Boron-Bridged Bis(oxazolines) and their Use in Copper-Catalyzed Reactions

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Dekan

A mes parents

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Contents

Abbreviations

3-NBA	3-nitro-benzyl alcohol (matric for FAB-MS)
Å	Ångström (10^{-10} m)
Ar	aryl
BINAP	2,2'-bis-(diphenylphosphino)-1,1'-bi-naphthalene
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
BOX	bis(oxazoline)
Bn	benzyl
br	broad (NMR)
Bu	butyl
c	concentration
cat.	catalyst
Cbz	carbobenzyloxy
COD	1,5-cyclooctadien
Cy	cyclohexyl
δ	chemical shift
d	day
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact ionization (MS)
ent	enantiomer
Et	ethyl
equiv.	equivalent
ESI	electronspray ionization
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC	gas chromatography
h	hour
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
i	iso
J	coupling constant
L*	chiral ligand
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
m	*meta*
M	molar (mol/L)
Me	methyl
m.p.	melting point
MS	mass spectroscopy
m/z	mass-to-charge ratio
n.d.	not determined
NMR	nuclear magnetic resonance
o	*ortho*
Oxa	oxazolidine
p	*para*
Ph	phenyl
PHOX	phoshinooxazoline
ppm	parts per million
Pr	propyl
R_f	retention factor
rt	room temperature
t	tertiary
TADDOL	tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethyl silyl
TBME	*t*-butylmethylether
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TSOH	toluenesulfonic acid
t_r	retention time
w	weak
$\tilde{\upsilon}$	wave number (IR)
	used to illustrate relative stereochemistry
	used to illustrate absolute stereochemistry

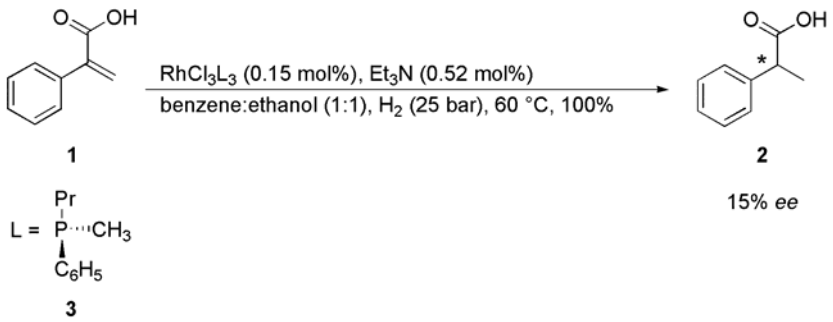
Chapter 1

Introduction

1 Introduction

1.1 Asymmetric Catalysis Breakthrough

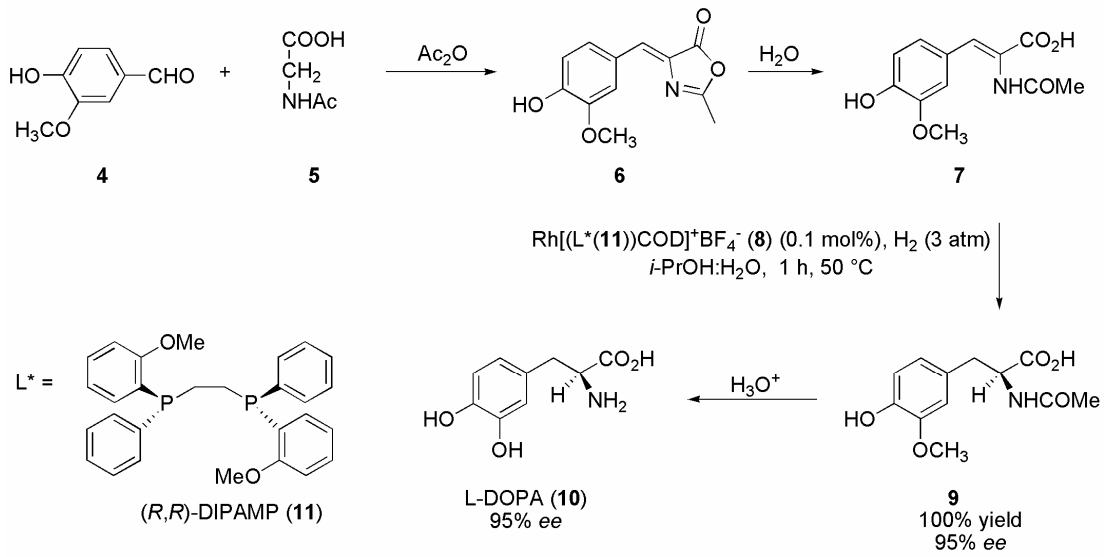
In 1848, Pasteur introduced the revolutionary concept of "dissymmetry" after he carried out the first enzymatic kinetic resolution. Starting from racemic ammonium tartrate, the organism *Penicillium glauca* selectively metabolized (*d*)-ammonium tartrate.[1] Since then, a wide variety of different routes have been developed to access enantiomerically pure compounds; chiral pool strategy, asymmetric synthesis based on chiral auxiliaries, enantioselective reactions by means of chiral reagents, chiral synthetic catalysts or enzymes. In 1968 Knowles, inspired by Horner's syntheses of chiral phosphines, was at the origin of the major breakthrough in asymmetric catalysis.[2] He showed that it was possible to induce enantioselectivity with a synthetic asymmetric rhodium complex derived from Wilkinson's catalyst.[3] The hydrogenation of styrene derivatives such as α-phenylacrylic acid (**1)** gave the optically active hydratropic acid (**2**) with an enantiomeric excess of 15% using an enantiopure methylpropylphenylphosphine ligand (**3**) (Scheme 1).



Scheme 1.

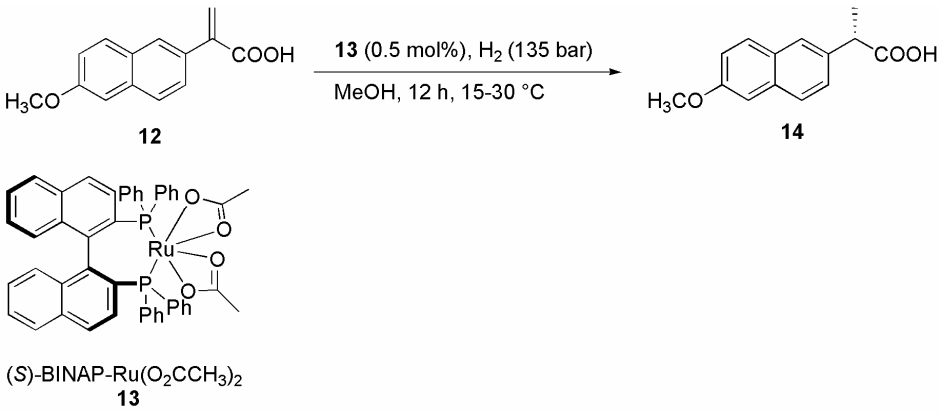
1.2 Industrial Applications of Chiral Transition-Metal Complexes

Knowles and co-workers later developed a chiral diphosphine-rhodium complex **8** that gave much higher *ee* and that catalyzed the hydrogenation of enamide **7** to a precursor of L-DOPA (**9**), used in the treatment of Parkinson's disease. This led to the first commercial use of a chiral transition-metal complex (Scheme 2).[4]



Scheme 2.

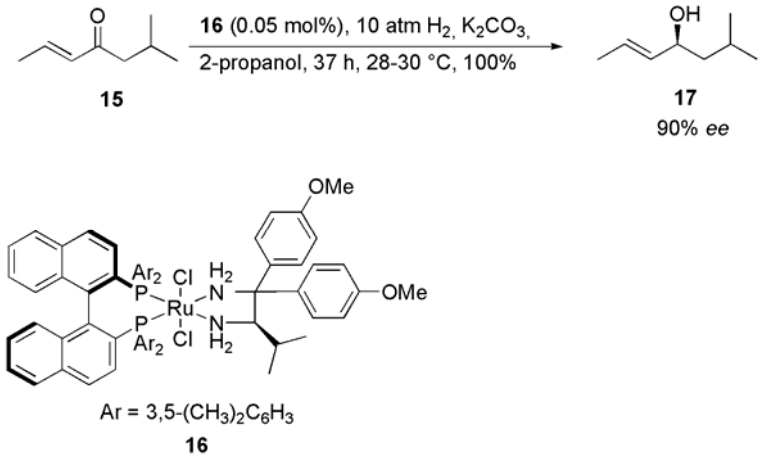
The expansion of asymmetric catalysis owes a great deal to Noyori's work. Nowadays, a number of transition-metal catalyzed reactions are highly enantioselective in the presence of diphosphine-binaphtyl ligand (BINAP) (**31b**).[5] In particular, BINAP-ruthenium(II) complexes catalyzed the hydrogenation of β,γ-unsaturated carboxylic acids[6], β-keto carboxylic esters[7] and functionalized ketones[8] to form highly enantioenriched products. For example, the BINAP-ruthenium(II) catalyst **13** was useful to catalyze the hydrogenation of the unsaturated carboxylic acid **12** to the anti-inflammatory agent naproxen[9] (**14**) in a yield of 92% and an enantiomeric excess of 97% (Scheme 3).



Scheme 3.

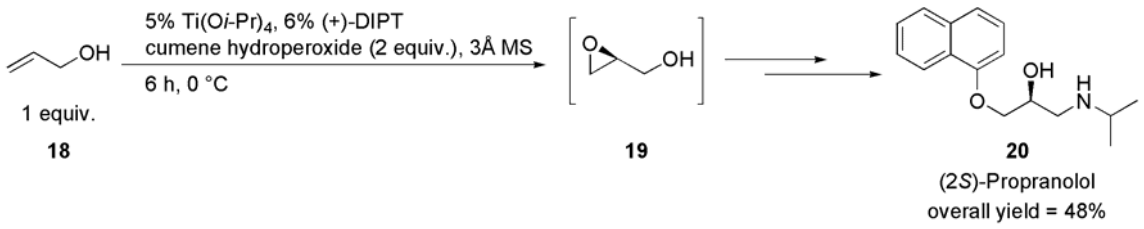
The research group of Noyori[10] demonstrated later that the *trans*-$RuCl_2$-(phosphine)$_2$(1,2-diamine) complex **16** preferentially hydrogenated the carbonyl group of an α,β-unsaturated

ketone instead of the double bond in a solution of 2-propanol in the presence of a weak base. This reaction was applied to the synthesis of compound **17**, a key building block for the preparation of the side chain of vitamin E (Scheme 4).



Scheme 4.

Parallel to the research on asymmetric hydrogenation, Sharpless's group developed transition-metal tartrate catalysts for the asymmetric epoxidation of allylic alcohols in 1980.[11] Later on, Sharpless and co-workers discovered that molecular sieves[12] could be used to further improve the efficiency of this asymmetric epoxidation. This process was applied on ton-scale in the industrial production of (*R*)- and (*S*)-glycidols, used to synthesize *β*-blockers based on (2*S*)-propranolol[13] (**20**) (Scheme 5). The alcohol **20** was synthesized in 5 steps from allylic alcohol **18** and was obtained in enantiomerically pure form after recrystallization in an overall yield of 48%.



Scheme 5.

More recently, Sharpless and co-workers devised a highly enantioselective osmium-catalyzed dihydroxylation of olefins.[14] They pre-mixed $K_2OsO_4.2H_2O$, a non volatile source of OsO_4,

$(DHQD)_2$-PHAL (**21**) or $(DHQ)_2$-PHAL (**22**), K_2CO_3 and $K_3Fe(CN)_6$ to form the active catalyst, which is easily prepared or commercially available (Figure 1).

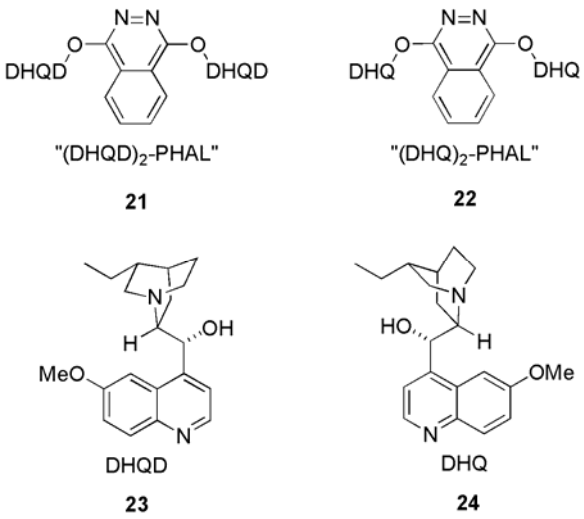
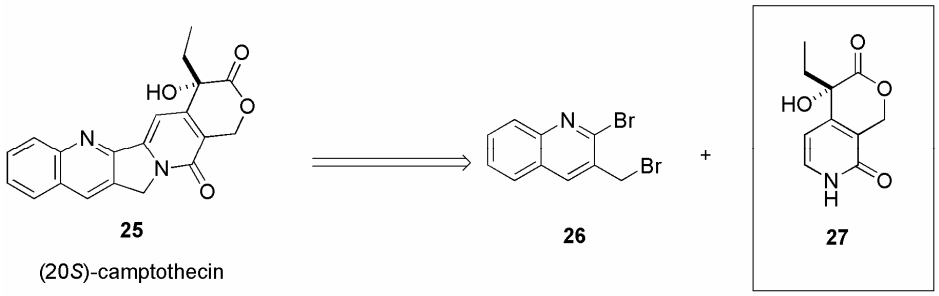


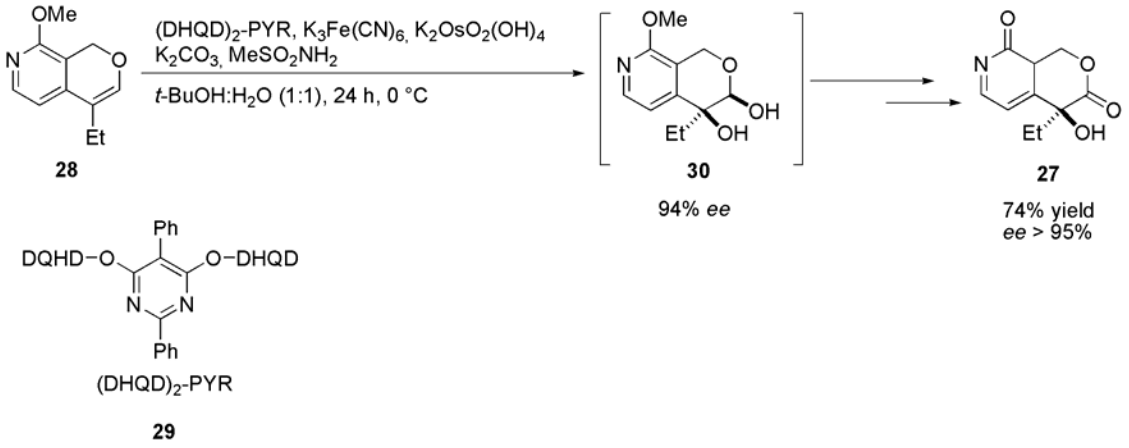
Figure 1.

An asymmetric dihydroxylation was used in the synthesis of (20*S*)-Camptothecin[13b] (**25**) which showed promising results in preclinical studies as an anticancer agent. Analogues of this alkaloid are now commercially available[15]. In 1992, Comins[16] proposed compound **27** as a key chiral intermediate (Scheme 6).



Scheme 6.

To prepare this intermediate Fang *et al.*[17] focused on the enol ether **28**, which was dihydroxylated under standard conditions using ligand $(DHQD)_2$-PYR (**29**) to give, after 2 additional steps, the corresponding pyridone **27** with an enantiomeric excess of >95% (Scheme 7).



Scheme 7.

Sharpless's epoxidation and dihydroxylation showed that synthetic catalysts could combine enzyme-like selectivity with sufficient generality for a wide range of substrates.

The successful work of Knowles, Noyori and Sharpless on asymmetric catalysis had obviously a great impact on academic research and the development of new drugs. All three were awarded with the Nobel Prize in chemistry in 2001.

1.3 Privileged Ligands in Asymmetric Catalysis

Enantiomerically pure compounds are in widespread use as pharmaceuticals, vitamins, agrochemicals, flavors and fragrances. Their synthesis using asymmetric catalysis requires a vast array of chiral ligands. Most of these are characterized by a "lock and key" specificity[18], which is also an enzyme feature. Therefore research scientists focused on the synthesis of chiral catalysts that would be selective for a broad range of reactions and substrates. Ligands of this kind are the so-called privileged ligands.[19] Important members include BINOL (**31a**), BINAP (**31b**), DuPhos (**32**), TADDOL (**33**), PHOX (**34**), BOX (**35a**), salen (**36**) and cinchona alkaloids (**37**) ligands (Figure 2).

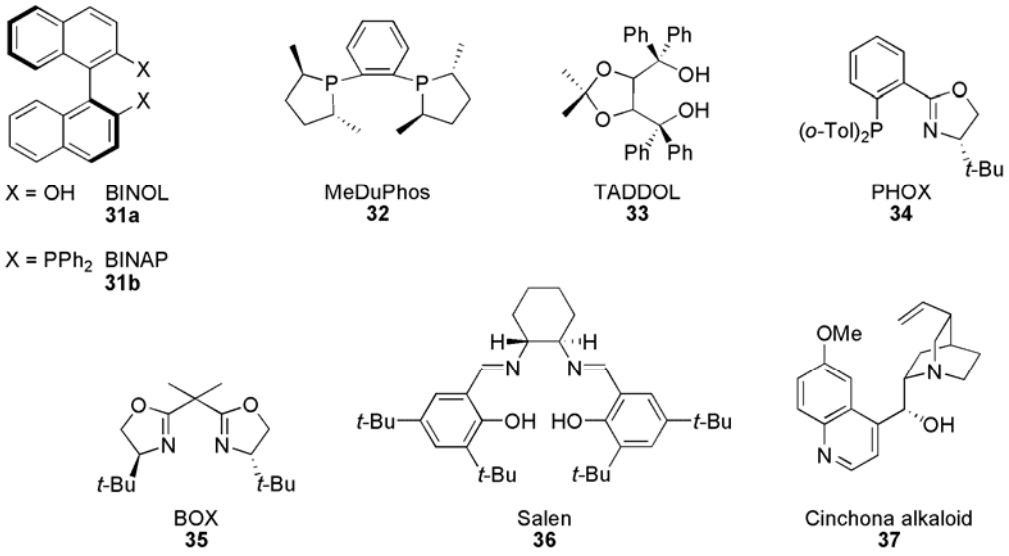


Figure 2.

One important characteristic of these ligands is the ease and flexibility of their synthesis. TADDOL **33** is derived from tartaric acid and is obtained in only two steps. Salen **36** and PHOX **34** ligands are synthesized from inexpensive chiral diamines and amino alcohols. Most of them possess C_2-symmetry which limits the number of possible catalyst-substrate arrangements and therefore reduces the number of competing reaction pathways. However, this feature does not necessarily imply that the ligand will be a privileged one. Ligands which are not C_2-symmetric can be highly efficient too; cinchona alkoloid derivatives[20] **37** for example are very selective for the aminohydroxylation of olefins,[21] heterogeneous hydrogenation of α-ketoesters[22] and phase transfer catalysis.[23]

The lack of common features for these ligands makes the identification of new privileged ligands problematic. High-throughput screening of catalyst libraries is still the most efficient way to discover new ligands.

1.4 Anionic and Neutral Ligands in Asymmetric Catalysis

Chiral ligands in asymmetric catalysis can be classified in two types: anionic and neutral ligands which form, in the presence of a metal, zwitterionic **38** and cationic complexes **39** (Figure 3).

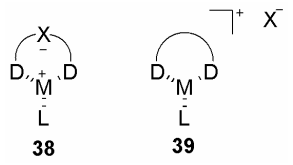


Figure 3.

The counterion of the cationic complex **39** is not necessarily a spectator. In many cases, it has an influence on the catalytic process.[24] First, the counterion competes with the substrate for coordination to the metal. Second, ion pairing may also influence stereochemistry.[24] For neutral ligands, the counterion is an additional variable to take into account for finding optimized reaction conditions. The zwitterionic complex **38** has obviously no counterion effect and this minimizes the number of parameters to screen.

1.5 Objectives of this Work

As one of the most versatile ligand structures, bis(oxazoline) ligands **35** have played a very important role in asymmetric catalysis over the last 25 years. To further develop its potential, a zwitterionic analogue, the borabox ligand **40**, was synthesized in the Pfaltz group.[25] The carbon bridging the two oxazoline units was replaced by a boron atom (Figure 4).

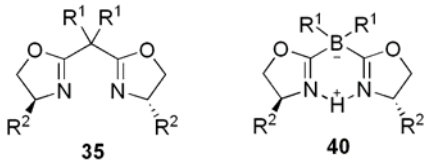


Figure 4.

The aim of this thesis was to demonstrate that the borabox ligands **40** were a valuable addition to the existing BOX ligands **35** with novel structural features.

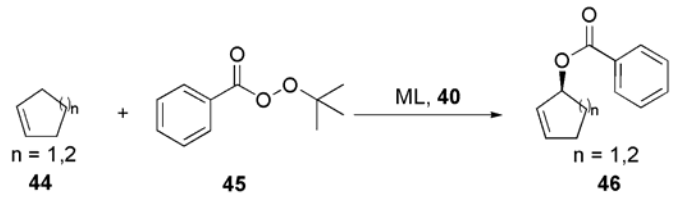
To obtain information about the characteristics of the borabox ligands **40** and its differences to the BOX ligands **35** crystallographic- and NMR-studies were performed.

This new ligand class was thought to show a similar versatility in asymmetric catalysis, but it was hoped to have a different or complementary behaviour compared to the BOX ligands due to the zwitterionic character of the corresponding metal complexes. Therefore several reactions were investigated in the presence of borabox ligands **40**.

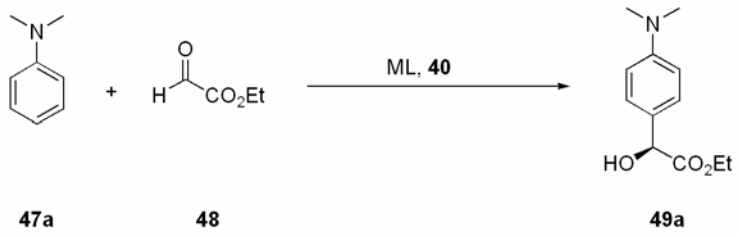
We studied first the Diels-Alder reaction, a benchmark reaction, and found suitable catalytic conditions (Scheme 8).

Scheme 8.

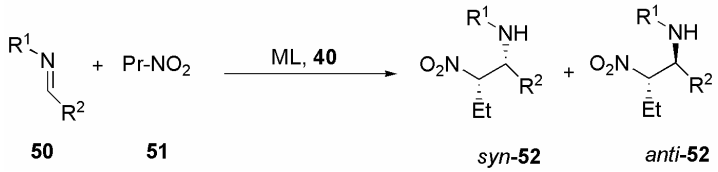
We became also interested in allylic oxidations, Friedel-Crafts and aza-Henry reactions (Schemes 9, 10 and 11), for which the reported enantioselectivities to date were still moderate.



Scheme 9.

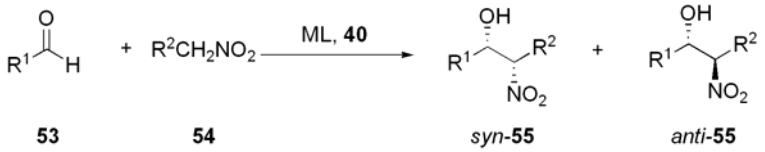


Scheme 10.



Scheme 11.

The Henry reaction was studied in greater detail (Scheme 12). After finding the optimal reaction conditions, the scope of the reaction was investigated.



Scheme 12.

Subsequently, C5,C5'-disubstituted borabox ligands (**56**) were synthesized (Figure 5). The objective was to improve the selectivity obtained in the Henry reaction by varying the substitution pattern of the ligand **56**.

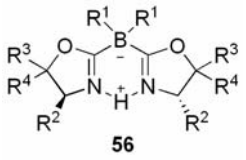


Figure 5.

Chapter 2

BOX and Zwitterionic Ligands in Asymmetric Catalysis

2 BOX and Zwitterionic Ligands in Asymmetric Catalysis

2.1 BOX Ligands in Asymmetric Catalysis

2.1.1 General Aspects

In 1986, Pfaltz and co-workers developed a new class of bidentate ligands, semicorrins **57** (Figure 6).[26] These C_2-symmetric ligands possess a rigid scaffold defined by the planar π system and the two pyrrolidine rings. This feature makes them attractive ligands for asymmetric catalysis. Indeed, semicorrin complexes induce high enantioselectivity in copper-catalyzed asymmetric cyclopropanation of olefins[27] and the cobalt-catalyzed conjugate addition of α,β-unsaturated esters and amides.[28]

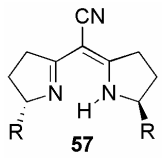


Figure 6.

The electron-rich vinylogous amidine group gives this class of ligands an electron donating character, reducing the electrophilicity of the metal center. But, for some reactions, it is preferable to have a weak electron donor or even a π-acceptor ligand.[29] In order to decrease this electron-donating character, neutral analogues of the semicorrins **57**, the bis(oxazolines) (**35**) and other ligands such as bioxazolines and aza-semicorrins[27] were independently developed by several groups in 1991 (Figure 7).[30,31] These bis(oxazolines) **35** were then successfully applied to both cyclopropanation of olefins and Diels-Alder reactions.

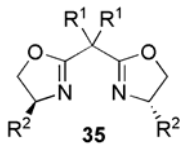
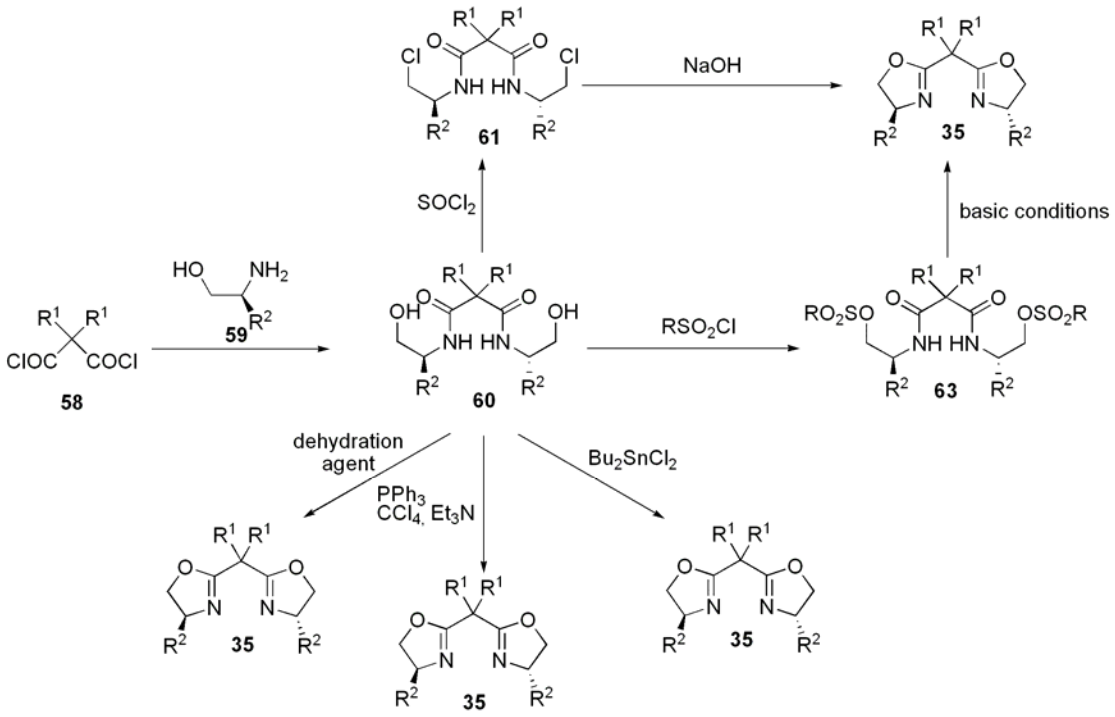


Figure 7.

Since then, the BOX ligands (**35**) have received increasing attention. In 2005, around 400 papers about BOX ligands were published.[32] This popularity can be explained by two factors, ease of the synthesis and the catalytic activity. The ligands **35** are readily formed in a simple 2-3 steps procedure (Scheme 13). In the first step, the addition of 2 equivalents of a *β*-amino alcohol (**59**) to a disubstituted malonic dichloride (**58**) led to the formation of bis-amide **60**. From this point, a variety of options are available.[32] In Corey's approach[31], compound **60** was converted to the bis-dichloride **61** in the presence of $SOCl_2$, and then cyclized to the BOX ligand (**35**) upon treatment with NaOH. Addition of RSO_2Cl (**62**) to bis-amide **60** gave access to intermediate **63**, leading to the BOX ligand (**35**) again under basic conditions. The BOX ligand (**35**) can also be synthesized in just one step from the bis-amide **60**. The Masamune protocol[33] gives access to the bis(oxazoline) system (**35**) by employing Bu_2SnCl_2 in refluxing toluene, whereas Evans[34] uses $Ph_3P/CCl_4/Et_3N$ as reagents. Dehydration reagents (methanesulfonic acid with CaH_2 for example) have also been used to cyclize compound **60** into the desired ligand **35**.[32]



Scheme 13.

More than 140 BOX ligands (**35**) have been developed so far.[32] In addition to the simple bis(oxazoline) ligands described before, C5-substituted ligands **64** and **65** have also been synthesized (Figure 8).[32]

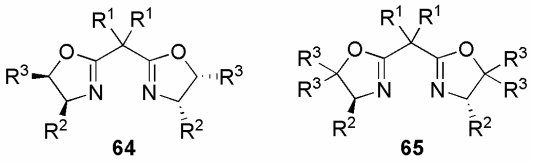


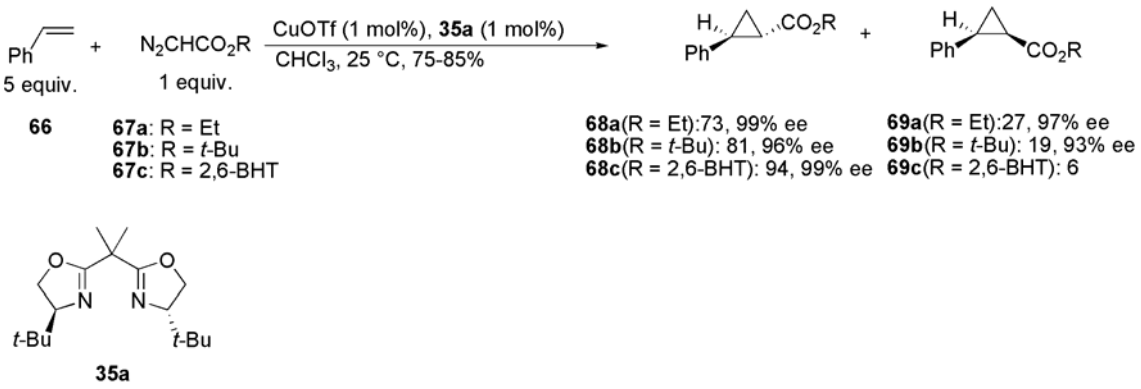
Figure 8.

The other, and major, reason for the popularity of the BOX ligands (**35**) are the high enantioselectivities they induce in Diels-Alder, aziridination, cycloproponation, allylic substitution, 1,3-dipolar cycloaddition, Mukayama-aldol, Michael, carbonyl ene and radical reactions.[32] Many of these processes have been successfully developed with copper-BOX complexes as catalysts. The next section will give a brief overview of the use of these systems in asymmetric catalysis (the Diels-Alder reaction will be examined in chapter 4).

2.1.2 BOX Ligands in Copper Asymmetric Catalysis

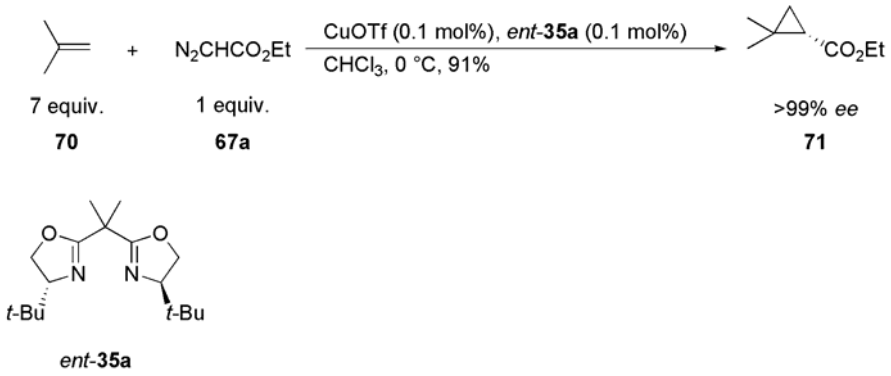
2.1.2.1 Cyclopropanation

Cyclopropanes have emerged as versatile precursors in organic synthesis.[35] Indeed, cyclopropane derivatives can undergo a variety of ring opening reactions (in the presence of electrophiles, nucleophiles, radicals, and by heat or light) and thus are useful intermediates for the synthesis of complex molecules.[35] The first enantioselective version of the cyclopropanation of olefins was reported by Nozaki and co-workers in 1966.[36] The reaction between styrene (**66**) and a variety of diazo compounds **67**, catalyzed by chiral copper-salicylaldimine complexes, gave only low *ee*'s but laid the groundwork for many other processes.[37] Among them, the use of copper complexes derived from the bis(oxazoline) ligand **35** in the cyclopropanation of olefins showcased the potential of this ligand.[30] The reactions between styrene (**66**) and the diazoacetates **67** were catalyzed by copper (I) triflate and the ligand **35a** affording cyclopropane derivatives **68** and **69** in good yields, *trans*:*cis* ratios and enantioselectivities (Scheme 14). The *trans*:*cis* ratio was increased in the presence of a bulky group on the diazoacetate **67** like 2,6-di-*tert*-butyl-4-methylphenyl (BHT). The *trans* cyclopropane derivative **68c** was then formed with a selectivity of 94:6 and 99% *ee*.



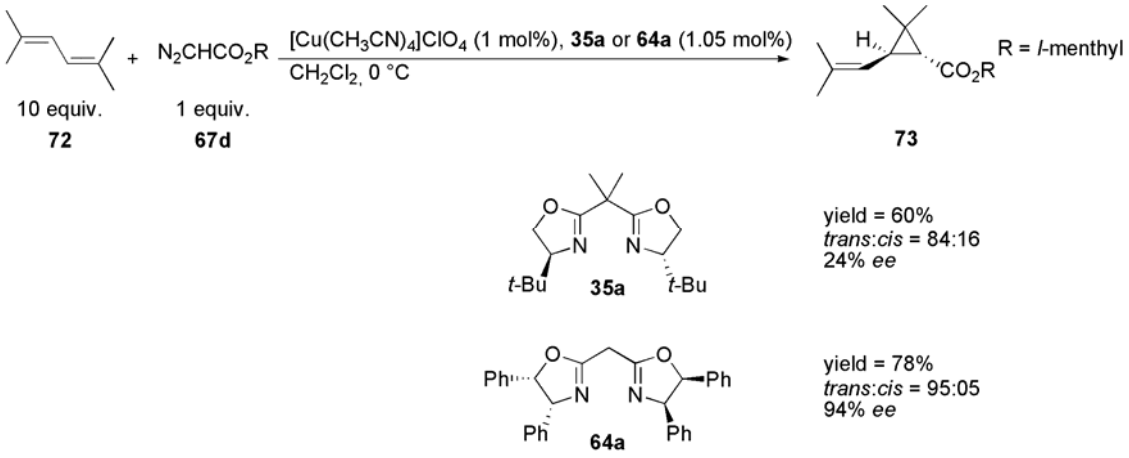
Scheme 14.

The cyclopropanation of 1,1-disubstituted olefins also proceeded with high selectivity in the presence of the BOX ligand **35a** (Scheme 15). 2-methylpropene (**70**) reacted with diazoacetate **67a** to give compound **71** with an *ee* >99%.



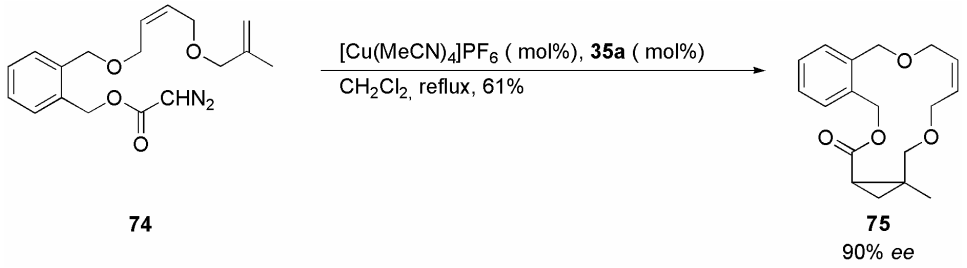
Scheme 15.

Nowadays, the BOX ligand **35a** is still the most versatile ligand used for the cyclopropanation of mono- and disubstituted terminal olefins. However, for trisubstituted and 1,2-disubstituted (*Z*)-olefins, C5-monosubstituted ligand **64a** has been found to induce higher selectivity (Scheme 16).[33b]



Scheme 16.

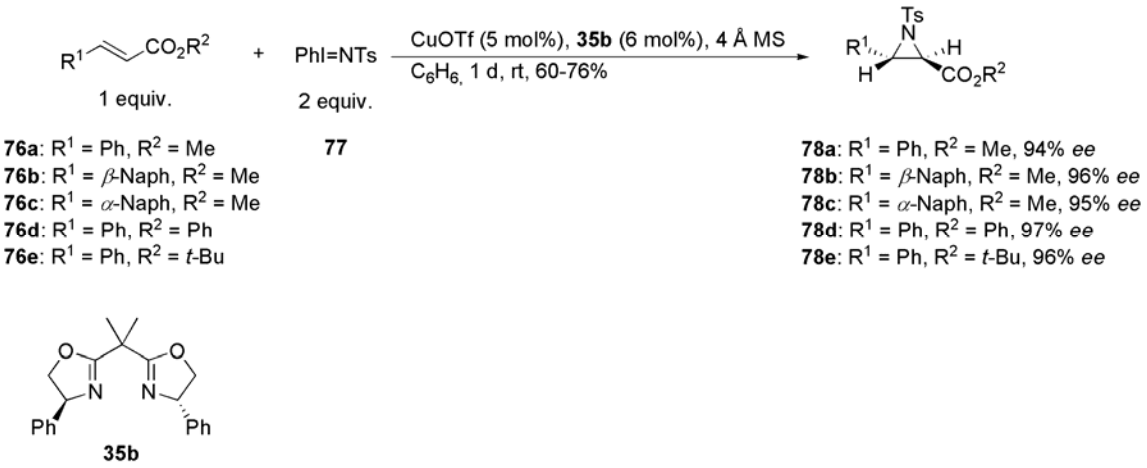
Copper complexes derived from BOX ligand **35a** are also efficient in the intramolecular cyclopropanation of olefins, especially in the synthesis of macrocycles.[38] The 15-membered ring product **75** was formed with exceptionally high regioselectivity (>50:1, competition between the formation of 10- and 15-membered rings), diastereoselectivity (>50:1 (*Z*)- *versus* (*E*)-cyclopropane geometry) and enantioselectivity (90% *ee*) (Scheme 17).[39]



Scheme 17.

2.1.2.2 Aziridination

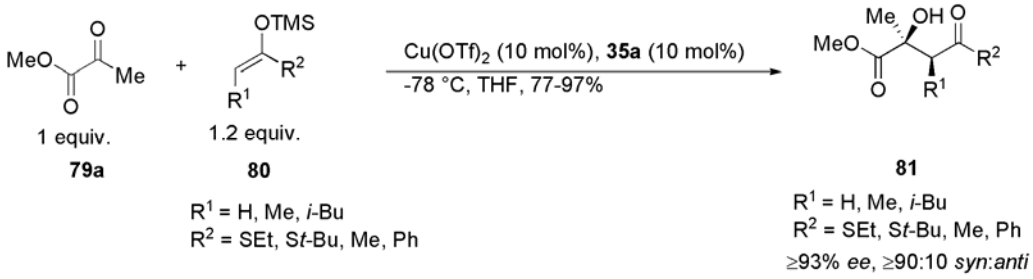
Contrary to cyclopropanation, aziridination of olefins is only at the beginning of its development. Enantioselective versions of the reaction via imido transfer catalysis have been explored.[40] Evans *et al.* studied the aziridination of cinnamate ester derivatives **76** in the presence of BOX complexes (Scheme 18).[41] High levels of enantioselectivity were observed (94-97% *ee*) with both aryl and ester substituents. However, no further applications with other substrates have so far been developed.



Scheme 18.

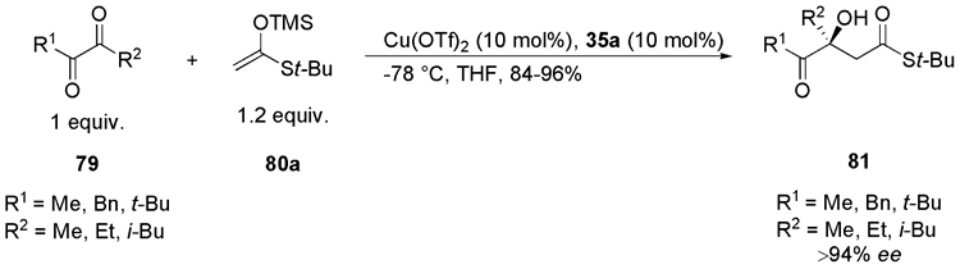
2.1.2.3 Mukaiyama Aldol Reaction

Aldol reactions are extremely popular in asymmetric catalysis as one reaction can simultaneously establish two new stereocenters. In the mid 70's, Mukaiyama developed a new type of aldol reaction, employing silyl enol ethers as enolate equivalents in Lewis acid-catalyzed aldol additions.[42] Evans then studied this reaction in the presence of copper (II)-BOX complexes, which were found to be effective catalysts for the addition of enolsilanes (**80**) to methyl pyruvate (**79a**, Scheme 19).[43] The tertiary alcohol product **81** was obtained with high diastereoselectivity and enantioselectivity regardless of the enolsilane **80** used (≥90:10 *syn*:*anti*, ≥93% *ee*).



Scheme 19.

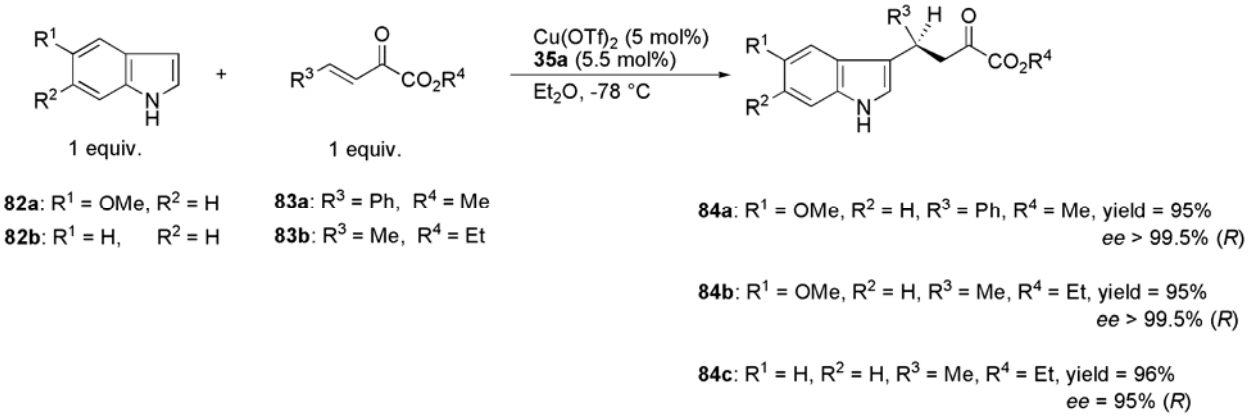
The reaction was also very selective with a broad range of α-ketoesters **79** (Scheme 20).[43] The generality of this process is a perfect example of the versatility shown by the privileged ligand **35a**.



Scheme 20.

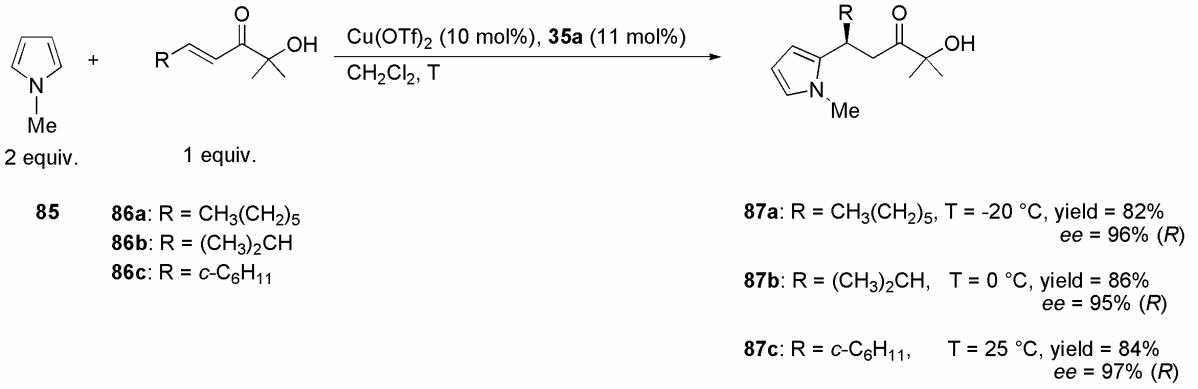
2.1.2.4 Michael Reaction

The 1,4-addition of stabilized carbanions to electrophilic π-systems has emerged as a powerful method for asymmetric catalysis.[44] BOX ligands (**35**) have been found to be particularly selective for the conjugate addition of cyclic compounds such as indoles (**82**) to *β,γ*-unsaturated *α*-ketoesters (**83**). Optically-active aryl-substituted compounds **84** were synthesized in high yields and with high enantioselectivities (Scheme 21).[45]



Scheme 21.

The BOX ligand **35a** was also the ligand of choice for the 1,4-addition of methyl-pyrroles **85** to *α*-hydroxy enones **86** (Scheme 22).[46]

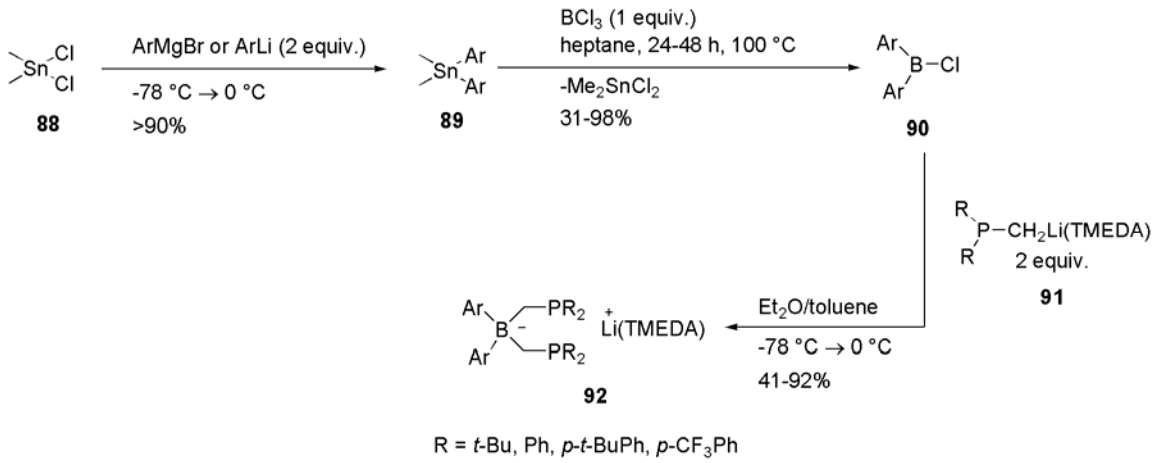


Scheme 22.

These copper (II)-BOX catalyzed Michael reactions are characterized by their great flexibility and are capable of synthesizing pyrrole and indole skeletons, which are very important moieties found in natural products and medicinal agents.[47]

2.2 Zwitterionic Complexes in Asymmetric Catalysis

In recent years, zwitterionic organometallic complexes of cationic metals have received increasing attention. Many of them were synthesized for catalytic purposes. Indeed, they were expected to provide reactivity advantages over analogous cationic complexes. In 2001, Peters developed the anionic version of the phosphine ligands by incorporating a boron atom into the ligand framework.[48] The general method for synthesizing these bis(phosphino)borates[49] **92** is based on the attack of a phosphinoalkyl carbanion **91** on a borane electrophile **90** (Scheme 23). For generating the latter, a two-step procedure was used. First, the dimethyldiaryltin reagent **89** was formed via reaction with either a *Grignard* or an organolithium reagent and then the tin intermediate **89** attacked BCl_3 to give the boron electrophile **90**. Finally, the addition of the phosphine carbanion **91** to intermediate **92** afforded the bis(phosphino)borate **92** in moderate to good yields.



Scheme 23.

To compare the electronic properties of bis(phosphino)borate **92** to a cationic analogue **93**, the carbonyl complexes **94** and **95** were synthesized (Figure 9). IR data were reported and the CO stretching frequency for the neutral complex **94** was lower in energy than the one for the cationic complex **95**, meaning that the phosphino(borate) ligand **92** is more electron-releasing than **93**.

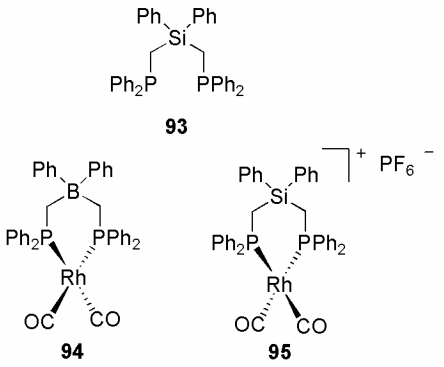


Figure 9.

The same trend was reported for bis(amino)borate **96**, an anionic equivalent of tertiary diamine, which was synthesized following a similar method to that used for the bis(phosphino)borate ligand **92** (Figure 10).[50]

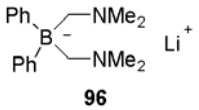
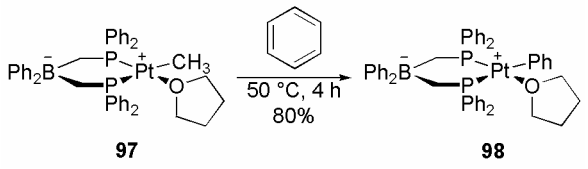


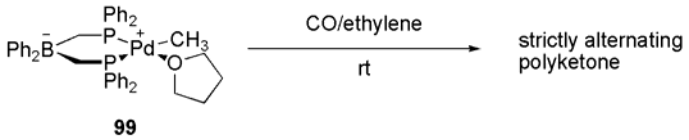
Figure 10.

The increased electron-richness of the zwitterionic complexes derived from ligands **92** and **96** as compared to the analogous cationic complex does not impede their ability to mediate catalytic reactions. Indeed, similar reactivities were observed in hydroacylation of 4-methyl-4-pentenal, hydrogenation, hydroboration, and hydrosilylation of styrene (**66**).[51] However, there does exist a difference in the activities of the cationic and zwitterionic complexes depending on the solvent. The activity of the zwitterionic phosphane and amine rhodium systems stayed highly constant in a wide range of polar and non-polar solvents whereas the analogous cationic complex showed high reactivity only in specific solvents.

The anionic ligand **92** was also applied in other catalytic reactions. Platinum (II) complex **97** promoted benzene C-H activation[48] (Scheme 24) and the zwitterionic palladium (II) complex **99**[52] was very active for the copolymerization of CO and ethylene, competing with the corresponding cationic complex (Scheme 25).

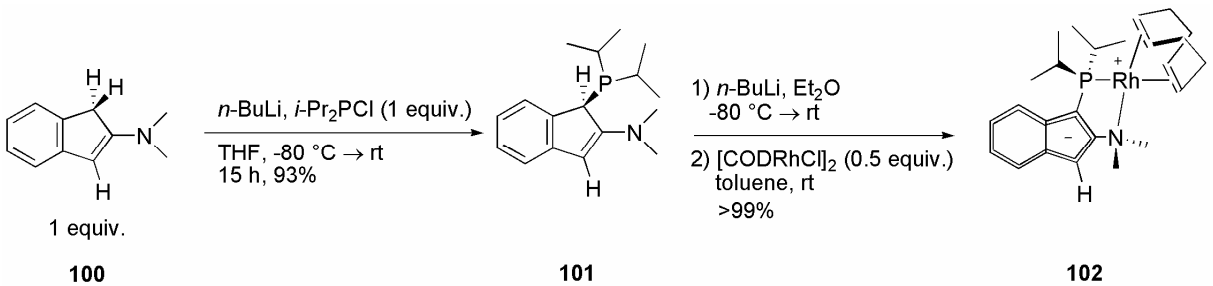


Scheme 24.



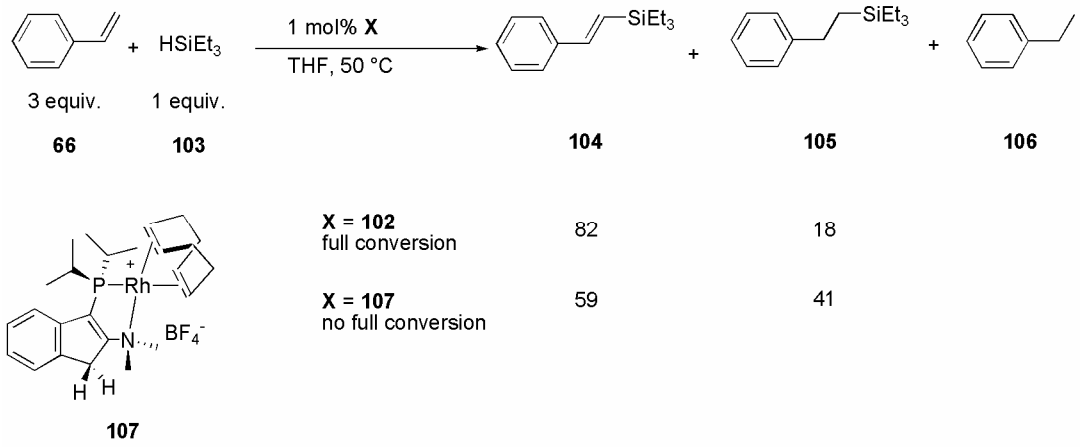
Scheme 25.

As a further variation, Stradiotto *et al.* have developed a P,N-substituted indenide ligand **101**, which was synthesized in one step from 2-methylaminoindene **100** (Scheme 26).[53]



Scheme 26.

The catalytic performance of the corresponding Rh(I) complex **102** was tested in the dehydrogenative silylation of styrene (**66**) and compared with the reactivity of the cationic Rh(I) species **107** (Scheme 27). Full conversion and good selectivity for dehydrogenative silylation over hydrosilylation (preferred formation of **104** over **105**) were obtained in the presence of the complex **102**. In contrast, the reaction was both incomplete and poorly selective when it was catalyzed by the cationic complex **107**.



Scheme 27.

Ligand **101** was also applied to the hydrogenation of alkenes and zwitterionic complex **108** was found to be active in a broad range of solvents (Figure 11).[54]

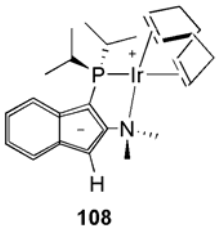


Figure 11.

In general, zwitterionic complexes compete well with their cationic analogues but they can also outperform them under certain conditions. They are usually little influenced by the polarity of the solvent used and, unlike the cationic complexes, they avoid an undesirable counterion effect which can unpredictably affect the performance of the catalyst.[55]

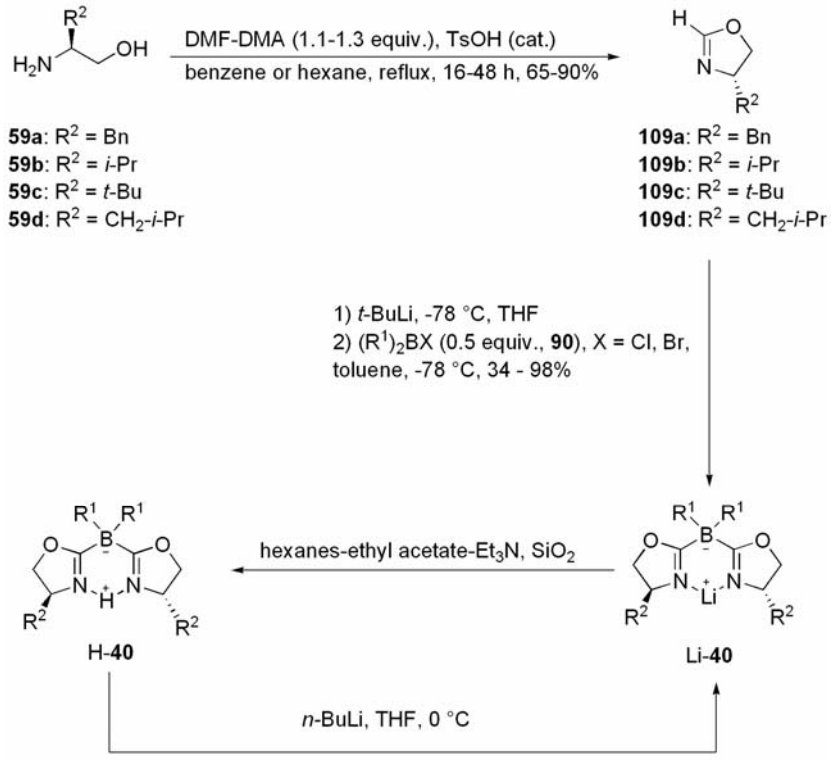
Chapter 3

Characteristics of Borabox Ligands

3 Characteristics of Borabox Ligands

3.1 Synthesis of Borabox Ligands

The synthesis of the borabox ligands **40** differs from known synthetic approaches to bis(oxazolines) **35**.[32] The desired ligand **40** was obtained in only two steps in a very straightforward fashion. In the first step, the amino alcohol **59** cyclized into the 2*H*-oxazoline **109**, in the presence of DMF-DMA and TsOH as catalyst (Scheme 28).[56] Lithiation of **109** according to Meyers' procedure[57], followed by treatment with 0.5 equivalents of dialkyl or diaryl haloboranes **90** gave access to the lithium salt Li-**40** of borabox ligand. The pure protonated form H-**40** could be easily isolated after column chromatography on silica using a hexanes/ethyl acetate/triethylamine eluent as a 10/1/0.5 mixture. The lithium salt Li-**40** can be quantitatively regenerated by treatment of the ligand H-**40** with *n*-butyllithium in tetrahydrofuran at 0 °C.



Scheme 28.

Thirteen borabox ligands were synthesized following this procedure in moderate to good yields (Table 1).

Table 1.

Entry	R^1	R^2	Ligand	Yield[a] [%]
1	Cy	*i*-Pr	**40a**	70
2	Et	*i*-Pr	**40b**	65
3	Ph	*i*-Pr	**40c**	63
4	3,5-bis(trifluoromethyl)phenyl	*i*-Pr	**40d**	45
5	Cy	*t*-Bu	**40e**	51
6	Et	*t*-Bu	**40f**	65
7	Ph	*t*-Bu	**40g**	72
8	3,5-bis(trifluoromethyl)phenyl	*t*-Bu	**40h**	89
9	Et	Bn	**40i**	78
10	Ph	Bn	**40j**	31
11	3,5-bis(trifluoromethyl)phenyl	Bn	**40k**	44
12	Cy	Bn	**40l**	39
13	Ph	CH_2-*i*-Pr	**40m**	19

[a] Isolated yields of the protonated borabox ligand H-**40**.

Variation of the substituents both at the boron atom and the stereocenters of the oxazoline rings allow for the tuning of electronic and steric factors. A proper choice of the substituent R^2 allows the control of the coordination sphere. Futhermore, DFT calculations (B3LYP, 6-31G*, LALN2DZ) showed that the Lewis acidic character of the metal center could be adjusted by variation of the nature of the substituent R^1 (Figure 12).[58] Indeed, the more electrowithdrawing is the substituent R^1, the more Lewis acidic is the metal center.

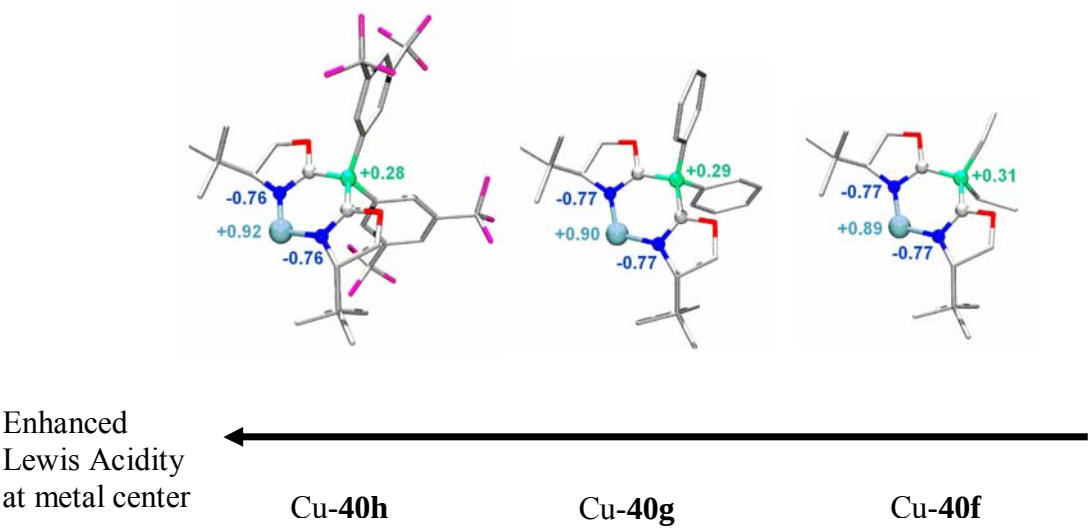
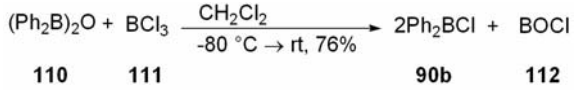


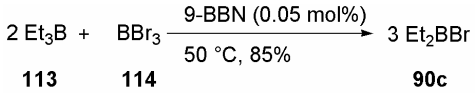
Figure 12.

The borabox ligands **40** were prepared using Cy_2BCl (**90a**), Ph_2BCl (**90b**), Et_2BBr (**90c**) and bis((3,5-trifluormethyl)phenyl)-chloroboran (**90d**). Chlorodicyclohexylborane **90a** is commercially available as a solution, and the corresponding diphenylborane chloride **90b** can be easily prepared in only one step and high yield by the addition of boron trichloride **111** to diphenylborinic anhydride **110** (Scheme 29).[59]



Scheme 29.

Diethylboron bromide **90c** was synthesized from triethylborane **113** and boron tribromide **114** in the presence of 9-BBN as catalyst in 85% yield (Scheme 30).[60]



Scheme 30.

The synthesis of diaryl haloborane **90** was already mentioned in section 2.2, and bis((3,5-trifluormethyl)phenyl)-chloroboran **90d** was obtained with a yield of 18% over two steps.

3.2 Determination of the pK_a of the Borabox Ligand

Unique to borabox ligand **40** is the ability to prepare, store and use the protonated and the lithiated form of this ligand. These two forms are both very efficient in catalysis. The lithium salts of borabox complexes successfully catalyzed the cyclopropanation of styrene (**66**), whereas protonated borabox ligands competed well with BOX ligands in the kinetic resolution of 1,2-diols (see section 3.4). From a practical point of view, the protonated ligand is usually preferred as it can be stored under air and is easily handled. We wished to determine the pK_a of the borabox ligand H-**40**. This was done by NMR studies, which are part of this thesis.

One equivalent of ligand **40c** was mixed with one equivalent of base in C_6D_6 and the resulting solution was analysed by ^1H NMR and ^{11}B NMR. The Schwesinger bases, which are

uncharged polyaminophosphazenes, were chosen as deprotonating agents.[61] Indeed, variation of the substituents of these bases allow to adjust quite easily the pK_a and then to cover a wide range of pK_a (Figure 13). When **P_4** (pK_a of 42.7 in acetonitrile) was added to ligand **40c** in C_6D_6 a shift in both ^1H NMR and ^{11}B NMR was observed (Figure 14 and Table 2). The boron signal was moving by 0.39 ppm in lower field (entry 2, Table 2). The deprotonation experiments were repeated with two other Schwesinger bases **P_1** and **P_2** (pK_a = 26.88 and 33.49 in acetonitrile respectively, entries 3 and 4, Table 2). No changes were observed using **P_1** but the addition of **P_2** to the borabox ligand **40c** caused a change in both ^1H and ^{11}B NMR signals ($\delta(^{11}B)$ =-13.27 ppm, entry 4, Table 2).

Borabox ligand **40c** was therefore assigned a pK_a in the range of 26-33.

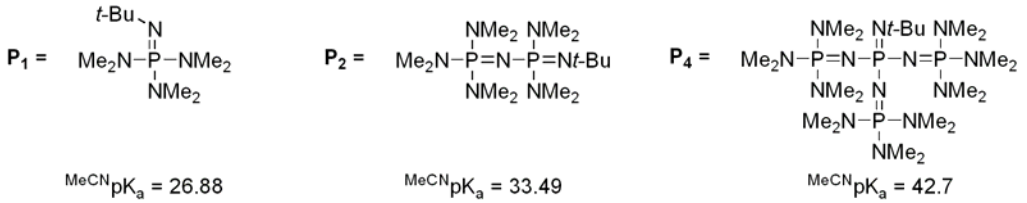


Figure 13.

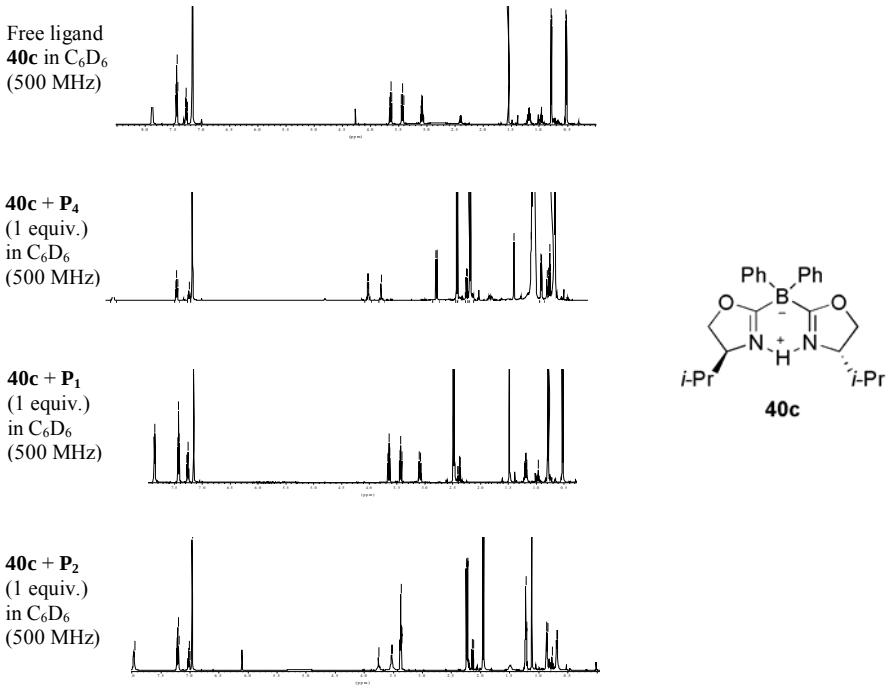


Figure 14.

Table 2.

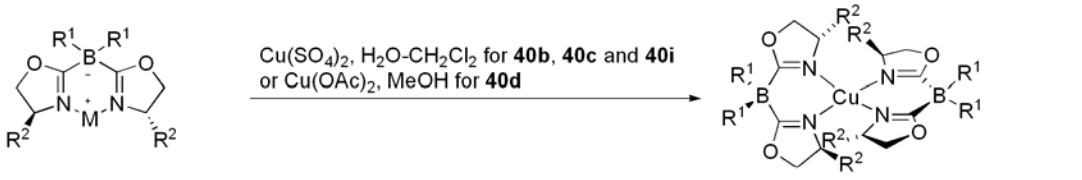
Entry	Base	$^{MeCN}pK_a$	$^{DMSO}pK_a$	δ^{11}B NMR[a] [ppm]
1	none	-	-	-13.52
2	**P_4**	42.7	30.2	-13.13
3	**P_1**	26.88	-	-13.48
4	**P_2**	33.49	21.5	-13.27

[a] In C_6D_6 (161 MHz) and using $B(OMe)_3$ as internal reference $\delta(^{11}B) = 18.72$ ppm.

3.3 Crystal Structures of Borabox Ligands

3.3.1 Homoleptic Borabox Complexes

Stable complexes of Cu^{II}, Zn^{II}, Pd^{II}, Rh^{I} and Ir^{I} could be prepared from the lithium salt Li-**40** or the protonated form H-**40** of the borabox ligand (Scheme 31).[25] The homoleptic borabox copper complexes **115** were synthesized by Clément Mazet in our group by reaction of the lithium salt Li-**40** with one equivalent of $CuSO_4.H_2O$ in a biphasic mixture of water and dichloromethane, or by reaction of the protonated ligand H-**40** with one equivalent of $Cu(OAc)_2$ in methanol.[62]

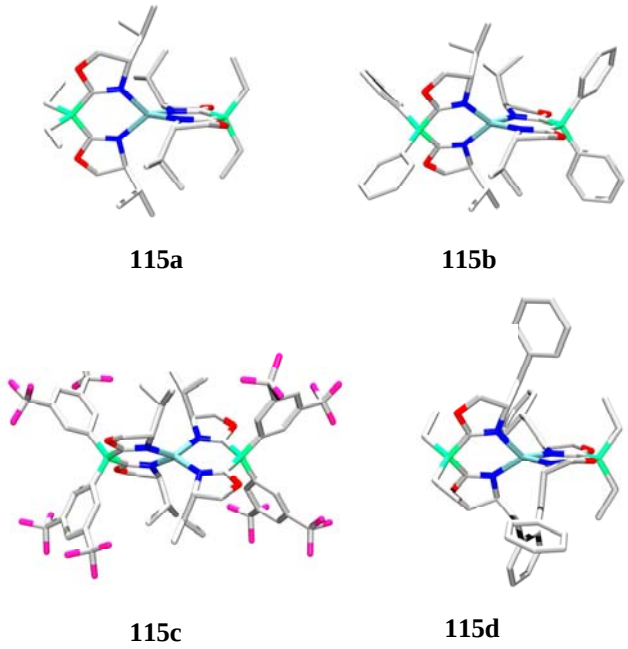


40b: R^1 = Et, R^2 = *i*-Pr
40c: R^1 = Ph, R^2 = *i*-Pr
40d: R^1 = 3,5-$(CF_3)_2C_6H_3$, R^2 = *i*-Pr
40i: R^1 = Et, R^2 = Bn

115a: R^1 = Et, R^2 = *i*-Pr
115b: R^1 = Ph, R^2 = *i*-Pr
115c: R^1 = 3,5-$(CF_3)_2C_6H_3$, R^2 = *i*-Pr
115d: R^1 = Et, R^2 = Bn

Scheme 31.

All complexes adopt a distorted tetrahedral geometry (Figure 15). The average bond lengths between the bridging boron atom and the oxazoline rings vary from 1.61 Å (**115a**, **115b** and **115d**) to 1.62 Å (**115c**). C=N bond lengths are in the range of 1.28 Å (**115a**) to 1.30 Å (**115d**). The angles C_{oxa}-B-C_{oxa} are close to the ideal tetrahedral angle with values between 109.0° (**115a**) and 110.4° (**115c**).



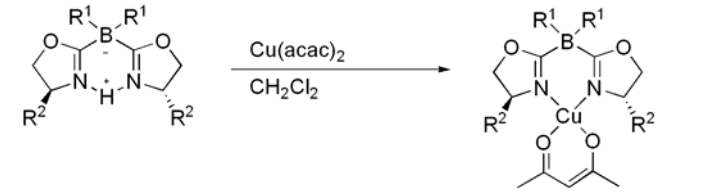
115a **115b**

115c **115d**

Figure 15.

3.3.2 Monomeric Borabox Complexes

In an analogous fashion to the formation of semicorrins complexes[63], the monomeric complexes **116** were prepared by mixing stoichiomeric amounts of borabox ligand **40** with copper (II) acetylacetonate in dichloromethane (Scheme 32).



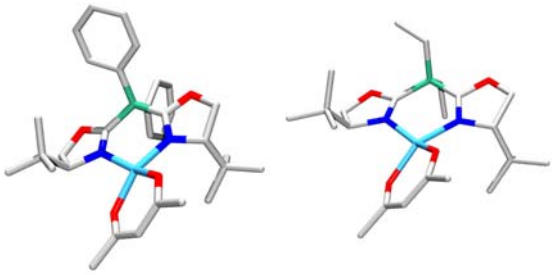
40f: R^1 = Et,R^2 = *t*-Bu
40g: R^1 = Ph, R^2 = *t*-Bu

116a: R^1 = Et,R^2 = *t*-Bu
116b: R^1 = Ph, R^2 = *t*-Bu

Scheme 32.

These monomeric complexes **116** adopt a very similar square-planar distorted geometry (Figure 16). The bond lengths B-C_{oxa} vary from 1.62 Å to 1.63 Å and the bond length N-Cu is 1.95 Å for both. The bite angles, defined as the angle about the copper and the two nitrogen atoms (N-Cu-N), are between 95.2° (**116b**) and 97.8° (**116a**). These crystallographic

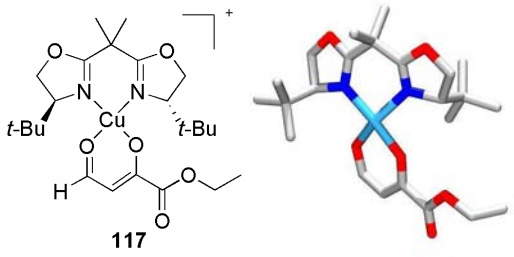
parameters suggest that variation of the boron substituents results in little change of the solid state structure.



116b **116a**

Figure 16.

The previously reported BOX complex **117**[64] shows a lesser distorted square planar geometry compared to the borabox complexes **116** (d(C-C_{oxa}) = 1.50 Å and d(N-Cu) = 1.98 Å), with a bite angle of 91.4° closer to an ideal square planar angle (Figure 17).



117

Figure 17. The triflate counterion and hydrogens have been omitted for clarity.

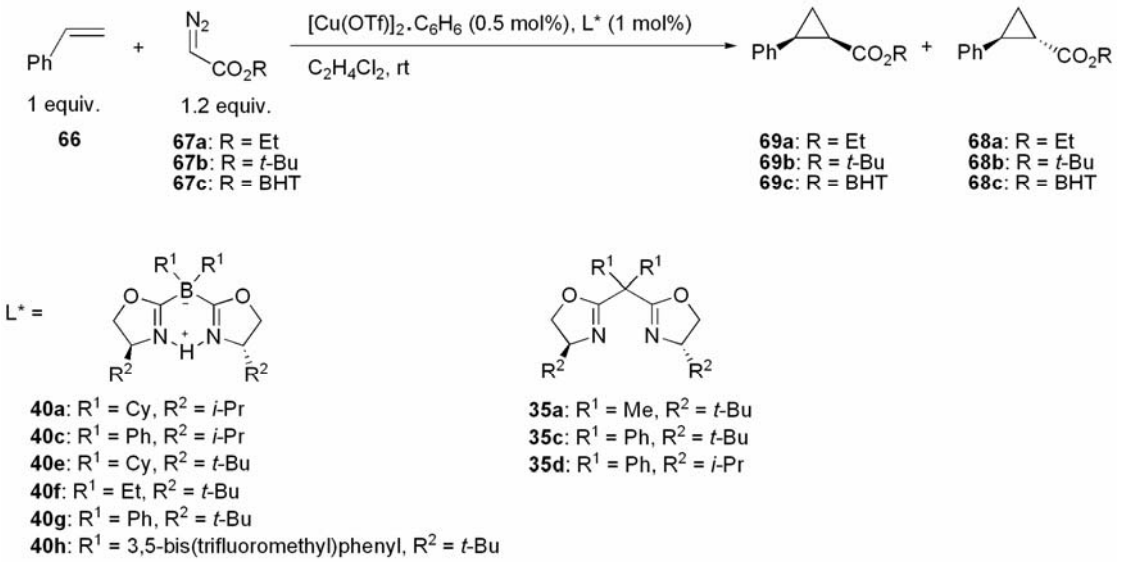
3.4 Borabox Ligands in Asymmetric Catalysis

Borabox ligands **40** were used in the Pfaltz' group for the cyclopropanation of olefins[25], desymmetrization of meso diols and kinetic resolution of 1,2-diols.[65] Although the palladium-borabox complex was found to be completely inactive in asymmetric allylic alkylation[62], the investigations of this reaction gave an insight into some interesting features of the borabox ligand **40**.

3.4.1 Cyclopropanation of Olefins

For testing the reactivity and selectivity of the borabox ligand, the cyclopropanation of olefins was investigated. Pfaltz and co-workers carried out a comparative study of the cyclopropanation of styrene (**66**) in the presence of borabox **40** and analogous BOX ligands **35**.[25] In general, these two kinds of ligand gave similar reactivities (63-89% yield, Table 3). In the presence of ethyl diazoacetate (**67a**), the enantioselectivities induced by the borabox ligands **40** were inferior to those obtained using the BOX ligands **35** (entries 1 to 9, Table 3). However, in the reaction with *tert*-butyl diazoacetate **67b** and 2,6-di-*tert*-butyl-4-methylphenyl (BHT) diazoacetate **67c**, the enantiomeric excesses obtained with the borabox ligands **40** were comparable to those obtained using the BOX ligands **35**. Interestingly, higher *cis*:*trans* ratios were obtained with borabox ligands **40** (entries 10 to 17, Table 3). The best result was obtained when the bulkier BHT-diazoacetate **67c** was used, in the presence of the ligand possessing perfluorinated aryl groups at the boron atom **40h** (98% *ee*, *cis*:*trans* ratio of 1:99, 89% yield, entry 17, Table 3).

Table 3.



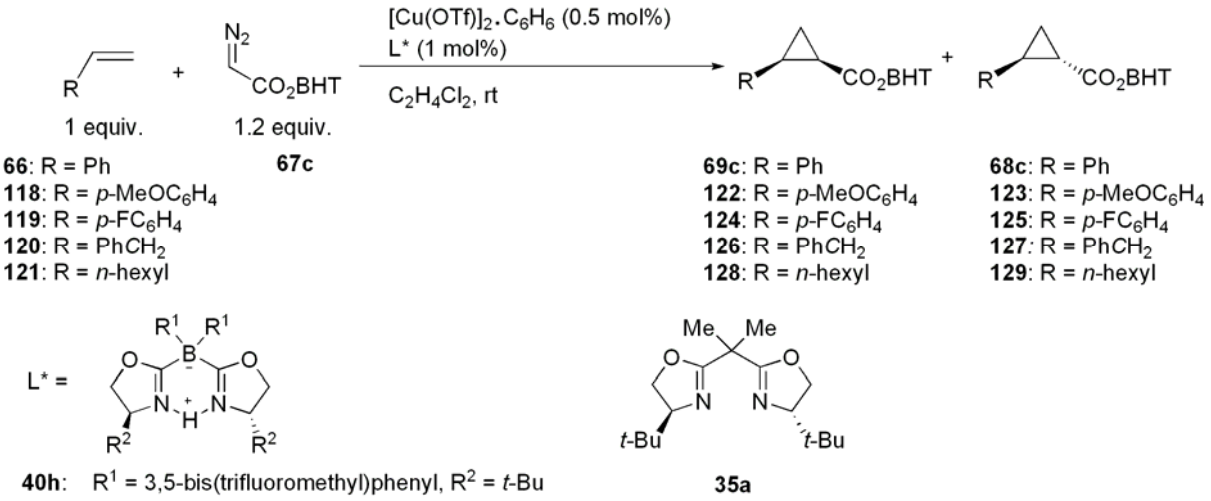
Entry	Ligand	Diazoester	*cis:trans*[a]	*ee* (*cis*) [b] [%]	*ee* (*trans*)[b] ee [%]	Yield [%][c] (*cis*+*trans*)
1	**35d**	**67a**	36:64	54	51	85
2	**35c**	**67a**	33:67	91	89	72
3	**35a**	**67a**	27:73	97	99	77
4	**40c**	**67a**	29:71	58	65	77
5	**40g**	**67a**	30:70	66	70	84
6	**40a**	**67a**	32:68	24	33	68
7	**40f**	**67a**	28:72	59	72	75

Entry	Ligand	Diazoester	*cis:trans*[a]	*ee* (*cis*) [b] [%]	*ee* (*trans*)[b] ee [%]	Yield [%][c] (*cis*+*trans*)
8	**40e**	**67a**	28:72	78	66	79
9	**40h**	**67a**	32:68	68	77	89
10	**35c**	**67b**	21:79	93	90	70
11	**35a**	**67b**	19:81	93	96	75
12	**40g**	**67b**	15:85	77	67	77
13	**40f**	**67b**	13:87	76	73	65
14	**40e**	**67b**	9:91	82	73	63
15	**40h**	**67b**	17:83	86	92	65
16	**35a**	**67c**	4:96	-	99	85
17	**40h**	**67c**	1:99	-	98	89

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by chiral GC or HPLC. [c] Isolated yields.

Borabox ligands **40** also performed well with other alkenes (Table 4). The enantioselectivities induced were similar to those obtained with BOX ligands **35** and the diastereoselectivities were generally higher with the borabox ligands **40** (compare entry 1 to 2, 5 to 6, 9 to 10, Table 4).

Table 4.



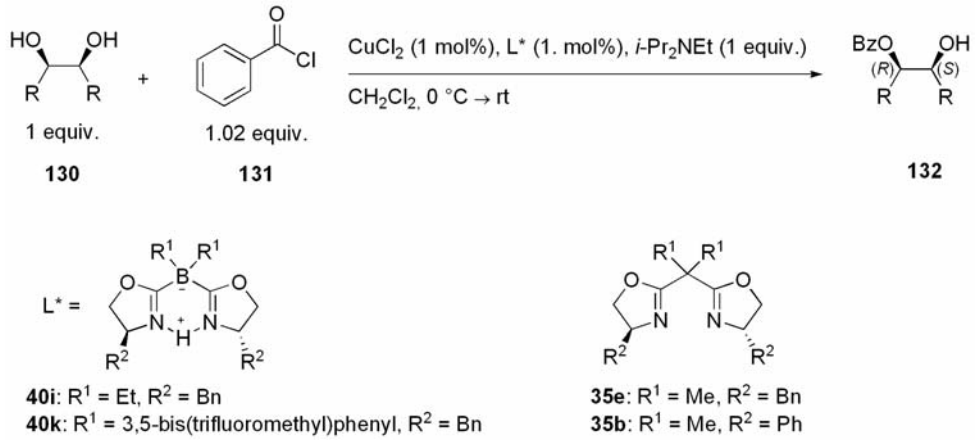
Entry	Ligand	alkene	*cis:trans*[a]	*ee* (*trans*) [%][b]	Yield [%][c] (*cis*+*trans*)
1	**35a**	**66**	4:96	99	85
2	**40h**	**66**	1:99	98	89
3	**35a**	**118**	4:96	96	35
4	**40h**	**118**	4:96	97	65
5	**35a**	**119**	4:96	99.4	89
6	**40h**	**119**	1:99	99.5	91
7	**35a**	**120**	7:93	99	ng[d]
8	**40h**	**120**	8:92	97	66
9	**35a**	**121**	2:98	99	51
10	**40h**	**121**	1:99	95	68

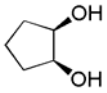
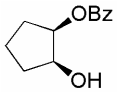
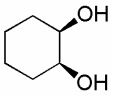
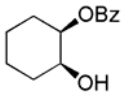
[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC. [c] After chromatography. [d] ng = not given.

3.4.2 Desymmetrization of *meso*-Diols

In 2003, Matsumura *et al.* developed the first example of an enantioselective copper (II)-mediated activation of *meso* 1,2-diols.[66] Catalyzed by the complex derived from the BOX ligand **35b** and copper (II) chloride, the reaction gave high enantioselectivities. The same conditions were used when carrying out the reaction with borabox ligand **40** (Table 5).[25] In most of the cases better selectivities and yields were obtained in the presence of the borabox ligands **40i** and **40k** (compare entries 1 and 2 to 3 and 4, 5 and 6 to 7 and 8, 9 and 10 to 11 and 12, Table 5). The three benzoate products **132a**, **132b** and **132c** were formed with higher enantioselectivities when the reaction was carried out with the borabox ligand **40k** which clearly outperformed the BOX ligands **35** (entries 4, 8 and 12, Table 5).

Table 5.



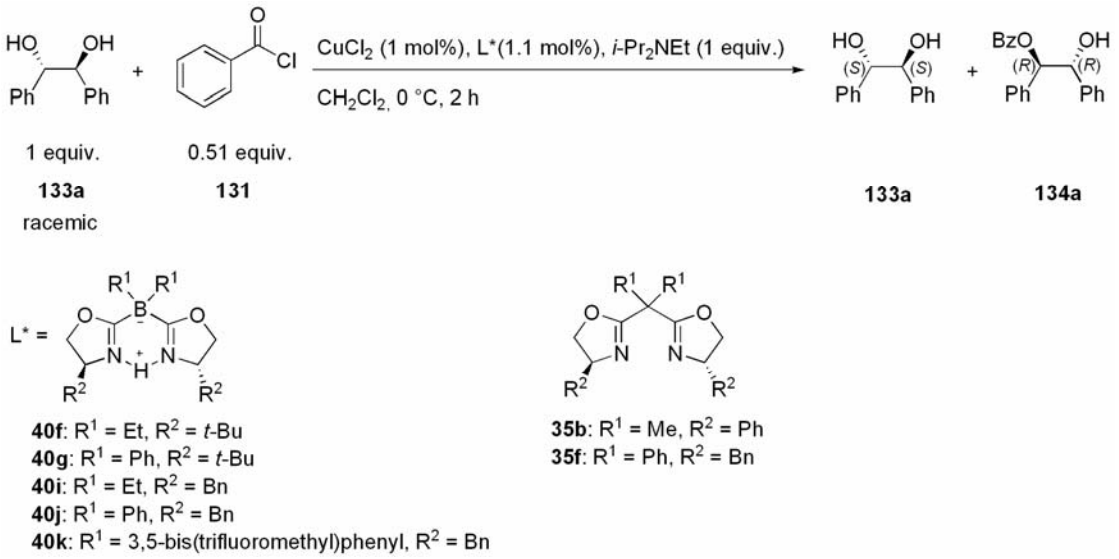
Entry	Ligand	*meso* 1,2-diol	Product	Yield [%][a]	*ee* [%][b]
1	**35e**			70	33[c]
2	**35b**			58	13
3	**40i**			79	40
4	**40k**	**130a**	**132a**	73	76
5	**35e**			74	85
6	**35b**			62	22
7	**40i**			75	47
8	**40k**	**130b**	**132b**	83	90
9	**35e**			68	84[c]
10	**35b**			58	86
11	**40i**			62	92
12	**40k**	**130c**	**132c**	65	94

[a] Average of two runs. [b] *ee* and absolute configuration values were determined by chiral HPLC according to the literature data. [c] The enantiomer of **130** was used in this case and, therefore, a product of opposite configuration was obtained.

3.4.3 Kinetic Resolution of 1,2-Diols

Due to the good results obtained for the desymmetrization of *meso* 1,2-diols, the kinetic resolution of 1,2-diols catalyzed by borabox ligands **40** was investigated.[65] Under similar conditions and with 1,2-diphenylethane-1,2-diol (**133a**) as substrate, borabox ligand **40k** induced the highest enantioselectivities (98% *ee* for **133a** and 96% *ee* for **134a**, entry 7, Table 6) and selectivity factor[67] *S* (*S* = 225, entry 7, Table 6). These results compete well with the one obtained with the BOX ligand **35b** (95% *ee* for **133a**, 96% *ee* for **134a** and a selectivity factor *S* of 182, entry 1, Table 6).

Table 6.

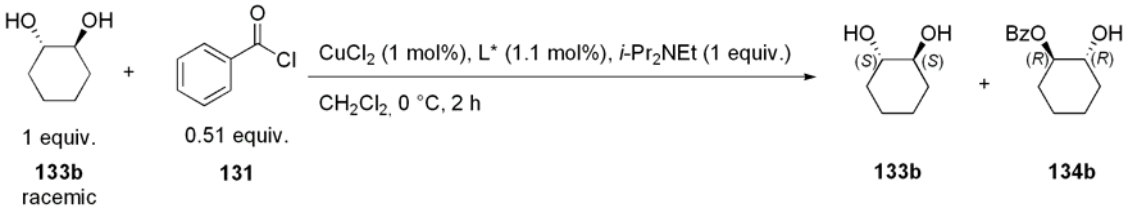


Entry	Ligand	*ee* (**133a**) [%][a]	*ee* (**134a**) [%][a]	Conversion [%][b]	*S* [b]
1	**35b**	95	96	50	182
2	**35f**	96	95	50	217
3	**40f**	14	39	27	3
4	**40g**	38	45	46	4
5	**40j**	80	86	48	32
6	**40i**	82	93	47	71
7	**40k**	98	96	51	225

[a] Determined by chiral HPLC. [b] See ref. 67.

With 1,2-cyclohexanediol **133b** as substrate, the benzoate **134b** was synthesized with comparable enantioselectivities when the reaction was carried out with the borabox ligands (**40i** and **40k**) or with the BOX ligand **35b**. Higher conversions and enantioselectivities for the compound **133b** were obtained in the presence of the borabox ligands **40i** and **40k** compared to those obtained with the BOX ligand **35b** (compare entry 1 to 2 and 1 to 3, Table 7).

Table 7.



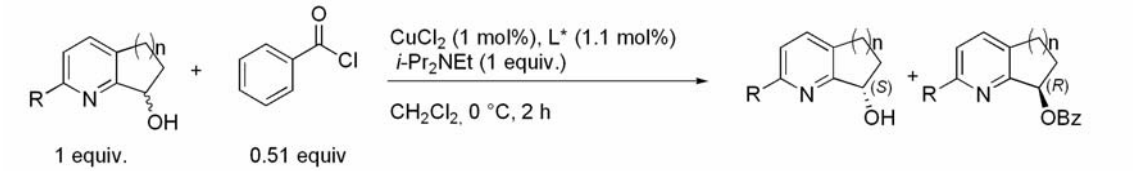
40i: R^1 = Et, R^2 = Bn
40k: R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = Bn

Entry	Ligand	*ee* (**133b**) [%][a]	*ee* (**134b**) [%][a]	Conversion [%][b]	*S* [b]
1	**35b**	17	86	17	16
2	**40i**	74	79	48	19
3	**40k**	64	83	44	21

[a] Determined by chiral HPLC. [b] See ref. 67.

Chiral pyridyl alcohols **135** are useful intermediates in the synthesis of chiral P,N ligands, which induce high enantioselectivities in the iridium-catalyzed hydrogenation of unfunctionalized olefins.[68] The benzoylation of these compounds was therefore investigated. A screening of substituted pyridyl alcohols **135** showed an increase of the selectivity factor *S* when a phenyl ring was attached at the α position of the pyridine ring (entries 4 to 6 and 10 to 12, Table 8). The ligands **40i** and **40k** gave the highest selectivity factors *S* for the substrate **135d** (92 and 125 respectively, entries 11 and 12, Table 8).

Table 8.



135a: R = H, n = 1
135b: R = Ph, n = 1
135c: R = H, n = 2
135d: R = Ph, n = 2
135e: R = Cl, n = 2

135a: R = H, n = 1
135b: R = Ph, n = 1
135c: R = H, n = 2
135d: R = Ph, n = 2
135e: R = Cl, n = 2

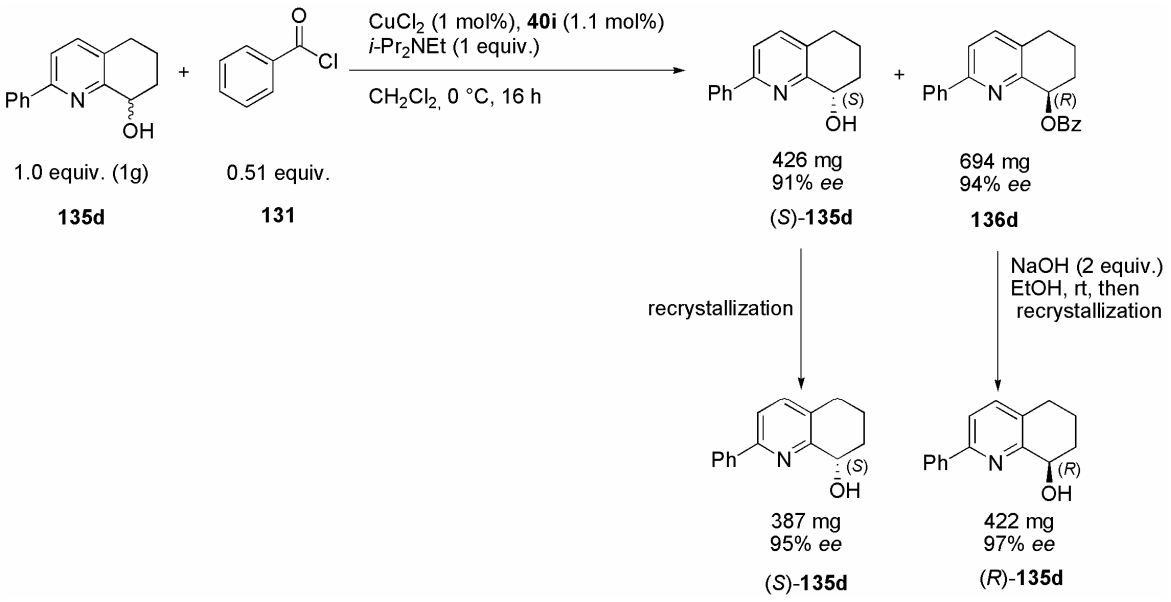
136a: R = H, n = 1
136b: R = Ph, n = 1
136c: R = H, n = 2
136d: R = Ph, n = 2
136d: R = Cl, n = 2

40i: R^1 = Et, R^2 = Bn
40k: R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = Bn

Entry	Substrate	Ligand	*ee* (alcohol) [%][a]	*ee* (benzoate) [%][a]	Conversion [%][b]	*S* [b]
1	**135a**	**35f**	1	1	50	1
2	**135a**	**40i**	16	33	33	2
3	**135a**	**40k**	5	5	46	1
4	**135b**	**35f**	8	26	24	2
5	**135b**	**40i**	50	84	36	18
6	**135b**	**40k**	76	91	45	51
7	**135c**	**35f**	3	8	27	1
8	**135c**	**40i**	>99	60	62	9
9	**135c**	**40k**	83	76	52	19
10	**135d**	**35f**	3	17	15	2
11	**135d**	**40i**	61	96	39	92
12	**135d**	**40k**	70	97	42	125
13	**135e**	**35f**	6	6	53	1
14	**135e**	**40i**	62	80	44	17
15	**135e**	**40k**	58	65	47	8

[a] Determined by chiral HPLC. [b] See ref. 67.

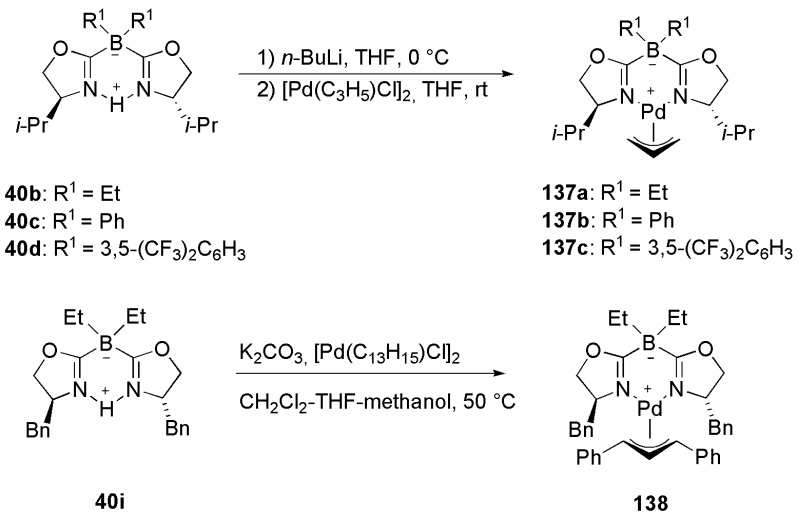
The kinetic resolution of substrate **135d** was carried out on a 1 g scale in the presence of ligand **40i** (Scheme 33). The alcohols (*S*)- and (*R*)-**135** were both isolated with high enantiomeric excesses (95% *ee* and 97 % *ee* respectively after recrystallization) and yields (39% and 42% respectively).



Scheme 33.

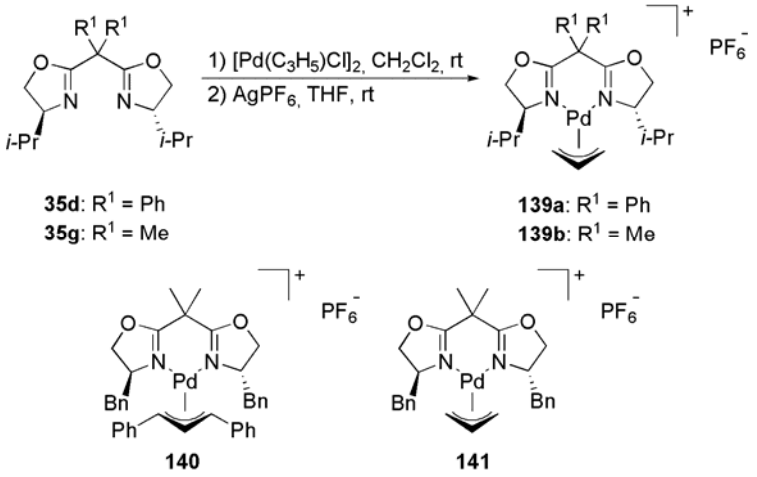
3.4.4 Allylic Substitution Reaction

The palladium-catalyzed allylic substitution has emerged as a versatile asymmetric transformation for carbon-carbon bond formation.[69] In order to test the reactivity of the borabox ligands **40** in this reaction, palladium complexes **137** were synthesized (Scheme 34).[62]



Scheme 34.

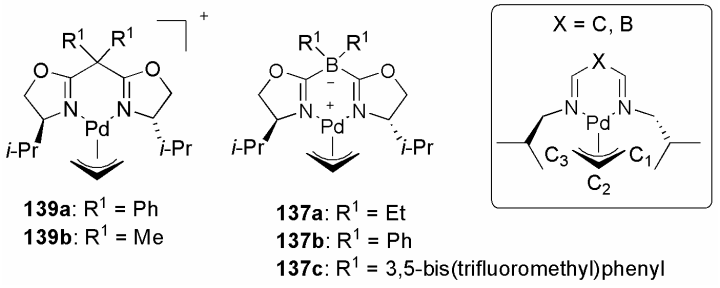
In the presence of these complexes **137** and **138**, the allylic substitution between *rac*-(*E*)-1,3-diphenyl-2-propenyl-1-acetate and dimethyl malonate was attempted, but no product was observed. To understand this behaviour, a comparative study of borabox and BOX complexes was performed. BOX complexes were synthesized following published procedures (Scheme 35).[70]



Scheme 35.

It has been reported that small coordinating anions like chloride and fluoride cause the allyl rotation of Pd complexes.[71] This effect was observed by ^{1}H NMR in the case of the BOX complex **139b**. Presumably, this is due to the brine wash in the synthesis of this ligand.[70] However, no allyl rotation could be detected for borabox complex **137b**, maybe due to a lower electrophilicity of the palladium atom, which therefore has a weaker tendency to coordinate a choride ion.

Some additional information about borabox complexes was obtained via ^{13}C NMR and DFT calculations. These showed that allyl C-atoms of the borabox complexes resonate at higher field, implying that the allyl moiety is more electron-rich than for the BOX complexes (Figure 18). The same tendency was revealed by DFT calculations.[62]



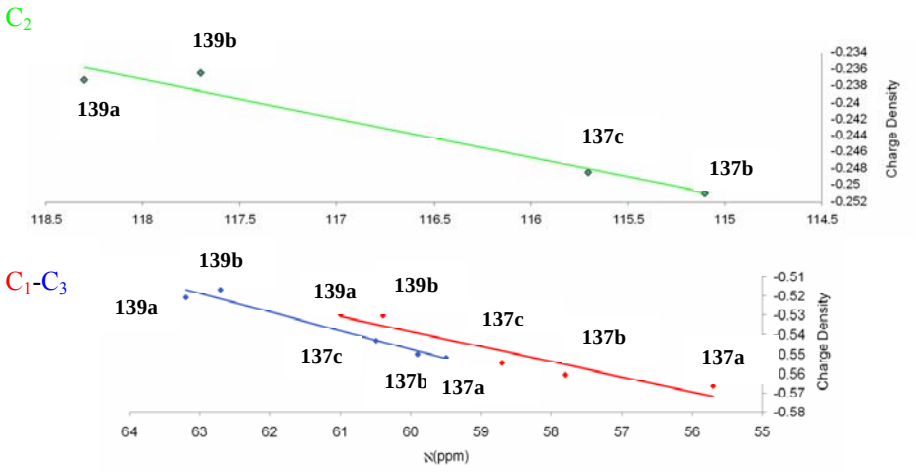


Figure 18.

The higher electron density in the allyl fragment could explain the lack of catalytic activity of palladium-borabox complexes for allylic substitution.

Chapter 4

Application of Borabox Ligands in Asymmetric Catalysis

4 Application of Borabox Ligands in Asymmetric Catalysis

4.1 Chiral Lewis Acid Catalysis of the Diels-Alder Reaction

4.1.1 Literature

4.1.1.1 Introduction

In 1950, Otto Paul Hermann Diels and his student Kurt Alder were awarded the Nobel Prize in chemistry for their research on the [4+2] cycloaddition reaction.[72] This so called Diels-Alder reaction enables, in one step, starting from a diene and a dienophile, the rapid preparation of a six-membered ring compound. Up to four stereocenters can be constructed simultaneously in this reaction that is widely considered to be one of the most powerful reactions in organic synthesis.[73]

Many enantioselective versions[74] of this process have been developed but chiral Lewis acid based reactions[75] have seen increased attention in the past few years.[76] When catalyzed by a Lewis acid, the activation energy of the Diels-Alder reaction can be lowered as much as 10 kcal/mol.[77] In the normal demand Diels-Alder reaction, on which we will focus here, the coordination of the Lewis acid to the dienophile **142** reduces the electron density of the double bond and lowers the LUMO energy of the carbonyl substrate. Thus, the complexation enhances the interaction with the HOMO of the diene **144** (Figure 19).[78]

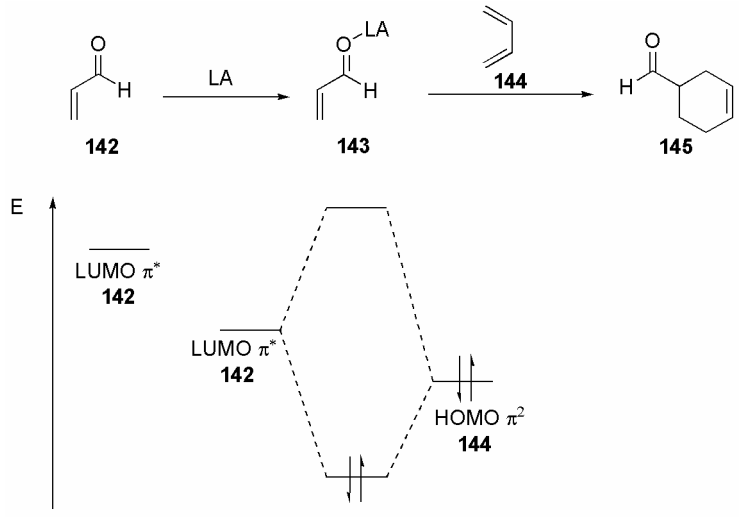


Figure 19.

4.1.1.2 Mechanistic aspects

The mechanism of the Diels-Alder reaction and an explanation for the usually favored *endo* approach of the dienophile towards the diene has been the subject of much debate. In 1973, Houk and co-workers claimed that the *endo* selectivity was due to secondary orbital interactions[78], as originally proposed by Woodward and Hoffmann[79], a theory which has since been refined. Further studies proved that the stabilizing diene HOMO-dienophile LUMO interaction leads to a destabilizing substantial charge donation.[80] However, the geometry of the *endo* transition state minimizes the physical separation of the induced charges and is thus favored. Furthermore, the Lewis acid catalyzed Diels-Alder reaction is often described as a concerted but asynchronous process.[80] In the transition structure, the bond formation at the dienophile terminus is more advanced than for the internal carbon.

In a Diels-Alder reaction catalyzed by a Lewis acid, the nature of the transition structure is largely influenced by the coordination mode of the Lewis acid to the dienophile (η^1- *vs* η^2-complex), the regiochemistry of Lewis acid complexation to the dienophile and the conformation of the dienophile (Figure 20).

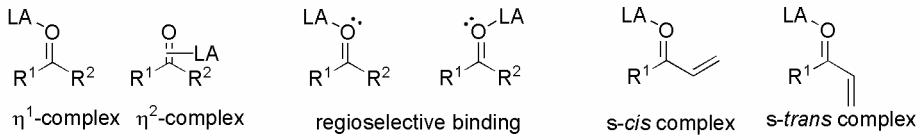


Figure 20.

4.1.1.2.1 Mode of Coordination of the Lewis Acid to the Dienophile

The Lewis acid can coordinate to the dienophile in a σ-fashion (η^1-complex) or π-fashion (η^2-complex). Both coordination modes have been observed by X-ray structural analysis.[81] However, in the case of the η^2-complex, the electron density of the carbonyl will be increased due to a HOMO (metal)-LUMO (carbonyl) interaction. In a normal demand Diels-Alder reaction, this will obviously disfavor the reaction. As a consequence, η^1-complexes will be considered to be the active species in all normal demand Diels-Alder reactions.[91]

4.1.1.2.2 Regiochemistry of the Complexation of the Lewis Acid to the Dienophile

When the dienophile is an aldehyde, numerous reports confirmed the *syn* geometrical preference of the Lewis acid to the formyl proton.[82] Along with steric reasons, the anomeric effect[83] and formyl hydrogen bond[84] have been as well proposed as explanations of this preferred conformation (Figure 21).

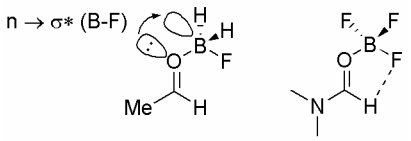


Figure 21.

In esters, complexation of the Lewis acid occurs *anti* to the OR^1- moiety, this was shown by X-ray diffraction (Figure 22).[85] Furthermore, (*Z*)-ester conformation is favored by a HOMO(oxygen lone pair)-LUMO(σ^*C-O) interaction.[76]

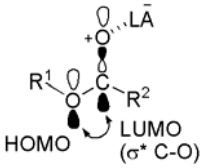
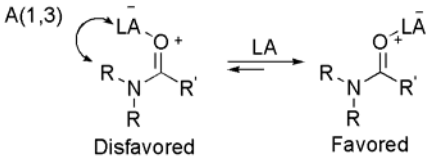


Figure 22.

Lewis acid complexation is also oriented *anti* to NR_2-moiety in the case of amides. Indeed, allylic strain stongly disfavors Lewis acid complexation *syn* to the NR_2-moiety (Scheme 36).[81]

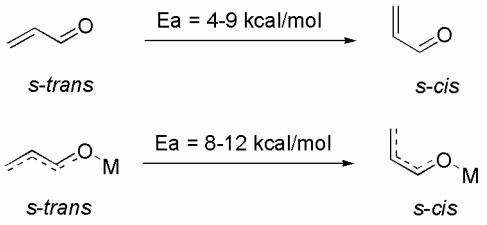


Scheme 36.

4.1.1.2.3 Conformation of the Dienophile

The geometry of the dienophile-Lewis acid complex determines the *s-cis vs. s-trans* conformation of α,β-unsaturated carbonyl compound, which is an important issue. Indeed, the observed enantioselectivity is a direct consequence of the shielding of one face by the dienophile-Lewis acid complex. In 1987, Houk and co-workers demonstrated that the Lewis

acid complexation of acrylates dramatically stabilizes the *s-trans* conformation of the dienophile by electronic or steric effects (Scheme 37).[86]



Scheme 37.

Many examples in the literature illustrated the general preference for the *s-trans* conformation of the complexes derived from α,β-unsaturated aldehydes[82] and esters.[87] A few exceptions showed that the *s-cis* dienophile is favored for certain chiral acrylates complexed by bidentate Lewis acids.[88]

Concerning acyl-1,3-oxazolidin-2-ones **41**, which are widely used in Diels-Alder reactions[76], four complexes might be present in equilibrium depending on the nature of the Lewis acid (propensity of the metal for 1- or 2-point binding) but also on steric and electronic interactions in the transition state (Figure 23). It was assumed that the *s-cis* conformers were the favored complexes avoiding non bonding interactions present in the *s-trans* compounds. Experimental evidence showed the participation of the *s-cis* complex **146a**.[89] However, complexes **146b** and **146c** were also considered to be involved in order to explain the observed enantioselectivities in some Diels-Alder reactions.[90]

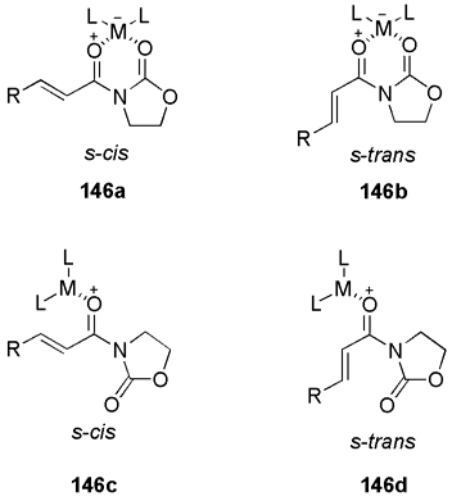


Figure 23.

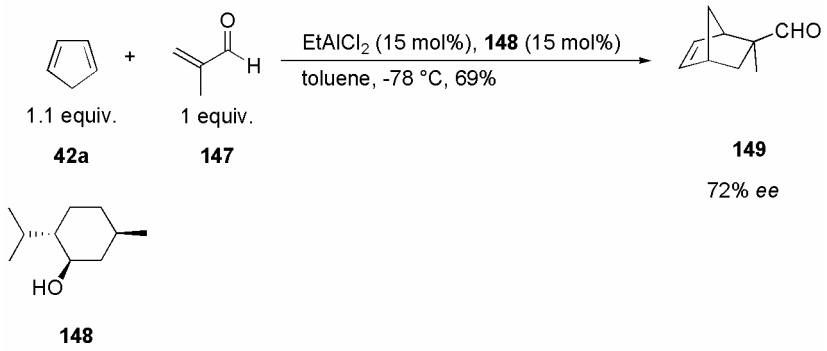
At this point, it is important to notice that the preferred ground state conformations described here will not necessarily describe the transition state structures of the Diels-Alder reaction.

Indeed *ab initio* calculations conducted by Houk showed that, even if the *s-trans* conformer was favored, the activation energy for the reaction between 1,3-butadiene and borane-bound acrolein from the *s-cis* configuration was lower.[80] Many proposed transition structures in the literature are also derived from higher energy complexed dienophiles.[91]

4.1.1.3 Lewis Acid Catalysts for the Enantioselective Diels-Alder Reaction

4.1.1.3.1 Introduction

In 1979, Koga and co-workers published the first example of a catalytic enantioselective Diels-Alder reaction in the presence of a chiral aluminium catalyst (Scheme 38).[92] The reaction of cyclopentadiene (**42a**) and methacrolein (**147**) catalyzed by 15 mol% of menthyloxyaluminium dichloride gave the *exo* product **149** in 72% *ee*.



Scheme 38.

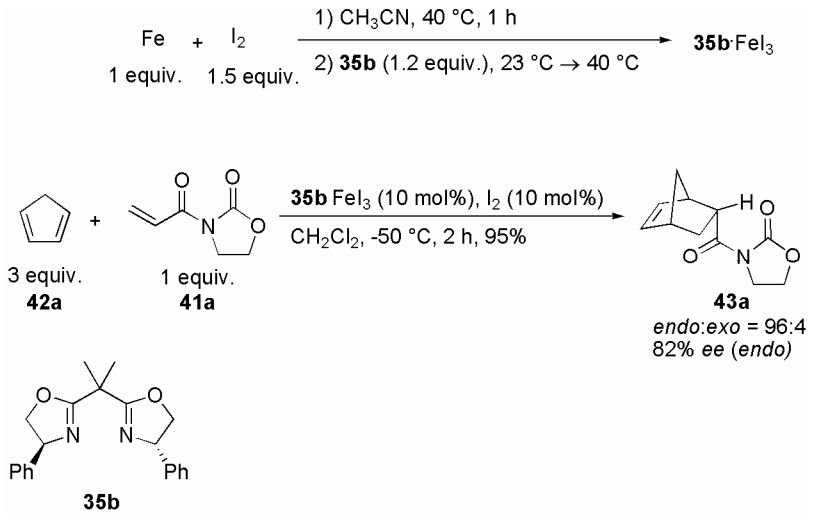
Since then, many different catalytic systems were applied to the Diels-Alder reaction. Among them, the most efficient catalysts for this process were complexes derived from the privileged ligands and chiral boron Lewis acids.

4.1.1.3.2 Lewis Acid Catalysts Derived from Privileged Ligands

4.1.1.3.2.1 Bis(oxazoline) Ligands and Derivatives

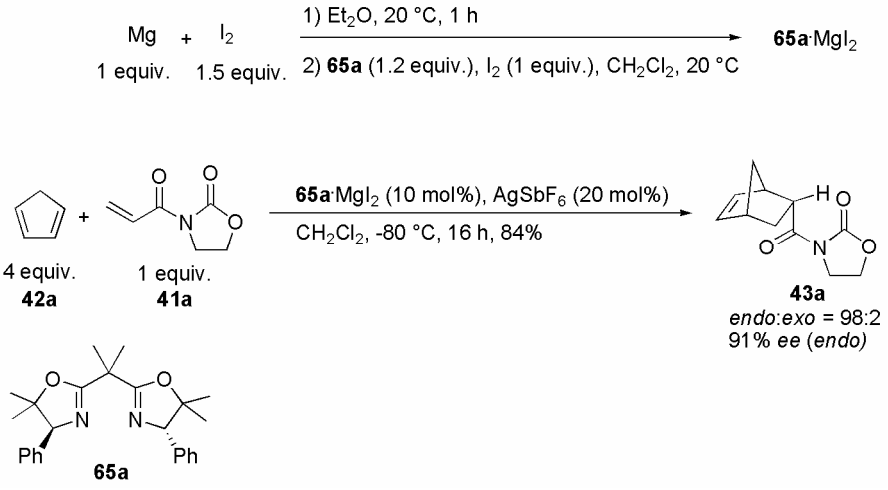
Corey and his group carried out the Diels-Alder reaction between cyclopentadiene (**42a**) and 3-acryloyl-1,3-oxazolidin-2-one (**41a**) in the presence of 10 mol% of the complex **35b**.FeI_3.[31] This catalyst was prepared by the reaction of FeI_3 (made *in situ* from powdered iron and I_2)

with ligand **35b** (Scheme 39). The *endo* adduct **43a** was obtained with high diastereoselectivity and with an enantioslectivity of 82%. The reaction time was improved by addition of I_2 as co-catalyst. However, the octahedral geometry of the iron complex complicated the mechanistic investigations.



Scheme 39.

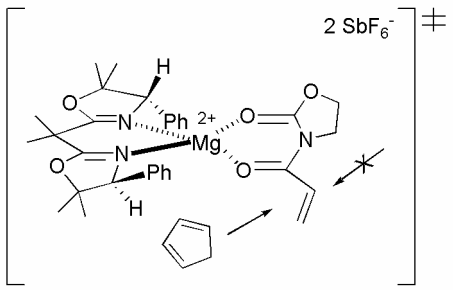
To get an insight of the mechanism, the same reaction was carried out in the presence of a tetrahedral magnesium complex derived from BOX ligand **65a** (Scheme 40).[93] With $AgSbF_6$ as co-catalyst, the major *endo* product **43a** was synthesized with a high enantiomeric excess of 91%.



Scheme 40.

The proposed transition state **150** for this reaction showed a tetrahedral arrangement of donor groups about the metal and the *s-cis* conformation of 3-acryloyl-1,3-oxazolidin-2-one **41a**

(Figure 24). The back side of the complex is blocked by the phenyl moiety of the BOX ligand **65a**. The diene **42a** approaches from the front side leading to the observed *endo* product **43a**.

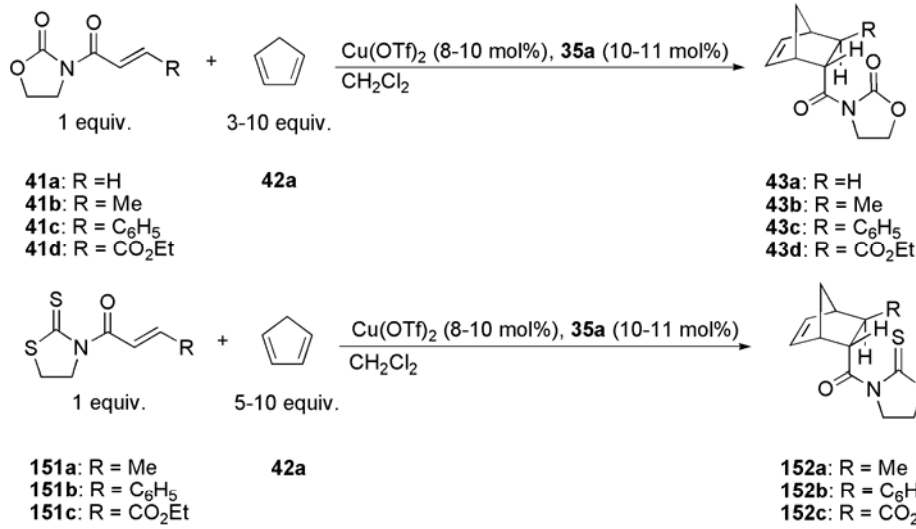


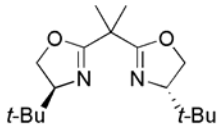
150

Figure 24.

In 1993, Evans *et al.* demonstrated the efficiency of copper (II)-BOX complexes as Lewis acids in the Diels-Alder reaction of imides **41** with cyclopentadiene (**42a**).[94] Contrary to the reactions with iron and magnesium complexes mentioned earlier, the best results were obtained in the presence of ligand **35a** with *t*-butyl groups at the C4 positions of the oxazoline rings. The scope of the reaction was enlarged with substituted imides **41** and thiazolidine-2-thione analogous **151** (Table 9). The highest enantiomeric excess was observed for the cycloadduct **43a** which was prepared with an *ee* greater than 98% and a diastereoselectivity of 98:2 (entry 1, Table 9). For the other substrates, the enantioselectivities measured were higher than 90% and the diastereoselectivities showed a high preference for the *endo* adduct (≥84:16, entries 2 to 7, Table 9).

Table 9.



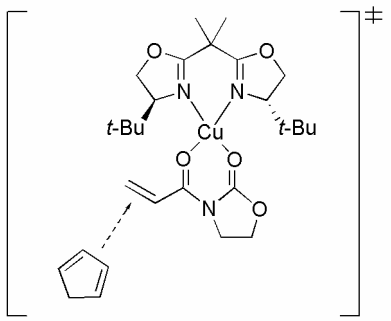


35a

Entry	Substrate	Time [hours]	T [°C]	Yield [%][a]	*endo*:*exo*	*ee (endo)* [%][b]
1	**41a**	18	-78	86	98:02	>98
2	**41b**	30	-15	85	96:04	97
3	**41c**	24	25	85	90:10	90
4	**41d**	20	-55	92	94:06	95
5	**151a**	36	-45	82	96:04	94
6	**151b**	72	-35	86	92:08	97
7	**151c**	20	-55	88	84:16	96

[a] Isolated yields. [b] Determined by chiral GC or HPLC.

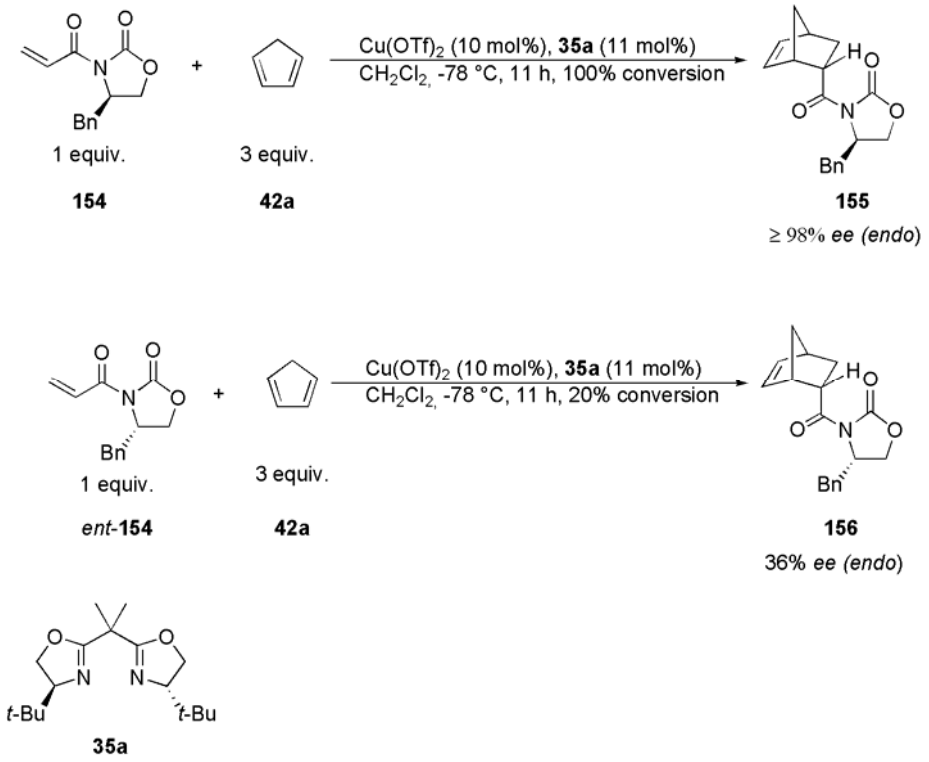
To explain this selectivity, a square planar transition state **153** was proposed (Figure 25). The approach of cyclopentadiene (**42a**) occurs from the *si*-face of the dienophile, the other face being blocked by the *t*-butyl group of the BOX ligand **35a**.



153

Figure 25.

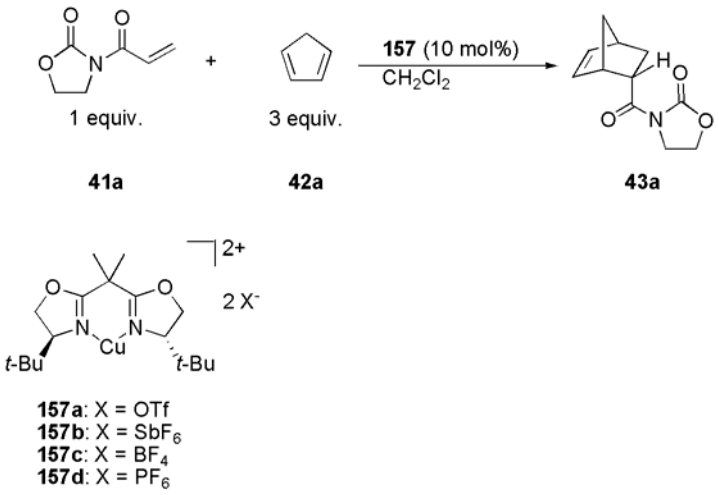
To rationalize this transition structure, Evans and co-workers performed under the same conditions the reaction with the chiral imides **154** and *ent*-**154** (Scheme 41).[94] The reaction with compound **154** clearly corresponded to the matched case. Indeed, the *t*-butyl group of the oxazoline and the benzyl group of the dienophile are on the same face, allowing the synthesis of the cycloadduct **155** with high enantioselectivity of ≥98%. In the case of the imide *ent*-**154**, the reaction only proceeded with 20% conversion and the enantiomeric excess was much lower (36%). The *t*-butyl group of the oxazoline and the benzyl group of the dienophile are on opposite faces hindering the approach of the diene from one or the other face. These studies confirmed the square planar geometry of the catalyst. Indeed, if the reaction was proceeding *via* a tetrahedral transition structure, the opposite result would have been expected. The nature of the compound **156** obtained in the mismatched case shows clearly that the catalyst dominates obviously the sense of induction.



Scheme 41.

Evans and his group also investigated the influence of different counterions on the Diels-Alder reaction.[95] Whereas complexes **157c** and **157d** exhibited the same catalytic activity compared to copper complex **157a**, the catalyst **157b** displayed enhanced efficiency (Table 10). With **157b** the reaction proceeded faster and allowed the synthesis of the cycloadduct **43a** with the same or even higher enantioselectivity (compare entry 1 to 2 and 3 to 4, Table 10). However, the diastereoselectivity is slightly lowered in the presence of this catalyst (*endo*:*exo* ratio of 98:2 and 96:4 for **157a** and **157b** respectively, entries 1 and 2, Table 10).

Table 10.

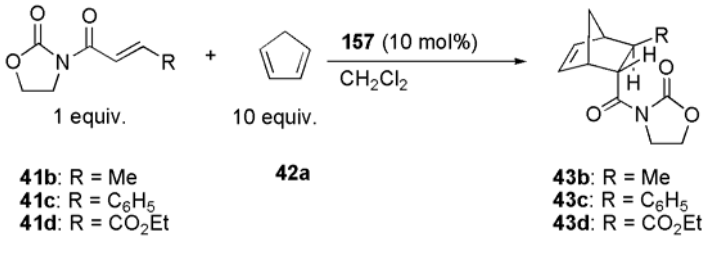


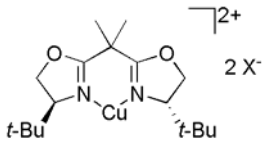
Entry	Catalyst	Time[a]	T [°C]	*endo*:*exo*[b]	*ee* (*endo*) [%][c]
1	**157a**	10 h	-78	98:02	>98
2	**157b**	4 h	-78	96:04	>98
3	**157a**	15 min	25	88:12	86
4	**157b**	10 min	25	86:14	94

[a] 100% conversion. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

With β-substituted dienophiles **41b-d**, the same trend was observed (Table 11). In particular, the cycloadduct **43b** was obtained with a remarkable *ee* of 99% in the presence of the catalyst **157b** (entry 2, Table 11). The copper complex **157b** gave a considerable increase in the reactivity of the reaction with the imide **41c** in comparison to the application of catalyst **157a** (compare entry 3 and 4, Table 11). The enantioselectivity was also increased to 98% but with a lower diastereoselectivity of 88:12 (entry 4, Table 11). The reaction of imide **41d** with the catalyst **157b** proceeded with a lower *ee* compared to the triflate catalyst **157a** (compare entry 5 and 6, Table 11). To explain this unusual behaviour, it was postulated that the catalyst **157b** activated the ester function of the imide **41d**, lowering the selectivity of the substrate.

Table 11.





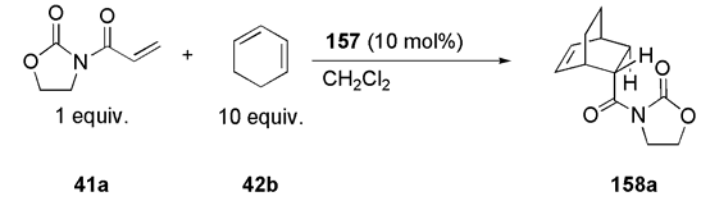
Entry	Substrate	Catalyst	Time	T [°C]	Yield [%][a]	*endo*:*exo*	*ee (endo)* [%][b]
1	**41b**	**157a**	30 h	-15	85	96:04	97
2	**41b**	**157b**	20 h	-15	99	85:15	99
3	**41c**	**157a**	48 h	-10	16	93:07	94
4	**41c**	**157b**	48 h	-10	77	88:12	98
5	**41d**	**157a**	20 h	-55	92	94:06	95
6	**41d**	**157b**	20 h	-55	88	82:18	87

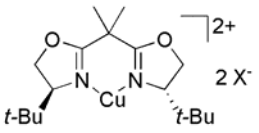
[a] Isolated yields. [b] Determined by chiral HPLC.

The Diels-Alder reaction was also carried out with less reactive dienes, such as cyclohexadiene (**42b**, Table 12).[95] Fourty hours were needed for complete conversion in the reaction between cyclohexadiene (**43b**) and the imide **41a** catalyzed by **157a** at 25 °C. The cycloadduct **158a** was obtained with 82% *ee* for the *endo* isomer and a diastereoselectivity of 98:2 (entry 1, Table 12). After only 5 hours, the same reaction catalyzed by **157b** was

complete and whereas the diastereoselectivity was lower (*endo*:*exo* ratio of 95:5, entry 2, Table 12) the enantiomeric excess increased (93% *ee* (*endo*), entry 2, Table 12). Under the same conditions at -10 °C, the selectivities were slightly increased (95% *ee* (*endo*) and *endo*:*exo* ratio of 95:5, entry 3, Table 12).

Table 12.





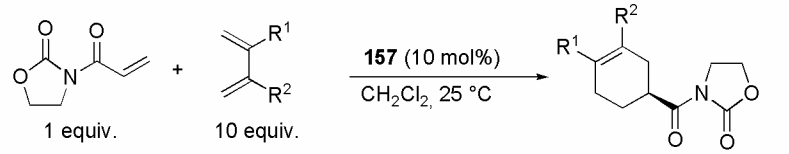
157a: X = OTf
157b: X = SbF_6

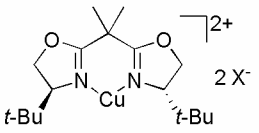
Entry	Catalyst	Time	T [°C]	Yield [%][a]	*endo*:*exo*	*ee* (*endo*) [%][b]
1	**157a**	40 h	25	90	98:02	82
2	**157b**	5 h	25	90	95:05	93
3	**157b**	46 h	-10	49	96:04	95

[a] Isolated yields. [b] Determined by chiral HPLC.

Acyclic dienes **159** could be converted into their corresponding cycloadducts **160** with moderate selectivities (59-65% *ee*, Table 13).[95]

Table 13.



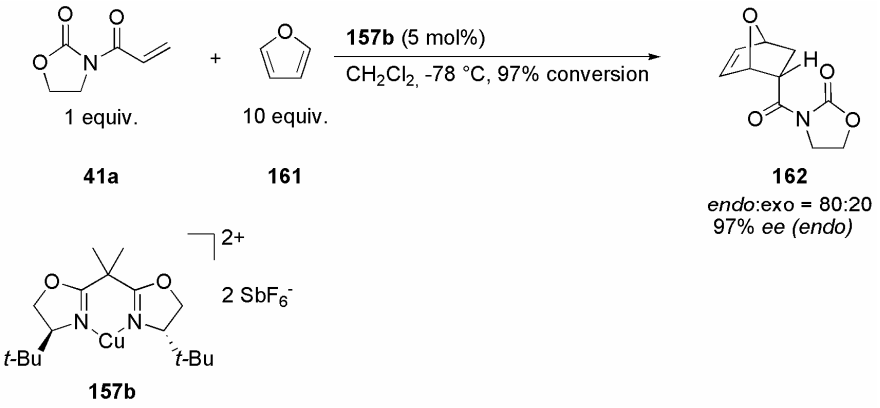


157a: X = OTf
157b: X = SbF_6

Entry	Substrate	Catalyst	Time	Yield [%]	(1,4):(1,3) regioisomer ratio	*ee* [%][a]
1	**159a**	**157a**	24 h	95	97:03	60
2	**159a**	**157b**	12 h	81	96:04	59
3	**159b**	**157a**	24 h	95	-	60
4	**159b**	**157b**	24 h	78	-	65

[a] Enantiomer ratios of the primary adduct.

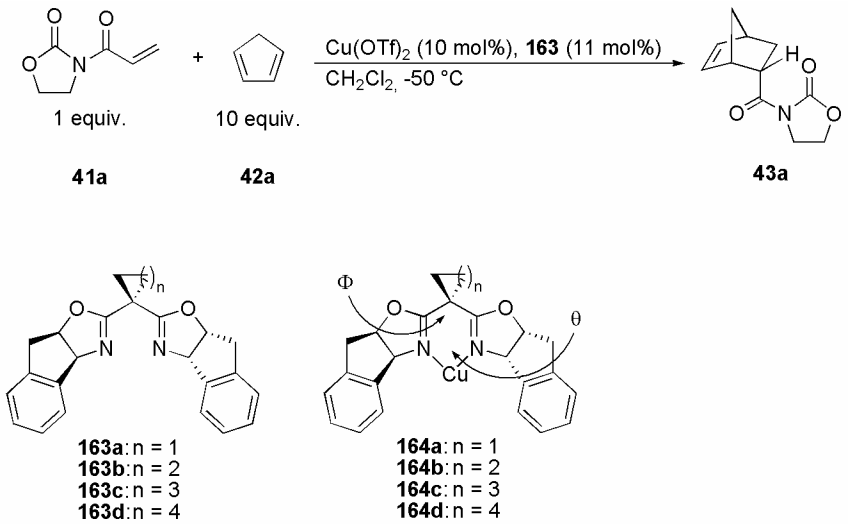
Evans and co-workers also reported the highly enantioselective Diels-Alder reaction of furan (**161**) with the acrylimide **41a** (Scheme 42).[95] With 5 mol% of catalyst **157b**, the product **162** was obtained in an 80:20 mixture of *endo*:*exo* isomers with an enantioselectivity as high as 97% *ee* for the *endo* adduct.



Scheme 42.

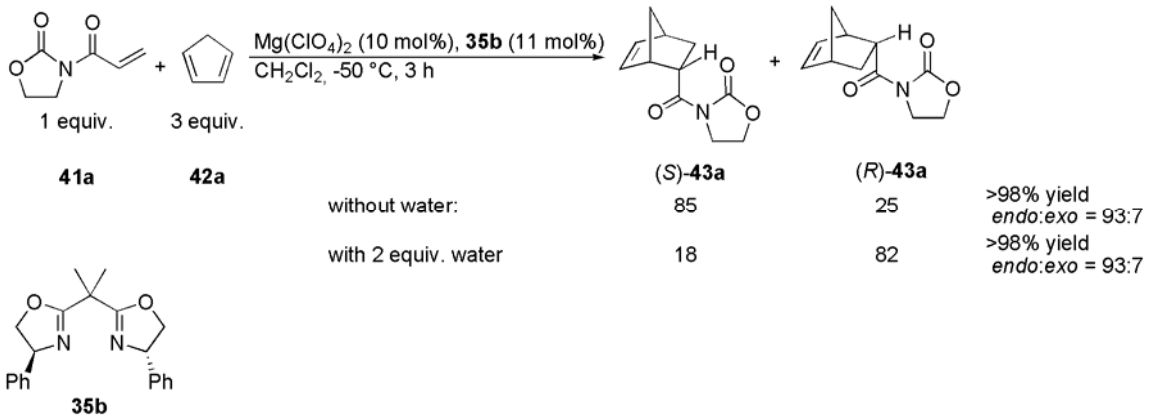
In 1996, a group at Merck Research Laboratories found an interesting correlation between the bite angle of the bis(oxazoline) ligands **163** and the enantiomeric excess induced in the copper catalyzed Diels-Alder reaction.[96] Table 14 shows that the larger the angle Φ (and by consequence the larger the bite angle θ), the higher are the enantioselectivity and diasteroselectivity observed.

Table 14.



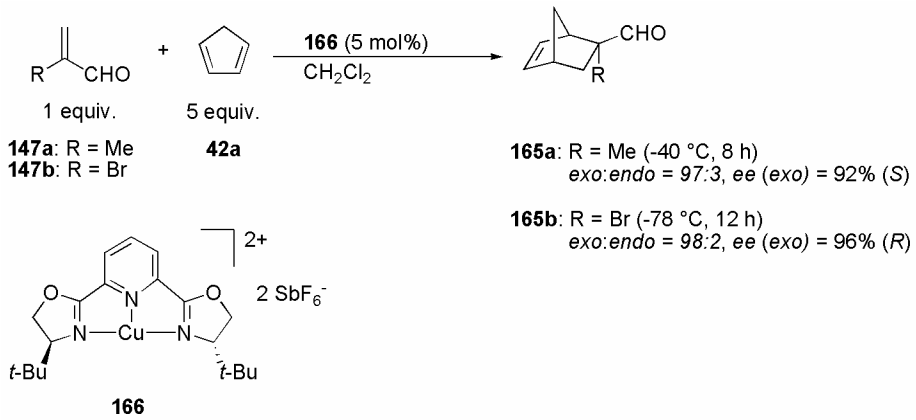
Entry	Ligand	Φ [°]	*endo*:*exo*	*ee* (*endo*) [%]
1	**163a**	110.6	44:1	96.3
2	**163b**	108.0	38:1	92.0
3	**163c**	105.8	37:1	89.5
4	**163d**	103.7	26:1	83.0

Desimini and co-workers developed a method to synthesize both enantiomers of the Diels-Alder product with the same bis-(oxazoline)-magnesium perchlorate chiral catalyst (Scheme 43).[97] The tetrahedral coordination of the catalyst and the dienophile **41a** gave the expected product (*S*)-**43a**. But when 2 equivalents of water were added to the catalyst, (*R*)-**43a** was obtained as a major product. It was postulated that the water favored the octahedral coordination of the catalyst and the dienophile **41a**. However, the selectivities obtained for this same reaction can not compete with those obtained by Evans and co-workers.[94]



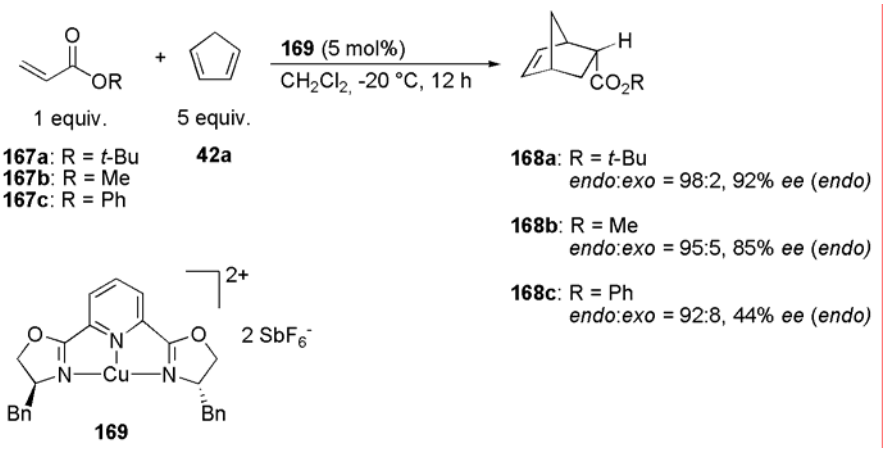
Scheme 43.

The Diels-Alder reaction of 2-substituted acrolein derivatives **147** with cyclopentadiene (**42a**) was studied in the presence of bis-(oxazolinyl)-pyridine catalyst (Pybox) **166** (Scheme 44). The *exo* adducts **165** were obtained as major products (*exo*:*endo* ratio of 97:3 and 98:2 respectively) with high enantioselectivity (92% and 96% *ee* (*exo*) respectively).



Scheme 44.

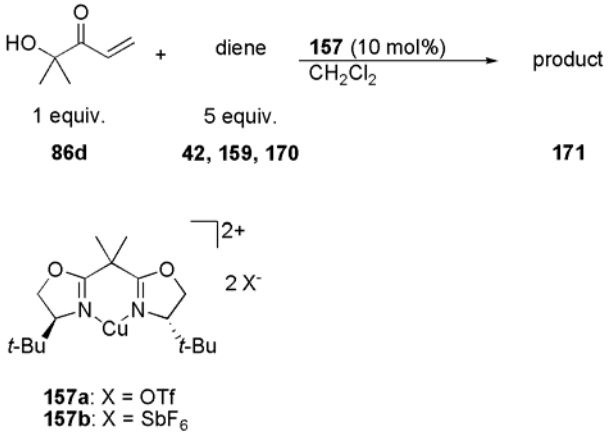
The Pybox complex **169** is also an efficient catalyst for the conversion of acrylate esters **167** with cyclopentadiene (**42a**) to their corresponding cycloadducts **168** (Scheme 45). High enantioselectivities were obtained for **168a** and **168b** (92% and 85% respectively for the *endo* isomers), whereas phenyl acrylate **167c** underwent cycloaddition with lower selectivity (44% *ee* (*endo*)).

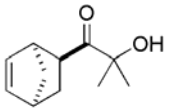
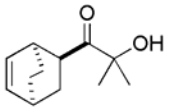
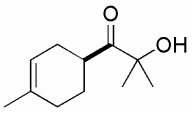
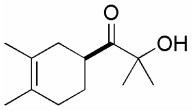
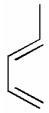
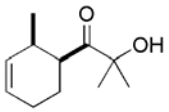


Scheme 45.

Palomo and co-workers employed α'-hydroxy enones **86d** as dienophiles for the Diels-Alder reaction.[98] These substrates were expected to form well ordered transition structures upon combination with chiral Lewis acids. Indeed, the reaction of α'-hydroxy enones **86d** with dienes catalyzed by copper (II)-BOX complexes gave the corresponding cycloadducts **171** with high yields and selectivities (Table 15). Starting from cyclopentadiene (**66**), compound **171a** was synthesized in >99% *ee* and a >99:1 *endo*:*exo* ratio (entry 1, Table 15). The reaction with the less reactive cyclohexadiene (**42b**) was highly selective as well (>99:1 for the *endo*:*exo* ratio and ≥98% *ee* (*endo*), entry 2, Table 15). Cycloadducts **171c**, **171d** and **171e** derived from acyclic dienes **159a**, **159b** and **170** were obtained with high enantioselectivity and diastereoselectivity (entries 3 to 5, Table 15).

Table 15.

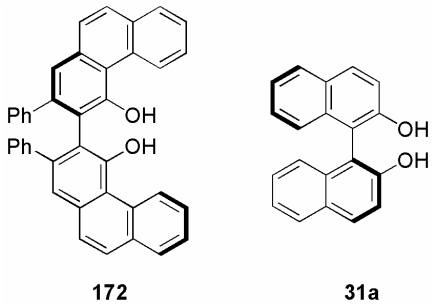


Entry	Diene	Catalyst	T [°C]	Time [h]	isomer ratio[a]	*endo*:*exo*	Product	Yield [%]	*ee* (*endo*) [%]
1	 **42a**	**157a**	-78	2.5	-	>99:01	 **171a**	99	>99
2	 **42b**	**157b**	25	2	-	>99:01	 **171b**	93	≥98
3	 **159a**	**157b**	-20	14	>99:01	-	 **171c**	85	94
4	 **159b**	**157b**	-20	13	-	-	 **171d**	80	94
5	 **170**	**157b**	-10	15	88:12	-	 **171e**	95	>99

[a] Ratio of regio- or *cis*:*trans* isomers as applicable.

4.1.1.3.2.2 Biaryl Derivatives

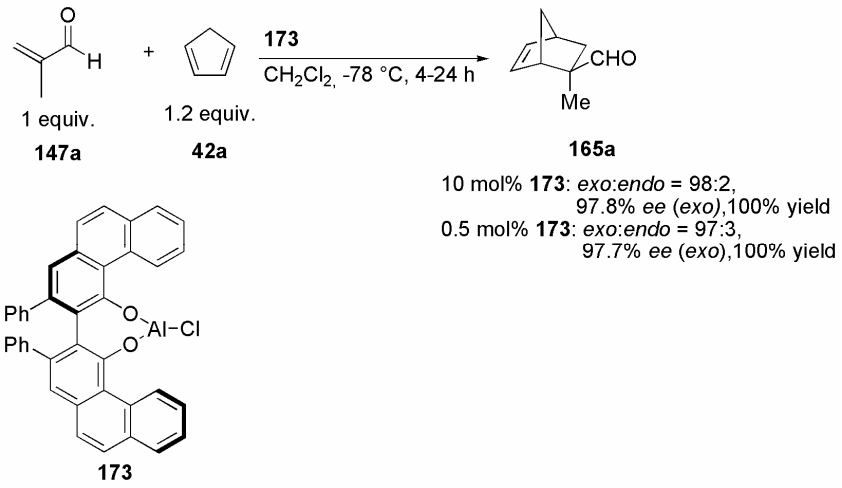
In 1993, Wulff *et al.* described the synthesis of vaulted 3,3'-biphenantrol **172** and its use as chiral ligand in the Diels-Alder reaction of methacrolein (**147a**) and cyclopentadiene (**42a**) (Figure 26).[99] The aromatic rings of the ligand **172** definite the walls of the "chiral pocket" that is deeper than that of BINOL ligand **31a**.



172 **31a**

Figure 26.

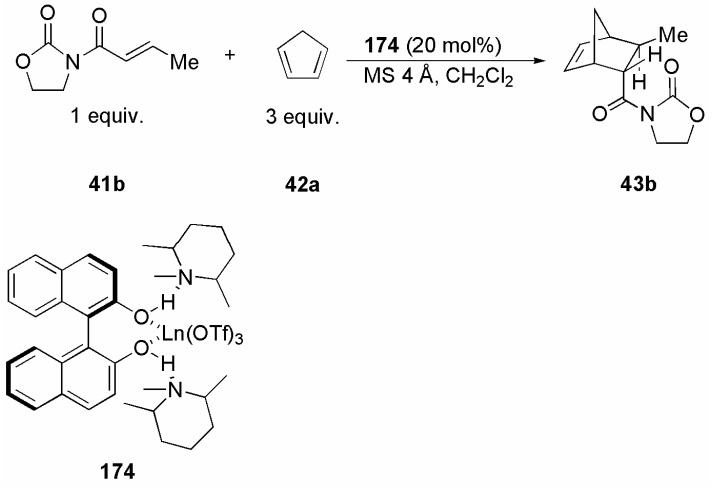
With only 0.5 mol% of catalyst **173**, one of the lowest catalyst loading for a catalytic Diels-Alder reaction, the enantiomeric excess of compound **165a** was up to 97.7% *ee* (Scheme 46).



Scheme 46.

Kobayashi and co-workers reported the use of a chiral lanthanide (III) triflate complex **174** as an efficient catalyst for the Diels-Alder reaction.[100] They observed that the enantioselectivity induced by the catalyst diminished rapidly with increasing ionic radius of the lanthanide used (Table 16).

Table 16.

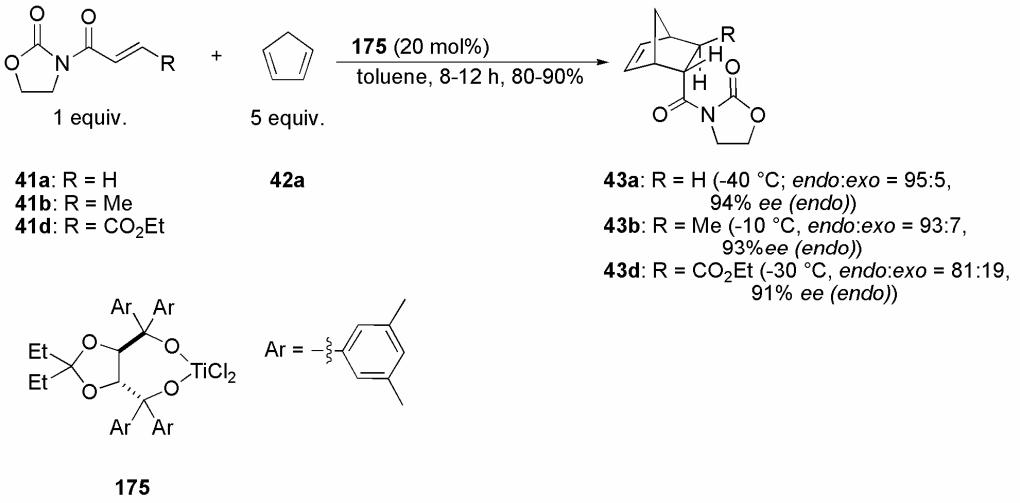


Entry	Ln	Yield [%]	*endo*:*exo*	*ee* (*endo*) [%]
1	Lu	60	89:11	93
2	Yb	77	89:11	93
3	Tm	46	86:14	75
4	Er	24	83:17	69
5	Ho	12	73:27	25
6	Y	6	70:30	20
7	Gd	0	-	-

Titanium complexes derived from binaphtol type ligands are also highly selective in the Diels-Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene[101] (**66**) and of methacrolein (**147a**) with alkoxydienes[102].

4.1.1.3.2.3 TADDOL Derivatives

The reaction of cyclopentadiene (**42a**) with the oxazolidinones **41** in the presence of a modified version of the Narasaka[103] catalyst synthesized by Corey and his group afforded the Diels-Alder cycloadducts **43** in high yields and with good selectivities[104] (Scheme 47). To explain the selectivity observed, the authors proposed a *s-trans* geometry for the dienophile **41**.



Scheme 47.

4.1.1.3.3 Chiral Boron Lewis Acids

Yamamoto[105] and Helmchen[106] reported the first use of chiral oxazaborolidines in Diels-Alder reactions (Figure 27). Catalysts **176-178** induced moderate enantioselectivities in the cycloadditions of α,β-unsaturated aldehydes with dienes.

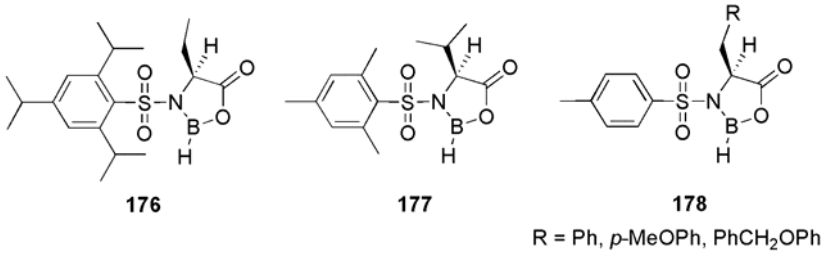
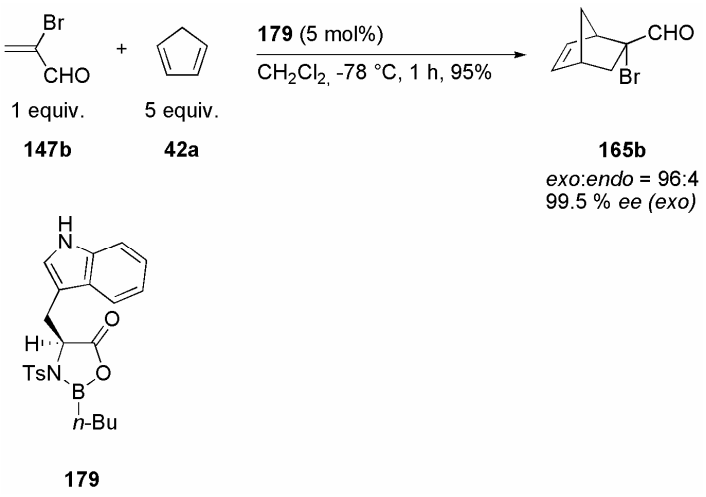


Figure 27.

Remarkable enantioselectivities were obtained by Corey and co-workers when employing the catalyst **179** (Scheme 48).[107] 2-bromoacrolein (**147b**) and cyclopentadiene (**42a**) underwent Diels-Alder reaction to give the (*R*)-bromo aldehyde **165b** in 95% yield and with 99.5% *ee* for the *exo* isomer.



Scheme 48.

Corey proposed the transition structure **180** to explain the high *ee* observed (Figure 28).[108] The bright orange-red colour of the complex **180** is indicative of a charge transfer complex between the α,β-enal and the indole ring. By consequence, the aldehyde **147b** is complexed to the face of boron that is in the proximity of the indole ring. This interaction is missing in the catalysts **176-178** developed by Helmchen and Yamamoto and could therefore explain the high enantioselectivity obtained with catalyst **179**. It was also postulated that the dienophile **147b** prefers the *s-cis* conformation over the *s-trans* due to the steric interactions between α-bromine substituent and the indole ring.

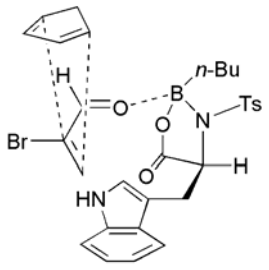
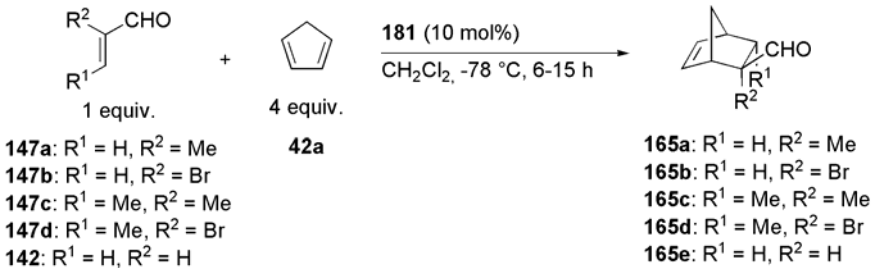


Figure 28.

Derivatives of this catalyst **179** were applied successfully in many synthetic applications.[109] A triflic acid activated chiral oxazaborolidine was developed by Corey in 2002.[110] These new chiral Lewis superacids induced high enantioselectivities in the Diels-Alder reaction of 2-bromoacrolein (**147b**) and several dienes.

Chiral (acyloxy)-borane (CAB) catalysts **181** developed by Yamamoto and co-workers were also efficient catalysts in the Diels-Alder reaction of cyclopentadiene (**42a)** with aldehydes **147**.[111] Cycloadducts **165** were obtained with high *ee*'s and yields for a broad range of aldehydes (Table 17).

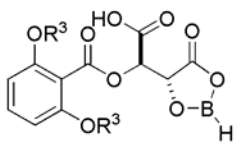
Table 17.



147a: R^1 = H, R^2 = Me
147b: R^1 = H, R^2 = Br
147c: R^1 = Me, R^2 = Me
147d: R^1 = Me, R^2 = Br
142: R^1 = H, R^2 = H

42a

165a: R^1 = H, R^2 = Me
165b: R^1 = H, R^2 = Br
165c: R^1 = Me, R^2 = Me
165d: R^1 = Me, R^2 = Br
165e: R^1 = H, R^2 = H



181a: R^3 = Me
181b: R^3 = *i*-Pr

Entry	Catalyst	Dienophile	Yield [%]	*exo*:*endo*	*ee* [%][a]
1	**181a**	**147a**	85	89:11	96
2	**181a**	**142**	90	12:88	84
3	**181a**	**147d**	91	97:03	90
4	**181b**	**147b**	100	94:06	95
5	**181b**	**147c**	100	>99:01	98

[a] *ee* of the major diastereomer.

4.1.2 Diels-Alder Reaction Catalyzed by Borabox Complexes

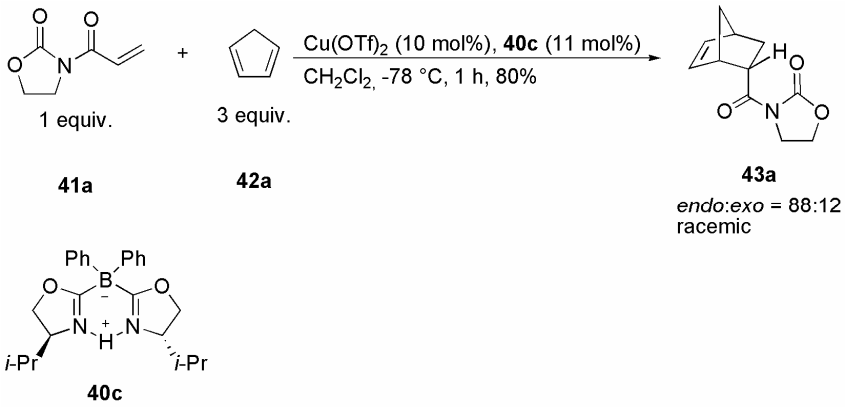
4.1.2.1 Objectives

The Diels-Alder reaction has been very popular over the last 50 years and the selectivities obtained, as shown in section 4.1.1, are remarkably high especially with bis(oxazoline) ligand **35a**. The objective of this chapter was not so much to improve the results already obtained in

the literature but to develop general conditions for the use of the borabox ligands **40** in Lewis acid-mediated asymmetric catalysis.

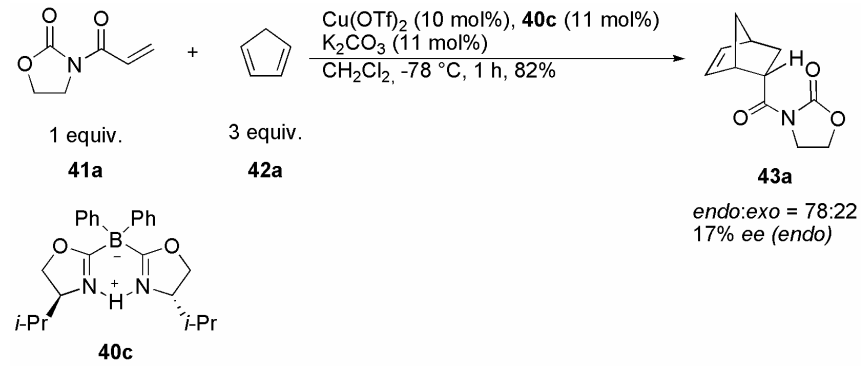
4.1.2.2 Initial Screening and Role of the Base

The Diels-Alder reaction between the imide **41a** and cyclopentadiene (**42a**) was performed with 10 mol% of copper (II) triflate and 11 mol% of ligand **40c** in dichloromethane at -78 °C (Scheme 49). In one hour, the reaction was complete but the cycloadduct **43a** was obtained with a moderate diasteroselectivity and as a racemate.



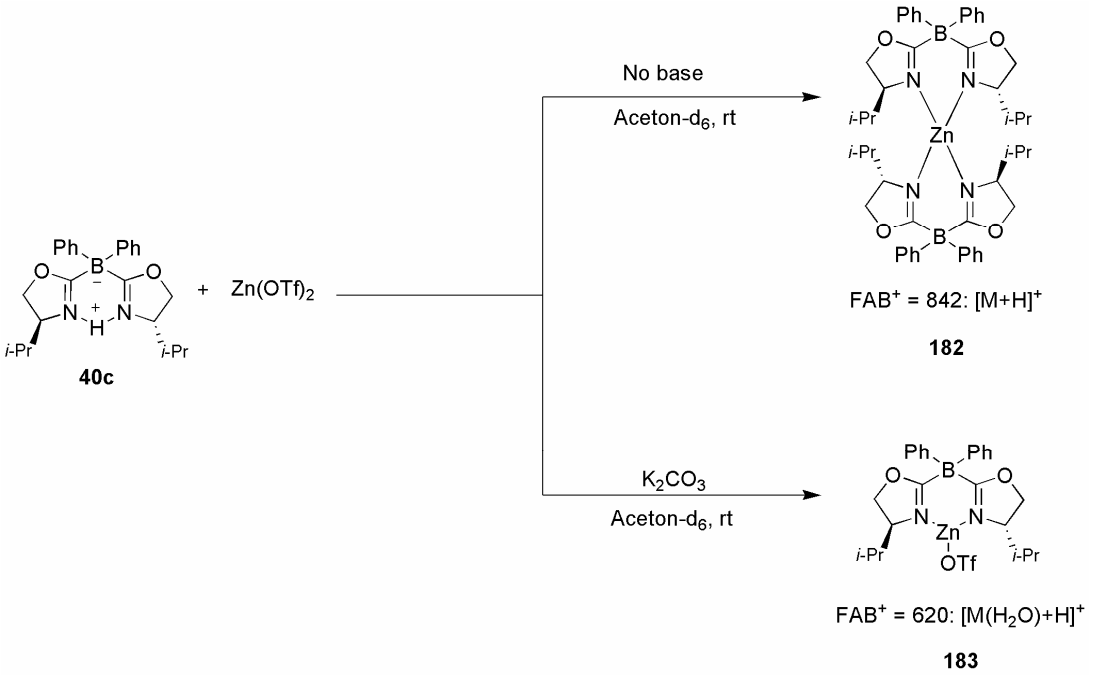
Scheme 49.

With the idea of removing the proton of the borabox ligand in order to facilitate the complexation of **40c** with the copper (II) triflate and the dienophile **41a**, one equivalent of potassium carbonate, with respect to ligand **40c**, was added during the complexation (Scheme 50). The reaction afforded the cycloadduct **43a** with an enantiomeric excess of 17% and a slightly decreased diastereoselectivity (*endo*:*exo* ratio of 78:22 and 17% *ee* (*endo*)).



Scheme 50.

A NMR study was performed to gain some insight into the complexation process of the borabox ligand **40c**. NMR- and mass spectra of a catalyst, formed by mixing an equimolar amount of borabox **40c** and zinc (II) triflate in acetone-d_6 (Scheme 51) proved the formation of a dimeric species **182**. However, when one equivalent of potassium carbonate was added to the reaction solution, the monomer **183** was observed. Addition of the base during the complexation prevents thus the formation of the non-selective homoleptic species.

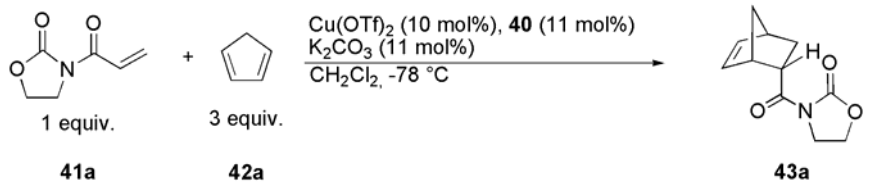


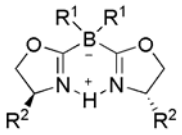
Scheme 51.

4.1.2.3 Conditions Screening and Results

Further screening of borabox ligands **40** demonstrated that ligand **40j** induced a very low enantioselectivity after 18 hours at -78 °C (entry 2, Table 18). When the reaction was conducted in the presence of ligands **40e-g** with *t*-butyl groups on the oxazoline rings, higher enantiomeric excesses were observed (entries 3 to 5, Table 18). In the presence of ligand **40g**, the Diels-Alder reaction gave the cycloadduct **43a** with a good enantioselectivity of 64% (entry 3, Table 18). Variations of the substituents on the boron center showed that the ligand **40f** catalyzed the reaction with the highest enantioselectivity and diastereoselectivity (85% *ee* (*endo*), *endo*:*exo* ratio of 92:08, entry 5, Table 18). This result could be improved by employing dry potassium carbonate (99.995% purity). The cycloadduct **43a** was then formed in 92% yield with 98% *ee* for the *endo* isomer (entry 6, Table 18).

Table 18.





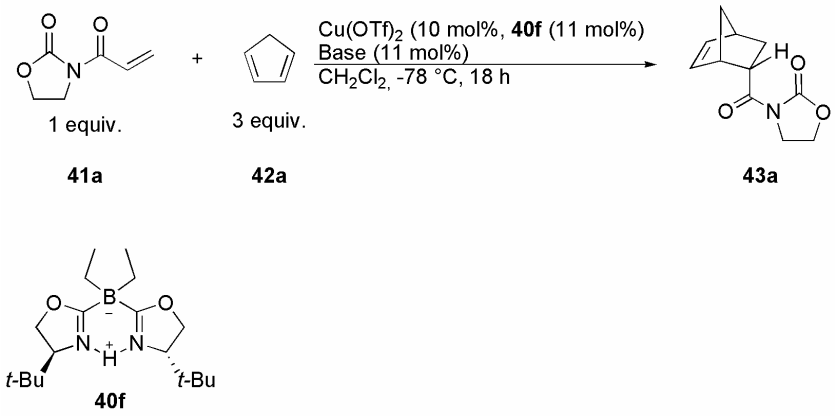
40c: R^1 = Ph, R^2 = *i*-Pr
40e: R^1 = Cy, R^2 = *t*-Bu
40f: R^1 = Et, R^2 = *t*-Bu
40g: R^1 = Ph, R^2 = *t*-Bu
40j: R^1 = Ph, R^2 = Bn

Entry	Ligand	Time [h]	Yield [%][a]	*endo*:*exo*[b]	*ee* (*endo*) [%][c]
1	**40c**	1	82	78:22	17
2	**40j**	18	92	87:13	9
3	**40g**	18	84	88:12	64
4	**40e**	18	>99	89:11	43
5	**40f**	18	96	92:08	85
6	**40f**[d]	18	92	94:06	98

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC. [d] Dry K_2CO_3 was used (99.995% purity).

In the presence of ligand **40f**, a screening of different bases was performed (Table 19). As expected, the reaction proceeded with low enantioselectivity when carried out without base (17% *ee*, entry 1, Table 19). With the amine derivatives, triethylamine and Hünig's base, the product **43a** was obtained in high yields but with moderate diastereoselectivities and low enantioselectivities (*endo*:*exo* ratio of 89:11 and 86:14, 72 and 46% *ee,* respectively, for the *endo* isomer, entry 2 and 3, Table 19). Cesium fluoride was used as an additive in the Diels-Alder reaction. It was thought that the fluoride ion could change the coordination geometry of the copper-borabox complex and could improve the reactivity and selectivity of the reaction. However, the addition of cesium fluoride to the reaction mixture lowered yield and selectivities (41% yield, *endo*:*exo* ratio of 92:08 and 65% *ee* for the *endo* isomer, entry 5, Table 19). The base of choice for this Diels-Alder reaction is therefore potassium carbonate which allows the synthesis of **43a** in 92% yield with an *endo*:*exo* ratio of 94:06 and 98% *ee* for the *endo* isomer (entry 6, Table 19).

Table 19.

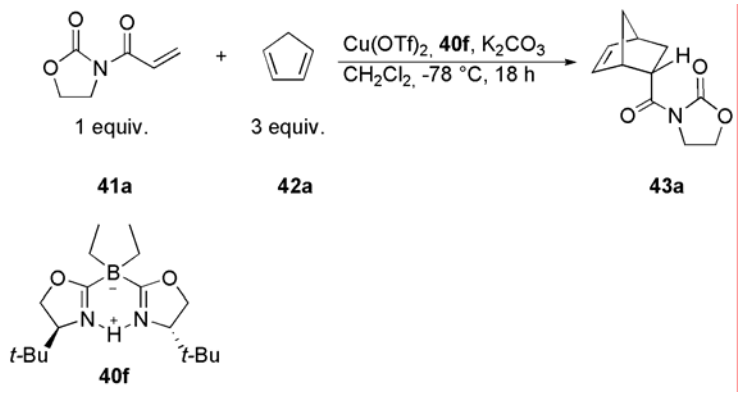


Entry	Base	Yield [%][a]	*endo*:*exo*[b]	*ee* (*endo*) [%][c]
1	-	43	90:10	17
2	Et_3N	93	89:11	72
3	$(i\text{-}Pr)_2NEt$	91	86:14	46
4	K_2CO_3	92	94:06	98
5	$CsF + K_2CO_3$[a]	41	92:08	65

[a] Isolated yields. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC. [d] 11 mol% of K_2CO_3 and 11 mol% of CsF were added during the complexation.

By lowering the catalyst loading, a dramatic decrease in the reaction of yield and enantioselectivity was observed (entry 2 and 3, Table 20). Therefore, all remaining reactions were carried out with a catalyst loading of 10 mol%.

Table 20.



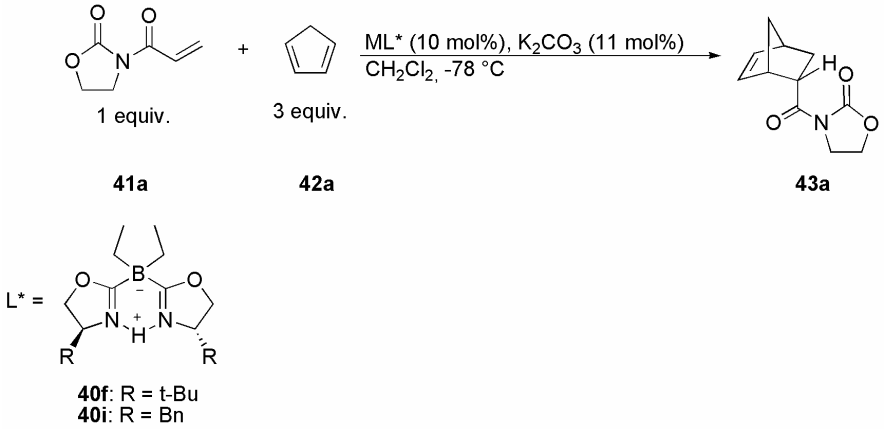
Entry	Catalyst loading [mol%]	Yield [%][a]	*endo*:*exo*[b]	*ee* (*endo*) [%][c]
1	10	92	94:06	98
2	5	54	90:10	18
3	2	60	90:10	5

[a] Isolated yields. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC.

Evans showed that the phenyl-substituted bis(oxazoline) ligands **35** were the optimal ligands for a tetrahedral metal system like zinc or magnesium, inducing better selectivities than any other bisoxazolines **35**.[95] A π stacking interaction, between the phenyl substituent of the BOX ligand **35** and the alkene moiety of the oxazolidinone **41**, was proposed to stabilize the

corresponding complex. This theory was tested in the presence of borabox ligands **40f** and **40i** (Table 21). When the Diels-Alder reaction was carried out using the complex derived from zinc (II) triflate and the borabox ligand **40f**, product **43a** was obtained in poor yield and with a very low enantioselectivity of 5% (entry 1, Table 21). In the presence of the ligand **40i**, the enantiomeric excess increased to 18% with no effect on the diastereoselectivity and the yield remained low (entry 2, Table 21). This little improvement in the enantioselectivity is possibly due to a π-stacking interaction between the benzyl group of the ligand **40i** and the alkene moiety of the oxazolidinone **41a**. In the case of magnesium catalysts, the *endo* cycloadduct **43a** was obtained as a racemic mixture with both ligands **40f** and **40i** (entry 3 and 4, Table 21). This is presumably indicative of a more distorted tetrahedral geometry of magnesium complexes compared to zinc complexes. None of the ligands tested here in combination with iron salt induced any enantioselectivity to the reaction. In the case of copper (II) triflate, the ligand **40f** was the most efficient ligand allowing the synthesis of the cycloadduct **43a** in 98% ee (entry 7, Table 21). This supports the observation of Evans that *t*-butyl susbstituted BOX ligands **35** are optimal in a copper square planar complex.[95]

Table 21.

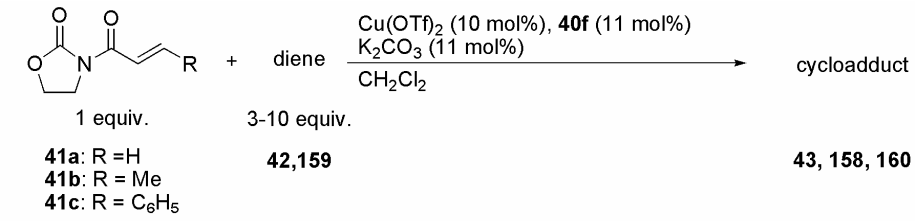


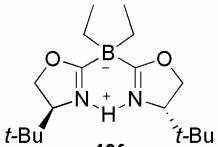
Entry	Metal salt	Ligand	Yield [%][a]	*endo:exo*[b]	*ee* (*endo*) [%][c]
1	$Zn(OTf)_2$	**40f**	32	92:08	5
2	$Zn(OTf)_2$	**40i**	57	92:08	18
3	$MgI_2.I_2$	**40f**	88	97:03	1
4	$MgI_2.I_2$	**40i**	>99	97:03	2
5	$FeI_3.I_2$	**40f**	88	91:09	2
6	$FeI_3.I_2$	**40i**	85	90:10	6
7	$Cu(OTf)_2$	**40f**	92	96:04	98
8	$Cu(OTf)_2$	**40i**	67	82:18	1

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC.

The scope of the Diels-Alder reaction catalyzed by copper (II)-borabox complexes was then investigated (Table 22). The substituted imides **41b** and **41c** were used as substrates in the reaction catalyzed by **40f**. The broader bite angle of the borabox ligand **40** compared to that of BOX ligand **35** (section 3.3.2) was expected to define a deeper chiral pocket able to anchor more effectively bulkier dienophiles such as **41b** and **41c**. The enantioselectivity for the cycloadducts **43b** and **43c** would then be enhanced when the reaction is catalyzed by the borabox ligand **40f** compared to the BOX ligand **35a**. However, only low enantioselectivities were obtained for these two substrates (entry 2 and 3, Table 22). The Diels-Alder reaction was then conducted with less reactive dienes as cyclohexadiene (**42b**), isoprene (**159a**) and 2,3-dimethylbutadiene (**159b**) (entries 4 to 6, Table 22). Cycloadducts **158a** and **159b** were formed with poor selectivity (39 and 35% *ee* respectively, entry 4 and 6, Table 22). The reaction with isoprene (**159a**) proceeded with 61% *ee* (entry 6, Table 22), which was identical to the enantioselectivity obtained using BOX ligand **35a**.[95]

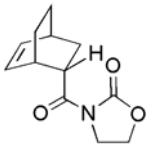
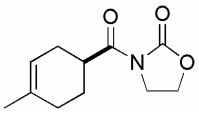
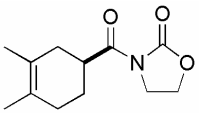
Table 22.





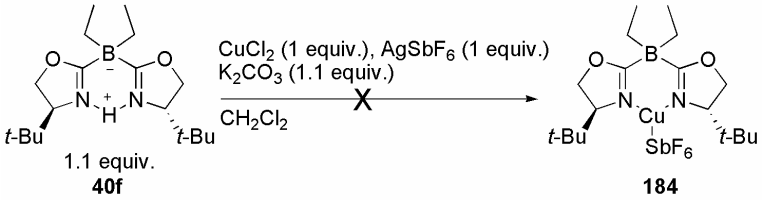
40f

Entry	R	Diene	Cycloadduct	T [°C]	t[a]	Yield [%][b]	*endo:exo*[c]	*ee* (*endo*) [%][d]
1	H	**42a**	**43a**	-78	18 h	92	96:04	98
2	Me	**42a**	**43b**	-15	3 d	90	87:13	40
3	Ph	**42a**	**43c**	25	7 d	87	82:18	49

Entry	R	Diene	Cycloadduct	T [°C]	t[a]	Yield [%][b]	*endo:exo*[c]	*ee* (*endo*) [%][d]
4	H	 **42b**	 **158a**	25	40 h	94	97:03	39
5	H	 **159a**	 **160a**	25	24 h	97	98:02[e]	61
6	H	 **159b**	 **160b**	25	16 h	85	-	35

[a] h for hours and d for days. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC. [e] Values refer to (1,4):(1,3) regioisomer ratio.

Evans and co-workers showed the influence of the counterion on the reactivity and selectivity of the Diels-Alder reaction.[95] In particular, complex **157b** derived from $Cu(SbF_6)_2$ and ligand **35a** increased the rate of the reaction between imide **41a** and cyclopentadiene (**42a**). The borabox complex **184** was postulated to behave similarly. But after addition of copper (II) chloride and silver hexafluoroantimonate to a solution of the borabox complex **40f**, a black precipitate was observed (Scheme 52). Filtration of this mixture afforded a clear solution that was used as a reaction medium for the Diels-Alder reaction but the enantioselectivity was very low (74% yield after 16 hours, 92:08 as *endo*:*exo* ratio and 7% *ee* (*endo*)).

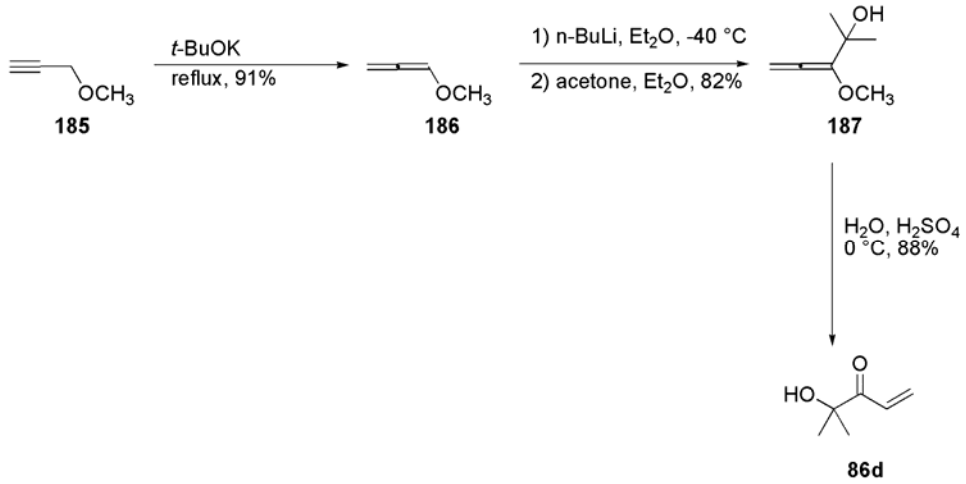


Scheme 52.

4.1.2.4 α'-Hydroxy Enones as Substrates for the Diels-Alder Reaction

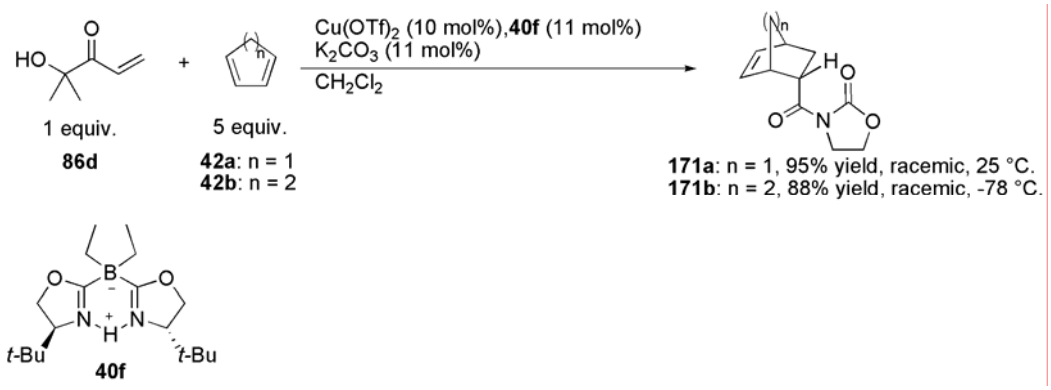
The kinetic resolution of 1,2-diols was highly selective when catalyzed by copper (II)-borabox complexes (section 3.2.3). It was envisaged that 1,2 bidentate substrates like α'-hydroxy enones **86d** would be more suitable dienophiles than the 1,3 bidentate imides **41**. 4-Hydroxy-4-methylpent-1-en-3-one (**86d**) was synthesized in three steps (Scheme 53). 3-Methoxypropa-1,2-diene (**186**) was formed in 91% yield after treatment of methyl

propargyl ether (**185**) with *t*-BuOK at reflux.[112] Subsequent treatment with *n*-BuLi followed by the addition of acetone to **186** gave 3-methoxy-2-methylpenta-3,4-dien-2-ol (**187**) in 82% yield. 4-Hydroxy-4-methylpent-1-en-3-one (**86d**) was obtained in 88% yield after treatment with sulfuric acid.[98]



Scheme 53.

The α'-hydroxy enone **86d** was used as the substrate in the Diels-Alder reaction with cyclopentadiene (**42a**) or cyclohexadiene (**42b**). Unfortunately, only racemic cycloadducts were obtained (Scheme 54). Presumably, the α'-hydroxy enone **86d** does not coordinate to the copper (II)-borabox complex and so no enantioselectivitity could be induced.



Scheme 54.

4.1.2.5 Conclusion

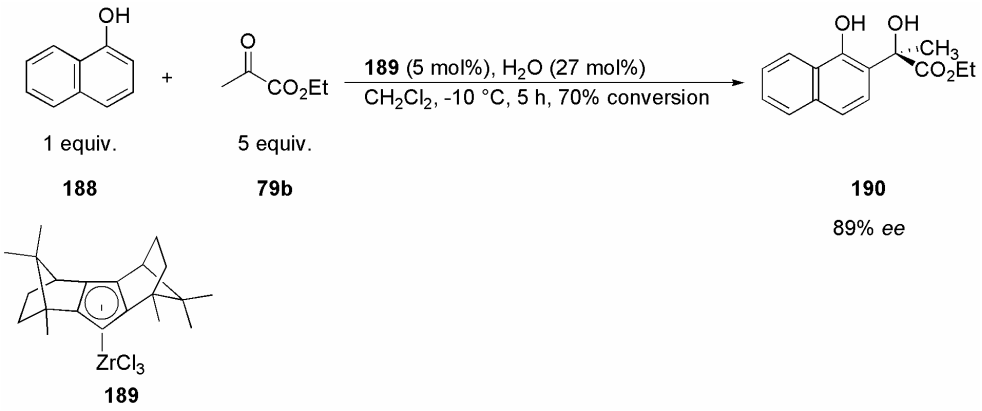
Ligand **40f**, with *t*-butyl substituents at the C4 positions of the oxazoline rings, was found to be the most efficient ligand borabox for the copper-catalyzed Diels-Alder reaction catalyzed by copper salts. The addition of one equivalent of base, with respect to the ligand **40f**, was

crucial to form the monomeric species **183** and not the dimeric species **182** which is non-selective. Iron, zinc and magnesium complexes were also tested as potential catalysts but were found to be unselective. For the reactions between imide **41a** and cyclopentadiene (**42a**) or isoprene (**159a**), the borabox ligand **40f** could compete with the BOX ligand **35a**. But in general, the selectivities induced by the borabox ligand **40f** were lower. Furthermore, 1,2 dienophiles as α'-hydroxy enones **86d** were unsuitable substrates for the Diels-Alder reaction catalyzed by copper (II)-borabox complexes, only racemic *endo* cycloadducts were formed.

4.2 Friedel-Crafts Reaction

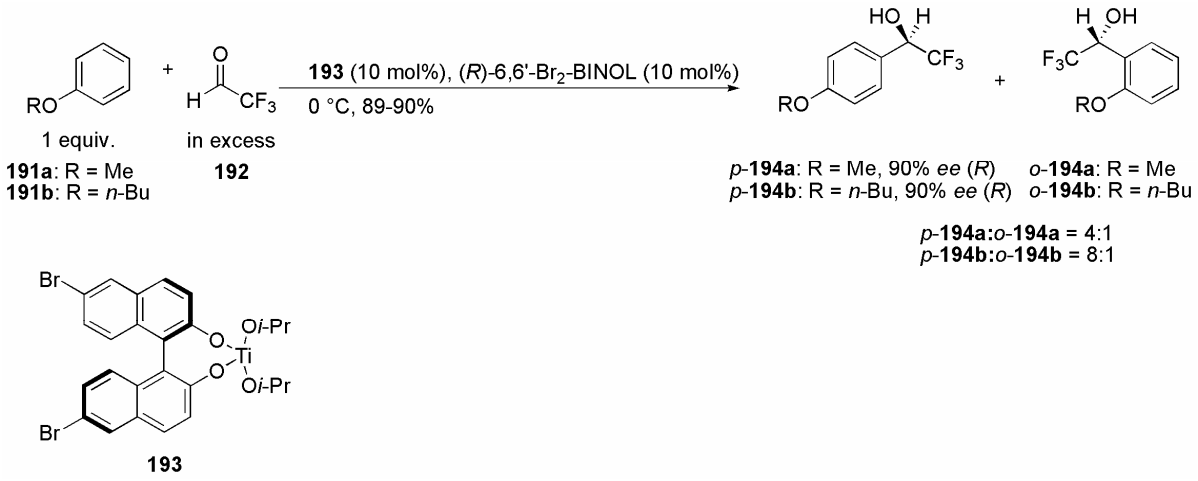
4.2.1 Literature

A wide range of substituted aromatic compounds have been prepared using the Friedel-Crafts reaction, one of the most fundamental C-C bond forming reactions in organic synthesis.[113] However, only a few catalytic enantioselective versions of Friedel-Crafts reaction have been developed to date. The first enantioselective catalytic Friedel-Crafts reaction was carried out using a zirconium trichloride Lewis acid **189** (Scheme 55).[114] The pharmacologically interesting 2-(2-hydroxyaryl)lactic ester **190** was prepared from pyruvic ester **79b** and hydroxylarene **188** in 89% *ee*.



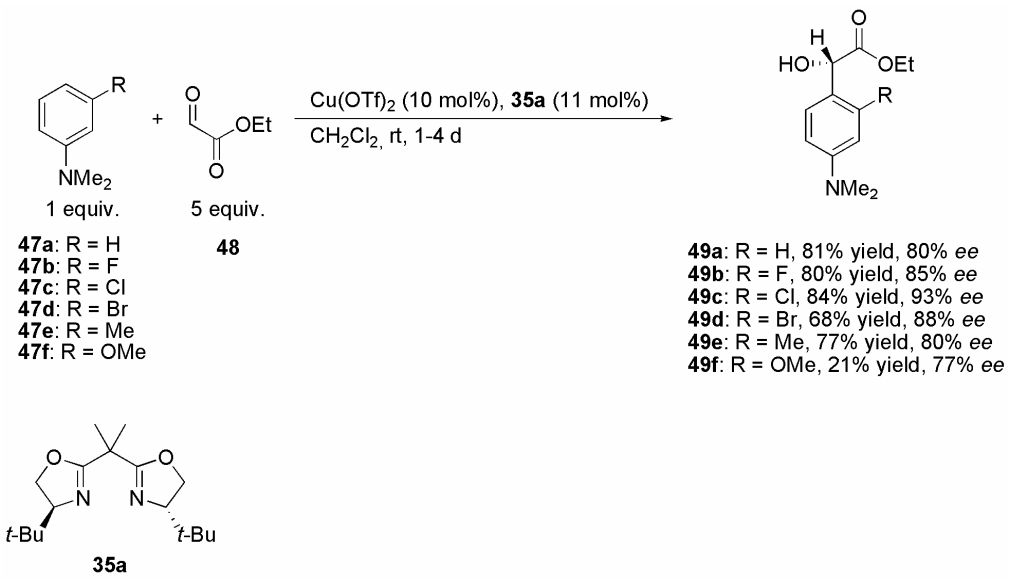
Scheme 55.

In 2000, Mikami and co-workers reported the first example of an asymmetric catalytic Friedel-Crafts reaction with fluoral **192**.[115] Chiral 1-aryl-2,2,2-trifluroroethanol derivatives **194** were synthesized in high yields and with good enantioselectivities by using the enantioenriched binaphtol-derived titanium catalyst **193** *via* asymmetric activation with a BINOL derivative (Scheme 56).[116]



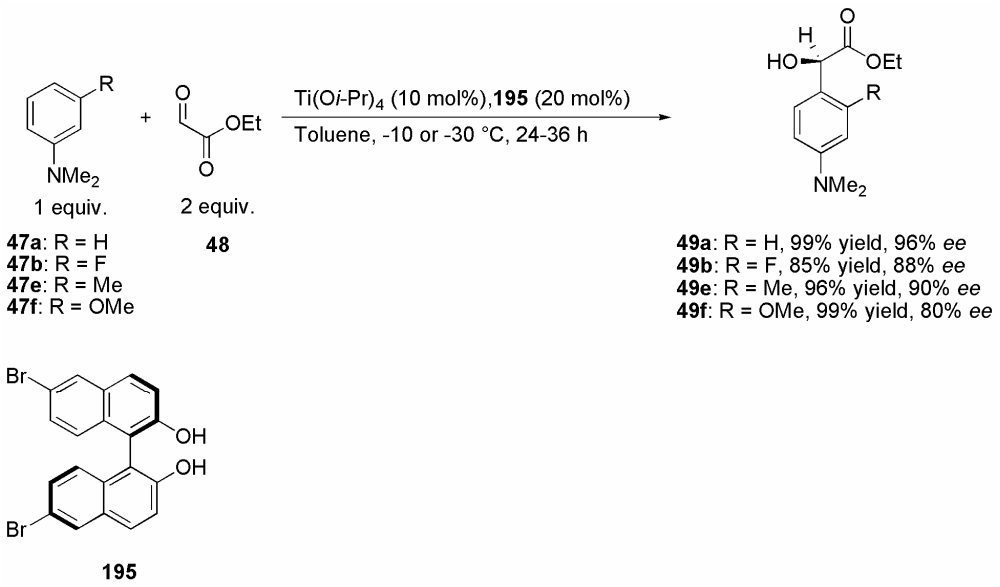
Scheme 56.

Jørgensen[117] developed an asymmetric reaction of aromatic amines with α-dicarbonyl compounds that gave substituted mandelic acid compounds **49a-f** with pharmacological activity[118]. The reaction of *N*,*N*-dimethylaniline derivatives **47a-f** and ethyl glyoxylate (**48**) catalyzed by copper (II) triflate and the BOX ligand **35a** afforded the compounds **49a-f** in good yields and enantioselectivities (Scheme 57).



Scheme 57.

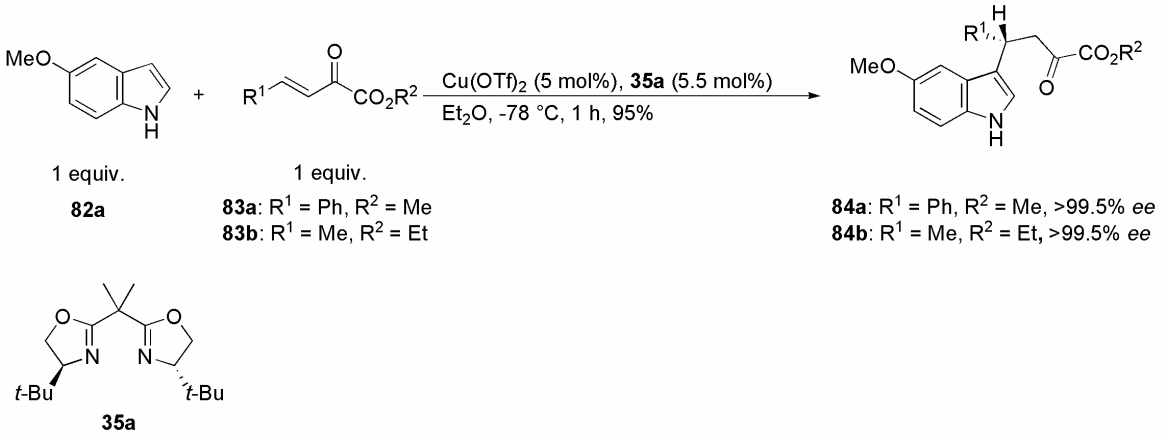
Ding and co-workers improved the results obtained by Jørgensen by using a catalyst derived from BINOL derivative **195** and Ti(O*i*-Pr)$_4$ (Scheme 58).[119] The compounds **49** were synthesized with good to high enantioselectivities (80-96% *ee*) and in high yields.



Scheme 58.

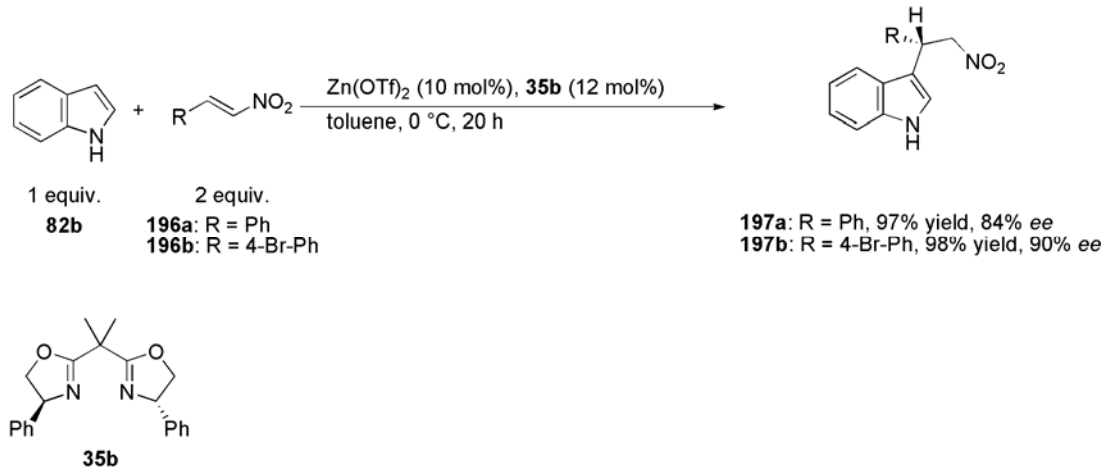
The Friedel-Crafts reaction catalyzed by chiral calixarene-like salen ligand also gave the substituted mandelic acid compounds **49** but with lower enantiomeric excesses.[120]

As well as ethyl glyoxylate (**48**) and fluoral (**192**), many other compounds were found to be suitable substrates for this Friedel-Crafts reaction. β,γ-Unsaturated α-ketoesters[45], α-hydroxy enones[121], acyl phosphonates[122], alkylidiene malonates[123], 2-acyl imidazoles[124] all underwent successful reaction with indole derivatives **82** to afford the corresponding Friedel-Crafts products in high enantioselectivities. In particular, Jørgensen developed the reaction of indole derivative **82a** with β,γ-unsaturated α-ketoesters **83** catalyzed by a copper (II)-bis(oxazoline) complex (Scheme 59).[45] The reaction was complete after only 1 hour and the products **84** formed with an *ee* greater than 99.5%.



Scheme 59.

Recently, nitroalkenes were successfully used as new substrates in the Friedel-Crafts alkylation.[125] The reaction between indole **82b** and nitroalkenes **196a** and **196b** catalyzed by zinc (II) triflate and the BOX ligand **35b** gave the products **197** in high yield and with good enantioselectivity (Scheme 60).



Scheme 60.

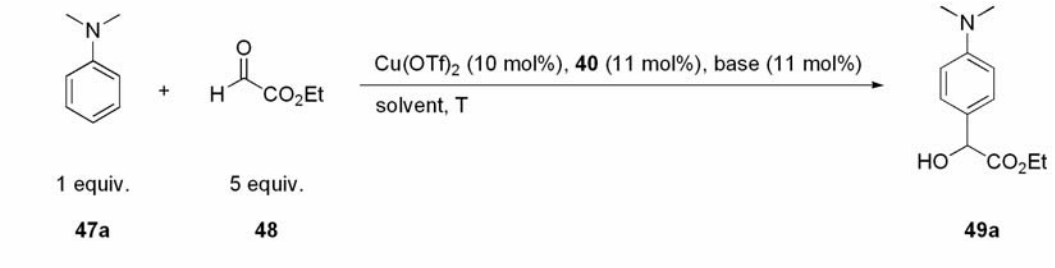
4.3.2 Results

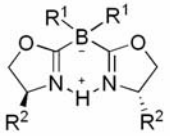
Good enantioselectivities have been obtained in the Friedel-Crafts reaction, particularly with BOX ligands **35**. However, in the case of the reaction between indole (**82b**) and nitroalkenes **196** (Scheme 60) and between *N*,*N*-dimethylaniline derivatives **47** and ethyl glyoxylate (**48)** (Scheme 58), the selectivities can still be improved.

The reaction between *N*,*N*-dimethylaniline (**47a**) and ethyl glyoxylate (**48**) was therefore performed with 10 mol% of copper (II) triflate, 11 mol% of borabox ligand **40** and 11 mol% of base.[117] A screening of differentially substituted borabox ligands, bases and solvents was performed (Table 23). With ligand **40f**, which gives the best result in the Diels-Alder reaction, no reactivity was observed at all (entry 1, Table 23). In the presence of the ligand **40g**, the Friedel-Crafts product was obtained in low yield and low enantioselectivity (10% yield, 30% *ee*, entry 2, Table 23) even after a reaction time of 2 days. With the same ligand **40g**, different solvents were tested (dichloromethane, nitromethane, entry 3 and 4, Table 23). Whereas in nitromethane no product was obtained, the reaction's reactivity and selectivity in dichloromethane was comparable with that obtained in tetrahydrofuran (23% yield and 22% *ee*, entry 3, Table 23). When the reaction was performed in the presence of ligand **40g** and triethylamine in tetrahydrofuran, the Friedel-Crafts product was obtained with a high yield of 96% and a moderate *ee* of 61% after 4 days (entry 5, Table 23). Variation of the substituents

at the stereogenic center and the boron atom of the ligand caused a decrease in both reactivity and selectivity of the reaction (entries 6 to 8, Table 23).

Table 23.



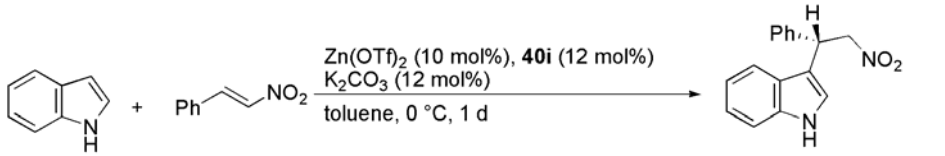


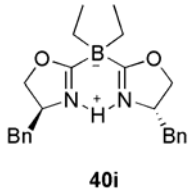
40c: R^1 = Ph; R^2 = *i*-Pr
40e: R^1 = Cy; R^2 = *t*-Bu
40f: R^1 = Et; R^2 = *t*-Bu
40g: R^1 = Ph; R^2 = *t*-Bu
40i: R^1 = Et; R^2 = Bn

Entry	**40**	Base	Solvent	T [°C]	Time [days]	Yield [%][a]	*ee* [%] [b]
1	**40f**	K_2CO_3	THF	0	-	-	-
2	**40g**	K_2CO_3	THF	0	2	10	30
3	**40g**	K_2CO_3	DCM	0	4	23	22
4	**40g**	K_2CO_3	$MeNO_2$	0	-	-	-
5	**40g**	Et_3N	THF	0	4	96	61
6	**40e**	Et_3N	THF	0	4	15	37
7	**40i**	Et_3N	THF	0	4	13	37
8	**40c**	Et_3N	THF	0	4	45	12

[a] Isolated yields. [b] Determined by chiral HPLC.

The reaction of indole (**82b**) with the nitroalkene **196a** was also tested in the presence of the borabox ligand **40i** but no selectivity was observed (Scheme 61).





40i

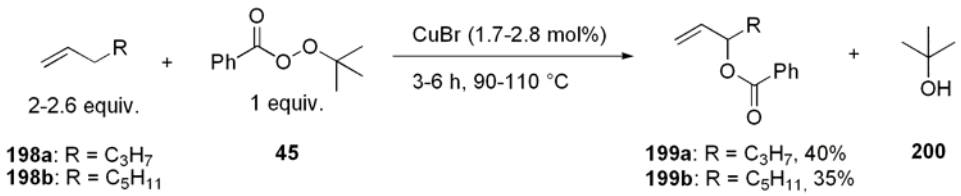
Scheme 61.

Due to the lack of reactivity of borabox ligand **40** in the Friedel-Crafts reaction and the poor enantioselectivity obtained for the mandelic acid and indole derivatives **49** and **197**, the reaction was not further studied.

4.3 Allylic Oxidation

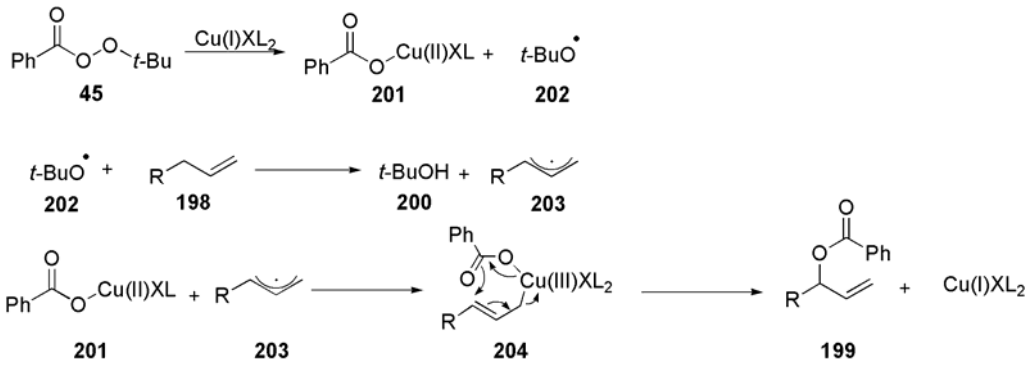
4.3.1 Literature

For many years, stereoselective C-H oxidations were limited to biochemical reactions using enzymes or microorganisms.[126] σ-Bond oxidations in particular required harsh conditions or a highly reactive oxidizing agent, making the control of stereoselectivity difficult. Due to the low reactivity of the C-H bond, the first oxidation processes employing transition metal catalysts were carried out on activated allylic C-H bonds. In 1958, Kharasch and co-workers investigated the allylic oxidation of olefins with peroxy esters in the presence of copper salts (Scheme 62).[127] In the case of terminal olefins, this led to the formation of only one regioisomer, the thermodynamically less stable allylic esters **199**.



Scheme 62.

This regiospecificity is quite unusual for a peroxy ester reaction, which generally gives the thermodynamically more stable non-terminal double bond.[128] To explain this, a mechanism involving an organo-copper intermediate was proposed (Scheme 63).[129] Reductive homolysis of the O-O bond of *t*-butyl peroxybenzoate **45** by a copper (I) salt gives copper (II) benzoate **201** and *t*-butoxy radical **202**. The latter abstracts an allylic hydrogen atom yielding the allylic radical **203**. Copper (II) benzoate **201** then rapidly attacks the allyl radical **203** at the least hindered terminal position forming the copper (III) species **204**. Finally, a pericyclic reaction leads to the formation of the thermodynamically unfavoured allylester product **199** and regenerates the copper (I) catalyst.

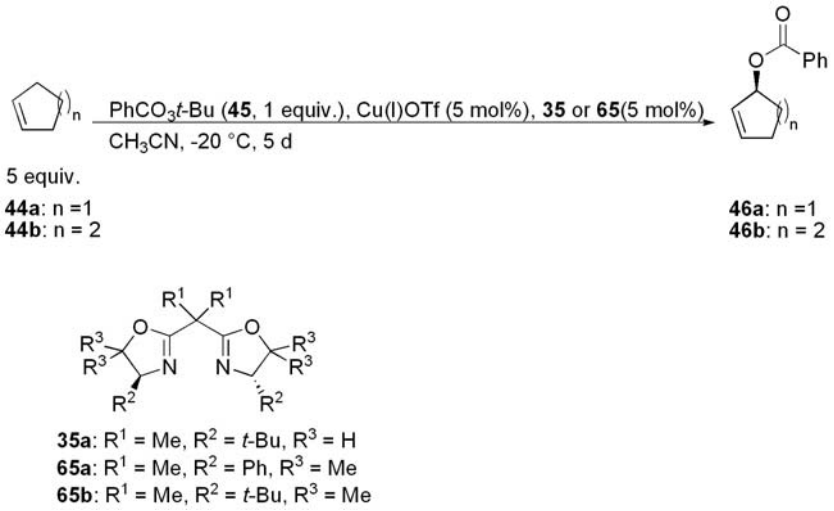


Scheme 63.

A few enantioselective versions of the allylic oxidation were developed in the 60's and 70's, but without great success.[130] The enantioselectivities obtained did not reach more than 17% *ee*. Later, Muzart[131] and Feringa[132] used copper complexes of optically-active amino acids as catalysts for the allylic oxidation of olefins. In the presence of a copper (II) complex of (*S*)-proline, cyclopentene and cyclohexene oxides **46a** and **46b** were synthesized with 54% and 63% *ee*, respectively.

In 1995, the emergence of bis(oxazoline) ligands **35** allowed for improved enantioselectivity in these reactions. Andrus and co-workers employed these ligands **35** and **65** with copper (I) triflate in acetonitrile at -20 °C (Table 24).[129] Starting from cyclopentene (**44a**), a high enantioselectivity was obtained with the C5,C5'-disubstituted ligand **65a** (49% yield, 81% *ee*, entry 3, Table 24). Cyclohexene oxide **46b** was also synthesized in high *ee* using ligand **35a** (80% *ee*, entry 4, Table 24).

Table 24.

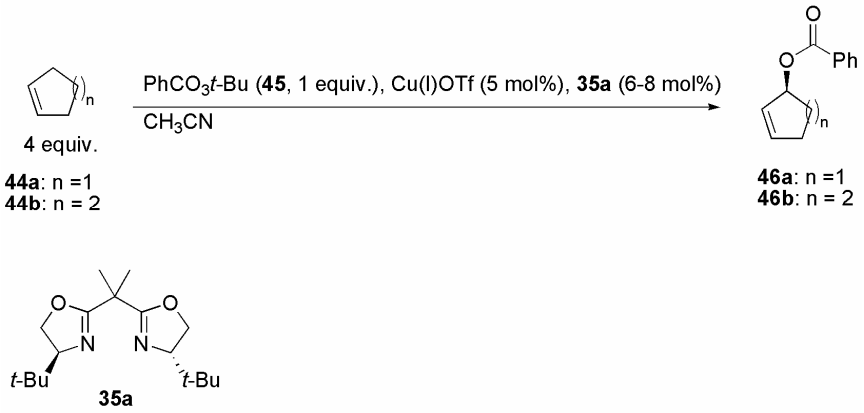


Entry	Substrate	Ligand	Yield [%][a]	*ee* [%][b]
1	**44a**	**35a**	44	70
2	**44a**	**65b**	41	42
3	**44a**	**65a**	49	81
4	**44b**	**35a**	43	80
5	**44b**	**65b**	49	67
6	**44b**	**65a**	44	47

[a] Isolated yields based on consumed perester. [b] Integration of ^{1}H NMR(500 MHz) signal for *o*-protons of the benzoate with chiral shift reagent Eu(hfc)3 and compared to spectra of the racemic compound.

Pfaltz and co-workers have also developed a practical catalyst system for the allylic oxidation of cyclohexene and cylopentene employing BOX ligand **35a** (Table 25).[133] Despite the high enantioselectivities obtained (84% and 77% *ee* for cyclopentene and cyclohexene oxides **46a** and **46b** respectively, entry 2 and 4, Table 25), reactivity remained a major problem in allylic oxidation. For cyclopentene for example, a reaction time of 3 weeks is required to obtain 68% conversion at -20 °C.

Table 25.



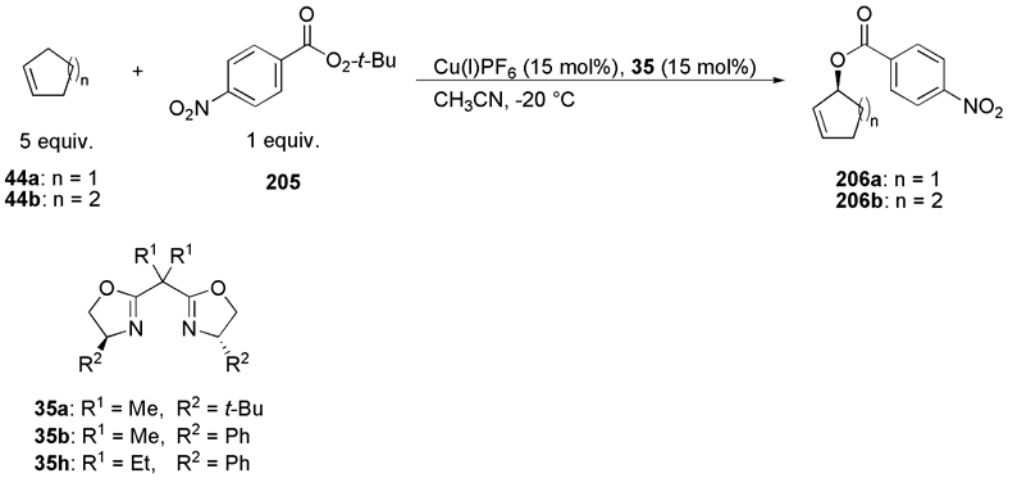
Entry	Substrate	Time [days]	T [°C]	Conversion [%]	Yield [%][a]	*ee* [%][b]
1	**44a**	4	23	88	68	74
2	**44a**	22	-20	68	61	84
3	**44b**	7	23	63	68	60
4	**44b**	15	7	77	64	77

[a] Yield based on consumed perester. [b] Determined by chiral HPLC. All products have (*S*)-configuration.

With the aim of improving the rate of this reaction, Andrus introduced the electron deficient peresters **205** (Table 26).[134] With this modification, it was expected that the perester bond will be weakened, leading to faster bond homolysis. The reaction was carried out in the presence of copper (I) hexafluorophosphate-BOX complexes in acetonitrile at -20 °C with 5 equivalents of olefin. For cyclopentene (**44a**), the application of ligand **35h** was reported to give product **206a** with very high selectivity (41% yield after 8 days, 99% *ee*, entry 3, Table 26) with the electron deficient perester **205**. The cyclohexenyl ester **206b** was also obtained

with very high enantiomeric excess but again conversion was low (44% yield after 17 days, 96% *ee*, entry 5, Table 26). However, a very strange increase of the *ee* from 70% (41% yield) after 3 days to 95% (55% yield) after 17 days was observed, which could not be explained.

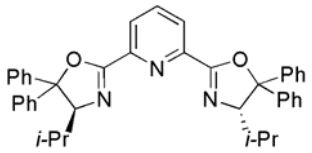
Table 26.



Entry	Substrate	Ligand	Time [days]	Yield [%][a]	*ee* [%][b]
1	**44a**	**35a**	10	52	79
2	**44a**	**35b**	10	49	82
3	**44a**	**35h**	8	41	99
4	**44b**	**35a**	7	61	84
5	**44b**	**35b**	17	44	96
6	**44b**	**35h**	13	50	75

[a] Yields are for isolated, chromatographed materials and based on the perester. [b] Determined by chiral HPLC.

Besides bis(oxazoline) ligands **35**, the pyridine bis(oxazoline) type ligand[135] (Pybox) **207** was also studied in allylic oxidation and was found to be a competitive system[136] (Figure 29).



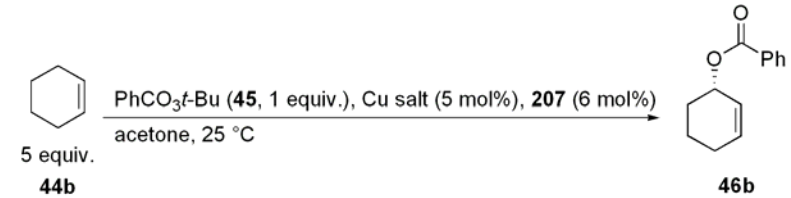
207

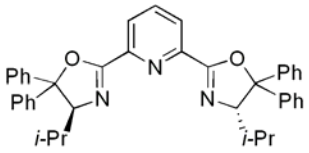
Figure 29.

An initial screening of conditions revealed that the rate of the reaction was highly dependent on the method of preparation of the copper (I) triflate complex (Table 27).[137] When copper (I) triflate was added directly to the solution of ligand **207** in acetone, cyclohexene oxide **46b** was synthesized with an enantiomeric excess of 91% and in 67% yield after 39 hours (entry 1, Table 27). But, when copper (I) triflate was prepared *in situ* by reducing copper (II) triflate with phenylhydrazine, the reaction was much faster. After 1 hour, the cyclohexene oxide **46b** was obtained in 67% yield and with the same enantioselectivity (91%, entry 2, table 27). It

thus appears that the use of phenylhydrazine increases the rate of the reaction, but the reasons remain unclear.

Table 27.





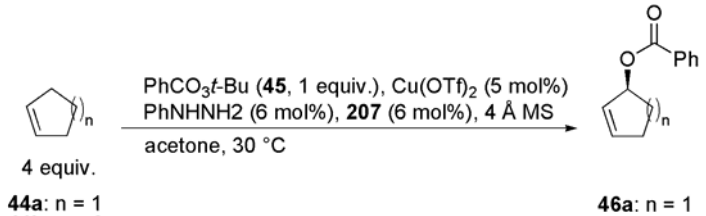
207

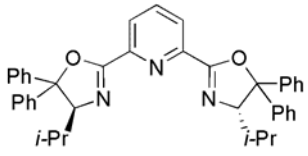
Entry	Cu salt	Time [hours]	Yield [%][a]	*ee* [%][b]
1	$(CuOTf)_2PhH$	39	67	91
2	[Cu(I)OTf][d]	1	67	91

[a] Isolated yields. [c] Determined by chiral HPLC. [b] Prepared *in situ* by reducing the Cu(II)OTf complex with $PhNHNH_2$.

The reaction was then extended to other olefins (Table 28). In the case of cyclopentene (**44a**), the reaction was complete after 3 hours and the product **46a** was formed with an enantiomeric excess of 70% (entry 1, Table 28). Cyclohexene and cycloheptene oxides **46b** and **46c** were synthesized with *ee*'s of 91 and 86% respectively (entries 2 and 3, Table 28). Six hours only were needed for completion in the case of cyclooctene (**44d**) and the enantioselectivity attained was remarkably high (94% *ee*, entry 4, Table 28).

Table 28.





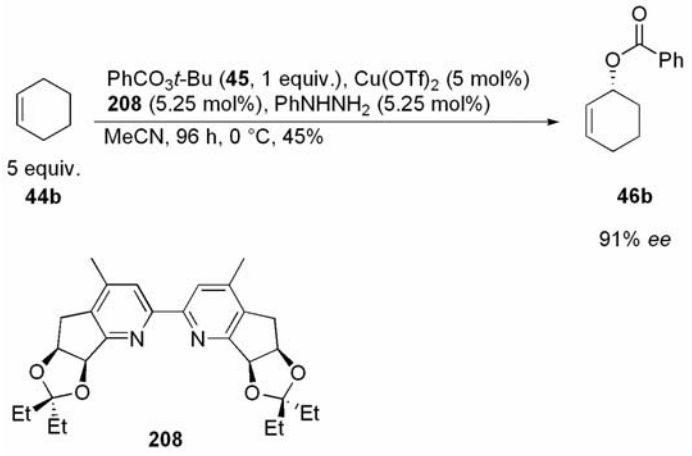
207

Entry	Olefins	Time [hours]	Yield [%][a]	*ee* [%][b]
1	**44a**	3	76	70
2	**44b**	1	67	91
3	**44c**	6	47	86
4	**44d**	6	34	94

[a] Isolated yields. [b] Determined by chiral HPLC.

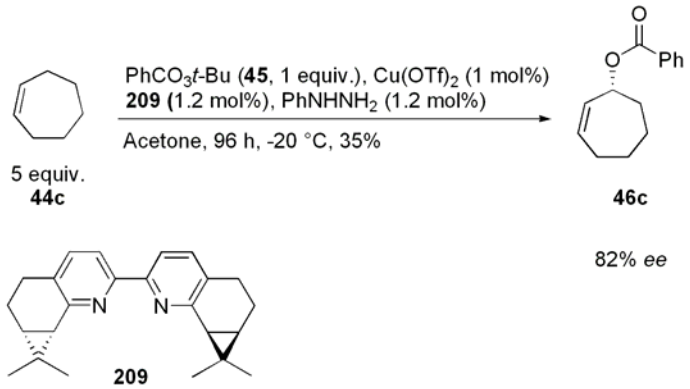
In 2000, Katsuki performed the allylic oxidation of olefins with tris(oxazoline) ligand and regardless of the ring size of the substrate, high enantioselectivities (81-93% ee) were obtained.[138]

Other ligands were also tested, but with less success. Wilson performed the allylic oxidation of olefins with bipyridyl ligand copper (I) complex and obtained cyclohexene oxide **46b** with an *ee* of 91% (Scheme 64).[139] However, when the same conditions were applied to other cyclic olefins, the enantioselectivities were very poor.



Scheme 64.

Andersson and co-workers used a chiral bicyclic amino acid as ligand, but the results were disappointing.[140] Recently, Kočovský synthesized the new chiral 2,2'-bypiridine ligand **209** and applied it in the allylic oxidation reaction.[141] High enantioselectivity was achieved only with cycloheptene (**44c**) as substrate (Scheme 65).



Scheme 65.

4.3.2 Allylic Oxidation Catalyzed by Borabox Complexes

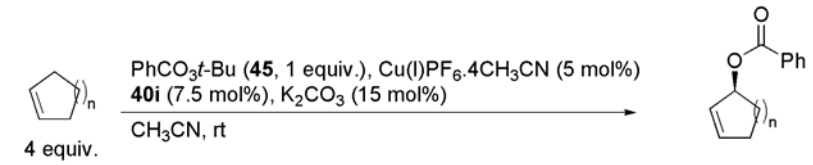
4.3.2.1 Objectives

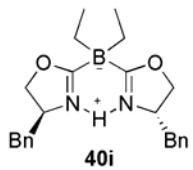
The major drawbacks of the allylic oxidation of olefins, as mentioned earlier, are slow reaction rate and selectivities which generally do not exceed 80% *ee*. This chapter seeks to determine suitable conditions for the allylic oxidation of olefins in the presence of borabox ligand **40** to improve both the enantioselectivity and reactivity of this reaction.

4.3.2.2 Results

The allylic oxidation of cyclic olefins was first studied by Valentin Köhler.[142] Initial investigations showed that, in contrast to the BOX ligand **35**, *t*-butyl groups at the C4 positions of the oxazoline rings of the borabox ligand **40** were not suitable for this reaction. The allylic oxidation of cyclopentene (**44a**) and cyclohexene (**44b**) was carried out with 5 mol% of copper (I) hexafluorophosphate tetracetonitrile, 7.5 mol% of ligand **40i** and 15 mol% of potassium carbonate in acetonitrile (Table 29). Good enantioselectivities were obtained (82% and 79% *ee* for **46a** and **46b** respectively, Table 29).

Table 29.





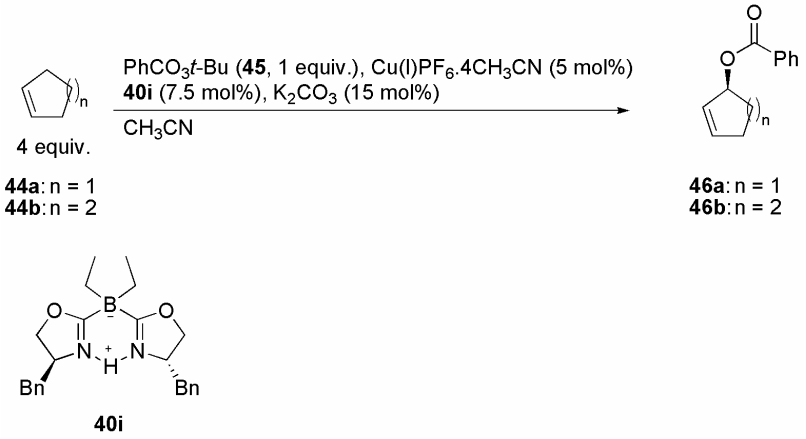
40i

Entry	Olefins	Time [days]	Yield [%][a]	*ee* [%][b]
1	**44a**	2	79	82
2	**44b**	10	69	79

[a] Isolated yields. [b] Determined by chiral HPLC.

Furthermore, the allylic oxidation of cyclopentene (**44a**) in the presence of borabox ligand **40i** showed a weak dependence on the temperature which is not the case for cyclohexene (**44b**, Table 30).[62] At 80 °C, after only one hour, cyclopentene oxide **46a** could still be obtained with an *ee* of 76% and 69% yield (entry 6, Table 30).

Table 30.

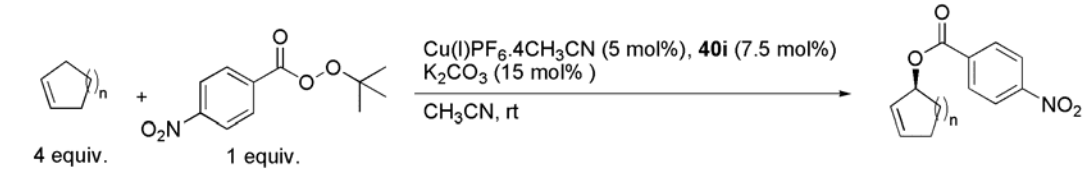


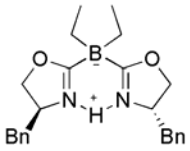
Entry	Olefins	T [°C]	Time [hours]	Yield [%][a]	*ee* [%][b]
1	**44a**	-15	360	30	86
2	**44a**	5	141	80	82
3	**44a**	25	48	79	82
4	**44a**	40	8	78	81
5	**44a**	60	2	70	78
6	**44a**	80	1	69	76
7	**44b**	25	219	69	79
8	**44b**	60	86	72	68
9	**44b**	80	11	61	65

[a] Isolated yields. [b] Determined by chiral HPLC.

In an effort to increase the reaction rate of the allylic oxidation of cycloalkenes, the reaction was carried out with Andrus' nitroperoxybenzoate (**205**) in the presence of ligand **40i** (Table 31). The enantioselectivity obtained for cyclopentene oxide **206a** in the presence of nitroperoxybenzoate (**205**) was improved compared to the one obtained with *tert*-butylperbenzote (**45**) (86% *ee*, entry 1, Table 31 and 82% *ee*, entry 3, Table 30). Unexpectedly, however, the reaction took longer to reach the same range of yields (77% in 3 days, entry 1, Table 31 and 79% in 2 days, entry 3, Table 30). In contrast, the reaction between cyclohexene (**44b**) and nitroperoxybenzoate (**205**) proceeded with the same enantioselectivity as with *tert*-butylperoxybenzoate (**45**) (79% *ee*, entry 2, Table 31) but with the expected reduced reaction time (3 days against 10 days, entry 2, Table 31 and entry 7, Table 30).

Table 31.



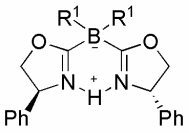


40i

Entry	Olefins	Time [days]	Yield [%][a]	*ee* [%][b]
1	**44a**	3	77	86
2	**44b**	3	85	79

[a] Isolated yields. [b] Determined by chiral HPLC.

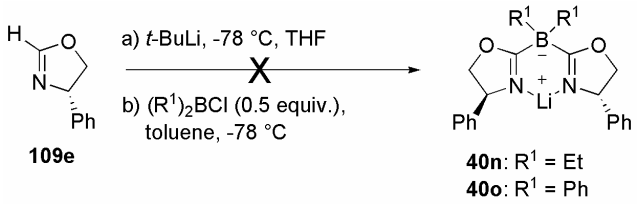
As mentioned earlier, Andrus and co-workers showed that ligand **65a** with phenyl groups at the C4 positions of the oxazoline rings induced high enantioselectivity for cyclopentene (**44a**).[129] It was therefore expected that the complex formed with ligand **40n** or **40o** (Figure 30) would catalyze the allylic oxidation in a highly enantioselective manner.[62]



40n: R^1 = Et
40o: R^1 = Ph

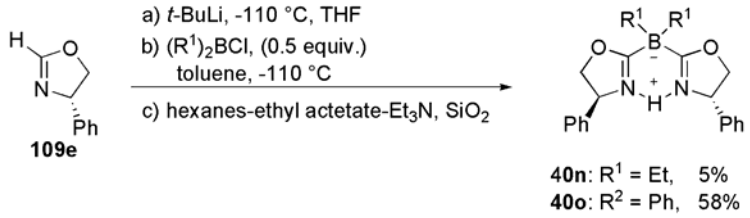
Figure 30.

However, attempts to synthesize these two new ligands **40n** and **40o**, following the usual procedure for borabox ligands failed (Scheme 66). The reaction mixture turned black and no formation of product was observed. The reason for this is still unclear, but it was supposed that under these conditions the benzylic position of the oxazoline ring was deprotonated by *t*-BuLi.



Scheme 66.

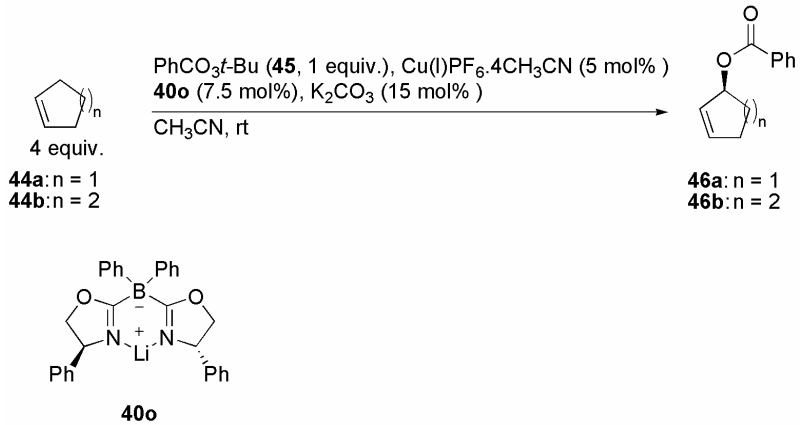
This issue was resolved by conducting the reaction at -110 °C instead of -78 °C, whereupon the borabox **40o** was formed in good yield. Ligand **40n** was also synthesized in this fashion but with a very poor yield (Scheme 67).



Scheme 67.

Ligand **40o** was then tested in the allylic oxidation of both cyclohexene (**44b**) and cyclopentene (**44a**) (Table 32). In the presence of ligand **40o**, cyclopentene oxide **46a** was obtained with comparable yield and enantioselectivity to reactions employing ligand **40i**. In the case of cyclohexene (**44b**), the rate of the reaction was increased with ligand **40o** (78% yield after 2 days, entry 2, Table 32 and 69% yield after 10 days, entry 2, Table 29), but the enantiomeric excess remained low (65% *ee* with **40o** and 79% *ee* with **40i**).

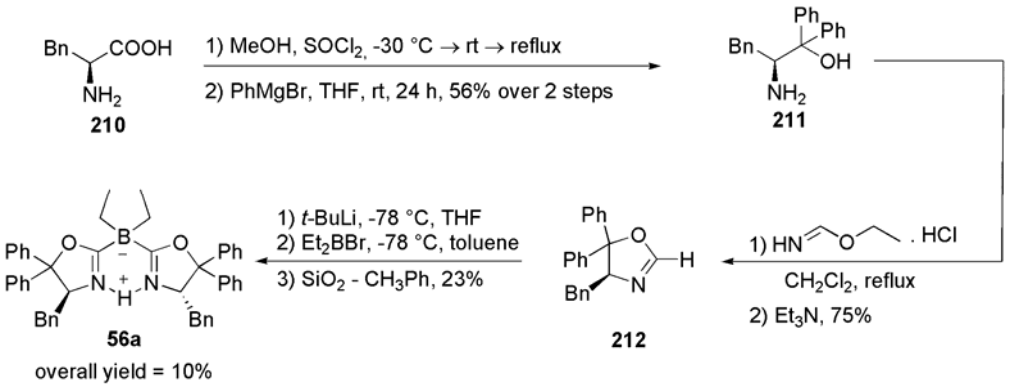
Table 32.



Entry	Olefins	Time [days]	Yield [%][a]	*ee* [%][b]
1	**44a**	2	75	78
2	**44b**	2	78	65

[a] Isolated yields. [b] Determined by chiral HPLC.

Another efficient ligand for this transformation is the Pybox ligand **207** (described in section 4.3.1) susbstituted with two phenyl groups at the C5 position of the oxazoline rings.[136] It was then decided to synthesize the corresponding borabox ligand **56a**[62], with benzyl groups at the stereogenic centers and ethyl groups at the boron like the ligand **40i**, which gave interesting results as mentioned earlier (Scheme 68).

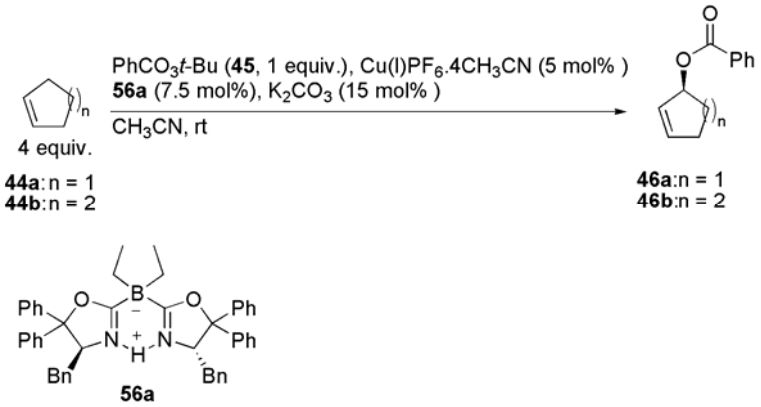


Scheme 68.

After methyl esterification[143] of phenylalanine **210**, the amino methylester was treated with an excess of phenylmagnesium bromide to give the corresponding amino alcohol **211** with an overall yield of 56% for these two steps. The cyclization into the 2*H*-oxazoline **212** was performed in the presence of ethyl formimidate hydrochloride. After addition of triethylamine, the intermediate **212** was obtained with 75% yield. The formation of borabox **56a** was carried out under the same conditions employed with C5-unsubstituted borabox ligands. The only change was in its purification by column chromatography, which was performed with toluene and not with the usual mixture of hexanes/ethyl acetate/triethylamine. The intermediate **212** was then coupled with Et_2BBr (**90c**) in a 3 step procedure to give borabox **56a** in 23% yield.

When applied to the allylic oxidation of cyclopentene (**44a**), ligand **56a** induced a better enantioselectivity than ligand **40i** and all the BOX ligands **35** used for this reaction (Table 33). Even at room temperature, the enantiomeric excess of cyclopentene oxide **46a** reached 86% with a yield of 87% after 3 days (entry 1, Table 33). Cyclohexene oxide **46b** was similarly synthesized with a high enantiomeric excess of 78% (entry 2, Table 33).

Table 33.



Entry	Olefins	Time [days]	Yield [%][a]	*ee* [%][b]
1	**44a**	3	87	86
2	**44b**	5	20	78

[a] Isolated yields. [b] Determined by chiral HPLC.

4.3.2.3 Conclusion

Borabox ligand **40i** has been shown to be an efficient ligand for the copper catalyzed allylic oxidation of olefins, principally because of the fast reaction rate it induces. Whereas complexes derived from BOX ligands **35** needed days at low temperature to form cyclopentene oxide **46a** with an *ee* in the range of 70%, borabox **40i** induced the same enantioselectivity in only one hour at 80 °C. Furthermore, ligand **56a** could compete in terms of enantioselectivity and reactivity with the privileged ligand **35a**.

Chapter 5

Henry and Aza-Henry Reactions

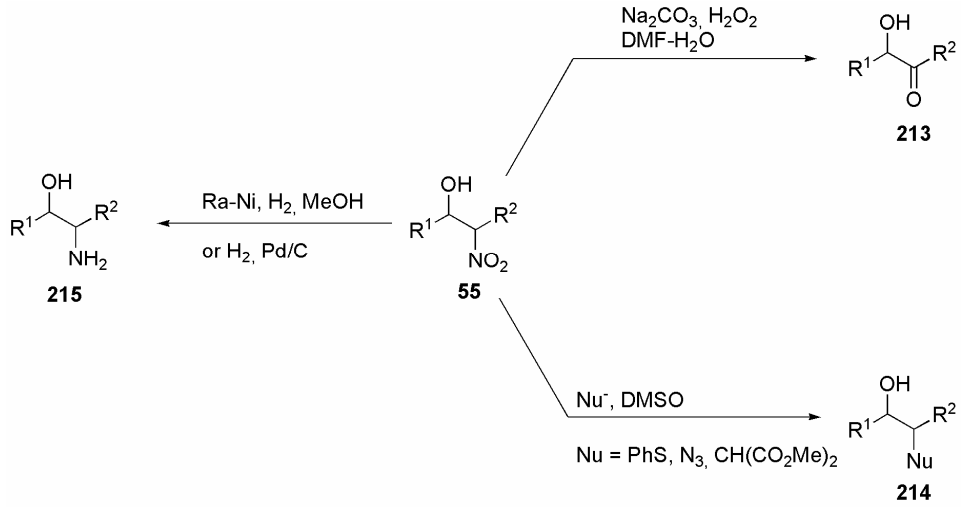
5 Henry and Aza-Henry Reactions

5.1 Asymmetric Henry Reaction

5.1.1 Literature

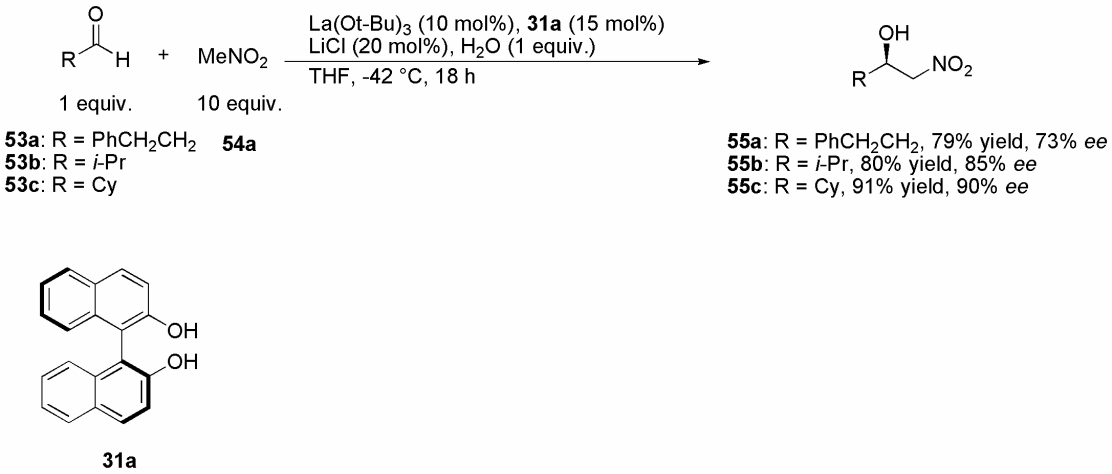
5.1.1.1 Introduction

In 1895, Henry reported the first addition reaction of nitroalkanes to aldehydes furnishing 1,2-functionalized nitroalcohols.[144] The nitroaldol or Henry reaction is one of the classical C-C bond forming processes and affords products which are frequently used as intermediates in organic synthesis.[145] Indeed, the nitro moiety of the nitroalcohol **55** can be converted into the corresponding ketone **213** (Nef reaction), the amino compound **215** (hydrogenation), or other derivatives **214** through substitution of the nitro group (Scheme 69).[146]



Scheme 69.

Almost 100 years after the discovery of the Henry reaction, no enantioselective version of the Henry reaction had been developed. The main obstacle was the lack of selectivity in this reaction due to its reversibility and the easy epimerization at the nitro-substituted C-atom. A major breakthrough in the enantioselective nitroaldol reaction was achieved by Shibasaki and co-workers in 1992.[147] They synthesized the nitroalcohols **55** with good enantiomeric excess by using BINOL **31a** in combination with lanthanum alkoxide as a catalyst (Scheme 70).

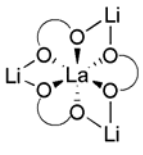


Scheme 70.

This catalyst became a new lead in the asymmetric Henry reaction. Afterwards, many other successful catalysts were developed. High enantioselectivities were obtained employing in particular bis(oxazoline) complexes, chiral dinuclear zinc semi-azacrown complexes, zinc-(+)-*N*-methyl ephedrine complexes and organocatalysts.

5.1.1.2 Rare Earth Metal Catalysts

With the successful application of the lanthanide complex derived from La(O*t*-Bu)$_3$ and (*S*)-BINOL **31a** to the Henry reaction[147], Shibasaki and co-workers developed the concept of multifunctional catalysis for artificial systems. Indeed, lanthanide complexes **216** exhibit both Lewis acidic and Brønsted basic features (Figure 31). It is likely that the lanthanum metal acts as a Lewis acid and the lithium binaphtoxide moiety functions as a Brønsted base.



216

Figure 31.

A mechanism for the Henry reaction in the presence of complex **216** was proposed (Figure 32). Nitromethane (**54a**) is first deprotonated by the lithium binaphtoxide moiety to give a lithium nitronate **217**. Then the aldehyde **53** is activated by the lanthanum metal leading to **218**. Finally, after the attack of the nitromethane (**54a**) to the aldehyde **53** forming the complex **219**, the nitroalcohol **55** is obtained and the catalyst **216** regenerated.

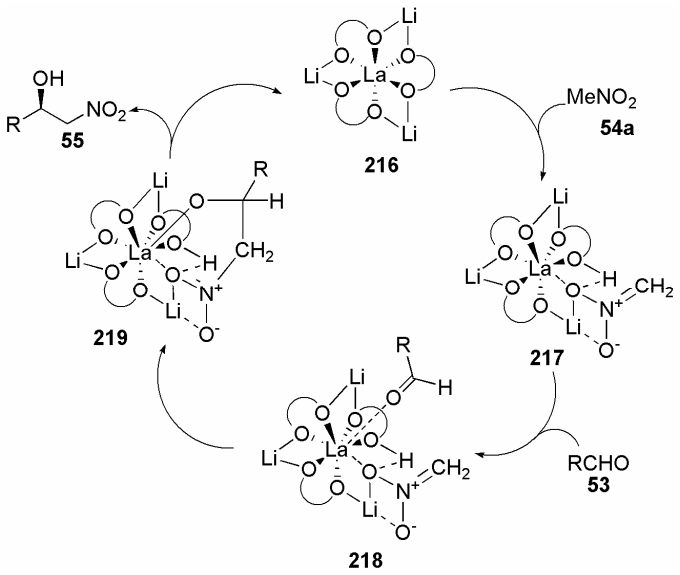


Figure 32. H_2O is omitted for clarity.

Starting from BINOL derivatives **220**, new catalysts **217** were synthesized (Figure 33).[148]

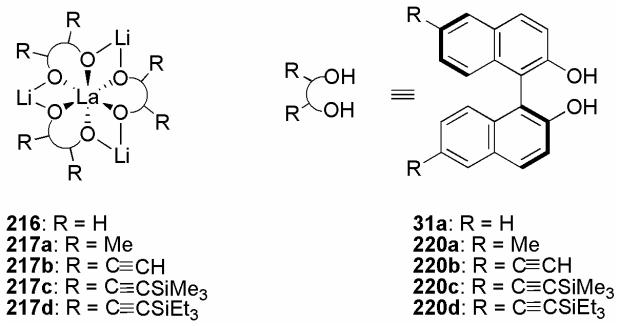
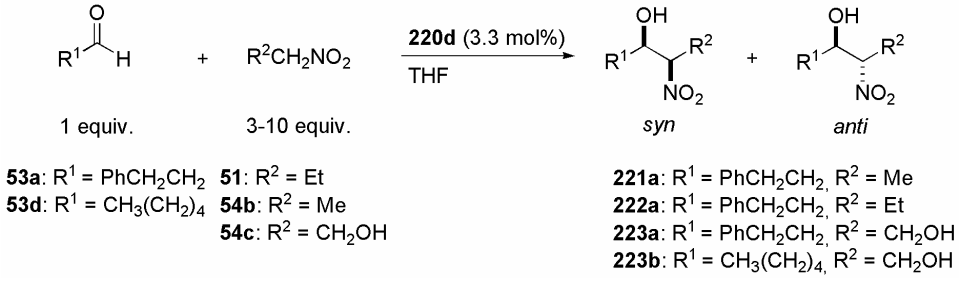


Figure 33.

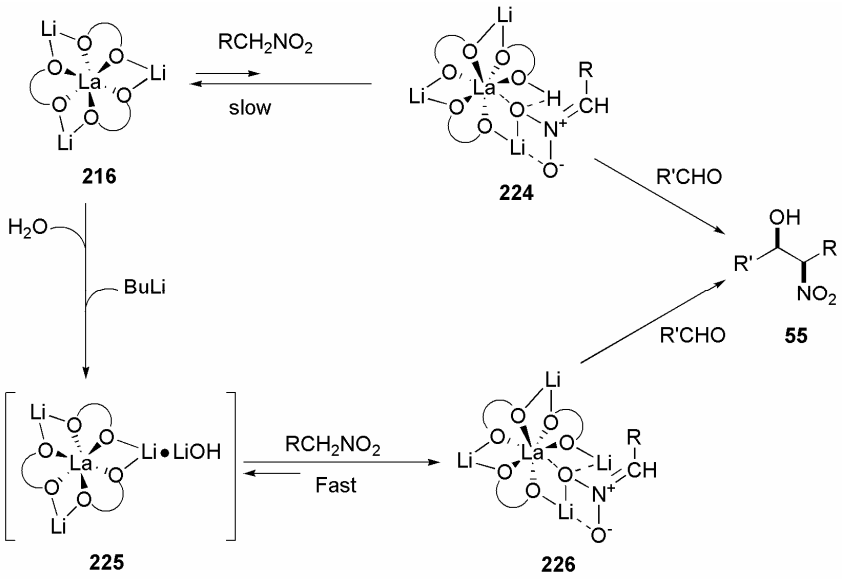
The catalyst **220d** allows to reach remarkable enantioselectivities in the reaction of several nitroalkanes **51**, **54** with aldehydes **53** (*syn*:*anti* ratio ≥ 89:11 and *ee* (*syn*) ≥ 93%, Table 34).

Table 34.



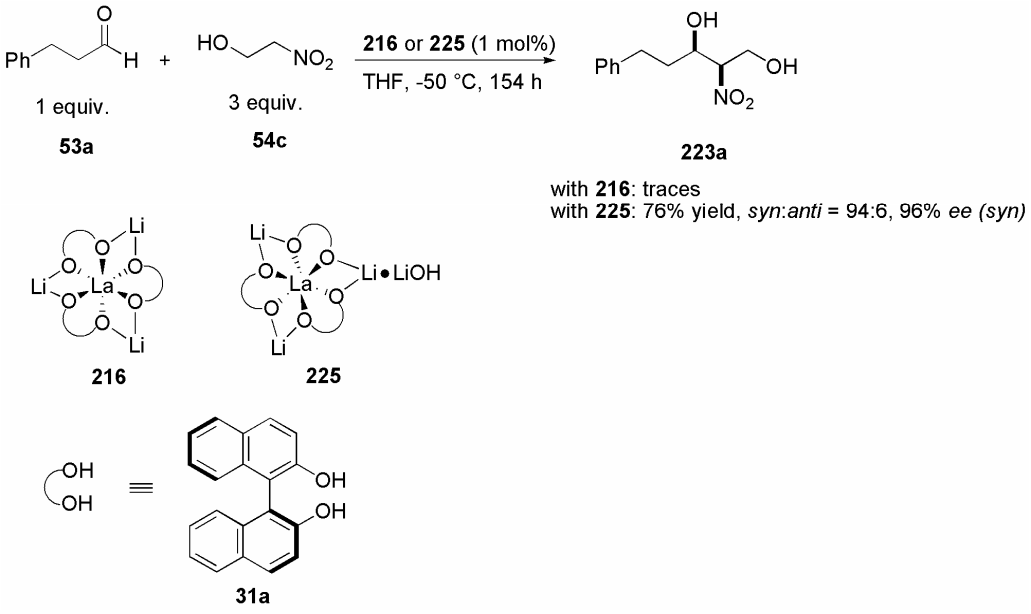
Entry	Aldehyde	Nitroalkane	Time [h]	T [°C]	Product	Yield [%]	*syn*:*anti*	*ee* (*syn*) [%]
1	**53a**	**54b**	75	-20	**221**	70	89:11	93
2	**53a**	**51**	138	-40	**222**	85	93:07	95
3	**53a**	**54c**	111	-40	**223a**	97	92:08	97
4	**53b**	**54c**	93	-40	**223b**	96	92:08	95

The long reaction time of this reaction was postulated to be due to the slow formation of the intermediate **224** (Scheme 71). The OH group of the intermediate **224** could effectively protonate the nitronate to regenerate the nitroalkane and the catalyst **216**. In order to avoid this, Shibasaki *et al.* developed the second generation of heterobimetallic catalyst **225** prepared from the catalyst **216**,[149] *n*-BuLi and H_2O. The formation of the intermediate **226** is faster and leads to the nitroalcohol **55**.



Scheme 71.

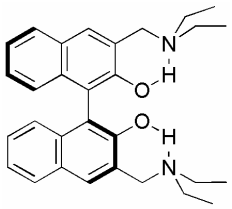
The application of catalyst **225** did not only accelerate the reaction but allowed also to lower the catalyst loading to 1 mol% without affecting the enantioselectivity (Scheme 72).



Scheme 72.

The asymmetric Henry reaction catalyzed by these lanthanum derivatives was successfully applied to the synthesis of β-blockers,[150] phenylnorstatine[151] and (*R*)-arbutamine.[152]

More recently, new lanthanum based catalysts with BINOL ligands **227** bearing aminoethyl side arms have been reported (Figure 34).[153] High enantioselectivities were induced for the reactions of nitromethane (**54a**) with aliphatic aldehydes (typically above 90%), whereas aromatic and α,β-unsaturated aldehydes gave poor results.

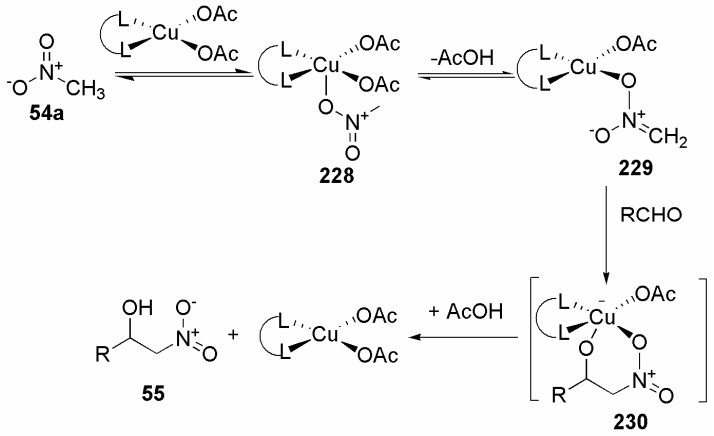


227

Figure 34.

5.1.1.3 Copper Complexes in the Asymmetric Henry Reaction

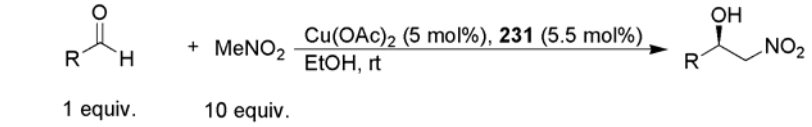
Evans and his group reported the use of copper acetate-bis(oxazoline) complexes in the enantioselective Henry reaction.[154] The acetate ligand serves as a Brønsted base, deprotonating nitromethane (**54a**, Scheme 73). Subsequently the resulting intermediate **229** reacts with the aldehyde to form complex **230**. In the last step, the catalyst is regenerated and the nitroalcohol **55** is obtained.



Scheme 73.

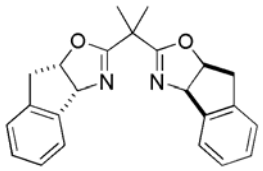
The Henry reaction of nitromethane (**54a**) with various aldehydes catalyzed by the copper acetate-bis(oxazoline) complex proceeded with high enantioselectivities. The nitroalcohols **55** were all obtained with *ee* in the range of 90% (Table 35).

Table 35.



53a: R = $PhCH_2CH_2$ **54a**
53b: R = *i*-Pr
53c: R = Cy
53e: R = Ph
53f: R = 2-MeC_6H_4
53g: R = 2-$MeOC_6H_4$
53h: R = 2-$NO_2C_6H_4$
53i: R = 2-ClC_6H_4
53j: R = 1-naphthyl
53k: R = 4-FC_6H_4
53l: R = 4-ClC_6H_4
53m: R = 4-PhC_6H_4
53n R = *i*-Bu
53o: R = *t*-Bu
53p: R = *n*-Bu

55a: R = $PhCH_2CH_2$
55b: R = *i*-Pr
55c: R = Cy
55e: R = Ph
55f: R = 2-MeC_6H_4
55g: R = 2-$MeOC_6H_4$
55h: R = 2-NoC_6H_4
55i: R = 2-ClC_6H_4
55j: R = 1-naphthyl
55k: R = 4-FC_6H_4
55l: R = 4-ClC_6H_4
55m: R = 4-PhC_6H_4
55n R = *i*-Bu
55o: R = *t*-Bu
55p: R = *n*-Bu



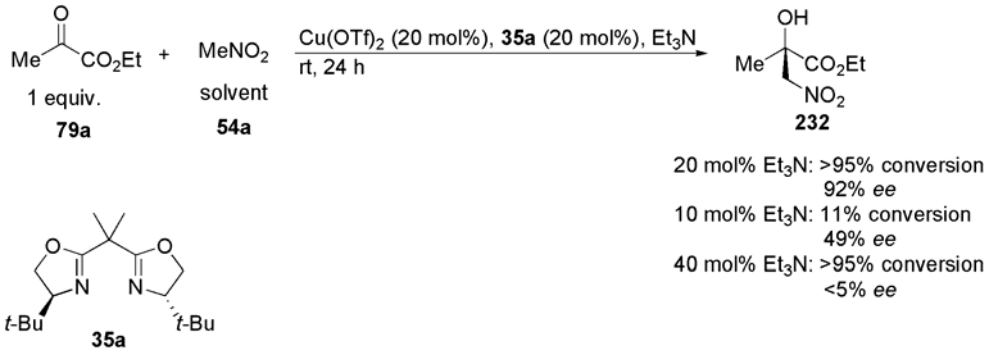
231

Entry	Aldehyde	Time [h]	Yield [%]	*ee* [%][a]
1	**53a**	24	81	90
2	**53b**	48	86	94
3	**53c**	48	95	93
4	**53e**	22	76	94
5	**53f**	42	72	93
6	**53g**	27	91	93
7	**53h**	4	86	89
8	**53i**	15	88	91
9	**53j**	15	66	87
10	**53k**	45	70	92
11	**53l**	21	73	90
12	**53m**	20	70	91
13	**53n**	48	86	92
14	**53o**	96	83	94
15	**53p**	48	87	93

[a] Determined by chiral HPLC, (*R*)-enantiomers.

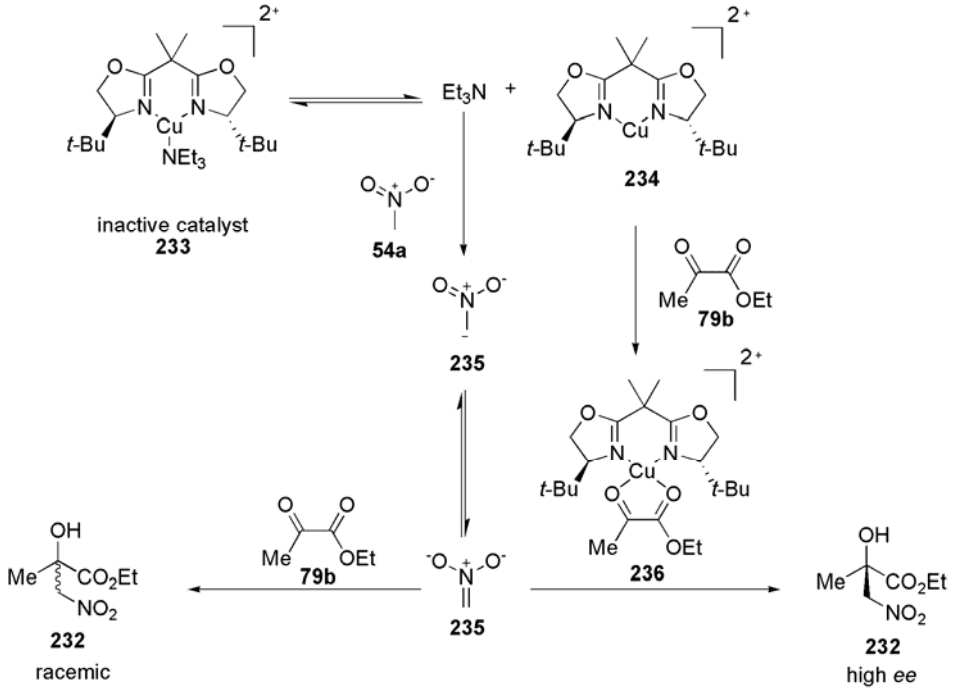
Jørgensen and co-workers extended the scope of the Henry reaction to α-ketoesters **79** as substrates.[155] These compounds are more challenging than the aldehydes because of the lower reactivity of the carbonyl group and the strong tendency of the corresponding product to undergo a retro-nitroaldol reaction under basic conditions.[146] A combination of the privileged ligand with copper (II) triflate induced high enantioselectivities for the reaction of alkyl-substituted 2-keto esters and electron-poor aromatic 2-keto esters with nitromethane (**54a**).[156] Interestingly, the *ee*'s observed were depending on the amount of base used for the deprotonation of nitromethane (**54a**, Scheme 74). One equivalent of base relative to the catalyst (20 mol%) gave the highest enantiomeric excess for the nitroalcohol **232** (>95%

conversion and 92% *ee*). When 40 mol% of triethylamine were used, the reaction became completely unselective (<5% *ee*) but the reaction rate stayed high (>95%). When 10 mol% of triethylamine was used, the product was formed with low conversion and moderate enantiomeric excess (11% conversion, 49% *ee*).



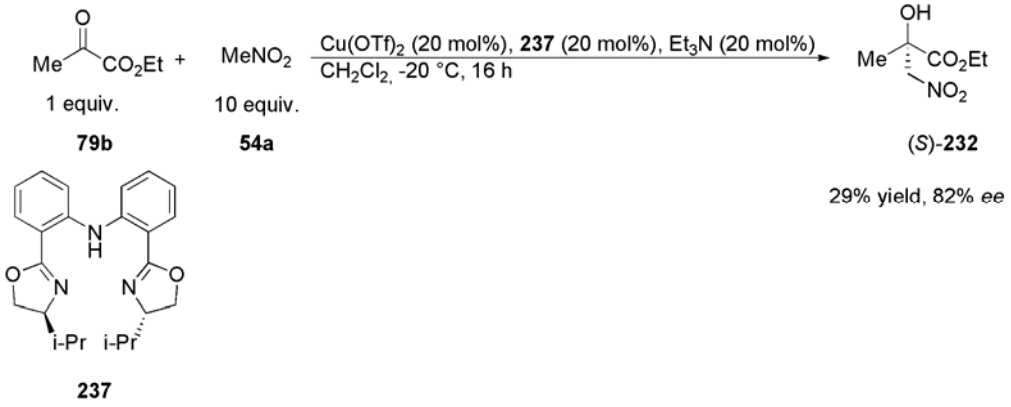
Scheme 74.

In order to explain the dependence of the enantioselectivity on the amount of base applied, Jørgensen proposed an equilibrium between the inactive catalyst **233** and the complex **234** (Scheme 75).[156] When an excess of triethylamine is used, the equilibrium is directed towards the formation of the inactive catalyst **233**. The remaining triethylamine deprotonates nitromethane (**54a**), which can then attack ethyl pyruvate (**79b**) leading to the formation of the racemic compound **232**. With an excess amount of catalyst **234**, the Henry reaction proceeds *via* a less effective reaction pathway giving lower conversion and poor enantioselectivity.



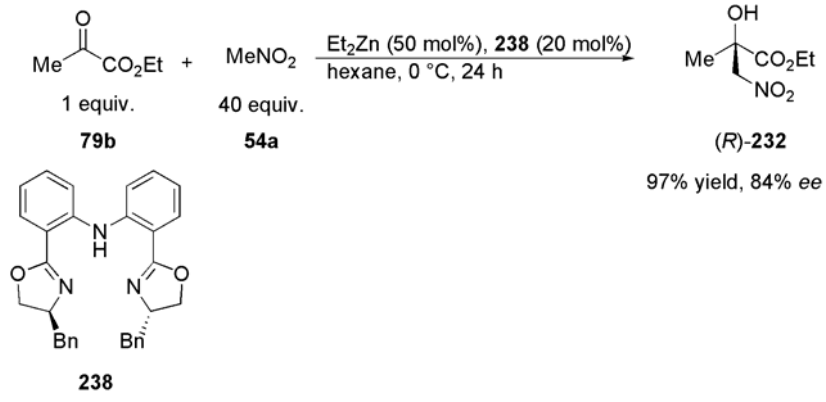
Scheme 75.

In 2005, Du *et al.* reported a procedure allowing the synthesis of both enantiomers of the nitroalcohol **232** by employing the same ligand.[157] The reversal of selectivity was achieved by changing the transition metal from copper to zinc. Following the procedure of Jørgensen,[156] the nitroalcohol **232** with the (*S*) configuration was obtained in up to 82% *ee* when catalyzed by the complex derived from copper (II) triflate and the tridentate bis(oxazoline) ligand **237** (Scheme 76).[158]



Scheme 76.

The nitroalcohol **232** with the (*R*) configuration was synthesized by replacing copper (II) triflate by Et_2Zn (Scheme 77). High yield and enantioselectivity were reached when ligand **238** was used (97% yield and 84% *ee*).



Scheme 77.

Recently, many copper (II) catalysts employed in the Henry reaction of nitromethane (**54a**) with various aldehydes have been reported. The copper Schiff-base complexes **239** and the copper-iminopyridine catalyst **240** developed by Zhou[159] and Pedro[160], respectively, induced

only poor selectivities, whereas copper complexes of (-)-sparteine **241**[161] and chiral diamines **242**[162] formed the nitroalcohols **55** with good to high *ee*'s (Figure 35).

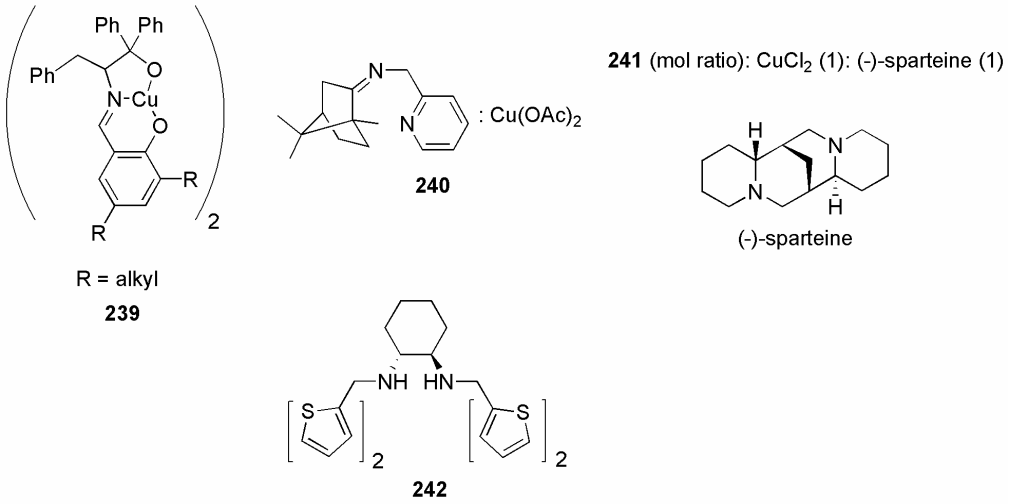
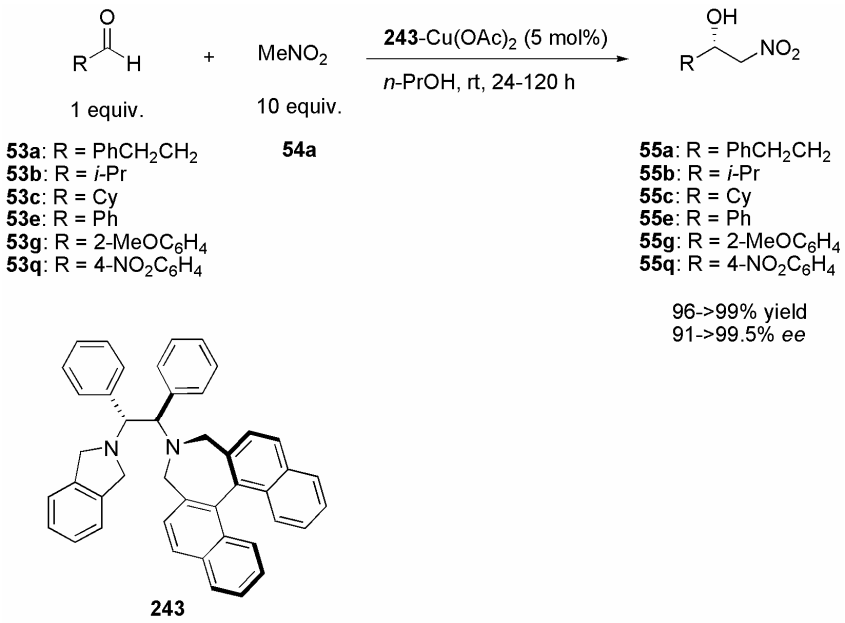


Figure 35.

In 2006, Arai *et al.* proposed a new system for high-throughput screening to test the efficiencies of catalysts[163] and found that the chiral diamine-$Cu(OAc)_2$ complex[164] was very efficient in the Henry reaction (Scheme 78). Nitroalcohols **55** could be synthesized in up to 99.5% *ee*.

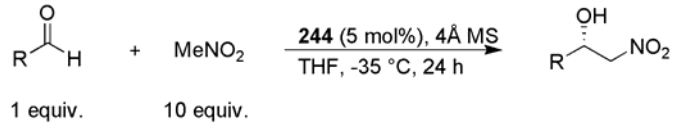


Scheme 78.

5.1.1.4 Zinc Complexes in the Asymmetric Henry Reaction

In 2002, Trost and his co-workers reported the use of the dinuclear zinc complex **244** as efficient catalyst for the nitroaldol reaction between nitromethane (**54a**) and various aldehydes **53** (Table 36).[165] Aromatic and aliphatic aldehydes **53** were converted into the corresponding nitroalcohols **55** and were isolated with yields ranging from 56 to 84% and enantioselectivities of up to 93% *ee*.

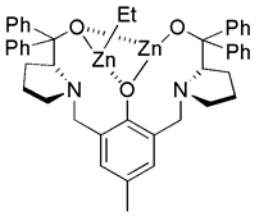
Table 36.



53a: R = $PhCH_2CH_2$
53b: R = *i*-Pr
53c: R = Cy
53e: R = Ph
53j: R = 1-naphthyl
53n: R = *i*-Bu
53o: R = *t*-Bu

54a

55a: R = $PhCH_2CH_2$
55b: R = *i*-Pr
55c: R = Cy
55e: R = Ph
55j: R = 1-naphthyl
55n: R = *i*-Bu
55o: R = *t*-Bu



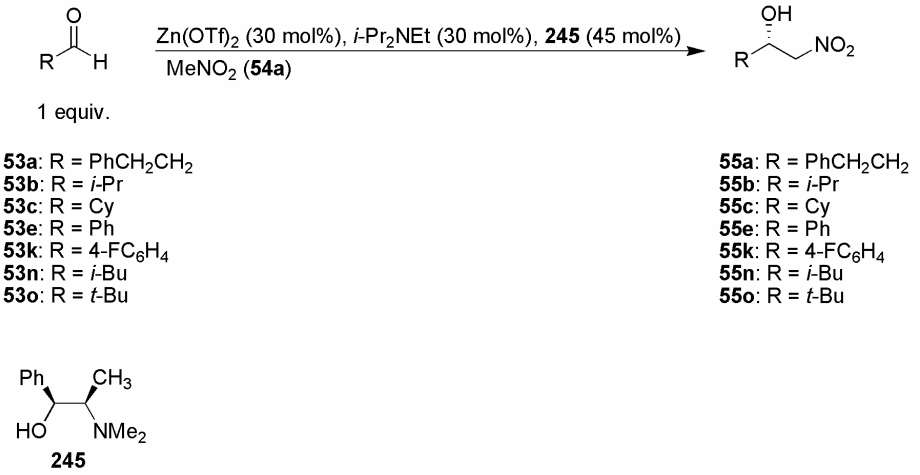
244

Entry	Aldehyde	Yield [%]	*ee* [%]
1	**53a**[a]	56	85
2	**53b**[b]	58	88
3	**53c**	75	85
4	**53e**	75	91
5	**53j**	71	93
6	**53n**	84	87
7	**53o**[b]	88	93

[a] Reaction performed using 15 equiv. of $MeNO_2$ and for 2 days. [b] Reaction performed using 5 equiv. $MeNO_2$ at -60 °C.

In 2005, Palomo reported a highly enantioselective nitroaldol reaction using zinc (II) triflate, diisopropylethylamine and (+)-*N*-methylephedrine **245**.[166] Contrary to the dinuclear zinc complex[165] developed by Trost, the acid and the basic centers are not integrated in the same molecular entity, allowing an easier screening of different combinations. The chiral amino alcohol **245** plays the double role of chiral inductor and base. Aromatic and aliphatic aldehydes **53** were both tolerated in the reaction with nitromethane (**54a**) and the enantioselectivities obtained were all around 90% *ee* (Table 37).

Table 37.



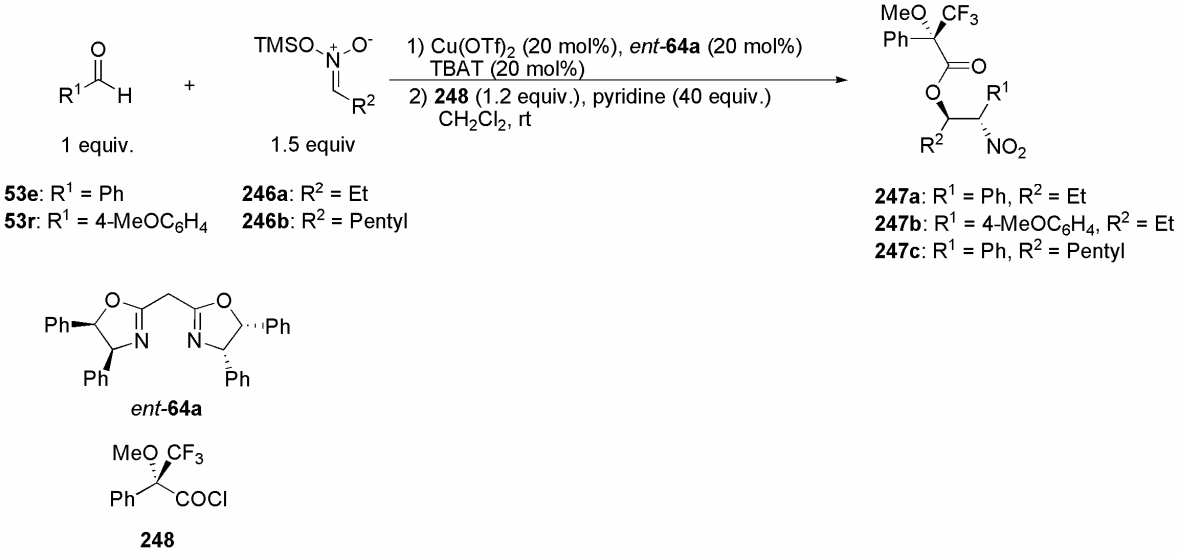
Entry	Aldehyde	T [°C]	t [h]	Yield [%]	*ee* [%]
1	**53a**	-20	16	90	90
2	**53b**	-20	15	68	97
3	**53c**	-20	16	72	90
4	**53e**[a]	-60	45	82	92
5	**53k**[a]	-60	45	68	89
6	**53n**	-30	16	75	92
7	**53o**	-20	16	71	96

[a] Using a 1:1 mixture of nitromethane and CH_2Cl_2 as solvent and a ratio of 1:1:1:1.5 of aldehyde/$Zn(OTf)_2$/*i*-Pr_2NEt/ligand.

Reiser and Lin showed as well that the Henry reaction can be promoted by Et_2Zn with various amino alcohols.[167] In another report, macrocyclic thioaza ligands[168] have been described as new chiral auxiliaries for the Henry reaction. However, very poor results were obtained with all these catalysts.

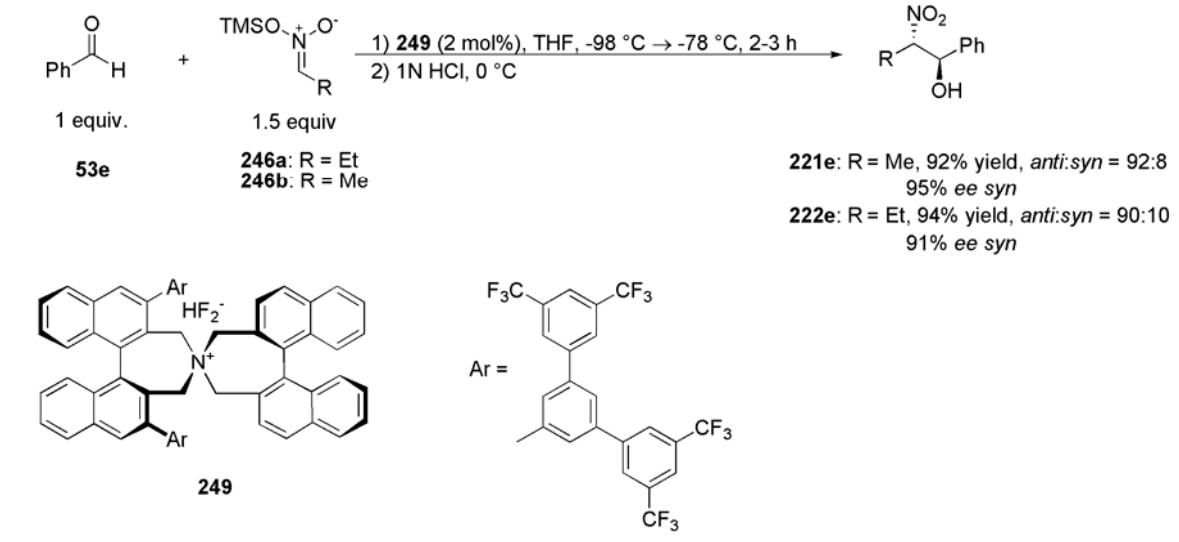
5.1.1.5 Catalytic Asymmetric Henry Reactions of Silyl Nitronates with Aldehydes

The use of silyl nitronates **246** as alternative substrates to nitroalkanes **54** for the enantioselective Henry reaction was reported by Jørgensen and his group in 2003.[169] The scope of the reaction, which was mainly restricted to nitromethane (**54a**), could be enlarged. The combination of copper (II)-bisoxazoline complex and tetrabutylammonium triphenylsilyl difluorosilicate[170] (TBAT) induced moderate enantioselectivities for the preferentially formed *anti* adduct **247** (Scheme 79). Due to the instability of the nitroalcohols under these conditions, they were converted to the Mosher esters **247**.



Scheme 79.

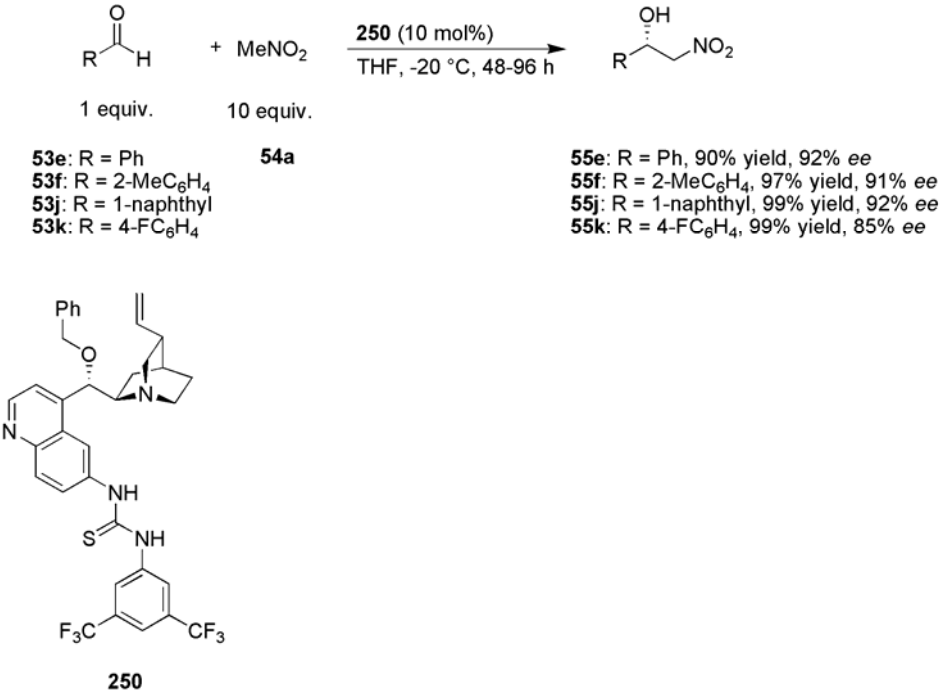
Maruoka *et al.* developed the addition of trimethylsilyl nitronates **246** to aromatic aldehydes **53** in the presence of 2 mol% of the chiral quaternary ammonium fluoride salt **249** to give the products **221e** and **222e** with *anti*:*syn* ratio usually higher than 90:10 and with more than 90% *ee* (Scheme 80). Unfortunately, aliphatic aldehydes were not suitable substrates for this reaction giving only poor enantioselectivities.



Scheme 80.

5.1.1.6 Asymmetric Organocatalytic Henry Reaction

Until recently, the use of metal-free catalysts in the Henry reaction did not induce enantiomeric excesses higher than 54%.[171] The cinchona derivative **250**, synthesized by Hiemstra and his group, allowed to considerably increase the enantioselectivity observed in the organocatalytic nitroaldol reaction.[172] The aromatic nitroalcohols **55** were obtained in good yields and with enantioselectivities ranging from 85 to 92% (Scheme 81).



Scheme 81.

The mode of action of the catalyst **250** is still unclear. But probably the thiourea moiety of the catalyst activates the aldehyde through double hydrogen bonding while nitromethane is activated by the basic quinuclidine (Figure 36).

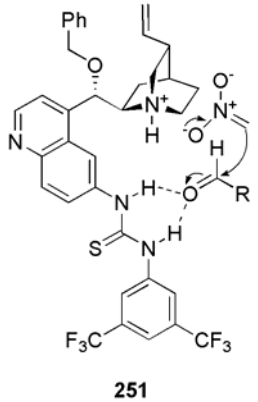
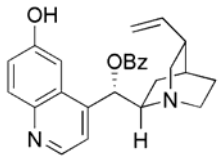


Figure 36.

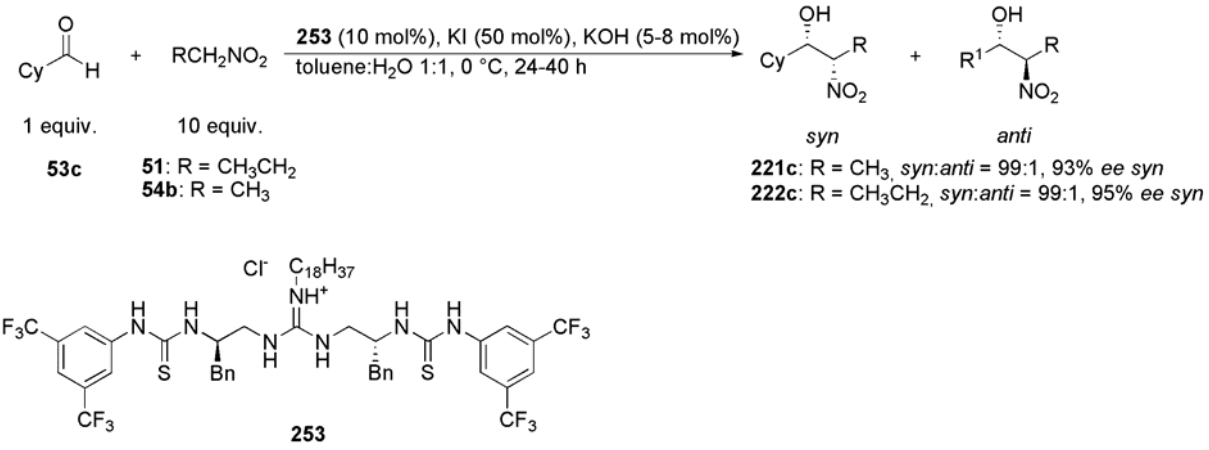
Cinchona alkaloids **252** are also very effective in the Henry reaction of α-ketoesters **79** inducing *ee*'s in the 90's range (Figure 37).[173]



252

Figure 37.

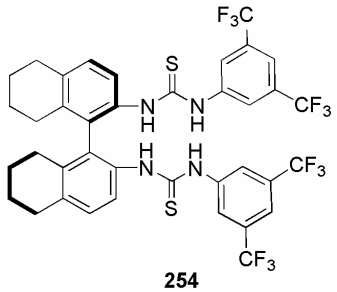
In 2006, Nagasawa reported a highly enantioselective Henry reaction catalyzed by the guanidine-thiourea bifunctionnal catalyst **253**.[174] Interestingly, this reaction was carried out in the presence of nitroalkanes other than nitromethane (**54a**). The nitroalcohols **221c** and **222c** were formed with a *syn*:*anti* selectivity of 99:1 and with 84-99% *ee* for the *syn* isomer (Scheme 82).



253

Scheme 82.

As a further variation, the axially chiral bis(arylthiourea)-based organocatalyst **254** has been reported but the enantioselectivities stayed poor (Figure 38).[175]

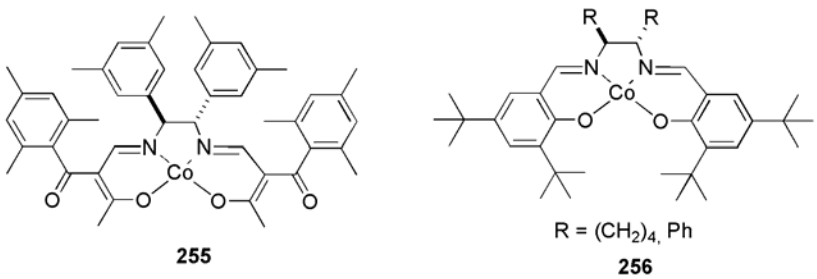


254

Figure 38.

5.1.1.7 Other Catalysts for the Asymmetric Henry Reaction

Chiral ketoamino **255** and salen cobalt complexes **256** were employed by Yamada in the asymmetric Henry reaction (Figure 39).[176] High enantioselectivities in the range of 73-92% could be induced.



255 **256**

Figure 39.

Other methods with metal complexes on solid support[177] and a chiral tetraaminophosphonium salt[178] were also reported for the asymmetric nitroaldol reaction.

5.1.2 Henry Reaction Catalyzed by Borabox Ligands

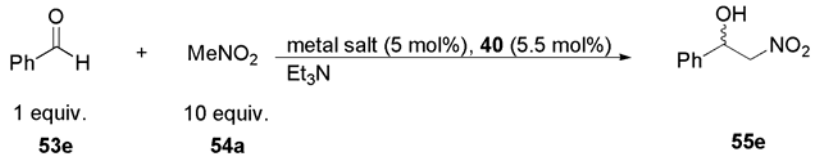
5.1.2.1 Objectives

The complexes developed by Shibasaki[147-152] and Nagasawa[174] are the only effective catalysts dealing with other nitroalkanes than nitromethane (**54a**). Most of the catalysts developed so far are substrate dependent and there is obviously a lack of a general method for the nitroaldol reaction. Therefore, the borabox ligands **40**, which were expected to have a comparable or even higher potential than the anologuous BOX ligands **35**, were applied to the asymmetric Henry reaction. In particular, the study focused on the development of a method for converting nitropropane (**51**) into the corresponding nitroalcohols **222** in a highly enantioselective fashion.

5.1.2.2 Initial Screening

Initially the reactivity and selectivity of various borabox complexes for the Henry reaction were investigated. The reaction between benzaldehyde (**53e**) and nitromethane (**54a**) in the

presence of 5 mol% of metal source, 5.5 mol% of borabox ligand **40** and triethylamine was chosen as a model system (Scheme 83).



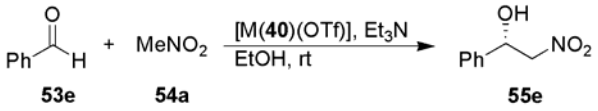
Scheme 83.

Zinc (II) and copper (II) triflate were the metal sources of choice since other metal salts like zinc (II) chloride, copper (II) chloride and copper (II) acetate induced lower enantioselectivities. Table 38 presents some representative results of the borabox ligands screening performed for these two metal sources. It was observed that the ratio of base to ligand influenced both the reactivity and selectivity of the catalyst (entry 1 to 3, Table 38). A coarse screening of the amount of base added after the complexation, showed that in the presence of zinc (II) triflate and ligand **40c**, 10.5 mol% of base allowed to reach the highest enantiomeric excess (70% yield, 24% *ee*, entry 2, Table 38). Taking into account the NMR studies of the complex derived from ligand **40c** and potassium carbonate (see section 4.1), it was supposed that 5.5 mol% of triethylamine was needed for the activation of the protonated borabox **40c** and 5 mol% for the deprotonation of nitromethane (**54a**). Consequently, the base was not added all at once after the complexation but in two portions: first 5.5 mol% during the complexation and then the second portion for the reaction itself. In the presence of copper (II) triflate and ligand **40g**, this new procedure allowed to increase the yield of the reaction and the product **55e** was formed with higher enantiomeric excess (70% *ee*, compare entry 6 to 7, Table 38).

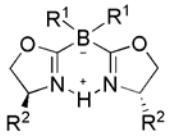
A further ligand screening showed that borabox ligands carrying a *tert*-butyl group at the C4 position of the oxazoline rings were the most effective ligands (entries 8, 9, 14 and 15, Table 38). The substituents at the boron did not have a pronounced effect on neither reactivity nor asymmetric induction. Borabox ligand **40o** in combination with zinc (II) triflate induced even lower enantiomeric excess than the complex formed by **40o** and copper (II) triflate (entry 16 and 17, Table 38). The opposite trend was actually expected since Evans' investigations concerning the Diels-Alder reaction demonstrated that the optimal ligand for a tetrahedral zinc complex was the gem-methyl phenyl bisoxazoline **35b** in the Diels-Alder reaction (see section 4.1).

In the following, all reactions were carried out in the presence of copper (II) triflate and ligand **40g** which induced the highest enantioselectivity in this model reaction.

Table 38.



53e **54a** **55e**



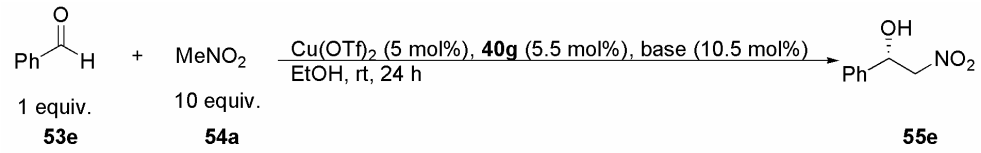
40c: R^1 = Ph; R^2 = *i*-Pr
40e: R^1 = Cy; R^2 = *t*-Bu
40f: R^1 = Et; R^2 = *t*-Bu
40g: R^1 = Ph; R^2 = *t*-Bu
40i: R^1 = Et; R^2 = Bn
40o: R^1 =Ph; R^2 = Ph
40p: R^1 = Et; R^2 = *i*-Bu

Entry	Ligand	Metal salt	Et_3N [mol %]	Yield [%][a]	*ee* [%][b]
1	**40c**	$Zn(OTf)_2$	5.5	59	2 (*R*)
2	**40c**	$Zn(OTf)_2$	10.5	70	24 (*S*)
3	**40c**	$Zn(OTf)_2$	15.5	75	22 (*S*)
4	**40c**	$Cu(OTf)_2$	10.5	90	1 (*R*)
5	**40g**	$Zn(OTf)_2$	10.5	86	3 (*R*)
6	**40g**	$Cu(OTf)_2$	10.5	85	35 (*S*)
7	**40g**	$Cu(OTf)_2$	10.5[c]	94	70 (*S*)
8	**40f**	$Zn(OTf)_2$	10.5[c]	50	25 (*R*)
9	**40f**	$Cu(OTf)_2$	10.5[c]	85	66 (*S*)
10	**40i**	$Zn(OTf)_2$	10.5[c]	81	3 (*R*)
11	**40i**	$Cu(OTf)_2$	10.5[c]	41	5 (*R*)
12	**40p**	$Zn(OTf)_2$	10.5[c]	50	6 (*R*)
13	**40p**	$Cu(OTf)_2$	10.5[c]	33	6 (*R*)
14	**40e**	$Zn(OTf)_2$	10.5[c]	56	17 (*R*)
15	**40e**	$Cu(OTf)_2$	10.5[c]	85	54 (*S*)
16	**40o**	$Zn(OTf)_2$	10.5[c]	63	3 (*R*)
17	**40o**	$Cu(OTf)_2$	10.5[c]	90	10 (*S*)

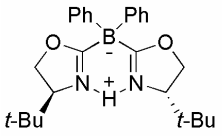
[a] Isolated yields. [b] Determined by chiral HPLC. The absolute configuration of **55e** was assigned by comparison to the one mentioned in the literature (see ref. 154). [c] 5.5 mol% of triethylamine were added during the complexation. After a stirring period of 3 to 5 hours and addition of benzaldehyde and nitromethane, 5 mol% of triethylamine were added.

Other bases were also tested for this reaction. Hünig's base and potassium carbonate gave lower enantioselectivities than triethylamine (compare entry 1 to 3 and 2 to 3, Table 39). As potassium carbonate is the base of choice for the formation of the selective catalyst in the Diels-Alder reaction (see section 4.1), it was expected that the addition of 5.5 mol% of potassium carbonate during the complexation and 5 mol% of triethylamine during the reaction would increase the enantioselectivity. Unfortunately, this combination was not successful (entry 4, Table 39). The Henry reaction was also carried out in the presence of (*L*)-sparteine which was expected to play the double role of base and chiral inductor similar to (+)-*N*-methylephedrine **245** (see section 6.1.1.3). However, only poor enantioselectivity was observed (entry 5, Table 39).

Table 39.



53e **54a** **55e**



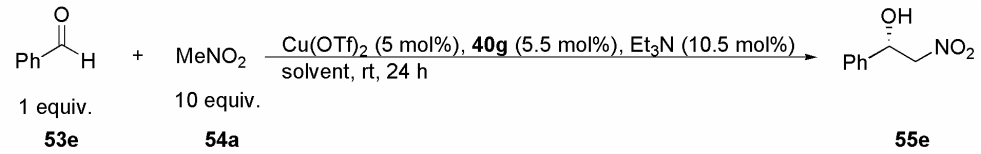
40g

Entry	Base	Yield [%][a]	*ee* [%][b]
1	K_2CO_3	47	2 (*R*)
2	*i*-Pr_2NEt	70	10 (*S*)
3	Et_3N	94	70 (*S*)
4	K_2CO_3 + Et_3N	80	21 (*S*)
5	(L)-sparteine	90	10 (*S*)

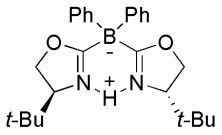
[a] Isolated yields. [b] Determined by chiral HPLC. The absolute configuration of **55e** was assigned by comparison to the one mentioned in the literature (see ref. 154).

A solvent screening showed that protic solvents like ethanol and methanol generally gave the best results (94 and 87% yield, 70 and 44% *ee*, respectively, entry 1 and 2, Table 40). When the Henry reaction is conducted in aprotic polar solvents (acetonitrile, acetone, nitromethane, entries 3 to 5, Table 40) or aprotic apolar solvents (dichloromethane and tetrahydrofuran, entry 6 and 7, Table 40), the nitroalcohol **55e** was obtained with lower yields (41-67% yield) and enantioselectivities (8-49% *ee*). In particular, when tetrahydrofuran was used, the product **55e** was obtained as a racemic mixture (entry 7, Table 40).

Table 40.



53e **54a** **55e**



40g

Entry	Solvent	Yield [%][a]	*ee* [%][b]
1	EtOH	94	70 (*S*)
2	MeOH	87	44 (*S*)
3	$MeNO_2$	41	31 (*S*)
4	$(CH_3)_2CO$	67	46 (*S*)
5	MeCN	41	49 (*S*)

Entry	Solvent	Yield [%][a]	*ee* [%][b]
6	CH_2Cl_2	64	30 (*S*)
7	THF	50	8 (*S*)

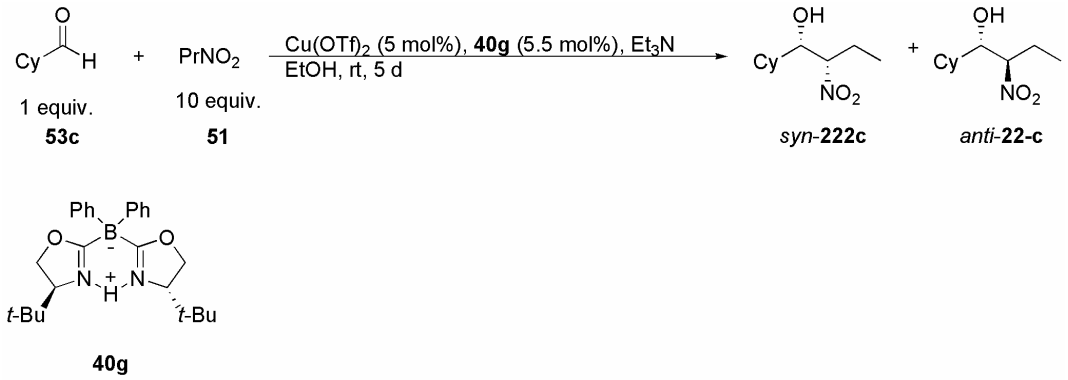
[a] Isolated yields. [b] Determined by chiral HPLC. The absolute configuration of **55e** was assigned by comparison to the one mentioned in the literature (see ref. 154).

5.1.2.3 Influence of the Amount of Base

Subsequently, the influence of the amount of triethylamine on the reactivity and selectivity of the Henry reaction was studied in greater detail. The quantity of base added during the complexation remained with 5.5 mol% constant (1 equivalent compared to the borabox ligand **40g**), whereas the amount of base used for the deprotonation of the nitroalkane was varied from 0 to 5.5 mol% (Table 41).

Applying the optimal reaction conditions described in Table 40, the reaction between cyclohexanecarboxaldehyde (**53c**) and nitropropane (**51**) afforded the corresponding nitroalcohol **222c** with good diastereoselectivity and enantioselectivity (*syn*:*anti* ratio of 90:10 and 84% *ee* (*syn*), entry 2, Table 41). The conversion increased to 64% but the selectivity decreased when 5.5 mol% of base was used (*syn*:*anti* ratio of 86:14 and 82% *ee* (*syn*), entry 1, Table 41). A slight reduction of the amount of triethylamine to 4.5 mol% allowed to increase both diastereoselectivity and enantioselectivity (*syn*:*anti* ratio of 92:08 and 91% *ee* (*syn*), entry 3, Table 41) with a minor increase of the conversion to 60%. By decreasing the amount of base to 3 and 1.5 mol% a slightly lower diastereoselectivity was observed whereas the enantioselectivity stayed constant (*syn*:*anti* ratio of 90:10 and 91:09 respectively and 91% *ee* (*syn*) for both, entries 4 and 5, Table 41). However, when adding no base at all, the diasteroselectivity stayed high but the enantioselectivity dropped to 75% (*syn*:*anti* ratio of 92:08, entry 6, Table 41).

Table 41.

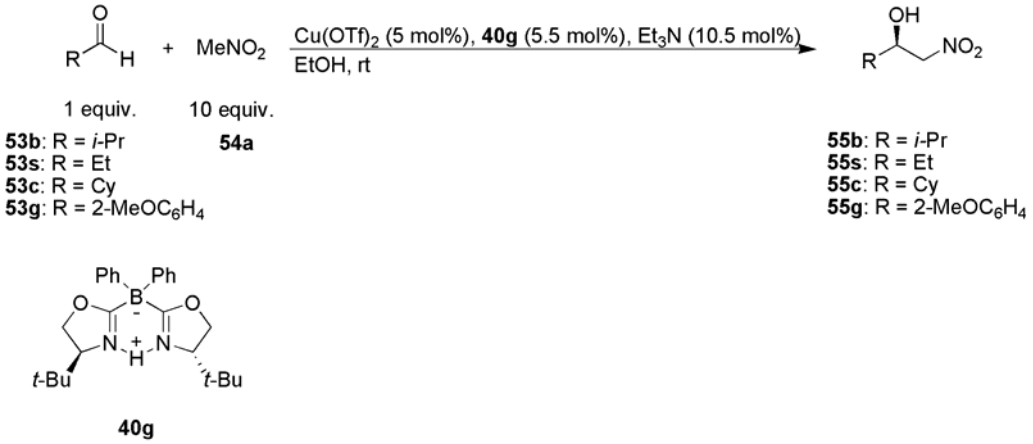


Entry	Et_3N [mol %]	Conversion [%][a]	*syn*:*anti*[a]	*ee* (*syn*) [%][b][c]	*ee* (*anti*) [%][b][d]
1	5.5	64	86:14	82 (1*S*,2*S*)	50 (1*S*,2*R*)
2	5.0	52	90:10	84 (1*S*,2*S*)	41 (1*S*,2*R*)
3	4.5	60	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
4	3.0	68	90:10	91 (1*S*,2*S*)	31 (1*S*,2*R*)
5	1.5	62	91:09	91 (1*S*,2*S*)	28 (1*S*,2*R*)
6	0.0	70	92:08	75 (1*S*,2*S*)	30 (1*S*,2*R*)

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. [c] The absolute configuration of *syn*-**222c** was determined by comparison with published HPLC retention times (see ref. 174). [d] The absolute configuration of *anti*-**222c** was determined by analogy with the absolute configuration of compound *anti*-**221e**.[179]

Subsequently, the reactions between several aldehydes and nitromethane (**54a**) were carried out in order to verify the general influence of this optimized procedure on the selectivity and reactivity of the reaction (Table 42). The application of the optimized reaction conditions allowed to considerably increase the enantioselectivity and slightly raised the conversion of the aliphatic aldehydes tested. The enantiomeric excess of the nitroalcohol **55b** derived for isobutyraldehyde (**53b**) increased from 38 to 56% (compare entries 1 and 2, Table 42). The same trend was observed for propionaldehyde (**53s**, from 38 to 55% *ee*, compare entries 3 and 4, Table 42) and cyclohexanecarboxaldehyde (**53c**, from 71 to 81% *ee*, compare entries 5 and 6, Table 42). However, for the aromatic aldehyde *ortho*-methoxybenzaldehyde (**53g**), the enantioselectivity did not change (65% against 68% *ee*, entries 7 and 8, Table 42).

Table 42.



Entry	R	Product	Et_3N [mol %]	Time [d]	Yield [%]	*ee* [%][b]
1	*i*-Pr	**55b**	5.0	5	78[a]	38 (*S*)
2	*i*-Pr	**55b**	4.5	5	83[a]	56 (*S*)
3	Et	**55s**	5.0	5	87[a]	38 (*S*)
4	Et	**55s**	4.5	5	90[a]	55 (*S*)
5	Cy	**55c**	5.0	5	85[a]	71 (*S*)
6	Cy	**55c**	4.5	5	93[a]	81 (*S*)
7	2-$MeOC_6H_4$	**55g**	5.0	1	82	65 (*S*)
8	2-$MeOC_6H_4$	**55g**	4.5	1	80	68 (*S*)

[a] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. The absolute configuration of nitroalcohol products **55** were assigned by comparison comparison to those mentioned in the literature (see ref. 154).

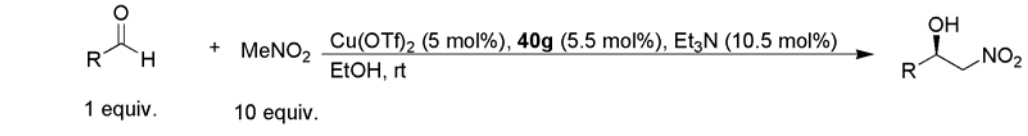
5.1.2.4 Scope of the Henry Reaction with Nitromethane

With the optimized procedure in hand, the scope of the Henry reaction with nitromethane was investigated (Table 43). The use of aromatic aldehydes bearing electron-withdrawing groups at the phenyl ring led to the formation of racemic compounds **55h** and **55q** (entries 2 and 3, Table 43). The nitroalcohols **55** derived from aldehydes carrying chloride, methyl and methoxy groups at the phenyl ring were isolated with low enantioselectivity (entries 4 to 8, Table 43). Examination of the results revealed that the chiral induction obtained with *ortho*-methoxybenzaldehyde was higher than the one obtained with *para*-methoxybenzaldehyde (**55g** and **55r**, 68% and 52% *ee* respectively, entries 7 and 8, Table 43). The reactions between nitromethane (**54a**) and *ortho*- and *para*-chlorobenzene (**53i** and **53l**)**,** respectively, were carried out to confirm this trend (entries 4 and 5, Table 43). But similar enantioselectivities were obtained for both substrates (**55i** and **55l**, 27 and 38% *ee*, entries 4 and 5, Table 43). Thus, the higher enantioselectivity obtained by using the *ortho*-methoxy substituted aldehyde (**53g**) is possibly not due to steric reasons but to a chelation of the metal to the methoxy group which is not possible with the *ortho*-chlorobenzaldeyde (**53i**).

Surprisingly, the use of aliphatic aldehydes led to nitroalcohols **55** with higher enantiomeric excess (entries 11 to 16, Table 43): the Henry product **55c** derived from cyclohexanecarboxaldehyde (**53c**) was synthesized with an enantiomeric excess of 81% and 93% conversion (entry 16, Table 43). Also bulky α-branched aldehydes like pivaldehyde (**53o**) reacted with nitromethane (**54a**) to give the corresponding nitroalcohol **55o** with a good enantioselectivity (89% conversion, 79% *ee*, entry 13, Table 43). Non-branched aldehydes (valeraldehyde **53p** and propionaldehyde **53s**) were converted to products **55p** and **55s** with lower selectivites (80% conversion, 60% *ee* and 90% conversion, 55% *ee,* respectively, entries 12 and 15, Table 43).

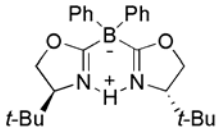
In general, the borabox ligands induced lower enantioselectivity for the Henry reaction with nitromethane (**54a**) than bis(oxazolines) ligands.[154] However, the promising results obtained with aliphatic aldehydes prompted us to carry out the Henry reaction with nitropropane (**51**) in the presence of borabox ligand **40g**, which gave the highest enantioselectivity for the reaction with nitromethane (**54a**).

Table 43.



53b: R = *i*-Pr
53c: R = Cy
53e: R = Ph
53g: R = 2-$MeOC_6H_4$
53h: R = 2-$NO_2C_6H_4$
53i: R = 2-ClC_6H_4
53j: R = 1-naphthyl
53l: R = 4-ClC_6H_4
53m: R = 4-PhC_6H_4
53n R = *i*-Bu
53o: R = *t*-Bu
53p: R = *n*-Bu
53q: R = 4-$NO_2C_6H_4$
53r: R = 4-$MeOC_6H_4$
53s: R = Et
53t: R = 3-MeC_6H_4

55b: R = *i*-Pr
55c: R = Cy
55e: R = Ph
55g: R = 2-$MeOC_6H_4$
55h: R = 2-$NO_2C_6H_4$
55i: R = 2-ClC_6H_4
55j: R = 1-naphthyl
55l: R = 4-ClC_6H_4
55m: R = 4-PhC_6H_4
55n R = *i*-Bu
55o: R = *t*-Bu
55p: R = *n*-Bu
55q: R = 4-$NO_2C_6H_4$
55r: R = 4-$MeOC_6H_4$
55s: R = Et
55t: R = 3-MeC_6H_4



40g

Entry	R	55	Time [days]	Yield [%]	*ee* [%][b]
1	Ph	**55e**	1	94	70 (*S*)
2	2-$NO_2C_6H_4$	**55h**	1	95	10 (*S*)
3	2-$NO_2C_6H_4$	**55q**	1	86	2 (*S*)
4	2-ClC_6H_4	**55i**	1	93	27 (*S*)
5	4-ClC_6H_4	**55l**	1	90	38 (*S*)
6	3-MeC_6H_4	**55t**	1	70	56 (*S*)
7	2-$MeOC_6H_4$	**55g**	1	80	68 (*S*)
8	4-$MeOC_6H_4$	**55r**	1	63	52 (*S*)
9	1-naphthyl	**55j**	1	95	46 (*S*)
10	4-PhC_6H_4	**55m**	1	89	53 (*S*)
11	*i*-Bu	**55n**	5	92[a]	57 (*S*)
12	*n*-Bu	**55p**	5	80[a]	60 (*S*)
13	*t*-Bu	**55o**	5	89[a]	79 (*S*)
14	*i*-Pr	**55b**	5	83[a]	56 (*S*)
15	Et	**55s**	5	90[a]	55 (*S*)
16	Cy	**55c**	5	93[a]	81 (*S*)

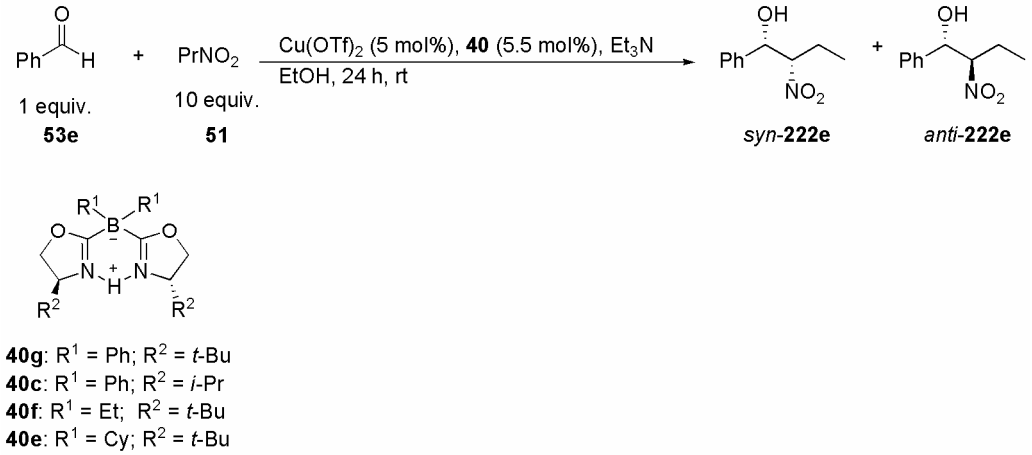
[a] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. The absolute configuration of nitroalcohol products **55** were assigned by comparison comparison to those mentioned in the literature (see ref. 154).

5.1.2.5 Asymmetric Henry Reaction with Nitropropane

As a preliminary study, a quick screening of borabox ligands **40** was conducted for the reaction of nitropropane (**51**) with benzaldehyde (**53e,** Table 44). The ligand **40g** induced higher diastereoselectivity and enantioselectivity than ligand **40c** (compare entry 1 to 2, Table 44). Furthermore, contrary to the reaction with nitromethane (**54a**), the substituent at the boron has an influence on the selectivity (compare entry 1 to 3 and 1 to 4, Table 44). As for nitromethane (**54a**), the ligand **40g** was the most efficient ligand in this reaction. The Henry

adduct **222e** was synthesized with low diasteroselectivity but with moderate enantioselectivity (*syn*:*anti* ratio of 62:38 and 65% *ee* (*syn*), entry 1, Table 44).

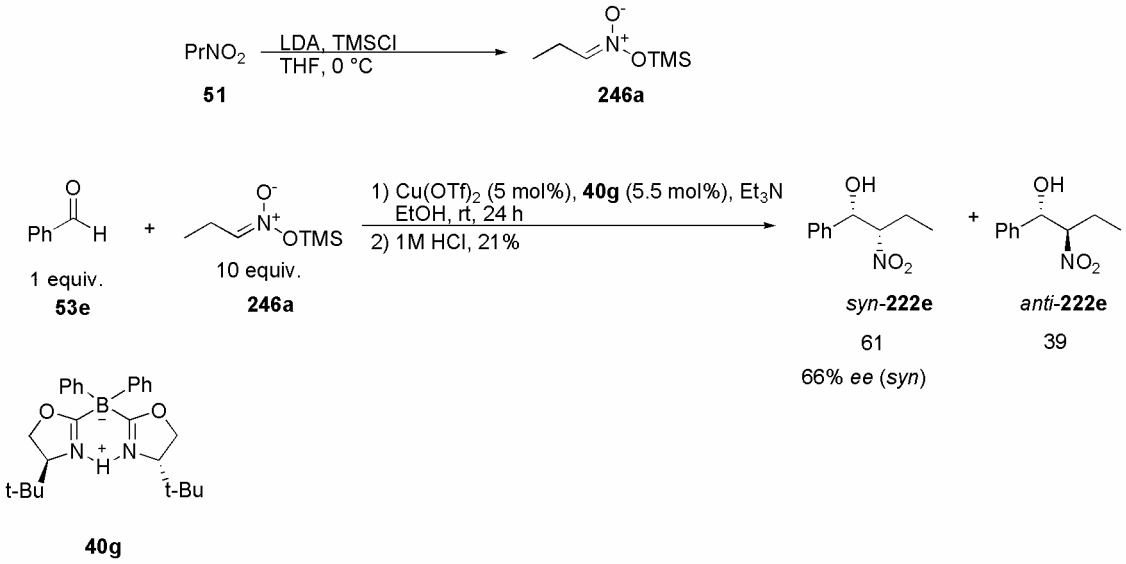
Table 44.



Entry	Ligand	Yield [%]	*syn*:*anti*[a]	*ee* (*syn*) [%][b]	*ee* (*anti*) [%][b]
1	**40g**	74	62:38	65 (1*S*,2*S*)	14 (1*S*,2*R*)
2	**40c**	80	74:26	<5 (1*S*,2*S*)	<5 (1*S*,2*R*)
3	**40f**	88	57:43	24 (1*S*,2*S*)	<5 (1*S*,2*R*)
4	**40e**	65	72:28	30 (1*S*,2*S*)	<5 (1*S*,2*R*)

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. [c] The absolute configuration of nitroalcohol products *syn*-**222e** were assigned by analogy with compound *syn*-**222c**. [d] The absolute configuration of nitroalcohol products *anti*-**222e** were assigned by analogy with compound *anti*-**221e** (see ref. 179).

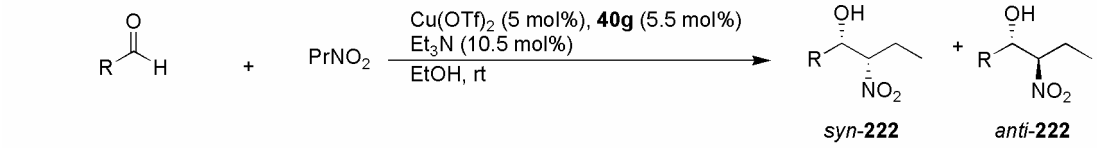
In order to improve the reactivity and the selectivity of this reaction, the silyl nitronate **246a** was used as substrate (Scheme 84). Unfortunately, the diastereoselectivity and enantioselectivity obtained (*syn*:*anti* ratio of 72:28 and 66% *ee* (*syn*)) were comparable to those obtained when nitropropane (**51**) was employed as substrate and the yield was even lower.



Scheme 84.

The scope of the reaction of nitropropane (**51**) and various aldehydes **53** was then investigated. Poor selectivities were obtained for aldehydes bearing electron-withdrawing groups at the aromatic ring as it was already observed when nitromethane (**54a**) was used (**222h** and **222q**, *syn*:*anti* ratio of 68:32 and 62:38, racemic *syn* and *anti* isomers, entries 2 and 3, Table 45). For the first time, good enantioselectivities were achieved in the formation of nitroalcohols **222g**, **222i**, **222j**, and **222r** derived from aldehydes carrying phenylmethoxy and phenylchloride substituents (entries 4 to 7, Table 45). In particular the *ortho*-chloride-substituted benzaldehyde (**53i**) and the *para*-methoxy-substituted benzaldehyde (**53r**) were converted to the corresponding Henry products **222i** and **222r** with high enantiomeric excesses of 85% and 82%, respectively, for the *syn* isomers (59 and 58% yields respectively, entries 4 and 7, Table 45). The *syn*:*anti* ratio was particularly low for the first one but moderate for the latter one (*syn*:*anti* ratio of 53:47 and 75:25, entries 4 and 7, Table 45). For nitromethane (**54a**), we observed the opposite trend: o*rtho*-methoxy- and *para*-chloride-substituted benzaldehyde **53g** and **53l** gave the highest enantiomeric excesses.
Concerning the aliphatic aldehydes, the selectivity was in general good: the major *syn* nitroalcohol **222b** derived from the α-branched aldehyde isobutyraldehyde (**53b**) was obtained with good enantiomeric excess of 75% (55% conversion, *syn*:*anti* ratio of 87:13, entry 12, Table 45). Especially high enantioselectivities were achieved when propionaldehyde and cyclohexanecarboxaldehyde were used (**53s** and **53c**, *syn*:*anti* ratio of 85:15 and 92:08, 87% and 91% *ee* (*syn*) respectively, entries 13 and 16, Table 45): to the best of our knowledge product **222s** was synthesized the first time in an enantioselective way. In order to increase the reactivity of the Henry reaction, the reactions with propionaldehyde (**53s**) and cyclohexanecarboxaldehyde (**53c**) were conducted at 35 °C (entries 15 and 18, Table 45). In the case of the cyclic aliphatic aldehyde **53c**, the diastereoselectivity dropped slightly to 85:15, but the enantiomeric excess of the major *syn* isomer was maintained at 91% with a higher conversion of 73% (entry 18, Table 45). Unfortunately, when the non branched aldehyde (**53s**) was used, both diastereoselectivity and enantioselectivity decreased significantly (97% conversion, *syn*:*anti* ratio of 61:39 and 30% *ee* (*syn*), entry 15, Table 45).
Futhermore, the reactions with these two aldehydes were carried out on a bigger scale (entries 14 and 17, Table 45) and the enantioselectivities were improved in both cases (89 and 91% *ee* for the *syn* isomers **222s** and **222c**).

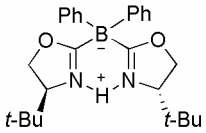
Table 45.



53a: R = $PhCH_2CH_2$
53b: R = *i*-Pr
53c: R = Cy
53e: R = Ph
53g: R = 2-$MeOC_6H_4$
53h: R = 2-$NO_2C_6H_4$
53i: R = 2-ClC_6H_4
53l: R = 4-ClC_6H_4
53n R = *i*-Bu
53p: R = *n*-Bu
53q: R = 4-$NO_2C_6H_4$
53r: R = 4-$MeOC_6H_4$
53s: R = Et
53u: R = 2-naphtyl

51

222a: R = $PhCH_2CH_2$
222b: R = *i*-Pr
222c: R = Cy
222e: R = Ph
222g: R = 2-$MeOC_6H_4$
222h: R = 2-$NO_2C_6H_4$
222i: R = 2-ClC_6H_4
222l: R = 4-ClC_6H_4
222n R = *i*-Bu
222p: R = *n*-Bu
222q: R = 4-$NO_2C_6H_4$
222r: R = 4-$MeOC_6H_4$
222s: R = Et
222u: R = 2-naphtyl

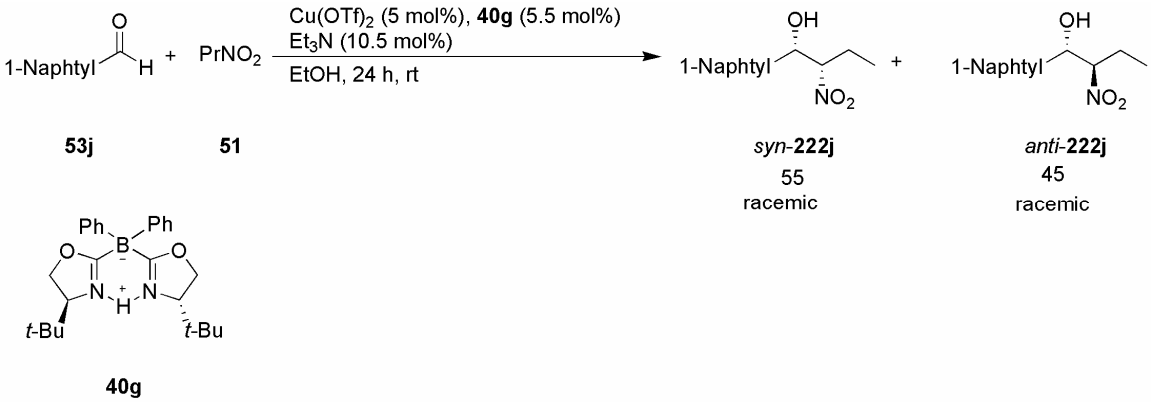


40g

Entry	R	222	Time [d]	Yield [%][a]	*syn*:*anti*[b]	*ee* (*syn*) [%][c][d]	*ee* (*anti*) [%][c][e]
1	Ph	**222e**	1	74	62:38	65 (1*S*,2*S*)	14 (1*S*,2*R*)
2	2-$NO_2C_6H_4$	**222h**	1	90	68:32	3 (1*S*,2*S*)	3 (1*S*,2*R*)
3	4-$NO_2C_6H_4$	**222q**	1	80	73:27	2 (1*S*,2*S*)	8 (1*S*,2*R*)
4	2-ClC_6H_4	**222i**	1	59	53:47	85 (1*S*,2*S*)	38 (1*S*,2*R*)
5	4-ClC_6H_4	**222l**	1	96	65:35	48 (1*S*,2*S*)	12 (1*S*,2*R*)
6	2-$MeOC_6H_4$	**222g**	1	83	61:39	50 (1*S*,2*S*)	10 (1*S*,2*R*)
7	4-$MeOC_6H_4$	**222r**	2	58	75:25	82 (1*S*,2*S*)	48 (1*S*,2*R*)
8	2-naphthyl	**222u**	1	70	63:37	54 (1*S*,2*S*)	2 (1*S*,2*R*)
9	$PhCH_2CH_2$	**222a**	2	45[f]	63:37	39 (3*S*,4*S*)	11 (3*S*,4*R*)
10	*i*-Bu	**222n**	5	53[f]	66:34	63 (4*S*,5*S*)	21 (4*S*,5*R*)
11	*n*-Bu	**222p**	4	64[f]	64:36	48 (3*S*,4*S*)	8 (3*R*,4*S*)
12	*i*-Pr	**222b**	5	55[f]	87:13	75 (3*S*,4*S*)	19 (3*S*,4*R*)
13	Et	**222s**	4	62[f]	85:15	87 (3*S*,4*S*)	49 (3*S*,4*R*)
14	Et	**222s**	4	55[g]	82:18	89 (1*S*,2*S*)	58 (1*S*,2*R*)
15	Et	**222s**	5	97[f][h]	61:39	30 (1*S*,2*S*)	8 (1*S*,2*R*)
16	Cy	**222c**	5	60[f]	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
17	Cy	**222c**	5	53[g]	93:07	94 (1*S*,2*S*)	74 (1*S*,2*R*)
18	Cy	**222c**	5	73[f][h]	85:15	91 (1*S*,2*S*)	27 (1*S*,2*R*)

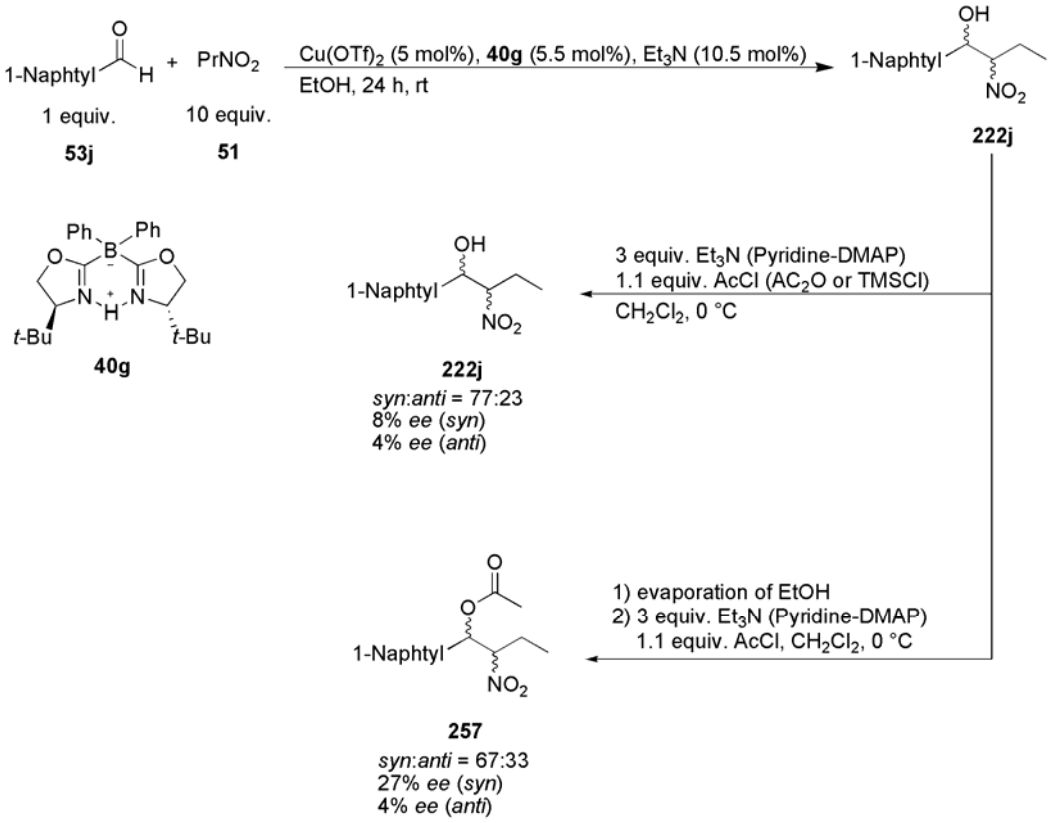
[a] Combined yields of *syn* and *anti* isomers. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC. [d] The absolute configuration of nitroalcohol products *syn*-**222** were assigned by analogy with compound *syn*-**222c**. [e] The absolute configuration of nitroalcohol products *anti*-**222** were assigned by analogy with compound *anti*-**221e** (see ref. 179). [f] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [g] Reactions were performed on a 2.5 mmol scale. [h] Reactions were carried out at 35 °C.

1-Naphtaldehyde (**53j**) was also tested as substrate in this reaction and the selectivities obtained for the compound **222j** were first quite promising (85% yield, *syn*:*anti* ratio of 92:08, 50% *ee* (*anti*), 93% *ee* (*syn*)). But the product **222j** was unstable and tended to epimerize and additionally underwent a retro-Henry reaction (Scheme 85).



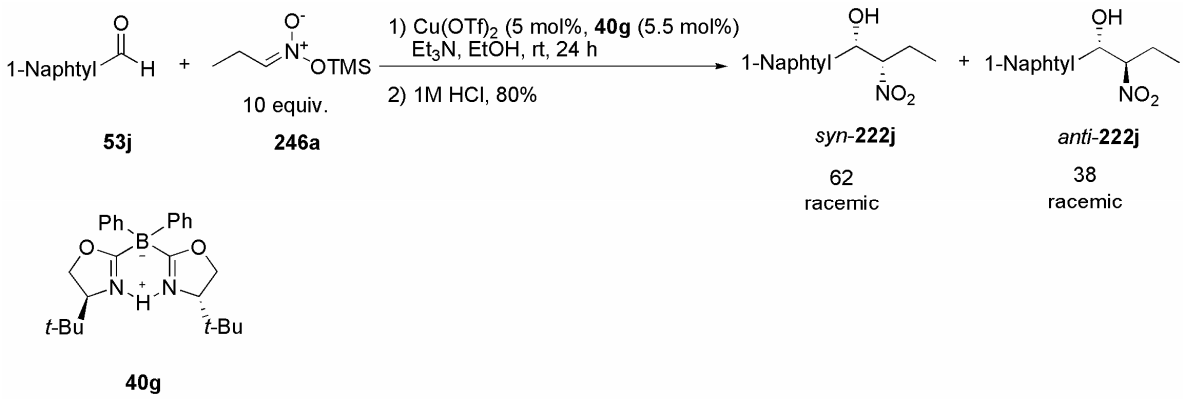
Scheme 85.

For preventing this epimerization, several attempts to convert the product **222j** into the acetate **257** were carried out (Scheme 86). When the acylating agent and the base were directly added to the reaction mixture, only racemic nitroalcohol **222j** was obtained. Several bases (triethylamine, pyridine with or without DMAP) and acylating agents (TMSCl, AcCl, Ac_2O) were tested without success. The desired compound **257** could be obtained by evaporating the ethanol prior to the addition of a solution of the acylating agent and the base in dichloromethane but the selectivity was lower than expected (*syn*:*anti* ratio of 67:33, 4% *ee* (*anti*), 27% *ee* (*syn*)).



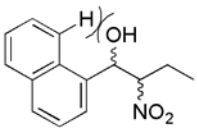
Scheme 86.

When the Henry reaction was carried out in the presence of silylated nitropropane **246a** instead of nitropropane (**51**), the compound **222j** was obtained with low diastereoselectivity and as a racemate (Scheme 87).



Scheme 87.

This epimerization was observed only with 1-naphtaldehyde (**53j**) whereas the product **222u** derived from 2-naphtaldehyde (**53u**) was perfectly stable. This instability is presumably due to a steric interaction between the proton of the aromatic ring and the OH group of the nitroalcohol **222j** (Figure 40).

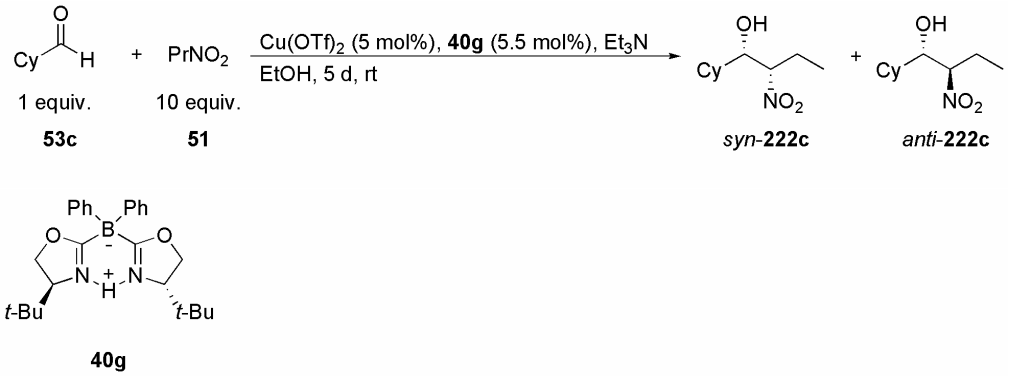


222j

Figure 40.

The reaction of nitropropane (**51**) with cyclohexanecarboxaldehyde (**53c**) catalyzed by the complex derived from copper (II) triflate and ligand **40g** afforded the nitroalcohol **222c** with high enantioselectivity. The influence of the aldehyde concentration of the solution was then investigated for this reaction (Table 46). An aldehyde concentration of 0.62 mol/L used all along these studies gave the best result (*syn*:*anti* ratio of 08:92, 33% *ee* (*anti*), 91% *ee* (*syn*)). Indeed, when the concentration was lowered to 0.5 mol/L or increased to 1 mol/L, the selectivities and the conversions dropped (30% conversion, *syn*:*anti* ratio of 82:18, 20% *ee* (*anti*), 84% *ee* (*syn*) and 8% conversion, *syn*:*anti* ratio of 84:16, 23% *ee* (*anti*), 81% *ee* (*syn*), respectively, entry 2 and 3, Table 46).

Table 46



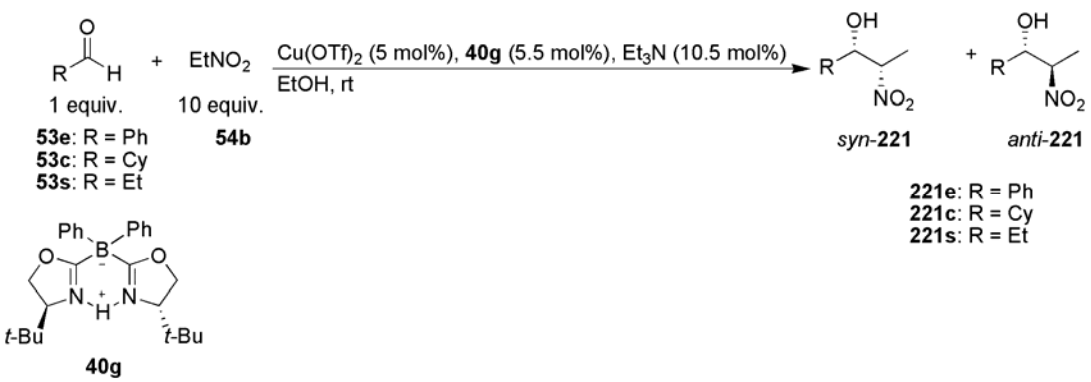
Entry	Concentration **53c** (mol/L)	Conversion [%][a]	*syn*:*anti*[a]	*ee* (*syn*) [%][b][c]	*ee* (*anti*) [%][b][d]
1	0.62	60	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
2	1.00	48	84:16	81 (1*S*,2*S*)	23 (1*S*,2*R*)
3	0.50	30	82:18	84 (1*S*,2*S*)	20 (1*S*,2*R*)

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. [c] The absolute configuration of nitroalcohol products *syn*-**222c** were assigned by comparison with published HPLC retention times (see ref. 174). [d] The absolute configuration of nitroalcohol products *anti*-**222c** were assigned by analogy with compound *anti*-**221e** (see ref. 179).

5.1.2.6 Asymmetric Henry Reaction with Nitroethane

In order to broaden the scope of nitroalkanes, we carried out the reaction between a few aldehydes and nitroethane (**54b**, Table 47). Once again the reaction with cyclohexanecarboxaldehyde (**53c**) was highly stereoselective (**221c**, *syn*:*anti* ratio of 90:10 and 90% *ee* (*syn*), 47% *ee* (*anti*), entry 2, Table 47). However, the Henry adducts **221e** and **221s** derived from benzaldehyde (**53e**) and propionaldehyde (**53s**) were synthesized with low diastereoselectivity and enantioselectivity (*syn*:*anti* ratio of 62:38 and 64:36, 21 and 51% *ee* (*syn*), respectively, entries 1 and 3, Table 47).

Table 47.



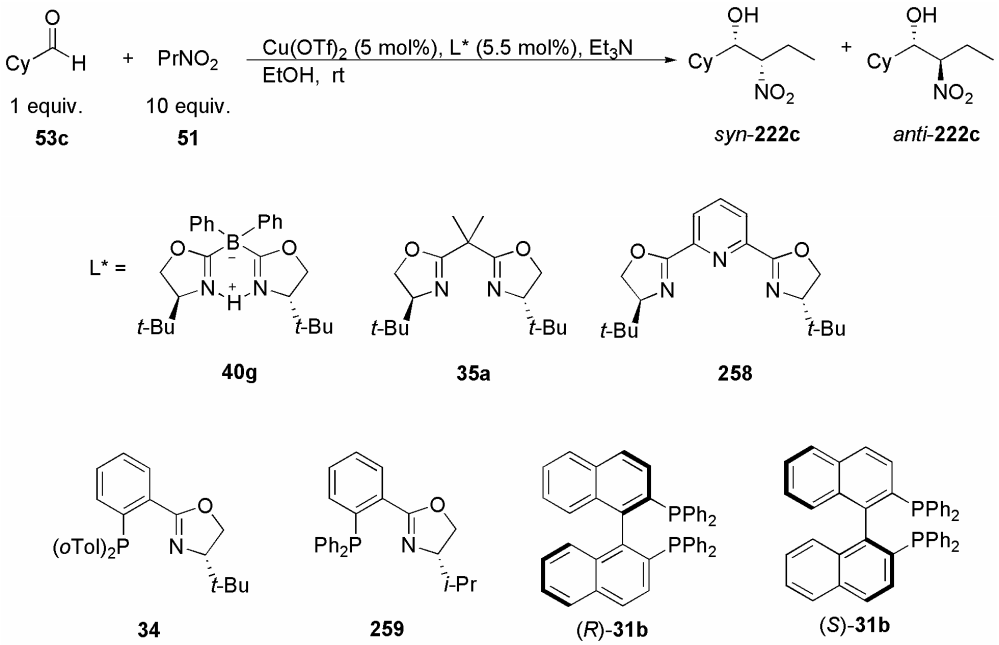
fEntry	**221**	Time [days]	Yield[%][a]	*syn*:*anti*[b]	*ee* (*syn*) [%][c][d]	*ee* (*anti*) [%][c][e]
1	**221e**	1	80	62:38	21 (1*S*,2*S*)	15 (1*S*,2*R*)
2	**221c**	5	82[f]	90:10	90 (1*S*,2*S*)	47 (1*S*,2*R*)
3	**221s**	5	80[f]	64:36	51 (2*S*,3*S*)	23 (2*R*,3*S*)

[a] Combined yield of *syn* and *anti* isomers. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC. [d] The absolute configuration of nitroalcohol products *syn*-**221** were assigned by analogy with compound *syn*-**222c**. [e] The absolute configuration of nitroalcohol products *anti*-**221** were assigned by analogy with compound *anti*-**221e** (see ref. 179). [f] Conversion determined by ^{1}H NMR spectroscopy of the crude product.

5.1.2.7 Comparison of Privileged Ligands and Borabox Ligands

Subsequently, the borabox ligand **40g** was compared to some privileged ligands (BOX ligand **35a**, Pybox **258**, PHOX **34**, **259** and BINAP ligand **31b,** Table 48) by applying them to the Henry reaction between cyclohexanecarboxaldehyde (**53c**) and nitropropane (**51**) using the optimized reaction conditions (Table 47). In general, these ligands generated more reactive catalysts than the borabox ligand: the reactions using (*R*)- and (*S*)-**31b** were complete after one day (entries 6 and 7, Table 48). However, the diasteroselectivities and enantioselectivities obtained could not compete with the one obtained with the borabox ligand **40g**: the diastereoselectivity did not exceed 79:21 and the enantioselectivity did not exceed 66% using BOX ligand **35a** (entry 2, Table 48).

Table 48.



Entry	Ligand	Time [days]	Conversion [%][a]	*syn*:*anti*[a]	*ee* (*syn*) [%][b][c]	*ee* (*anti*) [%][b][d]
1	**40g**	5	60	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
2	**35a**	2	65	79:21	66 (1*S*,2*S*)	16 (1*S*,2*R*)
3	**258**	4	98	73:27	17 (1*S*,2*S*)	2 (1*R*,2*S*)

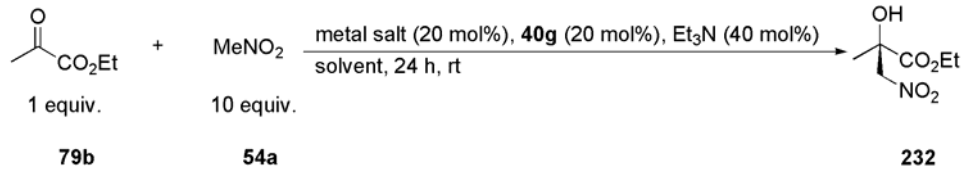
Entry	Ligand	Time [days]	Conversion [%][a]	*syn*:*anti*[a]	*ee* (*syn*) [%][b][c]	*ee* (*anti*) [%][b][d]
4	**34**	1	97	61:39	25 (1*R*,2*R*)	60 (1*R*,2*S*)
5	**259**	1	76	76:24	1 (1*S*,2*S*)	9 (1*S*,2*R*)
6	(*R*)-**31b**	1	>99	63:37	7 (1*R*,2*R*)	13 (1*R*,2*S*)
7	(*S*)-**31B**	1	>99	64:36	13 (1*S*,2*S*)	15 (1*S*,2*R*)

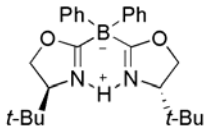
[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. [c] The absolute configuration of nitroalcohol products *syn*-**222c** were assigned by comparison with published HPLC retention times (see ref. 174). [d] The absolute configuration of nitroalcohol products *anti*-**222c** were assigned by analogy with compound *anti*-**221e** (see ref. 179).

5.1.2.8 α-Keto Esters as Substrates in the Asymmetric Henry Reaction

The Henry reaction of α-keto esters **79** with nitromethane (**54a**) was carried out in the presence of the borabox ligand **40g**. Poor enantioselectivity was obtained in the presence of copper (II) triflate and ethanol as solvent (17% *ee*, entry 1, Table 49). Changing the metal salt to zinc (II) triflate caused a decrease of the enantioselectivity (10% *ee*, entry 2, Table 49). When the reaction was carried out in nitromethane, the solvent of choice for the reaction developed by Jørgensen[156], or in dichloromethane, no improvement of the enantioselectivity was observed (entries 3 and 4, Table 49). Due to the lack of selectivity and the high catalyst loading, no further study was investigated with α-keto esters **79**.

Table 49.





40g

Entry	Metal salt	solvent	Yield [%][a]	*ee* [%][b][c]
1	$Cu(OTf)_2$	EtOH	60	17 (*R*)
2	$Zn(OTf)_2$	EtOH	65	10 (*R*)
3	$Cu(OTf)_2$	$MeNO_2$	98	10 (*R*)
4	$Cu(OTf)_2$	CH_2Cl_2	97	11 (*R*)

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. [c] The absolute configuration of nitroalcohol product **232** was assigned by comparison with the one mentioned in the literature (see ref. 157).

5.1.2.9 Conclusion

In this study, enantioselective Henry reactions catalyzed by boron-based bis(oxazolines) zinc (II)- and copper (II)-complexes were investigated. The drastic influence of the base in this reaction has been established: the study revealed that 1 equivalent of base compared to the ligand was needed for avoiding the formation of a non selective homoleptic complex and an additional 4.5 mol% of base, added during the reaction, was found to be the optimum amount for reaching high enantioselectivity.

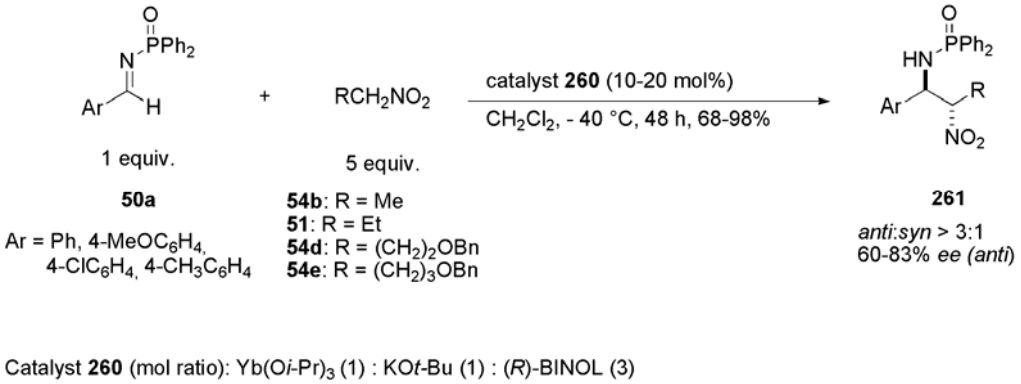
A screening of aldehydes in the presence of nitromethane (**54a**) revealed that the borabox ligand **40g** could not compete with the BOX ligand **35a**. However, further investigation showed that the borabox ligand **40g** allowed more pronounced stereocontrol of the Henry reaction when nitropropane (**51**) is used. High enantioselectivities were reached, allowing for the first time the enantioselective synthesis of the corresponding nitroalcohols. Concerning the reaction between nitropropane (**51**) and cyclohexanecarboxaldehyde (**53c**), the borabox ligand **40g** was found to be more selective than BOX and other privileged ligands.

5.2 Asymmetric Aza-Henry Reaction

5.2.1 Literature

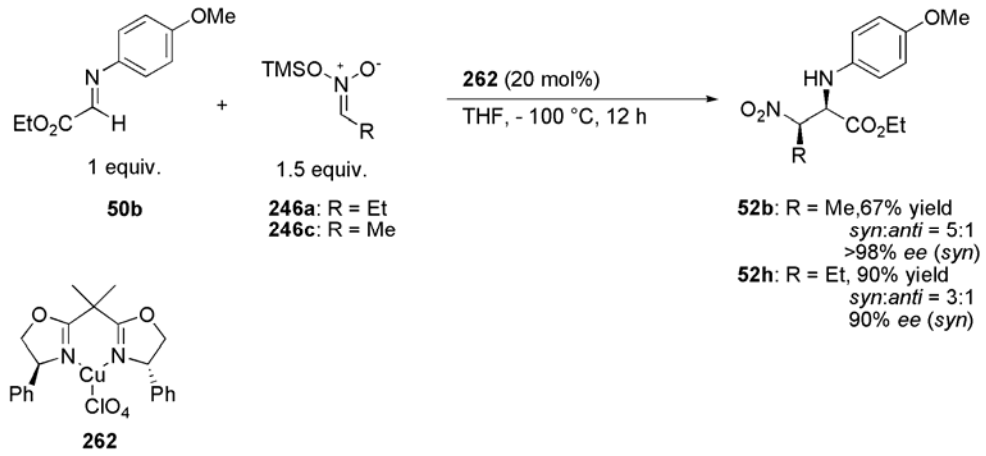
The nucleophilic addition of nitronates to imines, called the aza-Henry reaction[180], is an important tool for carbon-carbon bond formation that gives access to α-nitroamines, that can be easily converted to interesting synthetic building blocks such as 1,2-diamines[181] or α-amino acids[182].

The rare earth metal catalysts developed by Shibasaki *et al.*, already successful in the Henry reaction (see section 5.1), were applied to the aza-nitroaldol reaction.[183] The *N*-phosphinoylimines **50a** were found to be suitable substrates for this reaction as the P=O double bond can coordinate to the metal center of the heterobimetallic complex **260**.[184] The α-nitroamines **261** were synthesized in up to 83% *ee* for the major *anti* isomer (Scheme 88).



Scheme 88.

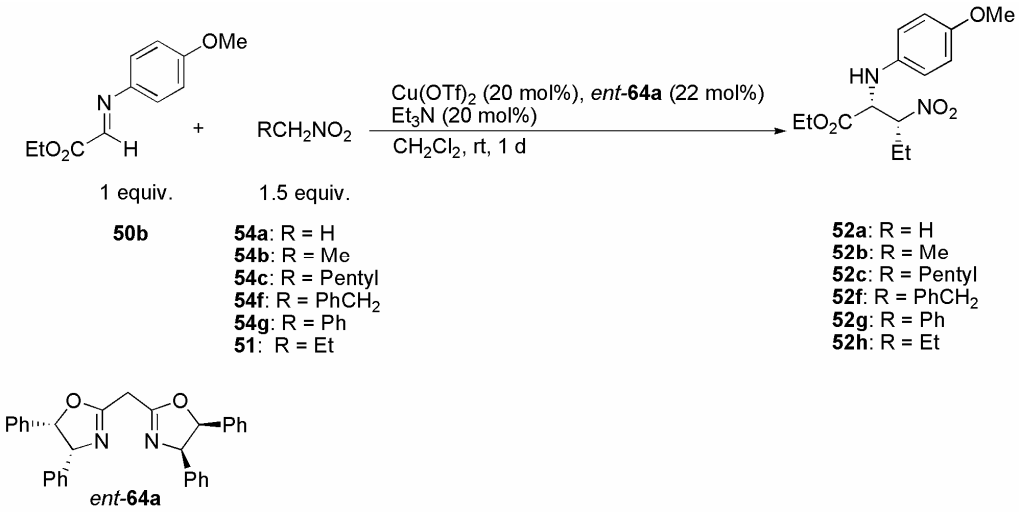
Jørgensen reported a very practicable method for the aza-Henry reaction using silyl nitronates **246**.[185] The application of copper (II)-bis(oxazoline) complex **262** led to the highly enantioselective formation of β-nitro-α-amino esters **52** (Scheme 89). Due to the high reactivity of silyl nitronates **246**, the reaction proceeded without catalyst even at -78 °C. Thus, a reaction temperature of -100 °C was required to suppress the unselective background reaction.



Scheme 89.

Later, Jørgensen *et al*. presented a simplified approach for this process.[186] The reaction was conducted at room temperature in the presence of nitroalkanes **51**, **54**, which are less reactive than silyl nitronates **246**, and a base. The products **52** were prepared in moderate to good yield and remarkable selectivities (Table 50). A serie of different *N*-protected α-imino esters were tested in the reaction. Electron-withdrawing substituents at the nitrogen atom gave products that decomposed during the workup. *N*-(*p*-methoxyphenyl)-α-imino ester **50b** led to a stable product and was therefore chosen as the test substrate.

Table 50.



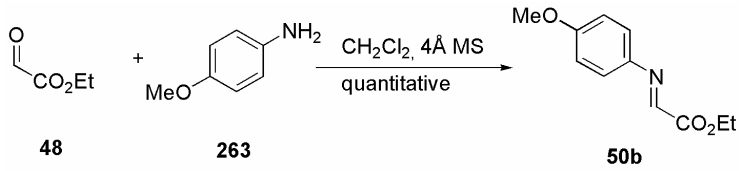
Entry	Nitroalkane	Yield [%]	*syn*:*anti*	*ee (syn)* [%]	*ee (anti)* [%]
1[a]	**54a**	38	-	87	-
2	**54b**	61	70:30	97	95
3	**51**	81	95:05	97	87
4	**54c**	52	93:07	97	89
5	**54f**	80	95:05	95	88
6	**54g**	59	55:45	74	77

[a] The reaction was performed at 0 °C.

Many organocatalytic methods for the enantioselective aza-Henry reaction have been reported.[187] In particular, a chiral thiourea catalyst allowed the synthesis of the aza-nitroaldol products with good yields and selectivities up to 97% *ee* for the *anti* isomer.[188]

5.2.2 Aza-Henry Reaction Catalyzed by Borabox Complexes

The good selectivities obtained in the Henry reaction of nitropropane (**51**) catalyzed by the copper complex derived from borabox ligand **40g** prompted us to investigate the aza-Henry reaction. The reaction of *N*-(*p*-methoxyphenyl)-α-imino ester **50b** with nitropropane (**51**) was chosen as a model reaction. The imine **50b** was synthesized in 90% yield from ethyl glyoxylate (**48**) and *p*-methoxyaniline (**263**) (Scheme 90).[185]

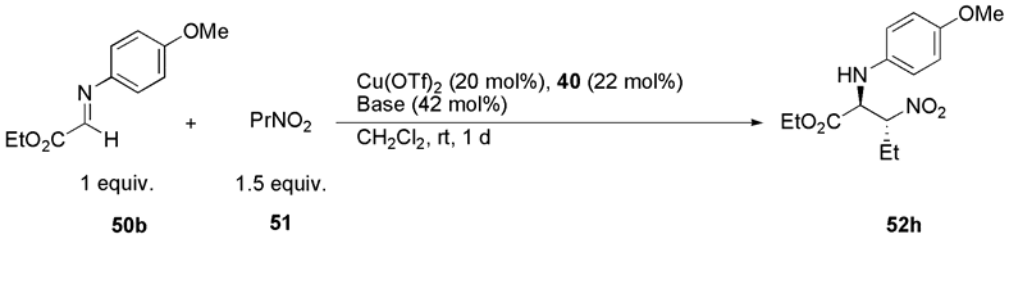


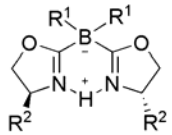
Scheme 90.

To rapidly determine the potential of the borabox ligands **40**, a quick screening was carried out (Table 51). Copper (II) bromide was chosen as the metal source for this reaction as copper (II) triflate gave only racemic compounds. In the presence of the borabox ligand **40i**, no product formation was observed when no base was added during the complexation (entry 1, Table 51). With potassium carbonate as base in the complexation and for the deprotonation of nitropropane (**51**), the *α*-nitroamine **52h** was formed in 89% yield and with modest diastereoselectivity and enantioselectivity (*anti:syn* ratio of 70:30, 16% *ee* (*anti*) and 12% *ee* (*syn*), entry 2, Table 51). Changing to triethylamine caused a decrease of yield but considerably increased the selectivities (56% yield, *anti:syn* ratio of 92:8, 59% *ee* (*anti*) and 57% *ee* (*syn*), entry 3, Table 51). The aza-Henry reaction was then carried out with ligand **40g**, which gave the best results in the Henry reaction. With potassium carbonate as the base

the formation of the product **52h** was not observed (entry 4, Table 51). In the presence of triethylamine, the product **52h** was obtained in 70% yield but with low selectivities (*anti:syn* ratio of 89:11, 1% *ee* (*anti*) and 13% *ee* (*syn*), entry 5, Table 51). A further screening of ligands **40** with triethylamine as base did not improve upon the result obtained with ligand **40i**. When catalyzed by copper complexes derived from ligands **40o**, **40c** and **40e**, the diastereoselectivities obtained were low (*anti*:*syn* ratio ≤76:24) and the *syn* and *anti* isomers were synthesized as racemic mixtures (entries 7 to 9, Table 51). In order to check the influence of the substituents at the boron center of the borabox ligand, the aza-nitroaldol reaction was conducted in the presence of the ligand **40l** (entry 10, Table 51). The product was obtained with a good yield of 86% but with very low diasteroselectivity (*anti:syn* ratio of 51:49). Furthermore, poor enantioselectivities for the *syn* and *anti* isomers were observed (26% *ee* (*anti*) and 19% *ee* (*syn*), entry 10, Table 51). With the ligand **40i**, which offered the best result, the reaction with silyl nitronate **246a** was carried out (entry 11, Table 51). Unfortunately, the compound **52h** was formed with lower selectivities (*anti:syn* ratio of 46:54, 15% *ee* (*anti*) and 18% *ee* (*syn*), entry 11, Table 51).

Table 51.





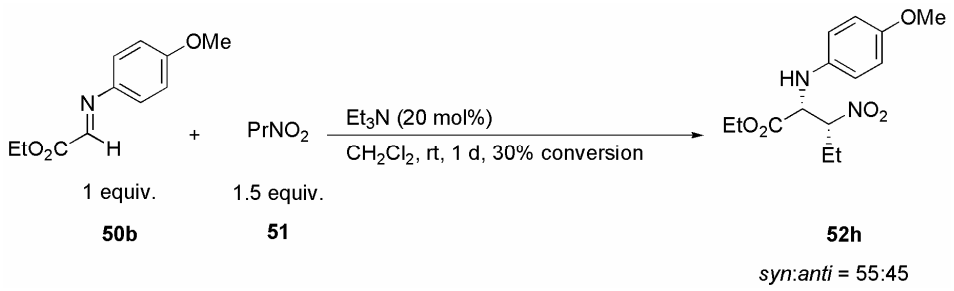
40c: R^1 = Ph; R^2 = *i*-Pr
40e: R^1 = Cy; R^2 = *t*-Bu
40g: R^1 = Ph; R^2 = *t*-Bu
40i: R^1 = Et; R^2 = Bn
40l: R^1 = Cy; R^2 = Bn
40o: R^1 =Ph; R^2 = Ph

Entry	Ligand	Base	Yield [%][a]	*anti:syn*[b]	*ee* (*anti*) [%][c]	*ee* (*syn*) [%][c]
1	**40i**	-	-	-	-	-
2[d]	**40i**	K_2CO_3	89	70:30	16	12
3	**40i**	Et_3N	56	92:08	59	57
4	**40g**	K_2CO_3	-	-	-	-
5	**40g**	Et_3N	70	89:11	1	13
6	**40o**	K_2CO_3	-	-	-	-

Entry	Ligand	Base	Yield [%][a]	*anti:syn*[b]	*ee* (*anti*) [%][c]	*ee* (*syn*) [%][c]
7	**40o**	Et_3N	15	64:36	3	2
8	**40c**	Et_3N	85	77:23	2	1
9	**40e**	Et_3N	90	76:24	4	5
10	**40l**	Et_3N	86	51:49	26	19
11[e]	**40i**	Et_3N	60	46:54	15	18

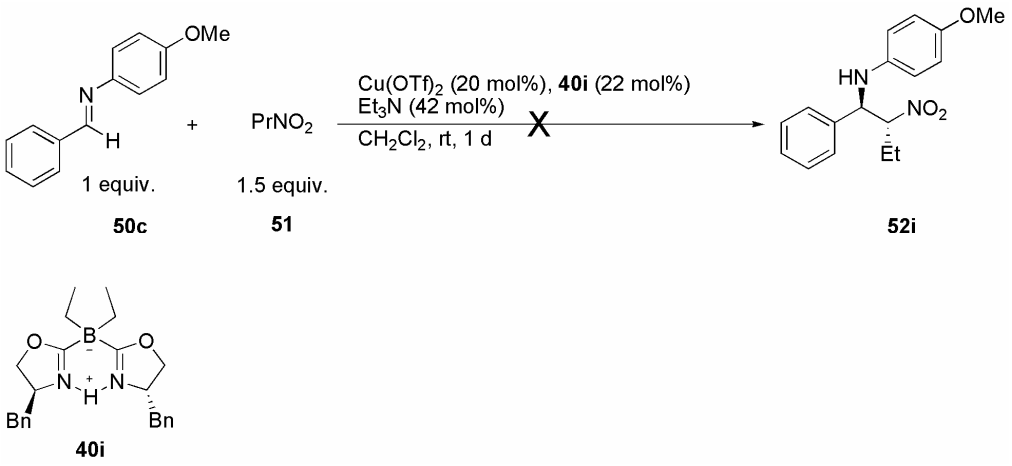
[a] Isolated yields. [b] Determined by ^{1}H-NMR and according to literature data (see ref. 186).[c] Determined by chiral HPLC. [d] Reaction time of 3 days. [e] Reaction conducted in the presence of silyl nitronate **246a**.

In the course of our study, we had difficulties in reproducing the results obtained when carrying out the aza-Henry reaction in the presence of borabox ligands **40**. Indeed, at room temperature the background reaction afforded the α-nitrosamine **52h** in 30% yield and with a diastereoselectivity of 55:45 (Scheme 91). Carrying out the reaction catalyzed by complex of borabox ligands **40** at lower temperature was not feasible due to the long reaction time already needed at room temperature.



Scheme 91.

The aza-Henry reaction was also conducted with *N*-benzylidene-*p*-anisidine[189] (**50c**) as the substrate but no product formation was observed (Scheme 92).



Scheme 92.

The difficulties to control the background reaction and the lack of rate acceleration by the borabox ligands **40** led us to stop any further study of the aza-Henry reaction catalyzed by complexes of borabox ligand **40**.

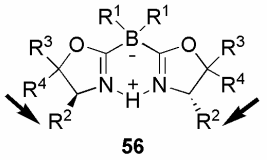
Chapter 6

Copper (II)-Complexes of C5-Substituted Borabox Ligands as Catalysts for the Asymmetric Henry Reaction

6 Copper (II)-Complexes of C5-Substituted Borabox Ligands as Catalysts for the Asymmetric Henry Reaction

6.1 Introduction

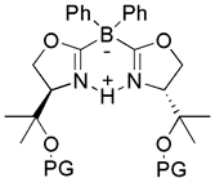
Ligand **56a**, a diphenyl C5-substituted ligand, was found to be highly efficient in the allylic oxidation of olefins (see section 4.2). Derivatives of this ligand were prepared in order to study the influence of substituents at the C5 position of the oxazoline rings on the enantioselectivity in the Henry reaction. The steric bulk of the substituents at the C5 position was expected to direct the groups at the C4 position towards the coordination sphere, allowing a better control of the selectivity (Figure 41).[190]



56

Figure 41.

The synthesis of ligand **264** was as well investigated (Figure 42) because analogous azasemicorrins gave interesting results in the cyclopropanation of olefins.[191] The protected alcohols at the stereogenic centers of the oxazoline rings were expected to coordinate to the copper atom influencing the selectivity and reactivity of the Henry reaction.



264

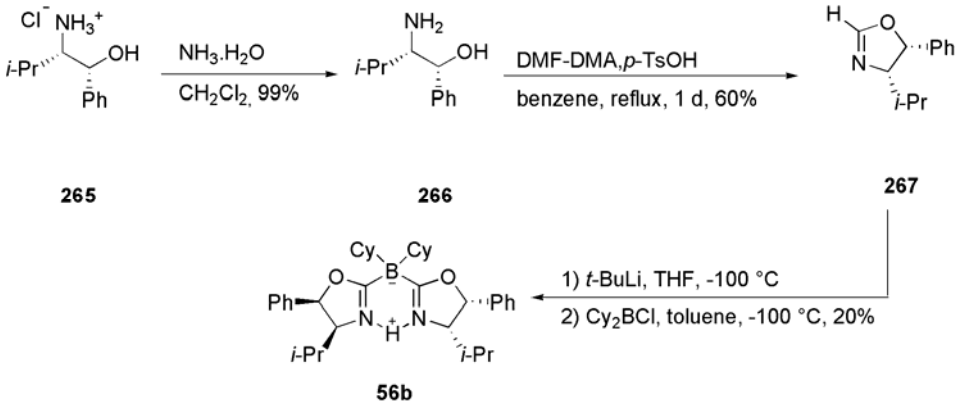
Figure 42.

6.2 Synthesis of C5-Substituted Borabox Ligands

6.2.1 Synthesis of Phenyl C5-Substituted Borabox Ligand

The synthesis of ligand **56b** was carried out starting from (1*R*, 2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol hydrochloride (**265**).[190] The free amino alcohol **266** was obtained in quantitative yield (Scheme 93). The cyclization into the 2*H*-oxazoline **267** in the presence of

DMF-DMA proceeded in 60% yield.[56] The synthesis of the corresponding borabox ligand **56b** was conducted according to the well established procedure except for the choice of the temperature.[25] Indeed, at -78 °C isomerization at the benzylic position occurred, leading to a mixture of diastereoisomers. By carrying out the reaction at -100 °C, the borabox ligand **56b** was obtained as a single isomer in 20% yield.



Scheme 93.

6.2.2 Synthesis of Dialkyl C5-Substituted Borabox Ligand

In the Henry reaction, ligand **40g** with *t*-butyl groups at the C4 position of the oxazoline rings induced the highest enantioselectivities (see section 5.1). Ligands **56c** and **56d** with two methyl groups at the C5 positions and *t*-butyl groups at the C4 positions were then expected to improve these results (Figure 43).

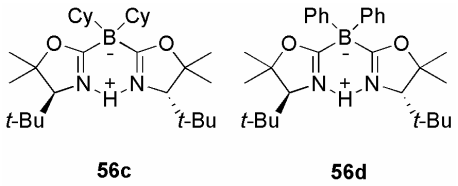
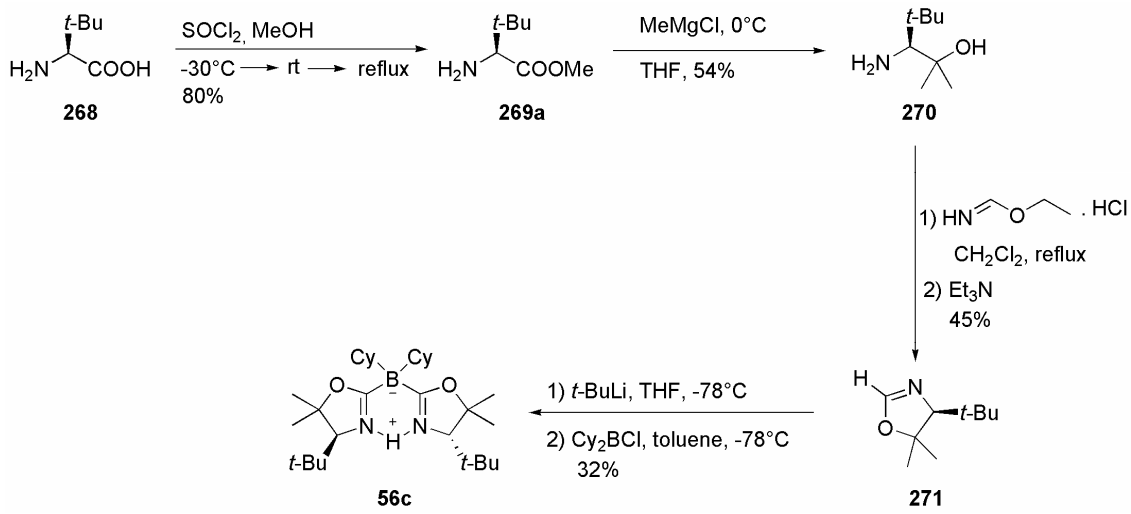


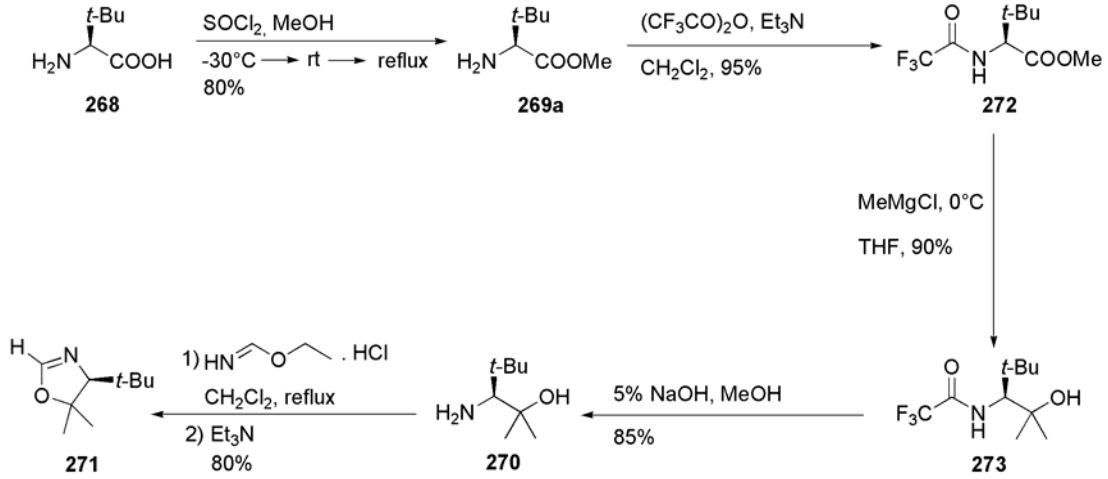
Figure 43.

The same procedure as for ligand **56a** was followed for the synthesis of ligand **56c** (Scheme 94). The amino-acid **268** was first converted to the amino-ester **269a** in 80% yield.[192] The addition of methyl magnesium chloride to the ester **269a** afforded the amino-alcohol **270** with a yield of 54%. The 2*H*-oxazoline **271** was obtained in 45% yield by treatment with ethyl formimidate hydrochloride and ligand **56c** was finally synthesized in 32% yield for the last step. An overall yield of 6% was obtained for this 4 step sequence.



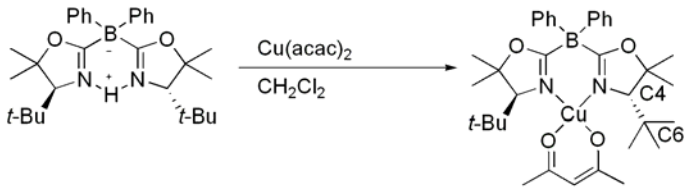
Scheme 94.

The low yields obtained especially in the second and third step are due to tedious purifications of intermediates **270** and **271**. In order to improve the yield of this synthesis, the protection of the amine of compound **269a**, before addition of the *Grignard* reagent, was carried out (Scheme 95).[193] After esterification of the amino-acid **268**, the amino-ester was protected with trifluoroacetic anhydride and compound **272** was obtained in 95% yield. The addition of the *Grignard* reagent proceeded in a high yield (90%). Deprotection of the amine by sodium hydroxide afforded the amino alcohol **270** which was converted to the 2*H*-oxazoline **271** in 80% yield. The borabox ligands **56c** and **56d** were obtained with 32 and 53% yield, respectively. In spite of the two additional steps, the overall yield for the formation of the borabox ligand **56c** was higher than for the first synthesis (overall yield of 6% without protection of the amine *versus* 15% with protection).



Scheme 95.

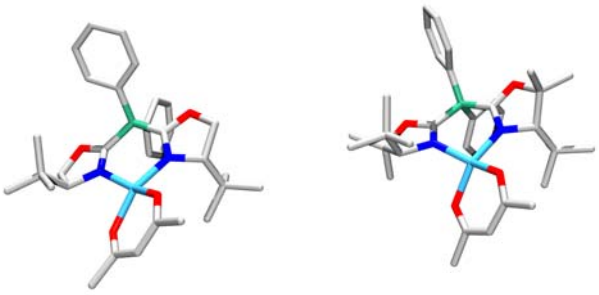
Complex **274** was obtained by reaction of 1 equivalent of ligand **56d** with 1 equivalent of copper (II) acetylacetonate following the procedure described in section 3.3 (Scheme 96).



56d **274**

Scheme 96.

The crystal structure of complex **274** was compared to the structure of complex **116b** (Figure 44). The influence of the substituents at the C5 positions of the oxazoline rings is directly visible by the measurement of the angles and bond distances. The monomeric complex **274** adopts a distorted square-planar geometry. The B-C_{oxa} and N-Cu bond lengths are 1.62 Å and 1.94 Å respectively. The bite angle (N-Cu-N) has a value of 95.5° which is similar to that of complex **116b** (see section 3.3.2). The angle (N-C4-C6) has a value of 109.6° in complex **274** and 110.4° in complex **116b**. The introduction of methyl groups at the C5 position of the oxazoline rings has therefore only a small influence on bond distances and angles in the solid state.



116b **274**

Figure 44.

6.2.3 Synthesis of Diaryl C5-Substituted Borabox Ligands

Bulkier substituents like substituted aryl groups were expected to have a stronger influence than methyl groups and to orientate more effectively the groups at the C4 position of the corresponding ligand towards the coordination sphere. For synthesizing the ligands **56e-h**, the

same procedure than for the C5,C5' dimethyl- substituted borabox ligands was followed (Figure 45).

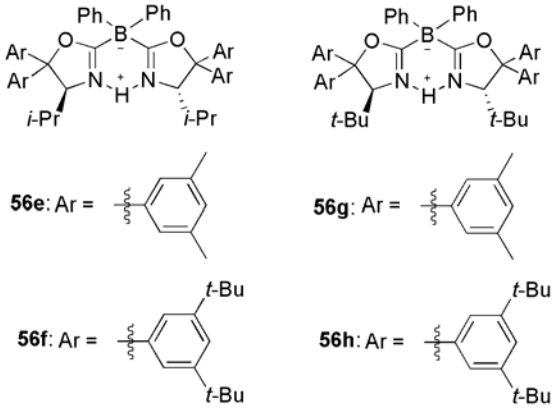
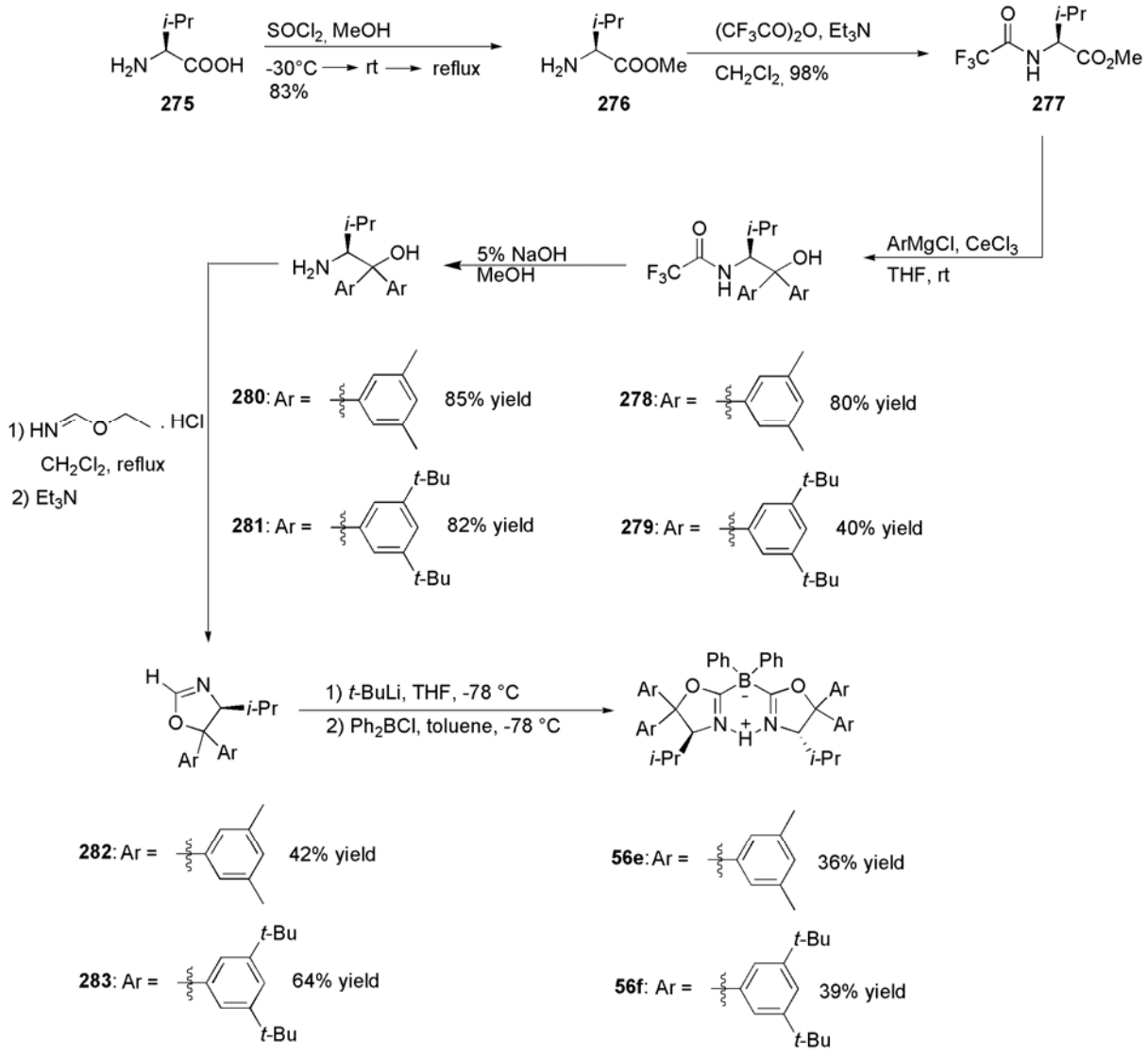


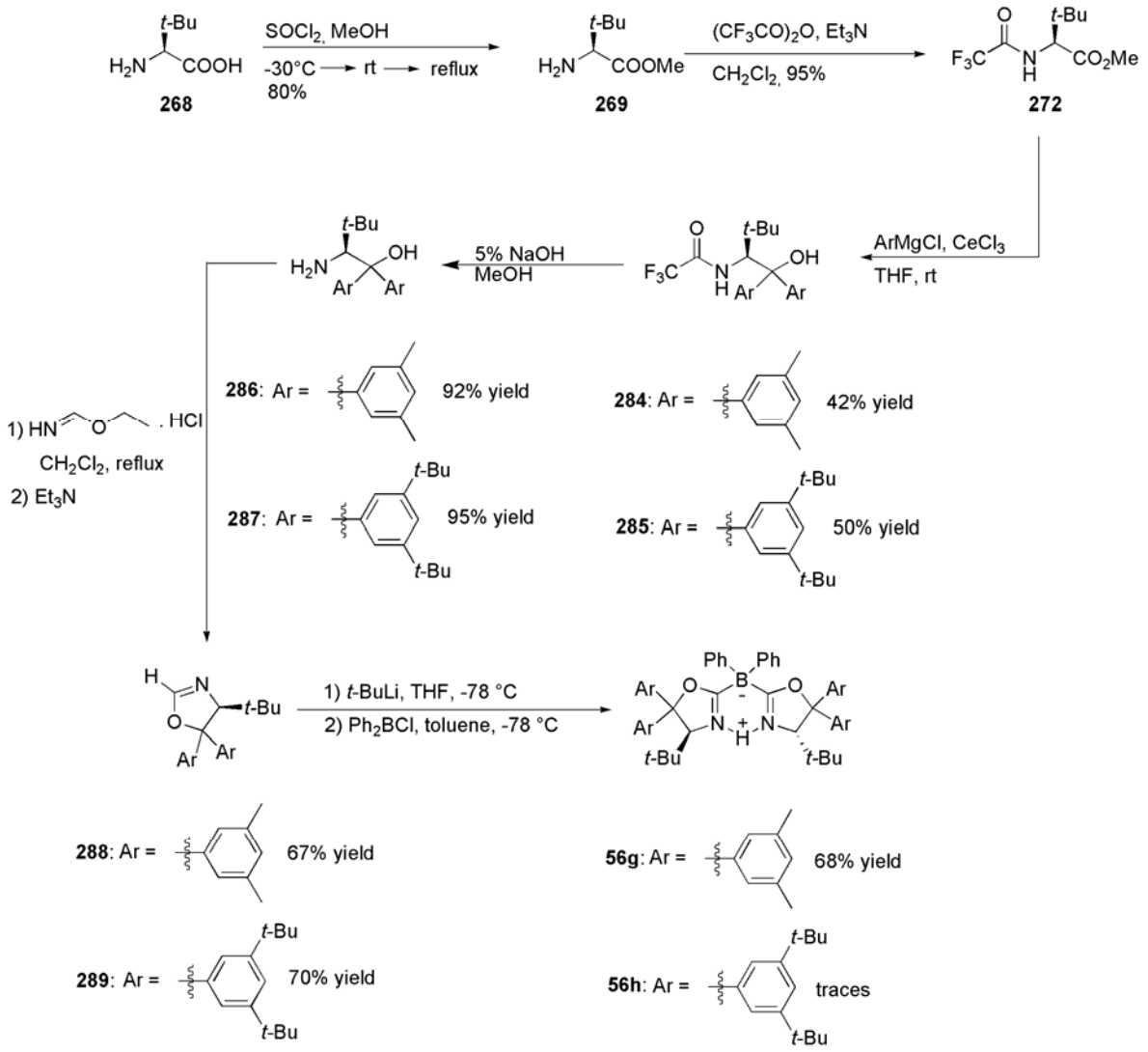
Figure 45.

The first two steps leading to the formation of the protected amine **277** were identical to the synthesis described before (section 6.2.2). Introduction of bulky groups like 3,5-dimethyl phenyl and 3,5-*t*-butyl phenyl groups was facilitated by the use of $CeCl_3$ in combination to the *Grignard* reagents (Scheme 97).[194] Amino-alcohols **278** and **279** were then synthesized in moderate to good yields (40 and 80% yields respectively). The protecting groups of the amines were subsequently easily removed and cyclization of the amino-alcohols **280** and **281** gave the 2*H*-oxazoline **282** and **283** in moderate yields. Finally, the two new disubstituted borabox ligands **56e** and **56f** were obtained in 36 and 39% yield, respectively.



Scheme 97.

Ligands **56g** and **56h** were prepared according to the same pathway (Scheme 98). The borabox ligand **56g** was obtained in 68% yield in the last step. Surprisingly, the final step for synthesizing ligand **56h** failed. Maybe due to steric hindrance between the substituents at the C4 and C5 positions, only traces of the desired ligand **56h** were obtained.



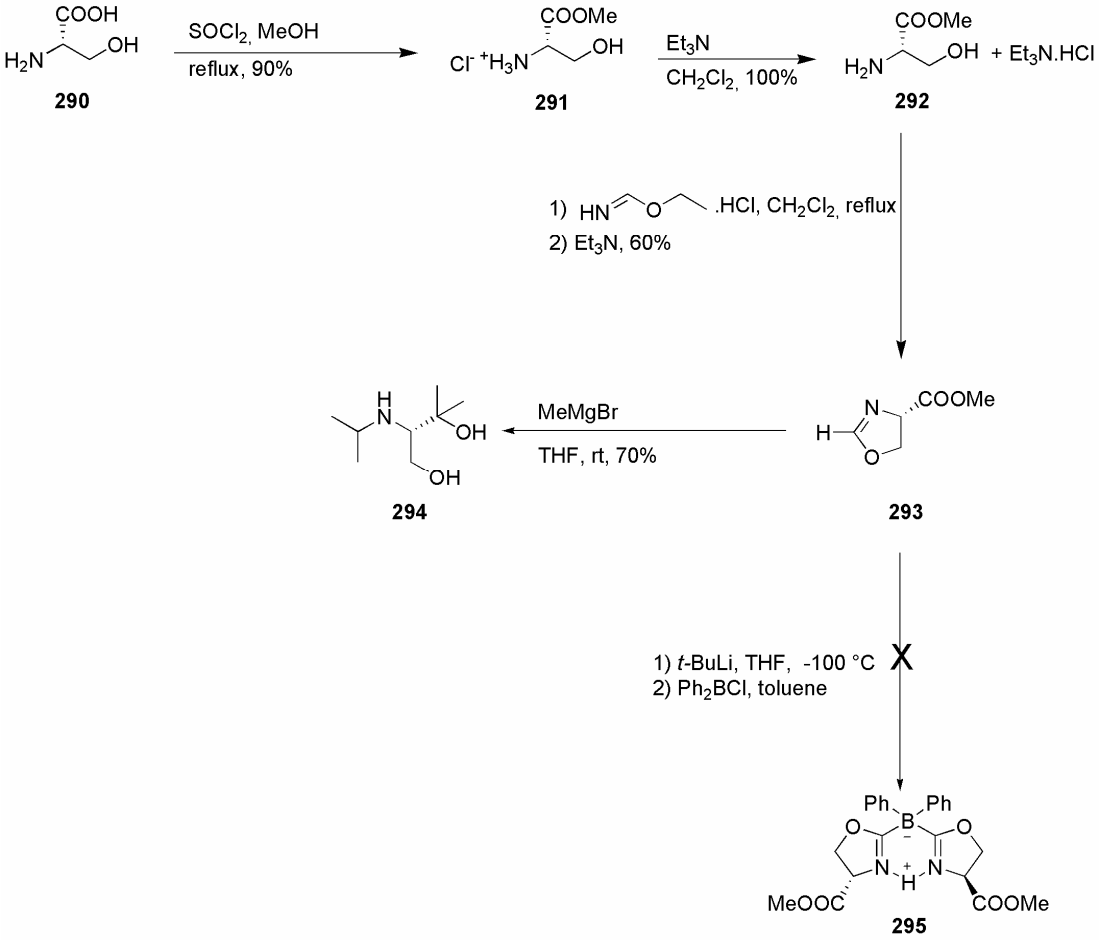
Scheme 98.

6.2.4 Synthesis of Hydroxyl-Substituted Borabox Ligand

In the Pfaltz group, alkyl and aryl substituted oxazoline carrying an alcohol group at the C4 position of the oxazoline moiety have already been synthesized.[195] These compounds were obtained after addition of a *Grignard* reagent to the oxazoline carrying an ester at the C4 position. The same procedure was followed in order to prepare ligand **264**.

Starting from (L)-serine, the methyl ester hydrochloride salt **291** was obtained in high yield (Scheme 99).[192] In order to isolate the free aminoalcohol, one equivalent of triethylamine in dichloromethane was added to the methyl ester hydrochloride salt **291.** A mixture of the free aminoalcohol and Et_3NHCl was obtained but it was not possible to separate them. Indeed the salt is insoluble in dichloromethane and purification by column chromatography did not afford any product. The cyclization was then carried out with the mixture of the free amino

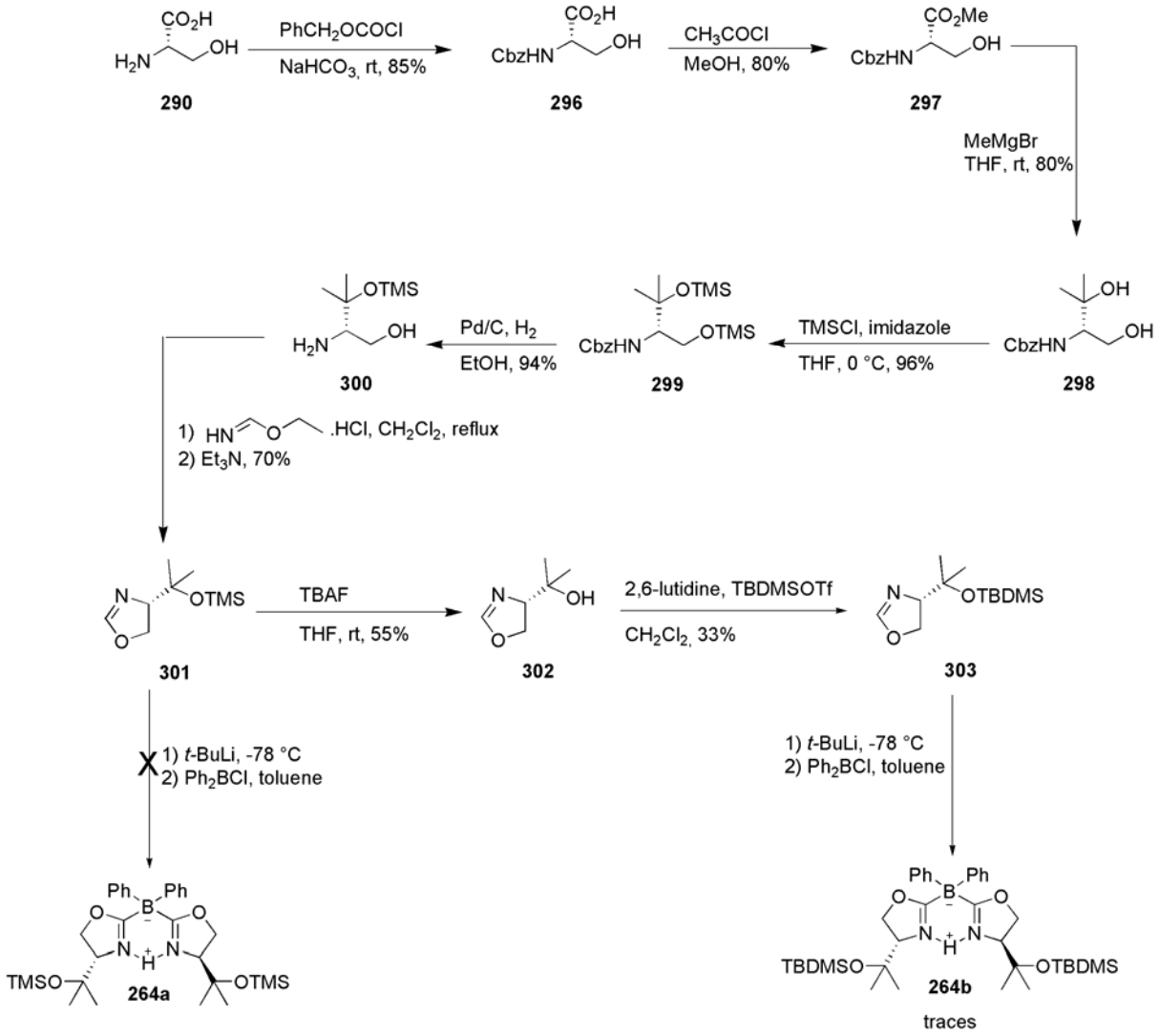
alcohol **292** and Et_3NHCl. In the presence of ethylformimidate hydrochloride, the 2*H*-oxazoline **293** was obtained in 60% yield. Addition of the methyl *Grignard* reagent to **293** did not afford the desired product but the diol **294** in 70% yield. Attempt to directly synthesize the borabox ligand **295** from the compound **293** failed as well.



Scheme 99.

Another route was then investigated. Starting from L-serine (**290**), the amino alcohol **300** was synthesized following a literature procedure.[196] After protection of the amino group of L-serine (**290**), the resulting carbamate **296** was esterified with acetyl chloride to give L-serine ester **297**. Addition of methylmagnesium bromide yielded 1,3-diol **298** which was subsequently protected to give the bis(trimethylsilyloxy) derivative **299**. Removal of the protecting group of the amine by hydrogenolysis afforded compound **300**. With the aminoalcohol in hand, the cyclization into the 2*H*-oxazoline was carried out in the presence of ethyl formimidate hydrochloride, and the desired compound **301** was successfully synthesized

in 70% yield. Attempts to obtain the borabox ligand **264a** unfortunately failed, possibly due to the instability of the TMS ether group. The synthesis of the 2*H*-oxazoline **303** using TBDMS, a more stable protecting group, was then carried out. Deprotection of the alcohol by TBAF followed by the addition of the new protecting group afforded the 2*H*-oxazoline **303**.[197] Unfortunately, the formation of the borabox ligand **264b** following the normal procedure led to only traces of the compound **264b**. Possibly, this is due to a deprotonation at the C4 position of the oxazoline ring, facilitated by the adjacent oxygen atom.



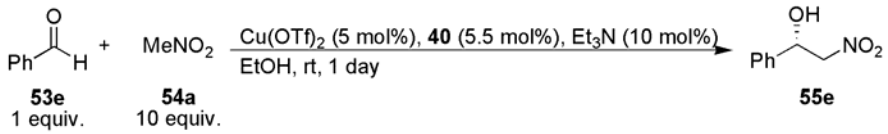
Scheme 100.

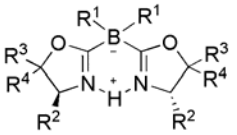
6.2.5 C5-Substituted Borabox Ligands in Asymmetric Henry Reaction

The new ligands **56b-d** were tested in the reaction of benzaldehyde (**53e**) with nitromethane (**54a**) and compared to the anologuous borabox ligands **40a**, **40e** and **40g** (Table 52). The nitroalcohol **55e** was obtained in 91% yield and 14% enantiomeric excess when employing

ligand **56b** (entry 2, Table 52). Compared to the ligand **40a**, a slight increase of yield but no improvement of *ee* were observed (compare entry 1 to 2, Table 52). The reaction catalyzed by ligand **40e** afforded compound **55e** in 37% yield and as a racemate (entry 3, Table 52). With the C5-substituted ligand **56c**, both yield and enantioselectivity could be improved (80% yield and 14% *ee*, entry 4, Table 52). Ligand **40g** is the most efficient ligand in this reaction affording **55e** in 94% yield and 70% *ee* (entry 5, Table 52). Ligand **56d** was expected to improve these results but unfortunately the enantiomeric excess was decreased to 47% *ee* (entry 6, Table 52).

Table 52.





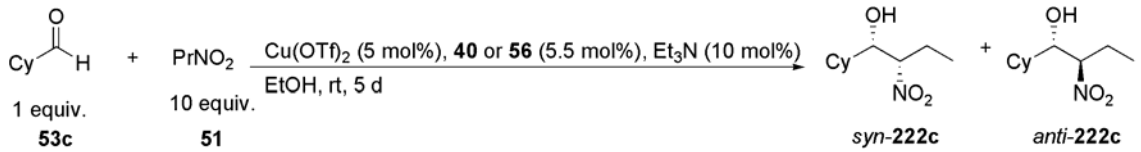
40a: R^1 = Cy; R^2 = *i*-Pr
40e: R^1 = Cy; R^2 = *t*-Bu
40g: R^1 = Ph; R^2 = *t*-Bu
56b: R^1 = Cy; R^2 = *i*-Pr, R^3 = Ph, R^4 = H
56c: R^1 = Cy; R^2 = *t*-Bu, R^3 = Me, R^4 = Me
56d: R^1 = Ph; R^2 = *t*-Bu, R^3 = Me, R^4 = Me

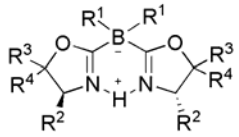
Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	**40a**	78	16 (*S*)
2	**56b**	91	14 (*S*)
3	**40e**	37	1 (*S*)
4	**56c**	80	14 (*S*)
5	**40g**	94	70 (*S*)
6	**56d**	91	47 (*S*)

[a] After column chromatography. [b] Determined by chiral HPLC. The absolute configuration of **55e** was assigned by comparison with literature compound (see ref. 154).

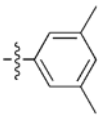
Ligand **56d** and C5-aryl substituted ligands (**56e-g**) were also tested in the reaction of nitropropane (**51**) with cyclohexylcarboxaldehyde (**53c**) (Table 53). In the presence of ligand **56d**, The *syn* nitroalcohol **222c** was synthesized with 84% *ee* which is lower than the enantiomeric excess reached with ligand **40g** (compare entry 1 to 2, Table 53). The C5,C5' disubstituted ligands **56e** and **56f** allowed to improve the selectivities obtained with the ligand **40c** (compare entry 3 to 4 and 5, Table 53). However, the *t*-butyl aryl disubstituted ligand **56g**, in contrast to our expectations, did not deliver compound **222c** with a higher *ee* than ligand **40g**.

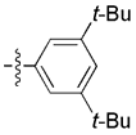
Table 53.





40g: R^1 = Ph; R^2 = *t*-Bu
40c: R^1 = Ph; R^2 = *i*-Pr
56d: R^1 = Cy; R^2 = *t*-Bu, R^3 = Me, R^4 = Me
56e: R^1 = Ph; R^2 = *i*-Pr, R^3 = Ar, R^4 = Ar
56f: R^1 = Ph; R^2 = *i*-Pr, R^3 = Ar', R^4 = Ar'
56g: R^1 = Ph; R^2 = *t*-Bu, R^3 = Ar, R^4 = Ar

Ar = 

Ar' = 

Entry	Ligand	Conversion [%][a]	*syn*:*anti*[a]	*ee* (*syn*) [%][b]
1	**40g**	60	92:08	91 (1*S*, 2*S*)
2	**56d**	54	86:14	84 (1*S*, 2*S*)
3	**40c**	62	74:26	21 (1*S*, 2*S*)
4	**56e**	66	84:16	74 (1*S*, 2*S*)
5	**56f**	52	84:16	82 (1*S*, 2*S*)
6	**56g**	58	75:25	44 (1*S*, 2*S*)

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC. The absolute configuration of *syn*-**222c** was determined by comparison with published HPLC retention times (see ref. 174).

6.3 Conclusion

The C5 substituted ligands **56b-g** were successfully synthesized. The application of the ligands **56e** and **56f** in the Henry reaction allowed an increase of the enantiomeric excess compared to the ligand **40c**. Unfortunately the same trend was not observed for ligand **56g**, and the highest enantioselectivity reached with ligand **40g** could not be improved.

Chapter 7

Boron-Bridged Bis(oxazolines) and their Use in Copper-Catalyzed Asymmetric Reactions

Boron-Bridged Bis(oxazolines) and their Use in Copper-Catalyzed Asymmetric Reactions (*Synopsis*)

Bis(oxazolines) ligands (BOX) **35** have established themselves as privileged chiral ligands for asymmetric catalysis. Boron-based variants of these ligands, borabox **40,** have been developed in the Pfaltz group and were expected to be a valuable addition to the BOX ligands **35** (Figure 46).[25]

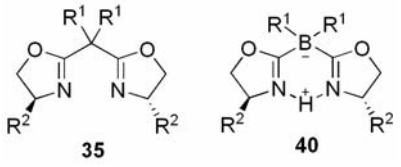
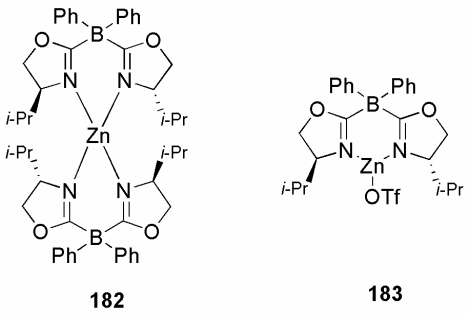


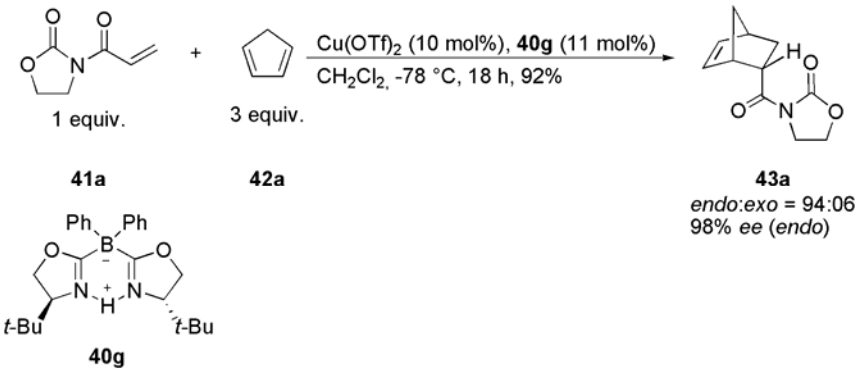
Figure 46.



Applied to Diels-Alder reaction, borabox ligands **40** were found to be selective only in the presence of an equimolar amount of base with respect to the ligand **40**. The addition of base prevents the formation of the unselective homoleptic complex **182** and gives access to the monomeric complex **183** (Figure 47).

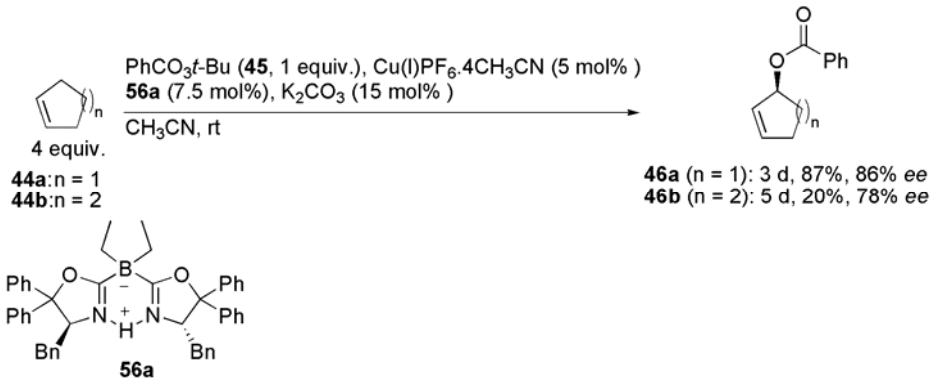
Figure 47.

When the Diels-Alder reaction was catalyzed by the copper complex derived from borabox ligand **40g**, the cycloadduct **43a** was prepared in 98% *ee* for the *endo* isomer and with an *endo*:*exo* ratio of 94:06 (Scheme 101).



Scheme 101.

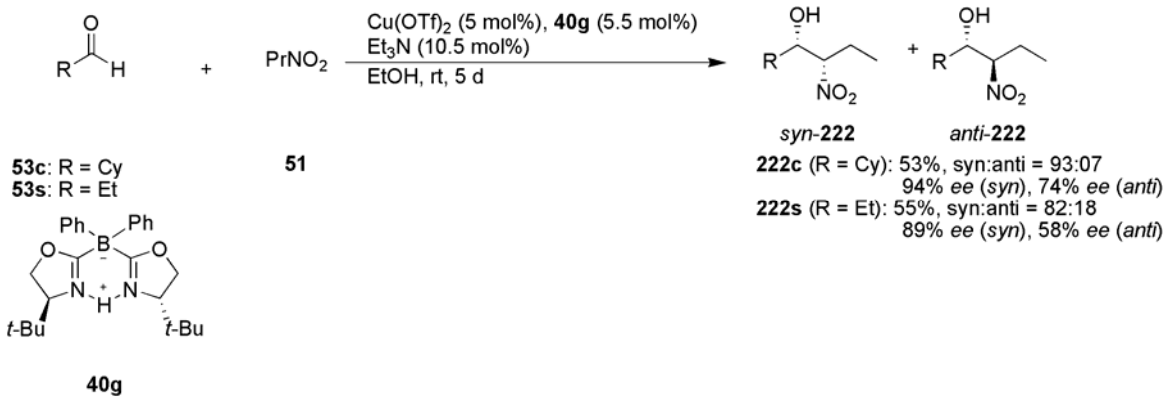
In the allylic oxidation of cyclic olefins, C5-disubstituted borabox ligand **56a** was equal to the privileged ligand **35a** in terms of reactivity and selectivity. Cyclopentene oxide **46a** and cyclohexene oxide **46b** were prepared in 86 and 78% *ee* respectively (Scheme 102).



Scheme 102.

The application of copper complexes derived from borabox ligands **40** to the Henry reaction showed the high potential of these ligands. A general method for the addition of nitropropane (**51**) to various aldehydes had yet to be developed. However, borabox ligand **40g** induced good selectivities for nitroalcohols prepared from aromatic or aliphatic aldehydes and nitropropane (**51**). The syn isomers of nitroalcohols **222c** and **222s** were prepared in 94% and 89% *ee* respectively (Scheme 103).

Scheme 103.



The synthesis of C5,C5'-disubstituted borabox ligands **56** was investigated (Figure 48). The steric bulk of the substituents at the C5 position was expected to orientate the groups at the C4 position towards the coordination sphere giving a better control of the selectivity. The ligands **56** were tested in the reaction of cyclohexanecarboxaldehyde (**53c**) with nitropropane (**51**). Whereas the complexes derived from borabox ligands **56e-f** improved the *ee* obtained with the ligand **40c**, lower selectivity was obtained with **56g** compared to **40f**.

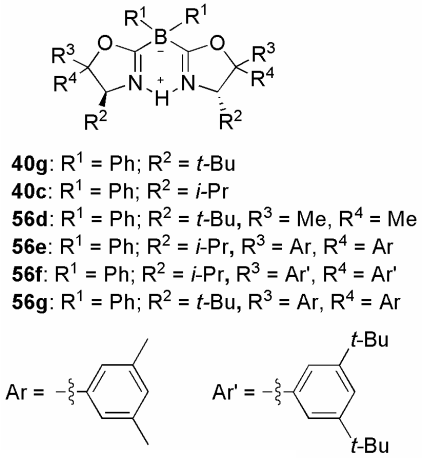


Figure 48.

Chapter 8

Experimental

8 Experimental

8.1 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 $CHCl_3$, 3.35 ppm and 4.78 ppm (^{1}H NMR) and 49.3 ppm (^{13}C NMR) for CH_3OH.[198] $CFCl_3$ and BF_3*OEt_2 were taken as external standards in a capillary respectively for ^{19}F NMR and ^{11}B NMR. The assignment of ^{1}H- and ^{13}C-signals was made by 2D-NMR, namely COSY, HMQC, HMBC and difference NOESY-spectrometry. ^{13}C until otherwise noted, were recorded ^{1}H-decoupled. Multiplets were assigned with s (singlet), d (doublet), t (triplet), ds (doublet of septet), m (multiplet).

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, HRMS spectra were measured by Stefan Schürch from the university of Bern on Sciex Qstar Pulsar. 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).

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.

8.2 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 (Argon).

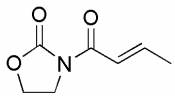
Solvents: Dichloromethane, diethyl ether, pentane, tetrahydrofuran and toluene were dried and degassed by reflux over an adequate drying agent under nitrogen.[199] Other solvents were purchased dry at Fluka or Aldrich in septum sealed bottles, kept under inert atmosphere and over molecular sieves. If 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[200] was performed.

8.3 Diels-Alder Reaction

8.3.1 Synthesis of Dienophiles

3-((*E*)-but-2-enoyl)oxazolidin-2-one (41b)[201]



General procedure I:

To a solution of oxazolidin-2-one (3.00 g, 34.4 mmol) in anhydrous tetrahydrofuran (100 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 21.5 mL, 34.4 mmol). After 15 minutes, freshly distilled crotonoyl chloride (3.60 mL, 37.8 mmol) was added. The mixture was stirred at -78 °C for 30 minutes and at 0 °C for 15 minutes. The reaction was quenched with excess saturated aqueous NH_4Cl and the resultant slurry was concentrated. The residue is diluted with diethyl ether and washed successfully with saturated aqueous sodium bicarbonate and then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (10 x 18 cm, $\mathbf{R_f}$ = 0.25, hexane : EtOAc 2 : 1) on silica to give **41b** as a colorless oil (4.59 g, 86%).

$C_7H_9NO_3$ (155.15 g/mol).

b.p. 115 °C (0.1 mmHg).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.27-7.14 (m, 2H, CH=CH), 4.41 (t, $^3J_{HH}$ = 8.1 Hz, 2H, OCH_2), 4.06 (t, $^3J_{HH}$ = 8.1 Hz, 2H, NCH_2), 1.96 (d, $^3J_{HH}$ = 6.1 Hz, 3H) ppm.

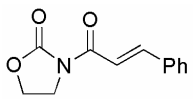
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 165.3 (NC=O), 153.7 (OC=O), 147.0 (CH=*C*HMe), 121.6 (*C*H=CHMe), 62.2 (OCH_2), 42.8 (NCH_2), 18.7 (CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3517m, 3090w, 2983m, 2922m, 1773s, 1686s, 1638s, 1521w, 1478s, 1444s, 1388s, 1292m, 1221s, 1125s, 1042s, 927m, 923m, 828m, 760m, 707m.

Elemental analysis calcd (%) for $C_7H_9NO_3$ (155.15 g/mol): C 54.19, H 5.85, N 9.03; found: C 53.96, H 5.82, N 9.07.

MS (EI, 70 eV): m/z (%) = 155 (15, M^+), 69 (100), 68 (38), 41 (29), 39 (15).

3-((*E*)-3-phenylacryloyl)oxazolidin-2-(41c)[201]



Compound **41c** was prepared according to **general procedure I** from oxazolidin-2-one (3.00 g, 34.4 mmol), *n*-BuLi (1.6 M in hexanes, 21.5 mL, 34.4 mmol) and cinnamoyl chloride (6.30 g, 37.8 mmol). The product was purified by column chromatography (10 x 18 cm**, R_f** = 0.25, hexane : EtOAc 2 : 1) on silica to give **41c** as a colorless solid (6.20 g, 84%).

$C_{12}H_{11}NO_3$ (217.22 g/mol).

m.p. 151-152 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.92 (d, $^3J_{HH}$ = 15.6 Hz, 1H, CH=C*H*Ph), 7.86 (d, $^3J_{HH}$ = 15.7 Hz, 1H, C*H*=CHPh), 7.64-7.61 (m, 2H, H_{Ph}), 7.40-7.38 (m, 3H, H_{Ph}), 4.46 (t, $^3J_{HH}$ = 8.3 Hz, 2H, OCH_2), 4.14 (t, $^3J_{HH}$ = 8.3 Hz, 2H, NCH_2) ppm.

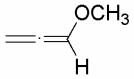
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 165.6 (NC=O), 153.7 (OC=O), 146.5 (CH=*C*HPh), 134.6 (C_{Ph}), 130.8 (CH_{Ph}), 129.0 (2C, CH_{Ph}), 128.5 (2C, CH_{Ph}), 116.7 (*C*H=CHPh), 62.2 (OCH_2), 42.8 (NCH_2) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 2926w, 1765s, 1678s, 1615s, 1480m, 1446w, 1392s, 1353s, 1285w, 1227s, 1106s, 1038s, 866w, 770m, 702m, 624w.

Elemental analysis calcd (%) for $C_{12}H_{11}NO_3$ (217.22 g/mol): C 66.35, H 5.10, N 6.45; found: C 66.14, H 5.15, N 6.23.

MS (EI, 70 eV): m/z (%) = 217 (29, M^+), 131 (100), 103 (28), 77 (13).

3-methoxypropa-1,2-diene (186)



Potassium *t*-butoxide (0.28 g, 2.50 mmol) was added to molecular sieves dried methyl propargyl ether (**185**, 7.00 g, 0.10 mol). The mixture was heated to reflux for 3 hours and then distilled under reduced pressure at room temperature to a dry-ice acetone cooled trap. Redistillation (**b.p.** 50-52 °C) afforded a colorless liquid (6.38 g, 91%).

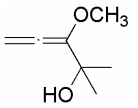
C_4H_6O (70.09 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.76 (t, $^{4}J_{HH}$ = 6.0 Hz, 1H, C*H*OCH_3), 5.48 (d, $^{4}J_{HH}$ = 5.8 Hz, 2H, CH_2), 3.41 (s, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 123.0 (CH_2=*C*=CH), 91.5 (*C*H_2=C=CH), 56.1 (CH_2=C=*C*H), 31.1 (OCH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3045w, 3004m, 2959s, 2832m, 2122w, 1945s, 1460s, 1351s, 1259s, 1219s, 1170s, 1050s, 889s, 860s, 799s, 668s.

2-methyl-3-methoxy-3,4-pentadien-2-ol (187)



To a solution of 3-methoxypropa-1,2-diene (**186**, 3.50 g, 50.0 mmol) in dry diethyl ether (100 mL) at -40 °C, *n*-BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol) was added under nitrogen and the reaction was stirred at -40 °C for 10 minutes. Then, acetone (4.04 mL, 55.0 mmol) in dry diethyl ether (55 mL) was added within 5 minutes. The reaction was stirred at the same temperature for 30 minutes and quenched with water (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 2-methyl-3-methoxy-3,4-pentadien-2-ol (**187**) as a yellow liquid (5.65 g, 82%) that was employed in the next step without further purification.

$C_7H_{12}O_2$ (128.17 g/mol).

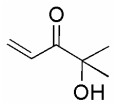
^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 5.55 (s, 2H, CH_2), 3.45 (s, 3H, OCH_3), 2.23 (s, 1H, OH), 1.20 (s, 6H, $C(CH_3)_2$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 195.6 (*C*OCH_3), 139.7 (CH_2=*C*=C), 92.9 (*C*H_2=C=C), 70.5 (COH), 56.7 (OCH_3), 27.9 (2C, $C(CH_3)_2$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3424s_{br}, 2978s, 2833m, 1953m, 1459s, 1367s, 1288m, 1232s, 1172s, 1124s, 1014m, 949m, 889m, 849w, 702w.

Elemental analysis calcd (%) for $C_7H_{12}O_2$ (128.17 g/mol): C 65.60, H 9.44, N 0.00; found: C 64.88, H 9.70, N <0.3.

4-hydroxy-4-methylpent-1-en-3-one (86d)

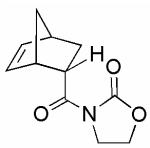


2-methyl-3-methoxy-3,4-pentadien-2-ol (**187**, 5.65 g, 44.0 mmol) was added dropwise to 5% aqueous H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 hours. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with diethyl ether (5 x 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation (**b.p.** 45 °C at 13 mmHg) afforded the enone as a colorless liquid (4.42 g, 88%).

$C_6H_{10}O_2$ (114.14 g/mol).
^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.74 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 10.4 Hz, 1H, C*H*H=CH), 6.53 (dd, $^2J_{HH}$ = 16.9 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CH*H*=CH), 5.85 (dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CHH=C*H*), 3.85 (s, 1H, OH), 1.40 (s, 6H, $C(CH_3)_2$) ppm.
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 202.6 (C=O), 131.4 (CH_2=CH), 129.0 (CH_2=*C*H), 75.5 (COH), 26.2 (2C, CH_3) ppm.
IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3455s, 2979s, 2935m, 2875w, 1697s, 1612s, 1463m, 1403s, 1370s, 1248s, 1170s, 1054s, 971s, 849w, 793w, 735w.
Elemental analysis calcd (%) for $C_6H_{10}O_2$ (114.14 g/mol): C 63.14, H 8.83, N 0.00; found: C 62.77, H 8.80, N 0.00.
MS (EI, 70 eV): m/z (%) = 114 (1, M^+), 59 (100), 56 (20), 43 (20), 41 (13).

8.3.2 Synthesis of Diels-Alder Adducts

***endo* 3-[(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-2-oxazolidinone (43a)**



General Procedure II:

Copper (II) triflate (18.0 mg, 0.05 mmol), ligand **40f** (17.7 mg, 0.055 mmol) and potassium carbonate (7.60 mg, 0.055 mmol) were combined in an inert atmosphere dry box. The sealed flask was then connected to an argon line. Anhydrous dichloromethane (1.5 mL) was added, whereupon a green solution was formed within 5 minutes. The solution was stirred overnight and then cooled down to -78 °C. 3-(2-Propenoyl)-2-oxazolidinone (**41a**, 71.0 mg, 0.50 mmol) was then added as a solution in 0.5 mL of dichloromethane *via* cannula. Immediately thereafter, cyclopentadiene (**42a**, 125 µL, 1.50 mmol) was added *via* syringue. After stirring 18 hours at -78 °C, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm, $\mathbf{R_f}$ = 0.23, hexane : EtOAc 2 : 1) on silica to give a colorless solid (95 mg, 92%).

$C_{11}H_{13}NO_3$ (207.23 g/mol).

m.p. 70-71 °C.

$[\alpha]_D^{20}$ = -158.5 (*c* = 0.23, $CHCl_3$, 98% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.22 (dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, CH=C*H*), 5.86 (dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 2.5 Hz, 1H, C*H*=CH), 4.43-4.34 (m, 2H, OCH_2), 4.02-3.89 (m, 3H, NCH_2 + CHC=O), 3.29 (brs, 1H, C*H*CH=CH), 2.92 (brs, 1H, C*H*CH=CH), 1.95 (ddd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, CHC*H*HCH), 1.48-1.37 (m, 3H, CHC*H*HCH + CH_2CHC=O) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 174.9 (NC=O), 153.5 (OC=O), 138.2 (*C*H=CH), 131.7 (CH=*C*H), 62.1 (OCH_2), 50.3 (*C*H_2CHC=O), 46.5 (*C*HCH=CH), 43.3 (*C*HCH=CH), 43.1 (NCH_2), 43.0 (*C*HC=O), 29.7 (CH*C*H_2CH) ppm.

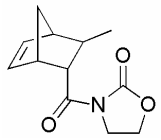
HPLC: OD-H, *n*-heptan : *i*-PrOH (95 : 05), 0.5 mL/min, 20 °C, 207 nm, t_R = 61.7 min (major), 69.4 min (minor).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3510w, 3449w, 3070w, 2980m, 2941m, 2875m, 1763s, 1689s, 1486m, 1387s, 1280m, 1215s, 1113s, 1038s, 1005m, 930w, 859w, 837w, 802w, 762m, 701s, 673m.

Elemental analysis calcd (%) for $C_{11}H_{13}NO_3$ (207.23 g/mol): C 63.76, H 6.32, N 6.76; found: C 63.64, H 6.34, N 6.83.

MS (EI, 70 eV): m/z (%) = 207 (11, M^+), 142 (63), 120 (23), 91 (16), 66 (100), 55 (28).

endo **3-[[(1*S*,2*S*,3*R*,4*R*)-3-Methylbicyclo[2.2.1]hept-5-en-2-yl]carbonyl]-2-oxazolidinone (43b)**



Product **43b** was prepared according to **general procedure II** from 3-((*E*)-but-2-enoyl)oxazolidin-2-one (**41b**, 77.0 mg, 0.50 mmol) and cyclopentadiene (**42a**, 625 µL, 5.00 mmol). After stirring 3 days at -15 °C, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.24, hexane : EtOAc 2 : 1) on silica to give a colorless solid (99 mg, 90%).

$C_{12}H_{15}NO_3$ (221.25 g/mol).

m.p. 88-89 °C.

$[\alpha]_D^{20}$ = -75 (*c* = 0.43, $CHCl_3$, 40% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.37 (dd, $^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, CH=C*H*), 5.78 (dd, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C*H*=CH), 4.40 (t, $^3J_{HH}$ = 7.8 Hz, 2H, OCH_2), 4.06-3.89 (m, 2H, NCH_2), 3.53 (dd, $^3J_{HH}$ = 4.0 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, CHC=O), 3.28 (brs, 1H, C*H*CH=CH), 2.53 (brs, 1H, C*H*CH=CH), 2.12-2.05 (m, 1H, C*H*Me), 1.70 (brd, $^3J_{HH}$ = 8.6 Hz, 1H, CHC*H*HCH), 1.46 (dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CHCH*H*CH), 1.12 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 174.9 (NC=O), 153.9 (OC=O), 140.1 (*C*H=CH), 131.3 (CH=*C*H), 62.3 (OCH_2), 51.7 (*C*HC=O), 49.9 (*C*HCH=CH), 47.9 ($CHCH_2CH$), 47.5 (CH=CH*C*H), 43.4 (NCH_2), 36.9 (*C*HMe), 20.8 (CH_3) ppm.

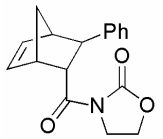
HPLC: AD-H, *n*-heptan : EtOH (90 : 10), 0.5 mL/min, 20 °C, 207 nm, t_R = 26.6 min (major), 35.2 min (minor).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3520w, 3058w, 975s, 2873m, 1769s, 1691s, 1486w, 1460w, 1381s, 1331m, 1293m, 1218s, 1119s, 1081m, 1035s, 96w, 898w, 834w, 803w, 761m, 699s, 606w.

HRMS (ESI^+): Exact Mass calcd for $C_{12}H_{15}NO_3Na$ $[M+Na]^+$, 244.0950. Found 244.0954.

MS (FAB, NBA): m/z (%) = 222 (59, $[M+H^+]$), 156 (100), 137 (11), 135 (24), 91 (11), 88 (11), 79 (11), 77 (11), 69 (73), 66 (20).

endo **3-[[(1*S*,2*R*,3*R*,4*R*)-3-Phenylbicyclo[2.2.1]hept-5-en-2-yl]carbonyl]-2-oxazolidinone (43c)**



Product **43c** was prepared according to **general procedure II** from 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one (**41c**, 109 mg, 0.50 mmol) and cyclopentadiene (**42a**, 625 µL, 5.00 mmol). After stirring 7 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.23, hexane : EtOAc 2 : 1) on silica to give a colorless solid (123 mg, 87%).

$C_{17}H_{17}NO_3$ (283.32 g/mol).

m.p. 95-96 °C.

$[\alpha]_D^{20}$ = -83.5 (*c* = 0.87, $CHCl_3$, 49% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.30-7.35 (m, 3H, H_{Ph}), 7.24-7.13 (m, 2H, H_{Ph}), 6.52 (dd, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*=CH), 5.91 (dd, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 2.5 Hz, 1H, CH=C*H*), 4.43-4.33 (m, 2H, OCH_2), 4.18 (dd, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, CHC=O), 4.04-3.92 (m, 2H, NCH_2), 3.46 (brs, 1H, C*H*CH=CH), 3.34 (dd, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CHPh), 2.99 (brs, 1H, C*H*CH=CH), 1.94 (brd, $^3J_{HH}$ = 8.6 Hz, 1H, CHC*H*HCH), 1.56 (brd, $^3J_{HH}$ = 7.3 Hz, 1H, CHCH*H*CH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 174.1 (NC=O), 153.5 (OC=O), 143.9 (C_{Ph}), 140.3 (*C*H=CH), 132.3 (CH=*C*H), 128.6 (2C, CH_{Ph}), 127.8 (2C, CH_{Ph}), 126.3 (CH_{Ph}), 62.1 (OCH_2), 50.4 (*C*HC=O), 49.9 (*C*HCH=CH), 48.3 (CH*C*H_2CH), 47.6 (CH=CH*C*H), 46.9 (CHPh), 43.2 (NCH_2) ppm.

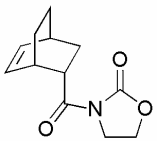
HPLC: AD-H, *n*-heptan : *i*-PrOH (80 : 20), 0.5 mL/min, 20 °C, 215 nm, t_R = 16.4 min (minor), 29.9 min (major).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3510m_{br}, 3059s, 2978s, 1767s, 1692s, 1620s, 1483s, 1452s, 1385s, 1222s, 1114s, 1035s, 918m, 874m, 801w, 757s, 700s.

Elemental analysis calcd (%) for $C_{17}H_{17}NO_3$ (283.33 g/mol): C 72.07, H 6.05, N 4.94; found: C 71.53, H 6.00, N 4.68.

MS (FAB, NBA): m/z (%) = 284 (31, [M+H$^+$]), 219 (14), 218 (100), 217 (11), 197 (19), 132 (10), 131 (88), 115 (12), 103 (11), 91 (25), 90 (11), 89 (19), 78 (11), 77 (26), 66 (36), 65 (15), 63 (12), 51 (15), 39 (22).

***endo* 3-[(1*S*, 2*S*, 4*S*)-Bicyclo[2.2.2]oct-5-en-2-ylcarbonyl]-2-oxazolidinone (158a)**



General procedure III:

Copper (II) triflate (18.0 mg, 0.05 mmol), ligand **40f** (17.7 mg, 0.055 mmol) and potassium carbonate (7.60 mg, 0.055 mmol) were combined in an inert atmosphere dry box. The sealed flask was then connected to an argon line. Anhydrous dichoromethane (1.5 mL) was added, whereupon a green solution was formed within 5 minutes. The solution was stirred overnight. To a solution of 3-(2-propenoyl)-2-oxazolidinone (**41a**, 71.0 mg, 0.50 mmol) in dichoromethane was added cyclohexadiene (**42b**, 477 µL, 5.00 mmol) and the solution was immediately cooled to -78 °C. The catalyst solution was added dropwise *via* syringue, down the side of the flask. The flask was then allowed to warm up at room temperature. After stirring 40 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.38, hexane : EtOAc 3 : 1) on silica to give a colorless solid (104 mg, 94%).

$C_{12}H_{15}NO_3$ (221.25 g/mol).

m.p. 49-50 °C.

$[\alpha]_D^{20}$ = -23 (*c* = 0.10, $CHCl_3$, 39% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.35 (t, $^3J_{HH}$ = 7.6 Hz, 1H, CH=C*H*), 6.16 (t, $^3J_{HH}$ = 7.3 Hz, 1H, CH=C*H*), 4.41-4.36 (m, 2H, OCH_2), 3.97 (t, $^3J_{HH}$ = 7.8 Hz, 2H, NCH_2), 3.76 (ddd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CHC=O), 2.83 (brd, $^3J_{HH}$ = 4.3 Hz, 1H, C*H*CH=CH), 2.62 (brt, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*CH=CH), 1.88-1.25 (m, 6H, CH_2CHC=O + CHCH_2CH_2CH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 175.8 (NC=O), 153.4 (OC=O), 135.1 (*C*H=CH), 131.5 (CH=*C*H), 62.0 (OCH_2), 43.1 (NCH_2), 42.2 (*C*HCH=CH), 32.9 (*C*HCH=CH), 30.3 (*C*H_2CHC=O), 29.6 (*C*HC=O), 25.8 (CH*C*H_2CH_2CH), 24.1 (CHCH_2*C*H_2CH) ppm.

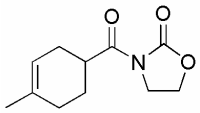
HPLC: AD-H, *n*-heptan : *i*-PrOH (95 : 05), 0.9 mL/min, 20 °C, 210 nm, t_R = 21.7 min (minor), 23.6 min (major).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3378w, 3044w, 2943s, 2867m, 1775s, 1697s, 1589w, 1552w, 1749m, 1384s, 1333m, 1256s, 1217s, 1111s, 1043s, 987w, 942w, 874w, 809w, 760m, 694s.

Elemental analysis calcd (%) for $C_{12}H_{15}NO_3$ (221.25 g/mol): C 65.14, H 6.83, N 6.33; found: C 65.07, H 6.84, N 6.28.

MS (EI, 70 eV): m/z (%) = 221 (30, M^+), 193 (22), 142 (56), 134 (20), 106 (28), 105 (21), 91 (11), 88 (29), 80 (100), 79 (50), 78 (20), 77 (21), 55 (14).

3-[(1*S*)-4-Methylcyclohex-3-en-1-ylcarbonyl]-2-oxazolidinone (160a)



Product **160a** was prepared according to **general procedure III** from 3-(2-propenoyl)-2-oxazolidinone (**41a**, 71.0 mg, 0.50 mmol) and isoprene (**159a**, 500 µL, 5.00 mmol). After stirring 24 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.25, hexane : EtOAc 3 : 1) on silica to give a colorless oil (101 mg, 97%).

$C_{11}H_{15}NO_3$ (209.24 g/mol).

$[\alpha]_D^{20}$ = -21 (*c* = 0.12, $CHCl_3$, 61% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 5.39 (brs, 1H, C*H*=C), 4.41 (t, $^3J_{HH}$ = 8.1 Hz, 3H, OCH_2), 4.02 (t, $^3J_{HH}$ = 8.1 Hz, 3H, NCH_2), 3.70-3.62 (m, 1H, CHC=O), 2.24-1.94 (m, 6H, H_{Cycle}), 1.66 (s, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 176.7 (NC=O), 153.3 (OC=O), 133.7 (*C*=CH), 119.1 (C=*C*H), 60.4 (NCH_2), 42.9 (OCH_2), 38.3 (*C*HC=O), 29.6 ($CH_{2\ cycle}$), 27.5 ($CH_{2\ cycle}$), 26.0 ($CH_{2\ cycle}$), 14.2 (CH_3) ppm.

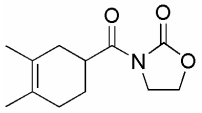
HPLC: OJ, *n*-heptan : *i*-PrOH (97 : 03), 1 mL/min, 20 °C, 220 nm, t_R = 48.6 min (minor), 52.7 min (major).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] =2983m, 1781s, 1739s, 1445m, 1377s, 1244s, 1105m, 1047s, 1105m, 1047s, 932w, 848w, 789w, 762w, 705w.

Elemental analysis calcd (%) for $C_{11}H_{15}NO_3$ (209.24 g/mol): C 63.14, H 7.23, N 6.69; found: C 73.21, H 7.33, N 6.90.

MS (EI, 70 eV): m/z (%) = 209 (44, M^+), 122 (72), 107 (12), 95 (35), 94 (100), 88 (67), 79 (56), 77 (14), 67 (11).

3-[(1*S*)-3,4-Methylcyclohex-3-en-1-ylcarbonyl]-2-oxazolidinone (160b)



Product **160b** was prepared according to **general procedure III** from 3-(2-propenoyl)-2-oxazolidinone (**41a**, 71.0 mg, 0.50 mmol) and 2,3-dimethyl-1,3-butadiene (**159b**, 566 µL, 5.00 mmol). After stirring 16 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.31, hexane : EtOAc 3 : 1) on silica to give a colorless oil (95 mg, 85%).

$C_{12}H_{17}NO_3$ (223.27 g/mol).

$[\alpha]_D^{20}$ = -14 (*c* = 0.58, $CHCl_3$, 35% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.38 (t, $^3J_{HH}$ = 7.8 Hz, 2H, OCH_2), 3.99 (t, $^3J_{HH}$ = 7.8 Hz, 3H, NCH_2), 3.70-3.62 (m, 1H, CHC=O), 2.26-2.05 (m, 4H, H_{Cy}), 1.95-1.85 (m, 2H, H_{Cy}), 1.61 (s, 6H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 176.8 (NC=O), 153.2 (OC=O), 125.4 (*C*=C), 123.9 (C=*C*), 62.0 (NCH_2), 42.9 (OCH_2), 39.2 (*C*HC=O), 33.6 ($CH_{2\ cycle}$), 31.3 ($CH_{2\ cycle}$), 26.3 ($CH_{2\ cycle}$), 19.1 (CH_3), 19.0 (CH_3) ppm.

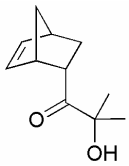
HPLC: AD-H, *n*-heptan : *i*-PrOH (97 : 03), 0.6 mL/min, 20 °C, 210 nm, t_R = 37.8 min (major), 44.6 min (minor).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] =3547w, 3463w, 2984s, 1885w, 1781s, 1742s, 1446s, 1374s, 1242s, 1102s, 1047s, 935m, 847m, 773w, 708w, 633m, 608m.

Elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.27 g/mol): C 64.55, H 7.67, N 6.27; found: C 64.76, H 7.83, N 6.64.

MS (EI, 70 eV): m/z (%) = 223 (36, M^+), 137 (12), 136 (100), 121 (11), 109 (27), 108 (96), 93 (70), 91 (16), 88 (26), 67 (12), 41 (11).

(1*S*, 2*S*, 4*S*)-2-(2-hydroxy-2methylpropanoyl)bicyclo[2.2.1]hept-5-ene (171a)



Product **171a** was prepared according to **general procedure II** from 4-hydroxy-4-methylpent-1-en-3-one (**86d**, 57.0 mg, 0.50 mmol) and cyclopentadiene (**42a**, 416 µL, 5.00 mmol). The reaction was stirred at -78 °C for 1 day and the volatile compounds were then removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.11, pentane : EtOAc 30 : 1) on silica to give a colorless oil (86 mg, 95%).

$C_{11}H_{16}O_2$ (180.24 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.25 (dd, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, CH=C*H*), 5.81 (dd, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 2.8 Hz 1H, CH=C*H*), 3.71 (brs, 1H, OH), 3.37 (ddd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, CHC=O), 3.18 (brs, 1H, C*H*CH=CH), 2.95 (brs, 1H, C*H*CH=CH), 1.86 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, CHC*H*HCH), 1.44 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.38-1.33 (m, 3H, CH_2CHC=O + CHCH*H*CH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 215.8 (C=O), 137.8 (*C*H=CH), 131.2 (CH=*C*H), 76.5 (COH), 50.7 (CH*C*H_2CH), 47.8 (*C*HCH=CH), 44.2 (CH=CH*C*H), 43.2 (*C*HC=O), 31.1 (*C*H_2CHC=O), 27.1 (CH_3), 26.7 (CH_3) ppm.

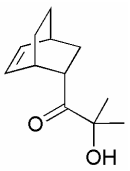
HPLC: OD-H, *n*-heptan : *i*-PrOH (100 : 00), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.2 min (major), 20.6 min (minor).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] =3472s, 3062w, 2975s, 2891w, 2870m, 1699s, 1571w, 1463m, 1340s, 1274w, 1167s, 1083s, 1041w, 1010w, 968m, 914s, 837w, 810w, 731s, 645m.

HRMS (ESI^+): Exact Mass calcd for $C_{11}H_{16}O_2Na$ $[M+Na]^+$, 203.1048. Found 203.1048.

MS (EI, 70 eV): m/z (%) = 180 (1, M^+), 122 (46), 93 (12), 79 (11), 66 (57), 59 (100), 55 (34).

(1*S*, 2*S*, 4*S*)-2-(2-hydroxy-2methylpropanoyl)bicyclo[2.2.2]oct-5-ene (171b)



Product **171b** was prepared according to **general procedure II** from 4-hydroxy-4-methylpent-1-en-3-one (**86d**, 57.0 mg, 0.50 mmol) and cyclohexadiene (**42b**, 477 µL, 5.00 mmol). The reaction was stirred at room temperature during 1 day and the volatile compounds were then removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.13, pentane : EtOAc 30 : 1) on silica to give a colorless oil (88 mg, 90%).

$C_{12}H_{20}O_2$ (196.29 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.33 (t, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*=CH), 6.16 (t, $^3J_{HH}$ = 6.8 Hz, 1H, CH=C*H*), 3.69 (brs, 1H, OH), 3.08 (ddd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 1.7 Hz, 1H, CHC=O), 2.68-2.65 (m, 1H, C*H*CH=CH), 2.64-2.61 (m, 1H, C*H*CH=CH), 1.79-1.72 (m, 2H, CHCH_2CH$_2$CH), 1.58-1.47 (m, 4H, CHCH$_2$CH_2CH + CH_2CHC=O), 1.41 (s, 3H, CH_3), 1.33 (s, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 216.5 (C=O), 134.4 (*C*H=CH), 131.5 (CH=*C*H), 76.5 (COH), 43.6 (*C*HC=O), 32.7 (*C*HCH=CH), 32.6 (CH*C*H$_2$CH$_2$CH), 29.6 (*C*HCH=CH), 26.8 (CH_3), 26.6 (CHCH$_2$*C*H$_2$CH), 26.5 (CH_3), 23.5 (*C*H$_2$CHC=O) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (99 : 01), 0.7 mL/min, 20 °C, 210 nm, t_R = 10.8 min (minor *exo*), 11.5 min (major *exo*), 12.3 min (minor *endo*), 12.9 min (major *endo*).

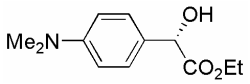
IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] =3490m, 3046w, 2942s, 2886m, 2868s, 1738s, 1450m, 1372s, 1244s, 1164m, 1047s, 966m, 848w, 792w, 733m, 701m, 633m.

Elemental analysis calcd (%) for $C_{12}H_{18}O_2$ (194.27 g/mol): C 74.19, H 9.34, N 0.00; found: C 74.28, H 9.60, N 0.00.

MS (FAB, NBA): m/z (%) = 195 (43, [M+H$^+$]), 177 (29), 161 (17), 159 (17), 137 (16), 136 (17), 107 (18), 97 (29), 93 (20), 91 (52), 89 (19), 81 (100), 80 (31), 79 (86), 78 (18), 77 (39), 67 (37), 65 (20), 59 (67), 43 (21), 41 ’28), 39 (31).

8.4 Friedel-Crafts Reaction

(*S*)-(4-Dimethylamino-phenyl)-2-hydroxy-acetic acid ethyl ester (49a)



To a flame dried Schlenk tube was added copper (II) triflate (18.1 mg, 0.05 mmol), ligand **40g** (23.0 mg, 0.055 mmol) and triethylamine (7.60 µL, 0.055 mmol). The mixture was dried under vacuum for 1-2 hours and freshly distilled anhydrous tetrahydrofuran (2.0 mL) was added and the solution was stirred for 0.5-1 hours. Freshly distilled ethyl glyoxylate (**48**, 255 mg, 2.50 mmol) and *N*,*N*-dimethylamine (**47a**, 33 µL, 0.50 mmol) were added. After stirring 4 days at 0 °C, the reaction mixture was filtered through a pad of silica with diethyl ether, concentrated in vacuo. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.10, petrolether : Et_2O 3 : 1) on silica to give a colorless solid (107 mg, 96%).

$C_{12}H_{17}NO_3$ (223.27 g/mol).

m.p. 101-103 °C.

$[\alpha]_D^{20}$ = +48.5 (*c* = 0.31, $CHCl_3$, 61% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.25 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 6.70 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 5.01 (s, 1H, C*H*OH), 4.26 (dq, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, C*H*HCH$_3$), 4.15 (dq, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, CH*H*CH$_3$), 2.95 (s, 6H, N(CH$_3$)$_2$), 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH$_2$C*H*$_3$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295K): δ = 174.6 (C=O), 151.0 (C_{Ar}), 128.0 (2C, CH_{Ar}), 126.6 (C_{Ar}), 112.8 (2C, CH_{Ar}), 73.1 (C*H*OH), 62.3 (O*C*H$_2$CH$_3$), 40.9 (2C, N(CH$_3$)$_2$), 14.5 (OCH$_2$*C*H$_3$) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (95:05), 0.9 mL/min, 20 °C, 255 nm, t_R = 18.3 min (major), 28.5 min (minor).

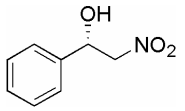
IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3445m, 2962m, 2807w, 2676w, 1732s, 1646w, 1615m, 1524m, 1464w, 1357m, 1272m, 1189s,1078m, 1016m, 942w, 862w, 802m, 772w, 706w, 673w, 573m, 523m.

Elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.27 g/mol): C 64.55, H 7.67, N 6.27; found: C 64.15, H 7.55, N 5.95.

MS (EI, 70 eV): m/z (%) = 223 (15, M^+), 151 (10), 150 (100).

8.5 Henry Reaction

(*S*)-1-phenyl-2-nitroethanol (55e)



General procedure IV:

Ligand **40f** (11.5 mg, 0.027 mmol), copper (II) triflate (9.00 mg, 0.025 mmol) and triethylamine (3.80 µL, 0.027 mmol) were added to a dry young tube containing a stir bar. Ethanol (0.8 mL) was added and the mixture was stirred for 3 to 5 hours. To the resulting dark green solution, nitromethane (**54a**, 0.27 mL, 5.00 mmol), benzaldehyde (**53e**, 50 µL, 0.50 mmol) and triethylamine (3 µL, 0.022 mmol) were added. After stirring 24 hours, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.28, CH_2Cl_2 : Et_2O 10 : 1) on silica to give a colorless oil (78 mg, 94%).

$C_8H_9NO_3$ (167.16 g/mol).

$[\alpha]_D^{20}$ = +13.5 (*c* = 0.68, $CHCl_3$, 70% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.42-7.36 (m, 5H, H_{Ph}), 5.47 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 2.3 Hz, 1H, C*H*OH), 4.62 (dd, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, CH*H*NO_2), 4.52 (dd, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, C*H*HNO_2), 2.80 (br s, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 138.2 (C_{Ph}), 129.2 (2C, CH_{Ph}), 129.1 (CH_{Ph}), 126.1 (2C, CH_{Ph}), 81.3 (CH_2NO_2), 71.1 (CHOH) ppm.

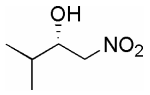
HPLC: OD-H, *n*-heptan : *i*-PrOH (85:15), 0.8 mL/min, 20 °C, 215 nm, t_R = 13.5 min (*R*), 16.1 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3420w_{br}, 3027m, 2973s, 2930s, 1688w, 1603w, 1521m, 1496w, 1452m, 1376m, 1339m, 1126s, 818w, 745m.

Elemental analysis calcd (%) for $C_8H_9NO_3$ (167.16 g/mol): C 57.48, H 5.43, N 8.38; found: C 57.27, H 5.57, N 8.19.

MS (FAB, NBA): m/z (%) = 168 (1, [M+H^+]), 150 (36), 138 (10), 137 (26), 121 (10), 120 (18), 104 (46), 91 (17), 77 (24), 39 (100).

(*S*)-3-Methyl-1-nitrobutan-2-ol (55b)



Product **55b** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), isobutyraldehyde (**53b**, 46 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.28, hexane : EtOAc 6 : 1) on silica to give a colorless oil (83% conversion).

$C_5H_{11}NO_3$ (133.15 g/mol).

$[\alpha]_D^{20}$ = +16 (*c* = 0.17, $CHCl_3$, 56% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.47 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 2.7 Hz, 1H, CH*H*NO_2), 4.41 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, C*H*HNO_2), 4.12-4.09 (m, 1H, CHOH), 2.46 (s, 1H, OH), 1.80 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 1.0 Hz, 1H, C*H*$(CH_3)_2$), 1.00 (app t, $^3J_{HH}$ = 6.9 Hz, 6H, CH_3) ppm.

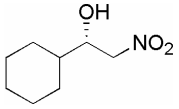
^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$, 295 K): δ = 79.3 (CH_2NO_2), 73.3 (CHOH), 31.7 (*C*H$(CH_3)_2$), 18.4 (CH_3), 17.5 (CH_3) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (98:02), 0.6 mL/min, 20 °C, 215 nm, t_R = 33.3 min (*R*), 37.3 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3450m, 2967s, 2935m, 2878m, 1724m, 1558s, 1417m, 1427m, 1382s, 1256m, 1139w, 1070m, 1047m, 1019w, 887w, 718w.

Elemental analysis calcd (%) for $C_5H_{11}NO_3$ (133.15 g/mol): C 45.10, H 8.33, N 10.52; found: C 44.78, H 8.14, N 10.40.

(*S*)-1-cyclohexyl-2-nitroethanol (55c)



Product **55c** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), cyclohexanecarboxaldehyde (**53c**, 60 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The

crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.07, hexane : EtOAc 6 : 1) on silica to give a colorless oil (93% conversion).

$C_8H_{15}NO_3$ (173.21 g/mol).

$[\alpha]_D^{20}$ = +9.8 (*c* = 0.49, $CHCl_3$, 81% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.48 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, CH*H*NO_2), 4.42 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.0Hz, 1H, C*H*HNO_2), 4.11-4.09 (m, 1H, C*H*OH), 2.46 (s, 1H, OH), 1.86-1.76 (m, 3H, H_{Cy}), 1.71-1.62 (m, 2H, H_{Cy}), 1.52-1.43 (m, 1H, H_{Cy}), 1.30-1.03 (m, 5H, H_{Cy}) ppm.

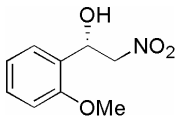
^{13}C{^{1}H} NMR (125.0 MHz, $CDCl_3$, 295 K): δ = 79.3 (CH_2NO_2), 72.8 (CHOH), 41.4 (CH_{Cy}), 28.8 (CH_{2Cy}), 27.9 (CH_{2Cy}), 26.1 (CH_{2Cy}), 25.9 (CH_{2Cy}), 25.7 (CH_{2Cy}) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (97:03), 0.8 mL/min, 20 °C, 215 nm, t_R = 28.0 min (*R*), 30.5 (*S*) min.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3417m_{br}, 2928s, 2855s, 1554s, 1449m, 1382m, 1273w, 1206w, 1108w, 1064w, 964w, 893w.

Elemental analysis calcd (%) for $C_8H_{15}NO_3$ (173.21 g/mol): C 55.47, H 8.73, N 8.09; found: C 55.60, H 8.74, N 8.11.

(*S*)-1-(2-Methoxyphenyl)-2-nitroethanol (55g)



Product **55g** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), 2-methoxybenzaldehyde (**53g**, 68 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.32, hexane : EtOAc 6 : 1) on silica to give a colorless oil (79 mg, 80%).

$C_9H_{11}NO_4$ (197.19 g/mol).

$[\alpha]_D^{20}$ = +7.3 (*c* = 0.79, $CHCl_3$, 68% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.43 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, H_{Ar}), 7.33 (td, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, H_{Ar}), 7.01 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H_{Ar}), 6.91 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, H_{Ar}), 5.62 (dd, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 3.3 Hz,

1H, C*H*OH), 4.64 (dd, $^{2}J_{HH}$ = 12.9 Hz, $^{3}J_{HH}$ = 3.2 Hz, 1H, CH*H*NO_2), 4.56 (dd, $^{2}J_{HH}$ = 13.1 Hz, $^{3}J_{HH}$ = 9.1 Hz, 1H, C*H*HNO_2), 3.88 (s, 3H, OC*H*$_3$), 3.21 (br s, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 156.4 (C_{Ar}), 130.2 (CH_{Ar}), 127.6 (CH_{Ar}), 126.4 (C_{Ar}), 121.6 (CH_{Ar}), 110.9 (CH_{Ar}), 80.2 (CHOH), 68.2 (CH_2NO_2), 55.8 (OCH_3) ppm.

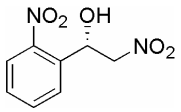
HPLC: OD-H, *n*-heptan : *i*-PrOH (90:10), 0.8 mL/min, 20 °C, 215 nm, t_R = 15.0 min (*R*), 17.9 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3522m, 2943m, 2841w, 1714m, 1598s, 1554s, 1492s, 1463s, 1379s, 1246s, 1119m, 1072s, 1028s, 940w, 897w, 852w, 788m, 759s, 706w, 613m.

Elemental analysis calcd (%) for $C_9H_{11}NO_4$ (197.19 g/mol): C 54.82, H 5.62, N 7.10; found: C 54.42, H 5.54, N 7.19.

MS (EI, 70 eV): m/z (%) = 197 (23, M^+), 150 (34), 137 (100), 135 (99), 107 (75), 91 (54).

(*S*)-2-nitro-1-(2-nitrophenyl) ethanol (55h)



Product **55h** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), 2-nitrobenzaldehyde (**53h**, 76 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.10, hexane : EtOAc 6 : 1) on silica to give a brown solid (101 mg, 95%).

$C_8H_8N_2O_5$ (212.16 g/mol).

$[\alpha]_D^{20}$ = -11.2 (*c* = 0.32, $CHCl_3$, 10% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 8.08 (dd, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.1 Hz, 1H, H_{Ar}), 7.96 (dd, $^{3}J_{HH}$ = 7.1 Hz, $^{4}J_{HH}$ = 1.0 Hz, 1H, H_{Ar}), 7.75 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H, CH_{Ar}), 7.55 (t, $^{3}J_{HH}$ = 8.5 Hz, 1H, H_{Ar}), 6.05 (dd, $^{3}J_{HH}$ = 9.1 Hz, $^{3}J_{HH}$ = 2.2 Hz, 1H, C*H*OH), 4.87 (dd, $^{2}J_{HH}$ = 14.0 Hz, $^{3}J_{HH}$ = 2.4 Hz, 1H, CH*H*NO_2), 4.56 (dd, $^{2}J_{HH}$ = 13.8 Hz, $^{3}J_{HH}$ = 9.0 Hz, 1H, C*H*HNO_2), 3.15 (br s, 1H, OH) ppm.

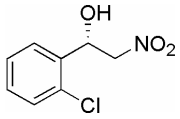
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 147.1 (C_{Ar}), 134.4 (CH_{Ar}), 133.9 (C_{Ar}), 129.7 (CH_{Ar}), 128.7 (CH_{Ar}), 125.0 (CH_{Ar}), 80.0 (CH_2NO_2), 66.8 (CHOH) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.8 mL/min, 20 °C, 215 nm, t_R = 20.0 min (*R*), 22.1 min (*S*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3408w_{br}, 1555s, 1527s, 1347m, 1096w, 908s.

HRMS (ESI^+): Exact Mass calcd for $C_8H_8N_2O_5Na$ $[M+Na]^+$, 235.0331. Found 235.0327.

(*S*)-2-chloro-1-(2-nitrophenyl) ethanol (55i)



Product **55i** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), 2-chlorobenzaldehyde (**53i**, 56 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.19, hexane : EtOAc 6 : 1) on silica to give a colorless oil (94 mg, 93%).

$C_8H_8ClNO_3$ (201.61 g/mol).

$[\alpha]_D^{20}$ = +12.8 (*c* = 0.54, $CHCl_3$, 27% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.67 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, H_{Ar}), 7.40-7.29 (m, 3H, H_{Ar}), 5.85 (d, $^3J_{HH}$ = 9.4 Hz, 1H, C*H*OH), 4.68 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 2.3 Hz, 1H, CH*H*NO_2), 4.46 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 9.6 Hz, 1H, C*H*HNO_2), 3.01 (br s, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 135.6 (C_{Ar}), 131.6 (C_{Ar}), 130.1 (CH_{Ar}), 129.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 79.4 (CH_2NO_2), 68.0 (CHOH) ppm.

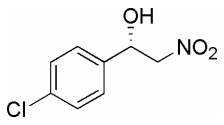
HPLC: OJ, *n*-heptan : *i*-PrOH (97 : 03), 0.8 mL/min, 20 °C, 215 nm, t_R = 59.8 min (*R*), 63.9 min (*S*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3465m_{br}, 1555s, 1527s, 1472m, 1441m, 1378s, 1270w, 1200w, 1087w, 1043m, 760s.

Elemental analysis calcd (%) for $C_8H_8ClNO_3$ (201.61 g/mol): C 47.66, H 4.00, N 6.95; found: C 47.25, H 4.10, N 6.78.

MS (EI, 70 eV): m/z (%) = 201 (3, M^+), 156 (33), 155 (13), 154 (100), 143 (17), 141 (69), 140 (20), 139 (63), 137 (21), 113 (22), 111 (23), 91 (42), 77 (62), 75 (25), 51 (17), 50 (14), 43 (16).

(*S*)-4-chloro-1-(2-nitrophenyl) ethanol (55l)



Product **55l** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5 mmol), 4-chlorobenzaldehyde (**53l**, 70 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.18, hexane : EtOAc 6 : 1) on silica to give a colorless oil (91 mg, 90%).

$C_8H_8ClNO_3$ (201.61 g/mol).

$[\alpha]_D^{20}$ = +8.1 (*c* = 0.51, CH_2Cl_2, 38% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.40-7.34 (m, 4H, H_{Ar}), 5.46 (dd, $^3J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C*H*OH), 4.58 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.4 Hz, 1H, CH*H*NO_2), 4.49 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*HNO_2), 2.89 (br s, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 136.6 (C_{Ar}), 135.0 (CH_{Ar}), 129.4 (2C, CH_{Ar}), 127.5 (2C, CH_{Ar}), 81.1 (CH_2NO_2), 70.4 (CHOH) ppm.

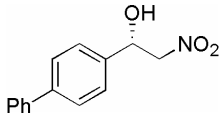
HPLC: OD-H, *n*-heptan : *i*-PrOH (85 : 15), 0.8 mL/min, 20 °C, 210 nm, t_R = 11.9 min (*R*), 14.8 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3448m_{br}, 1555s, 1492m, 1413m, 1379s, 1292w, 1210w, 1086s, 828m.

Elemental analysis calcd (%) for $C_8H_8ClNO_3$ (201.61 g /mol): C 47.66, H 4.00, N 6.95; found: C 47.47, H 4.16, N 7.03.

MS (EI, 70 eV): m/z (%) = 201 (3, M^+), 156 (25), 155 (12), 154 (75), 143 (18), 142 (21), 141 (86), 140 (56), 139 (100), 137 (18), 113 (20), 111 (31), 91 (46), 77 (60), 76 (16), 75 (28), 65 (12), 51 (23), 50 (21).

(*S*)-1-(4-phenylphenyl)-2-nitroethanol (55m)



Product **55m** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), 4-phenylbenzaldehyde (**53m**, 91 mg, 0.50 mmol). After stirring 1 day

at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.22, hexane : EtOAc 6 : 1) on silica to give a pale yellow crystalline solid (108 mg, 89%).

$C_{14}H_{13}NO_3$ (243.26 g/mol).

m.p.: 128 °C.

$[\alpha]_D^{20}$ = +14.8 (*c* = 0.58, CH_2Cl_2, 53% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.64-7.62 (m, 2H, H_{Ar}), 7.59-7.52 (m, 2H, H_{Ar}), 7.50-7.44 (m, 4H, H_{Ar}), 7.37 (tt, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, H_{Ar}), 5.53 (dt, $^3J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, C*H*OH), 4.66 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.6 Hz, 1H, CH*H*NO_2), 4.57 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C*H*HNO_2), 2.80 (d, $^3J_{HH}$ = 3.5 Hz, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 142.4 (C_{Ar}), 140.7 (C_{Ar}), 137.3 (C_{Ar}), 129.3 (2C, CH_{Ar}), 128.2 (2C, CH_{Ar}), 128.1 (CH_{Ar}), 127.5 (2C, CH_{Ar}), 126.8 (2C, CH_{Ar}), 81.6 (CHOH), 71.2 (CH_2NO_2) ppm.

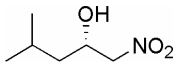
HPLC: OD-H, *n*-heptan : *i*-PrOH (85:15), 0.8 mL/min, 20 °C, 215 nm, t_R = 18.5 min (*R*), 21.6 min (*S*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3392m_{br}, 3030w, 2920w, 1551s, 1486w, 1418w, 1382m, 1322w, 1190w, 1074m, 1005w, 840m.

Elemental analysis calcd (%) for $C_{14}H_{13}NO_3$ (243.26 g/mol): C 69.13, H 5.39, N 5.76; found: C 69.19, H 5.22, N 5.80.

MS (EI, 70 eV): m/z (%) = 243 (8, M^+), 196 (15), 183 (24), 182 (100), 181 (99), 179 (11), 178 (14), 154 (15), 153 (43), 152 (70), 151 (17), 77 (12), 76 (14).

(*S*)-4-methyl-1-nitropentan-2-ol (55n)



Product **55n** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), isovaleraldehyde (**53n**, 54 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.42, hexane : EtOAc 6 : 1) on silica to give a colorless oil (92% conversion).

$C_6H_{13}NO_3$ (147.17 g/mol).

$[\alpha]_D^{20}$ = -8 (*c* = 0.24, $CHCl_3$, 57% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.42-4.32 (m, 3H, CH_2NO_2 + C*H*OH), 2.56 (br s, 1H, OH), 1.88-1.78 (m, 1H, CH*H*CHOH), 1.53-1.46 (m, 1H, C*H*HCHOH), 1.26-1.19 (m, 1H, C*H*$(Me)_2$), 0.96 (d, $^3J_{HH}$ = 5.8 Hz, 3H, CH_3), 0.94 (d, $^3J_{HH}$ = 5.8 Hz, 3H, CH_3) ppm.

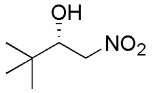
^{13}C{^{1}H} NMR (100.8 MHz, $CDCl_3$, 295 K): δ = 81.4 (CH_2NO_2), 67.3 (CHOH), 42.8 (*C*H_2CHOH), 24.7 (*C*HMe_2), 23.6 (CH_3), 22.1 (CH_3) ppm.

HPLC: OJ, *n*-heptan : *i*-PrOH (98:02), 0.6 mL/min, 20 °C, 215 nm, t_R = 39.6 min (*R*), 43.7 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3422s, 2960s, 2872s, 1716w, 1558s, 1469s, 1421m, 1385s, 1296w, 1205m, 1145m, 1090m, 1045w, 920w, 848w, 820w, 735w.

Elemental analysis calcd (%) for $C_6H_{13}NO_3$ (147.17 g/mol): C 48.97, H 8.90, N 9.52; found: C 49.18, H 8.70, N 9.23.

(*S*)-3,3-Dimethyl-1-nitrobutan-2-ol (55o)



Product **55o** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), pivalaldehyde (**53o**, 31 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.36, CH_2Cl_2 : Et_2O 100 : 1) on silica to give a colorless oil (89% conversion).

$C_6H_{13}NO_3$ (147.17 g/mol).

$[\alpha]_D^{20}$ = +13.5 (*c* = 0.27, $CHCl_3$, 79% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.52 (dd, $^3J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*HNO_2), 4.36 (dd, $^3J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 10.4 Hz, 1H, CH*H*NO_2), 4.02 (ddd, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*OH), 2.54 (d, $^3J_{HH}$ = 4.8 Hz, 1H, OH), 0.97 (s, 9H, $C(CH_3)_3$) ppm.

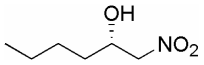
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 78.4 (CH_2NO_2), 76.3 (CHOH), 34.4 (*C*Me_3), 25.7 ($C(CH_3)_3$) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (98:02), 0.8 mL/min, 20 °C, 210 nm, t_R = 19.0 min (*R*), 22.5 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3548m_{br}, 2964s, 2876m, 1557s, 1476m, 1422m, 1381s, 1289w, 1192w, 1086m, 1022w, 922w, 881w, 699m.

Elemental analysis calcd (%) for $C_6H_{13}NO_3$ (147.17 g/mol): C 48.97, H 8.90, N 9.52; found: C 48.76, H 8.85, N 9.54.

(*S*)-1-Nitrohexan-2-ol (55p)



Product **55p** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), valeraldehyde (**53p**, 31 µL, 0.50 mmol). After stirring 4 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.14, hexane : EtOAc 6 : 1) on silica to give a colorless oil (80% conversion).

$C_6H_{13}NO_3$ (147.17 g/mol).

$[\alpha]_D^{20}$ = +3.5 (*c* = 0.63, $CHCl_3$, 60% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.43 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 2.7 Hz 1H, C*H*HNO_2), 4.37 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, CH*H*NO_2), 4.34-4.28 (m, 1H, C*H*OH), 2.55 (br s, 1H, OH), 1.52-1.33 (m, 6H, $(CH_2)_3CH_3$), 0.92 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3) ppm.

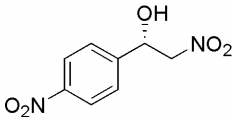
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 80.8 (CH_2NO_2), 68.8 (CHOH), 33.5 ($CH_2(CH_2)_2CH_3$), 27.4 ($CH_2CH_2CH_3$), 22.5 (CH_2CH_3), 14.0 (CH_3) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (98 : 02), 0.8 mL/min, 20 °C, 215 nm, t_R = 39.4 min (*R*), 51.5 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3394s_{br}, 2941m, 2880w, 1558s, 1469w, 1349s, 1093s.

Elemental analysis calcd (%) for $C_6H_{13}NO_3$ (147.17 g/mol): C 48.97, H 8.90, N 9.52; found: C 48.80, H 8.64, N 9.35.

(*S*)-2-nitro-1-(4-nitrophenyl) ethanol (55q)



Product **55q** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), 4-nitrobenzaldehyde (**53q**, 76 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.15, hexane : EtOAc 6 : 1) on silica to give an off-white solid (91 mg, 86%).

$C_8H_8N_2O_5$ (212.16 g/mol).

m.p. 83-85 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 8.28 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 7.63 (d, $^3J_{HH}$ = 8.3 Hz, 2H, H_{Ar}), 5.61 (dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, C*H*OH), 4.60 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.7 Hz, 1H, CH*H*NO_2), 4.56 (dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, C*H*HNO_2), 3.10 (br s, 1H, OH) ppm.

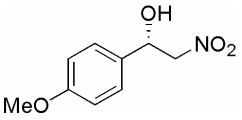
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 144.9 (C_{Ar}), 130.6 (C_{Ar}), 127.1 (2C, CH_{Ar}), 124.4 (2C, CH_{Ar}), 80.7 (CH_2NO_2), 70.1 (CHOH) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (85 : 15), 0.8 mL/min, 20 °C, 215 nm, t_R = 20.6 min (*R*), 25.6 min (*S*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3396m_{br}, 2930m, 2867w, 1554s, 1465w, 1381m, 1097m.

Elemental analysis calcd (%) for $C_8H_8N_2O_5$ (212.16 g/mol): C 45.29, H 3.80, N 13.20; found: C 45.01, H 3.81, N 13.23.

(*S*)-1-(4-Methoxyphenyl)-2-nitroethanol ethanol (55r)



Product **55r** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), 4-methoxybenzaldehyde (**53r**, 61 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The

crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.11, hexane : EtOAc 6 : 1) on silica to give a yellow oil (62 mg, 63%).

$C_9H_{11}NO_4$ (197.19 g/mol).

$[\alpha]_D^{20}$ = +18.3 (*c* = 0.58, $CHCl_3$, 52% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.32 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H_{Ar}), 6.92 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H_{Ar}), 5.42 (dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, C*H*OH), 4.61 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, C*H*HNO_2), 4.48 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, CH*H*NO_2), 3.82 (s, 3H, OCH_3), 2.71 (brs, 1H, OH) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 160.2 (C_{Ar}), 130.3 (C_{Ar}), 127.4 (2C, CH_{Ar}), 114.5 (2C, CH_{Ar}), 81.4 (CH_2NO_2), 70.8 (CHOH), 55.5 (OCH_3) ppm.

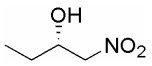
HPLC: OD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.8 mL/min, 20 °C, 215 nm, t_R = 25.1 min (*R*), 32.0 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3395m_{br}, 2927m, 1557s, 1514m, 1464w, 1369s, 1254m, 1096w.

Elemental analysis calcd (%) for $C_9H_{11}NO_4$ (197.19 g/mol): C 54.82, H 5.62, N 7.10; found: C 54.65, H 5.44, N 7.23.

MS (EI, 70 eV): m/z (%) = 197 (26, M^+), 151 (12), 150 (45), 137 (100), 136 (20), 135 (47), 109 (22), 108 (10), 94 (12), 91 (19), 77 (28), 65 (10).

(*S*)-1-nitrobutan-2-ol (55s)



Product **55s** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), propionaldehyde (**53s**, 36 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.20, hexane : EtOAc 6 : 1) on silica to give a colorless oil (90% conversion).

$C_4H_9NO_3$ (119.12 g/mol).

$[\alpha]_D^{20}$ = 1 (*c* = 0.56, $CHCl_3$, 55% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.43 (dd, $^3J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, C*H*HNO_2), 4.37 (dd, $^3J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, CH*H*NO_2), 4.27-4.21 (m, 1H,

C*H*OH), 2.57 (br s, 1H, OH), 1.60-1.53 (m, 2H, C*H*$_2$CH$_3$), 1.01 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_3$) ppm.

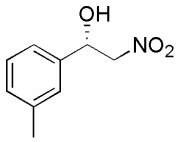
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 80.4 (CH_2NO_2), 70.0 (CHOH), 27.0 (CH_2), 9.7 (CH_3) ppm.

HPLC: OB-H, *n*-heptan : EtOH (98:02), 0.6 mL/min, 20 °C, 215 nm, t_R = 47.8 min (*S*), 51.8 min (*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3414s$_{br}$, 2973s, 2939s, 2883m, 1556s, 1463m, 1423m, 1386s, 1208w, 1130m, 1082m, 1028w, 990m, 876w, 726w.

Elemental analysis calcd (%) for $C_4H_9NO_3$ (119.12 g/mol): C 40.33, H 7.62, N 11.76; found: C 40.22, H 7.61, N 11.52.

(*S*)-1-(3-methylphenyl)-2-nitroethanol (55t)



Product **55t** was prepared according to **general procedure IV** from nitromethane (**54a**, 0.27 mL, 5.00 mmol), *m*-tolualdehyde (**53t**, 59 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.33, hexane : EtOAc 6 : 1) on silica to give a colorless oil (63 mg, 70%).

$C_9H_{11}NO_3$ (181.19 g/mol).

$[\alpha]_D^{20}$ = +7.7 (*c* = 1.07, $CHCl_3$, 56% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.29 (t, $^3J_{HH}$ = 7.6 Hz, 1H, H$_{Ar}$), 7.22-7.20 (m, 1H, H$_{Ar}$), 7.20-7.16 (m, 2H, H$_{Ar}$), 5.42 (brd, $^3J_{HH}$ = 9.6 Hz, 1H, C*H*OH), 4.60 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 9.6 Hz, 1H, C*H*HNO$_2$), 4.50 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, CH*H*NO$_2$), 2.85 (s, 1H, OH), 2.37 (s, 3H, CH$_3$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 139.3 (C$_{Ar}$), 138.5 (C$_{Ar}$), 130.1 (CH$_{Ar}$), 129.3 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 123.4 (CH$_{Ar}$), 81.7 (CHOH), 71.4 (CH_2NO_2), 21.8 (CH_3) ppm.

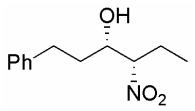
HPLC: OD-H, *n*-heptan : *i*-PrOH (85:15), 0.8 mL/min, 20 °C, 220 nm, t_R = 10.7 min (*R*), 12.4 min (*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3460m$_{br}$, 2984m, 2927m, 1735s, 1556s, 1423w, 1377s, 1247s, 1158w, 1046s, 918w, 889w, 848w, 790m, 707m.

Elemental analysis calcd (%) for $C_9H_{11}NO_3$ (181.19 g/mol): C 59.66, H 6.12, N 7.73; found: C 59.42, H 6.14, N 7.55.

MS (EI, 70 eV): m/z (%) = 181 (4, M^+), 134 (45), 121 (23), 120 (75), 119 (90), 117 (11), 93 (19), 92 (18), 91 (100), 77 (10), 65 (19), 61 (19), 43 (47).

(3*S*,4*S*)-4-Nitro-1-phenyl-hexan-3-ol (*syn*-222a)



Product *syn*-**222a** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 3-phenylpropionaldehyde (**53a**, 66 µL, 0.50 mmol). After stirring 2 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.42, hexane : TBME 3 : 1) on silica to give a colorless solid (30 mg, 27%).

$C_{12}H_{17}NO_3$ (223.27 g/mol).

$[\alpha]_D^{20}$ = +3 (*c* = 1.32, $CHCl_3$, 39% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.33-7.29 (m, 2H, H_{Ph}), 7.24-7.19 (m, 3H, H_{Ph}), 4.40 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 4.3 Hz, $CHNO_2$), 3.97-3.85 (m, 1H, C*H*OH), 2.88 (ddd, $^3J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 5.6 Hz, C*H*HPh), 2.74 (ddd, $^3J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 7.3 Hz, CH*H*Ph), 2.50 (d, $^3J_{HH}$ = 6.6 Hz, 1H, OH), 2.09-1.97 (m, 1H, C*H*HCH$_3$), 1.90-1.71 (m, 3H, C*H*$_2$CH$_2$Ph + CH*H*CH$_3$), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 140.9 (C_{Ph}), 128.7 (2C, CH_{Ph}), 128.5 (2C, CH_{Ph}), 126.3 (CH_{Ph}), 94.5 ($CHNO_2$), 71.1 (CHOH), 35.2 (*C*H$_2$CH$_2$Ph), 31.6 (*C*H$_2$Ph), 23.9 (*C*H$_2$CH$_3$), 10.2 (CH_3) ppm.

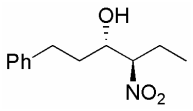
HPLC: OD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.500 mL/min, 20 °C, 215 nm, t_R = 23.3 min (*S*,*S*), 29.2 min (*R*,*R*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3590s$_{br}$, 3033w, 2920w, 1554s, 1452w, 1418w, 1379s, 1290w, 1066m, 764m.

Elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.27 g/mol): C 64.55, H 7.67, N 6.27; found: C 64.34, H 7.60, N 6.16.

MS (FAB, NBA): m/z (%) = 224 (47, [M+H$^+$]), 177 (14), 159 (27), 158 (12), 133 (13), 117 (28), 104 (10), 91 (100), 77 (16), 71 (46).

(3*S*,4*R*)-4-Nitro-1-phenyl-hexan-3-ol (*anti*-222a)



Product *anti*-**222a** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 3-phenylpropionaldehyde (**53a**, 66 µL, 0.50 mmol). After stirring 2 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.25, hexane : TBME 3 : 1) on silica to give a colorless oil (20 mg, 18%).

$C_{12}H_{17}NO_3$ (223.27 g/mol).

$[\alpha]_D^{20}$ = -3 (*c* = 1.20, $CHCl_3$, 11% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.32-7.28 (m, 2H, H_{Ph}), 7.23-7.18 (m, 3H, H_{Ph}), 4.36 (td, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 3.5 Hz, $CHNO_2$), 4.05-4.00 (m, 1H, C*H*OH), 2.89 (ddd, $^3J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 5.3 Hz, C*H*HPh), 2.70 (ddd, $^3J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.7 Hz, CH*H*Ph), 2.38 (d, $^3J_{HH}$ = 4.3 Hz, 1H, OH), 2.18-2.08 (m, 1H, C*H*HCH$_3$), 1.91-1.71 (m, 3H, C*H*$_2$CH$_2$Ph + CH*H*CH$_3$), 0.97 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 140.9 (C_{Ph}), 128.7 (2C, CH_{Ph}), 128.6 (2C, CH_{Ph}), 126.4 (CH_{Ph}), 93.9 ($CHNO_2$), 71.5 (CHOH), 34.8 (*C*H$_2$CH$_2$Ph), 31.9 (*C*H$_2$Ph), 21.6 (*C*H$_2$CH$_3$), 10.7 (CH_3) ppm.

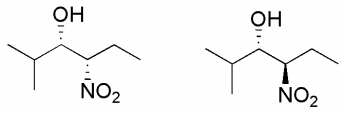
HPLC: OD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.5 mL/min, 20 °C, 215 nm, t_R = 18.8 min (*S*,*R*), 22.0 min (*R*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3440s$_{br}$, 3027w, 2938s, 1547s, 1456s, 1374s, 1307m, 1050m, 748m.

Elemental analysis calcd (%) for $C_{12}H_{17}NO_3$ (223.27 g/mol): C 64.55, H 7.67, N 6.27; found: C 64.74, H 7.54, N 6.13.

MS (FAB, NBA): m/z (%) = 224 (21, [M+H$^+$]), 177 (10), 159 (18), 117 (19), 107 (19), 92 (15), 91 (100), 77 (34), 71 (42).

(3*S*,4*S*)-2-Methyl-4-nitro-hexan-3-ol (*syn*-222b) and (3*S*,4*R*)-2-Methyl-4-nitro-hexan-3-ol (*anti*-222b)



Product **222b** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), isobutyraldehyde (**53b**, 46 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.21, hexane : EtOAc 6 : 1) on silica to give a colorless oil (55% conversion).

$C_7H_{15}NO_3$ (161.20 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.53 (ddd, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, $CHNO_2$, *syn*), 4.49 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, $CHNO_2$, *anti*), 3.76 (td, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*OH, *anti*), 3.63 (td, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, C*H*OH, *syn*), 2.19 (d, $^3J_{HH}$ = 4.5 Hz, 1H, OH, *anti*), 2.12 (d, $^3J_{HH}$ = 8.1 Hz, 1H, OH, *syn*), 2.18-2.09 (m, 1H, C*H*HCH$_3$, *anti*), 2.08-1.94 (m, 1H, C*H*HCH$_3$, *syn*), 1.97-1.91 (m, 1H, CH*H*CH$_3$, *anti*), 1.91-1.80 (m, 1H, CH*H*CH$_3$, *syn*), 1.73 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, C*H*(CH$_3$)$_2$, *syn*), 1.71 (ds, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$, *anti*), 1.02 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$CH$_3$), *syn*), 1.01 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH(C*H*$_3$CH$_3$), *anti*), 0.99 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH$_2$C*H*$_3$, *syn*), 0.98 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH$_2$C*H*$_3$, *anti*), 0.96 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH(CH$_3$C*H*$_3$), *syn*), 0.95 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(CH$_3$C*H*$_3$), *anti*) ppm.

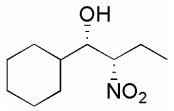
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 92.6 ($CHNO_2$, *syn*), 92.0 ($CHNO_2$, *anti*), 77.0 (CHOH, *anti*), 76.6 (CHOH, *syn*), 30.7 (*C*H(CH$_3$)$_2$, *anti*), 30.6 (*C*H(CH$_3$)$_2$, *syn*), 24.2 (*C*H$_2$CH$_3$, *syn*), 21.7 (*C*H$_2$CH$_3$, *anti*), 19.8 (CH(*C*H$_3$CH$_3$), *syn*), 19.4 (CH(*C*H$_3$CH$_3$), *anti*), 17.4 ((CH(CH$_3$*C*H$_3$), *anti*), 16.5 (CH(CH$_3$*C*H$_3$), *syn*), 10.7 (CH$_2$*C*H$_3$, *anti*), 10.4 (CH$_2$*C*H$_3$, *syn*) ppm.

HPLC: OB-H, *n*-heptan : *i*-PrOH (98:02), 0.6 mL/min, 20 °C, 215 nm, t_R = 17.3 min (*S*,*R*), 22.3 min (*R*,*S*), 25.1 min (*R*,*R*), 32.8 min (*S*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3432s$_{br}$, 2971m, 1639m, 1552s, 1464m, 1375m, 1264w, 1131w, 1010w, 804w.

Elemental analysis calcd (%) for $C_7H_{15}NO_3$ (161.20 g/mol): C 52.16, H 9.38, N 8.69; found: C 52.18, H 9.15, N 8.66.

(1*S*,2*S*)-1-cyclohexyl-2-nitro-butan-1-ol (*syn*-222c)



Product *syn*-**222c** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), cyclohexanecarboxaldehyde (**53c**, 60 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.29, hexane : EtOAc 6 : 1) on silica to give a colorless oil (50 mg, 50%).

$C_{10}H_{19}NO_3$ (201.26 g/mol).

$[\alpha]_D^{20}$ = +2.0 (*c* = 0.73, $CHCl_3$, 94% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.54 (ddd, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, $CHNO_2$), 3.63-3.58 (m, 1H, C*H*OH), 2.20 (d, $^3J_{HH}$ = 6.9 Hz , 1H, OH), 2.08-2.01 (m, 1H, C*H*HCH$_3$), 1.88-1.82 (m, 1H, CH*H*CH$_3$), 1.80-1.72 (m, 3H, H_{Cy}), 1.67-1.63 (m, 2H, H_{Cy}), 1.39-1.33 (m, 1H, H_{Cy}), 1.26-1.10 (m, 5H, H_{Cy}), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3) ppm.

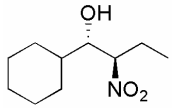
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 91.9 ($CHNO_2$), 75.9 (CHOH), 40.3 (CH_{Cy}), 29.8 (CH_{2Cy}), 26.8 (CH_{2Cy}), 26.1 (CH_{2Cy}), 26.0 (CH_{2Cy}), 25.7 (CH_{2Cy}), 24.0 (CH_2), 10.2 (CH_3) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (97 : 03), 0.8 mL/min, 20 °C, 215 nm, t_R = 18.9 min (*S*,*S*), 29.4 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3441s$_{br}$, 2929s, 2855s, 1550s, 1451m, 1378m, 1306w, 1109w, 1028w, 892w.

Elemental analysis calcd (%) for $C_{10}H_{19}NO_3$ (201.26 g/mol): C 59.68, H 9.51, N 6.96; found: C 59.88, H 9.35, N 6.79.

(1*S*,2*R*)-1-cyclohexyl-2-nitro-butan-1-ol (*anti*-222c)



Product *anti*-**222c** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), cyclohexanecarboxaldehyde (**53e**, 60 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.19, hexane : EtOAc 6 : 1) on silica to give a colorless oil (6 mg, 3%).

$C_{10}H_{19}NO_3$ (201.26 g/mol).

$[\alpha]_D^{20}$ = -1 (*c* = 0.12, $CHCl_3$, 74% *ee*).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.48 (ddd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.7 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, $CHNO_2$), 3.76 (t, $^3J_{HH}$ = 5.4 Hz, 1H, C*H*OH), 2.46 (brs, 1H, OH), 2.14-2.08 (m, 1H, C*H*HCH$_3$), 1.89-1.86 (m, 1H, CH*H*CH$_3$), 1.79-1.71 (m, 3H, H_{Cy}), 1.67-1.63 (m, 2H, H_{Cy}), 1.53-1.48 (m, 1H, H_{Cy}), 1.26-1.10 (m, 5H, H_{Cy}), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3) ppm.

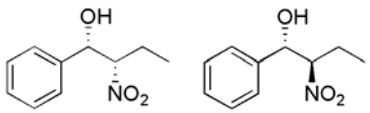
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 91.7 ($CHNO_2$), 76.4 (CHOH), 40.4 (CH_{Cy}), 29.4 (CH_{2Cy}), 28.1 (CH_{2Cy}), 26.1 (CH_{2Cy}), 25.8 (CH_{2Cy}), 25.5 (CH_{2Cy}), 24.2 (CH_2), 10.7 (CH_3) ppm.

HPLC: AD-H, *n*-heptan : EtOH (97:03), 0.5 mL/min, 20 °C, 215 nm, t_R = 31.4 min (*R*,*S*), 38.2 min (*S*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3448m$_{br}$, 2929s, 2855s, 1550s, 1451m, 1379m, 1306w, 1108m, 1058w, 893w.

Elemental analysis calcd (%) for $C_{10}H_{19}NO_3$ (201.26 g/mol): C 59.68, H 9.51, N 6.96; found: C 59.48, H 9.32, N 6.80.

(1*S*,2*S*)-2-nitro-1-phenylbutan-1-ol (*syn*-222e) and (1*S*,2*R*)-2-nitro-1-phenylbutan-1-ol (*anti*-222e)



Product **222e** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), benzaldehyde (**53e**, 50 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.12, hexane : EtOAc 6 : 1) on silica to give a colorless oil (72 mg, 74%).

$C_{10}H_{13}NO_3$ (195.22 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295K): δ = 7.34-7.30 (m, 10H, H_{Ph}, *syn* + *anti*), 5.18 (dd, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*OH, *anti*), 5.03 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C*H*OH, *syn*), 4.62 (ddd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, $CHNO_2$, *syn*), 4.58 (ddd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, $CHNO_2$, *anti*), 2.69 (d, $^3J_{HH}$ = 2.8 Hz, 1H, OH, *anti*), 2.48 (d, $^3J_{HH}$ = 3.5 Hz, 1H, OH, *syn*), 2.21-2.11 (m, 1H, C*H*HCH$_3$, *anti*), 1.94-1.86 (m, 1H, CH*H*CH$_3$, *anti*), 1.88-1.79 (m, 1H, C*H*HCH$_3$, *syn*), 1.47-1.37 (m, 1H, CH*H*CH$_3$, *syn*), 0.93 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3, *anti*), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3, *syn*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 138.8 (C_{Ph}, *syn*), 138.6 (C_{Ph}, *anti*), 129.4 (2C, CH_{Ph}, *anti*), 129.2 (2C, CH_{Ph}, *syn*), 128.9 (CH_{Ph}, *syn*), 128.8 (CH_{Ph}, *anti*), 127.0 (2C, CH_{Ph}, *syn*), 126.3 (2C, CH_{Ph}, *anti*), 95.3 ($CHNO_2$, *syn*), 94.8 ($CHNO_2$, *anti*), 75.7 (CHOH, *syn*), 74.4 (CHOH, *anti*), 24.1 (CH_2, *syn*), 21.4 (CH_2, *anti*), 10.5 (CH_3, *anti*), 10.2 (CH_3, *syn*) ppm.

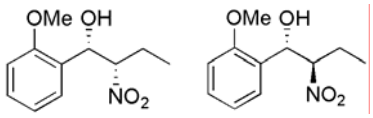
HPLC: AS, *n*-heptan : *i*-PrOH (98 : 02), 0.9 mL/min, 20 °C, 210 nm, t_R = 22.8 min (*S*,*R*), 26.6 min (*R*,*S*), 32.7 min (*S*,*S*), 49.3 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3441m$_{br}$, 3065w, 3033w, 2975m, 2938m, 2882w, 1964m, 1598w, 1551s, 1494w, 1452m, 1440w, 1374s, 1345m, 1311w, 1260w, 1203w, 1044m, 925w, 806m, 767m, 702s.

Elemental analysis calcd (%) for $C_{10}H_{13}NO_3$ (195.22 g/mol): C 61.53, H 6.71, N 7.18; found: C 61.36, H 6.81, N 6.99.

MS (EI, 70 eV): m/z (%) = 195 (1, M^+), 148 (12), 107 (70), 106 (94), 105 (100), 91 (11), 79 (20), 78 (12), 77 (85), 51 (22), 43 (19), 41 (16).

(1*S*,2*S*)-1-(2-Methoxy-phenyl)-2-nitro-butan-1-ol (*syn*-222g) and (1*S*,2*R*)-1-(2-methoxy-phenyl)-2-nitro-butan-1-ol (*anti*-222g)



Product **222g** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 2-methoxybenzaldehyde (**53g**, 68 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.19, 0.24, hexane : TBME 5 : 1) on silica to give a colorless oil (93 mg, 83%).

$C_{11}H_{15}NO_4$ (225.24 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.34-7.30 (m, 2H, H_{Ar}, *syn* + *anti*), 7.28-7.26 (m, 2H, H_{Ar}, *syn* + *anti*), 7.01-6.90 (m, 4H, H_{Ar}, *syn* + *anti*), 5.24 (d, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*OH, *anti*), 5.14 (t, $^3J_{HH}$ = 8.6 Hz, 1H, C*H*OH, *syn*), 4.84 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, $CHNO_2$, *syn*), 4.78 (ddd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, $CHNO_2$, *anti*), 3.90 (s, 3H, OCH_3, *syn*), 3.89 (s, 3H, OCH_3, *anti*), 3.24 (d, $^3J_{HH}$ = 8.6 Hz, 1H, OH, *syn*), 3.20 (brs, 1H, OH, *anti*), 2.20-2.09 (m, 1H, C*H*HCH_3, *anti*), 1.98-1.88 (m, 1H, C*H*HCH_3, *syn*), 1.97-1.87 (m, 1H, CH*H*CH_3, *anti*), 1.46-1.39 (m, 1H CH*H*CH_3, *syn*), 0.93 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *anti*), 0.88 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *syn*) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 295 K): δ = 156.9 (C_{Ar}, *syn*), 156.3 (C_{Ar}, *anti*), 130.2 (CH_{Ar}, *syn*), 129.8 (CH_{Ar}, *anti*), 129.1 (CH_{Ar}, *syn*), 128.5 (CH_{Ar}, *anti*), 126.3 (C_{Ar}, *syn*), 126.1 (C_{Ar}, *anti*), 121.4 (CH_{Ar}, *syn*), 121.1 (CH_{Ar}, *anti*), 111.1 (CH_{Ar}, *syn*), 110.7 (CH_{Ar}, *anti*), 94.5 ($CHNO_2$, *syn*), 92.7 ($CHNO_2$, *anti*), 73.7 (CHOH, *syn*), 72.3 (CHOH, *anti*), 55.6 (OCH_3, *syn*), 55.5 (OCH_3, *anti*), 24.3 (CH_2, *syn*), 21.9 (CH_2, *anti*), 10.4 (CH_3, *syn*), 10.6 (CH_3, *anti*) ppm.

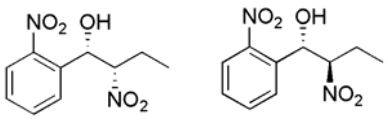
HPLC: AD-H, *n*-heptan : *i*-PrOH (99 : 01), 0.8 mL/min, 20 °C, 210 nm, t_R = 56.0 min (*S*,*R*), 67.2 min (*R*,*S*), 142.2 min (*R*,*R*), 156.5 min (*S*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3465m_{br}, 3079w, 2982s, 2942s, 1738s, 1560m, 1648s, 1464s, 1374s, 1245s, 1164w, 1047s, 938w, 833w, 803m, 759m.

Elemental analysis calcd (%) for $C_{11}H_{15}NO_4$ (225.24 g/mol): C 58.66, H 6.71, N 6.22; found: C 58.68, H 6.68, N 6.05.

MS (EI, 70 eV): m/z (%) = 225 (6, M^+), 137 (100), 136 (25), 135 (20), 121 (10), 107 (29), 77 (17).

(1*S*,2*S*) 2-Nitro-1-(2-nitro-phenyl)-butan-1-ol (*syn*-222h) and (1*S*,2*R*) 2-nitro-1-(2-nitro-phenyl)-butan-1-ol (*anti*-222h)



Product **222h** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 2-nitrobenzaldehyde (**53h**, 76 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude

product was purified by column chromatography (3 x 25 cm**, R_f** = 0.27, hexane : TBME 3 : 1) on silica to give a colorless oil (108 mg, 90%).

$C_{10}H_{12}N_2O_5$ (240.21 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 8.09 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, H_{Ar}, *anti*), 8.03 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H_{Ar}, *syn*), 7.88 (dd, $^3J_{HH}$ = 6.5 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, H_{Ar}, *anti*), 7.74-7.66 (m, 3H, H_{Ar}, *anti* + *syn*), 7.56-7.51 (m, 2H, H_{Ar}, *syn*), 5.84 (t, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*OH, *anti*), 5.74 (t, $^3J_{HH}$ = 6.3 Hz, C*H*OH, *syn*), 4.88-4.82 (m, 2H, $CHNO_2$, *syn* + *anti*), 3.42 (d, $^3J_{HH}$ = 3.8 Hz, 1H, OH, *anti*), 3.32 (d, $^3J_{HH}$ = 6.9 Hz, 1H, OH, *syn*), 2.29-2.13 (m, 2H, CH*H*CH_3, *anti* + *syn*), 1.89-1.80 (m, 1H, C*H*HCH_3, *anti*), 1.79-1.71 (m, 1H, C*H*HCH_3, *syn*), 1.00 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3, *syn*), 0.95 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3, *anti*) ppm.

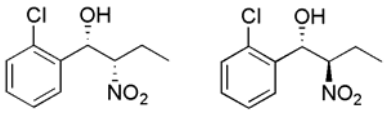
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 147.6 (C_{Ar}, *anti*), 147.1 (C_{Ar}, *syn*), 134.5 (C_{Ar}, *anti*), 134.2 (CH_{Ar}, *syn*), 134.1 (CH_{Ar}, *anti*), 133.9 (C_{Ar}, *syn*), 129.8 (CH_{Ar}, *syn*), 129.7 (CH_{Ar}, *anti*), 129.5 (CH_{Ar}, *anti*), 128.8 (CH_{Ar}, *syn*), 125.5 (CH_{Ar}, *anti*), 125.3 (CH_{Ar}, *syn*), 94.1 (*C*HNO_2, *syn*), 92.0 (*C*HNO_2, *anti*), 70.1 (*C*HOH, *syn*), 69.9 (*C*HOH, *anti*), 24.3 (*C*H_2CH_3, *syn*), 22.9 (*C*H_2CH_3, *anti*), 10.5 (CH_2*C*H_3, *anti*), 10.4 (CH_2*C*H_3, *syn*) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (96 : 04), 0.8 mL/min, 20 °C, 215 nm, t_R = 49.1 min (*S*,*R*), 51.5 min (*R*,*S*), 69.2 min (*S*,*S*), 74.4 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3523s_{br}, 2977m, 2940w, 2883w, 1610m, 1549s, 1460m, 1348s, 1190w, 1109w, 1038w, 861w, 792m, 751w, 708m.

Elemental analysis calcd (%) for $C_{10}H_{12}N_2O_5$ (240.21 g/mol): C 50.00, H 5.04, N 11.66; found: C 50.22, H 4.90, N 11.66.

(1*S*,2*S*)-1-(2-chlorophenyl)-2-nitrobutan-1-ol (*syn*-222i) and (1*S*,2*R*)-1-(2-chlorophenyl)-2-nitrobutan-1-ol (*anti*-222i)



Product **222i** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 2-chlorobenzaldehyde (**53i**, 56 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude

product was purified by column chromatography (3 x 25 cm**, R_f** = 0.34, hexane : EtOAc 6 : 1) on silica to give a colorless oil (68 mg, 59%).

$C_{10}H_{12}ClNO_3$ (229.66 g/mol).

^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ = 7.63 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H_{Ar}, *anti*), 7.49 (dd, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H_{Ar}, *syn*), 7.40-7.27 (m, 6H, H_{Ar}, *syn* + *anti*), 5.63 (t, $^3J_{HH}$ = 3.0 Hz, 1H, C*H*OH, *anti*), 5.58 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, C*H*OH, *syn*), 4.78-4.70 (m, 2H, $CHNO_2$, *syn* + *anti*), 3.16 (d, $^3J_{HH}$ = 3.6 Hz, 1H, OH, *anti*), 2.93 (d, $^3J_{HH}$ = 5.8 Hz, 1H, OH, *syn*), 2.25-2.14 (m, 1H, C*H*HCH_3, *anti*), 2.12-2.05 (m, 1H, C*H*HCH_3, *syn*), 1.73-1.63 (m, 1H, CH*H*CH_3, *anti*), 1.60-1.50 (m, 1H, C*H*HCH_3, *syn*), 0.93 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3, *syn*), 0.90 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *anti*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 136.5 (C_{Ar}, *syn*), 135.7 (C_{Ar}, *anti*), 132.8 (C_{Ar}, *syn*), 131.9 (C_{Ar}, *anti*), 130.2 (CH_{Ar}, *syn*), 130.0 (CH_{Ar}, *syn*), 129.9 (CH_{Ar}, *anti*), 129.8 (CH_{Ar}, *anti*), 128.4 (CH_{Ar}, *anti*), 128.3 (CH_{Ar}, *syn*), 127.8 (CH_{Ar}, *syn*), 127.4 (CH_{Ar}, *anti*), 94.8 ($CHNO_2$, *syn*), 91.5 ($CHNO_2$, *anti*), 71.3 (CHOH, *syn*), 71.0 (CHOH, *anti*), 23.7 (CH_2, *syn*), 19.9 (CH_2, *anti*), 10.6 (CH_3, *anti*), 10.4 (CH_3, *syn*) ppm.

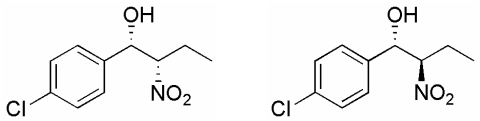
HPLC: AD-H, *n*-heptan:IPA (99:01), 0.8 mL/min, 20 °C, 220 nm, t_R = 40.5 min (*S*,*R*), 52.7 min (*R*,*S*), 99.9 min (*S*,*S*), 105.9 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3513s_{br}, 3069w, 2977s, 2939m, 2883w, 1693m, 1551s, 1466s, 1442s, 1374s, 1344s, 1304m, 1269m, 1197m, 1131m, 1035s, 926w, 806m, 761s.

Elemental analysis calcd (%) for $C_{10}H_{12}ClNO_3$ (229.66 g/mol): C 52.30, H 5.27, N 6.10; found: C 52.42, H 5.26, N 5.98.

MS (FAB, NBA): m/z (%) =230 (13, [M+H^+]), 225 (13), 214 (18), 212 (59), 183 (29), 168 (21), 166 (59), 155 (27), 153 (48), 141 (55), 139 (25), 138 (42), 137 (100), 107 (22), 91 (27), 90 (32), 89 (24), 77 (48).

(1*S*,2*S*) 1-(4-Chloro-phenyl)-2-nitro-butan-1-ol (*syn*-222l) and (1*S*,2*R*) 1-(4-chloro-phenyl)-2-nitro-butan-1-ol (*anti*-222l)



Product **222l** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 4-chlorobenzaldehyde (**53l**, 70 mg, 0.50 mmol). After stirring 1 day at

room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.31, hexane : EtOAc 6 : 1) on silica to give a colorless oil (110 mg, 96%).

$C_{10}H_{12}ClNO_3$ (229.66 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.40-7.31 (m, 8H, H_{Ar}, *anti* + *syn*), 5.17 (dd, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C*H*OH, *anti*), 5.03 (dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, C*H*OH, *syn*), 4.57 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, $CHNO_2$, *syn*), 4.53 (ddd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, $CHNO_2$, *anti*), 2.75 (d, $^3J_{HH}$ = 3.3 Hz, 1H, OH, *anti*), 2.53 (d, $^3J_{HH}$ = 4.5 Hz, 1H, OH, *syn*), 2.21-2.09 (m, 1H, C*H*HCH$_3$, *anti*), 1.92-1.83 (m, 1H, CH*H*CH$_3$, *anti*), 1.90-1.80 (m, 1H, C*H*HCH$_3$, *syn*), 1.48-1.38 (m, 1H, CH*H*CH$_3$, *syn*), 0.94 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *anti*), 0.88 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3, *syn*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 137.3 (C_{Ar}, *syn*), 137.1 (C_{Ar}, *anti*), 135.2 (C_{Ar}, *syn*), 134.7 (C_{Ar}, *anti*), 129.4 (2C, CH_{Ar}, *syn*), 129.1 (2C, CH_{Ar}, *anti*), 128.3 (2C, CH_{Ar}, *syn*), 127.7 (2C, CH_{Ar}, *anti*), 95.1 ($CHNO_2$, *syn*), 94.6 ($CHNO_2$, *anti*), 74.9 (CHOH, *syn*), 73.7 (CHOH, *anti*), 24.0 (CH_2, *syn*), 21.4 (CH_2, *anti*), 10.5 (CH_3, *anti*), 10.2 (CH_3, syn) ppm.

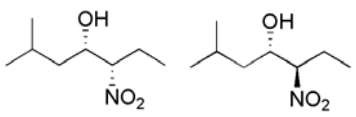
IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3440s$_{br}$, 3067w, 2974s, 2938s, 1718s, 1596m, 1551s, 1490s, 1460s, 1374s, 1342m, 1258s, 1091s, 1050s, 1014s, 832s, 806s, 726w.

HPLC: AD-H, *n*-heptan : *i*-PrOH (96 : 04), 0.8 mL/min, 20 °C, 215 nm, t_R = 27.7 min (*S*,*R*), 30.2 min (*R*,*S*), 39.3 min (*R*,*R*), 47.9 min (*S*,*S*).

Elemental analysis calcd (%) for $C_{10}H_{12}ClNO_3$ (229.66 g/mol): C 52.30, H 5.27, N 6.10; found: C 52.10, H 5.22, N 5.92.

MS (EI, 70 eV): m/z (%) = 229 (1, M^+), 182 (12), 143 (25), 142 (22), 141 (100), 140 (50), 139 (76), 113 (19), 111 (37), 77 (38), 75 (19), 57 (11), 51 (12), 50 (13), 43 (17), 41 (17).

(4*S*,5*S*)-2-Methyl-5-nitro-heptan-4-ol (*syn*-222n) and (4*S*,5*R*)-2-methyl-5-nitro-heptan-4-ol (*anti*-222n)



Product **222n** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), isovaleraldehyde (**53n**, 0.11 mL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude

product was purified by column chromatography (3 x 25 cm**, R_f** = 0.24, 0.30, hexane : EtOAc 6 : 1) on silica to give a colorless oil (53% conversion).

$C_8H_{17}NO_3$ (175.23 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.37-4.31 (m, 2H, $CHNO_2$, *syn* + *anti*), 4.13-4.08 (m, 1H, C*H*OH, *anti*), 3.99-3.92 (m, 1H, C*H*OH, *syn*), 2.24 (d, $^3J_{HH}$ = 4.8 Hz, OH, *anti*), 2.17-2.02 (m, 2H, C*H*HCHOH, *syn* + *anti*), 2.08 (brs, 1H, OH, *syn*), 1.92-1.78 (m, 4H, $(CH_3)_2CHCHHCHOH$, *syn* + *anti*), 1.51-1.37 (m, 2H, C*H*HCH$_3$, *syn* + *anti*), 1.29-1.15 (m, 2H, CH*H*CH$_3$, *syn* + *anti*), 1.02-0.91 (m, 18H, CH_3) ppm.

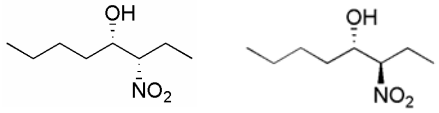
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 94.9 ($CHNO_2$, *syn*), 94.4 ($CHNO_2$, *anti*), 70.5 (CHOH, *anti*), 70.2 (CHOH, *syn*), 42.7 (CH_2CHOH, *syn*), 42.2 (CH_2CHOH, *anti*), 24.6 ($CH(CH_3)_2$, *anti*), 24.5 ($CH(CH_3)_2$, *syn*), 23.6 (CH_2CH_3, *syn*), 23.5 (CH_2CH_3, *anti*), 21.7 ($CH(CH_3CH_3)$, *syn*), 21.6 ($CH(CH_3CH_3)$, *anti*), 21.5 ($CH(CH_3CH_3)$, *syn* + *anti*), 10.7 (CH_2CH_3, *anti*), 10.3 (CH_2CH_3, *syn*) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (99 : 01), 0.6 mL/min, 20 °C, 207 nm, t_R = 41.7 min (*S*,*R*), 49.9 min (*R*,*S*), 58.8 min (*S*,*S*), 64.6 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3443s, 2959s, 2876s, 1708w, 1549s, 1463s, 1373s, 1307s, 1258m, 1144m, 1098m, 1056m, 1019m, 973w, 926w, 847w, 807s.

Elemental analysis calcd (%) for $C_8H_{17}NO_3$ (175.23 g/mol): C 54.84, H 9.78, N 7.99; found: C 54.59, H 9.55, N 7.88.

(3*S*,4*S*)- 3-Nitro-octan-4-ol (*syn*-222p) and (3*S*,4*R*)- 3-nitro-octan-4-ol (*anti*-222p)



Product **222p** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), valeraldehyde (**53p**, 31 µL, 0.50 mmol). After stirring 4 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.26, 0.34, hexane : TBME 5 : 1) on silica to give a colorless oil (64% conversion).

$C_8H_{17}NO_3$ (175.23 g/mol).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.38 (ddd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, $CHNO_2$, *syn*), 4.36 (ddd, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 3.6 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, $CHNO_2$, *anti*), 3.91-3.86 (m, 2H, C*H*OH, *syn* + *anti*), 2.31 (d, $^3J_{HH}$ = 4.7 Hz, 1H, OH, *anti*), 2.26 (d, $^3J_{HH}$ = 7.2 Hz, 1H, OH, *syn*), 2.15-2.07 (m, 1H, C*H*HCHNO$_2$, *anti*), 2.09-2.00 (m, 1H, C*H*HCHNO$_2$, *syn*), 1.92-1.84 (m, 1H, CH*H*CHNO$_2$, *anti*), 1.90-1.82 (m, 1H, CH*H*CHNO$_2$, *syn*), 1.55-1.28 (m, 6H, (CH_2)$_3$CH$_3$, *syn*), 1.53-1.29 (m, 6H, (CH_2)$_3$CH$_3$, *anti*), 0.99 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $CHNO_2CH_2CH_3$, *anti*), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $CHNO_2CH_2CH_3$, *syn*), 0.91 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $(CH_2)_3CH_3$, *syn*), 0.90 (t, $^3J_{HH}$ = 7.0 Hz, 3H, $(CH_2)_3CH_3$, *anti*) ppm.

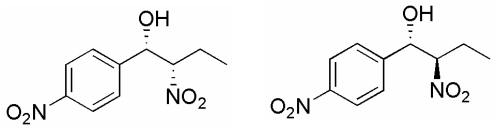
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 94.4 ($CHNO_2$, *syn*), 94.0 ($CHNO_2$, *anti*), 72.4 (CHOH, *anti*), 71.9 (CHOH, *syn*), 33.4 (CH_2CHOH, *syn*), 33.0 (CH_2CHOH, *anti*), 27.9 (CH_2CH_2CHOH, *anti*), 27.5 (CH_2CH_2CHOH, *syn*), 24.0 (CH_2CHNO_2, *syn*), 22.6 ($(CH_2)_2CH_2CH_3$, *syn*), 22.5 (CH_2CHNO_2, *anti*), 21.6 ($(CH_2)_2CH_2CH_3$, *anti*), 14.1 ($(CH_2)_3CH_3$, *anti*), 14.0 ($(CH_2)_3CH_3$, *syn*), 10.7 ($CH_3CH_2CHNO_2$, *anti*), 10.3 ($CH_3CH_2CHNO_2$, *syn*) ppm.

HPLC: AD-H, *n*-heptan : *i*-PrOH (99 : 01), 0.5 mL/min, 40 °C, 210 nm, t_R = 51.0 min (*S*,*R*), 56.5 min (*R*,*S*), 64.6 min (*S*,*S*), 74.8 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3419s$_{br}$, 2929s, 2865m, 1552s, 1460m, 1377m, 1262w, 1115w, 1057w, 806w.

Elemental analysis calcd (%) for $C_8H_{17}NO_3$ (175.23 g/mol): C 54.84, H 9.78, N 7.99; found: C 54.61, H 9.49, N 8.06.

(1*S*,2*S*) 2-Nitro-1-(4-nitro-phenyl)-butan-1-ol (*syn*-222q) and (1*S*,2*R*) 2-nitro-1-(4-nitro-phenyl)-butan-1-ol (*anti*-222q)



Product **222q** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 4-nitrobenzaldehyde (**53q**, 76 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.35, 0.40, hexane : TBME 3 : 1) on silica to give a colorless solid (96 mg, 80%).

$C_{10}H_{12}N_2O_5$ (240.21 g/mol).

m.p. 89-90 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 8.26 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H_{Ar}, *syn*), 8.24 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}, *anti*), 7.58 (m, 4H, H_{Ar}, *syn* + *anti*), 5.32 (d, $^3J_{HH}$ = 4.3 Hz, 1H, C*H*OH, *anti*), 5.17 (dd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*OH, *syn*), 4.61 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, $CHNO_2$, *syn*), 4.57 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.3 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, $CHNO_2$, *anti*), 3.11 (brs, 1H, OH, *anti*), 3.00 (d, $^3J_{HH}$ = 4.8 Hz, 1H, OH, *syn*), 2.23-2.12 (m, 1H, C*H*HCH_3, *anti*), 1.96-1.88 (m, 1H, C*H*HCH_3, *syn*), 1.85-1.77 (m, 1H, CH*H*CH_3, *anti*), 1.51-1.44 (m, 1H, CH*H*CH_3, *syn*), 0.94 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *anti*), 0.92 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *syn*) ppm.

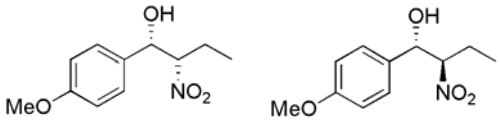
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 148.4 (C_{Ar}, *syn*), 148.1 (C_{Ar}, *anti*), 145.7 (C_{Ar}, *syn*), 145.6 (C_{Ar}, *anti*), 127.9 (2C, CH_{Ar}, *syn*), 127.4 (2C, CH_{Ar}, *anti*), 124.3 (2C, CH_{Ar}, *syn*), 124.1 (2C, CH_{Ar}, *anti*), 94.6 ($CHNO_2$, *syn*), 94.2 ($CHNO_2$, *anti*), 74.4 (CHOH, *syn*), 73.3 (CHOH, *anti*), 24.0 (CH_2, *syn*), 21.3 (CH_2, *anti*), 10.5 (CH_3, *anti*) 10.2 (CH_3, *syn*) ppm.

HPLC: AD-H, *n*-heptan : EtOH (90 : 10), 0.8 mL/min, 20 °C, 215 nm, t_R = 22.0 min (*S*,*R*), 27.6 min (*R*,*S*), 45.6 min (*R*,*R*), 70.3 min (*S*,*S*).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3461m, 3116w, 2981w, 2917w, 2850w, 1606m, 1558s, 1520s, 1462w, 1434w, 1345s, 1258w, 1227w, 1193w, 1105w, 1055m, 1007w, 931w, 854m, 802m, 757w, 703m.

Elemental analysis calcd (%) for $C_{10}H_{12}N_2O_5$ (240.21 g/mol): C 50.00, H 5.04, N 11.66; found: C 50.08, H 4.95, N 11.56.

(1*S*,2*S*) 1-(4-Methoxy-phenyl)-2-nitro-butan-1-ol (*syn*-222r) and (1*S*,2*R*) 1-(4-Methoxy-phenyl)-2-nitro-butan-1-ol (*anti*-222r)



Product **222r** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 4-methoxybenzaldehyde (**53r**, 61 µL, 0.50 mmol). After stirring 2 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.13, hexane : EtOAc 6 : 1) on silica to give a colorless oil (65 mg, 58%).

$C_{11}H_{15}NO_4$ (225.24 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.30-7.26 (m, 4H, H_{Ar}, *syn* + *anti*), 6.94-6.88 (m, 4H, H_{Ar}, *syn* + *anti*), 5.10 (dd, $^3J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*OH, *anti*), 4.99 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, C*H*OH, *syn*), 4.62-4.53 (m, 2H, $CHNO_2$, *syn* + *anti*), 3.82 (s, 3H, OCH_3, *syn*), 3.81 (s, 3H, OCH_3, *anti*), 2.62 (d, $^3J_{HH}$ = 2.0 Hz, 1H, OH, *anti*), 2.45 (d, $^3J_{HH}$ = 3.6 Hz, 1H, OH, *syn*), 2.01-1.91 (m, 1H, C*H*HCH_3, *anti*), 1.88-1.77 (m, 1H, C*H*HCH_3, *syn*), 1.45-1.33 (m, 2H, CH*H*CH_3, *syn* + *anti*), 0.95 (t, $^3J_{HH}$ = 7.4 Hz, CH_3, *anti*), 0.87 (t, $^3J_{HH}$ = 7.3 Hz, CH_3, *syn*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 160.3 (C_{Ar}, *syn*), 160.2 (C_{Ar}, *anti*),130.9 (C_{Ar}, *syn*), 130.8 (C_{Ar}, *anti*), 128.3 (2C, CH_{Ar}, *syn*), 127.6 (2C, CH_{Ar}, *anti*), 114.5 (2C, CH_{Ar}, *syn*), 114.3 (2C, CH_{Ar}, *anti*), 95.5 ($CHNO_2$, *syn*), 94.9 ($CHNO_2$, *anti*), 75.3 (CHOH, *syn*), 74.2 (CHOH, *anti*), 55.5 (OCH_3, *syn*), 55.4 (OCH_3, *anti*), 24.1 (CH_2CH_3, *syn*), 22.8 (CH_2CH_3, *anti*), 10.5 (CH_2CH_3, *anti*), 10.2 (CH_2CH_3, *syn*) ppm.

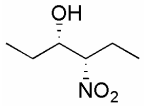
HPLC: OB-H, *n*-heptan : *i*-PrOH (91 : 09), 0.5 mL/min, 20 °C, 215 nm, t_R = 41.2 min (*R*,*S*), 44.1 min (*S*,*R*), 55.8 min (*S*,*S*), 63.3 min (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3466m_{br}, 3080w, 2981s, 2941m, 1738s, 1600m, 1548s, 1464s, 1374s, 1245s, 1164w, 1046s, 938w, 833w, 803w.

Elemental analysis calcd (%) for $C_{11}H_{15}NO_4$ (225.24 g/mol): C 58.66, H 6.71, N 6.22; found: C 58.72, H 6.71, N 6.18.

MS (EI, 70 eV): m/z (%) = 225 (4, M^+), 137 (100), 136 (12), 135 (23), 109 (18), 94 (10), 77 (23), 43 (13), 41 (12), 39 (12).

(3*S*,4*S*)-4-Nitro-hexan-3-ol (*syn*-222s)[202]



Product *syn*-**222s** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), propionaldehyde (**53s**, 36 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.24, hexane : EtOAc 6 : 1) on silica to give a colorless oil (33 mg, 45% yield).

$C_6H_{13}NO_3$ (147.17 g/mol).

$[\alpha]_D^{20}$ = -14 (*c* = 0.83, CH_2Cl_2, 89% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.40 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, $CHNO_2$), 3.87-3.79 (m, 1H, C*H*OH), 2.23 (d, $^3J_{HH}$ = 6.8 Hz, 1H, OH), 2.10-1.98 (m, 1H, C*H*HCHNO$_2$), 1.91-1.81 (m, 1H, CH*H*CHNO$_2$), 1.65-1.52 (m, 1H, C*H*HCHOH), 1.52-1.41 (m, 1H, CH*H*CHOH), 1.02 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CHOHCH$_2$C*H*$_3$), 0.98 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CHNO$_2$CH$_2$C*H*$_3$) ppm.

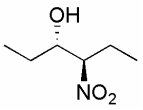
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 94.1 ($CHNO_2$), 73.2 (CHOH), 26.7 (CHOH*C*H$_2$CH$_3$), 24.0 (CHNO$_2$*C*H$_2$CH$_3$), 10.3 (CHNO$_2$CH$_2$*C*H$_3$), 9.8 (CHOHCH$_2$*C*H$_3$) ppm.

HPLC: OB-H, *n*-heptan : *i*-PrOH (98 : 02), 0.6 mL/min, 20 °C, 210 nm, t_R =37.0 min (*R*,*R*), 43.7 min (*S*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3439s, 2975s, 2940s, 2882m, 1707m, 1552s, 1461m, 1440m, 1377m, 1310m, 1261m, 1230w, 1129m, 979m, 929m, 888w, 810m, 734w.

Elemental analysis calcd (%) for $C_6H_{13}NO_3$ (147.17 g/mol): C 48.97, H 8.90, N 9.52; found: C 48.87, H 8.80, N 9.13.

(3*S*,4*R*)-4-Nitro-hexan-3-ol (*anti*-222s)[202]



Product *anti*-**222s** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), propionaldehyde (**53s**, 36 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.23, hexane : EtOAc 6 : 1) on silica to give a colorless oil (7 mg, 10% yield).).

$C_6H_{13}NO_3$ (147.17 g/mol).

$[\alpha]_D^{20}$ = -12 (*c* = 0.10, $CHCl_3$, 49% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.38 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 3.6 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, $CHNO_2$), 3.97-3.93 (m, 1H, C*H*OH), 2.25 (brs, 1H, OH), 2.18-2.08 (m, 1H, C*H*HCHNO$_2$), 1.94-1.84 (m, 1H, CH*H*CHNO$_2$), 1.56-1.48 (m, 2H, C*H*$_2$CHOH), 1.02 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CHOHCH$_2$C*H*$_3$), 1.00 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CHNO$_2$CH$_2$C*H*$_3$) ppm.

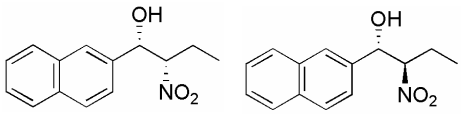
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 93.7 ($CHNO_2$), 73.7 (CHOH), 26.4 (CHOH*C*H$_2$CH$_3$), 21.6 (CHNO$_2$*C*H$_2$CH$_3$), 10.7 (CHNO$_2$*C*H$_2$CH$_3$), 10.2 (CHOH*C*H$_2$CH$_3$) ppm.

HPLC: OB-H, *n*-heptan : *i*-PrOH (98 : 02), 0.6 mL/min, 20 °C, 210 nm, t_R = 24.7 min (*S*,*R*), 31.4 min (*R*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3422m, 2974s, 2939s, 2882m, 1720w, 1550s, 1461m, 1378m, 1306w, 1260m, 1112m, 983w, 930w, 887w, 808m.

Elemental analysis calcd (%) for $C_6H_{13}NO_3$ (147.17 g/mol): C 48.97, H 8.90, N 9.52; found: C 48.90, H 8.85, N 9.25.

(1*S*,2*S*)- 1-Naphthalen-2-yl-2-nitro-butan-1-ol (*syn*-222u) and (1*S*,2*R*)- 1-naphthalen-2-yl-2-nitro-butan-1-ol (*anti*-222u)



Product **222u** was prepared according to **general procedure IV** from nitropropane (**51**, 0.44 mL, 5.00 mmol), 2-naphtaldehyde (**53u**, 78 mg, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.19, hexane : EtOAc 6 : 1) on silica to give a colorless oil (86 mg, 70%).

$C_{14}H_{15}NO_3$ (245.27 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.92-7.81 (m, 8H, H_{Ar}, *syn* + *anti*), 7.53-7.45 (m, 6H, H_{Ar}, *syn* + *anti*), 5.38 (dd, $^3J_{HH}$ = 4.0 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*OH, *anti*), 5.22 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 4.0 Hz, 1H, C*H*OH, *syn*), 4.73 (ddd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, $CHNO_2$, *syn*), 4.69 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, $CHNO_2$, *anti*), 2.79 (d, $^3J_{HH}$ = 2.8 Hz, 1H, OH, *anti*), 2.52 (d, $^3J_{HH}$ = 4.1 Hz, 1H, OH, *syn*), 2.27-2.19 (m, 1H, C*H*HCH_3, *anti*), 1.94-1.87 (m, 1H, C*H*HCH_3, *syn*), 1.95-1.90 (m, 1H, CH*H*CH_3, *anti*), 1.50-1.39 (m, 1H, CH*H*CH_3, *syn*), 0.94 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3, *anti*), 0.88 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3, *syn*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 136.1 (C_{Ar}, *syn*), 136.0 (C_{Ar}, *anti*), 133.7 (C_{Ar}, *syn*), 133.5 (C_{Ar}, *anti*), 133.3 (C_{Ar}, *syn*), 133.2 (C_{Ar}, *anti*), 129.3 (CH_{Ar}, *syn*), 128.9 (CH_{Ar}, *anti*), 128.3 (CH_{Ar}, *anti*), 128.2 (CH_{Ar}, *syn*), 128.0 (CH_{Ar}, *syn*), 127.9 (CH_{Ar}, *anti*), 126.9 (2C, CH_{Ar}, *syn*), 126.8 (CH_{Ar}, *syn*), 126.7 (2C, CH_{Ar}, *anti*), 125.8 (CH_{Ar}, *anti*), 124.0 (CH_{Ar}, *syn*), 123.6 (CH_{Ar}, *anti*), 95.3 ($CHNO_2$, *syn*), 94.7 ($CHNO_2$, *anti*), 75.9 (CHOH, *syn*), 74.5 (CHOH, *anti*), 21.3 (CH_2, *syn*), 21.2 (CH_2, *anti*), 10.6 (CH_3, *anti*), 10.2 (CH_3, *anti*) ppm.

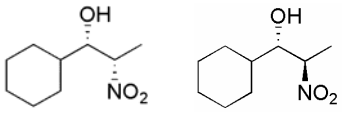
HPLC: AD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.5 mL/min, 20 °C, 215 nm, t_R = 22.0 min (*S,R*), 22.9 min (*R,S*), 31.9 (*R,R*), 34.2 (*S,S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3451s_{br}, 3056m, 2975s, 2937m, 2883m, 1689m, 1627w, 1600w, 1550s, 1511w, 1461m, 1371s, 1297m, 1264m, 1170w, 1124m, 1945s; 955w, 899m, 861s, 820s, 752s.

HRMS (EI^+): Exact Mass calcd for $C_{14}H_{15}NO_3$ [M^+], 245.10519. Found 245.10529.

MS (EI, 70 eV): m/z (%) = 245 (5, M^+), 157 (27), 156 (100), 155 (82), 129 (11), 128 (26), 127 (89), 126 (18), 43 (15), 41 (13).

(1*S*,2*S*) 1-Cyclohexyl-2-nitro-propan-1-ol (*syn*-221c) and (1*S*,2*R*) 1-cyclohexyl-2-nitro-propan-1-ol (*anti*-221c)



Product **221c** was prepared according to **general procedure IV** from nitroethane (**54b**, 0.36 mL, 5.00 mmol), cyclohexanecarboxaldehyde (**53c**, 60 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.45, pentane : EtOAc 6 : 1) on silica to give a colorless oil (82% conversion).

$C_9H_{17}NO_3$ (187.24 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.72 (app quintet, $^3J_{HH}$ = 6.8 Hz, 1H, $CHNO_2$, *syn*), 4.64 (qd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, $CHNO_2$, *anti*), 3.95 (ddd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 4.8 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, CHOH, *anti*), 3.65 (app td, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, CHOH, *syn*), 2.16 (d, $^3J_{HH}$ = 4.8 Hz, 1H, OH, *anti*), 2.11 (d, $^3J_{HH}$ = 7.6 Hz, 1H, OH, *syn*), 1.83-1.74 (m, 4H, H_{Cy}, *syn* + *anti*), 1.71-1.62. (m, 6H, H_{Cy}, *syn* + *anti*), 1.56 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3, *syn*), 1.54 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3, *anti*) 1.46-1.37 (m, 2H, H_{Cy}, *syn* + *anti*), 1.28-1.17 (m, 10H, H_{Cy}, *syn* + *anti*) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 85.6 ($CHNO_2$, *syn*), 84.4 ($CHNO_2$, *anti*), 77.4 (CHOH, *anti*), 76.4 (CHOH, *syn*), 40.3 (CH_{Cy}, *anti*), 40.0 (CH_{Cy}, *syn*), 30.1 (CH_{2Cy}, *anti*

+ *syn*), 29.1 (CH_{2Cy}, *anti*), 29.0 (CH_{2Cy}, *syn*), 26.3 (CH_{2Cy}, *syn* + *anti*), 26.2 (CH_{2Cy}, *syn*), 26.1 (CH_{2Cy}, *anti*), 25.9 (CH_{2Cy}, *syn*), 25.7 (CH_{2Cy}, *anti*), 16.6 (CH_3, *syn*), 12.0 (CH_3, *anti*) ppm.

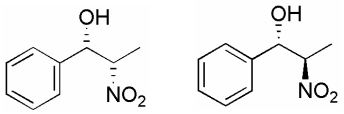
HPLC: AD-H, *n*-heptan : *i*-PrOH (97 : 03), 0.8 mL/min, 20 °C, 215 nm, t_R = 20.2 min (1*R*, 2*S*), 21.6 min (1*S*, 2*S*), 23.6 min (1*S*, 2*R*), 33.0 min (1*R*, 2*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3449m_{br}, 2929s, 2855s, 1551s, 1409s, 1392s, 1359m, 1300m, 1185w, 1119m, 1030w,985m, 870w.

Elemental analysis calcd (%) for $C_9H_{17}NO_3$ (187.24 g/mol): C 57.73, H 9.15, N 7.48; found: C 57.87, H 9.04, N 7.34.

MS (FAB, NBA): m/z (%) = 188 (83, [M+H^+]), 186 (13), 170 (11), 141 (41), 138 (24), 135 (14), 123 (56), 95 (22), 91 (18), 76 (100).

(1*S*,2*S*)-2-nitro-1-phenylpropan-1-ol (*syn*-221e) and (1*S*,2*R*)-2-nitro-1-phenylpropan-1-ol (*anti*-221e)



Product **221e** was prepared according to **general procedure IV** from nitroethane (**54b**, 0.36 mL, 5.00 mmol), benzaldehyde (**53e**, 50 µL, 0.50 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.47, hexane : EtOAc 6 : 1) on silica to give a colorless oil (72 mg, 80%).

$C_9H_{11}NO_3$ (181.19 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295K): δ = 7.38-7.31 (m, 10H, H_{Ph}, *syn* + *anti*), 5.41 (dd, $^3J_{HH}$ = 3.5 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*OH, *anti*), 5.04 (dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*OH, *syn*), 4.78 (dq, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, $CHNO_2$, *syn*), 4.52 (dq, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, $CHNO_2$, *anti*), 2.66 (d, $^3J_{HH}$ = 3.5 Hz, 1H, OH, *anti*), 2.52 (d, $^3J_{HH}$ = 3.8 Hz, 1H, OH, *syn*), 1.53 (d, $^3J_{HH}$ = 6.8 Hz, 1H, CH_3, *anti*), 1.33 (d, $^3J_{HH}$ = 6.8 Hz, 1H, CH_3, *syn*) ppm**.**

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 138.4 (C_{Ph}, *syn*), 138.2 (C_{Ph}, *anti*), 129.4 (2C, CH_{Ph}, *anti*), 129.2 (2C, CH_{Ph}, *syn*), 128.9 (CH_{Ph}, *syn*), 128.7 (CH_{Ph}, *anti*), 127.1 (2C, CH_{Ph}, *syn*), 126.1 (2C, CH_{Ph}, *anti*), 88.5 ($CHNO_2$, *syn*), 87.6 ($CHNO_2$, *anti*), 76.4 (CHOH, *syn*), 74.0 (CHOH, *anti*), 16.6 (CH_3, *syn*), 12.2 (CH_3, *anti*) ppm.

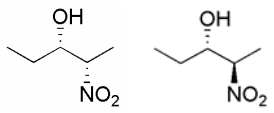
HPLC: AD-H, *n*-heptan : *i*-PrOH (90 : 10), 0.9 mL/min, 20 °C, 210 nm, t_R = 9.3 min (*S*,*R*), 10.3 min (*R*,*S*), 12.0 min (*S*,*S*), 13.3 (*R*,*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3503m_{br}, 3379m, 2961s, 2906w, 1696m, 1551s, 1453m, 1390m, 1361s, 1289w, 1248w, 1202w, 1171w, 1051m, 1022m, 902w, 871w, 765m, 702s.

Elemental analysis calcd (%) for $C_9H_{11}NO_3$ (181.19 g/mol): C 59.66, H 6.12, N 7.73; found: C 59.36, H 6.11, N 7.81.

MS (FAB, NBA): m/z (%) = 182 (1, [M+H^+]), 57 (100), 41 (24).

(2*S*,3*S*)-2-nitropentan-3-ol (*syn*-221s) and (2*R*,3*S*)-2-nitropentan-3-ol (*anti*-221s)



Product **221s** was prepared according to **general procedure IV** from nitroethane (**54b**, 0.36 mL, 5.00 mmol), propionaldehyde (**53s**, 36 µL, 0.50 mmol). After stirring 5 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.44, hexane : EtOAc 6 : 1) on silica to give a colorless oil (80% conversion).

$C_5H_{11}NO_3$ (133.15 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.56 (quint, $^3J_{HH}$ = 6.8 Hz, 1H, $CHNO_2$, *syn*), 4.53 (dq, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, $CHNO_2$, *anti*), 4.11-4.08 (m, 1H, C*H*OH, *anti*), 3.88-3.81 (m, 1H, C*H*OH, *syn*), 2.28 (d, $^3J_{HH}$ = 4.8 Hz, 1H, OH, *anti*), 2.19 (d, $^3J_{HH}$ = 6.8 Hz, 1H, OH, *syn*), 1.65-1.43 (m, 4H, C$H_2$$CH_3$, *syn* + *anti*), 1.04 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3, *syn*), 1.03 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3, *anti*) ppm.

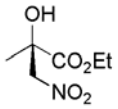
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 87.5 ($CHNO_2$, *syn*), 86.2 ($CHNO_2$, *anti*), 74.2 (CHOH, *syn*), 73.6 (CHOH, *anti*), 26.3 (CH_2, *anti*), 26.2 (CH_2, *syn*), 16.4 (CH_3NO_2, *syn*), 12.5 (CH_3NO_2, *anti*), 10.3 (CH_2CH_3, *anti*), 9.6 (CH_2CH_3, syn) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (98 : 02), 0.5 mL/min, 20 °C, 210 nm, t_R =27.7 min (*R*,*S*), 31.5 min (*S*,*R*), 33.1 min (*R*,*R*), 36.2 min (*S*,*S*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3421s_{br}, 2973s, 2942s, 1551s, 1459s, 1392s, 1360s, 1301w, 1257w, 1111m, 1051w, 978s, 933w, 872w, 780w.

Elemental analysis calcd (%) for $C_5H_{11}NO_3$ (133.15 g/mol): C 45.10, H 8.33, N 10.52; found: C 44.95, H 8.17, N 10.30.

(*R*)-2-hydroxy-2-methyl-3-nitro-propionic acid ethyl ester (232)



Ligand **40f** (23.0 mg, 0.055 mmol), copper (II) triflate (18.1 mg, 0.050 mmol) and triethylamine (7.6 µL, 0.055 mmol) were added to a dry young tube containing a stir bar. Ethanol (1.5 mL) was added and the mixture was stirred for three to five hours. To the resulting dark green solution, ethyl pyruvate (**79b**, 28 µL, 0.250 mmol), nitromethane (**54a**, 0.27 mL, 2.50 mmol) and triethylamine (7 µL, 0.05 mmol) were added. After stirring 24 hours, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.34, CH_2Cl_2 : Et_2O 9 : 1) on silica to give a pale yellow oil (26 mg, 60%).

$C_6H_{11}NO_5$ (177.16 g/mol).

$[\alpha]_D^{20}$ = +2 (*c* = 0.23, $CHCl_3$, 17% *ee*).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 4.84 (d, $^2J_{HH}$ = 13.6 Hz, 1H, C*H*HNO_2), 4.56 (d, $^2J_{HH}$ = 13.6 Hz, 1H, CH*H*NO_2), 3.72 (s, 1H, OH), 4.38-4.30 (m, 2H, OC*H*$_2$$CH_3$), 1.46 (s, 3H, CCH_3), 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 173.6 (C=O), 81.1 (CH_2NO_2), 72.6 (COH), 63.3 (OCH_2), 24.0 (CCH_3), 14.2 (OCH_2CH_3) ppm.

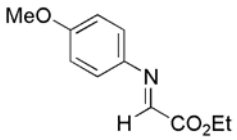
HPLC: OB-H, *n*-heptan : *i*-PrOH (90 : 10), 0.9 mL/min, 20 °C, 215 nm, t_R =16.1 min (*S*), 19.2 min (*R*).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3492m_{br}, 2987m, 2938w, 1739s, 1561s, 1454m, 1416m, 1381s, 1276m, 1227s, 1173m, 1016m, 960w, 911s, 861w, 773w, 734s, 656w.

Elemental analysis calcd (%) for $C_6H_{11}NO_5$ (177.15 g/mol): C 40.68, H 6.26, N 7.91; found: C 40.85, H 6.16, N 7.91.

8.6 Aza-Henry Reaction

N- (*p*-Methoxyphenyl)- α- imino ester (50b)



In 20 mL of dichloromethane were added ethyl glyoxylate (**48**, 6.60 g, 65.0 mmol) (freshly distilled over P_2O_5), *p*-methoxyaniline (**263**, 7.90 g, 65.0 mmol) and 4Å molecular sieves. The mixture was stirred at room temperature during one day. After filtration, the solution was concentrated to give almost pure imine. A chromatography (10 x 18 cm**)** on silica using dichloromethane as eluent afforded the imine (13.5 g) as a yellow oil in a quantitative yield.

$C_{11}H_{13}NO_3$ (207.23 g/mol).

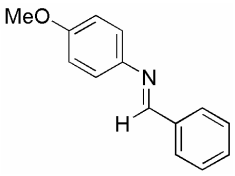
R_f = 0.23 (cyclohexane : EtOAc 80 : 20).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.94 (s, 1H, N=CH), 7.36 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 6.93 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 4.41 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 3.83 (s, 3H, OCH_3), 1.40 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_2CH_3) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 164.0 (C=N), 160.9 (C=O), 148.4 (C_{Ar}), 141.8 (C_{Ar}), 124.0 (2C, CH_{Ar}), 114.9 (2C, CH_{Ar}), 62.3 (CH_2CH_3), 55.9 (OCH_3), 14.6 (CH_2CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3389w, 3054w, 2982m, 2837w, 1731s, 1588m, 1512s, 1463m, 1400w, 1318m, 1249s, 1192s, 1094m, 1034s, 942w, 829s, 736s.

N-benzylidene-*p*-anisidine (50c)

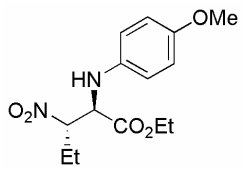


A 100-mL flask was charged with 45 mL of dichloromethane and benzaldehyde (**53e**, 3.00 mL, 30.0 mmol), and then was cooled in an ice-water bath while a solution of *p*- methoxyaniline (**263,** 3.50 g, 28.0 mmol) in 5 mL of dichloromethane was added dropwise

via syringe over 15 minutes. After 30 minutes, 7.5 g of anhydrous $MgSO_4$ was added in one portion. The ice-water bath was removed, and the reaction mixture was stirred at room temperature for 2 hours. The resulting mixture was then filtered through a sintered glass funnel with the aid of two 5-mL portions of dichloromethane, and the filtrate was concentrated at reduced pressure by rotary evaporation at room temperature to give a pale brown powder. This material was dissolved in 150 mL of ethanol heated in an 80°C oil bath while 270 mL of hot water was added with stirring. The resulting solution was allowed to cool to room temperature and then was cooled in an ice-water bath for 2 hours. Filtration provided *N*-benzylidene-*p*-anisidine (5.31 g, 88%) as brown metallic plates.

$C_{14}H_{13}NO$ (211.26 g/mol).
m.p. 63-64 °C.
^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 8.50 (s, 1H, N=CH), 7.90-7.87 (m, 2H, H_{Ar}), 7.47-7.45 (m, 3H, H_{Ar}), 7.25-7.23 (m, 2H, H_{Ar}), 6.95-6.92 (m, 2H, H_{Ar}), 3.84 (s, 3H, OCH_3) ppm.
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 158.6 (C=N), 158.4 (C_{Ar}), 145.1 (C_{Ar}), 136.6 (C_{Ar}), 131.2 (CH_{Ar}), 128.9 (2C, CH_{Ar}), 128.7 (2C, CH_{Ar}), 122.3 (2C, CH_{Ar}), 114.5 (2C, CH_{Ar}), 55.6 (OCH_3) ppm.
IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3351w, 2954m, 2908w, 2833w, 1654m, 1620s, 1573m, 1503s, 1447m, 1363w, 1291m, 1247s, 1184m, 1109m, 1072w, 1028s, 972w, 879w, 833s, 752m, 718w, 686s, 542s, 492w.
MS (EI, 70 eV): m/z (%) = 211 (100, M^+), 210 (13), 197 (13), 196 (91), 167 (13).

Ethyl 2- (4-Methoxyphenyl) amino-3-nitropentanoate (52h)



Ligand **40i** (4.30 mg, 0.011 mmol), copper (II) bromide (2.20 mg, 0.01 mmol) and triethylamine (1.50 µL, 0.011 mmol) were added to a dry young tube containing a stir bar. Dichloromethane (2 mL) was added and the mixture was stirred 5 hours. To the resulting solution, *N*- (*p*-methoxyphenyl)- α- imino ester (**50b**, 41 mg, 0.20 mmol), triethylamine (1.50 µL, 0.011 mmol) and nitropropane (**51**, 27 µL, 0.30 mmol) were added. After stirring 24 hours, the reaction was quenched with ethanol (0.5 mL). The catalyst was removed by

filtration through silica gel, and the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.19, CH_2Cl_2 : pentane 1 : 1) on silica to give a yellow oil (33 mg, 56%).

$C_{14}H_{20}N_2O_5$ (296.32 g/mol).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.78 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 6.65 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H_{Ar}), 4.72 (td, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, $CHNO_2$), 4.47 (d, $^3J_{HH}$ = 5.8 Hz, 1H, C*H*NH), 4.27-4.18 (m, 2H, O$CH_2$$CH_3$), 3.74 (s, 3H, OCH_3), 2.27-2.19 (m, 1H, CHC*H*HCH_3), 2.03-1.97 (m, 1H, CHCH*H*CH_3), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3), 1.03 (t, $^3J_{HH}$ = 7.3 Hz, 3H, $CHCH_2CH_3$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 170.4 (C=O), 154.1 (C_{Ar}), 140.0 (C_{Ar}), 116.7 (2C, CH_{Ar}), 115.3 (2C, CH_{Ar}), 90.7 (CHNH), 62.7 (O$CH_2$$CH_3$), 61.1 ($CHNO_2$), 56.0 ($OCH_3$), 23.5 (CH$CH_2$$CH_3$), 14.4 ($OCH_2CH_3$), 11.0 ($CHCH_2CH_3$) ppm.

HPLC: OD-H, *n*-heptan : *i*-PrOH (97:03), 0.5 mL/min, 20 °C, 215 nm, t_R = 30.2 min (minor *anti*), 37.9 min (major *anti*), 41.2 min (minor *syn*), 49.2 min (major *syn*).

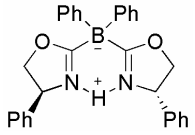
IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3372m, 2979s, 2940s, 2836m, 1738s, 1553s, 1515s, 1462s, 1372s, 1244s, 1199s, 1105m, 1034s, 940w, 824s, 738w.

Elemental analysis calcd (%) for $C_{14}H_{20}N_2O_5$ (296.32 g/mol): C 56.75, H 6.80, N 9.45; found: C 56.55, H 6.75, N 9.56.

MS (EI, 70 eV): m/z (%) = 296 (100, M^+), 208 (36), 178 (12), 177 (100), 176 (21), 162 (38), 134 (51), 122 (11).

8.7 Synthesis of Borabox ligands

[$Ph_2B(Oxa\text{-}Ph)_2$][H] (40o)



General Procedure V: *t*-BuLi (1.7 M in hexanes, 1.78 mL, 3.03 mmol) was added at -100 °C over a 10 minutes period to a solution of (*S*)-4,5-dihydro-4-phenyloxazole (**109e**, 405 mg, 2.75 mmol) in 100 mL of tetrahydrofuran, resulting in a pale yellow solution. After stirring for 30 minutes at this temperature, a solution of Ph_2BCl (**90b**, 276 mg, 1.38 mmol) in toluene

(5 mL) was added through a cannula and the cooling bath immediately removed after addition. After 12 hours, the reaction volatile compounds were removed under vacuum. The ligand was then purified by column chromatography (3 x 25 cm**, R_f** = 0.13, hexane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give compound **40o** as a colorless solid (367 mg, 58%).

$C_{30}H_{27}BN_2O_2$ (458.36 g/mol).

$[\alpha]_D^{20}$ = -91 (c = 0.28, CH_2Cl_2).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 8.59 (bs, 1H, NHN), 7.49 (m_c, 4H, H_{Ph}), 7.34 (m_c, 10H, H_{Ph}), 7.23 (m_c, 6H, H_{Ph}), 5.13 (dd, $^2J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.6 Hz, 2H, OC*H*H), 4.73 (dd, $^2J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 9.1 Hz, 2H, OCH*H*), 4.23 (dd, $^3J_{HH}$ = 9.1, $^3J_{HH}$ = 7.7 Hz, 2H, CHPh) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 195.9 (2C, N=C_{oxa}), 140.8 (2C, C_{Ph}), 134.0 (4C, CH_{Ph}), 129.1 (4C, CH_{Ph}), 128.3 (2C, CH_{Ph}), 127.4 (4C, CH_{Ph}), 126.7 (4C, CH_{Ph}), 125.6 (2C, CH_{Ph}), 76.5 (2C, OCH_2), 64.7 (2C, CHPh) ppm. (one quaternary C-atom is not visible).

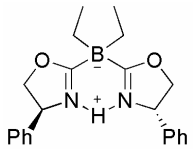
^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = –13.1 (s).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 2962, 2903, 2360, 1952, 1882, 1811, 1579, 1489, 1261, 1158, 803, 700.

Elemental analysis calcd (%) for $C_{30}H_{27}BN_2O_2$ (458.37 g/mol): C 78.61, H 5.94, N 6.11; found: C 78.46, H 6.10, N 5.98.

MS (FAB, NBA): m/z (%) = 459 ([M^+ + H], 100), 312 ([M^+ – oxa], 79).

[Et_2B(Oxa-Ph)$_2$][H] (40n)



Product **40n** was prepared according to **general procedure V** from (*S*)-4,5-dihydro-4-phenyloxazole (**109e**, 405 mg, 2.75 mmol), *t*-BuLi (1.7 M in hexanes, 1.78 mL, 3.03 mmol) and Et_2BBr (**90c**, 205 mg, 1.38 mmol). After stirring 12 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.31, hexane : EtOAc : Et_3N 10 : 1 : 0.5) over silica gel to give a colorless solid (25 mg, 5%).

$C_{22}H_{27}BN_2O_2$ (362.27 g/mol).

$[\alpha]_D^{20}$ = -35 (c = 0.11, CH_2Cl_2).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295K): δ = 7.36 (m_c, 4H, H_{Ph}), 7.30 (m_c, 2H, H_{Ph}), 7.23 (m_c, 4H, H_{Ph}), 5.09 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, OC*H*H), 4.72 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 8.8 Hz, 2H, OCH*H*), 4.19 (dd, $^3J_{HH}$ = 8.9, $^3J_{HH}$ = 7.4 Hz, 2H, CHPh)), 0.84 (t, $^3J_{HH}$ = 7.6 Hz, 6H, CH_3), 0.62 (q, $^3J_{HH}$ = 7.5 Hz, 4H, C*H*$_2$CH$_3$) ppm.

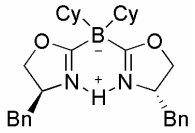
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295K): δ = 141.2 (2C, C_{Ph}), 129.0 (4C, CH_{Ph}), 128.1 (2C, CH_{Ph}), 126.6 (4C, CH_{Ph}), 76.1 (2C, OCH_2), 64.8 (2C, CHPh), 14.8 (*C*H$_2$CH$_3$), 12.3 (CH_3). (one quaternary C-atom is not visible).

^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = –15.3 (s).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 2933, 2360, 1954, 1884, 1733, 1577, 1457, 1409, 1261, 1161, 803, 698.

MS (FAB, NBA): m/z (%) = 363 ([M$^+$ + H], 100), 216 ([M$^+$ – oxa], 19).

[Cy$_2$B(Oxa-Bn)$_2$][H] (40l)



General Procedure VI: *t*-BuLi (1.7 M in hexanes, 1.78 mL, 3.03 mmol) was added at -78 °C over a 10 minutes period to a solution of (*S*)-4-benzyl-4,5-dihydrooxazole (**109a**, 443 mg, 2.75 mmol) in 100 mL of tetrahydrofuran, resulting in a pale yellow solution. After stirring for 30 minutes at this temperature, a solution of Cy_2BCl (**90a**, 1 M in hexanes, 1.40 mL, 1.40 mmol) in toluene (5 mL) was added through a cannula and the cooling bath immediately removed after addition. After 12 hours, the reaction volatile compounds were removed under vacuum. The ligand was then purified by column chromatography (3 x 25 cm**, R_f** = 0.23, hexane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give compound **40l** as a colorless solid (488 mg, 70%).

$C_{32}H_{43}BN_2O_2$ (498.51 g/mol).

m.p. 49-50 °C.

$[\alpha]_D^{20}$ = -87 (c = 0.11, $CHCl_3$).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 7.31 (t, $^3J_{HH}$ = 7.1 Hz, 4H, H_{Ph}), 7.26-7.23 (m, 2H, H_{Ph}), 7.17 (d, $^3J_{HH}$ = 6.9 Hz, 4H, H_{Ph}), 4.35 (dd, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 8.9 Hz, 2H, OC*H*H),

4.25-4.19 (m, 2H, CHBn), 4.10 (dd, $^2J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 6.5 Hz, 2H, OCH*H*), 2.28 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 7.1 Hz, 2H, C*H*HPh), 2.70 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 7.1 Hz, 2H, CH*H*Ph), 1.66-1.64 (m, 6H, H_{Cy}), 1.49-1.41 (m, 4H, H_{Cy}), 1.24-1.11 (m, 6H, H_{Cy}), 0.91-0.81 (m, 4H, H_{Cy}), 0.66-0.61 (m, 2H, H_{Cy}) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 198.3 (2C, C=N_{oxa}), 137.5 (2C, C_{Ph}), 129.1 (4C, CH_{Ph}), 128.6 (4C, CH_{Ph}), 126.7 (2C, CH_{Ph}), 72.7 (2C, OCH_2), 62.1 (2C, CHBn), 42.3 (2C, CH_2Ph), 31.7 (4C, $CH_{2\,Cy}$), 31.3 (4C, $CH_{2\,Cy}$), 29.1 (2C, CH_{Cy}), 27.9 (2C, $CH_{2\,Cy}$) ppm.

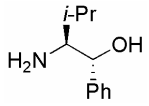
^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = -13.4 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3425m, 3028w, 2915s, 2842s, 1577s, 1496w, 1443m, 1406m, 1296w, 1266w, 1202w, 1153w, 1112w, 1024m, 963m.

Elemental analysis calcd (%) for $C_{32}H_{43}BN_2O_2$ (498.51 g/mol): C 77.10, H 8.69, N 5.62; found: C 76.84, H 8.66, N 5.36.

MS (FAB, NBA): m/z (%) = 499 (40, [M+H^+]), 256 (27), 174 (100), 117 (72), 91 (90), 77 (25), 57 (26), 55 (30), 43 (21), 41 (39), 39 (32).

(1*R*, 2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol (266)



To a solution of (1*R*, 2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol hydrochloride (**265**, 11.0 g, 50.0 mmol) in dichloromethane (100 mL), $NH_3.H_2O$ (20 mL) was added carefully. After separating the two layers, the organic layer was dried over $MgSO_4$ and concentrated. The compound **266** was obtained as a colorless solid (8.87 g, 99%).

$C_{11}H_{17}NO$ (179.26 g/mol).

m.p. 65-66 °C.

$[\alpha]_D^{20}$ = -15.0 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.35-7.30 (m, 5H, H_{Ph}), 4.66 (d, $^3J_{HH}$ = 6.0 Hz, 1H, CHPh), 2.76 (t, $^3J_{HH}$ = 6.1 Hz, 1H, NH_2C*H*), 1.68-1.60 (m, 1H, C*H*(CH_3)$_2$), 1.58 (brs, 3H, NH_2 + OH), 1.04 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 0.91 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3) ppm.

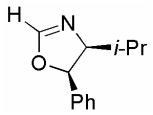
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 142.0 (C_{Ph}), 128.5 (2C, CH_{Ph}), 127.8 (CH_{Ph}), 127.2 (2C, CH_{Ph}), 77.4 (CHPh), 62.0 (NH_2CH), 29.6 (*C*H(CH_3)$_2$), 20.8 (CH_3), 17.4 (CH_3) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3342m_{br}, 3295m, 2960s, 2885s, 1598m, 1462m, 1371w, 1317w, 1279w, 1247w, 1181w, 1093m, 1042s, 1010s, 939s, 903s, 798w, 755s, 697s, 634m, 547w.

Elemental analysis calcd (%) for $C_{11}H_{17}NO$ (179.26 g/mol): C 73.70, H 9.56, N 7.81; found: C 73.44, H 9.35, N 7.75.

MS (FAB, NBA): m/z (%) = 180 (100, [M+H^+]), 162 (44), 107 (11), 91 (21), 77 (15), 72 (64), 41 (10), 39 (18).

(4*S*, 5*R*)-4,5-dihydro-4-isopropyl-5-phenyloxazole (267)



(1*R*, 2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol (**266**, 2.47 g, 13.8 mmol), DMF-DMA (1.83 mL, 13.8 mmol), and TsOH (5 mg) in benzene were refluxed for 48 hours in a flask equipped with a liquid/solid extraction apparatus containing 15 g of 4Å molecular sieves. The reaction mixture was filtered of resin, washed with 10% $KHCO_3$ (30 mL) and brine (30 mL), and dried over $MgSO_4$. The solution was concentrated and purified by column chromatography (10 x 18 cm**,** $\mathbf{R_f}$ = 0.26, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give compound **267** as a colorless solid (1.60 g, 60%).

$C_{12}H_{15}NO$ (189.25 g/mol).

m. p. 81-82 °C.

$[\alpha]_D^{20}$ = -36.0 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.37-7.31 (m, 3H, H_{Ph}), 7.29-7.26 (m, 2H, H_{Ph}), 7.07 (d, $^4J_{HH}$ = 2.3 Hz, 1H, CH=N), 5.54 (d, $^3J_{HH}$ = 10.4 Hz, 1H, CHPh), 4.02 (ddd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, NCH), 1.57-1.55 (m, 1H, C*H*$(CH_3)_2$), 0.84 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3), 0.73 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3).

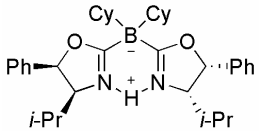
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 154.4 (C=N), 141.3 (C_{Ph}), 128.3 (2C, CH_{Ph}), 128.2 (CH_{Ph}), 127.3 (2C, CH_{Ph}), 83.2 (CHPh), 75.3 (NCH), 28.9 (*C*H$(CH_3)_2$), 21.2 (CH_3), 19.3 (CH_3) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3426m_{br}, 3081w, 3030w, 2950m, 2878m, 1632s, 1456m, 1386w, 1312m, 1204w, 1085s, 1010m, 929m, 852w, 807w, 741m, 697s, 600m; 524m.

HRMS (ESI^+): Exact Mass calcd for $C_{12}H_{16}NO$ [M+H] $^+$, 190.1232. Found 190.1237.

MS (FAB, NBA): m/z (%) = 190 (91, [M+H$^+$]), 162 (24), 145 (37), 137 (11), 107 (17), 105 (11), 100 (28), 91 (40), 89 (13), 79 (14), 78 (12), 77 (26), 72 (13), 65 (14), 63 (12), 55 (12), 51 (16), 43 (11), 41 (14).

Borabox ligand 56b



Compound **56b** was prepared according to **general procedure V** from *t*-BuLi (1.7 M in hexanes, 1.78 mL, 3.03 mmol), (4*R*, 5*S*)-4,5-dihydro-4-isopropyl-5-phenyloxazole (**267**, 520 mg, 2.75 mmol) and Cy_2BCl (**90a**, 1.38 mL, 1 M in hexanes, 1.38 mmol). The ligand was purified by column chromatography (3 x 25 cm**, R_f** = 0.44, hexane : Et_3N 95.5 : 0.5) on silica to give compound **56b** as a colorless solid (153 mg, 20%).

$C_{36}H_{51}BN_2O_2$ (554.61 g/mol).

$[\alpha]_D^{20}$ = -102 (c = 0.15, $CHCl_3$).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 7.37-7.35 (m, 6H, CH_{Ph}), 7.34-7.29 (m, 4H, CH_{Ph}), 5.70 (d, $^3J_{HH}$ = 10.4 Hz, 2H, OCHPh), 3.95 (dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 8.3 Hz, 2H, NCH), 1.68 (d, $^3J_{HH}$ = 10.5 Hz, 8H, CH_{Cy}), 1.60-1.52 (m, 4H, CH_{Cy} + $CH_{i\text{-}Pr}$), 1.26-1.18 (m, 6H, CH_{Cy}), 1.12-1.02 (m, 6H, CH_{Cy}), 0.87 (d, $^3J_{HH}$ = 6.6 Hz, 6H, CH_3), 0.61 (d, $^3J_{HH}$ = 6.5 Hz, 6H, CH_3) ppm.

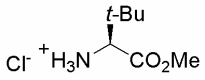
^{13}C NMR (125.6 MHz, $CDCl_3$, 295 K): δ = 187.8 (2C, C=N_{oxa}), 136.3 (2C, C_{Ph}), 128.1 (4C, CH_{Ph}), 127.7 (4C, CH_{Ph}), 125.5 (2C, CH_{Ph}), 84.6 (2C, OCHPh), 70.7 (2C, NCH), 31.9 (4C, $CH_{2\ Cy}$), 31.5 (4C, $CH_{2\ Cy}$), 30.3 (2C, CH_{Cy}), 29.1 (2C, $CH_{2\ Cy}$), 29.0 (2C, $CH_{i\text{-}Pr}$), 20.7 (2C, CH_3), 19.8 (2C, CH_3) ppm.

^{11}B {^{1}H} NMR (160 MHz, $CDCl_3$): δ = -13.2 (s) ppm.

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3023m, 2923s, 1769w, 1712m, 1639s, 1448s, 1371s, 1259m, 1186w, 1104s, 1066s, 1038s, 920w, 829w, 751m, 699s.

HRMS (ESI$^+$): Exact Mass calcd for $C_{36}H_{52}BN_2O_2$ [M+H]$^+$, 555.4122. Found 555.4114.

L-*tert*-leucine methyl ester hydrochloride (269b)



General procedure VII:

To a mixture of L-*tert*-leucine (**268,** 7.00 g, 58.8 mmol) in 300 mL methanol was given dropwise at -30 °C $SOCl_2$ (21.5 mL, 295 mmol). After warming up to room temperature the reaction mixture was refluxed for two hours. The organic solvent was concentrated in vacuum affording the hydrochloride salt **269b** as a colorless solid (9.10 g, 85%). Then the residue was introduced with $NH_3.H_2O$ into pH 9.0 or so. The mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The compound **269a** was obtained as a colorless oil (6.80 g, 80%) and used without further purification.

$C_7H_{16}ClNO_2$ (181.66 g/mol).

$[\alpha]_D^{20}$ = -6.5 (c = 0.49, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 8.81 (s, 3H, NH_3^+), 3.82 (s, 3H, OCH_3), 1.17 (s, 9H, $C(CH_3)_3$) ppm.

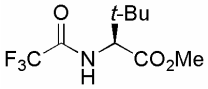
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 186.4 (C=O), 62.3 ($CHNH_3^+$), 52.9 (OCH_3), 33.9 (CMe_3), 27.0 (3C, $C(CH_3)_3$) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3394w, 2960s, 1732s, 1472m, 1368m, 1166s.

Elemental analysis calcd (%) for $C_7H_{16}ClNO_2$ (181.66 g/mol): C 46.28, H 8.88, N 7.71; found: C 46.60, H 8.56, N 7.62.

MS (FAB, NBA): m/z (%) = 146 (100, [M+H$^+$]), 86 (44).

(*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3,3-dimethylbutanoate (272)



General procedure VIII:

Trifluoroacetic anhydride (4.30 mL, 26.2 mmol) was added dropwise to a solution of L-*tert*-leucine methyl ester (**269a**, 4.70 g, 26.2 mmol) and triethylamine (4.00 mL, 28.6

mmol) in dichloromethane (50 mL) at -74 °C over 5 minutes. After complete addition the reaction mixture was stirred at -74 °C for 3 hours, quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and allowed to warm to room temperature. The mixture was extracted with dichloromethane (3 x 30 mL), the combined organic extracts were washed with water (50 mL), dried ($MgSO_4$), and filtered. The solution was concentrated and compound **272** was obtained as a colorless oil (6.00 g, 95%).

$C_9H_{14}F_3NO_3$ (241.21 g/mol).

$[\alpha]_D^{20}$ = +18.2 (c = 1.45, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.78 (br s, 1H, NH), 4.49 (d, $^3J_{HH}$ = 9.6 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 1.00 (s, 9H, CH_3 *t*-Bu) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 170.7 ($C{=}O_{ester}$), 157.0 (q, $^3J_{CF}$ = 47 Hz, CF_3), 115.9 (q, $^3J_{CF}$ = 360 Hz, $C{=}O_{amide}$), 60.5 (CHNH), 52.5 (OCH_3), 35.5 (CMe_3), 26.5 (3C, CH_3 *t*-Bu) ppm.

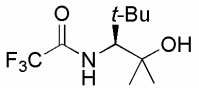
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -76.9 ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3423m, 3334s, 3078w, 2969s, 2912m, 1726s, 1543s, 1475m, 1442m, 1403w, 1373m, 1300s, 1218s, 1170s, 1098w, 1039w, 993w, 939w, 855w, 727w.

Elemental analysis calcd (%) for $C_9H_{14}F_3NO_3$ (241.21 g/mol): C 44.82, H 5.85, N 5.81; found: C 44.92, H 5.87, N 5.80.

MS (FAB, NBA): m/z (%) = 242 (47, [M+H$^+$]), 230 (10), 210 (17), 182 (39), 167 (12), 149 (43), 146 (95), 144 (13), 102 (21), 86 (41), 69 (18), 57 (35), 55 (17), 43 (15), 41 (41), 39 (26).

(*S*)-2,2,2-Trifluoro-*N*-(2-hydroxy-2,4,4-trimethylpentan-3-yl)acetamide (273)



A solution of (*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3,3-dimethylbutanoate (**272**, 6.00 g, 24.9 mmol) in tetrahydrofuran (30 mL) was added dropwise to methylmagnesium bromide (3M in Et_2O, 41 mL, 124 mmol) in 40 mL of tetrahydrofuran over 1 hour. The reaction mixture was heated to reflux for 6 hours and then was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution (30 mL), and extracted with TBME (4 x 40 mL). The combined organic extracts were washed with brine (120 mL), dried ($MgSO_4$) and filtered. Concentration of the filtrate gave a yellow oil (5.40 g, 90%) which was used without further purification.

$C_{10}H_{18}F_3NO_2$ (241.25 g/mol).

$[\alpha]_D^{20}$ = -26.5 (*c* = 0.35, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.85 (brs, 1H, NH), 3.70 (d, $^3J_{HH}$ = 10.1 Hz, 1H, CH*t*-Bu), 1.48 (s, 3H, $CH_{3\ gem}$), 1.23 (s, 3H, $CH_{3\ gem}$), 1.08 (s, 9H, $CH_{3\ t\text{-}Bu}$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 157.4 (q, $^3J_{CF}$ = 36 Hz, CF_3), 116.4 (q, $^3J_{CF}$ = 288 Hz, C=O), 74.4 (COH), 63.8 (CHNH), 36.3 ($C_{t\text{-}Bu}$), 31.2 ($CH_{3\ gem}$), 28.7 (3C, $CH_{3\ t\text{-}Bu}$), 29.7 ($CH_{3\ gem}$) ppm.

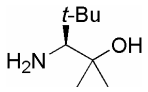
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -76.8 ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3414s, 3093w, 2973s, 1713s, 1539s, 1478m, 1373s, 1277m, 1168s, 1060w, 1023w, 950w, 907w, 859w, 795w, 710m.

Elemental analysis calcd (%) for $C_{10}H_{18}F_3NO_2$ (241.25 g/mol): C 49.79, H 7.52, N 5.81; found: C 49.39, H 7.42, N 5.88.

MS (FAB, NBA): m/z (%) = 242 (39, [M+H^+]), 225 (12), 224 (100), 168 (70), 138 (12), 137 (55), 77 (14), 69 (27), 59 (23), 57 (87), 55 (17), 43 (15), 41 (31), 39 (21).

(*S*)-3-amino-2,4,4-trimethylpentan-2-ol (270)



General procedure IX:

(*S*)-2,2,2-trifluoro-*N*-(-2-hydroxy-2,4,4-trimethylpentan-3-yl)acetamide (**273**, 5.40 g, 22.3 mmol) was heated to reflux in 5% methanolic NaOH solution (40 mL) for 5 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was dissolved in dichloromethane (25 mL) and partitioned with water (50 mL), and the aqueous phase was extracted with dichloromethane (6 x 30 mL). The combined organic extracts were washed with brine (50 mL), and the aqueous phase was back-extracted with dichloromethane (2 x 30 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was distilled (**b.p.** 130 °C at 0.2 mbar) and a colorless oil was obtained (2.70 g, 85%).

$C_7H_{15}NO_2$ (145.24 g/mol).

$[\alpha]_D^{20}$ = +21.7 (*c* = 0.43, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 2.36 (s, 1H, C*H*NH_2), 1.94 (brs, 3H, NH_2 + OH), 1.32 (s, 3H, C(C*H*$_3$CH$_3$)), 1.15 (s, 3H, C(CH$_3$C*H*$_3$)), 1.02 (s, 9H, C(CH$_3$)$_3$) ppm.

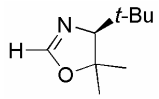
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 72.4 (COH), 68.4 ($CHNH_2$), 35.1 (*C*(CH$_3$)$_3$), 30.0 (C(*C*H$_3$CH$_3$)), 28.9 (3C, C(*C*H$_3$)$_3$), 25.8 (C(CH$_3$*C*H$_3$)) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3045s$_{br}$, 2964s, 1745m, 1590w, 1478s, 1371s, 1238m, 1164s, 1074w, 1034w, 964s, 859s, 736s.

Elemental analysis calcd (%) for $C_7H_{15}NO_2$ (145.24 g/mol): C 66.16, H 13.19, N 9.64; found: C 65.54, H 12.87, N 9.22.

MS (FAB, NBA): m/z (%) = 146 (100, [M+H$^+$]), 136 (21), 116 (20), 89 (20), 86 (23), 77 (22), 72 (92), 57 (50), 41 (33), 39 (29).

(*S*)-4-tert-butyl-4,5-dihydro-5,5-dimethyloxazole (271)



General procedure X:

(*S*)-3-amino-2,4,4-trimethylpentan-2-ol (**270**, 2.10 g, 14.7 mmol) and ethyl formimidate hydrochloride (1.60 g, 14.9 mmol) were refluxed in dichloromethane (300 mL) over night. After cooling, triethylamine (10.3 mL, 72.0 mmol) was added and the reaction mixture was washed with saturated aqueous $NaHCO_3$-solution (180 mL). The organic phase was dried over Na_2SO_4 and after removal of volatiles compound **271** was obtained as a colorless oil (1.80 g, 80%).

$C_9H_{17}NO$ (155.24 g/mol).

$[\alpha]_D^{20}$ = 24 (*c* = 0.04, $CHCl_3$).

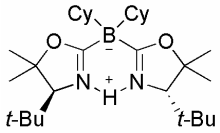
^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.80 (d, $^4J_{HH}$ = 2.3 Hz, 1H, HC=N), 3.36 (d, $^4J_{HH}$ = 2.3 Hz, 1H, CH*t*-Bu), 1.46 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.06 (s, 9H, C(CH$_3$)$_3$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 153.4 (C=N), 86.8 (CMe_2), 81.7 (CH*t*-Bu), 33.7 (*C*(CH$_3$)$_3$), 30.8 (CH_3), 27.8 (3C, C(*C*H$_3$)$_3$), 23.3 (CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3255m$_{br}$, 2971s, 2874s, 1750s, 1677m, 1633s, 1470s, 1371s, 1303w, 1250w, 1208w, 1160m, 1096s, 1006w, 932w, 883w, 811w, 779w, 732m.

HRMS (ESI$^+$): Exact Mass calcd for $C_9H_{18}NO$ [M+H]$^+$, 156.1388. Found 156.1390.

Borabox ligand 56c



Product **56c** was prepared according to **general procedure VI** from (*S*)-4-tert-butyl-4,5-dihydro-5,5-dimethyloxazole (**271**, 600 mg, 3.80 mmol), *t*-BuLi (1.7 M in hexanes, 2.30 mL, 4.00 mmol) and Cy_2BCl (**90a**, 1 M in hexanes, 1.90 mL, 1.90 mmol). After stirring 1 day at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.44, hexane : Et_3N 95.5 : 0.5) on silica to give a colorless solid (300 mg, 32%).

$C_{30}H_{55}BN_2O_2$ (486.58 g/mol).

m.p. 190-192 °C.

$[\alpha]_D^{20}$ = -11 (c = 0.10, $CHCl_3$).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 3.36 (s, 2H, NCH), 1.65-1.60 (m, 8H, H_{Cy}), 1.48 (s, 6H, C(C*H*$_3$CH$_3$)), 1.42 (s, 6H, C(CH$_3$C*H*$_3$)), 1.41-1.37 (m, 2H, H_{Cy}), 1.25-1.10 (m, 6H, H_{Cy}), 1.06 (s, 18H, C(CH$_3$)$_3$), 0.97-0.87 (m, 4H, H_{Cy}), 0.58 (m, 2H, H_{Cy}) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 196.4 (2C, C=N), 87.2 (2C, O*C*Me$_2$), 77.7 (2C, CH*t*-Bu), 33.2 (2C, *C*Me$_3$), 31.7 (4C, $CH_{2\ Cy}$), 31.3 (2C, C(*C*H$_3$CH$_3$)), 31.0 (4C, $CH_{2\ Cy}$), 29.2 (2C, CH_{Cy}), 28.2 (2C, $CH_{2\ Cy}$), 27.7 (6C, C(*C*H$_3$)$_3$), 23.5(2C, C(CH$_3$*C*H$_3$)) ppm.

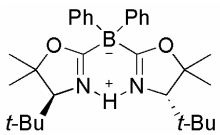
^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = -14.3 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3421w, 2972s, 2916s, 2840s, 1574s, 1468m, 1395s, 1308w, 1257w, 1210m, 1110m, 1019m, 986w, 938w, 873w, 837w, 701w, 647w.

Elemental analysis calcd (%) for $C_{30}H_{55}BN_2O_2$ (486.58 g/mol): C 74.05, H 11.39, N 5.76; found: C 73.93, H 11.23, N 5.47.

MS (FAB, NBA): m/z (%) = 487 (100, [M+H$^+$]), 486 (25), 250 (11), 168 (24), 57 (17).

Borabox ligand 56d



Product **56d** was prepared according to **general procedure VI** from (*S*)-4-tert-butyl-4,5-dihydro-5,5-dimethyloxazole (**271**, 0.60 g, 3.80 mmol), *t*-BuLi (1.7 M in hexanes, 2.30 mL, 4.00 mmol) and Ph_2BCl (**90b**, 380 mg, 1.90 mmol). After stirring 12 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.32, hexane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (0.48 g, 53%).

$C_{30}H_{43}BN_2O_2$ (474.49 g/mol).

m.p. 165-167 °C.

$[\alpha]_D^{20}$ = -16 (*c* = 0.30, $CHCl_3$).

^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 7.35 (d, $^3J_{HH}$ = 7.0 Hz, 4H, CH_{Ph}), 7.17 (t, $^3J_{HH}$ = 6.6 Hz, 4H, CH_{Ph}), 7.09 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_{Ph}), 3.44 (s, 2H, CHN), 1.38 (s, 6H, $CH_{3\ gem}$), 1.35 (s, 6H, $CH_{3\ gem}$), 1.07 (s, 18H, $CH_{3\ t\text{-Bu}}$) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 134.0 (4C, CH_{Ph}), 127.0 (4C, CH_{Ph}), 124.8 (2C, CH_{Ph}), 88.7 (2C, $OCMe_2$), 78.0 (2C, CH*t*-Bu), 33.7 (2C, *C*Me_3), 30.7 (2C, $CH_{3\ gem}$), 27.7 (6C, $CH_{3\ t\text{-Bu}}$), 22.9 (2C, $CH_{3\ gem}$) ppm. (two quaternary C-atoms are not visible).

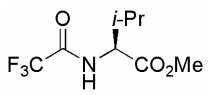
^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = -12.8 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3047m, 2968s, 2871s, 1943w, 1876w, 1811w, 1584s, 1467s, 1398s, 1296m, 1252m, 1205s, 168w, 1129w, 1018m, 949s, 868s, 756m, 740m, 700s, 656w, 631w, 556w, 523w.

Elemental analysis calcd (%) for $C_{30}H_{43}BN_2O_2$ (474.49 g/mol): C 75.94, H 9.13, N 5.90; found: C 75.87, H 8.97, N 5.76.

MS (EI, 70 eV): m/z (%) = 474 (83, M^+), 473 (51), 334 (28), 320 (79), 319 (25), 277 (22), 167 (30), 165 (50), 158 (100), 114 (38), 112 (35), 111 (26), 105 (19), 104 (32), 97 (33), 69 (31), 57 (94), 55 (41), 41 (28).

(*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3-methylbutanoate (277)



Product **277** was prepared according to **general procedure VIII** from trifluoroacetic anhydride (4.30 mL, 26.2 mmol), L-valine methyl ester hydrochloride (**276**, 3.40 g, 26.2

mmol) and triethylamine (4.00 mL, 28.6 mmol) in dichloromethane (50 mL). The product was obtained as a colorless oil (5.80 g, 98%).

$C_8H_{12}F_3NO_3$ (227.18 g/mol).

$[\alpha]_D^{20}$ = +33 (c = 0.279, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.79 (brs, 1H, NH), 4.58 (dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 4.6 Hz, 2H, CH*i*-Pr), 3.80 (s, 3H, OCH_3), 2.26 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 2.2 Hz, 1H, C*H*$(CH_3)_2$), 0.97 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 0.94 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 171.1 ($C{=}O_{ester}$), 157.1 (q, $^3J_{CF}$ = 37 Hz, $C{=}O_{amide}$), 115.9 (q, $^1J_{CF}$ = 287 Hz, CF_3), 57.6 (CHNH), 52.8 (OCH_3), 31.5 (*C*H$(CH_3)_2$), 18.8 (CH_3), 17.7 (CH_3) ppm.

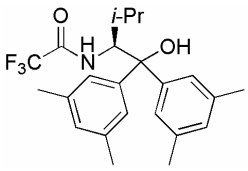
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -76.9 (m) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3327m, 3080w, 2970s, 2881m, 2706w, 1724s, 1675s, 1550s, 1467m, 1440m, 1305s, 1270s, 1212s, 1018w, 937w, 830w, 727m.

Elemental analysis calcd (%) for $C_8H_{12}NO_3F_3$ (227.18 g/mol): C 42.30, H 5.32, N 6.17; found: C 41.96, H 5.62, N 6.12.

MS (FAB, NBA): m/z (%) = 228 (3, [M+H^+]), 107 (13), 102 (100), 91 (14), 90 (14), 89 (26), 79 (13), 78 (15), 77 (36), 69 (18), 67 (12), 65 (17), 63 (18), 57 (28), 55 (29), 51 (23), 50 (12).

2,2,2-trifluoro-*N*-((*S*)-1-hydroxy-3-methyl-1,1-bis(3,5-dimethylphenyl)butan-2-yl)acetamide (278)



General procedure XI:

$CeCl_3 \cdot 7H_2O$ (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 tetrahydrofuran (80.0 mL) and stirred for 30 minutes before a 2M *Grignard* solution (15.0 mL, 30.0 mmol) in tetrahydrofuran was added drop wise. After the reaction mixture was stirred for 2 hours at 0 °C, (*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3-methylbutanoate (**277**, 1.20 g, 5.00 mmol) was added and the mixture was stirred over night at room temperature. The mixture was carefully quenched by a 1 M 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 (10 x 18 cm**,** $\mathbf{R_f}$ = 0.27, hexane : EtOAc 6 : 1) on silica to give a colorless solid (1.60 g, 80%).

$C_{23}H_{27}F_3NO_2$ (407.47 g/mol).

m.p. 163-165 °C.

$[\alpha]_D^{20}$ = -40 (*c* = 0.82, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.02 (s, 2H, CH_{Ph}), 6.96 (s, 2H, CH_{Ph}), 6.88 (s, 1H, CH_{Ph}), 6.83 (s, 1H, CH_{Ph}), 6.71 (d, $^3J_{HH}$ = 9.8 Hz, 1H, NH), 4.85 (dd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, C*H*NH), 2.43 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OH), 2.30 (s, 6H, $Ph(CH_3)_2$), 2.25 (s, 6H, $Ph(CH_3)_2$), 1.89 (dsept, $^3J_{HH}$ = 6.8 Hz , $^3J_{HH}$ = 2.0 Hz, 1H, C*H*$(CH_3)_2$), 0.91 (d, $^3J_{HH}$ = 4.0 Hz, 3H, CH_3), 0.89 (d, $^3J_{HH}$ = 4.0 Hz, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 157.4 (q, $^2J_{CF}$ = 36 Hz, C=O), 145.1 (C_{Ph}), 144.6 (C_{Ph}), 138.3 (C_{Ph}), 138.2 (C_{Ph}), 129.2 (CH_{Ph}), 129.1 (CH_{Ph}), 123.0 (CH_{Ph}), 122.8 (CH_{Ph}), 116.1 (q, $^1J_{CF}$ = 286 Hz, CF_3), 82.0 (CHOH), 58.8 (CHNH), 29.0 (*C*H$(CH_3)_2$), 22.8 (CH_3), 21.7 ($PhCH_3$), 21.6 ($PhCH_3$), 17.5 (CH_3) ppm.

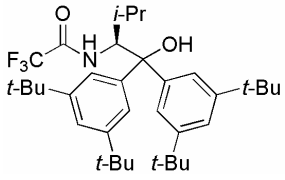
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -77.1 (m) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3496s, 3353s, 2965m, 2920w, 2876w, 1691s, 1598m, 1565m, 1467m, 1379w, 1312w, 1213s, 1175s, 859m, 759m, 716m.

Elemental analysis calcd (%) for $C_{23}H_{27}F_3NO_2$ (407.47 g/mol): C 67.80, H 6.93, N 3.44; found: C 67.55, H 6.83, N 3.19.

MS (FAB, NBA): m/z (%) = 407 (1, [M+H^+]), 390 (36), 277 (29), 240 (20), 239 (100), 230 (24), 223 (13), 133 (64), 105 (23), 91 (12), 77 (15), 55 (22), 43 (12), 39 (13).

N-((*S*)-1,1-bis(3,5-di-tert-butylphenyl)-1-hydroxy-3-methylbutan-2-yl)-2,2,2-trifluoroacetamide (279)



Product **279** was prepared according to **general procedure XI** from $CeCl_3 \cdot 7H_2O$ (11.2 g, 30.0 mmol), 2M *Grignard* solution (15.0 mL, 30.0 mmol) in tetrahydrofuran and

(*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3-methylbutanoate (**277**, 1.20 g, 5.00 mmol). After stirring 3 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (10 x 18 cm**, R_f** = 0.17, pentane : TBME 100 : 1) on silica to give a colorless solid (1.10 g, 40%).

$C_{35}H_{52}F_3NO_2$ (575.79 g/mol).

m.p. 155-159 °C.

$[\alpha]_D^{20}$ = -6 (*c* = 0.20, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.28-7.27 (m, 3H, CH_{Ar}), 7.24-7.23 (m, 3H, CH_{Ar}), 6.61 (d, $^3J_{HH}$ = 9.8 Hz, 1H, NH), 4.94 (dd, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, CH*i*-Pr), 2.41 (s, 1H, OH), 1.98 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, C*H*$(CH_3)_2$), 1.29 (s, 18H, CH_3 *t*-Bu), 1.26 (s, 18H, CH_3 *t*-Bu), 0.94 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 0.86 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3) ppm.

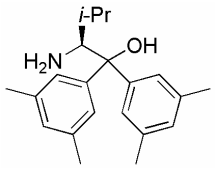
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 157.0 (q, $^2J_{CF}$ = 37 Hz, C=O), 150.8 (2C, C_{Ar}), 150.7 (2C, C_{Ar}), 143.7 (C_{Ar}), 143.6 (C_{Ar}), 121.1 (CH_{Ar}), 121.0 (CH_{Ar}), 119.5 (2C, CH_{Ar}), 119.2 (2C, CH_{Ar}), 115.9 (q, $^1J_{CF}$ = 289 Hz, CF_3), 82.5 (CHOH), 59.4 (CHNH), 35.0 (2C, Ph*C*$(CH_3)_3$), 34.9 (2C, Ph*C*$(CH_3)_3$), 31.5 (6C, PhC(*C*$H_3)_3$), 31.3 (6C, PhC(*C*$H_3)_3$), 28.8 (*C*H$(CH_3)_2$), 23.0 (CH(*C*H_3CH_3)), 17.6 (CH(*C*H_3CH_3)) ppm.

^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -77.0 (m) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm-1] = 3504w, 3378w, 3081w, 2966s, 2905w, 2870w, 1719m, 1700s, 1655w, 1600m, 1550m, 1477m, 1394w, 1364m, 1250s, 1203s, 1168s, 1027w, 898m, 880m, 744m, 710m.

Elemental analysis calcd (%) for $C_{35}H_{52}F_3NO_2$ (575.79 g/mol): C 73.01, H 9.10, N 2.43; found: C 73.00, H 9.09, N 2.22.

(*S*)-2-amino-3-methyl-1,1-bis(3,5-dimethylphenyl)butan-1-ol (280)



Product **280** was prepared according to **general procedure IX** from 2,2,2-trifluoro-*N*-((*S*)-1-hydroxy-3-methyl-1,1-bis(3,5-dimethylphenyl)butan-2-yl)acetamide (**278**, 1.60 g, 3.90 mmol). The crude product was purified by column chromatography (10 x 18 cm**, R_f** = 0.58, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (1.00 g, 85%).

$C_{21}H_{29}NO$ (311.46 g/mol).

m.p. 153-155 °C.

$[\alpha]_D^{20}$ = -39 (*c* = 0.75, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.20 (s, 2H, CH_{Ph}), 7.10 (s, 2H, CH_{Ph}), 6.81 (brs, 1H, CH_{Ph}), 6.79 (brs, 1H, CH_{Ph}), 4.26 (s, 1H, OH), 3.77-3.76 (m, 1H, C*H*NH_2), 2.29 (s, 6H, $Ph(CH_3)_2$), 2.27 (s, 6H, $Ph(CH_3)_2$), 1.75 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, C*H*$(CH_3)_2$), 1.08 (d, $^3J_{HH}$ = 3.2 Hz , 2H, NH_2), 0.93 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 0.88 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3) ppm.

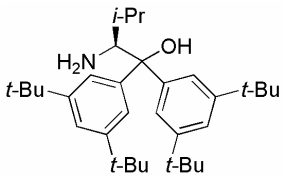
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 148.1 (C_{Ph}), 145.0 (C_{Ph}), 137.8 (2C, C_{Ph}), 137.4 (2C, C_{Ph}), 128.3 (CH_{Ph}), 128.1 (CH_{Ph}), 123.8 (CH_{Ph}), 123.3 (CH_{Ph}), 79.8 (COH), 60.3 ($CHNH_2$), 27.9 (*C*H$(CH_3)_2$), 23.2 (CH_3), 21.8 ($PhCH_3$), 21.7 ($PhCH_3$), 16.3 (CH_3) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3401s, 3396s, 2955s, 2920m, 2872m, 1602s, 1592s, 1459s, 1375m, 1351m, 1278w, 1157s, 1032m, 860s, 738s, 622m.

Elemental analysis calcd (%) for $C_{21}H_{29}NO$ (311.47 g/mol): C 80.98, H 9.38, N 4.50; found: C 80.92, H 9.30, N 4.27.

MS (FAB, NBA): m/z (%) = 312 (32, [M+H^+]), 294 (51), 133 (15), 72 (100), 55 (16), 43 (10), 41 (10).

(*S*)-1,1-bis(3,5-di-tert-butylphenyl)-2-amino-3-methylbutan-1-ol (281)



Product **281** was prepared according to **general procedure IX** from *N*-((*S*)-1,1-bis(3,5-di-tert-butylphenyl)-1-hydroxy-3-methylbutan-2-yl)-2,2,2-trifluoroacetamide (**279**, 1.00 g, 1.70 mmol). The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.45, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (660 mg, 82%).

$C_{33}H_{53}NO$ (479.78 g/mol).

m.p. 117-120 °C.

$[\alpha]_D^{20}$ = -18 (*c* = 0.30, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.49 (d, $^4J_{HH}$ = 1.8 Hz, 2H, CH_{Ph}), 7.38 (d, $^4J_{HH}$ = 1.8 Hz, 2H, CH_{Ph}), 7.22 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ph}), 7.20 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ph}), 4.23 (s, 1H, OH), 3.75 (d, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*NH_2), 1.76 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*$(CH_3)_2$), 1.30 (s, 18H, CH_3 *t*-Bu), 1.29 (s, 18H, CH_3 *t*-Bu), 0.91 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 0.83 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3) ppm.

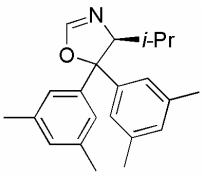
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 150.3 (2C, C_{Ph}), 149.8 (2C, C_{Ph}), 146.9 (C_{Ph}), 144.1 (C_{Ph}), 120.4 (CH_{Ph}), 120.2 (2C, CH_{Ph}), 120.2 (2C, CH_{Ph}), 119.8 (CH_{Ph}), 80.6 (COH), 61.5 ($CHNH_2$), 35.1 (2C, *C*$(CH_3)_3$), 35.0 (2C, *C*$(CH_3)_3$), 31.8 (6C, C(*C*$H_3)_3$), 31.7 (6C, C(*C*$H_3)_3$), 28.0 (*C*H$(CH_3)_2$), 23.3 (CH(*C*$H_3)_2$), 16.5 (CH(*C*$H_3)_2$) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3397m, 3332w, 3073w, 2963s, 2904s, 2868s, 1597s, 1540w, 1747s, 1393s, 1362s, 1290w, 1247s, 1202m, 1183m, 1059w, 896m, 878s, 737s, 714s, 612m.

Elemental analysis calcd (%) for $C_{33}H_{53}NO$ (479.79 g/mol): C 82.61, H 11.13, N 2.92; found: C 82.57, H 10.93, N 2.76.

MS (FAB, NBA): m/z (%) = 480 (34, [M+H^+]), 463 (36), 462 (100), 72 (11), 57 (27).

(*S*)-4,5-dihydro-4-isopropyl-5,5-bis(3,5-dimethylphenyl)oxazole (282)



Product **282** was prepared according to **general procedure X** from (*S*)-2-amino-3-methyl-1,1-bis(3,5-dimethylphenyl)butan-1-ol (**280**, 1.00 g, 3.21 mmol), ethyl formimidate hydrochloride (355 mg, 3.24 mmol) and triethylamine (2.20 mL, 16.0 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.62, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (430 mg, 42%).

$C_{22}H_{27}NO$ (321.46 g/mol).

m.p. 85-88 °C.

$[\alpha]_D^{20}$ = -162 (*c* = 0.25, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.08-7.06 (m, 3H, CH_{Ar}), 6.93 (s, 1H, HC=N), 6.87 (brs, 3H, CH_{Ar}), 4.57 (dd, $^3J_{HH}$ = 4.6 Hz, $^3J_{HH}$ = 2.1 Hz, 1H, CH*i*-Pr), 2.32 (s, 3H,

$PhCH_3$), 2.28 (s, 3H, $PhCH_3$), 1.78 (ds, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*$(CH_3)_2$), 1.01 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$CH$_3$)), 0.57 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH(CH_3C*H*$_3$)) ppm.

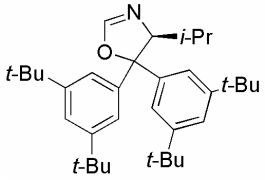
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 152.7 (C=N), 145.4 (C_{Ar}), 140.3 (C_{Ar}), 137.8 (2C, C_{Ar}), 137.1 (2C, C_{Ar}), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 124.9 (2C, CH_{Ar}), 124.2 (2C, CH_{Ar}), 91.9 (CAr_2), 78.3 (CH*i*-Pr), 29.6 (*C*H$(CH_3)_2$), 22.1 (CH(*C*H$_3$CH$_3$)), 21.7 (2C, $PhCH_3$), 21.6 (2C, $PhCH_3$), 17.0 (CH(CH_3*C*H$_3$)) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 2981m, 2960s, 2922s, 2870m, 1649s, 1603s, 1459m, 1384w, 1363w, 1352w, 1310w, 1274w, 1187w, 1120s, 1037w, 976w, 932w, 916w, 852m, 822m, 776w, 726m.

Elemental analysis calcd (%) for $C_{22}H_{27}NO$ (321.46 g/mol): C 82.20, H 8.47, N 4.36; found: C 81.80, H 8.67, N 4.08.

MS (EI, 70 eV): m/z (%) = 321 (2, M^+), 240 (18), 239 (100), 133 (50).

(*S*)-5,5-bis(3,5-di-tert-butylphenyl)-4,5-dihydro-4-isopropyloxazole (283)



Product **283** was prepared according to **general procedure X** from (*S*)-1,1-bis(3,5-di-tert-butylphenyl)-2-amino-3-methylbutan-1-ol (**281**, 660 mg, 1.04 mmol), ethyl formimidate hydrochloride (115 mg, 1.05 mmol) and triethylamine (0.70 mL, 5.00 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.26, pentane : Et_3N 10 : 0.5) on silica to give a colorless solid (320 mg, 64%).

$C_{34}H_{51}NO$ (489.77 g/mol).

m.p. 103-105 °C.

$[\alpha]_D^{20}$ = -28 (*c* = 0.26, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.35 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}), 7.31 (d, $^4J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 7.27 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}), 7.15 (d, $^4J_{HH}$ = 2.0 Hz, 1H, HC=N), 7.05 (d, $^4J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 4.47 (dd, $^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, CH*i*-Pr), 1.75 (ds, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 2.0 Hz, 1H, C*H*$(CH_3)_2$), 1.31 (s, 18H, CH_3 *t*-Bu), 1.25 (s, 18H, CH_3 *t*-Bu), 0.91 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH(C*H*$_3$CH$_3$)), 0.63 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH(CH_3C*H*$_3$)) ppm.

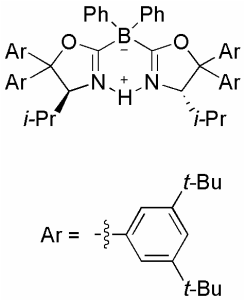
$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 152.8 (C=N), 150.5 (2C, C_{Ar}), 149.7 (2C, C_{Ar}), 144.7 (C_{Ar}), 139.4 (C_{Ar}), 121.9 (2C, CH_{Ar}), 121.7 (CH_{Ar}), 120.8 (3C, CH_{Ar}), 92.7 (CAr_2), 80.7 (*C*H*i*-Pr), 35.1 (2C, *C*$(CH_3)_3$), 35.0 (2C, *C*$(CH_3)_3$), 31.6 (6C, C(*C*$H_3)_3$), 31.5 (6C, C(*C*$H_3)_3$), 30.4 (C*H*$(CH_3)_2$), 22.0 (CH(C*H*$_3$CH$_3$)), 18.0 (CH(CH$_3$C*H*$_3$)), ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3422w, 3072w, 2963s, 2869m, 1701w, 1686w, 1648m, 1598m, 1477m, 1449w, 1393w, 1363m, 1249m, 1203w, 1129s, 1026w, 954w, 898w, 880m, 855w, 825w, 716m.

Elemental analysis calcd (%) for $C_{34}H_{51}NO$ (489.78 g/mol): C 83.38, H 10.50, N 2.86; found: C 83.41, H 10.47, N 2.65.

MS (FAB, NBA): m/z (%) = 490 (8, [M+H^+]), 462 (12), 57 (100), 41 (25).

Borabox ligand 56f



Product **56f** was prepared according to **general procedure VI** from (*S*)-5,5-bis(3,5-di-tert-butylphenyl)-4,5-dihydro-4-isopropyloxazole (**283**, 300 mg, 0.60 mmol), *t*-BuLi (1.7 M in hexanes, 0.37 mL, 0.63 mmol) and Ph_2BCl (**90b**, 60.0 mg, 0.30 mmol). After stirring 12 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.13, pentane : Et_3N 10 : 0.5) on silica to give a colorless solid (267 mg, 39%).

$C_{80}H_{111}BN_2O_2$ (1143.56 g/mol).

m.p. 100-104 °C.

$[\alpha]_D^{20}$ = -26 (*c* = 0.10, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.38-7.36 (m, 4H, CH_{Ph}), 7.32 (d, $^4J_{HH}$ = 1.8 Hz, 4H, CH_{Ph}), 7.14 (t, $^3J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 7.07-6.98 (m, 8H, CH_{Ar}), 6.76 (d, $^3J_{HH}$ = 1.8 Hz, 4H, CH_{Ar}), 4.48 (d, $^3J_{HH}$ = 6.8 Hz, 2H, CHN), 1.60 (ds, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 6.6 Hz, 2H, C*H*$(CH_3)_2$), 1.30 (s, 36H, Ph*t*-Bu), 1.06 (s, 36H, Ph*t*-Bu), 0.80 (d, $^3J_{HH}$ = 6.6 Hz, 6H, CH(C*H*$_3$CH$_3$)), 0.65 (d, $^3J_{HH}$ = 6.6 Hz, 6H, CH(CH$_3$C*H*$_3$)) ppm.

$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 192.8 (2C, C=N), 150.4 (4C, C_{Ar}), 149.5 (4C, C_{Ar}), 144.0 (2C, C_{Ar}), 138.8 (2C, C_{Ar}), 134.6 (4C, CH_{Ph}), 127.2 (4C, CH_{Ph}), 125.7 (2C, C_{Ph}), 124.9 (2C, CH_{Ph}), 122.4 (4C, CH_{Ar}), 122.1 (2C, CH_{Ar}), 121.0 (4C, CH_{Ar}), 120.6 (2C, CH_{Ar}), 95.3 (2C, $OCAr_2$), 77.3 (2C, CH*i*-Pr), 35.1 (4C, Ph*C*Me_3), 34.8 (4C, Ph*C*Me_3), 31.7 (12C, CH_3 *t*-Bu), 31.4 (12C, CH_3 *t*-Bu), 30.9 (2C, *C*H$(CH_3)_2$), 30.5 (2C, *C*H$(CH_3)_2$), 21.5 (4C, *C*H$(CH_3)_2$), 22.9 (4C, *C*H$(CH_3)_2$) ppm.

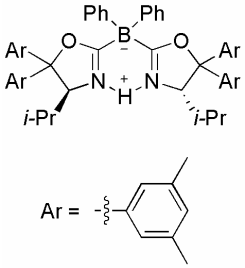
$^{11}B\{^{1}H\}$ NMR (160.8 MHz, $CDCl_3$, 295 K): δ = -13.7 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448m, 3069w, 2964s, 2868m, 1595s, 1570w, 1561w, 1476m, 1458w, 1438w, 1396m, 1363s, 1248s, 1202w, 1085w, 1032w, 949w, 893w, 841w, 748w, 717m, 700s.

Elemental analysis calcd (%) for $C_{80}H_{111}BN_2O_2$ (1143.58 g/mol): C 84.02, H 9.78, N 2.45; found: C 83.90, H 9.72, N 2.24.

MS (FAB, NBA): m/z (%) = 1144 (5, [M+H^+]), 57 (>100), 41 (15).

Borabox ligand 56e



Product **56e** was prepared according to **general procedure VI** from (*S*)-4,5-dihydro-4-isopropyl-5,5-bis(3,5-dimethylphenyl)oxazole (**282**, 430 mg, 1.30 mmol), *t*-BuLi (1.7 M in hexanes, 0.82 mL, 1.40 mmol) and Ph_2BCl (**90b**, 130 mg, 0.65 mmol). After stirring 12 hours at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.61, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (188 mg, 36%).

$C_{56}H_{63}BN_2O_2$ (806.92 g/mol).

m.p. 88-90 °C.

$[\alpha]_D^{20}$ = -126 (*c* = 0.13, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.46 (d, $^{3}J_{HH}$ = 8.1 Hz, 4H, CH_{Ph}), 7.16-7.13 (m, 6H, CH_{Ph}), 7.06 (s, 4H, CH_{Ar}), 6.93 (s, 2H, CH_{Ar}), 6.72 (s, 2H, CH_{Ar}), 6.53 (s, 2H, CH_{Ar}), 4.43 (d, $^{3}J_{HH}$ = 6.3 Hz, 2H, CH*i*-Pr), 2.30 (s, 12H, $PhCH_3$), 2.06 (s, 12H, $PhCH_3$), 1.65 (ds, $^{3}J_{HH}$ = 6.6 Hz, $^{3}J_{HH}$ = 6.3 Hz, 2H, C*H*$(CH_3)_2$), 0.88 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H, CH_3 *i*-Pr), 0.57 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H, CH_3 *i*-Pr) ppm.

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 144.9 (2C, C_{Ar}), 139.8 (2C, C_{Ar}), 137.8 (4C, C_{Ar}), 137.0 (4C, C_{Ar}), 134.9 (4C, CH_{Ph}), 129.4 (2C, CH_{Ar}), 129.0 (2C, CH_{Ar}), 126.9 (4C, CH_{Ph}), 125.2 (4C, CH_{Ar}), 125.1 (2C, CH_{Ph}), 124.2 (4C, CH_{Ar}), 94.1 (2C, $OCAr_2$), 76.5 (2C, CH*i*-Pr), 30.2 (2C, $CH(CH_3)_2$), 21.8 (2C, $CH(CH_3)_2$), 21.7 (4C, $PhCH_3$), 21.5 (4C, $PhCH_3$), 18.3 (2C, $CH(CH_3)_2$) ppm. (three quaternary C-atoms are not visible).

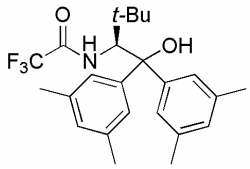
^{11}B {^{1}H} NMR (160.8 MHz, $CDCl_3$, 295 K): δ = -13.7 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3066w, 3042w, 2962s, 2916s, 2868m, 1598s, 1561w, 1466m, 1450w, 1398m, 1320w, 1195w, 1162m, 1034w, 955m, 851m, 730m, 711s.

Elemental analysis calcd (%) for $C_{58}H_{67}BN_2O_2$ (834.99 g/mol): C 83.43, H 8.09, N 3.36; found: C 81.82, H 7.57, N 3.38.

MS (FAB, NBA): m/z (%) = 807 (100, [M+H^+]), 806 (27), 486 (20), 458 (17).

(*S*)-2,2,2-trifluoro-*N*-(1-hydroxy-3,3-dimethyl-1,1-bis(3,5-dimethylphenyl)butan-2-yl)acetamide (284)



Product **284** was prepared according to **general procedure X** from $CeCl_3 \cdot 7H_2O$ (11.2 g, 30.0 mmol), 2M *Grignard* solution (15.0 mL, 30.0 mmol) in tetrahydrofuran and (*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3,3-dimethylbutanoate (**272**, 1.20 g, 5.00 mmol). After stirring 3 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (10 x 18 cm**, R_f** = 0.64, pentane : EtOAc 6 : 1) on silica to give a colorless solid (0.88 g, 42%).

$C_{24}H_{30}F_3NO_2$ (421.50 g/mol).

m.p. 188-190 °C.

$[\alpha]_D^{20}$ = -86 (*c* = 0.23, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.08 (s, 2H, CH_{Ar}), 7.00 (s, 2H, CH_{Ar}), 6.82 (s, 1H, CH_{Ar}), 6.79 (brs, 2H, CH_{Ar} + NH), 4.86 (d, $^{3}J_{HH}$ = 10.1 Hz , 1H, CH*t*-Bu), 2.61 (s, 1H, OH), 2.28 (s, 6H, $PhCH_3$), 2.24 (s, 6H, $PhCH_3$), 0.83 (s, 9H, *t*-Bu) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 157.0 (q, $^{2}J_{CF}$ = 36 Hz, C=O), 146.6 (C_{Ar}), 144.8 (C_{Ar}), 138.2 (2C, C_{Ar}), 137.8 (2C, C_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 123.3 (2C, CH_{Ar}),

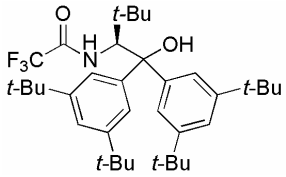
122.0 (2C, CH_{Ar}), 116.0 (q, $^{1}J_{CF}$ = 286 Hz, CF_3), 82.3 (COH), 61.6 (CHNH), 37.6 ($C(CH_3)_3$), 29.4 (3C, $CH_{3\ t\text{-Bu}}$), 21.7 (2C, PhCH_3), 21.6 (2C, PhCH_3) ppm.

$^{19}F\{^{1}H\}$ NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -77.4 (m) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3557w, 3514w, 3440w, 3414w, 2963m, 2917m, 1715s, 1603w, 1538m, 1478w, 1369w, 1335w, 1266m, 1218s, 1166s, 1097w, 1026w, 938w, 891w, 855w, 757w, 716w, 610w.

Elemental analysis calcd (%) for $C_{24}H_{29}F_3NO_2$ (420.49 g/mol): C 68.55, H 6.95, N 3.33; found: C 68.62, H 7.03, N 3.04.

N-((*S*)-1,1-bis(3,5-di-tert-butylphenyl)-1-hydroxy-3,3-dimethylbutan-2-yl)-2,2,2-trifluoroacetamide (285)



Product **285** was prepared according to **general procedure XI** from $CeCl_3 \cdot 7H_2O$ (11.2 g, 30.0 mmol), 2M *Grignard* solution (15.0 mL, 30.0 mmol) in tetrahydrofuran and (*S*)-methyl 2-(2,2,2-trifluoroacetamido)-3,3-dimethylbutanoate (**272**, 1.20 g, 5.00 mmol). After stirring 3 days at room temperature, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (10 x 18 cm**, R_f** = 0.56, pentane : EtOAc 6 : 1) on silica to give a colorless solid (1.47 g, 50%).

$C_{36}H_{54}F_3NO_2$ (589.81 g/mol).

m.p. 167-169 °C.

$[\alpha]_D^{20}$ = -11 (*c* = 0.22, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.39 (d, $^{4}J_{HH}$ = 1.5 Hz, 2H, CH_{Ar}), 7.32 (d, $^{4}J_{HH}$ = 1.5 Hz, 2H, CH_{Ar}), 7.23 (t, $^{4}J_{HH}$ = 1.5 Hz, 1H, CH_{Ar}), 7.21 (t, $^{3}J_{HH}$ = 1.5 Hz, 1H, CH_{Ar}), 6.71 (d, $^{3}J_{HH}$ = 10.3 Hz , 1H, NH), 4.92 (d, $^{3}J_{HH}$ = 10.1 Hz, 1H, CH*t*-Bu), 2.66 (s, 1H, OH), 1.29 (s, 18H, PhC$(CH_3)_3$), 1.27 (s, 18H, PhC$(CH_3)_3$), 0.82 (s, 9H, CHC$(CH_3)_3$) ppm.

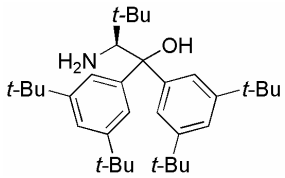
$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 156.6 (q, $^{2}J_{CF}$ = 46 Hz, C=O), 150.8 (2C, C_{Ar}), 150.5 (2C, C_{Ar}), 145.2 (C_{Ar}), 144.0 (C_{Ar}), 121.1 (CH_{Ar}), 120.8 (CH_{Ar}), 119.7 (2C, CH_{Ar}), 118.4 (2C, CH_{Ar}), 116.0 (q, $^{1}J_{CF}$ = 361 Hz, CF_3), 82.8 (CHOH), 62.4 (CHNH), 37.5 ($CH(CH_3)_3$), 35.1 (2C, Ph$C(CH_3)_3$), 35.0 (2C, Ph$C(CH_3)_3$), 31.6 (6C, PhC$(CH_3)_3$), 31.5 (6C, PhC$(CH_3)_3$), 29.4 (3C, CH$(CH_3)_3$) ppm.

$^{19}F\{^{1}H\}$ NMR (376.5 MHz, $CDCl_3$, 295 K): δ = -77.4 (m) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3504m, 3379m, 2963s, 2872m, 1699s, 1599m, 1548w, 1477m, 1395w, 1366m, 1282w, 1249m, 1170s, 1094w, 1025w, 969w, 878w, 825w, 746w, 715m, 650w.

Elemental analysis calcd (%) for $C_{36}H_{54}F_3NO_2$ (589.82 g/mol): C 73.31, H 9.23, N 2.37; found: C 73.29, H 9.09, N 2.14.

(*S*)-1,1-bis(3,5-di-tert-butylphenyl)-2-amino-3,3-dimethylbutan-1-ol (287)



Product **287** was prepared according to **general procedure IX** from *N*-((*S*)-1,1-bis(3,5-di-tert-butylphenyl)-1-hydroxy-3,3-dimethylbutan-2-yl)-2,2,2-trifluoroacetamide (**285**, 1.20 g, 2.00 mmol). The crude product was purified by column chromatography (10 x 18 cm**, R_f** = 0.61, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (0.94 g, 95%).

$C_{34}H_{55}NO$ (493.81 g/mol).

m.p. 97-99 °C.

$[\alpha]_D^{20}$ = -51 (*c* = 0.14, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.57 (d, $^{3}J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 7.49 (d, $^{3}J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 7.19 (t, $^{3}J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}) 7.15 (d, $^{3}J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}), 4.24 (s, 1H, OH), 3.74 (s, 1H, CH*t*-Bu), 1.31 (s, 18H, Ph(*t*-Bu)$_2$), 1.28 (s, 18H, Ph(*t*-Bu)$_2$), 0.74 (s, 9H, *t*-Bu) ppm.

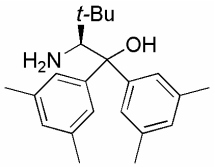
$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 150.4 (2C, C_{Ph}), 149.5 (2C, C_{Ph}), 148.6 (C_{Ph}), 144.2 (C_{Ph}), 120.9 (2C, CH_{Ph}), 120.3 (CH_{Ph}), 119.7 (2C, CH_{Ph}), 119.6 (CH_{Ph}), 80.7 (COH), 64.9 ($CHNH_2$), 35.6 ($C(CH_3)_3$), 35.1 (2C, Ph$C(CH_3)_3$), 35.0 (2C, Ph$C(CH_3)_3$), 31.8 (3C, PhC(CH_3)$_3$), 31.6 (3C, PhC(CH_3)$_3$) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3423m, 3074w, 2961s, 2869s, 1729w, 1597s, 1476s, 1393m, 1365s, 1289w, 1249s, 1174s, 1074w, 1020w, 994w, 875s, 830w, 782w, 734s, 712s, 624w.

Elemental analysis calcd (%) for $C_{34}H_{55}NO$ (493.81 g/mol): C 82.70, H 11.23, N 2.84; found: C 82.60, H 11.15, N 2.76.

MS (FAB, NBA): m/z (%) = 494 (39, [M+H^+]), 476 (14), 421 (25), 420 (75), 217 (12), 86 (55), 77 (10), 57 (100), 41 (24), 39 (15).

(*S*)-2-amino-3,3-dimethyl-1,1-bis(3,5-dimethylphenyl)butan-1-ol (286)



Product **286** was prepared according to **general procedure IX** from (*S*)-2,2,2-trifluoro-*N*-(1-hydroxy-3,3-dimethyl-1,1-bis(3,5-dimethylphenyl)butan-2-yl)acetamide (**284**, 0.70 g, 1.70 mmol). The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.58, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless solid (0.51 g, 92%).

$C_{22}H_{31}NO$ (325.49 g/mol).

m.p. 176-178 °C.

$[\alpha]_D^{20}$ = -165 (*c* = 0.27, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.25 (s, 2H, CH_{Ar}), 7.15 (s, 2H, CH_{Ar}), 6.79 (s, 1H, CH_{Ar}), 6.74 (s, 1H, CH_{Ar}), 4.29 (s, 1H, OH), 3.74 (t, $^3J_{HH}$ = 3.3 Hz, 1H, CH*t*-Bu), 2.30 (s, 6H, Ph(Me)$_2$), 2.25 (s, 6H, Ph(Me)$_2$), 1.27 (d, $^3J_{HH}$ = 3.3 Hz, 2H, NH_2), 0.78 (s, 9H, *t*-Bu) ppm.

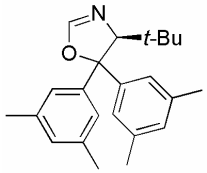
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 149.9 (C_{Ph}), 145.2 (C_{Ph}), 137.9 (2C, C_{Ph}), 136.9 (2C, C_{Ph}), 128.2 (CH_{Ph}), 127.9 (CH_{Ph}), 124.0 (2C, CH_{Ph}), 123.4 (2C, CH_{Ph}), 79.9 (COH), 63.7 ($CHNH_2$), 35.6 ($C(CH_3)_3$), 29.3 (3C, CH_3 *t*-Bu), 21.8 (2C, $PhCH_3$), 21.7 (2C, $PhCH_3$) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3410m, 2953s, 2913s, 2860s, 1753w, 1600s, 1468s, 1368m, 1281w, 1223w, 1155m, 1065w, 1022m, 972w, 850s, 816m, 735s, 588w.

Elemental analysis calcd (%) for $C_{22}H_{31}NO$ (325.49 g/mol): C 81.18, H 9.60, N 4.30; found: C 81.26, H 9.44, N 4.10.

MS (FAB, NBA): m/z (%) = 326 (93, [M+H^+]), 253 (21), 252 (100), 251 (12), 133 (11), 86 (21).

(*S*)-4-tert-butyl-4,5-dihydro-5,5-bis(3,5-dimethylphenyl)oxazole (288)



Product **288** was prepared according to **general procedure X** from (*S*)-2-amino-3,3-dimethyl-1,1-bis(3,5-dimethylphenyl)butan-1-ol (**286**, 0.40 g, 1.20 mmol), ethyl formimidate hydrochloride (133 mg, 1.21 mmol) and triethylamine (0.80 mL, 6.00 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.28, pentane : Et_3N 10 : 0.5) on silica to give a colorless oil (270 mg, 67%).

$C_{23}H_{29}NO$ (335.48 g/mol).

$[\alpha]_D^{20}$ = -417 (*c* = 0.18, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.12 (brs, 2H, CH_{Ar}), 7.09 (d, $^3J_{HH}$ = 2.3 Hz, 1H, CH_{Ar}), 6.93-6.90 (m, 3H, CH_{Ar}), 6.85 (brs, 1H, HC=N), 4.52 (d, $^3J_{HH}$ = 2.0 Hz, 1H, CH*t*-Bu), 2.32 (s, 3H, $PhCH_3$), 2.24 (s, 3H, $PhCH_3$), 0.81 (s, 9H, $C(CH_3)_3$)ppm.

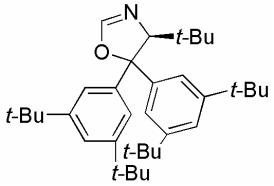
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 152.5 (C=N), 146.3 (C_{Ar}), 139.9 (C_{Ar}), 137.6 (2C, C_{Ar}), 136.6 (2C, C_{Ar}), 129.5 (CH_{Ar}), 129.1 (CH_{Ar}), 126.8 (2C, CH_{Ar}), 124.5 (2C, CH_{Ar}), 92.3 (CAr_2), 81.2 (CH*t*-Bu), 34.9 ($C(CH_3)_3$), 28.0 (3C, $C(CH_3)_3$), 21.7 (2C, $PhCH_3$), 21.6 (2C, $PhCH_3$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3410w, 2953s, 2871s, 2735w, 1719w, 1645s, 1603s, 1471s, 1367m, 1301w, 1246w, 1202w, 1121s, 1038s, 968m, 939m, 896w, 852s, 826m, 786m, 726m.

Elemental analysis calcd (%) for $C_7H_{15}NO_3$ (161.20 g/mol): C 52.16, H 9.38, N 8.69; found: C 51.98, H 9.00, N 8.80.

MS (FAB, NBA): m/z (%) = 336 (39, [M+H^+]), 281 (22), 280 (100), 252 (30), 240 (16), 239 (71), 174 (13), 133 (27), 91 (11), 77 (11), 57 (37), 41 (18), 39 (14).

(*S*)-4-tert-butyl-5,5-bis(3,5-di-tert-butylphenyl)-4,5-dihydrooxazole (289)



Product **289** was prepared according to **general procedure X** from (*S*)-1,1-bis(3,5-di-tert-butylphenyl)-2-amino-3,3-dimethylbutan-1-ol **(287**, 0.80 g, 1.62 mmol), ethyl formimidate hydrochloride (179 mg, 1.64 mmol) and triethylamine (1.10 mL, 8.00 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude

product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.26, pentane : Et_3N 10 : 0.5) on silica to give a colorless solid (571 mg, 70%).

$C_{35}H_{53}NO$ (503.80 g/mol).

m.p. 146-147 °C.

$[\alpha]_D^{20}$ = -287 (*c* = 0.10, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.40 (d, $^4J_{HH}$ = 1.8 Hz, 2H, CH_{Ar}), 7.34 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}), 7.23 (t, $^4J_{HH}$ = 1.8 Hz, 1H, CH_{Ar}), 7.20 (d, $^4J_{HH}$ = 2.3 Hz, 1H, CH_{Ar}), 7.13 (brs, 2H, CH_{Ar} + HC=N), 4.52 (d, $^4J_{HH}$ = 2.3 Hz, 1H, CH*t*-Bu), 1.32 (s, 9H, $Ph(CH_3)_3$), 1.22 (s, 9H, $Ph(CH_3)_3$), 0.79 (s, 9H, $C(CH_3)_3$) ppm.

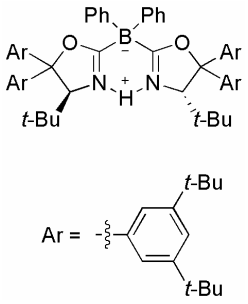
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 152.6 (C=N), 150.2 (2C, C_{Ar}), 149.0 (2C, C_{Ar}), 145.4 (C_{Ar}), 138.8 (C_{Ar}), 123.7 (2C, CH_{Ar}), 121.6 (CH_{Ar}), 121.0 (2C, CH_{Ar}), 120.9 (CH_{Ar}), 93.1 (CAr_2), 83.3 (CH*t*-Bu), 35.1 (Ph*C*$(CH_3)_3$), 34.9 (Ph*C*$(CH_3)_3$), 34.8 (*C*$(CH_3)_3$), 31.7 (6C, PhC(*C*$H_3)_3$), 31.4 (6C, PhC(*C*$H_3)_3$), 28.1 (3C, C(*C*$H_3)_3$) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3424m, 3074w, 2960s, 2870s, 2714w, 1653s, 1597s, 1543w, 1477s, 1393m, 1363s, 1285w, 1248s, 1207w, 1135s, 1027w, 961m, 930w, 881m, 854w, 831w, 800w, 753w, 714m, 686w, 606w, 552w.

HRMS (ESI^+): Exact Mass calcd for $C_{35}H_{54}NO$ $[M+H]^+$, 504.4205. Found 504.4202.

MS (FAB, NBA): m/z (%) = 504 (8, $[M+H^+]$), 494 (36), 476 (20), 449 (21), 448 (61), 421 (33), 420 (100), 407 (53), 217 (26), 89 (22), 77 (35), 63 (22), 57 (63), 51 (23), 41 (37), 39 (45).

Borabox ligand 56h



Product **56h** was prepared according to **general procedure VI** from **(***S*)-4-tert-butyl-4,5-dihydro-5,5-bis(3,5-dimethylphenyl)oxazole (**289**, 200 mg, 0.60 mmol), *t*-BuLi (1.7 M in hexanes, 0.37 mL, 0.63 mmol) and Ph_2BCl (**90b**, 60 mg, 0.30 mmol). After stirring 12 hours at room temperature, the volatile compounds were removed under reduced pressure. The

crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.37, pentane : Et_3N 10 : 0.5) on silica to give a colorless solid (170 mg, 68%).

$C_{58}H_{67}BN_2O_2$ (834.98 g/mol).

m.p. 113-114 °C.

$[\alpha]_D^{20}$ = -58 (c = 0.20, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.44 (d, $^3J_{HH}$ = 7.6 Hz, 4H, CH_{Ar}), 7.18-7.15 (m, 10H, CH_{Ar}), 6.96 (s, 2H, CH_{Ar}), 6.70 (s, 2H, CH_{Ar}), 6.57 (s, 4H, CH_{Ar}), 4.52 (s, 2H, CHN), 2.33 (s, 12H, $PhCH_3$), 2.03 (s, 12H, $PhCH_3$), 0.70 (s, 18H, $CH_{3\ t\text{-Bu}}$) ppm.

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 146.1 (2C, C_{Ar}), 139.0 (2C, C_{Ar}), 137.6 (4C, C_{Ar}), 136.4 (4C, C_{Ar}), 135.1 (4C, CH_{Ph}), 129.4 (2C, CH_{Ar}), 129.0 (2C, CH_{Ar}), 126.9 (4C, CH_{Ph}), 125.2 (4C, CH_{Ar}), 124.5 (4C, CH_{Ar}), 124.4 (2C, CH_{Ph}),94.1 (2C, $OCAr_2$), 79.7 (2C, CHN), 35.3 (2C, $C(CH_3)_3$), 27.6 (6C, $C(CH_3)_3$), 21.8 (2C, $PhCH_3$), 21.4 (2C, $PhCH_3$). (three quaternary C-atoms are not visible).

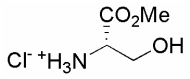
^{11}B {^{1}H} NMR (160 MHz, $CDCl_3$, 295 K): δ = -13.7 (s) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3425m_{br}, 3041w, 2956s, 2868m, 1772w, 1600s, 1475m, 1397m, 1201w, 1162m, 1035w, 955m, 894w, 853m, 792w, 728m, 701m.

Elemental analysis calcd (%) for $C_{58}H_{67}BN_2O_2$ (834.99 g/mol): C 83.43, H 8.09, N 3.36; found: C 83.05, H 8.33, N 3.30.

MS (FAB, NBA): m/z (%) = 835 (82, [M+H^+]), 834 (21), 500 (39), 444 (21), 416 (21), 338 (45), 252 (28), 220 (23), 165 (49), 57 (100), 41 (33).

L-serine methyl ester hydrochloride (291)



Product **291** was prepared according to **general procedure VII** from (L)-serine (**290**, 6.10 g, 58.8 mmol) and $SOCl_2$ (21.53 mL, 295 mmol). The hydrochloride salt **291** was obtained as a colorless solid (8.20 g, 90%).

$C_4H_{10}ClNO_3$ (155.58 g/mol).

m.p. 154 °C (decomposition).

$[\alpha]_D^{20}$ = +3 (c = 0.32, MeOH).

^{1}H NMR (400.1 MHz, CD_3OD, 295 K): δ = 4.16 (t, $^3J_{HH}$ = 3.8 Hz, 1H, C*H*CO_2Me), 4.01 (dd, $^2J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C*H*HOH), 3.95 (dd, $^2J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, CH*H*OH), 3.85 (s, 3H, CH_3) ppm.

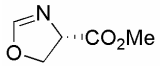
^{13}C{^{1}H} NMR (125.8 MHz, CD_3OD, 295 K): δ = 169.4 (C=O), 60.6 (CH_2OH), 56.1 (*C*HCO_2Me), 53.7 (CO_2CH_3) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3356s_{br}, 2952s_{br}, 2749m, 2662m, 2553w, 2490w, 1935m, 1749s, 1596s, 1513s, 1446m, 1385w, 1346w, 1299m, 1256s, 1159m, 1128w, 1094m, 1039s, 971m, 899w, 842w, 794w.

Elemental analysis calcd (%) for $C_4H_{10}ClNO_3$ (155.58 g/mol): C 30.88, H 6.48, N 9.00; found: C 30.48, H 6.32, N 8.88.

MS (FAB, NBA): m/z (%) = 120 (100, [M-Cl^-]), 89 (11), 77 (14), 60 (16), 51 (10).

(*S*)-methyl 4,5-dihydrooxazole-4-carboxylate (293)



Product **293** was prepared according to **general procedure X** from L-serine methyl ester hydrochloride (**291**, 763 mg, 4.91 mmol), ethyl formimidate hydrochloride (544 mg, 4.97 mmol) and triethylamine (3.40 mL, 24.0 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**, R_f** = 0.22, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless oil (380 mg, 60%).

$C_5H_7NO_3$ (129.11 g/mol).

$[\alpha]_D^{20}$ = +158.2 (*c* = 0.58, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.94 (d, $^4J_{HH}$ = 3.2 Hz, 1H, HC=N), 4.76 (ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, CHCO_2Me), 4.49 (dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, C*H*HCHCO_2Me), 4.39 (dd, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, CH*H*CHCO_2Me), 3.80 (s, 3H, OCH_3) ppm.

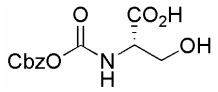
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 171.3 (C=O), 157.2 (C=N), 68.5 (OCH_2), 67.3 (*C*HCO_2Me), 52.9 (OCH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3463w, 3238w, 3079w, 2957m, 2912w, 2851w, 1742s, 1627s, 1440s, 1348s, 1281s, 1213s, 1113s, 1057s, 943s, 874w, 841w, 722w, 729m.

Elemental analysis calcd (%) for $C_5H_7NO_3$ (129.11 g/mol): C 46.51, H 5.46, N 10.85; found: C 46.07, H 5.53, N 10.81.

MS (FAB, NBA): m/z (%) = 130 (17, $[M+H^+]$), 120 (59), 107 (23), 102 (11), 91 (16), 90 (21), 89 (34), 88 (21), 78 (14), 77 (32), 65 (17), 63 (16), 60 (48), 57 (13), 51 (19), 41 (16), 39 (32).

N-(Benzyloxycarbonyl)-L-serine (296)



Benzyl chloroformate (50 mL, 50 wt-% solution in toluene, 148 mmol) was added to a solution of L-serine (**290**, 10.5 g, 100 mmol) in saturated aqueous sodium hydrogen carbonate (400 mL). The mixture was stirred vigorously for 4 hours at ca. 20 °C and the aqueous phase was extracted with ether (2 x 400 mL). The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 400 mL), and the organic phase was dried over Na_2SO_4 and concentrated to give the compound **296** as a colorless solid (20.3 g, 85%), used without further purification.

$C_{11}H_{13}NO_5$ (239.22 g/mol).

m.p. 118-119 °C.

$[\alpha]_D^{20} = +7$ ($c = 0.29$, $(CH_3)_2CO$).

^{1}H NMR (400.1 MHz, CD_3COCD_3, 295 K): δ = 7.50-7.31 (m, 5H, CH_{Ar}), 6.37 (d, $^3J_{HH}$ = 7.6 Hz, 1H, NH), 5.10 (s, 2H, $PhCH_2O$), 4.36 (ddd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 4.3 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C*H*CO_2H), 3.95 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C*H*HOH), 3.91 (d, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 3.9 Hz 1H, CH*H*OH) ppm.

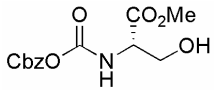
^{13}C{^{1}H} NMR (100.6 MHz, CD_3COCD_3, 295 K): δ = 172.2 ($C{=}O_{acid}$), 157.0 ($C{=}O_{amid}$), 138.1 (C_{Ar}), 129.2 (2C, CH_{Ar}), 128.6 (3C, CH_{Ar}), 66.8 ($PhCH_2$), 63.9 (CH_2OH), 57.2 (NCH) ppm.

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3445m, 3332s, 3207m, 2947w, 2774w, 1748m, 1690s, 1531m, 1479w, 1399w, 1349w, 1307w, 1247m, 1210w, 1059w, 1027w, 964w, 911w, 837w, 785w, 696w, 608w.

Elemental analysis calcd (%) for $C_{11}H_{13}NO_5$ (239.23 g/mol): C 55.23, H 5.48, N 5.86; found: C 54.93, H 5.42, N 5.82.

MS (FAB, NBA): m/z (%) = 240 (70, $[M+H]^+$), 196 (22), 137 (20), 92 (11), 91 (100).

_N_-(Benzyloxycarbonyl)-L-serine methyl ester (297)



Acetyl chloride (16.05 mL, 225 mmol) was added dropwise to a solution of *N*-(benzyloxycarbonyl)-L-serine (**296**, 18.0 g, 75.0 mmol) in methanol (100 mL) at 0 °C. The mixture was heated at reflux for 16 hours and then cooled to ca. 20 °C. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (190 mL) and washed with saturated aqueous sodium hydrogen carbonate (2 x 75 mL). The organic phase was dried over $MgSO_4$ and concentrated to give **297** as a colorless oil (19.0 g, 80%).

$C_{12}H_{15}NO_5$ (253.25 g/mol).

$[\alpha]_D^{20} = +6$ ($c = 0.19$, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.37-7.32 (m, 5H, CH_{Ar}), 5.69 (d, $^3J_{HH}$ = 7.9 Hz, 1H, NH), 5.13 (s, 2H, $PhCH_2O$), 4.42 (ddd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 3.6 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, C*H*CO_2Me), 3.99 (dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, C*H*HOH), 3.92 (dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, CH*H*OH), 3.79 (s, 3H, OCH_3), 2.09 (brs, 1H, OH) ppm.

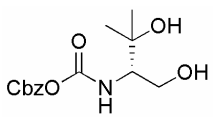
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 171.1 ($C{=}O_{ester}$), 156.4 ($C{=}O_{amid}$), 136.2 (C_{Ar}), 128.7 (2C, CH_{Ar}), 128.4 (3C, CH_{Ar}), 67.4 ($PhCH_2$), 63.4 (CH_2OH), 56.2 (NCH), 52.9 (CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3408s, 3033w, 2954m, 2890w, 1723s, 1527s, 1452m, 1343s, 1216s, 1063s, 979w, 912w, 742m, 699m.

Elemental analysis calcd (%) for $C_{12}H_{15}NO_5$ (253.25 g/mol): C 56.91, H 5.97, N 5.53; found: C 56.88, H 5.97, N 5.32.

MS (FAB, NBA): m/z (%) = 254 (74, $[M+H]^+$), 210 (48), 137 (11), 107 (12), 92 (12), 91 (100), 78 (10), 77 (20), 65 (12), 63 (10), 51 (11), 39 (15).

(*S*)-2-*N*-(Benzyloxycarbonylamino)-3-methyl-1,3-butanediol (298)



A solution of *N*-(benzyloxycarbonyl)-L-serine methyl ester (**297**, 10.5 g, 41.5 mmol) in anhydrous tetrahydrofuran (60 mL) was added dropwise at 0 °C to MeMgBr (3M in THF, 246 mmol) in anhydrous diethyl ether (120 mL). The white suspension was stirred at ca. 20 °C for a further 90 minutes. The reaction mixture was cooled to 0 °C, cautiously quenched by addition of ether (90 mL) and 1 M HCl (200 mL), and poured into a separating funnel. The aqueous phase was extracted with diethyl ether (3 x 200 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by chromatography on silica gel to give **298** as a colorless oil (8.41 g, 80%).

$C_{13}H_{19}NO_4$ (253.29 g/mol).

$[\alpha]_D^{20} = +14$ ($c = 0.23$, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.37-7.30 (m, 5H, CH_{Ar}), 5.64 (d, $^3J_{HH}$ = 8.3 Hz, 1H, NH), 5.12 (s, 2H, OCH_2), 4.05 (td, $^3J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, C*H*NH), 3.86-3.81 (m, 1H, C*H*HOH), 3.55-3.51 (m, 1H, CH*H*OH), 2.57 (s, 1H, $C(CH_3)_2O\mathit{H}$), 2.44 (t, $^3J_{HH}$ = 4.0 Hz, 1H, $CH_2O\mathit{H}$), 1.36 (s, 3H, CH_3), 1.25 (s, 3H, CH_3) ppm.

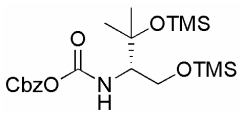
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 156.9 (C=O), 136.5 (C_{Ar}), 128.7 (2C, CH_{Ar}), 128.3 (3C, CH_{Ar}), 73.8 ($PhCH_2$), 67.1 (CH_2OH), 60.6 (NCH), 58.3 ($\mathit{C}(CH_3)_2OH$), 27.8 (CH_3), 27.7 (CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3391s_{br}, 3066m, 3034m, 2975s, 1695s, 1534s, 1460s, 1376s, 1335s, 1254s, 1156s, 1054s, 947m, 724s, 698s.

Elemental analysis calcd (%) for $C_{13}H_{19}NO_4$ (253.30 g/mol): C 61.64, H 7.56, N 5.53; found: C 60.97, H 7.30, N 5.65.

MS (FAB, NBA): m/z (%) = 254 (47, $[M+H]^+$), 236 (17), 92 (10), 91 (100).

(*S*)-2-*N*-(Benzyloxycarbonylamino)-3-methyl-1,3-bis(trimethylsilyloxy)butane (299)



Chlorotrimethylsilane (2.28 mL, 18 mmol) was added dropwise to a solution of (*S*)-2-*N*-(benzyloxycarbonylamino)-3-methyl-1,3-butanediol (**298**, 1.52 g, 6.00 mmol) and imidazole (2.45 g, 36.0 mmol) in anhydrous tetrahydrofuran (33 mL) at 0 °C. After 16 hours at 0 °C, a mixture of ether/petroleum ether/triethylamine (2:98:5) (50 mL) was added to this

suspension. Filtration through a pad of silica gel (15 g), washing with ether/petroleum ether/triethylamine (50:50:5) (75 mL), and removal of the organic solvents under vacuum afforded **299** as a colorless liquid (2.40 g, 96%). Because of migration of the silyl function during prolonged storage at 0 °C, **299** was stored at -27 °C and used within two weeks.

$C_{19}H_{35}NO_4Si_2$ (397.66 g/mol).

$[\alpha]_D^{20} = +3$ ($c = 4.3$, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 7.37-7.32 (m, 5H, CH_{Ar}), 5.13 (d, $^2J_{HH}$ = 12.1 Hz, 1H, C*H*HOC=O), 5.10 (d, $^2J_{HH}$ = 12.1 Hz, 1H, CH*H*OC=O), 5.03 (d, $^3J_{HH}$ = 10.1 Hz, 1H, NH), 3.77 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C*H*HOSiMe$_3$), 3.65 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, CH*H*OSiMe$_3$), 3.54 (ddd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C*H*NH), 1.29 (brs, 3H, CH_3), 1.22 (s, 3H, CH_3), 0.11 (s, 9H, Si(CH_3)$_3$), 0.09 (s, 9H, Si(CH_3)$_3$) ppm.

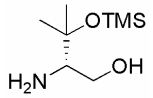
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 156.7 (C=O), 136.9 (C_{Ar}), 128.6 (2C, CH_{Ar}), 128.2 (3C, CH_{Ar}), 75.5 ($PhCH_2$), 66.7 (CH_2OSiMe_3), 61.6 (NCH), 60.7 ($C(CH_3)_2OSiMe_3$), 27.9 (CH_3), 27.7 (CH_3), 2.5 (3C, $C(CH_3)_2OSi(CH)_3$), -0.4 (3C, $CH_2OSi(CH)_3$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3445m, 3340m, 3033w, 2957s, 1725s, 1503s, 1463m, 1370w, 1335m, 1252s, 1170s, 1109s, 1039s, 843s, 751m, 695w.

Elemental analysis calcd (%) for $C_{19}H_{35}NO_4Si_2$ (397.66 g/mol): C 57.39, H 8.87, N 3.52; found: C 57.31, H 8.77, N 3.52.

MS (FAB, NBA): m/z (%) = 398 (10, $[M+H]^+$), 308 (13), 131 (39), 103 (11), 91 (100), 73 (54).

(*S*)-2-amino-3-methyl-3-(trimethylsilyloxy)butan-1-ol (300)



Pd/C (10%, 0.60 g) was added to a solution of (*S*)-2-*N*-(benzyloxycarbonylamino)-3-methyl-1,3-bis(trimethylsilyloxy)butane (**299**, 0.60 g, 1.50 mmol) in anhydrous ethanol (6 mL). The mixture was hydrogenated at ca. 20 °C and at atmospheric pressure for 18 hours. The catalyst was removed by filtration through Celite and, after washing of the solid with 95% ethanol (3 mL), the filtrate was concentrated under vacuum to give **300** as a colorless oil (287 mg,

94%). Because of migration of the silyl function during prolonged storage at 0 °C, **300** was stored at -27 °C and used within two weeks.

$C_8H_{21}NO_2Si$ (191.34 g/mol).

$[\alpha]_D^{20}$ = -15 (*c* = 2.5, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 3.66 (dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C*H*HOH), 3.41 (dd, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, CH*H*OH), 2.54 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C*H*NH_2), 1.26 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 0.12 (s, 9H, $Si(CH_3)_3$) ppm.

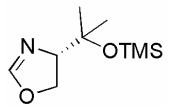
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 76.0 (CH_2OH), 62.8 (NCH), 61.4 ($C(CH_3)_2OSiMe_3$), 27.4 (CH_3), 26.9 (CH_3), 2.6 (3C, $SiMe_3$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3362s_{br}, 2965s, 1584m, 1463m, 1370s, 1253s, 1161s, 1035s, 843s, 755m, 683w.

Elemental analysis calcd (%) for $C_8H_{21}NO_2Si$ (191.34 g/mol): C 50.22, H 11.06, N 7.32; found: C 50.70, H 10.77, N 7.31.

MS (FAB, NBA): m/z (%) = 192 (86, $[M+H]^+$), 136 (15), 131 (59), 102 (48), 91 (11), 89 (14), 77 (17), 73 (100), 72 (17), 70 (11), 57 (14), 41 (14), 39 (15).

Compound 301



Product **301** was prepared according to **general procedure X** from **(***S*)-2-amino-3-methyl-3-(trimethylsilyloxy)butan-1-ol (**300**, 250 mg, 1.31 mmol), ethyl formimidate hydrochloride (145 mg, 1.33 mmol) and triethylamine (0.90 mL, 6.00 mmol). After stirring 1 day at reflux, the volatile compounds were removed under reduced pressure. The crude product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.48, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give a colorless oil (185 mg, 70%).

$C_9H_{19}NO_2Si$ (201.34 g/mol).

$[\alpha]_D^{20}$ = +180.0 (*c* = 0.10, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.81 (d, $^4J_{HH}$ = 2.0 Hz, 1H, HC=N), 4.24 (t, $^3J_{HH}$ = 8.6 Hz, 1H, NCH), 4.13 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, OC*H*H), 3.97 (dd, $^2J_{HH}$ = 10.1

Hz, $^{3}J_{HH}$ = 8.6 Hz, 1H, OCH*H*), 1.31 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 0.10 (s, 9H, $Si(CH_3)_3$) ppm.

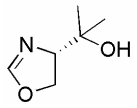
$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 155.3 (C=N), 75.3 (NCH), 67.9 (OCH_2), 53.6 (*C*OSiMe$_2$*t*-Bu), 28.8 (CH_3), 24.6 (CH_3), 2.6 (3C, $Si(CH_3)_3$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3351s, 2965s, 1723m, 1632s, 1462s, 1377s, 1253m, 1165w, 1109s, 1041m, 906w, 842w, 753w, 686w.

HRMS (ESI^+): Exact Mass calcd for $C_9H_{19}NO_2NaSi$ $[M+Na]^+$, 224.1083. Found 224.1077.

MS (FAB, NBA): m/z (%) = 202 (5, $[M+H^+]$), 149 (19), 131 (36), 102 (30), 84 (11), 75 (16), 73 (69), 72 (13), 60 (11), 57 (22), 55 (11), 43 (12), 41 (12).

2-((*S*)-4,5-dihydrooxazol-4-yl)propan-2-ol (302)



To a solution of **301** (180 mg, 0.80 mmol) in tetrahydrofuran (15 mL) was added TBAF (1 M in THF, 1.20 mL, 1.20 mmol) at room temperature, and the mixture was stirred for 30 minutes at the same temperature. Then, the solvent was removed under reduced pressure and the crude was filtered through a short column of silica gel using dichloromethane as eluant. The solvent was removed under reduced pressure to give **302** as a colorless oil (57 mg, 55%).

$C_6H_{11}NO_2$ (129.16 g/mol).

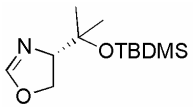
$[\alpha]_D^{20}$ = +16.4 (*c* = 0.45, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.90 (d, $^{4}J_{HH}$ = 1.3 Hz, 1H, HC=N), 4.23 (dd, $^{2}J_{HH}$ = 10.4 Hz, $^{3}J_{HH}$ = 8.6 Hz, 1H, OC*H*H), 4.16 (t, $^{3}J_{HH}$ = 8.6 Hz, 1H, NCH), 4.06-4.02 (m, 1H, OCH*H*), 1.30 (s, 3H, CH_3), 1.16 (s, 3H, CH_3) ppm.

$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 156.1 (C=N), 77.4 (NCH), 74.5 ($C(CH_3)_2OH$), 67.7 (OCH_2), 30.4 (CH_3), 25.4 (CH_3) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3377s_{br}, 2968s, 1726m, 1630s, 1463s, 1375s, 1273m, 1119s, 1045m, 952m, 871w, 739w, 698w.

Compound 303[191]



To a solution of 2-((*S*)-4,5-dihydrooxazol-4-yl)propan-2-ol (**302**, 55.0 mg, 0.42 mmol) in 20 mL dichloromethane was added under argon 2,6-lutidin (0.04 mL, 4.20 mmol) and *tert*-butyldimethylsilyltriflat (0.29 mL, 1.27 mmol). After stirring 14 hours at room temperature, the reaction was quenched with 30 mL NH_4Cl solution, and extracted with 60 mL ethyl acetate. The organic layers were washed with 25 mL 0.1 M HCl, $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the volatiles, the product was purified by column chromatography (3 x 25 cm**,** $\mathbf{R_f}$ = 0.43, pentane : EtOAc : Et_3N 10 : 1 : 0.5) on silica to give compound **303** as a colorless oil (34 mg, 33%).

$C_{12}H_{25}NO_2Si$ (243.42 g/mol).

$[\alpha]_D^{20}$ = +21.0 (*c* = 0.15, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 6.81 (d, $^4J_{HH}$ = 1.0 Hz, 1H, HC=N), 4.27 (t, $^3J_{HH}$ = 6.6 Hz, 1H, OC*H*H), 4.13 (t, $^3J_{HH}$ = 8.6 Hz, 1H, OCH*H*), 3.98-3.94 (m, 1H, NCH), 1.29 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 0.83 (s, 9H, $C(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$) ppm.

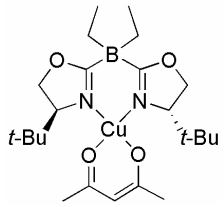
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 155.2 (C=N), 75.5 (NCH), 74.3 (*C*O$SiMe_2$*t*-Bu), 67.8 (OCH_2), 28.7 (CH_3), 25.8 (3C, $C(CH_3)_3$), 25.0 (CH_3), -2.02 ($SiCH_3$), -2.01 ($SiCH_3$) ppm.

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3334m_{br}, 2954s, 2908s, 2857s, 1678w, 1632s, 1466m, 1383m, 1365m, 1253s, 1166s, 1107s, 1047s, 936w, 888m, 834s, 773s, 663s.

MS (FAB, NBA): m/z (%) = 244 (6, [M+H^+]), 204 (10), 173 (24), 136 (23), 130 (59), 112 (25), 107 (11), 100 (24), 90 (12), 89 (26), 84 (12), 77 (17), 75 (52), 73 (100), 59 (12), 57 (16), 51 (10), 41 (17), 39 (17).

8.8 Synthesis of Borabox Complexes

Borabox Complex 116a



General procedure XII:

Copper (II) acetylacetonate (78 mg, 0.3 mmol) was added to a solution of borabox ligand **40f** (100 mg, 0.3 mmol) in dichloromethane (20 mL). After one hour at room temperature, the solution was filtrated, washed with ethyl acetate and concentrated. The remaining green crystalline solid was dissolved in a minimum amount of diethylether and layered with hexane. After 1 week, green plates started to grow. They were collected and subjected to single crystal analysis.

$C_{23}H_{41}B_1Cu_1N_2O_4$ (483.94 g/mol).

m.p. 230 °C (decomposition).

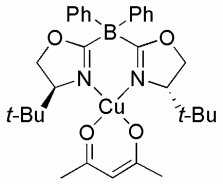
$[\alpha]_D^{20}$ = -816 (c = 0.047, $CHCl_3$).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3450m, 3121w, 2958s, 2869s, 2824m, 1561s, 1475s, 1380s, 1275m, 1179s, 1048s, 1021s, 952m, 793m, 731w, 677w, 586w.

Elemental analysis calcd (%) for $C_{23}H_{41}BCuN_2O_4$ (483.94 g/mol): C 57.08, H 8.54, N 5.79; found: C 56.34, H 8.29, N 5.42.

MS (FAB, NBA): m/z (%) = 484 (12, [M+H^+]), 457 (18), 456 (43), 455 (46), 454 (82), 453 (24), 426 (23), 357 (33), 356 (20), 355 (64), 329 (21), 328 (31), 326 (36), 324 (21), 323 (100), 322 (26), 190 (21), 83 (51), 82 (20), 73 (65), 69 (34), 57 (86), 55 (62), 43 (39), 41 (54).

Borabox Complex 116b



Compound **116b** was prepared according to **general procedure XII** from copper (II) acetylacetonate (78 mg, 0.3 mmol) and borabox ligand **40g** (125 mg, 0.3 mmol). After 2 days, green plates started to grow. They were collected and subjected to single crystal analysis.

$C_{31}H_{41}B_1Cu_1N_2O_4$ (580.03 g/mol).

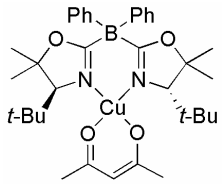
m.p. 240 °C (decomposition).

$[\alpha]_D^{20}$ = -340 (c = 0.12, $CHCl_3$).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449w, 3047w, 2996m, 2959s, 1566s, 1521s, 1476s, 1428s, 1376s, 1277m, 1192s, 1068w, 1021m, 972s, 936m, 872w, 790w, 729m, 701m, 644w.

MS (FAB, NBA): m/z (%) = 580 (11, [M+H^+]), 502 (40), 483 (43), 482 (38), 481 (100), 480 (32), 479 (29), 419 (43), 405 (25), 403 (52), 376 (20), 354 (33), 292 (37), 190 (30), 165 (38), 130 (30), 83 (23), 57 (29), 55 (31), 41 (33).

Borabox Complex 274



Compound **274** was prepared according to **general procedure XII** from copper (II) acetylacetonate (78 mg, 0.3 mmol) and borabox ligand **56d** (142 mg, 0.3 mmol). After 2 weeks, green plates started to grow. They were collected and subjected to single crystal analysis.

$C_{35}H_{49}BCuN_2O_4$ (636.13 g/mol).

m.p. 250 °C (decomposition).

$[\alpha]_D^{20}$ = -216 (c = 0.07, $CHCl_3$).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3447w, 3047w, 2962s, 1565s, 1517s, 1469m, 1433m, 1383s, 1258m, 1220m, 1136m, 1019m, 979m, 943m, 870w, 812w, 733m, 699s.

MS (FAB, NBA): m/z (%) = 636 (4, [M+H^+]), 558 (19), 475 (70), 165 (21), 136 (24), 97 (21), 91 (21), 89 (24), 77 (33), 57 (100), 55 (55), 43 (35), 41 (61), 39 (41).

Chapter 9

Appendix

9 Appendix

9.1 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[203], or the dirax/view/EvalCCD programs from Utrecht University.[204] The structure was solved with either SIR92[205] or SIR97[206] and refined in Crystals.[207] The absolute configuration and enantiopurity could be determined by refinement of the flack parameter.[208] The refined structures were checked with checkcif.[209]

Compound	**40f**	**40g**
Molecular Formula	$C_{23}H_{41}B_1Cu_1N_2O_4$	$C_{31}H_{41}B_1Cu_1N_2O_2$
Formula Weight	483.95	580.03
Shape	Plate	Plate
Colour	Green	Green
Temperature (K)	173	173
Crystal size (mm^3)	0.10 x 0.16 x 0.20	0.09 x 0.12 x 0.39
Crystal system	Hexagonal	Orthorhombic
Space group	$P\,6_5$	$P\,2_1\,2_1\,2_1$
a (Å)	19.8196(1)	11.32130(10)
b (Å)	19.8196(1)	18.0426(2)
c (Å)	34.0180(2)	29.9568(3)
α (Å)	90	90
β (Å)	90	90
γ (Å)	120	90
Volume ($Å^3$)	11572.55(11)	6119.15(11)
Z	18	8
Density (calc.)($Mg\ m^{-3}$)	1.250	1.259
Absorption coeff. (mm^{-1})	0.878	0.750
Radiation type (λ [Å])	$Mo_{K\alpha}$ (0.71073)	$Mo_{K\alpha}$ (0.71073)
F (000)	4662	2456
Θ range of data collection (°)	1.186-27.497	1.317-27.943
Completeness to Θmax (%)	0.999	0.997
Limiting indices (measured)	-21≤h≤0 0≤k≤25 -44≤l≤44	-14≤h≤14 0≤k≤23 0≤l≤39
Reflections measured	100656	46164
Reflections independent	17691 (R_{int} = 0.144)	14624 (R_{int} = 0.041)
Reflection used	9400	10733
Number of parameters	875	704
R (observed data)	0.0393 ($I > 1\ \sigma(I)$)	0.0255 ($I > 3\ \sigma(I)$)
wR (all data)	0.0439	0.0269
Goodness of fit on F	1.0565	1.1121
Residual density ($e\ Å^{-3}$)	-0.64/0.51	-0.48/0.24
Flack-parameter	0.014(9)	0.008(6)
CCDC deposition code	-	-

Compound	**56d**
Molecular Formula	$C_{35}H_{49}B_1Cu_1N_2O_4$
Formula Weight	636.14
Shape	Plate
Colour	Green
Temperature (K)	173
Crystal size (mm^3)	0.09 x 0.14 x 0.39
Crystal system	Monoclinic
Space group	$P\ 2_1$
a (Å)	10.3175(1)
b (Å)	16.1318(1)
c (Å)	21.4164(2)
α (Å)	90
β (Å)	100.5714(5)
γ (Å)	90
Volume ($Å^3$)	3504.04(5)
Z	4
Density (calc.)(Mg m^{-3})	1.206
Absorption coeff. (mm^{-1})	0.661
Radiation type (λ [Å])	$Mo_{K\alpha}$ (0.71073)
F (000)	1356
Θ range of data collection (°)	1.590-27.847
Completeness to Θmax (%)	0.999
Limiting indices (measured)	-13≤h≤13 -21≤k≤20 0≤l≤28
Reflections measured	29995
Reflections independent	16365 (R_{int} = 0.028)
Reflection used	13332
Number of parameters	776
R (observed data)	0.0275 ($I > 3\ \sigma(I)$)
wR (all data)	0.0363
Goodness of fit on F	1.1069
Residual density (e $Å^{-3}$)	-0.70/0.45
Flack-parameter	0.007(5)
CCDC deposition code	-

Chapter 10

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Education

Since Oct. 2004	**Doctorate in Organic Chemistry and Asymmetric Catalysis** in the research group of Prof. A. Pfaltz, at the University of Basel, Switzerland: "Boron Bridged Bisoxazolines Ligands and their Applications in Asymmetric Catalysis".
July 2004	**DEA (equivalent master) in Organic Chemistry**, Université Pierre et Marie Curie, Paris, France.
June 2004	**Diploma in Engineering at the Ecole Supérieure de Physique et de Chimie Industrielles** (E.S.P.C.I). Major in chemistry, biology and physics.
Jan. 2004 – June 2004	**DEA work at Université Pierre et Marie Curie, Paris, France** under the supervision of Prof. Max Malacria and Dr. Emmanuel Lacôte: "Asymmetric Synthesis and Reactivity of Sulfonimidates".
2000 – 2004	**Student at the Ecole Supérieure de Physique et de Chimie Industrielles**. E.S.P.C.I. is a graduate level engineering school.
1997 – 2000	**Intensive undergraduate studies in chemistry, physics, and maths** to prepare for competitive exams for admission the French "Grandes Ecoles" (joined E.S.P.C.I.).
July 1997	Obtained the **French Baccalauréat** with honours Bien).

Professional Experience

Since 2005	**Teaching assistant in Organic Chemistry, University of Basel,** for advanced chemistry students.
July – Sept. 2003	**Internship in quality direction of EMC distribution, Paris**: study of chemical compounds (glycol ethers, phthalate and nitrosamine) which are potentially hazardous for human health.
April – June 2003	**Internship at E.S.P.C.I. in the research group of Prof. J. Cossy, Paris, France**: "Synthesis of a New Oxidation Catalyst": Ullmann reaction.
July – Nov. 2002	**Engineering internship at Eli Lilly (Indianapolis, USA) in Organic Chemistry**: "MRP-1 Pump Inhibitor's Synthesis with a View to a New Cancer Treatment".
Jan – May 2002	**Bibliographic research for Pfizer** on the pharmaceutical properties of salts with the E.S.P.C.I. Student Enterprise: solubility studies, dissolution rates.

Publications

"Enantioselective Henry Reaction Catalysed by Boron-based Bisoxazolines"

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"Chiral Boron-Bridged Bisoxazoline (borabox) Ligands: Structure and Reactivity of Pd and Cu Complexes"

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Posters and Courses Attended

Sept. 2007	• 2007 CUSO's Summer School in Villars, Switzerland: "Target Synthesis: Challenges, Strategies and Methods". • Fall Meeting of the Swiss Chemical Society, Lausanne – Poster presentation.
Nov. 2006	Fall Meeting of the Swiss Chemical Society, Zürich – Poster presentation.
August 2006	1st European Chemistry Congress, Budapest, Hungary – Poster presentation.
Sept. 2005	*Regio-symposium*, Sornetan, Switzerland – Poster presentation.
July 2005	OMCOS-13, Geneva, Switzerland – Poster presentation.
Sept. 2004	JCO 2004, "Journées de Chimie Organique", Paris, France – Poster presentation.
August 2003	5 Day Graduate Course given by Prof. Stephen L. Buchwald and Prof. Eric. N. Jacobsen, Indianapolis, USA: "Organometallic Chemistry and its application to Organic Synthesis".

I declare that I wrote this thesis "Boron-Bridged Bis(oxazolines) and their Use in Copper-Catalyzed Asymmetric Reactions" with the help indicated and only handed it in to the faculty of Science of the University of Basel and to no other faculty and no other University

Basel, 1st February 2008 Aurélie Toussaint