Synthesis and Applications of Azabis(oxazoline)-Ligands

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Meiner Familie

Immanuel Kant (1724-1804)

„Was kann wohl meiner Hand oder meinem Ohr ähnlicher, und in allen Stücken gleicher sein, als ihr Bild im Spiegel? Und dennoch kann ich eine solche Hand, als im Spiegel gesehen wird, nicht an die Stelle ihres Urbildes setzen …“

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Abbrevations:

abs	absolute
AD	asymmetric dihydroxylation
Ar	aryl
atm.	atmosphere
AzaBOX	azabis(oxazoline)
BINOL	1,1´-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
Bz	benzoyl
Cbz	carboxybenzyloxy
CI	chemical ionization (MS)
COD	1,5-cyclooctadiene
d	days
DCM	dichloromethane
Diglyme	bis(2-methoxyethyl) ether
DIPEA	N,N-diisopropylethylamine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EE	ethyl acetate
EI	electron impact (MS)
ent	enantiomer
eq.	equivalent
ESI	electrospray ionization (MS)
Et	ethyl
EtOH	ethanol
GC	gas chromatography
h	hour
HPLC	high performance liquid chromatography
^{i}Pr	*iso*-propyl
IR	infrared spectroscopy
LDA	lithium diisopropylamide
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MeOPEG	polyethylene glycol monomethyl ether
min	minute
MS	mass spectrometry
^{n}Bu	*n*-butyl
n-BuLi	*n*-butyl lithium
nd	not determined
NLE	non linear effect
NMR	nuclear magnetic resonance
^{n}Pr	*n*-propyl
OAc	acetate
TBS	*tert*-butyl silyl
OTf	triflate
PE	hexanes
Ph	phenyl
PMMH	phenoxy-methyl(methyl-hydrazono)
ppm	part per million
p-TSA	*para*-toluene sulfonic acid
quant.	quantitative
R	arbitrary rest
r.t.	room temperature
rac	racemic
^{t}Bu	*tert*-butyl
^{t}BuOH	*tert*-butanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	tetramethylsilyl

A. Introduction

Already in the beginning of the 19th century the French physicist Biot discovered, that certain inorganic and organic compounds are able to rotate the plane of polarized light.[1,2] Later Pasteur revealed that the sodium ammonium salt of tartaric acid precipitates into enantiomorphic crystals. He was able to mechanically separate the two types of crystals and made the discovery that the solutions of the crystals rotate plane polarized light by the same value but in opposite directions. His explanation for these observations was that the crystals consist of molecules which are nonsuperimposable mirror images of one another. He established that the phenomenon of optical activity is correlated to an asymmetric grouping of atoms within a molecule.

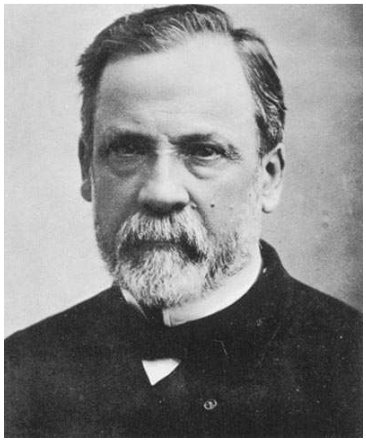


***Figure 1*:** Louis Pasteur (1822-1895).

All this took place even before it was known that carbon is tetravalent, a finding which was established by Kekulé about 40 years later.[3] After the postulates of van't Hoff and Le Bel, which independently reported that tetravalent carbon has a tetrahedral structure, the stage was set for the fundamental feature of organic molecules, their ability to exist in two mirror image configurations. This architecture can result when the central carbon is connected to four different substituents and this stereogenic carbon atom is said to be "chiral" (Figure 2). The expression "chirality" was introduced already more than one century ago by Lord Kelvin, but it took several decades until it became a key word in chemical text books.[4]

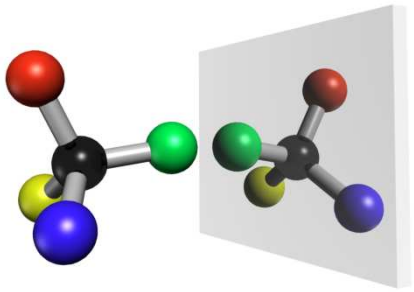


***Figure 2*:** The two mirror image forms of a stereogenic tetrahedral carbon atom.

Ever since the seminal discoveries of Pasteur, van't Hoff and Le Bel it was one of the biggest goals of organic chemists to be able to synthesize only one of the possible stereoisomeric forms, so to produce enantiomerically pure products. Especially in the last few decades, more and more efforts were made concerning the asymmetric synthesis of molecules. Particularly for the pharmaceutical industry the synthesis of single enantiomers of chiral compounds is of great interest, not only because of the thalidomide tragedies. This fact is reflected in Figure 3, showing that in 1989 the amounts of racemates and single enantiomers used in drugs was almost equal, whereas in 2000 there were almost ten times more single enantiomers applied.

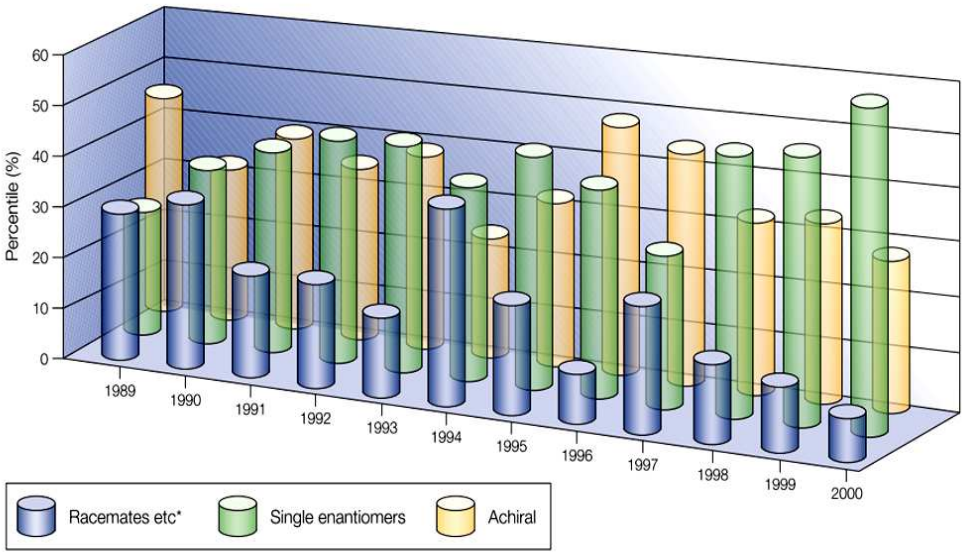
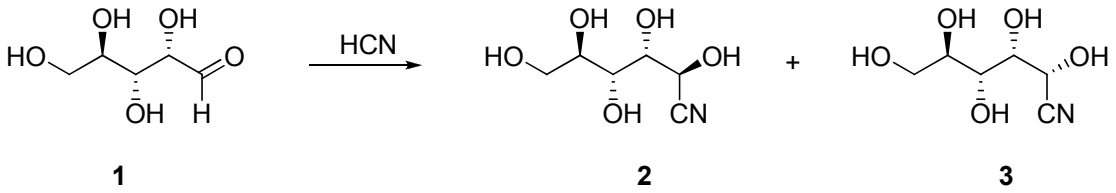


***Figure 3*:** Annual distribution of worldwide approved drugs according to chirality character (1989–2000). * Including diastereomeric mixtures.[5]

Up to date the access to enantiomerically pure compounds relies largely on biologic and biochemical transformations. However, these methods often suffer from drawbacks such as limited substrate scope or instability of the biocatalyst (enzyme, microorganism) in the reaction media. In order to produce new stereogenic centers several chemical methodologies are known: (a) substrate control, (b) auxiliary control and (c) reagent control. The first asymmetric reactions that were conducted used substrate control. This means, that an existing chiral center of the substrate influences the stereochemical outcome of the formation of a new stereocenter during the reaction with an achiral reagent. The first observations in this field were made by E. Fischer in the reaction of hydrogen cyanide with D-arabinose (**1**). The resulting nitriles **2** and **3** were formed in a diastereoselective manner (**2**:**3** = 66:34) (Scheme1).

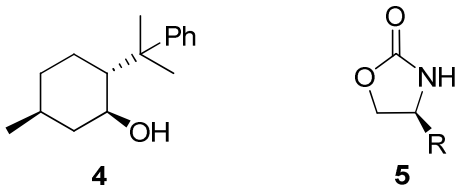


1 **2** **3**

***Scheme 1*:** Diastereoselective addition of HCN to D-arabinose.[6]

After these first results it took more than 50 years until a deeper insight into asymmetric induction in substrate controlled reactions was gained. In 1952 Cram published 'The rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems'[7] which was the basis for a rational interpretation and control of the stereochemical outcome of substrate controlled reactions.

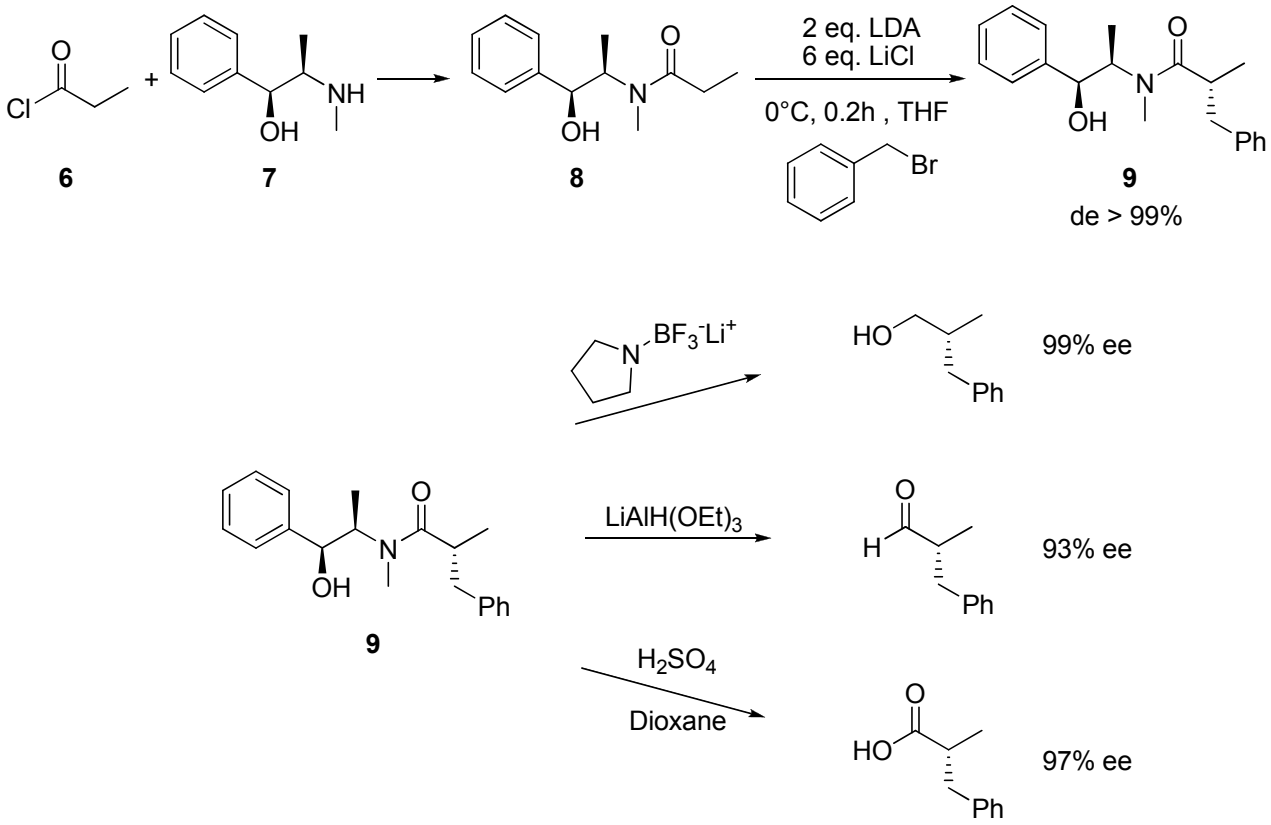
Another approach to the synthesis of chiral compounds was the use of chiral auxiliaries. For this purpose, a chiral, nonracemic molecule (the chiral auxiliary) is covalently attached to the substrate. In the second step, the substrate reacts with an achiral reactant and the stereochemical outcome is controlled by the auxiliary. After the transformation the auxiliary is cleaved to obtain the enantiomerically enriched product. Chiral auxiliaries were introduced by Corey, who used (1*S*,2*R*,5*S*)-2-(1-methyl-1-phenylethyl)-5-methyl-cyclohexanol (**4**) as directing group in 1978.[8] Up to date, the most prominent auxiliaries are the Evans-auxiliaries (**5**), so molecules derived from oxazolidinones, which were used, for example, for enantioselective Aldol-reactions.[9]



4 **5**

***Figure 4*:** Different types of chiral auxiliaries.

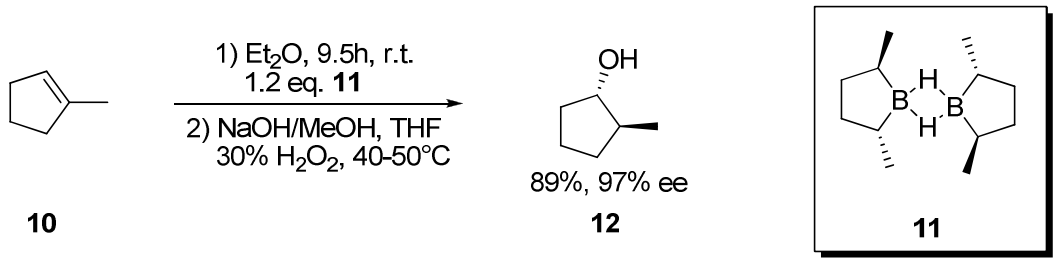
But also other molecules can serve as chirality transmitting groups. Myers et al. reported the use of both enantiomers of pseudoephedrine (**7**) as auxiliaries.[10] For the enantioselective reaction pseudoephedrine **7** first was attached to the substrate to form the amide **8**. After enolization of the amide, a subsequent substitution with benzyl bromide afforded very good diastereoselectivity. The intermediate **9** could be converted into different products with high enantioselectivities (Scheme 2).



***Scheme 2*:** Use of pseudoephedrine as chiral auxiliary according to Myers et al.[9]

The major disadvantages of this methodology were the introduction of two additional synthetic steps into the reaction sequence and the need for stoichiometric amounts of the auxiliary, which usually cannot be recycled.

The third possibility to implement enantioselectivity in a reaction was the application of reagent control. These asymmetric transformations can be divided into two methodologies: (a) the chiral reagent is used in stoichiometric amounts; and (b) the chiral compound is used in sub-stoichiometric quantities (chiral catalysis). In these types of asymmetric reactions, the stereochemical outcome of the reaction is coined by the chirality of the reagent. A very elegant example for asymmetric reactions with reagent control was published by Masamune et al.[11] They used the chiral dialkyl borane **11** for the hydroboration of different alkenes. Applying this methodology also tri-substituted alkenes could be transformed to the corresponding alcohols with almost perfect control of the two new stereocenters (Scheme 3).



***Scheme 3*:** Hydroboration of a tri-substituted alkene by Masamune et al.[10]

Although the deployment of chiral reagents is an elegant way to obtain enantioselective products, it would be more desirable to use the reagent in a sub-stoichiometric amount, as a catalyst that is not consumed during the reaction. Asymmetric catalysis can again be divided into two main fields: the organocatalysis and catalysis employing metal complexes. Since the introduction of the term “organocatalysis” by MacMillan in 2000 it has become a great field of interest for organic chemists and the number of publications concerning this type of chemistry is increasing each year (Figure 5). This is mainly due to the facts that no (possibly) toxic metal has to be used and many catalysts are derived from readily available substances of the chiral pool (amino acids, sugars, terpenes, etc.).

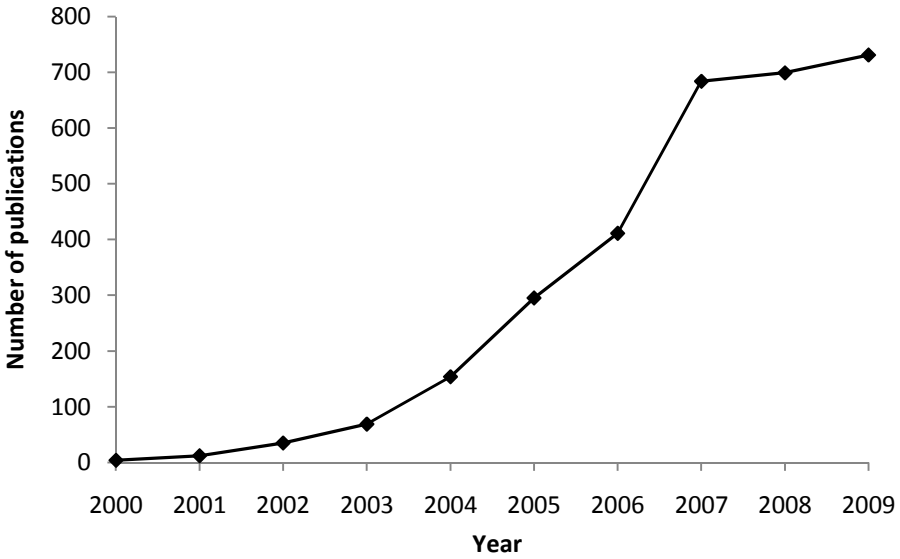
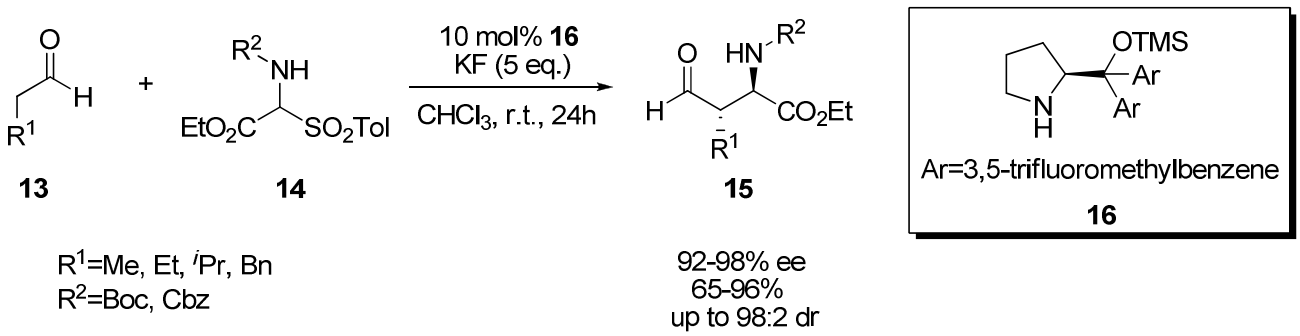


***Figure 5*:** Number of publications using the keyword "organocatalysis" in title or abstract since the year 2000 (from SciFinder, 23.11.2009).

Organocatalysts, which are usually small organic molecules, can increase the reaction rate by different interactions with the substrate, i.e. covalent bonding or non-covalent interactions like hydrogen bonding. The most important mode of action is the covalent bonding of the catalyst to the substrate. Herein, the enamine and the iminium catalysis play the most prominent role. The enamine-type is prevalent in the majority of proline or proline-derived catalysis (Scheme 4). Under these circumstances, the catalyst and the carbonyl compound form an enamin, which is amenable to a nucleophilic attack.



***Scheme 4*:** Highly enantioselective *anti*-Mannich reaction.[12]

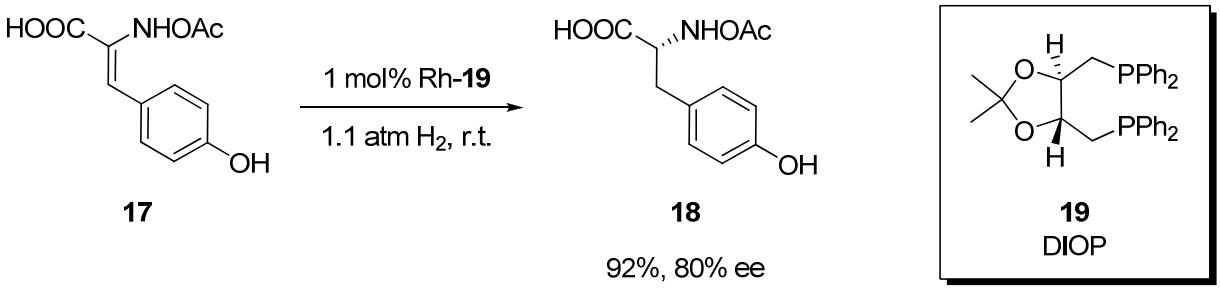
In the second case, the iminium ion catalysis, the secondary amine catalyst and the carbonyl compound will form an iminium ion. The active species then is able to

accomplish a number of reactions, like Diels-Alder-reactions, Michael-additions, Friedel-Crafts-alkylations, to mention only few.

Although the impact of organocatalysis was expanding in the last years, a number of reactions cannot be performed without the use of metal ions so far. For that reason, a lot of research is dedicated to the field of organo-metallic catalysis and great efforts and improvements have been made to enable synthesis of more active and selective catalytic systems. However, enantioselective catalysis is not just a tool in academic research but suitable for large scale synthesis, since there are already a lot of processes catalyzed by metal-organic compounds which are conducted on industrial scale.[13]

1. Historical remarks on organo-metallic, asymmetric catalysis

The first example of homogeneous enantioselective catalysis in literature dates back to 1966.[14] In this reaction, the cyclopropanation of styrene with ethyl diazoacetate, an enantiomeric ratio of 53:47 (regarding the trans isomer) was achieved. Two years later, in 1968, Knowles et al.[15] and Horner et al.[16] independently reported on the hydrogenation of prochiral olefins using Rh complexes of the Wilkinson type, containing optically active phosphines. However, only poor enantioselectivities were achieved using these monodentate ligands, which were chiral on the phosphorus atom. One of the milestones in asymmetric catalysis was the synthesis of DIOP (**19**), a diphosphine ligand derived from tartaric acid that was synthesized by Kagan and coworkers.[17] This represented the first C_2-symmetric ligand, which was able to reduce the number of possible conformations due to bidentate coordination.



17 **18** **19** DIOP

***Scheme 5*:** Asymmetric hydrogenation using DIOP.[16]

Under these conditions it was possible to hydrogenate dehydro *N*-acetyl-tyrosine **17** to afford the corresponding *N*-protected (*R*)-amino acid **18** in good yields and with good enantioselectivities (Scheme 5). These promising results stimulated the research worldwide and as a result many new chiral diphosphines were developed (Figure 6).[18]

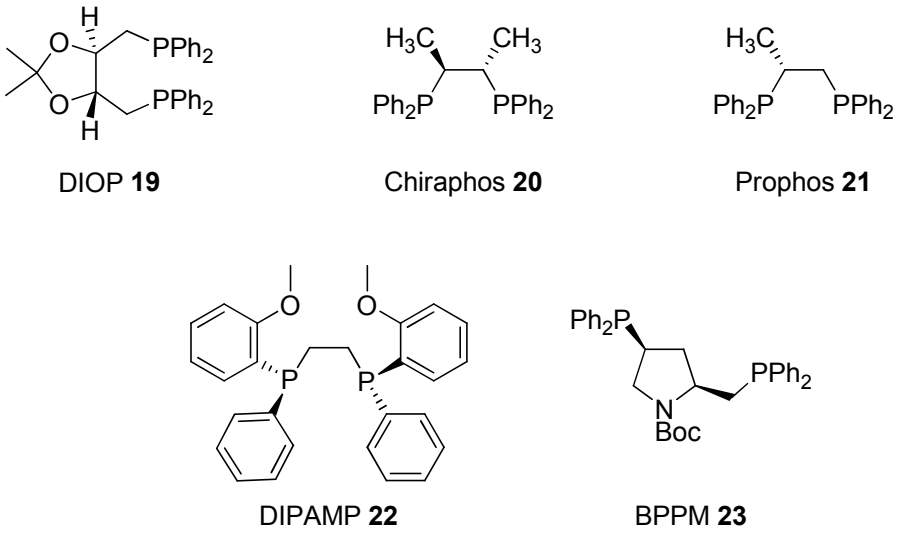
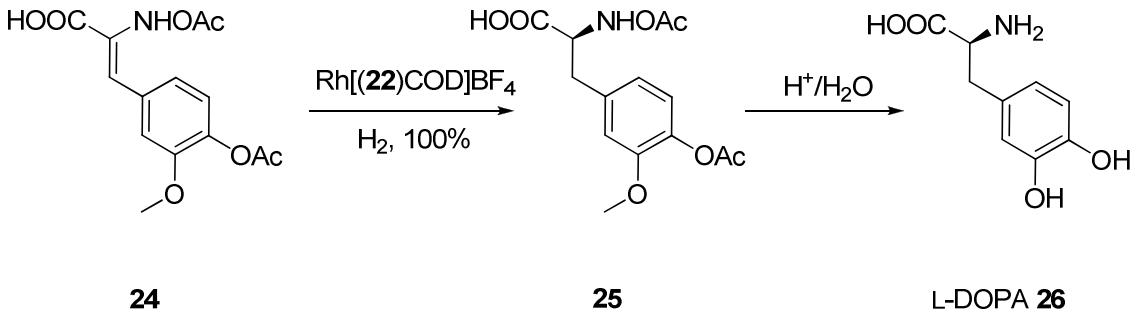


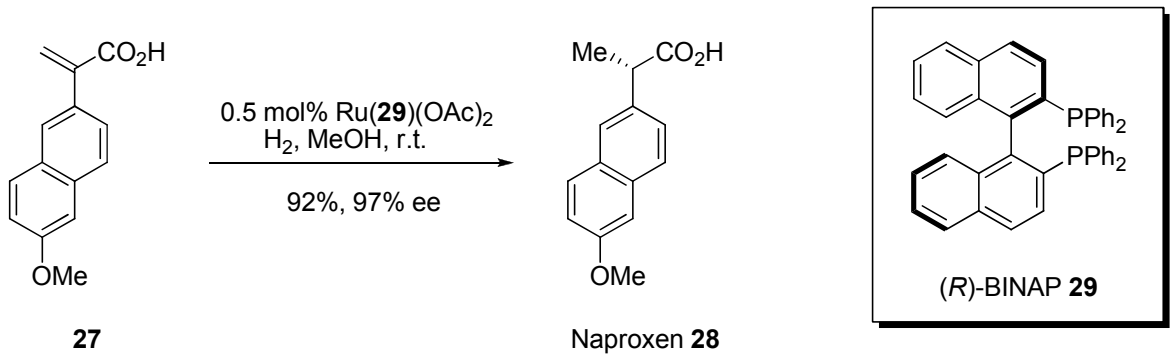
***Figure 6*:** Prominent optically active diphosphines.[19]

A special role plays the DIPAMP ligand **22**, because this compound was used for the first catalytic asymmetric process on industrial scale, namely the synthesis of L-DOPA. In a rhodium(I)-catalyzed reaction, unsaturated amino acid **24** was reduced to the intermediate **25**, which furnished the desired product after hydrolysis of the protecting groups (Scheme 6).



***Scheme 6*:** The asymmetric synthesis of L-DOPA using a C_2-symmetric ligand.[20]

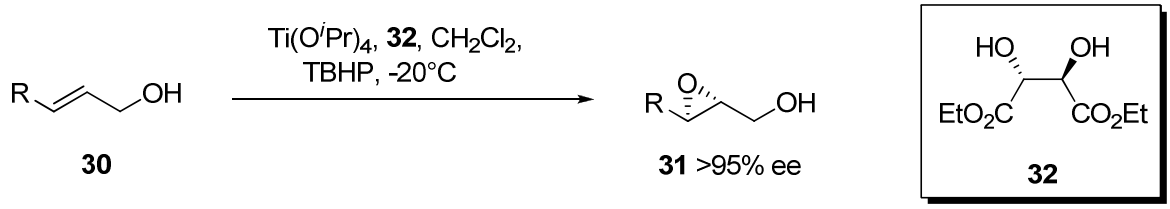
Another benchmark for asymmetric hydrogenations was set by Noyori in 1980, when he introduced the axially chiral C_2-symmetric ligand BINAP **29**, whose rhodium(I) and ruthenium(II) complexes were also used for hydrogenation reactions. Currently several chiral drugs are produced using these catalytic systems. For instance, the anti-inflammatory drug naproxen **28** is prepared from α-arylacrylic acid **27** in a highly enantioselective process (Scheme 7).



27 Naproxen **28**

***Scheme 7*:** Asymmetric synthesis of naproxen **28**.[21]

But not only hydrogenations were successfully applied in asymmetric catalysis, as shown for example by Sharpless and Katsuki, who were able to selectively epoxidize allylic alcohols (Scheme 8).

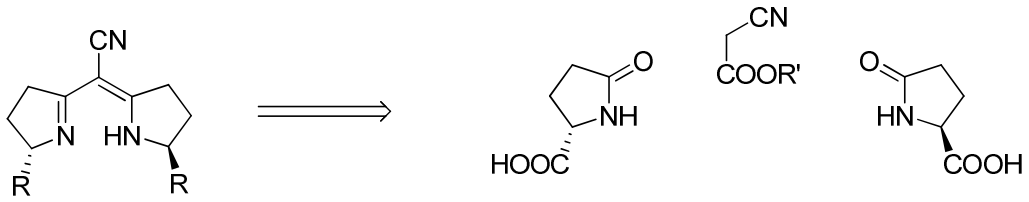


30 **31** >95% ee

***Scheme 8*:** Sharpless-Katsuki asymmetric epoxidation of allylic alcohols.[22]

In this reaction several allylic alcohols could be epoxidized by the Ti-complex of tartrate **32**. For their great contributions to asymmetric catalysis, Noyori and Knowles were awarded the Nobel Prize in 2001, for their achievements in asymmetric hydrogenation reactions, next to Sharpless for his work on the asymmetric oxidation of alkenes.[23]

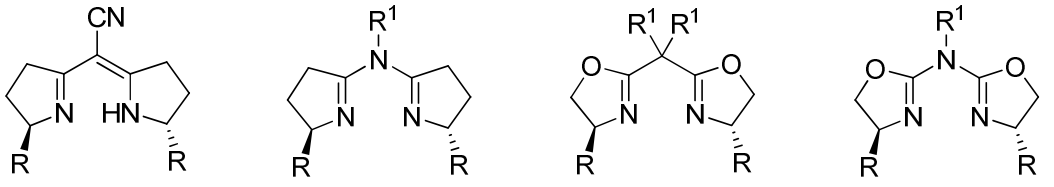
A new class of ligands was developed by Pfaltz et al. in 1986, with the *pseudo* C_2-symmetric semicorrin ligand **33a**, which was inspired by naturally occuring structural motifs of corrinoid and porphinoid metal complexes.[24] The ligand is derived from pyroglutamic acid **34**, a compound which is commercially available in both enantiomeric forms (Scheme 9).



33a **34** **34**

***Scheme 9*:** Retrosynthetic analysis of semicorrin ligand **33a**.[24]

The structural motif of nitrogen containing bidentate ligands found a wide range of applications and a plethora of new catalysts were developed on the basis of this concept. Some of them are shown in Figure 7. The most prominent representatives of bidentate *N*-containing ligands were established almost simultaneously by Masamune et al.[25] and Evans et al.[26], when they published the synthesis of bis(oxazoline) (BOX) ligands **35**. They represent the consequent enhancement of ligands based on the structural element of oxazolines, which was implemented by Brunner et al.[27] The bis(oxazolines) are among the most useful ligands for asymmetric catalysis due to their ability to coordinate a large number of metals.[28] These ligands were successfully applied in a manifold of reactions, such as cyclopropanations, Diels-Alder reactions, allylic substitutions or 1,3-dipolar cycloadditions.[29]



33a semicorrin **33b** aza-semicorrin **35** bis(oxazoline) **36** azabis(oxazoline)

***Figure 7*:** Bidentate nitrogen containing ligands.

Another class of *N*-containing ligands are the azabis(oxazoline) (AzaBOX) ligands **36**, which were developed in our group.[30] They combine the relatively simple synthesis, like the bis(oxazolines), starting from the corresponding amino alcohols, and the possibility of a functionalization on the central nitrogen, like the aza-semicorrins. Furthermore, due to the different electronic properties, they are less prone to metal-leaching compared to bis(oxazolines).[31] These attributes qualify azabis(oxazolines) for anchoring to different solid supports, in order to recycle the catalyst. Several approaches have been accomplished successfully, where the ligands were bound to supports like MeOPEG,[29a,32] Merrifield-resin, fluorous tags,[33] dendrimers[34] or nanoparticles.[35] The metal complexes showed their usefulness in a variety of reactions like cyclopropanations,[29a] benzoylation of 1,2-diols,[32] conjugate reductions[36] or Michael-additions.[37]

The goal of this research project was to synthesize new azabis(oxazoline) ligands and extend the scope of their usability in different transformations.

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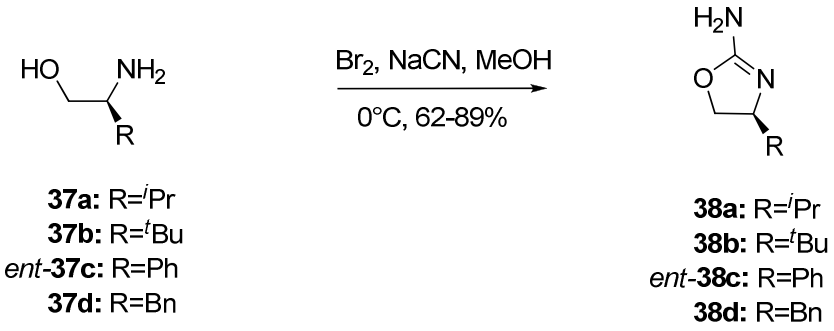
B. Main Part

1. Ligand Synthesis

For the synthesis of azabis(oxazoline) (AzaBOX) ligands two main routes are established. Both start from β-amino alcohols, which are readily available from the chiral pool by simple reduction of the corresponding amino acid. For the conversion of these amino alcohols into 2-aminooxazolines (**38**) several strategies are known, for example the reaction of the amino alcohol with in situ formed BrCN, following the protocol of Poos et al. (Scheme 10).[1]

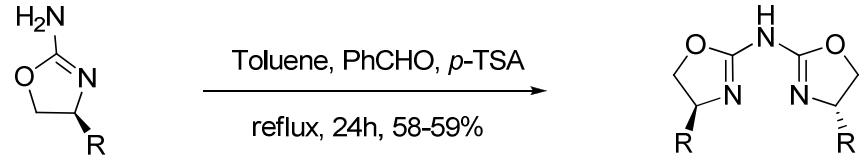


37a: R=^{i}Pr
37b: R=^{t}Bu
ent-**37c:** R=Ph
37d: R=Bn

38a: R=^{i}Pr
38b: R=^{t}Bu
ent-**38c:** R=Ph
38d: R=Bn

***Scheme 10*:** Synthesis of aminooxazolines following Poos et al.[1]

The likewise formed aminooxazolines originally should be converted to imines in the presence of benzaldehyde and *p*-toluenesulfonic acid, to produce new chiral building blocks for asymmetric catalysis. But instead, a condensation of two molecules of **38** took place, under the formal elimination of ammonia, and as a main product azabis(oxazolines) **36** were obtained (Scheme 11).[2]

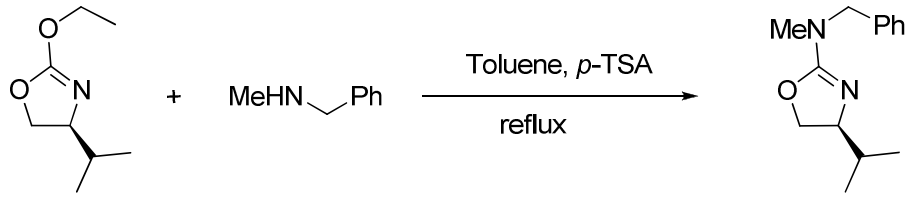


38a: R= ^{i}Pr
38b: R= ^{t}Bu

36a: R= ^{i}Pr
36b: R= ^{t}Bu

***Scheme 11*:** Synthesis of azabis(oxazolines) by M. Glos.[2]

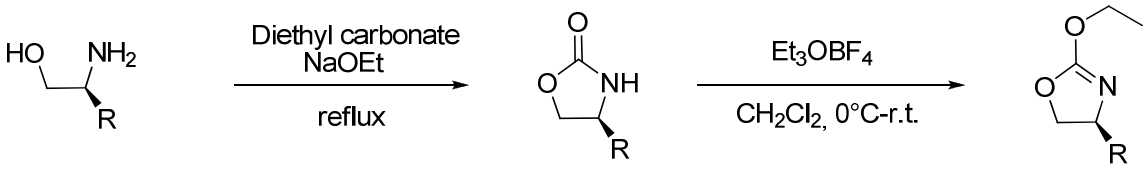
But this short and elegant synthesis turned out to be useful only in the case of ^{i}Pr and ^{t}Bu substituted azabis(oxazolines). Even in these cases the purification was often tedious and only moderate yields could be achieved. For that reasons a new synthetic route was developed by H. Werner[3] which gave access to new AzaBOX-ligands. The new methodology was based on the results of Gawley et al.,[4] who examined the reactivity of ethoxyoxazolines **39** towards *sec*. amines (Scheme 12).



39a **40** **41**

***Scheme 12*:** Reaction of ethoxyoxazoline **39a** with *sec*. amine.[4]

The synthesis of the ethoxyoxazoline starts from the easy accessible oxazolidinone, which can be formed from the amino alcohol by a multitude of possible ways. One of them is the reaction of amino alcohol **37** with diethyl carbonate in the presence of sodium ethanolate. Subsequently, the oxazolidinones **42** can be alkylated on the carbonyl oxygen by use of Meerwein salt (Scheme 13).

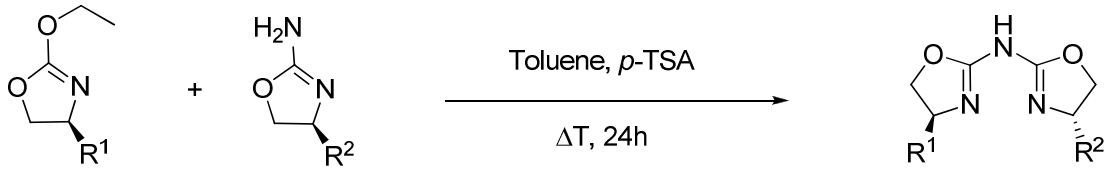


37 **42** **39**

***Scheme 13*:** Synthesis of ethoxyoxazolines **39**.[5]

The hereof obtained ethoxyoxazolines **39** usually are quite unstable, therefore they are directly reacted with the aminooxazoline **38** to form the azabis(oxazolines) (Table 1).

***Table 1*:** Azabis(oxazolines) synthesized by H. Werner[a] and A. Gissibl[b].[3,6]



39a: R^1= ^{i}Pr
39b: R^1= ^{t}Bu
ent-**39c:** R^1= Ph
39d: R^1= Bn

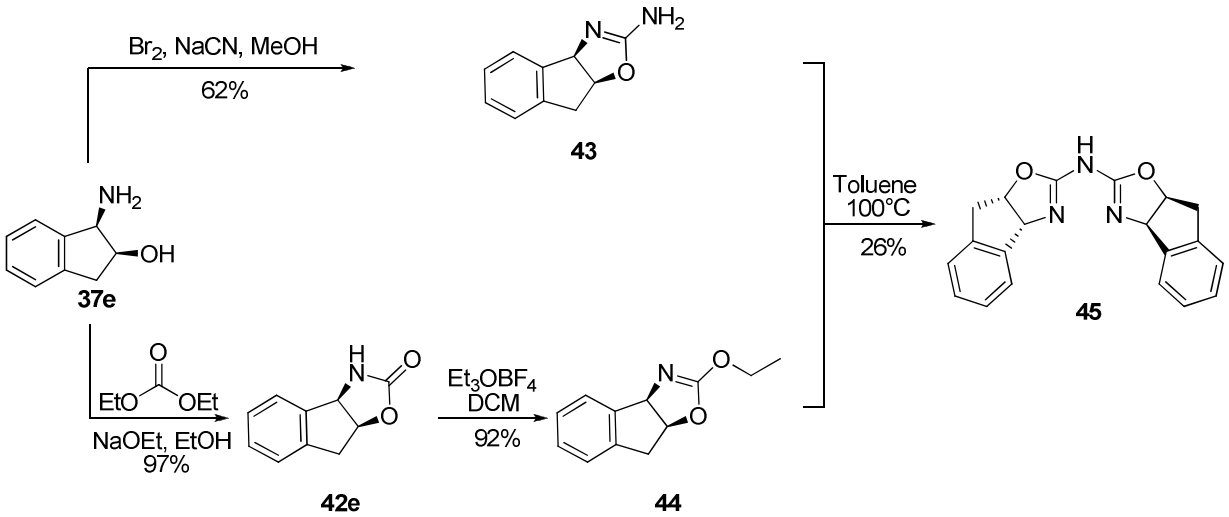
38a: R^2= ^{i}Pr
38b: R^2= ^{t}Bu
ent-**38c:** R^2= Ph
38d: R^2= Bn

36a,b,d,e
ent-**36c**

Entry	Product	R^1	R^2	Temperature (℃)	Yield (%)
1[a]	**36a**	^{i}Propyl-	^{i}Propyl-	110	50
2[a]	**36b**	^{t}Butyl-	^{t}Butyl-	110	92
3[a]	*ent*-**36c**	Phenyl-	Phenyl-	50	35
4[a]	**36e**	^{t}Butyl-	Phenyl-	50	64
5[b]	**36d**	Benzyl-	Benzyl-	110	35

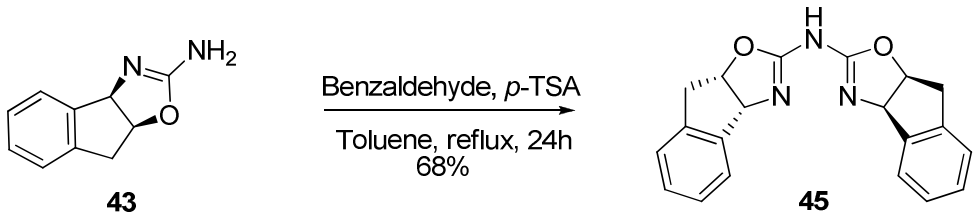
Following this procedure it was even possible to synthesize unsymmetrical substituted ligands (Table 1, entry 4).

One goal of this work was to create new azabis(oxazoline) ligands and apply them in asymmetric catalysis. For that reason the commercially available amino alcohol (1*R*,2*S*)-1-amino-2-indanol **37e** was chosen as starting point, because the analog bis(oxazoline) ligand has already found application in different catalytic reactions like Henry reactions,[7] Diels-Alder reactions,[8] Nazarov reactions[9] or conjugate additions.[10] In the beginning the route of Werner was attempted, exhibiting usually high compatibility towards different substitution patterns on the oxazoline ring and giving often superior yields (Scheme 14).



***Scheme 14*:** Synthesis of the indanyl-substituted AzaBOX **45** following the procedure of H. Werner.

Therefore the aminooxazoline **43** was formed under standard conditions in moderate yield after recrystallisation. In a second reaction the amino alcohol **37e** was converted to the oxazolidinon **42e** in very good yield. Subsequently, the oxazolidinon was transformed into the ethoxyoxazoline **44** in good yield. Unfortunately, the coupling of the two fragments **43** and **44** turned out to be problematic. The desired product **45** could only be isolated in 26% yield. One explanation could be the surprisingly high stability of the ethoxyoxazoline, which could be reisolated as a crystalline product even after column chromatography. Usually these kinds of compounds decompose within some days at room temperature. Due to this result the strategy was changed and the protocol of Glos was applied using only the aminooxazoline **43** (Scheme 15).



***Scheme 15*:** Synthesis of indanyl-substituted AzaBOX following the protocol of Glos.

Under these conditions the yield could be considerably increased to 68% and the product was obtained in pure form after recrystallisation. This result led to the

suggestion, that already in the first case (Scheme 14) the achieved product can be ascribed only to the coupling of the aminooxazoline fragments.
The structure of ligand **45** could be confirmed by X-ray analysis as shown in Figure 8.

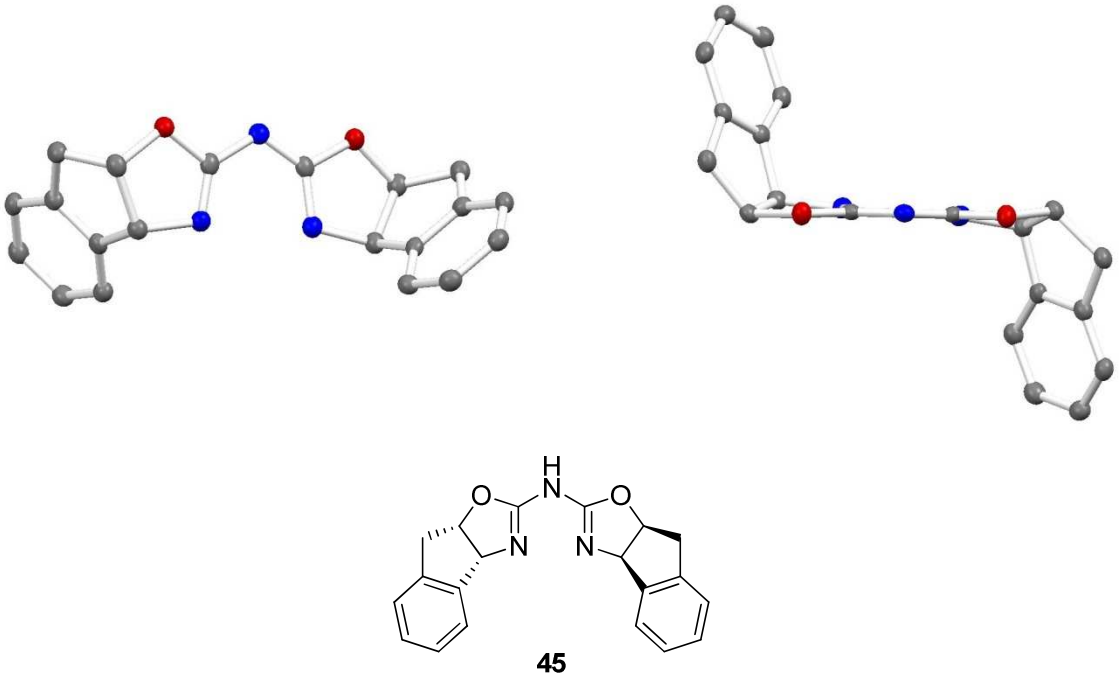
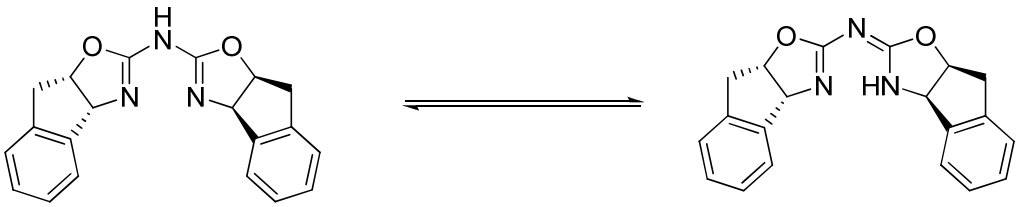


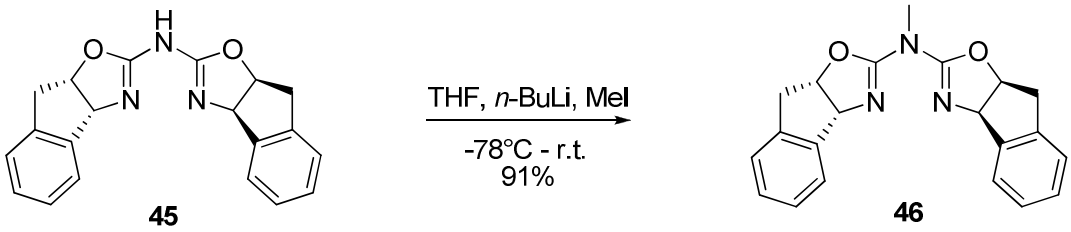
***Figure 8*:** X-ray structures of the indanyl-AzaBOX **45** (protons are omitted for clarity).

According to the already known structures the two oxazoline rings form an almost planar system. This fact can be ascribed to a possible amine-imine-tautomerism of the central bridging nitrogen and one of the oxazoline nitrogens (Scheme 16).



***Scheme 16*:** Possible tautomeric forms of azabis(oxazoline) **45**.

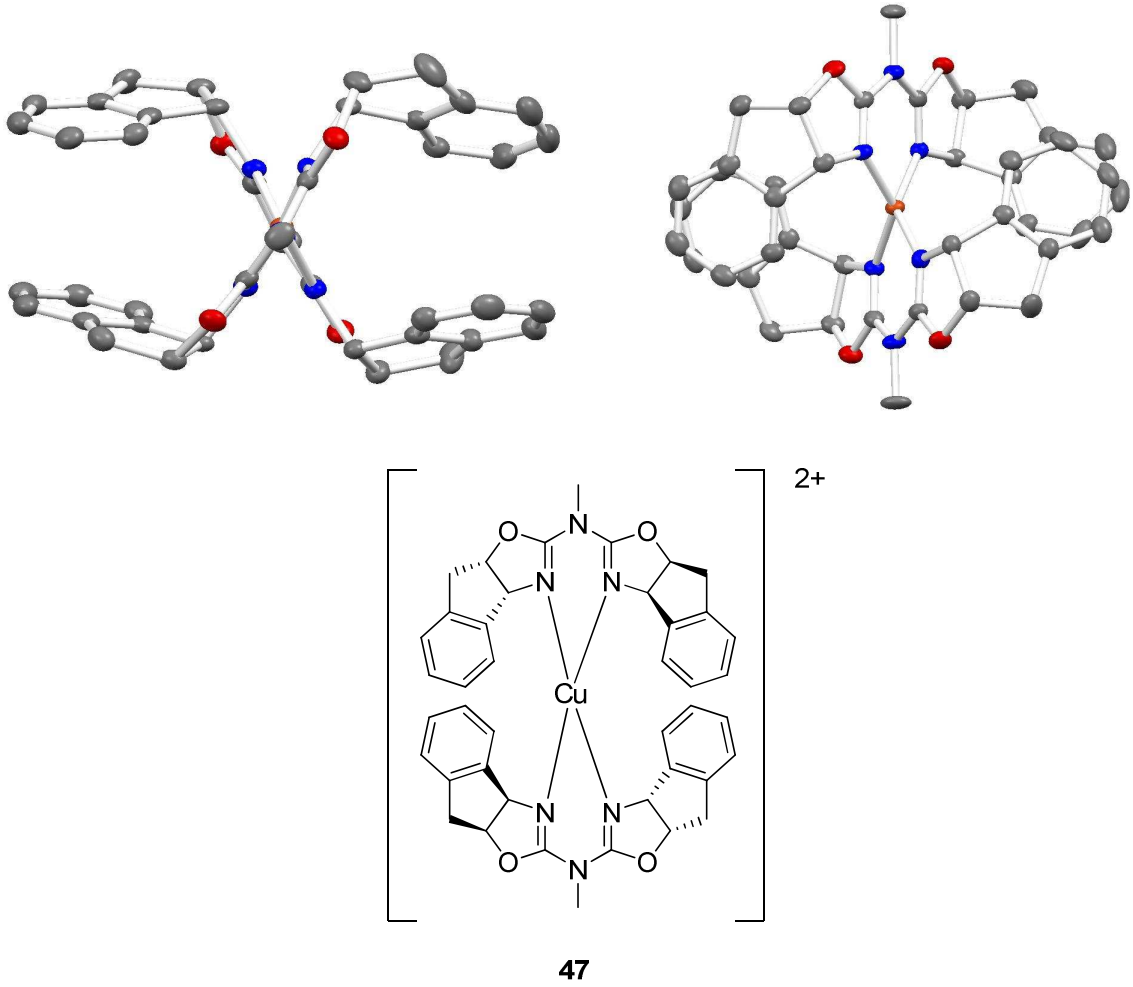
The obtained ligand **45** furthermore was methylated on the central nitrogen bridge, using standard conditions, to give compound **46** (Scheme 17).



45 **46**

***Scheme 17*:** Methylation of ligand **45**.

For the methylated ligand it was not possible to grow a single crystal for X-ray analysis, but after the complexation with $Cu(ClO_4)_2$ utilizable crystals could be obtained (Figure 9).

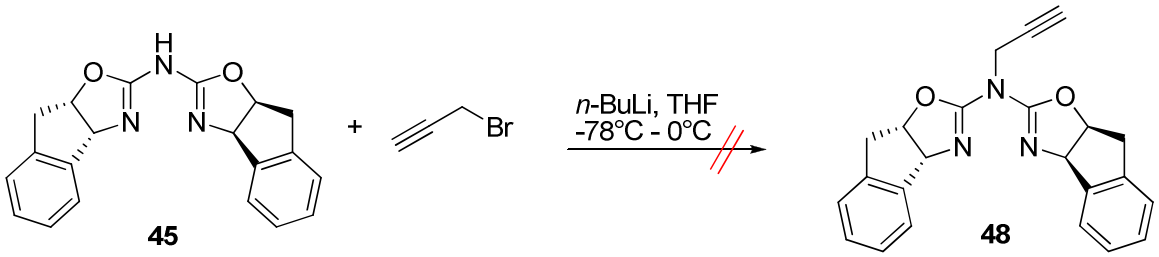


47

***Figure 9*:** X-ray structure of complex **47** (counter ions and protons are omitted for clarity).

In analogy to other complexes of azabis(oxazolines)[2,6] the ligand **46** and the copper-salt form a 2:1 complex in the solid state, although the compounds were mixed in a 1:1 ratio.

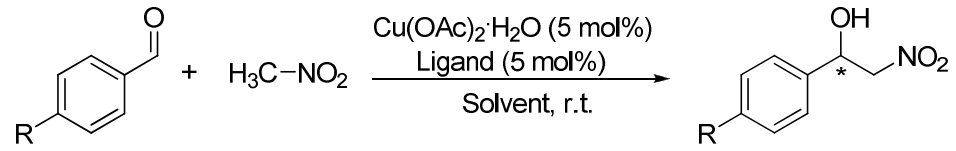
It was also envisaged to propargylate the ligand **45** on the central nitrogen, to be able to immobilize it via 'click'-reaction on different solid supports (Scheme 18). But during the addition of propargyl bromide the substrate precipitated from the reaction mixture and couldn't be redissolved even at higher temperatures. The same problem occurred when the reaction was reiterated under more diluted conditions.



***Scheme 18*:** Attempt to propargylate the ligand **45**.

In order to validate the catalytic activity of the new ligands, the Henry reaction was chosen as test reaction, being known to give very good enantioselectivities with the indanyl-substituted BOX-ligand **52**. The results are summarized in Table 2.

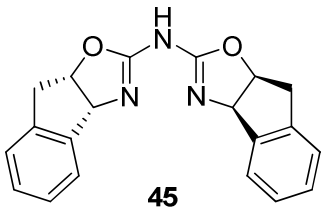
***Table 2*:** Asymmetric Henry reaction.[a]



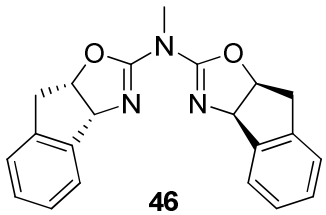
49a: R=H
49b: R=NO_2

50

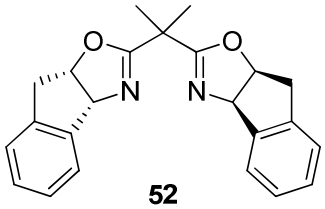
51a: R=H
51b: R=NO_2



45



46



52

Entry	Ligand	Solvent	Substrate	Yield (%)[b]	ee (%)[c]
1	**45**	EtOH	**49b**	9	0
2	**45**	THF	**49a**	–	–
3	**46**	EtOH	**49b**	94	75
4[d]	**52**	EtOH	**49b**	85	78
5[d]	**52**	EtOH	**49a**	76	94

[a] Reagents and conditions: aldehyde (0.5 mmol), nitro methane (5 mmol), r.t., 1 mL solvent. [b] Isolated yield of **51**. [c] Determined by chiral HPLC. [d] Taken from ref. 7.

The results show, that the unmethylated ligand **45** is catalytic inactive under the given conditions (Table 2, entries 1 and 2). This can be ascribed to the poor solubility of this compound in the most common organic solvents. In contrast, the methylated ligand **46** is soluble and therefore is able to perform the reaction in high yield and with an enantioselctivity which is comparable to the literature value (Table 2, entries 3 and 4). Because of this promising result the new ligands were tested in several transformations, which will be shown later.

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2. Immobilization on water-soluble dendrons

For the application of catalytic systems on industrial scale one prerequisite is often the ability of catalyst recycling. Especially organo-metallic compounds frequently suffer from the drawback of being cost-intensive. Therefore, many approaches have been made to graft the catalytically active species to different supports in order to facilitate their recovery. The attachment can be done by a multitude of methods, i.e. covalent bonding, electrostatic interactions[1] or encapsulation.[2] One general possibility is to connect the catalyst to an insoluble support, like nanoparticles, clays, alumina, zeolithes or highly branched organic polymers (polystyrene, polyacrylate). In these cases the recuperation can be achieved by a simple filtration or magnetic decantation (nanoparticles). The major disadvantage of the heterogeneous catalysts is their often reduced activity and selectivity compared to the unbound counterpart. To circumvent these drawbacks soluble, linear polymers (polyethylenglycol, polystyrene) and organic macromolecules (dendrimers) have been developed, which give rise to homogeneous reaction conditions. The catalyst recovery can be done after precipitation of the polymer using unpolar solvents. As already mentioned, both types of solid supports have been applied successfully for azabis-(oxazolines) (Figure 10).

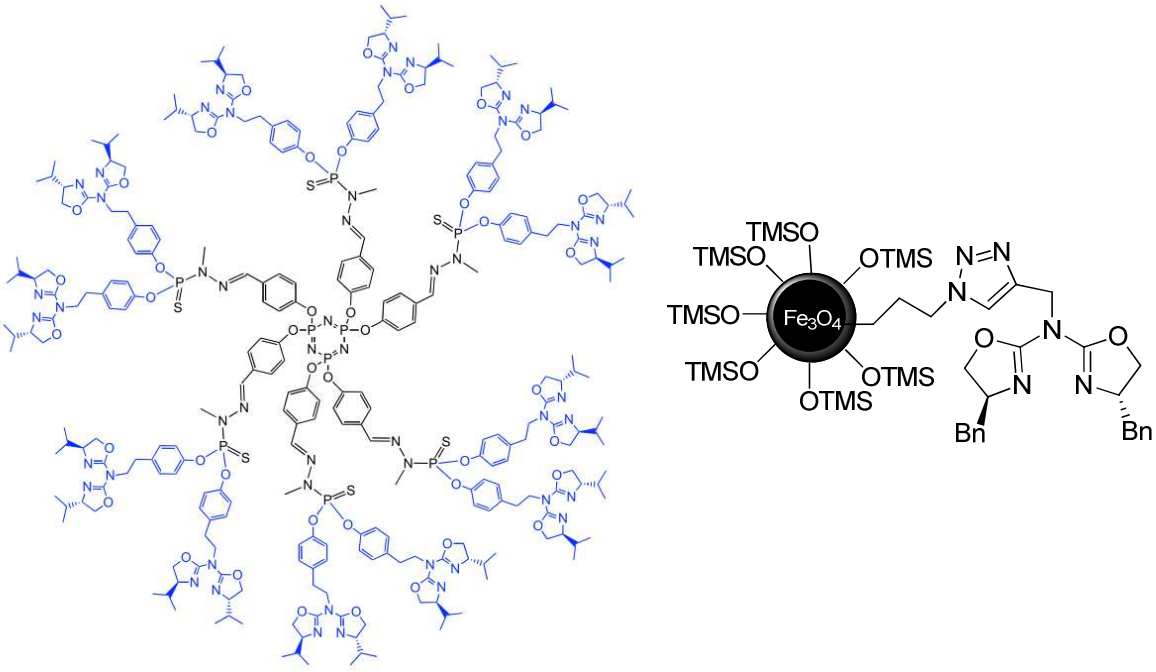
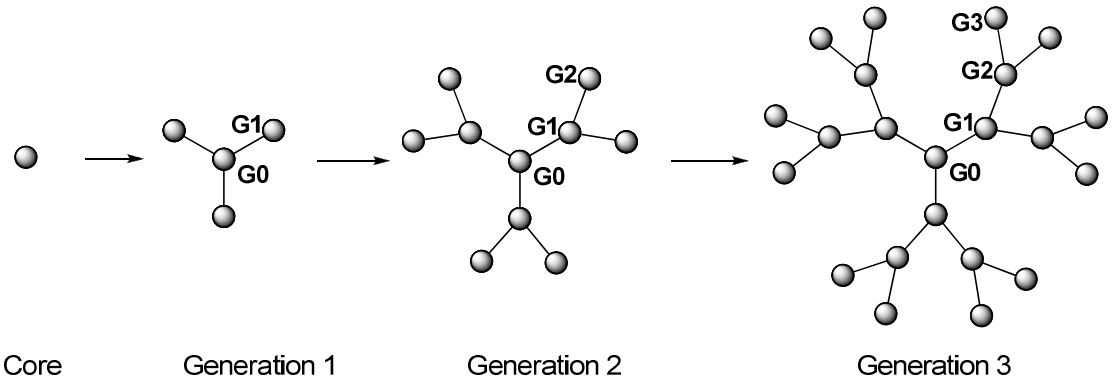


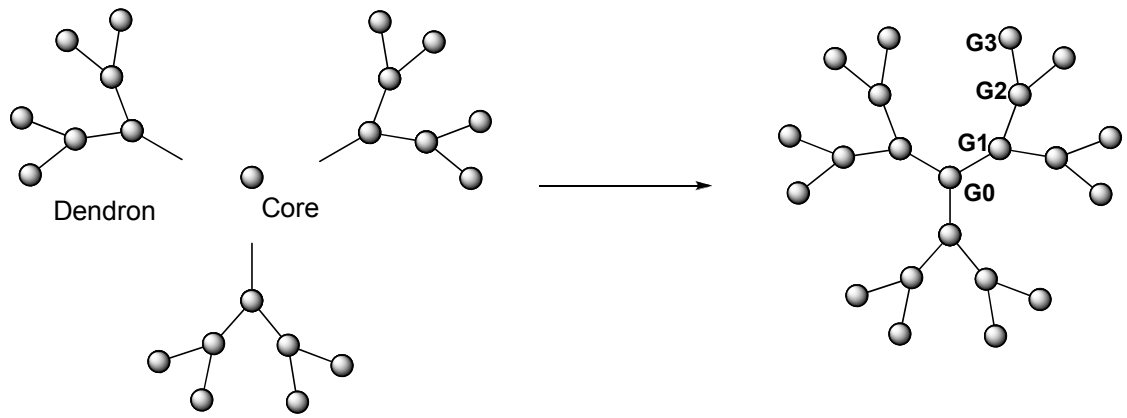
***Figure 10*:** Examples of immobilized azabis(oxazolines) (left: on dendrimer, right: on magnetic nanoparticles).[3,4]

Dendrimers, as depicted in Figure 10 (left), are repeatedly branched, monodisperse and usually highly symmetric macromolecules. For the synthesis of dendrimers two major routes are known, the divergent synthesis and the convergent synthesis.[5] In the divergent synthesis the molecule is assembled from the core by stepwise addition of monomers (Scheme 19).



***Scheme 19*:** Divergent synthesis of dendrimers.

In contrast, the convergent route starts from the surface and proceeds inwards. In the end the synthesized dendrons are attached to the core (Scheme 20). The advantage of this approach is the relatively easy separation of defective dendrimers, but especially for dendrimers of higher generation this synthesis becomes challenging, due to the increasing steric bulk of the dendrons.

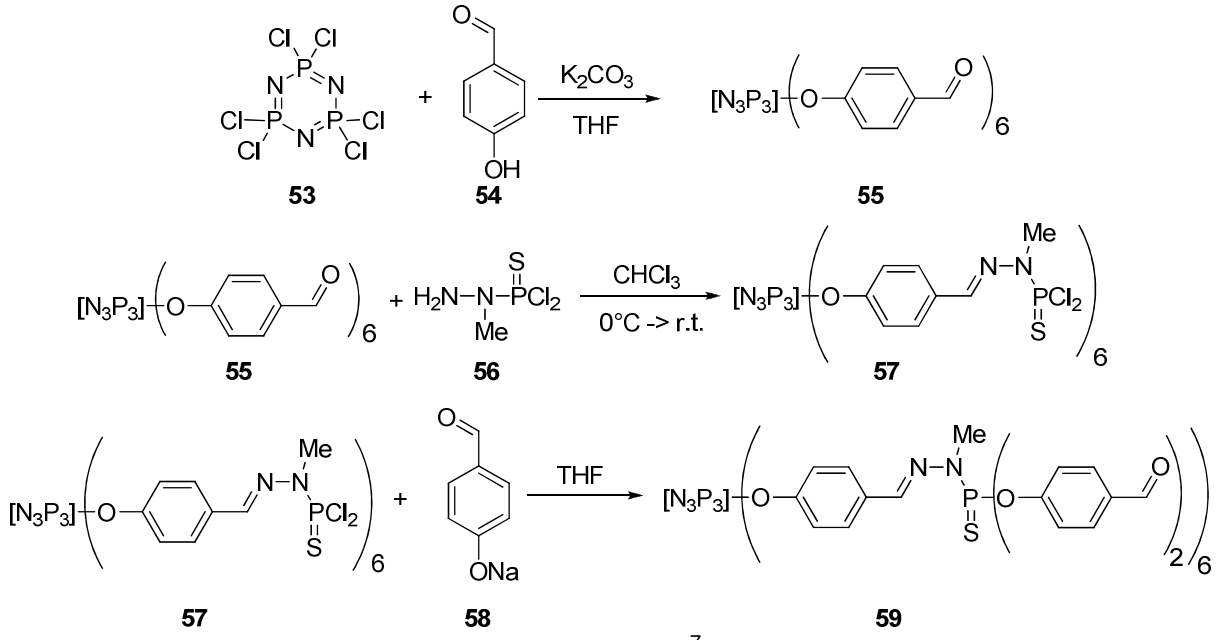


***Scheme 20*:** Last step of the convergent dendrimer synthesis.

If dendrimers are used for transition metal catalysis the catalyst can be attached at different positions on the dendrimer, for example on the surface or in the core of the molecule. But also catalysts immobilized on dendrons have already found

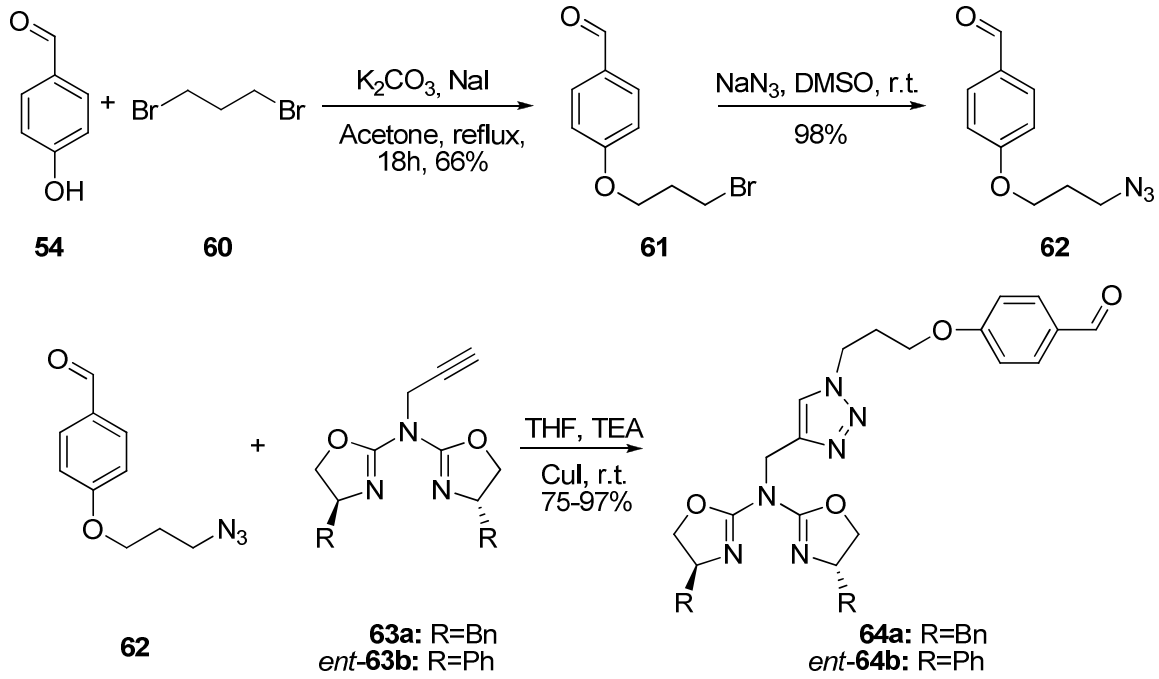
application.[6] For that reason and on the basis of the results of F. Jaroschik[3] and A. Gissibl, [6,3] who attached azabis(oxazolines) to the surface of the PMMH-dendrimer, investigations were made to connect AzaBOX-ligands to water soluble dendrons. This project was carried out under the supervision of J.-P. Majoral at the LCC in Toulouse.

The AzaBOX bearing dendron was planned to be built up in analogy to the synthesis of the PMMH (PhenoxyMethyl(MethylHydrazono)) dendrimer, which is depicted briefly in Scheme 21.



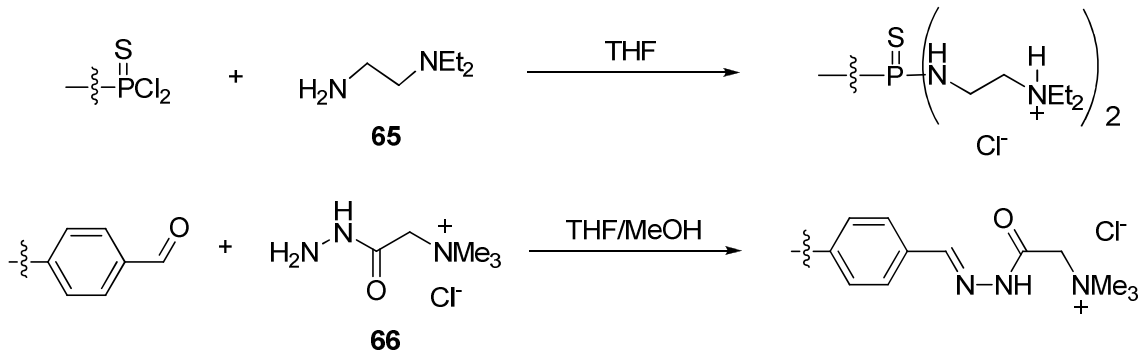
***Scheme 21*:** Synthesis of the PMMH-dendrimer.[7]

The intended synthesis started from propargylated azabis(oxazolines) **63**, which would undergo a click reaction with the aldehyde fragment **62**, that was derived from *p*-hydroxybenzaldehyde **54** (Scheme 22).



***Scheme 22*:** Intended synthesis of water soluble dendrons (part 1).

With the compound **64** in hands the synthesis of higher generations should be accomplished as shown in Scheme 23. To make the dendrons water soluble two different strategies were suggested as depicted in Scheme 23.

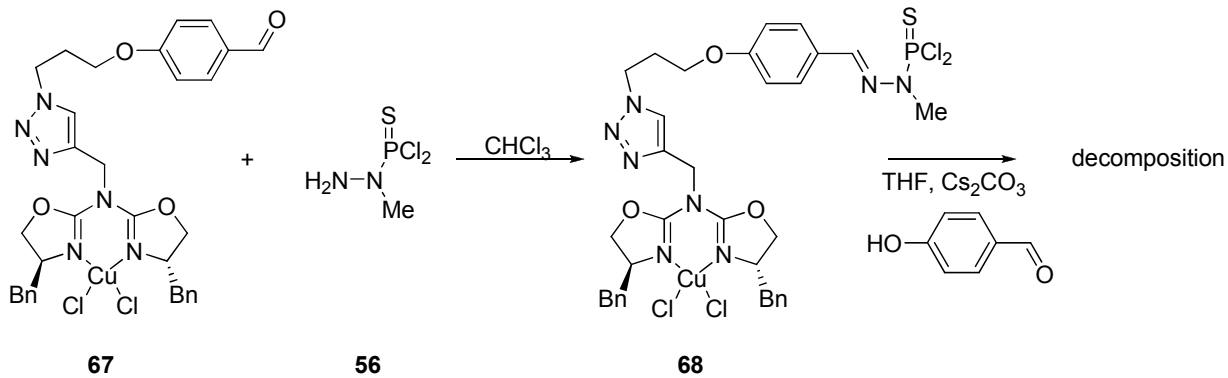


***Scheme 23*:** Intended synthesis of water soluble dendrons (part 2).

Depending on the functional group on the surface either ethylendiamine (**65**) or the Girard's reagent T (**66**) were planned to be used for establishing a quaternary ammonium ion function on the surface.

Unfortunately, during the synthesis it turned out that the oxazoline moieties of the ligand are unstable against the hydrazide **56**. To circumvent this problem the ligand was complexed with $CuCl_2$ in order to stabilize the oxazoline rings. Indeed the ^{31}P-NMR spectrum of the obtained product **68** showed only one peak, but during the

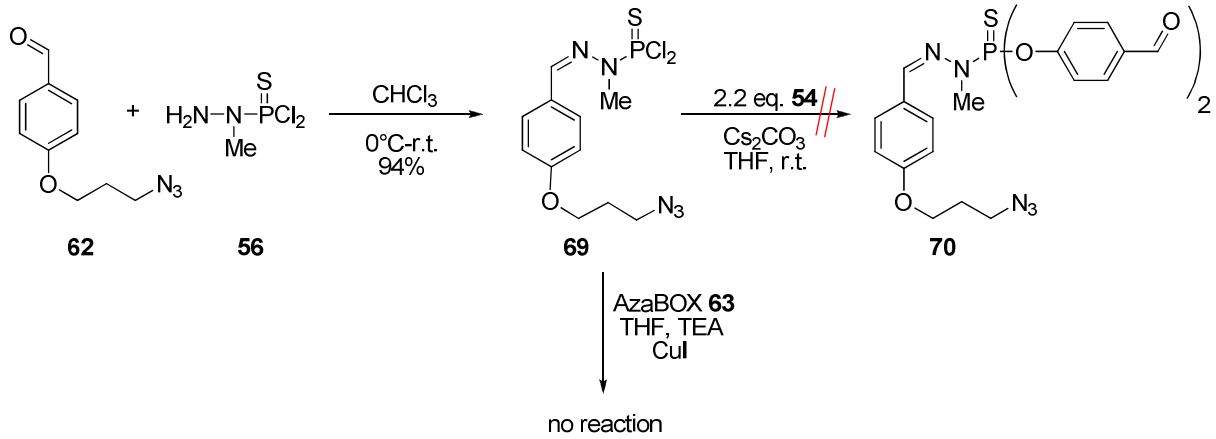
next coupling step with the *p*-hydroxybenzaldehyde decomposition was observed (Scheme 24).



67 **56** **68**

***Scheme 24*:** Synthesis with AzaBOX-$CuCl_2$ complex.

As a consequence of these results the synthetic strategy was changed. The idea was to construct the dendron first and connect the ligand to it right before the introduction of the ammonium groups. But now a new problem arose, the click reaction didn't proceed even with dendrons of first generation (**69**). This fact was ascribed to the reactive $PSCl_2$ unit, therefore it was tried to react this group with *p*-hydroxybenzaldehyde **54**. Unfortunatelly, the attempted reaction resulted in a decomposition of the material.



62 **56** **69** **70**

***Scheme 25*:** Attempted new strategy for the dendron synthesis.

Due to the instability of the ligand against the conditions of the dendron synthesis and a lack of time no further investigations could be made to achieve the goal of having water soluble ligands for asymmetric catalysis.

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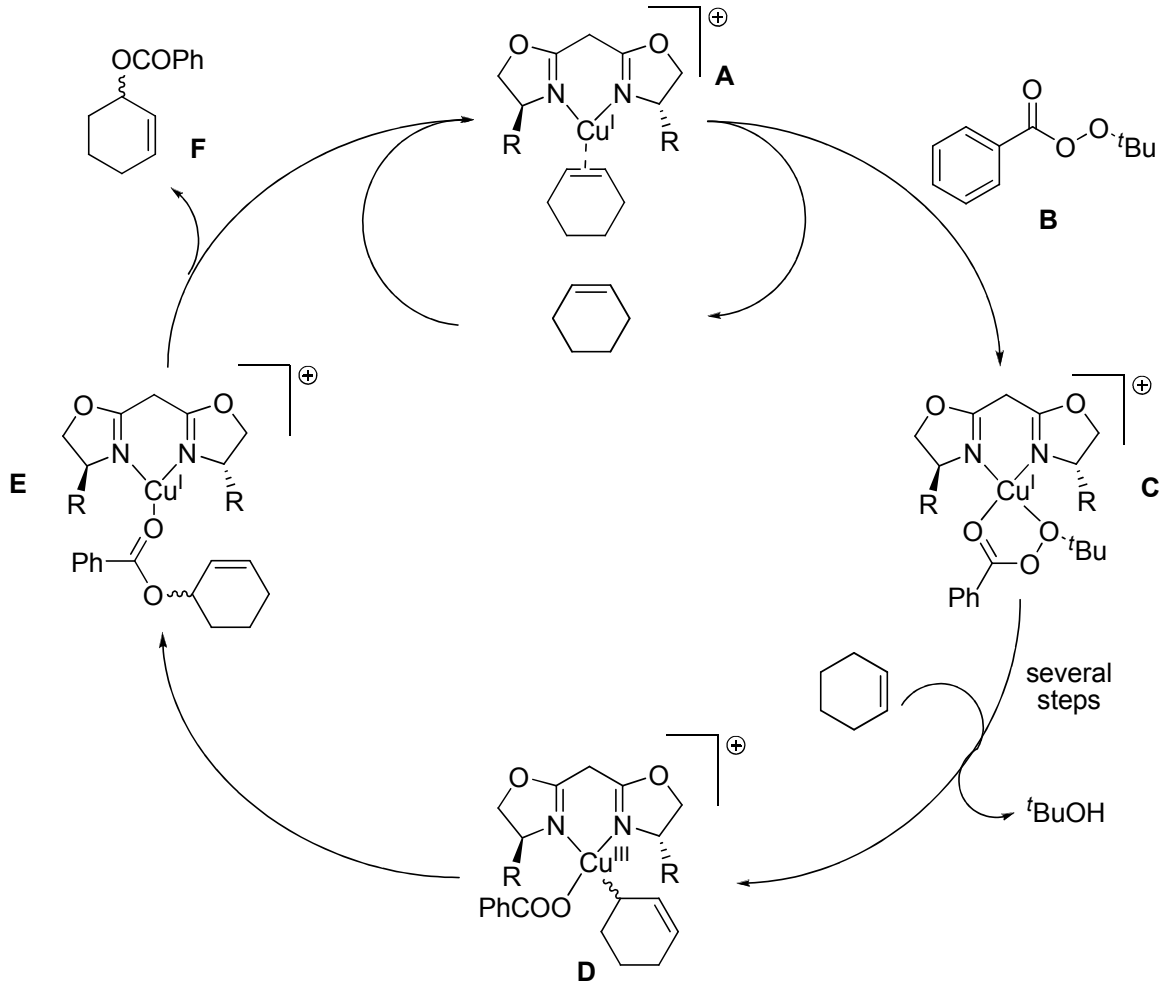
3. Catalysis

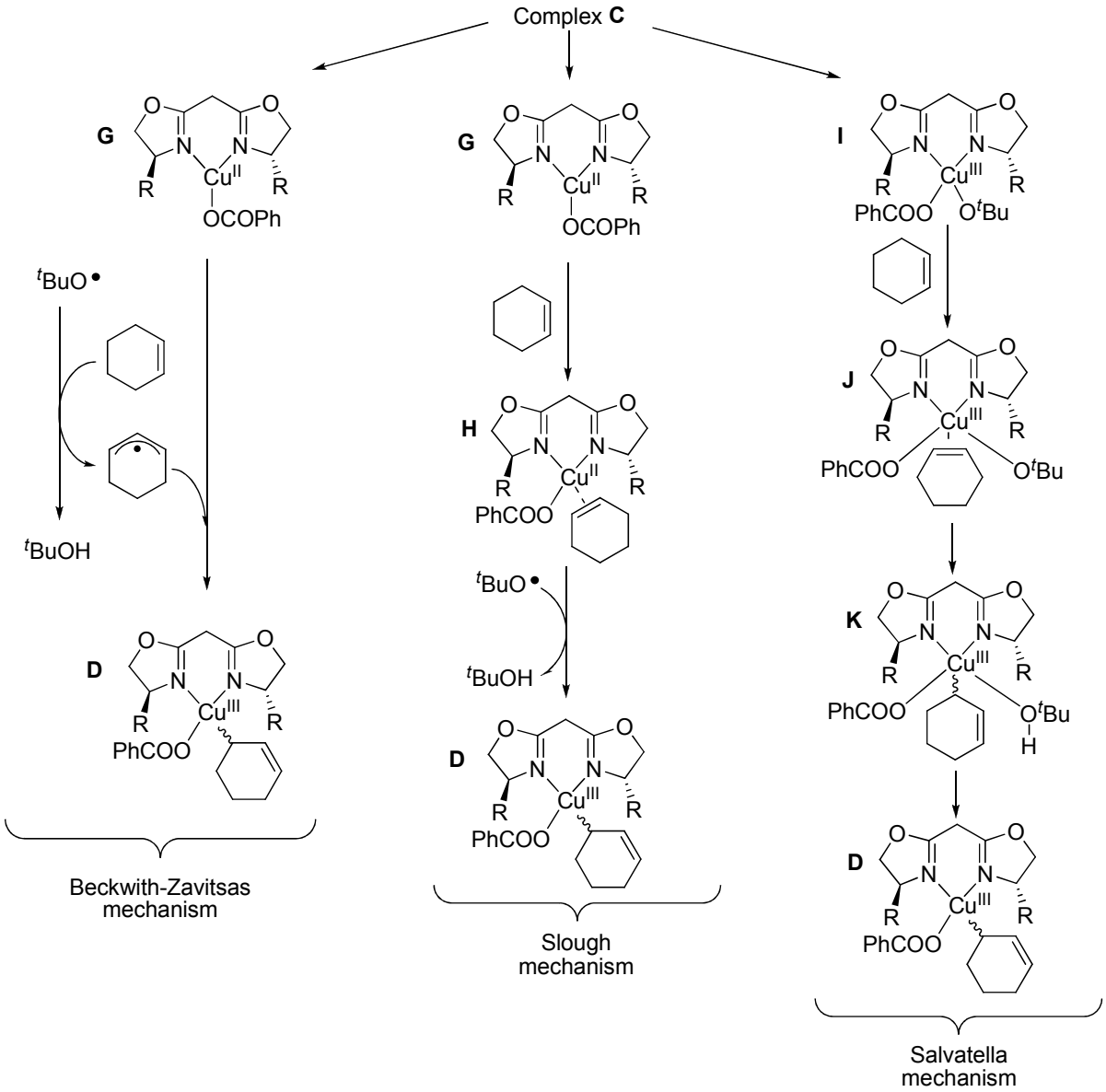
3.1 Asymmetric Kharasch-Sosnovsky-reaction

The Kharasch-Sosnovsky-reaction, also known as allylic oxidation, is a reaction of *t*butyl perbenzoate with olefins under transition metal catalysis.[1] The obtained products are of special interest because they can be easily transformed into allylic alcohols by a simple saponification of the ester. These allylic alcohols represent versatile building blocks for the synthesis of biological active compounds, for instance the (*S*)-enantiomer of cyclohex-2-enyl benzoate (**82**) represents a key intermediate in the leukotriene B_4 synthesis.[2] The transformation is usually catalyzed by Cu(I) or Cu(II) species. The global mechanism for the Cu(I)-bis(oxazoline) catalyzed reaction between cyclohexene and *t*butyl perbenzoate is depicted in Scheme 26.



***Scheme 26*:** Global mechanism of the Cu(I)-BOX catalyzed allylic oxidation.[3]

In the catalytic cycle a variation of the oxidation state of the copper is involved. The cycle starts from the copper(I)-alkene complex **A**,[4] since a large excess of olefin is present under the standard reaction conditions. After ligand exchange the oxidant is bound to the metal to form complex **C**, which subsequently reacts with cyclohexene to the species **D** through a mechanism involving several steps. After reductive elimination of the copper(III)-complex and decomplexation of the product the catalyst is regenerated for the next cycle. Three different mechanisms are postulated for the reaction of species **C** to complex **D**, as depicted in Scheme 27.

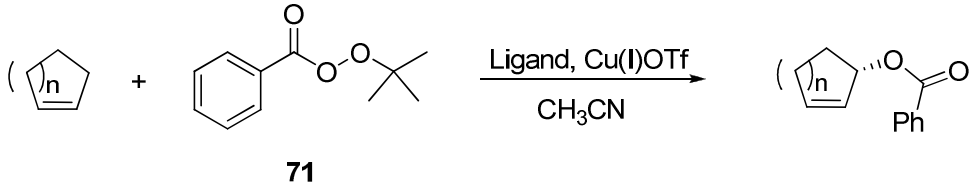


***Scheme 27*:** Mechanism proposed by Beckwith-Zavitsas (left), Slough (middle) and Salvatella (right) for the generation of the allyl-copper(III) key intermediate.[3]

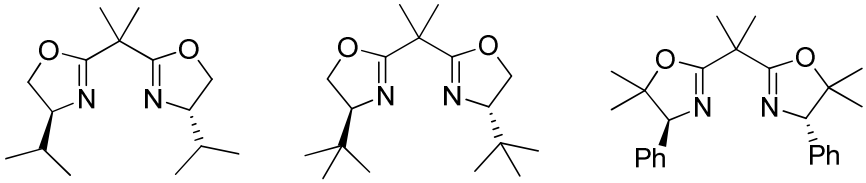
In the proposed mechanism of Beckwith and Zavitsas from 1986,[5] an allylic hydrogen from a cyclohexene molecule is abstracted by a *t*-butoxyl radical, leading to the cyclohexenyl radical and *t*-BuOH. In a subsequent step, the allylic radical binds to the copper atom of the benzoate-copper(II) species to generate the corresponding allyl-copper(III) key intermediate **D**. In the Slough mechanism[6] the hydrogen is abstracted by the *t*-butoxyl radical from the ligand bound cyclohexene in complex **H**, a process that incorporates a formal π-bond migration in the organo-metallic species. In contrast, the Salvatella mechanism comprises an oxidative addition of the oxidant to give species **I**, which subsequently coordinates the cyclohexene (complex **J**). After hydrogen transfer from the cyclohexene to the *t*-butoxy-group, resulting in the benzoate-η^1-cyclohex-2-enyl-copper(III) complex **K**, and release of *t*-BuOH from the latter complex the key intermediate **D** is formed.
During the course of the Kharasch-Sosnovsky-reaction mainly one allylic benzoate is formed, in contrast to normal radical reactions of unsymmetrical substituted olefins, due to a favored addition of the Cu(II)-benzoate at the less hindered position.[7] The mechanism of the Cu(II) catalyzed reaction is not clarified completely up to now.

The first attempts of doing an asymmetric allylic oxidation gave only low enantioselectivities of 15-30%.[8] A significant improve was made by Andrus et al. and Pfaltz et al. with the use of BOX-ligands.[7,9] Some of the results are summarized in Table 3.

***Table 3*:** Selected results of allylic oxidations using BOX-ligands.



71

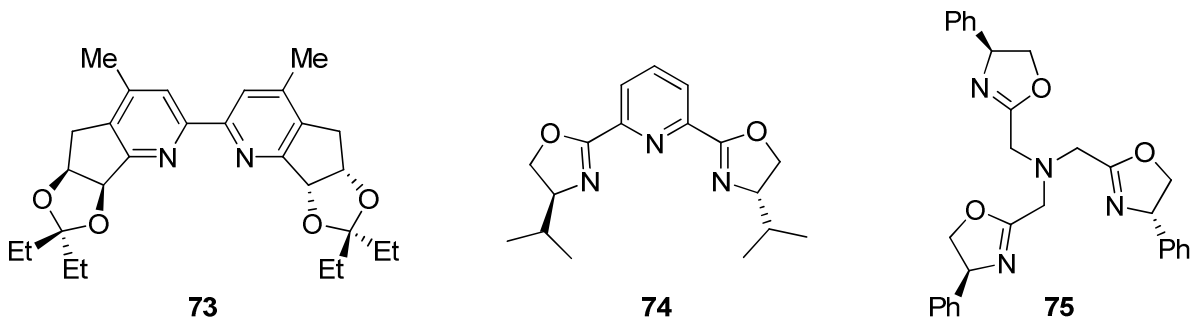


35a **35b** **72**

Entry	Substrate	Ligand	Time	Temperature	Yield (%)	ee (%)
1[a]	n=1	**72**	5d	-20℃	49	81
2[a]	n=2	**35b**	5d	-20℃	43	80
3[a]	n=4	**35b**	5d	-20℃	44	13
4[b]	n=1	**35b**	22d	-20℃	61	84
5[b]	n=2	**35b**	15d	7℃	64	77
6[b]	n=3	**35a**	14d	7℃	44	82

[a] Taken from ref. 7. [b] Taken from ref. 9.

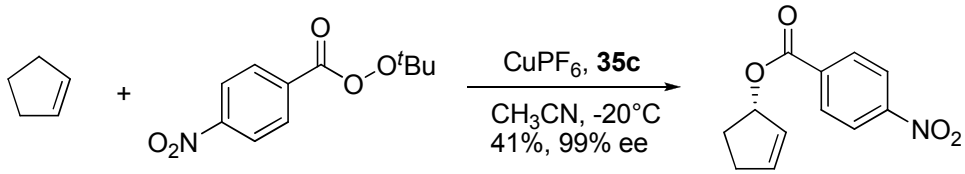
Besides the problem of moderate enantioselectivities long reaction times were needed because of low reaction rates. This problem was solved by the introduction of different additives like phenyl hydrazine or molecular sieves.[10] Numerous ligands have been designed and found application in the Kharasch-Sosnovsky reaction. Some of them are depicted in Figure 11. The best enantioselectivity obtained so far for the title reaction using cyclohexene was published by Wilson et al.[11] applying the bipyridyl-ligand **73**.



73 **74** **75**

***Figure 11*:** Ligands used for the allylic oxidation.[9,10,11]

With small variations of the reactants and reaction conditions even selectivities of up to 99% could be obtained.[12]

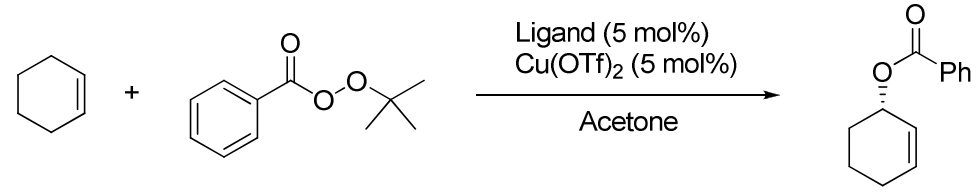


76 **77** **78**

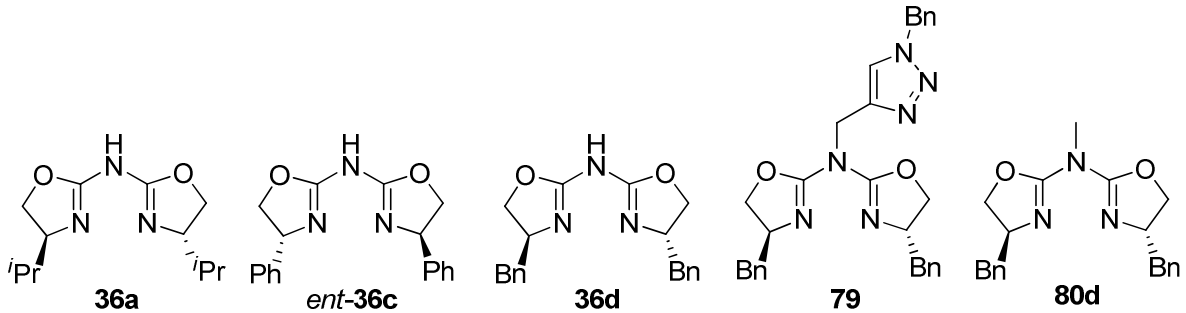
***Scheme 28*:** Allylic oxidation of cyclopentene according to Andrus et al.[12]

Because of the promising results of bis(oxazoline) ligands and the close structural relationship of azabis(oxazolines) investigations were undertaken to see the viability of these ligands. On the basis of the results obtained by A. Gissibl[13] the reactions were carried out using acetone as solvent. A series of different azabis(oxazoline) ligands was applied in order to find the best catalytic system. For all experiments copper(II)-triflate was chosen as metal source. Some of the results were already gained during the diploma thesis, they are summarized in Table 4.

***Table 4*:** Results of the allylic oxidation[a].



81 **82** **83**



36a *ent*-**36c** **36d** **79** **80d**

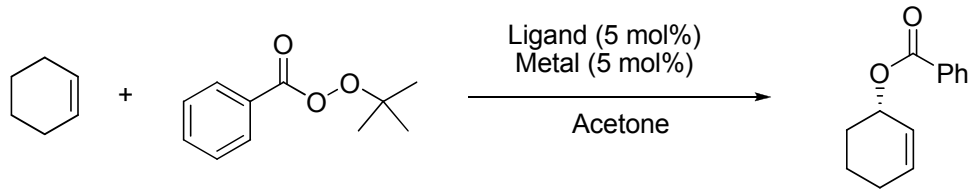
Entry	Ligand	Time	Temp.	$PhNHNH_2$	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)[c]
1[d]	**36a**	1 h	r.t.	yes	67	-128.3	55
2[d]	**36a**	16 h	0℃	yes	64	-117.9	66
3[d]	*ent*-**36c**	20 h	r.t.	no	33	+126.8	56
4[d]	*ent*-**36c**	20 h	r.t.	yes	43	+146.0	61
5[d]	**36d**	20 h	r.t.	no	51	-119.5	51
6[d]	**36d**	2 h	r.t.	yes	74	-168.0	75
7[d]	**36d**	16 h	0℃	yes	68	-161.1	74
8[d]	**79**	16 h	0℃	yes	74	-173.0	78
9	**80d**	16 h	r.t.	yes	54	-174.0	78

[a] Reagents and conditions: 10 mmol cyclohexene, 1 mmol *t*-butyl perbenzoate, 1 drop of phenyl hydrazine, 5 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Results of the diploma thesis.[14]

The results indicate that the AzaBOX ligands provide selectivities that are comparable to those obtained with the BOX analogues. Remarkable are the relative short reactions times, especially when phenyl hydrazine was used, compared to the literature values. Besides the drastic increase in reaction rate a small improve of selectivity can be accomplished by the addition of phenyl hydrazine. The best ees are obtained with the benzyl-substituted ligands **36d, 80d** and the ligand **79** which is bearing an additional triazole moiety (Table 4, entries 6, 8 and 9). To explore the

importance of the metal source experiments were carried out using different copper (I) and (II) species. The results are summarized in Table 5.

***Table 5*:** Influence of the metal source.[a]



81 **82** **83**

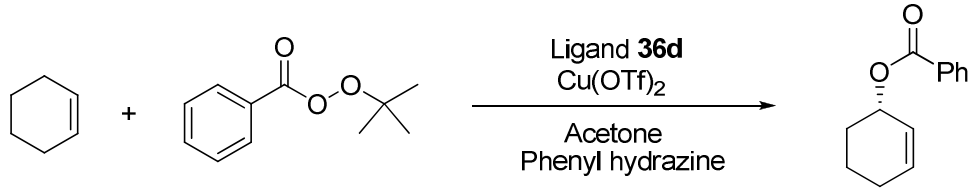
Entry	Metal source	Time (h)	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)[c]
1	$Cu(OTf)_2$	20	51	-119.5	51
2	CuI	20	---	---	---
3	$(CuOTf)_2 \bullet C_6H_6$	20	55	-78.1	34
4	$Cu(OTf)_2$+$PhNHNH_2$	2	66	-167.5	72

[a] Reagents and conditions: 10 mmol cyclohexene, 1 mmol *t*-butyl perbenzoate, 5 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC.

These results clearly demonstrate that the *in situ* reduced copper (II) triflate gives the best enantioselectivity (Table 5, entry 4). The use of copper(I)-triflate benzene complex (entry 3) gave the product with a considerable diminished enantioselectivity of 34% after 20h. Another observation is the substantial higher reaction rate when phenyl hydrazine is used, in this case the product was obtained with higher yield in a much shorter reaction time.

Furthermore, it could be shown that the ligand to metal ratio doesn't play a crucial role in the Kharasch-Sosnovsky reaction, as demonstrated for the Michael-Addition of malonate and indole.[15] For these investigations the optimized conditions were applied (ligand **36d**, $Cu(OTf)_2$, $PhNHNH_2$).

***Table 6*:** Influence of ligand to metal ratio.[a]14

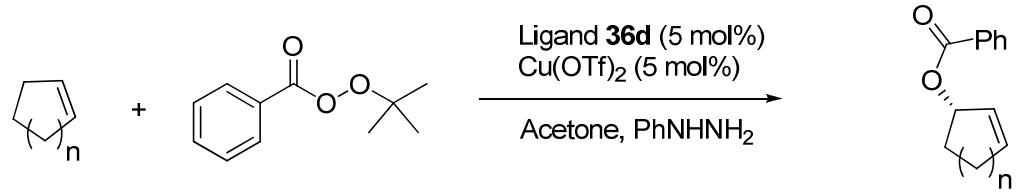


81 **82** **83**

Entry	Cu/Ligand	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)[c]
1	1/1.1	71	-177.6	76
2	1/1.3	74	-174.1	76
3	1/1.5	71	-175.2	78

[a] Reagents and conditions: 10 mmol cyclohexene, 1 mmol *t*-butylperbenzoate, 1 drop of phenyl hydrazine, 5 mL acetone. [b] Isolated yield. [c] Determined by chiral HPLC.

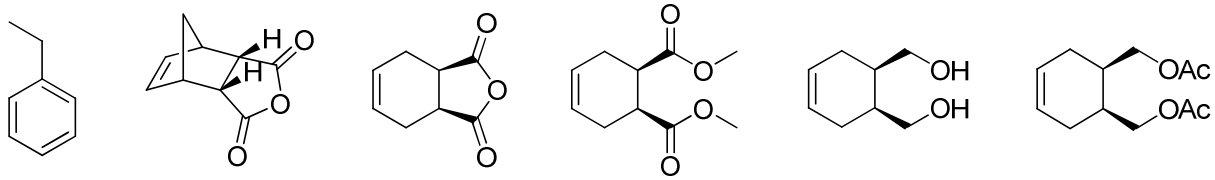
To explore the synthetic usefulness and to further improve the obtained enantioselectivities different substrates were screened. As a first modification only the ring size of the olefin was varied. Therefore cyclopentene and cycloheptene were chosen as substrates.



84a: n=1
84b: n=3 **82** **85a**: n=1
85b: n=3

***Scheme 29*:** Allylic oxidation using different substrates.[16]

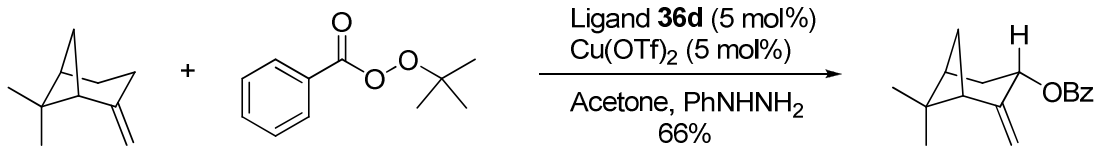
Both substrates gave only low yields 34% for cyclopentene and 33% for cycloheptene respectively. Moreover, the obtained selectivities were only moderate (55% ee for cylopentene, 75% ee for cycloheptene). To further investigate the scope of substrates different olefins (Figure 12) were tested under the standard conditions.



86 **87** **88** **89** **90** **91**

***Figure 12*:** Substrates for allylic oxidation.

The investigations began with ethyl benzene **86**, to see if the oxidation can also take place in benzylic position, but no reaction was observable. In the next step the Diels-Alder-adducts **87**-**89** were tested, again without any success. Unfortunately, there was no apparent reaction even after elongated reaction times. The suggestion was that this could be ascribed to the strong electron withdrawing effect of the anhydride or ester groups. Therefore the ester was reduced to the corresponding alcohol (**90**), which additionally was protected as acetate (**91**). In these two cases at least some conversion was observable, but the wanted product couldn't be isolated in pure form. As a last substrate (-)-β-pinene was used, since the application of bridged bicyclic alkenes in the asymmetric Kharasch-Sosnovsky-reaction was already reported in literature.[17]



92 **81** **93**

***Scheme 30*:** Allylic Oxidation of (-)-β-pinene.

In this case the procuct could be obtained in moderate yield as a single diastereomer, as confirmed by NOE-NMR.

The results illustrate that azabis(oxazolines) are able to perform the Kharasch-Sosnovsky reaction with moderate to good enantioselectivities, comparable to those in literature. One peculiarity is their high activity which is represented in the short reaction times compared to reported values. Regrettably, the scope of substrates is limited to olefins bearing no electron withdrawing groups, therefore the applicability of the transformation is constricted.

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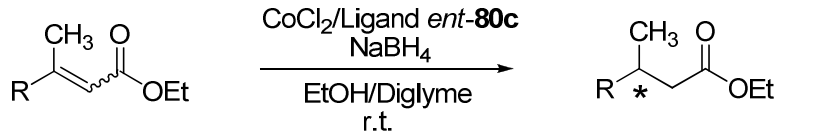
3.2 Asymmetric cobalt(II)-azabis(oxazoline) catalyzed reduction of carbonyl compounds

Reductions are among the most fundamental transformations in organic chemistry. Therefore, a plethora of catalytic, asymmetric ways is known for reducing prochiral carbonyl compounds, starting from hydrogenations, transfer-hydrogenations or reductions using boranes. Another approach that is frequently used is the application of hydride containing reducing agents like $NaBH_4$, $LiAlH_4$, NaH and so on. It is known in literature that cobalt can serve as a reduction catalyst in combination with sodium borohydride.[1] On the basis of this several reports have been published concerning the reductive potential of the latter system. Already in 1989 Pfaltz et al. published the use of semicorrin ligands (**33a**) in combination with $CoCl_2$ to effect the conjugate reduction of α,β-unsaturated esters and amides by sodium borohydride in high chemical yield and with high enantioselectivities.[2] Intrigued by these results C. Geiger of our group was able to accomplish the same reactions using azabis(oxazoline) ligands (Scheme 31).[3]



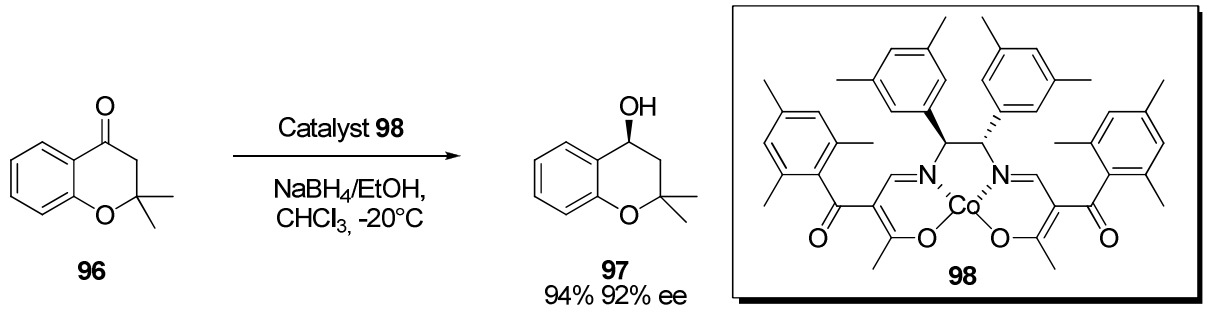
(*Z*)-**94a**: R=Ph
(*E*)-**94a**: R=Ph
(*Z*)-**94b**: R=CH_2CH_2Ph
(*E*)-**94b**: R=CH_2CH_2Ph

(*R*)-**95a**: 86% 92% ee
(*S*)-**95a**: 89% 94% ee
(*S*)-**95b**: 86% 97% ee
(*R*)-**95b**: 86% 93% ee

***Scheme 31*:** Selected results of the conjugate reduction of α,β-unsaturated esters according to C. Geiger.[3]

Motivated by these results we were interested to further broaden the scope of substrates, therefore carbonyl compounds were subjected to the given reaction conditions.

The first asymmetric reduction of ketones using sodium borohydride was published in 1995 by Mukaiyama et al.[4] In this paper the application of different cobalt-salen complexes was delineated, giving the products in high yields and in selectivities of up to 94% ee (Scheme 32).



***Scheme 32*:** Asymmetric reduction of ketones according to Mukaiyama et al.[4]

On the basis of these results a lot of investigations were conducted using different salen-cobalt complexes,[5] including macrocyclic[6] or unsymmetric salen[7] ligands as depicted in Figure 13.

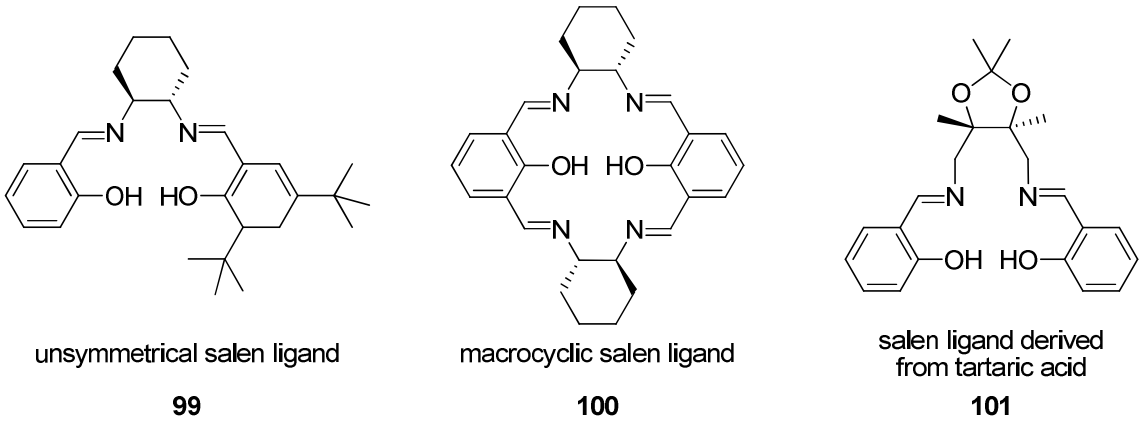
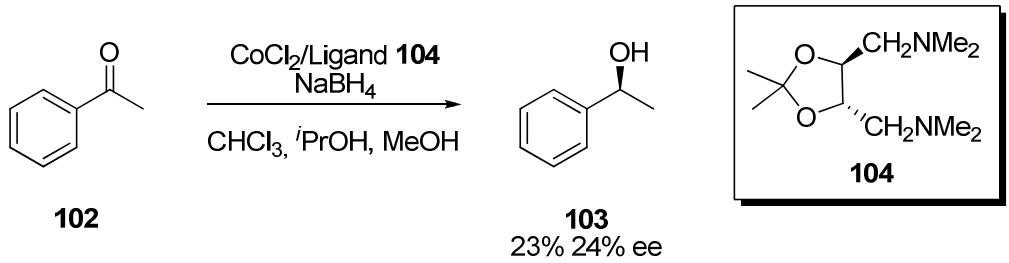


***Figure 13*:** Different salen ligands used in Co-catalyzed reductions.[5,6,7]

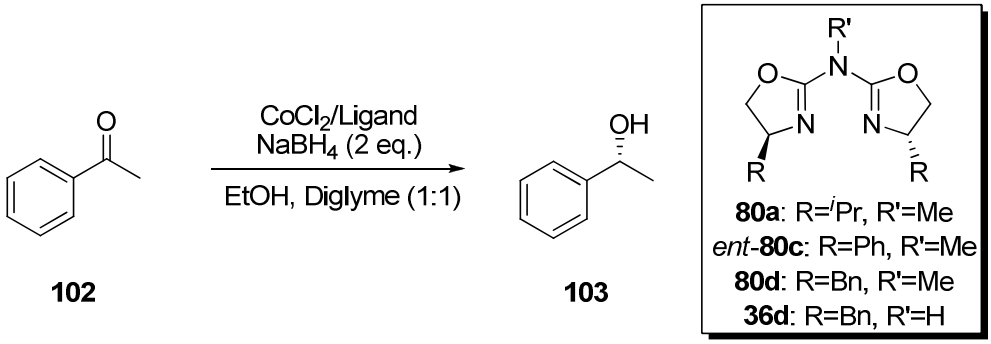
Apart from the use of salen ligands chiral cobalt(II)-diamine complexes were applied as promoters for the asymmetric reduction of carbonyl compounds using hydride donors. The chiral diamine was derived from tartaric acid, but in most cases only low yields and enantioselectivities were achieved for the reduction of acetophenone (Scheme 33).



***Scheme 33*:** Reduction of acetophenone using chiral diamine **104**.

In the beginning of our investigations the optimized conditions for the conjugate reduction utilized by C. Geiger were adopted. In first experiments different ligands were tested at varying temperatures. The results are shown in Table 7.

***Table 7*:** Results of the asymmetric Co(II)-AzaBOX catalyzed reduction of acetophenone.[a]



102 **103**

Entry	Ligand	Temp. (℃)	Yield (%)[b]	ee (%)[c]	Conformation
1	**80d**	30	13	48	(*R*)
2	**80d**	0	79	48	(*R*)
3	**80d**	-45	18	18	(*R*)
4[d]	**80d**	-45	66	0	(*R*)
5	**36d**	0	58	4	(*R*)
6	*ent*-**80c**	0	51	24	(*S*)
7	**80a**	0	66	44	(*R*)

[a] Reagents and conditions: 0.5 mmol acetophenone, 1.0 mmol $NaBH_4$, 5 mol% ligand, 5 mol% $CoCl_2 \bullet 6H_2O$, 1 mL EtOH, 1 mL diglyme. [b] Isolated yield. [c] Determined by chiral GC. [d] No diglyme was used.

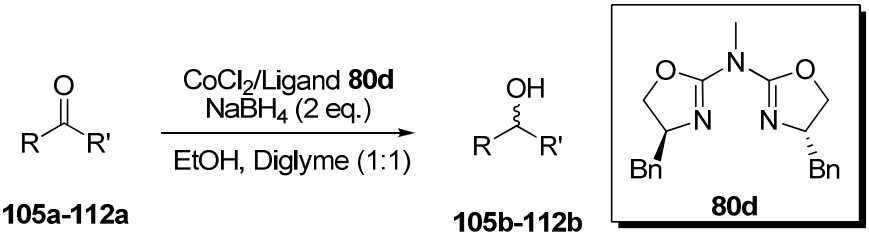
The first experiment was carried out at 30℃, givin g the product with 48%ee but in a low yield of only 13% (entry 1). Lowering the temperature to 0℃ didn't affect the resulting ee, but the yield was enhanced (entry 2). If the temperature was decreased even further (-45℃, entry 3) both, selectivity and yield were diminished. Entry 4 displays the situation if diglyme is omitted, in comparison to entry 3 the chemical yield is improved, but the product was obtained as a racemate.

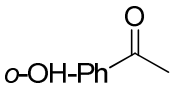
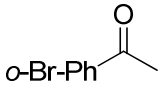
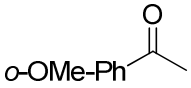
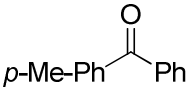
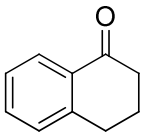
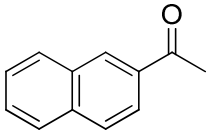
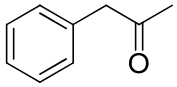
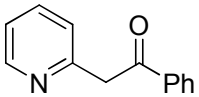
Furthermore, several ligands were tested, to evaluate the influence of the steric and electronic properties of the chiral promoter on the transformation. Ligand **36d**, bearing a proton on the central nitrogen bridge, paled in comparison to its methylated

counterpart **80d**, giving an almost racemic product (entry 5), which is in agreement with the results gained by C. Geiger.[3] Under the given reaction conditions this ligand most probably is deprotonated on the central nitrogen, forming an anionic species. The phenyl-substituted ligand *ent*-**80c** and the isopropyl-substituted **80a** gave results that were little inferior to those of **80d** (entries 6 and 7).

In subsequent investigations a variety of different ketones was tested under the optimized conditions.

***Table 8*:** Asymmetric reduction of ketones using AzaBOX **80d**.[a]

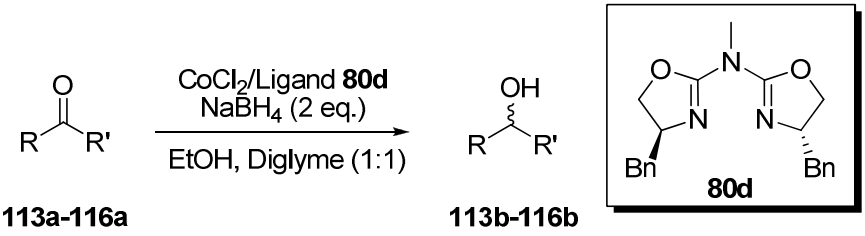


Entry	Ketone		Temp. (°C)	Yield (%) [b]	ee (%)[c]	Conformation[d]
1		**105a**	0	15	30	(*R*)
2		**106a**[e]	0	20	48	(*R*)
3		**107a**	0	66	52	(*R*)
4		**108a**	0	62	0	–
5		**109a**	0	40	56	(*R*)
6		**110a**	rt	73	45	(*R*)
7		**111a**	0	56	8	(*S*)
8		**112a**	0	70	10	(*R*)

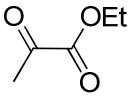
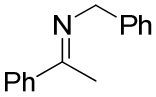
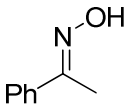
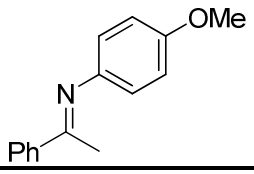
[a] Reagents and conditions: 0.5 mmol substrate, 1.0 mmol $NaBH_4$, 5 mol% ligand, 5 mol% $CoCl_2 \cdot 6H_2O$, 1 mL EtOH, 1 mL diglyme. [b] Isolated yield. [c] Determined by chiral GC or chiral HPLC. [d] The configuration was deduced by comparison of the optical rotation with literature values. [e] A partial dehalogenation occurred.

Different acetophenones **105**-**107** were tested, because in these cases the substituent in *ortho* position can represent an additional coordination point for the metal, giving rise to a better enantio-discrimination in the reaction intermediate. Unfortunately, no positive effect of the substituents could be observed (entries 1-3). In contrast, substrate **105**, bearing a hydroxyl group in *ortho* position, showed even diminished reactivity and selectivity (entry 1). The benzophenone derivative **108** was obtained in moderate yield without any ee, probably due to the low steric influence exhibited by the methyl group in *para* position (entry 4). The ketones **109** and **110** were reduced to the corresponding alcohol in low to moderate yield and with moderate enantioselectivity (entries 5 and 6), whereas the substrates **111** and **112** gave hardly any ee (entries 7 and 8). In further experiments more substrates like α-hydroxy esters, imines or oximes were screened (Table 9).

***Table 9*:** Attempted asymmetric reduction of different ketones and imines.



113a-116a **113b-116b**

Entry	Substrate		Temp. (℃)	Yield (%)	ee (%)
1		**113a**	0	40	0
2		**114a**	0	84	0
3		**115a**	50	no reaction	–
4		**116a**	60	no reaction	–

[a] Reagents and conditions: 0.5 mmol substrate, 1.0 mmol $NaBH_4$, 5 mol% ligand, 5 mol% $CoCl_2 \bullet 6H_2O$, 1 mL EtOH, 1 mL diglyme. [b] Isolated yield. [c] Determined by chiral GC or chiral HPLC.

Regrettably, only for the substrates **113** and **114** the wanted product was observed, albeit no enantioselectivity was induced (entries 1-2). However, no reaction was visible for the oxime **115** and the imine **116** even at elevated temperatures.

In conclusion, Co(II)-azabis(oxazoline) complexes are able to perform the asymmetric reduction of ketones using sodium borohydride with low to moderate yields and enantioselectivities. Nevertheless, the obtained ees are not capable of competing with the best values known in literature. Therefore, no further explorations regarding this transformation were undertaken.

1 (a) M. Green, S. Swinden, *Inorganica Chimica Acta* **1971**, *5*, 49; (b) M. Miura, M. Shinohara, M. Nomura, *Journal of Molecular Catalysis* **1988**, *45*, 151.

2 a) U. Leutenegger, A. Madin, A. Pfaltz, *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 60; b) P. v. Matt, A. Pfaltz, *Tetrahedron: Asymmetry* **1991**, *2*, 691; c) M. Misun, A. Pfaltz, *Helv. Chim. Acta* **1996**, *79*, 961.

3 (a) C. Geiger, P. Kreitmeier, O. Reiser, *Adv. Synth. Catal*. **2005**, *347*, 249; (b) C. Geiger, Dissertation **2006**, Universität Regensburg.

4 T. Nagata, K. Yorozu, T. Yamada, T. Mukaiyama, *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2145.

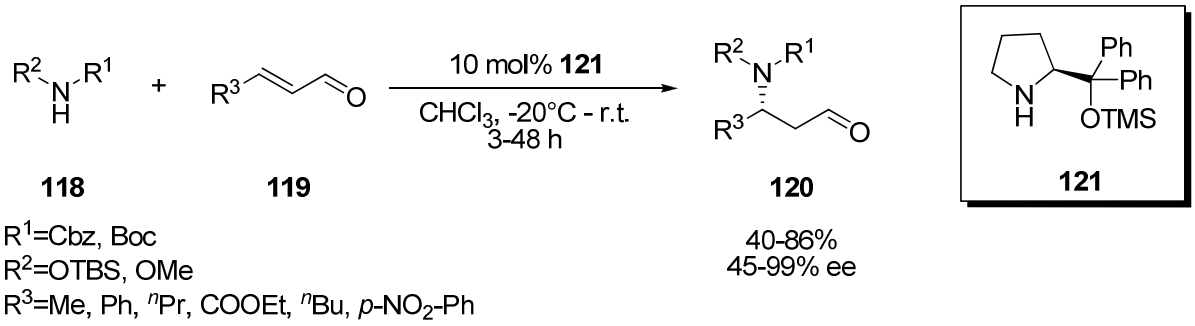
5 (a) W. Sun, C. - G. Xia, P. - Q. Zhao, *Journal of Molecular Catalysis A: Chemical* **2002**, *184*, 51; (b) L. O. Nindakova, F. M. Lebed', A. Yu. Zamazei, B. A. Shainyan, *Russian Journal of Organic Chemistry* **2007**, *43*, 1322; (c) T. Yamada, T. Nagata, K. D. Sugi, K. Yorozu, T. Ikeno, Y. Ohtsuka, D. Miyazaki, T. Mukaiyama, *Chem. Eur. J*. **2003**, *9*, 4485; (d) I. Iwakura, M. Hatanaka, A. Kokura, H. Teraoka, T. Ikeno, T. Nagata, T. Yamada, *Chem. Asian J*. **2006**, *1*, 656; (e) A. Kokura, S. Tanaka, H. Teraoka, A. Shibahara, T. Ikeno, T. Nagata, T. Yamada, *Chemistry Letters* **2007**, *36*, 26.

6 G. - J. Kim, D. - W. Park, Y. - S. Tak, *Catalysis Letters* **2000**, *65*, 127.

7 G. - J. Kim, J. - H. Shin, *Catalysis Letters* **1999**, *63*, 83.

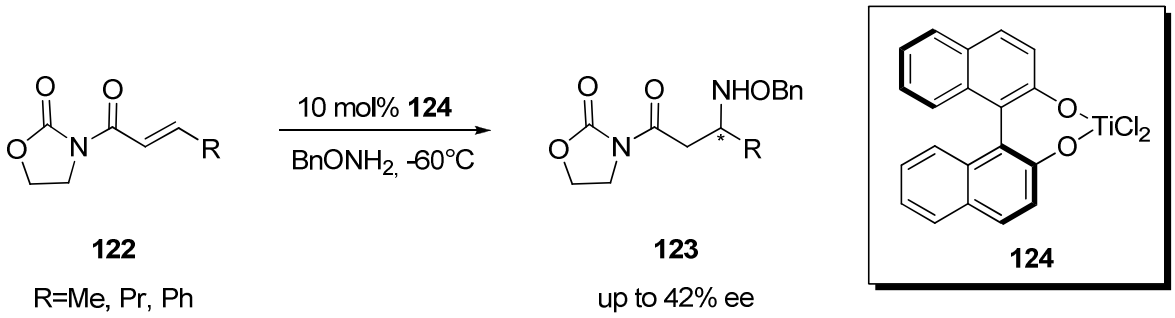
3.3 Asymmetric aza-Michael addition

The so-called Michael addition represents one of the most important and best studied transformations in organic chemistry.[1] Even before the discovery of the actual Michael addition in 1887[2] conjugate additions using heteroatom nucleophiles were reported. In 1878 the oxa-Michael addition was published by Loydl[3] and even earlier, in 1874, the aza-Michael addition was dicovered by Heintz, Sokoloff and Latschinoff.[4] This transformation constitutes an especially important variant, since the thereof derived products, including β-amino acids[5] and β-lactams[6], are of great synthetical and pharmaceutical value. The first asymmetric aza-Michael additions mainly focused on the use of chiral amines,[7] chiral substrates[8] or chiral auxiliaries.[9] Since the first catalytic asymmetric aza-Michael addition reported by Jørgensen et al.[10] a manifold of new catalytic systems has been developed.[11] Especially in the field of organocatalysis great improvements have been achieved in conducting enantioselective aza-Michael additions. Therefore mainly proline-derivatives or cinchona alkaloids were used as catalysts. One example represents the aza-Michael addition of carbamates **118** to α,β-unsaturated aldehydes reported by Córdova et al. (Scheme 34).[12]



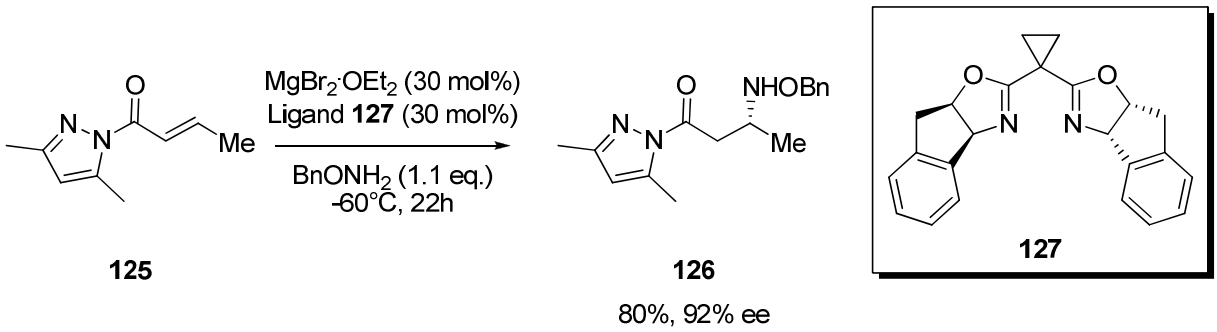
***Scheme 34*:** Aza-Michael addition of carbamates **118** to enals.[12]

Nevertheless, great effort has been undertaken in the field of organo-metallic catalysis as well, starting with the already mentioned report of Jørgensen in 1996, in which he published the application of titanium-BINOL catalyst **124** in the addition of $BnONH_2$ to *N*-acyloxazolidinones **122**.[10] The resulting product was obtained in high yield, albeit accompanied by moderate enantioselectivity (Scheme 35).



***Scheme 35*:** The first asymmetric organo-metallic aza-Michael addition as reported by Jørgensen.[10]

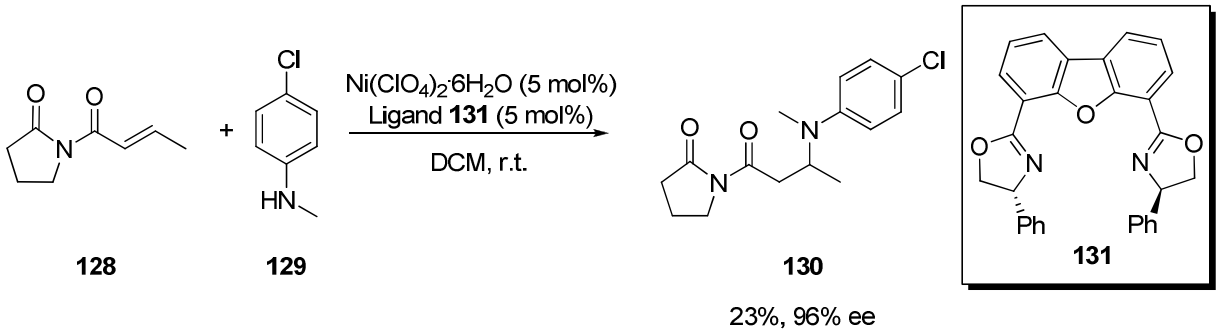
Besides the use of BINOL as chiral catalyst for the asymmetric aza-Michael addition, several reports focused on the application of different bis(oxazoline) ligands. One interesting example represented the contribution of Sibi et al.,[13] in which bis(oxazoline) **127** was used in combination with $MgBr_2 \bullet OEt_2$ as Lewis acid. Good chemical yields and selectivities up to 97% were achieved in the addition of *O*-benzylhydroxylamine to a 3,5-dimethylpyrazole-derived enoate **125** (Scheme 36).



***Scheme 36*:** Aza-Michael addition according to Sibi et al.[13]

It is noteworthy, that in the latter case the opposite enantiomer of product **126** was obtained when a lanthanide salt was employed as Lewis acid instead of magnesium, although the reversed sense of stereoinduction could not be explained by the authors.

The first stereoselective addition of secondary amines to acylpyrrolidinones **128** was investigated by Jørgensen et al.,[14] showing that DBFOX ligand **131** is capable of performing the reaction with selectivities up to 96% (Scheme 37).

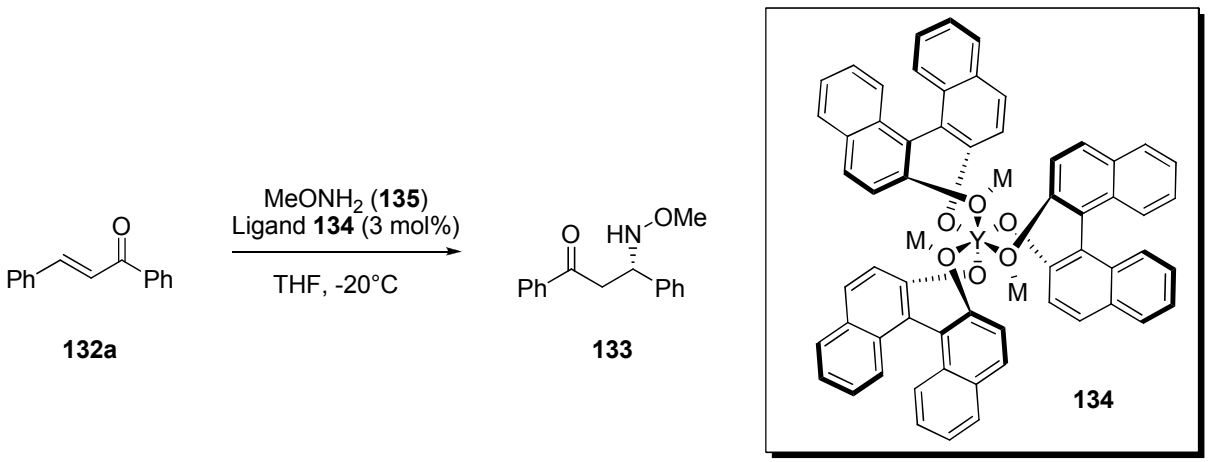


128 **129** **130** **131**

23%, 96% ee

***Scheme 37*:** Addition of secondary aromatic amine **129** to acylpyrrolidinones **128** according to Jørgensen et al.[14]

In all the studies comprising bis(oxazoline) ligands the α,β-unsaturated carbonyl compound contained two groups which could coordinate to the metal center. In the approach made during the course of this work the use of the simple chalcones **132** was intended, as these substrates are easily accessible via common aldol condensation reactions. Shibasaki et al. could accomplish the asymmetric aza-Michael addition of *O*-alkylhydroxylamine **135** to chalcones using the heterobimetallic multifunctional catalyst **134**.[15]



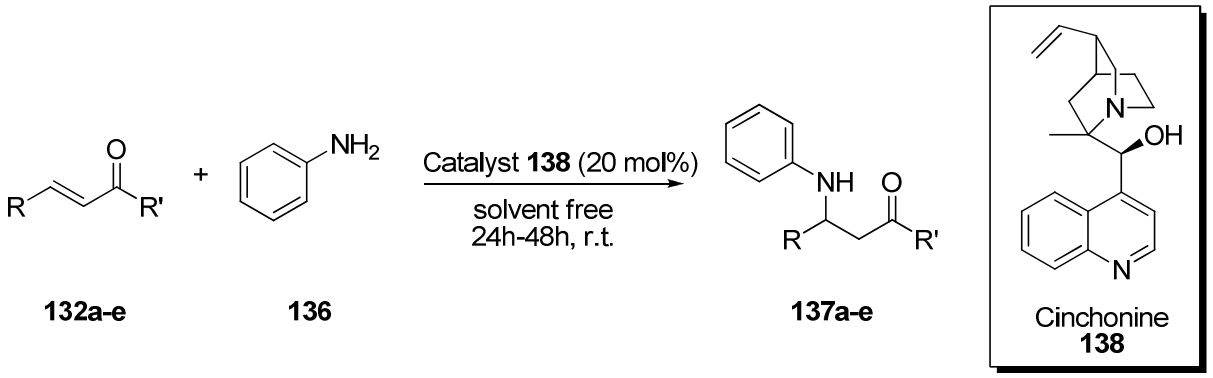
132a **133** **134**

***Scheme 38*:** Asymmetric aza-Michael addition of *O*-alkylhydroxylamine **135** to chalcone according to Shibasaki et al.[15]

For the investigations simple anilines served as nitrogen nucleophile, since the use of aromatic amines has not been thoroughly studied up to now.[16] The combined use of these simple starting materials, chalcones and anilines, is rather unexplored so far. To the best of the author's knowledge, only one report dealing with these substrates

was published yet by Scettri et al.[17] In this approach cinchona alkaloids were used as catalysts under solvent free conditions. Cinchonine **138** was identified as the catalyst giving superior enantioselectivities, although only values up to 58% ee were obtained. Some of the results are depicted in Table 10.

Table 10**:** Selected results from the addition of aniline to chalcones catalyzed by cinchonine. [a]17



132a-e **136** **137a-e**

Entry	R	R′	Substrate	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	**132a**	24	>99	58
2	Ph	*p*-Cl-Ph	**132b**	24	>99	31
3	Ph	*p*-Me-Ph	**132c**	24	50	52
4	*p*-MeO-Ph	Ph	**132d**	48	44	49
5	*p*-Cl-Ph	Ph	**132e**	24	72	27

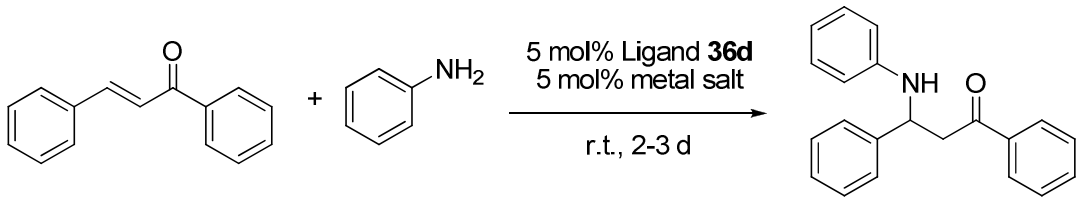
[a] Reagents and conditions: 0.25 mmol chalcone, 0.5 mmol aniline, 0.05 mmol catalyst, 24h-48h, r.t. [b] Isolated yield. [c] Determined by chiral HPLC.

The best result was achieved for the unsubstituted substrates **132a** and **136** (entry 1), giving excellent yields but only moderate enantioselectivity. Furthermore, an electron withdrawing group on either of the two aromatic rings of the chalcone lead to a diminished selectivity (entries 2 and 5).

The investigations started with the search for an appropriate metal salt. Therefore, different copper salts were screened without any ligand. The Lewis-acids that have been chosen were $CuCl_2$, $Cu(OTf)_2$, $Cu(OAc)_2•H_2O$ and $Cu(ClO_4)_2•6H_2O$. Unfortunately, only in the case of $Cu(OAc)_2•H_2O$ some conversion was observed after 24h. For that reason the experiment was repeated in different solvents and in

the presence of azabis(oxazoline) ligand, to examine if the process was ligand accelerated. The results are shown in Table 11.

***Table 11*:** Results of the aza-Michael addition between chalcone **132a** and aniline **136** in different solvents and with different metal salts.[a]



132a **136** **137a**

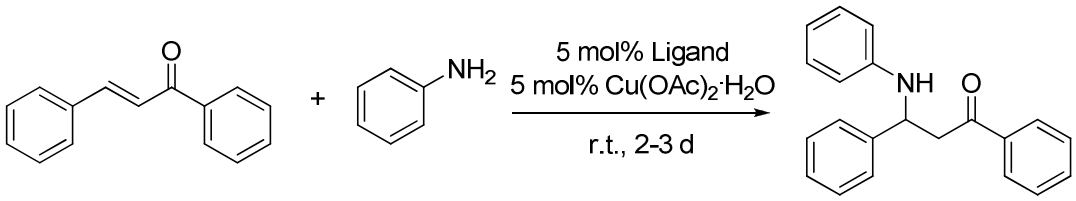
Entry	Metal salt	Solvent	Yield (%)[b]	ee (%)[c]
1	$CuCl_2$	CH_2Cl_2	–	–
2	$CuCl_2$	$CHCl_3$	–	–
3	$CuCl_2$	EtOH	–	–
4	$CuCl_2$	Toluene	5	nd
5	$Cu(OAc)_2•H_2O$	CH_2Cl_2	19	73
6	$Cu(OAc)_2•H_2O$	EtOH	22	68
7	$Cu(OAc)_2•H_2O$	Toluene	52	70
8	$Cu(OAc)_2•H_2O$	MeCN	19	66
9	$Zn(OTf)_2$	Toluene	5	nd
10	$Co(OAc)_2•4H_2O$	Toluene	6	nd
11	$SnCl_2$	Toluene	5	nd

[a] Reagents and conditions: 0.5 mmol chalcone, 1.0 mmol aniline, 5 mol% ligand **36d**, 5 mol% metal salt, 1 mL solvent, r.t. [b] Isolated yield. [c] Determined by chiral HPLC, nd = not determined.

The results indicated that only copper acetate was able to catalyze the reaction in moderate yields (entries 5-8). In all the other cases no conversion was observed or only poor yields of ca. 5% were obtained, which is only insignificantly more than the uncatalyzed background reaction.[17] The best results for the given substrates were gained in toluene (entry 7). Although DCM as solvent gave slightly superior selectivity (73%, entry 5) the yield paled in respect to toluene (19% vs. 52%). As a consequence of these results, the subsequent experiments were performed using $Cu(OAc)_2•H_2O$ as metal source and toluene as solvent.

In order to evaluate the scope of the catalytic system, different ligands were tested in the asymmetric aza-Michael addition (Table 12).

***Table 12*:** Ligand screening for the asymmetric aza-Michael addition of aniline **136** to chalcone **132a**.[a]



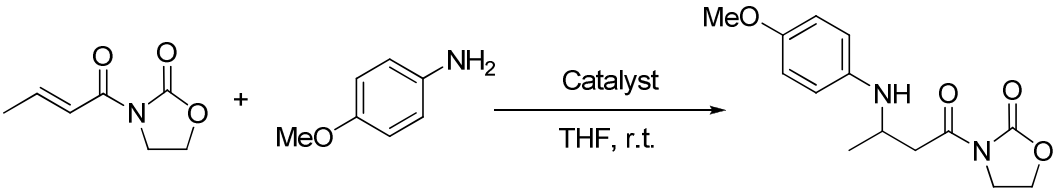
132a **136** **137a**

Entry	Ligand	Solvent	Yield (%)[b]	ee (%)[c]
1	**36a**	Toluene	39	18
2	**80a**	Toluene	58	9
3	**36d**	Toluene	52	70
4	**80d**	Toluene	19	39
5	*ent*-**36c**	Toluene	60	31
6	*ent*-**80c**	Toluene	47	21
7	**36b**	Toluene	29	10
8	**45**	EtOH	20	7
9	**46**	Toluene	29	22

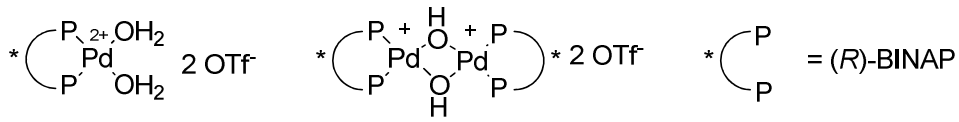
[a] Reagents and conditions: 0.5 mmol chalcone, 1.0 mmol aniline, 5 mol% ligand, 5 mol% $Cu(OAc)_2 \bullet H_2O$, 1 mL solvent, r.t. [b] Isolated yield. [c] Determined by chiral HPLC.

The results clearly indicated the supremacy of the benzyl substituted ligand **36d**. Although only a moderate yield of 52% was obtained entry 3 represented the best enantiomeric excess known so far for these substrates. All other ligands paled in comparison to **36d** regarding selectivity. In entry 8, ethanol was used as solvent due to the poor solubility of ligand **45** in toluene. An explanation for the preponderance of ligand **36d** might be found in π–π-interactions between the aromatic rings of the catalyst and the substrate. Such effects have been noted in literature.[18] However, the main problem remained the poor reactivity of the system, which can be ascribed to a possible deactivation of the Lewis acid by the excess of amine.[19] To circumvent this problem, Sodeoka et al. used the amine as a salt of trifluoromethanesulfonic acid (TfOH) and were able to increase both, yield and selectivity (Table 13).[19]

***Table 13*:** Representative results of the conjugate addition according to Sodeoka et al.[19]



139 **140** **141**



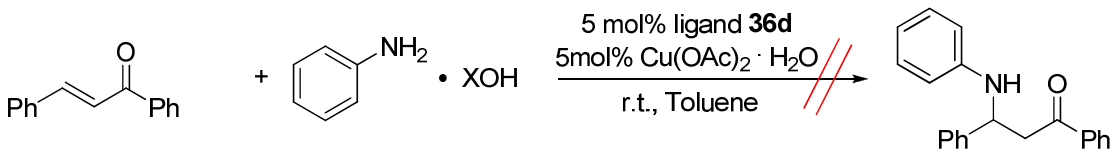
142-1 **142-2**

Entry	Catalyst	TfOH (equiv.)	Time (h)	Yield (%)	ee (%)
1	**142-1**	–	24	35	2
2	–	–	24	41	–
3[a]	**142-1**	1.0	24	25	88
4	**142-1**	0.5	24	98	4
5[a]	**142-2**	1.0	12	92	98

[a] TfOH was added as a salt of *p*-OMe-aniline.

Entries 3 and 5 unambiguously showed the effect of the utilization of an anilinium salt. Especially catalyst **142-2** exhibited high enantioselectivity combined with high chemical yield.

On the basis of these results it was investigated if the application of the corresponding anilinium salt lead to higher reactivity. Unfortunately, no conversion was observed neither for the use of the *p*-TSA-salt nor for the TfOH-salt (Scheme 39).



132a **143**: XOH=*p*-TSA **144**: XOH=TfOH **137a**

***Scheme 39*:** Attempts to use the amine as a salt of different acids.

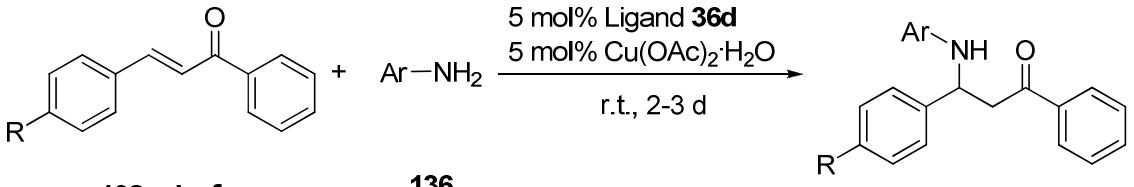
An explanation for these results could be the exchange of the counter ion of the metal salt, leading to a less active species, since an excess of anions resulting from

the added acid was present. At least $Cu(OTf)_2$ was known to be unable to catalyze the given process.

Furthermore, the comparability of the two catalytic systems (Pd-BINAP vs. Cu-AzaBOX) is limited.

In additional experiments different substrates were tested, to see how different electronic and steric properties would influence the reaction (Table 14).

***Table 14*:** Aza-Michael addition using different substituted chalcones and anilines.[a]



132a,d,e,f **136 145a-d** **137a,d,e,f 146a-d**

Entry	R	Ar-NH_2	Product	Solvent	Yield (%)[b]	ee (%)[c]
1	CF_3 (**132f**)	Ph (**136**)	**137f**	Toluene	49	55
2	Cl (**132e**)	Ph (**136**)	**137e**	Toluene	38	5
3	OMe (**132d**)	Ph (**136**)	**137d**	Toluene	33	13
4	H (**132a**)	3,5-OMe-aniline (**145a**)	**146a**	Toluene	41	0
5	H (**132a**)	2,6-^{i}Pr-aniline (**145b**)	**146b**	Toluene	–	–
6	H (**132a**)	2-OH-aniline (**145c**)	**146c**	EtOH	–	–
7	H (**132a**)	3-NO_2-aniline (**145d**)	**146d**	EtOH	–	–

[a] Reagents and conditions: 0.5 mmol chalcone, 1.0 mmol aniline, 5 mol% ligand, 5 mol% $Cu(OAc)_2 \bullet H_2O$, 1 mL solvent, r.t. [b] Isolated yield. [c] Determined by chiral HPLC.

Again, these results illustrate the problem of poor reactivity of the substrates. Only 33-49% yield were obtained. Furthermore, only low to moderate ees were gained. The best result was obtained with the *p*-CF_3-substituted chalcone **132f** (entry 1), giving 55% ee. For the different substituted anilines in entry 5-7 no reaction was observable, probably due to steric hindrance (entry 5) or electronic properties (entries 6 and 7). In the case of the 2-OH-substituted and the 3-NO_2-substituted aniline ethanol was used as solvent again, because these substrates were insoluble in toluene.

In conclusion, the asymmetric aza-Michael addition between chalcones and anilines was accomplished with the highest enantioselectivity known so far in literature using azabis(oxazolines). Nevertheless, the process suffered from low yields and the dependence on the right catalytic system. Only ligand **36d** was able to produce good selectivity in combination with $Cu(OAc)_2 \bullet H_2O$. Further studies are required in order to prove the value of the given process.

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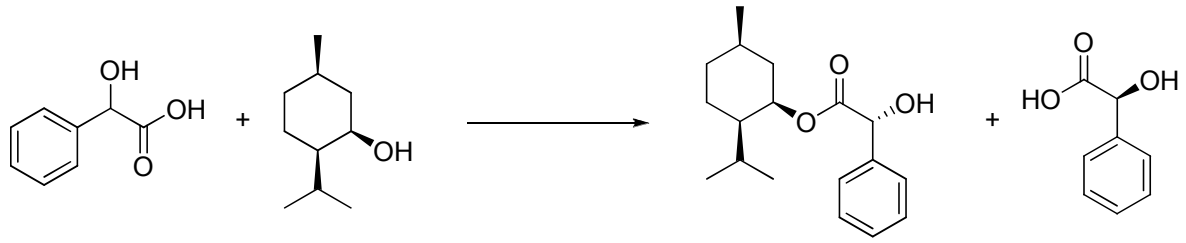
3.4 Kinetic resolution

Among the different possibilities of producing optically active compounds the kinetic resolution has the distinction of being the oldest. According to the 1996 IUPAC recommendation the definition of kinetic resolution follows: “The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)”.[1] The kinetic resolution can be divided onto two major fields, the enzyme catalyzed techniques and non-enzymatic processes. The enzyme catalyzed methods have gained tremendous importance due to their often very high selectivities and activities, but they also lack of the drawback that the enzyme selectivity cannot be predicted for a certain substrate. The first example of non-enzymatic kinetic resolution was published already in 1899 by Marckwald and McKenzie when they reported the enantioselective esterification of racemic mandelic acid **147** by (-)-menthol.[2]



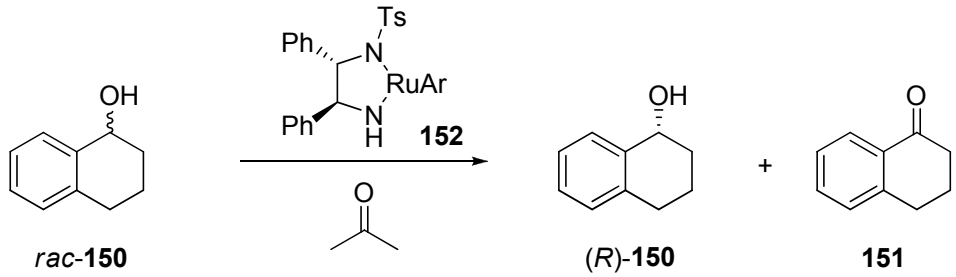
147 **148** **149** (*S*)-**147**

***Scheme 40*:** First non-enzymatic kinetic resolution according to Marckwald and McKenzie.[2]

In this reaction the (*R*)-enantiomer of the mandelic acid showed the higher reaction rate and the recovered (*S*)-enantiomer could be isolated in pure form after several recrystallization steps. An important fact regarding kinetic resolution is that the enantiomeric excess of the product is dependent on the conversion of the reaction, as shown for the first time by Dakin.[3] For obtaining high ees the maximum yield that can be obtained is 50%, if no racemisation process of the starting material is included (dynamic kinetic resolution). Kinetic resolutions can be applied to virtually every class of chiral substrates and can be used in combination with all methods of enantioselective synthesis.[4]

3.4.1 Kinetic resolution of alcohols

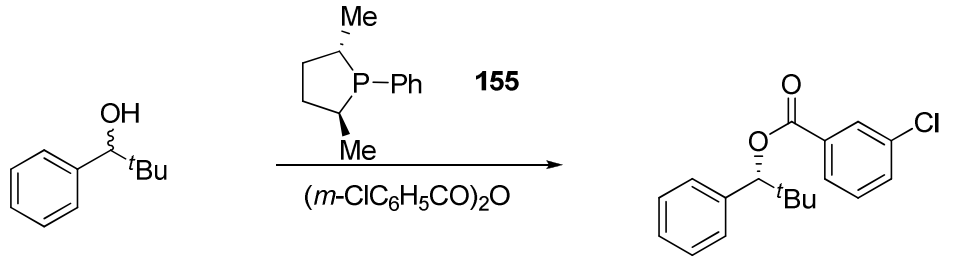
In the context of kinetic resolution alcohols are the functional groups that have received the most attention due to their broad applicability. One of the big advantages exhibited by alcohols is the possibility of a simple inversion of stereocenters, e.g. under Mitsunobu conditions. This might, in principle, lead to a higher efficiency, but stoichiometric amounts of chiral phosphines are needed for these processes.[5] Another method that has gained considerable interest in the field of kinetic resolution of alcohols is the oxidation of *sec.* alcohols to the corresponding ketones, as these can be easily recycled to the racemic starting material by simple reduction. The first broadly applicable approach was published by Noyori et al., as shown in Scheme 41.



***Scheme 41*:** Kinetic resolution of *sec*. alcohol by oxidation to the prochiral ketone.[6]

This reaction actually represents the reverse of the asymmetric hydrogenation of ketones, a method that employs the same catalyst together with isopropanol as a stoichiometric hydride donor. In the present case, which works best with benzylic alcohols, the chiral ruthenium catalyst abstracts a hydride form *rac*-**150** which is subsequently transferred to acetone as hydride acceptor.

The most prominent way for the kinetic resolution of alcohols is the transfer of acyl groups through activation of anhydrides or acid chlorides. The first experiments in this field can be traced back to the 1930s, when Wegler accomplished the enantioselective acylation with acetyl chloride and acetic anhydride under alkaloid catalysis.[7] The first non-enzymatic kinetic resolution of alcohols with eligible selectivity factors was published by Diver et al. in 1996.[8] Herein, the chiral phosphine **155** was employed to activate *m*-chlorobenzoic anhydride (Scheme 42).



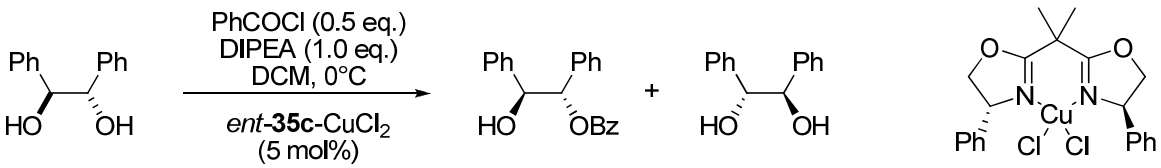
153 **154**

81% ee at 25% conversion

***Scheme 42*:** Enantioselective acylation catalyzed by chiral phosphine **155**.[8]

The product was obtained with 81% ee at a conversion of 25%, this corresponds to a selectivity factor >10.

In order to acylate alcohols with high enantiomeric excesses a multitude of enzymatic methods are known,[9] but organometallic or organocatalytic processes exist as well. One of the most prominent transition-metal catalyzed kinetic resolutions of 1,2-diols was published by Matsumura et al., using bis(oxazoline) ligands for the monobenzoylation of the latter alcohols.[10] The product was obtained with 49% yield (theoretical maximum: 50%) and >99% ee.



(±)-**156** (*S,S*)-**157** (*R,R*)-**156** *ent*-**35c**-$CuCl_2$

***Scheme 43*:** Asymmetric monobenzoylation of diol **156** with bis(oxazoline) ligands.[10]

To give an explanation for the high selectivities achieved, the authors postulated a transition state that is depicted in Figure 14. In the intermediate **B** the benzoyl chloride can access the alkoxide, which is generated from (*S,S*)-**156** with (*R,R*)-Ph-BOX-$CuCl_2$, more easily compared to the complex **A**, where more steric hindrance is present.

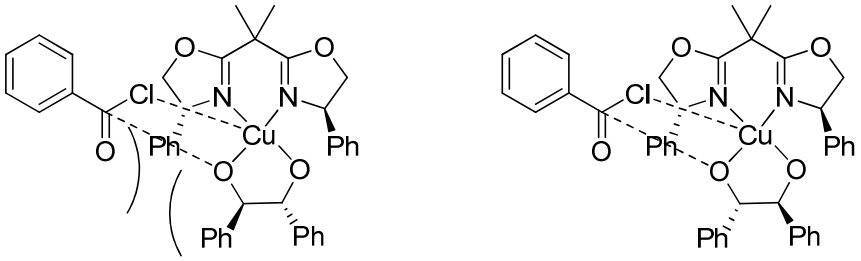
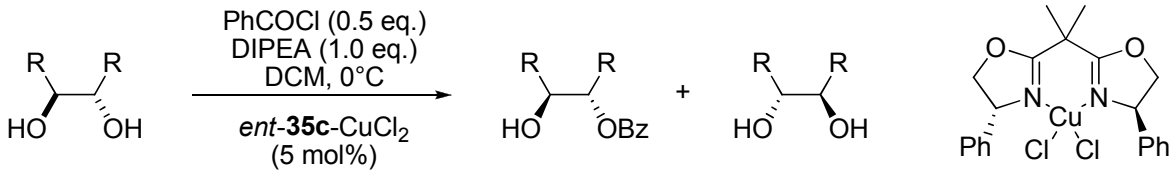


***Figure 14*:** Schematic representation of the unfavored (left) and favored (right) transition state of the asymmetric benzoylation.

Besides the excellent results for hydrobenzoin several other substances were used successfully as substrates. Some of the results are shown in Table 15.

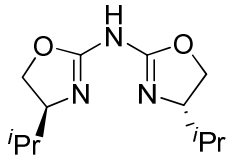
***Table 15*:** Selected results of the benzoylation according to Matsumura et al.



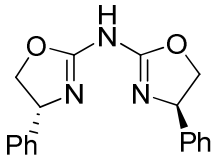
Entry	Substrate	Product	Yield (%)	ee (%)
1	*p*-Cl-hydrobenzoin (**158**)	**162**	48	>99
2	*p*-MeO-hydrobenzoin (**159**)	**163**	49	98
3	trans-1,2-cyclohexane diol (**160**)	**164**	37	80
4	trans-1,2-cycloheptane diol (**161**)	**165**	49	84

Due to the close structural relationship between bis(oxazolines) and azabis-(oxazolines) investigations were carried out to prove the viability of the latter ligands for these kind of processes. In a series of elegant experiments A. Gissibl could show that AzaBOX ligands are capable of performing the benzoylation of 1,2-diols with very high yields and enantioselectivities.[11] The scope of substrates was also examined and good results could be obtained as illustrated in Table 16.

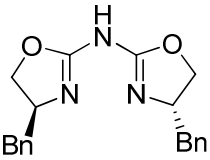
***Table 16*:** Selected results of the benzoylation carried out by A. Gissibl.[a]11



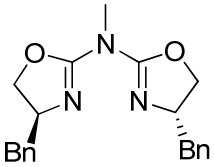
36a



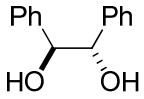
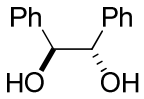
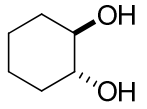
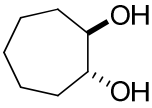
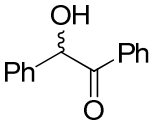
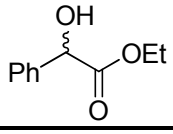
ent-**36c**



36d

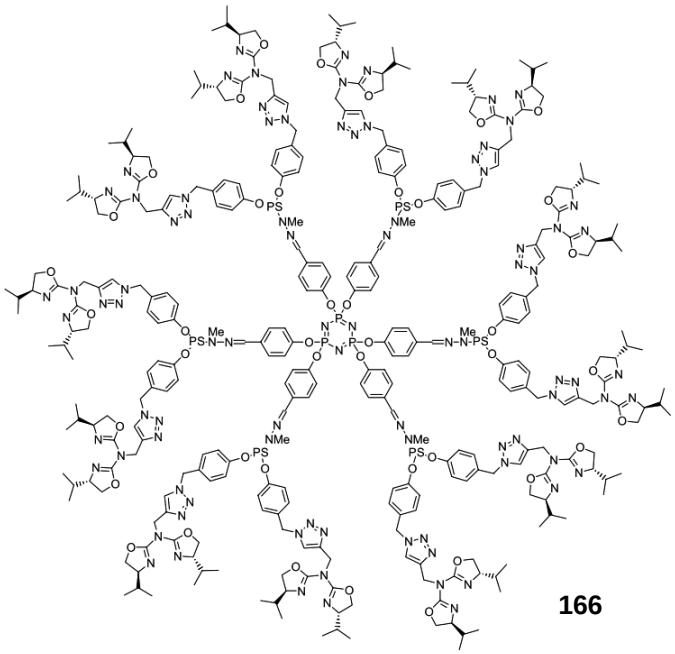


80d

Entry	Substrate	Ligand	Yield (%)	ee (%)	Configuration of the product	s[b]
1		**36d**	45	97	*R,R*	160
2		**80d**	49	99	*R,R*	751
3		*ent*-**36c**	46	83	*S,S*	22
4		**36a**	46	82	*R,R*	21
5		**36a**	43	79	*R*	16
6		**36a**	45	75	*R*	13

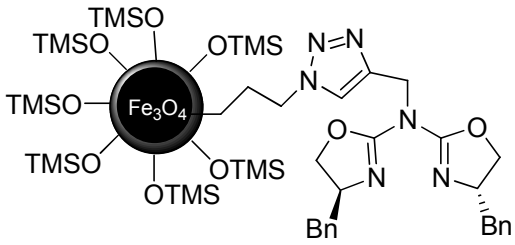
[a] Reagents and conditions: substrate (1 mmol), benzoylchloride (0.5 mmol), DIPEA (1 mmol), 0℃, CH_2Cl_2. [b] Ref. 12

In additional experiments it was shown that azabis(oxazolines) can be attached to a manifold of solid supports in order to be able to recycle and reuse the catalyst. For homogeneous reaction conditions the soluble supports MeOPEG 5000 and dendrimers were used, which could be recycled by precipitation and subsequent filtration. Especially the dendrimers could prove their usefulness, as they were able to perform the benzoylation with high selectivity in several cycles (Figure 15). Also heterogeneous catalytic processes were possible with the use of Merrifield-resin or magnetic nanoparticles as backbone for the ligands. The nanoparticles represent a very elegant possibility for catalyst recovery, as they are separated from the reaction mixture by simple magnetic decantation. They could be used in up to four cycles without any evident drop in yield or selectivity (Figure 15).



166

3 cycles
35-43%
99% ee



167

4 cycles
43-49%
95-98% ee

***Figure 15*:** Selected supported ligands that were used in the asymmetric benzoylation of hydrobenzoin (left: Gc1 bound AzaBOX, right: AzaBOX on magnetic nano-particle).[13,14]

3.4.2 Kinetic resolution of β-hydroxy amides

Inspired by the promising results obtained in the asymmetric benzoylation of 1,2-diols and α-hydroxy carbonyl compounds using azabis(oxazolines), investigations were carried out to further broaden the scope of substrates. β-Hydroxy carboxylic acid derivatives represent a class of high synthetic relevance, especially in enantiomerically pure form, as they are versatile precursors for pharmaceuticals and natural products.[15] Applying these substrates the intermediary built chelate would be a six membered ring instead of the five membered one in the case of 1,2-diols or α-hydroxy carbonyl compounds.

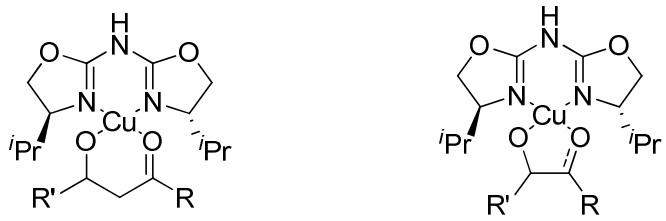
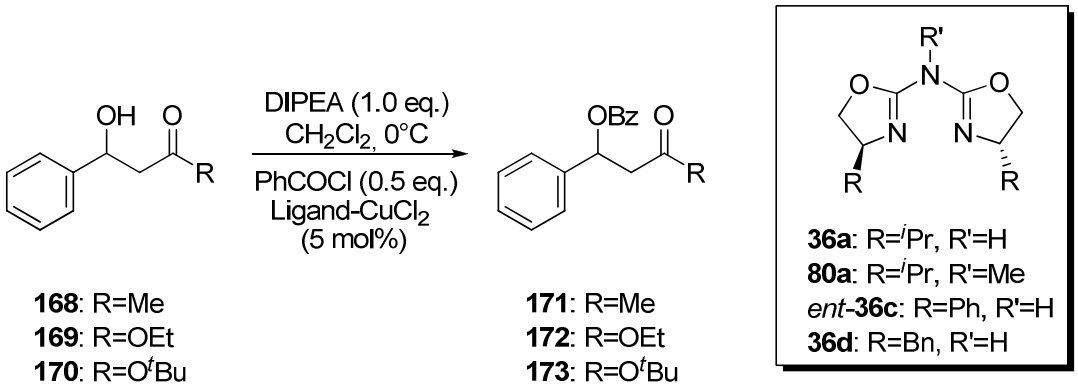


***Figure 16*:** Suggested chelates built during the benzoylation reaction.

The first experiments were carried out using β-hydroxy ketones and β-hydroxy esters. However, attempts to employ these classes of compounds were unsuccessful as depicted in Table 17.

***Table 17*:** Results of the benzoylation using β-hydroxy ketones and β-hydroxy esters.[a]



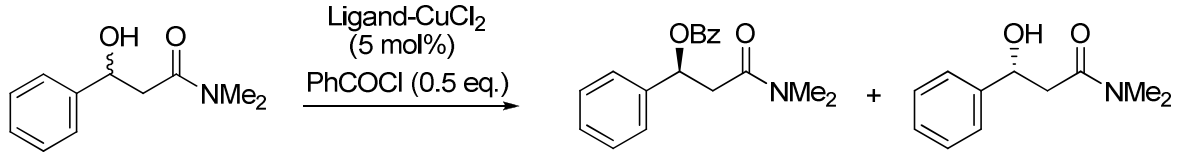
Entry	Ligand	R	Yield (%)[b]	ee (%)[c]
1	**36a**	Me	–	–
2	**36a**	OEt	28	38
3	**36a**	O^{t}Bu	27	46
4	*ent*-**36c**	O^{t}Bu	20	36
5	**36d**	O^{t}Bu	25	33
6[d]	**36d**	O^{t}Bu	18	35
7	**80a**	O^{t}Bu	15	56

[a] Reaction conditions: Substrate (0.5 mmol), ligand-Cu-complex (5 mol%), base (0.5 mmol), benzoylchloride (0.25 mmol) in 3 mL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Cu-complex was prepared in situ.

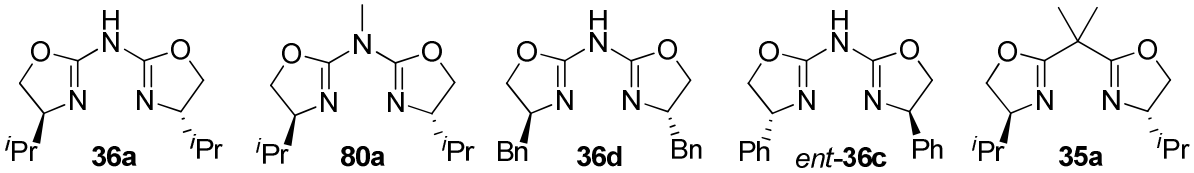
Not only low enantioselectivities were obtained, but an even more severe problem was represented by the low reactivity of these compounds. No reaction was

observable for the ketone **168** and only low to moderate yields were obtained utilizing different esters and catalysts. Intrigued by the reports of Onomura et al.,[16] that α-hydroxy amides represent superior substrates compared to α-hydroxy esters in the asymmetric tosylation with bis(oxazoline) ligands, investigations were started to apply β-hydroxy amides in asymmetric benzoylation reactions. The explorations were commenced using the protocol established for the benzoylation of α-hydroxy esters. Nevertheless, optimization studies were carried out using different solvents, bases and ligands.

***Table 18*:** Optimization studies for the benzoylation of β-hydroxy amides.[a]



174 **175** **174**



Entry	Ligand	Base	Solvent	Configuration[b]	Time	Yield (%)	ee (%)[c]
1	**36a**	K_2CO_3	MeCN	S	12 h	22	83
2	**36a**	DIPEA	MeCN	S	12 h	42	75
3	**36a**	K_2CO_3	CH_2Cl_2	S	12 h	49	82
4	**36a**	DIPEA	THF	S	24 h	–	–
5	**36a**	DIPEA	EtOAc	S	24 h	24	76
6	**36a**	DIPEA	EtOH	S	4 h	32	74
7	**36a**	DIPEA	CH_2Cl_2	S	12 h	48	83
8	**80b**[d]	DIPEA	CH_2Cl_2	S	12 h	39	69
9	**36d**	DIPEA	CH_2Cl_2	S	12 h	39	65
10	*ent*-**36c**	DIPEA	CH_2Cl_2	R	12 h	38	43
11	**35a**[d]	DIPEA	CH_2Cl_2	S	12 h	20	7

[a] Reaction conditions: Substrate (0.5 mmol), ligand-Cu-complex (5 mol%), base (0.5 mmol), benzoylchloride (0.25 mmol), 3 mL of solvent at r.t. [b] The absolute stereo configuration was deduced by comparing the optical rotation of the product with literature values.[17] [c] Determined by chiral HPLC. [d] Cu-complex was prepared in situ.

Although a high selectivity was obtained using K_2CO_3 in MeCN only a moderate yield of 22%, based on the substrate **174**, was achieved. The other tested solvents paled compared to DCM in both, enantioselectivity and yield. It is noteworthy, that in THF no reaction was observable even after elongated reaction times (entry 4). The influence of the employed base was found to be of minor importance, at least for DCM as solvent (entries 3 and 7). Nevertheless, DIPEA was chosen for the further investigations, due to an easier work-up procedure where no extraction was required. Among the different ligands used, the isopropyl substituted ligand **36a** gave the best results (entry 7). The difference of the results between the *N*-methylated ligand **80a** and its counterpart **35a** can be explained by the possible deprotonation of **35a** on the central nitrogen bridge, leading to different catalytic active species. An interesting fact is that the bis(oxazoline) ligand **35a** (entry 11) gave hardly any enantioselectivity and only a low yield of 20%.

Utilizing the optimized conditions several substrates were screened having different substituents in β-position or on the amide nitrogen.

***Table 19*:** Benzoylation of different substituted β-hydroxy amides.[a]

176a-h **177a-h** **176a-h**

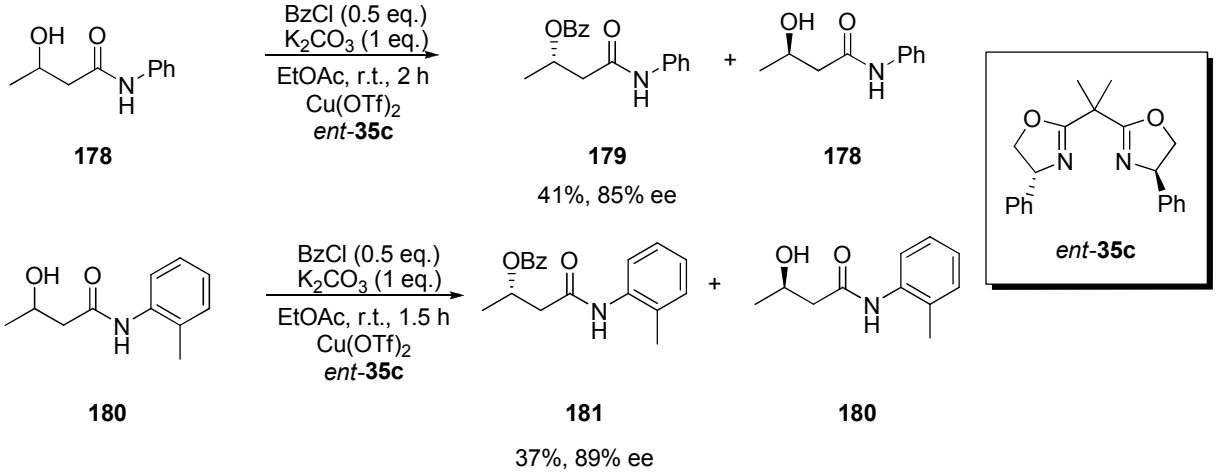
Entry	Substrate	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]
1	**176a**	Ph	^{i}Pr	**177a**	49	78
2	**176b**	Ph	Ph	**177b**	44	44
3	**176c**	Ph	-$(CH_2)_5$-	**177c**	42	70
4	**176d**	*p*-OMe-Ph	Me	**177d**	39	73
5	**176e**	*p*-Cl-Ph	Me	**177e**	40	75
6	**176f**	*p*-NO_2-Ph	Me	**177f**	46	38
7	**176g**	cyclohexyl	Me	**177g**	38	72[d]
8	**176h**	^{n}Pr	Me	**177h**	47	73[d]

[a] Reaction conditions: Substrate (0.5 mmol), ligand-Cu-complex (5 mol%), base (0.5 mmol), benzoylchloride (0.25 mmol) in 3 mL of solvent at r.t. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by chiral GC after cleavage of the Bz-group.

All the products could be received in acceptable to high yields. The influence of the substituent on the amide nitrogen can be seen in the entries 1-3. If an alkyl substituent is present no drastic changes in enantioselectivity are visible compared to the model substrate **174**. In contrast, an amide function bearing aromatic groups gives rise to inferior ees (entry 2), which can probably be ascribed to the electron withdrawing effect of these groups leading to a weaker coordination of the substrate to the catalyst. The influence of the substituents in β-position is only of subsidiary relevance as shown in the entries 4-8. Only the *p*-nitro substituted starting material **176f** gave a dimished ee compared to the others. This finding can be explained by the possible coordination of the nitro group to the copper center giving rise to an unselective reaction.

In conclusion, it could be demonstrated, that the copper catalyzed asymmetric benzoylation of β-hydroxy amides can be fulfilled using azabis(oxazoline) ligands. In this process high yields and good enantioselectivities up to 83% ee were obtained.

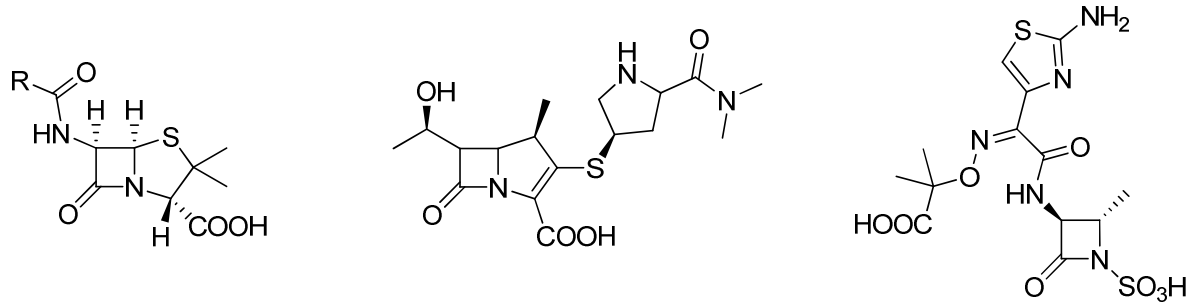
During the course of the investigations comparable results were published by Onomura et al., demonstrating that bis(oxazoline) *ent*-**35c** is also capable of performing the kinetic resolution of β-hydroxy amides.[17] Some of the results are shown in Scheme 44.



***Scheme 44*:** Kinetic resolution of β-hydroxy amides according to Onomura et al.[17]

3.4.3 Kinetic resolution of β-lactams

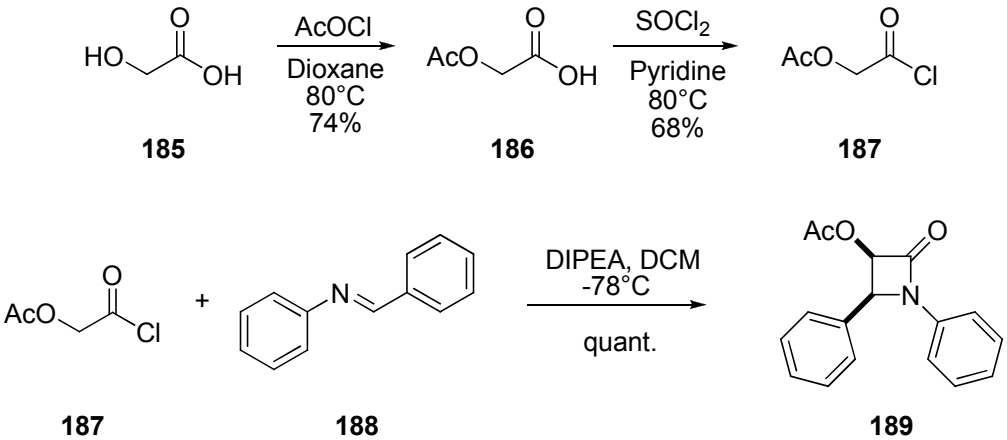
Intrigued by the results of the kinetic resolution using β-hydroxy amides another class of substrates should be examined. For that reason it was focused on β-lactams, cyclic amides which are additionally bearing a hydroxyl moiety in α-position to the carbonyl function. The structural motif of β-lactams can be found in a manifold of natural products and since the seminal discovery of Fleming, who introduces the β-lactam antibiotic penicillin in 1928,[18] many efforts have been made to synthesize this kind of compounds.



Penicillin **182** | Meropenem **183** | Aztreonam **184**

***Figure 17*:** Selected antibiotics containing a β-lactam unit.[19,20]

The synthesis of the β-lactam started from the readily available glycolic acid **185**, which was acetyl protected on the hydroxyl function to give **186** and afterwards converted to the acid chloride **187**, using standard techniques, in good yields. The obtained acid chloride was subsequently reacted with the imine **188** applying the protocol of Kingston et al.[21]

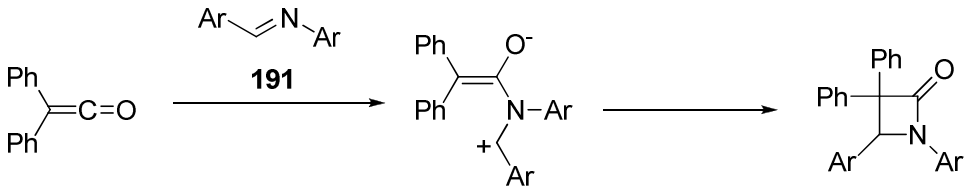


185 → **186** → **187**

187 + **188** → **189**

***Scheme 45*:** Synthesis of the β-lactam.

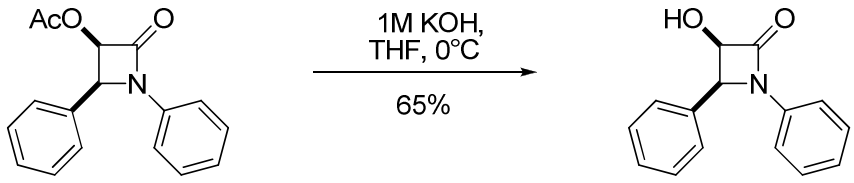
The selectivity of this reaction strongly depends on the reaction conditions and the used starting materials. Furthermore, a decisive criterion is that the reaction can proceed in different pathways. For instance, a concerted [2+2] cycloaddition or a two step process with the zwitterionic intermediate **192** are reasonable.[22]



190 **192** **193**

***Scheme 46*:** β-lactam formation with a zwitterionic intermediate.[22]

The product **189** was obtained as a single diastereomer. In the present case only the *cis* configured product was built in the [2+2] cycloaddition of ketene and imine. In the final step the acetyl protecting group was cleaved to give the α-hydroxy substituted β-lactam **194** in acceptable yield.

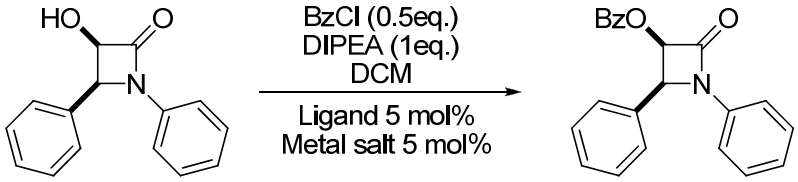


189 **194**

***Scheme 47*:** Deprotection of the OH-group.

The likewise obtained substrate was tested in the kinetic resolution using different azabis(oxazoline)-metal complexes. The results are summarized in Table 20.

***Table 20*:** Attempted benzoylation of β-lactam **194**.[a]



194 **195**

Entry	Ligand	Metal-salt	Temp.	Time	Yield (%)[b]	ee (%)[c]
1	**36d**	$CuCl_2$	r.t.	4 h	41	–
2	**45**	$CuCl_2$	r.t.	2.5 h	40	–
3	*ent*-**36c**	$Mg(OTf)_2$	r.t.	1 h	48	–
4	*ent*-**36c**	$Mg(OTf)_2$	-15℃	16 h	47	–

[a] Reaction conditions: Substrate (0.5 mmol), ligand (5.0 mol%), metal salt (4.8 mol%), base (0.5 mmol), benzoylchloride (0.25 mmol) in 5 mL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC.

In the first experiments the standard conditions of the benzoylation were used (entries 1 and 2). In these cases good yields were obtained, but no selectivity was observed at all. In further reactions $Mg(OTf)_2$ was used as metal source, because in that case the metal complex has a different geometry compared to the copper complex. Nevertheless, in none of the cases any enantioselectivity was obtained. An explanation for these results might be the weak coordination of the substrate to the catalyst, due to steric bulk or an unfavorable complex geometry. Therefore, it would be suggestive that in further experiments other substrates or metal sources should be tested. Maybe substrates bearing less hindered substituents could be used in additional studies. Another useful approach could be the employment of calcium as metal source, due to the higher ion radius a better chelatisation could be possible.

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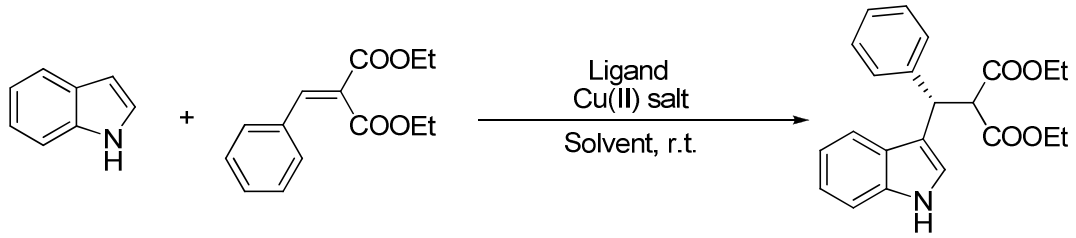
4. Assessment of Catalyst Activities

4.1 Asymmetric catalytic Michael-Addition

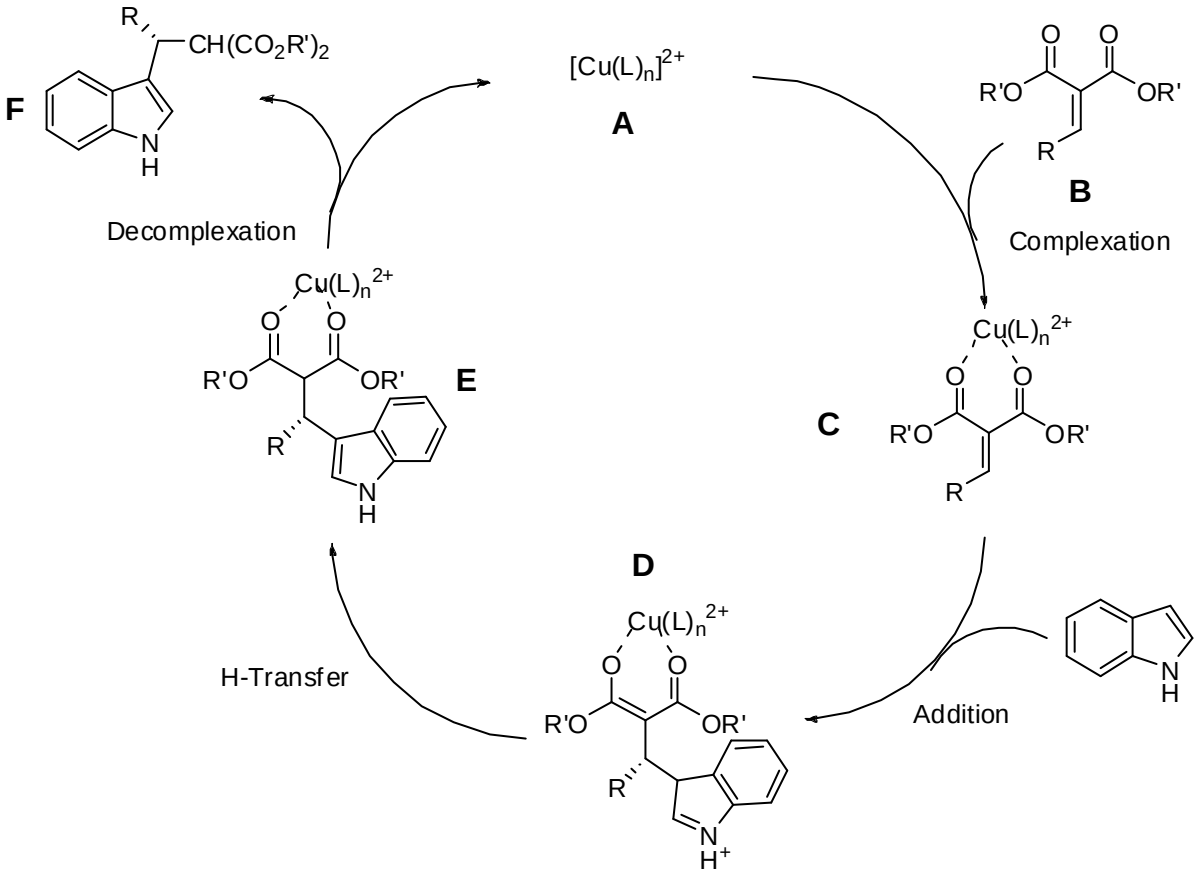
Michael-additions are among the most prominent processes for the formation of new C-C bonds and still a lot of research in done to improve existing methods or to find new ways for the enantioselective accomplishment of these reactions. In the case that an aromatic or heteroaromatic substance is added to the α,β-unsaturated carbonyl compound the reaction can also be regarded as Friedel-Crafts-alkylation. In the present case indole is used as substrate due to the high relevance of indole derivatives in pharmacological drugs.[1] The copper-bis(oxazoline) catalyzed process has been a great field of research starting with the pioneering work of Jørgensen et al., who was able to fulfill the addition of indole to α,β-unsaturated keto esters with perfect enantioselectivies of >99% ee.[2] In contrast, the 1,4-addition of indole to benzylidene malonate (Scheme 48) could only be accomplished with moderate selectivities (up to 69% ee) under the same reaction conditions.[3]



196 **197** **198**

***Scheme 48*:** Enantioselective Michael-addition of indole to benzylidene malonate.

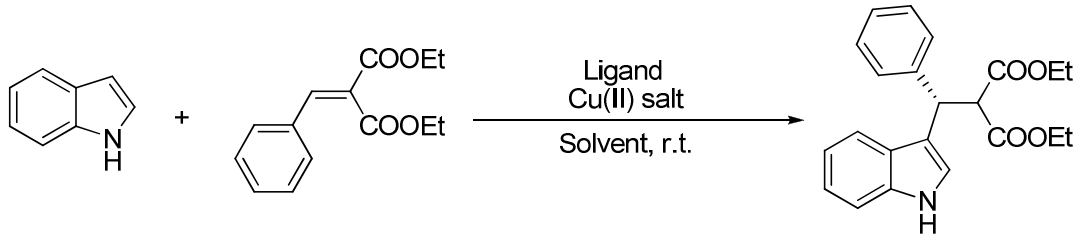
In subsequent studies Tang et al. could improve the selectivity of the latter reaction[4] and could also show that tris(oxazolines) **199** are superior ligands for this process.[5] With the optimized conditions selectivities of up to 93% ee were achieved and a penta-coordinated Cu(II)-species was postulated as the decisive intermediate for high enantioselectivities. The mechanism of the reaction is depicted in Scheme 49. It starts with the coordination of the malonate **B** to the copper source **A** to form the complex **C**. After addition of the indole, intermediate **D** is formed which then undergoes a proton transfer to give **E**. After decomplexation the product **F** is released and the catalyst is recovered for the next cycle.



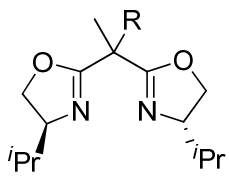
***Scheme 49*:** Mechanism of the enantioselective Friedel-Crafts alkylation.[5]

In studies that were conducted together with R. Rasappan it could be shown, that the addition of indole to benzylidene malonate can be done with simple bis(oxazolines) and azabis(oxazolines) with very high selectivities, if the metal/ligand ratio is adjusted meticulously. Some of the results are summarized in Table 21.

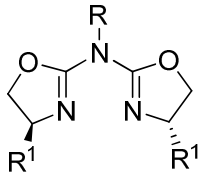
***Table 21*:** Dependence of enantioselectivity on copper(II)/ligand ratios in the asymmetric 1,4-addition to benzylidene malonates.[6]



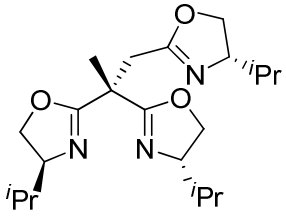
196 **197** **198**



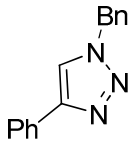
35a: R=Me
35e: R=H



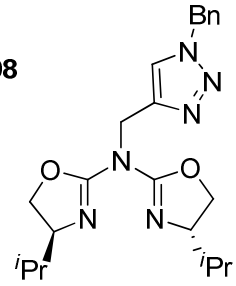
36a: R=H, R^1=^{i}Pr
36d: R=H, R^1=Bn
80a: R=Me, R^1=^{i}Pr



199



200



201

Entry	Cu-salt	Ligand	Cu/Ligand ratio	Cu/Ligand mol%	Solvent	Yield (%)	ee (%)[a]
1[b]	$Cu(OTf)_2$	**35a**	1/1.2	10/12	^{i}BuOH	85	79
2[c]	$Cu(OTf)_2$	**35b**	1/1.1	10/11	^{i}BuOH	99	82[d]
3[c]	$Cu(OTf)_2$	**35b**	1/1.1	10/11	EtOH	94	76
4[b]	$Cu(OTf)_2$	**199**	1/1.2	10/12	^{i}BuOH	90	93
5	$Cu(ClO_4)_2$	**201**	1/1.1	4.5/5.0	EtOH	93	95
6	$Cu(ClO_4)_2$	**80a**	1/1.1	4.5/5.0	EtOH	88	70
7	$Cu(ClO_4)_2$	**36a**	1/1.1	4.5/5.0	EtOH	85	66
8[e]	$Cu(ClO_4)_2$	**36a**	1/1.1	4.5/5.0	EtOH	92	81
9	$Cu(ClO_4)_2$	**36d**	1/1.3	3.8/5.0	EtOH	90	87
10	$Cu(ClO_4)_2$	**36d**	1/1.04	4.8/5.0	EtOH	96	95
11	$Cu(OTf)_2$	**36a**	1/1.3	3.8/5.0	EtOH	98	81
12	$Cu(OTf)_2$	**36a**	1/1.1	4.5/5.0	EtOH	93	85
13[f]	$Cu(OTf)_2$	**36a**	1/1.04	4.8/5.0	EtOH	97	>99
14	$Cu(OTf)_2$	**36a**	1/1	5.0/5.0	EtOH	90	98
15	$Cu(OTf)_2$	**36a**	1.1/1	5.5/5.0	EtOH	96	98
16	$Cu(OTf)_2$	**36a**	1.3/1	6.5/5.0	EtOH	95	91
17	$Cu(OTf)_2$			7.5/0	EtOH	90	0
18	$Cu(OTf)_2$	**35a**	1/1.04	4.8/5.0	EtOH	89	99

[a] Determined by chiral HPLC. [b] Taken from ref. 5d. [c] Taken from ref. 5c. [d] 75% yield, 93% ee at -25℃. [e] 5.5 mol% of triazole **200** were added. [f] Obtained in three runs.

The investigations began with the finding, that ligand **201** is able to catalyze the reaction with better enantioselectivity than the bis(oxazolines) (**35**) and the tris(oxazoline) **199** (Table 21, entry 5).[7] This was surprising, because a tridentate coordination, according to the tris(oxazolines), is not possible due to the rigidity of the triazole framework. Nevertheless, an intermolecular coordination of the triazole unit to a second metal center can take place as confirmed by X-ray analysis (Figure 18).

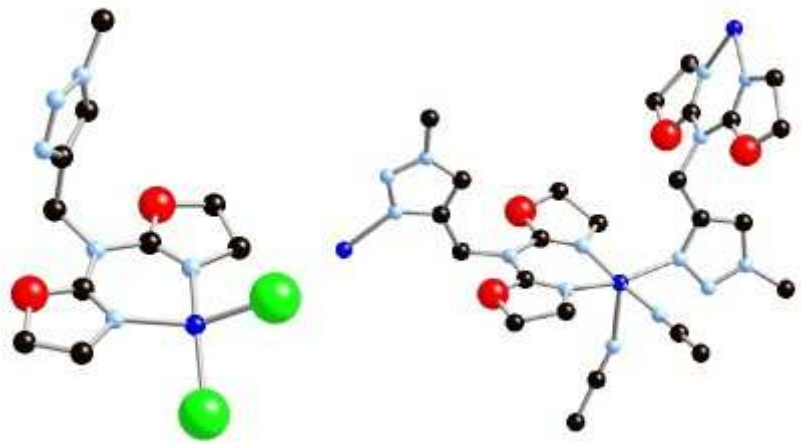
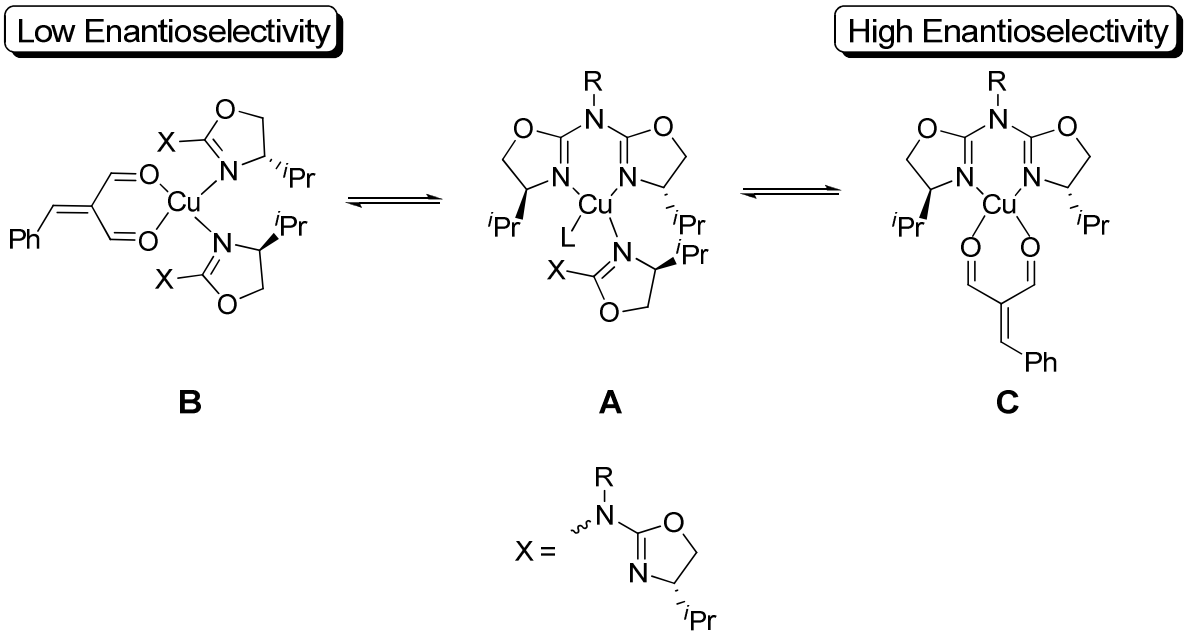


Figure 18**:** X-ray structures of $CuCl_2$•XY (left) and $[Cu(ClO_4)_2(CH_3CN)_2$•$XY]_n$ (right); ^{i}Pr, Ph, and ClO_4 groups are omitted for clarity.[6]

The X-ray structure shows a polymeric ligand structure (Figure 18, right picture) which is bridged by copper atoms. Consequently we suggested, that an external additive that is able to coordinate to the metal, should be sufficient to obtain high selectivities. However, a slight improve was visible (Table 21, entries 7 and 8) but the result could not equalize the performance of ligand **201**. With these observations a new mechanism for the title reaction was proposed: The coordination of three nitrogens to the copper might represent a resting state of the catalyst. In order to form the active species one of the ligands has to dissociate off. In the case of bis(oxazoline) ligands, the excess of ligand used might provide a third oxazoline (Scheme 50, complex **A**). If then one of the chelating oxazoline moieties dissociates off a species like **B** (Scheme 50) is created, which would give rise to low enantioselectivity. If now an additive is present that coordinates weaker, a species like **C** would be favored, resulting in high enantioselectivity.

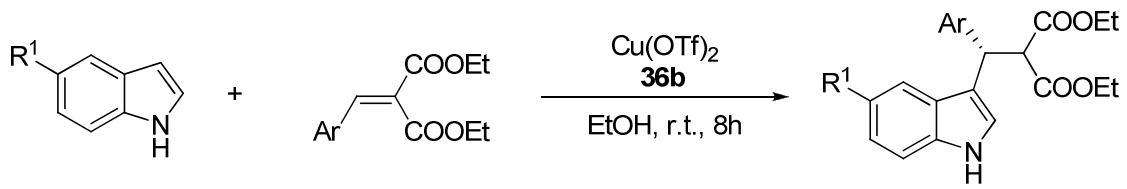


***Scheme 50*:** Mechanistic model for the asymmetric 1,4-addition to benzylidene malonates.

The superior results using the tris(oxazoline) ligands can also be understood, following this line of argument, since the dissociation of any oxazoline moiety would result in a species of type **C**.

The rational consequence of this finding would be that the copper/ligand ratio plays a fundamental role for obtaining high selectivities and an excess of ligand can be detrimental therefore. This is quite in contrast to the usually applied ligand excess, which is utilized to avoid any background reaction by uncomplexed metal. Indeed, a variation of the ligand/metal ratio exhibited a strong effect on the resulting ee (Table 21, entries 11-13). Applying this protocol enantioselectivities of 99% could be achieved for both, azabis(oxazolines) and bis(oxazolines). Using these standard conditions also different substrates were screened and good results were obtained as shown in Table 22.

***Table 22*:** Asymmetric Michael-addition using different indoles and benzylidene malonates. [a] 6



196: R=H
202: R=OMe

197
203-206

198
207-211

Entry	Ar	R^1	Product	Yield (%)[b]	ee (%)[c]
1	Ph (**197**)	H	**198**	97	99
2	*p*-Me-Ph (**203**)	H	**207**	80	93
3	*p*-Cl-Ph (**204**)	H	**208**	91	98
4	*o*-Br-Ph (**205**)	H	**209**	89	85
5	*p*-NO_2-Ph (**206**)	H	**210**	94	80
6	Ph (**197**)	OMe	**211**	80	90

[a] Reagents and conditions: benzylidene malonate 1.0 mmol, indole 1.2 mmol, 4 mL EtOH. [b] Isolated yield. [c] Determined by chiral HPLC.

All the products were obtained in high yields and with good to excellent selectivities. Only the *p*-NO_2-sustituted benzylidene malonate paled in regard of enantioselectivity. This finding at first was explained by a possible coordination of the nitro group to the metal center, which would lead to an unselective reaction.

In further experiments A. Schätz could show, that the influence of the ligand/metal ratio strongly depends on the substrate nature.[8] It was found out that only for electron rich benzylidene malonates a ligand surplus is detrimental for the optical yield of the reaction. In contrast if electron withdrawing groups are present even a ligand excess is required to get the optimal ee.

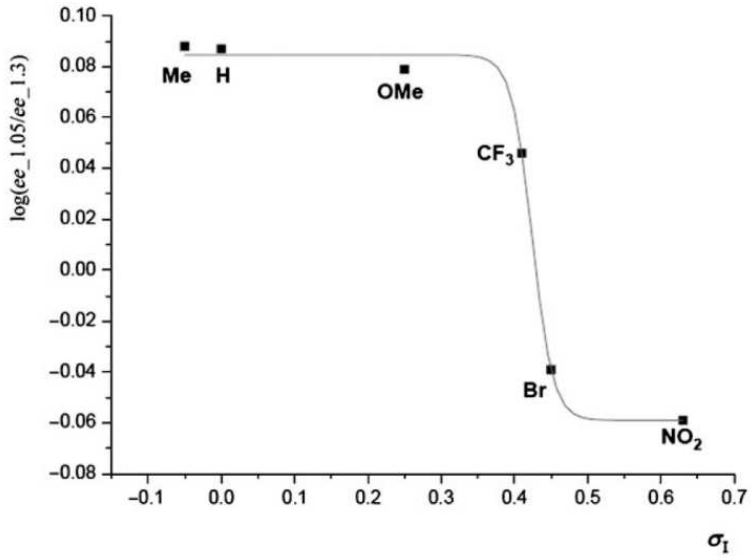
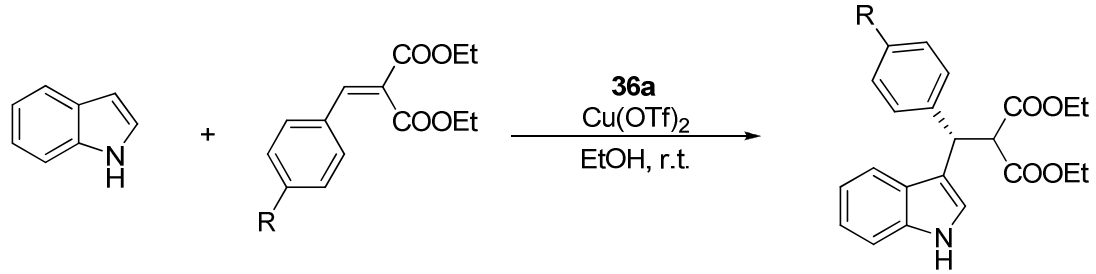


***Figure 19*:** Semi-logarithmic correlation of optical yield ratio versus σ_I values of para substituents in the reaction of indole with substituted benzylidene malonates.[8]

Furthermore, it could be shown that the influence of the ligand/metal ratio vanishes if an excess of triflate is used. The explanation therefore is that the triflate ion coordinates to the copper in apical position[9] and impedes the coordination of a third oxazoline moiety. Some of the results are summarized in Table 23.

***Table 23*:** Dependence of enantioselectivity on the ligand/metal ratio in the 1,4-addition of indole to benzylidene malonates; influence of triflate as an additive.[a]



196 **197**: R=H; **206**: R=NO_2 **198**: R=H; **210**: R=NO_2

Entry	Ligand/metal ratio	R	Li(OTf)$_2$/36a	Yield (%)	ee (%)[b]
1	1.04/1.0	H	-	97	>99[c]
2	1.05/1.0	H	5	90	93
3	1.3/1.0	H	-	98	81[c]
4	1.3/1.0	H	5	97	96
5	1.05/1.0	NO_2	-	92	82[c]
6	1.05/1.0	NO_2	5	89	96
7	1.3/1.0	NO_2	-	83	94[c]
8	1.3/1.0	NO_2	5	73	93

[a] Reaction conditions: 1.2 mmol indole, 1.0 mmol malonate, 5 mol % **36a**, 20℃, 8 h; 4 mL EtOH. [b] Determined by chrial HPLC. [c] Obtained by at least two independent runs.

In conclusion, simple copper(II)-bis(oxazoline) complexes are excellent catalysts for the asymmetric Michael-addition of indoles to benzylidene malonates, under the precondition of a precise adjustment of the ligand/metal ratio depending on the electronic properties of the substrates.

4.2 Determination of catalyst activities

As Noyori has pointed out, asymmetric catalysis is actually four-dimensional chemistry.[10] This means, that a high efficiency of a catalyst can only be achieved through a combination of an ideal three dimensional structure and suitable kinetics. Especially for applications on industrial scale it is important that the catalytic active species shows not only high selectivity but also high activity. Generally the activities

are determined by comparison of the reaction kinetics. The problem herein is the evaluation of the kinetic data; usually this comprises the meticulous measurement of increments over a potentially long period of time. This means that after defined intervals aliquots have to be taken from the reaction mixture, often followed by a work up procedure, before the actual measurement (i.e. HPLC, GC, NMR) can take place. The ideal way would be a real-time monitoring, without affecting the system in any way, but this often requires complicated and cost intensive reaction setups (Figure 20).

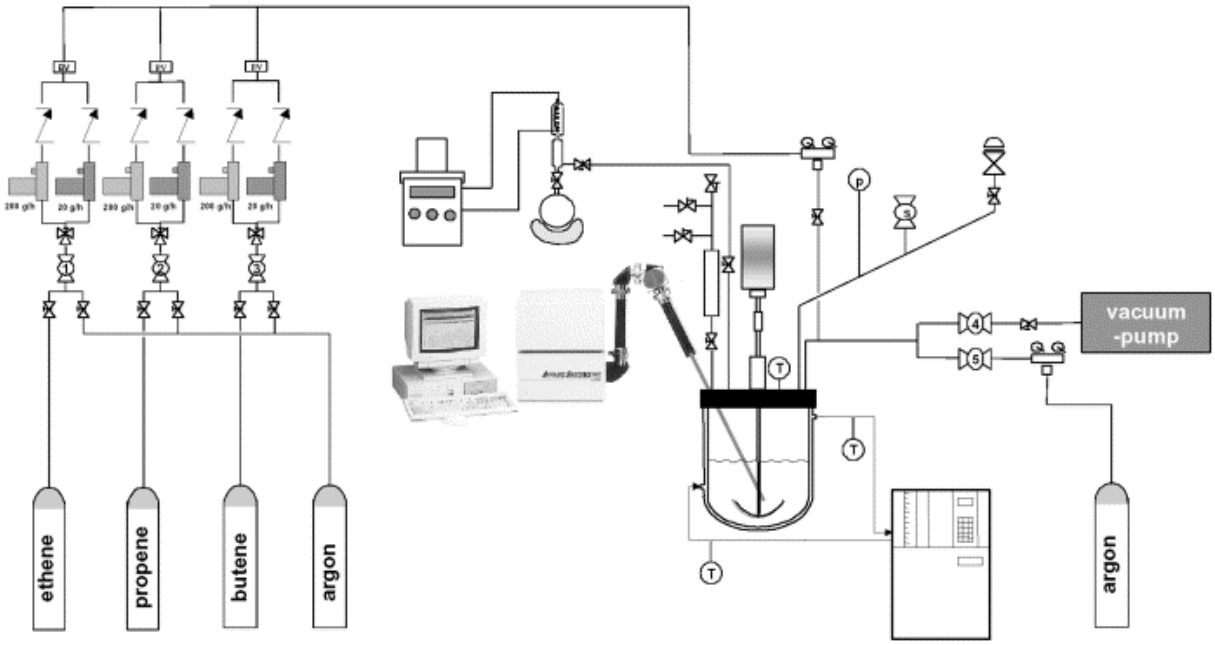


***Figure 20*:** Polymerization reactor with real-time monitoring.[11]

In our approach, which is rather unexplored so far, the goal was to deduce information about relative catalyst activities only from the level of enantioselectivity obtained. Therefore a simple experimental setup is sufficient, which does not call for a continuous recording. Nevertheless, it allows a precise assessment of relative reaction rates.

Our investigations mainly concentrated on the well explored Michael-addition of indole to benzylidene malonate, which was summarized in the previous paragraph, due to the fact that high yields and selectivities are obtained for both bis(oxazolines) and azabis(oxazolines). Hence, both ligands appear equally suited for the reaction under these conditions. The idea of the new approach was to have two chiral ligands

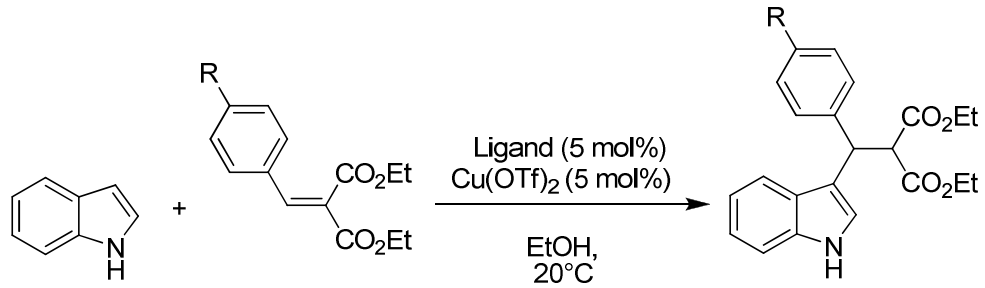
inside the reaction mixture which are producing the opposite enantiomers during the reaction. From the resulting ee and the known selectivities of the normal reactions (using only one ligand) the relative activities of the catalysts can be derived. For the calculation of the relative reaction rates the following formula was developed by S. Wittmann and F. Pein:

$$v_{rel} = \frac{ee_2 + ee_r}{ee_1 - ee_r}$$

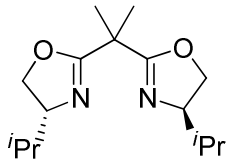
ν_{rel} = relative reaction rate
ee_1 = enantioselectivity of ligand 1
ee_2 = enantioselectivity of ligand 2
ee_r = resulting enantioselectivity using both ligands

As a first step the reactions were carried out using only one ligand because the preliminary results of the Friedel-Crafts alkylation were obtained with an optimal ligand/metal ratio of 1.04/1.0. For the intended experiments, however, a small excess of ligand is not suggestive, because this may lead to unequal amounts of the different complexes in the reaction mixture. For that reason a thoroughly preserved ratio of 1/1 was employed. The results are summarized in Table 24.

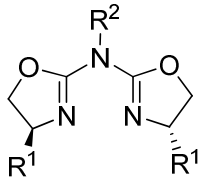
***Table 24*:** Asymmetric 1,4-addition of indole to benzylidene malonates catalyzed by different bis(oxazoline)- and azabis(oxazoline)-copper(II) complexes respectively.[a]



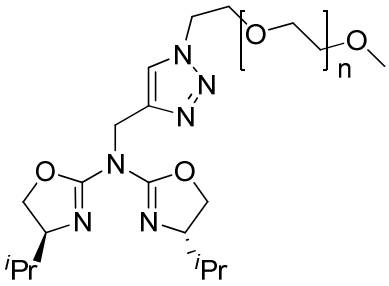
196 **197, 203 204, 212** **198, 207 208, 213**



ent-**35a**



36a: R^1 = ^{i}Pr, R^2 = H
36b: R^1 = ^{i}Pr, R^2 =Me
ent-**36c**: R^1 = Ph, R^2 = H
36d: R^1 = Bn, R^2 = H



214

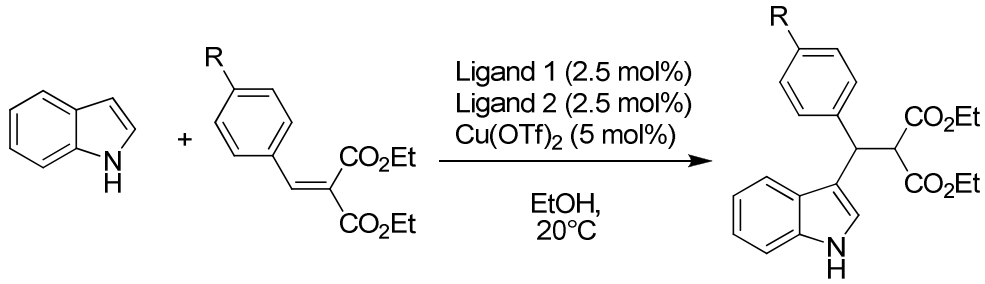
Entry	Ligand	R	Product	Yield (%)	ee (%)[b]
1[c]	**35a**	H (**197**)	**198**	89	- 99
2[c]	**36a**	H (**197**)	**198**	97	+ 99
3	*ent*-**35a**	H (**197**)	**198**	93	- 90
4	**36a**	H (**197**)	**198**	90	+ 98
5	**80a**	H (**197**)	**198**	84	+ 77
6	**36d**	H (**197**)	**198**	90	+ 81
7	*ent*-**36c**	H (**197**)	**198**	63	- 57
8	*ent*-**35a**	Cl (**204**)	**208**	84	- 80
9	**36a**	Cl (**204**)	**208**	87	+ 76
10	*ent*-**35a**	Me (**203**)	**207**	79	- 84
11	**36a**	Me (**203**)	**207**	66	+ 78
12	*ent*-**35a**	OMe (**212**)	**213**	80	- 83
13	**36a**	OMe (**212**)	**213**	47	+ 71
14	**214**	H (**197**)	**198**	81	+ 87

[a] Reagents and conditions: 1.2 mmol indole, 1.0 mmol benzylidene malonate, 5 mol% ligand, 5 mol% $Cu(OTf)_2$, 20℃, 16h, solvent: 4 mL EtOH. [b] Determined by chiral HPLC. [c] 4.8 mol% $Cu(OTf)_2$, Taken from ref. 6.

The results indicate that the selectivities are inferior to those obtained under optimized conditions (entries 1 and 2). Nevertheless, good to excellent ee's were achieved, with the exception of the phenyl-substituted AzaBOX ligand *ent*-**36c** (entry 7), for all ligands and substrates tested. The entries 3 and 4 clearly show a prevalence of the ^{i}Pr-substituted ligands *ent*-**35a** and **36a**, regarding enantioselectivity, for the unsubstituted benzylidene malonate. Therefore, only these ligands were used for the substrate screening experiments. The MeOPEG immobilized ligand **214** also showed results that are comparable with the unbound counterpart in regards of selectivity (Table 24, entry 14). For all these experiments elongated reaction times were applied to ensure a complete conversion.

Having these results, the next step was the utilization of two ligands in the reaction mixture. All the experiments were carried out twice to assure the reproducibility of the applied method.

***Table 25*:** Asymmetric 1,4-addition of indole to benzylidene malonates: Comparison between different bis(oxazolines) and azabis(oxazolines).[a]



196

197: R=H
203: R=Me
204: R=Cl
212: R=OMe

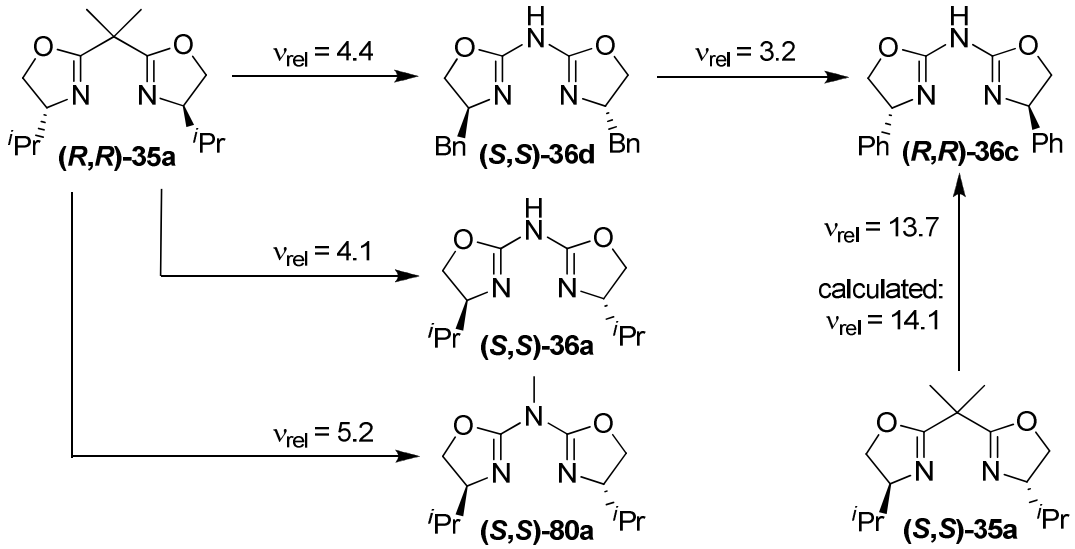
198: R=H
207: R=Me
208: R=Cl
213: R=OMe

Entry	Ligand 1	Ligand 2	R	Yield (%)[b]	ee (%)[c]	$\nu_{rel.}$
1	*ent*-**35a**	**36a**	H	90	- 53	4.1
2	*ent*-**35a**	**80a**	H	89	- 63	5.2
3	*ent*-**35a**	**36d**	H	90	- 58	4.4
4	**35a**	*ent*-**36c**	H	92	- 80	13.7
5	**36d**	*ent*-**36c**	H	84	+ 48	3.2
6	*ent*-**35a**	**36a**	Cl	87	- 41	3.0
7	*ent*-**35a**	**36a**	Me	65	- 49	3.7
8	*ent*-**35a**	**36a**	OMe	44	- 55	4.6
9[d]	*ent*-**35a**	**214**	H	71	- 52	3.6

[a] Reagents and conditions: 1.2 mmol indole, 1.0 mmol malonate, 2.5 mol% ligand 1, 2.5 mol% ligand 2, 5 mol% $Cu(OTf)_2$, 20℃, 16h, solvent: 4 mL EtOH. [b] Average of two runs. [c] Determined by chiral HPLC; average of two runs. [d] Results from S. Wittmann.

Within the two independent runs only negligible aberrance in isolated yield and selectivity was obtained. The conglomerated ee-values and the thereof derived reaction rates show a clear tendency. In all competitive experiments between BOX and AzaBOX ligands the resulting enantioselectivity is coined by the chirality of the BOX ligand. The ee-values vary from 53-80%, giving rise to relative reaction rates between 3.6 and 13.7. Interestingly the N-methylated ^{i}Pr-substituted AzaBOX ligand **80a** is a little slower than the unmethylated counterpart **36a** (entries 1 and 2). In contrast, the polymer supported ligand **214** shows more or less the same activity as the unbound ligand **36a** (entry 9). The Bn-substituted azabis(oxazoline) **36d** provides again activities compareable to **36a**. Only ligand *ent*-**36c** pales in regard of activity,

being 13.7 times slower than BOX **35a**. But it was pleasing to find that this results could be predicted almost exactly by the multiplication of the values in the entries 3 and 5 (calculated: 14.1). For a better visualization the results of the unsubstituted benzylidene malonates are depicted in Scheme 51.



***Scheme 51*:** Schematic representation of the correlation of rate ratios of bis(oxazoline)- and different azabis(oxazoline)-ligands derived from Table 25; arrows point towards the less active ligand.

An interesting tendency is observed for different substituted benzylidene malonates (Table 25, entries 6-8). The electronic nature of the substrate influences the rate ratio between the ligands. The rate-supremacy of the BOX ligand is decreased when an electron withdrawing substituent is present. This observation can be easily rationalized by the fact that these substrates are more active towards the addition of indole and therefore the difference in reaction rate is alleviated.

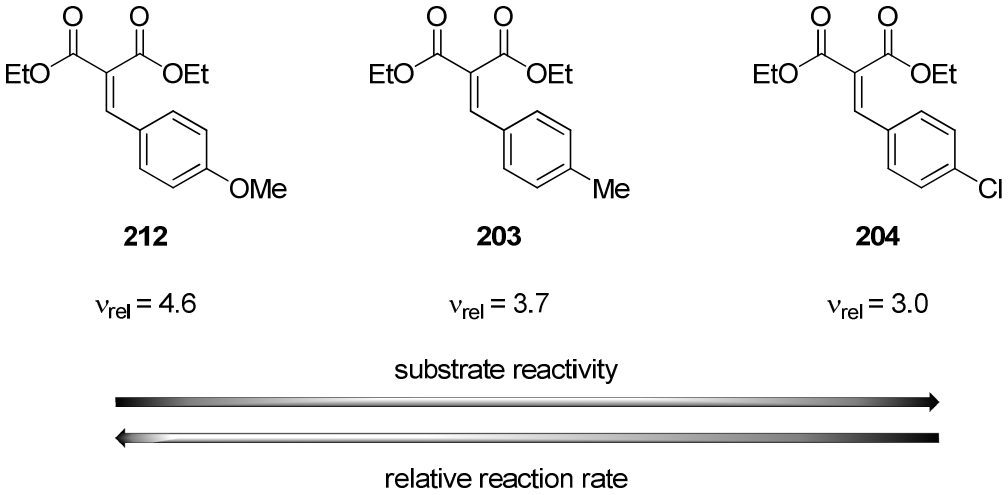


***Figure 21*:** Influence of the electronic properties of the substrate on the relative reaction rates.

To further extend the scope of the employed method experiments were planned where the ligands are used in uneven amounts. Therefore the formula to calculate the rate ratios had to be adjusted:

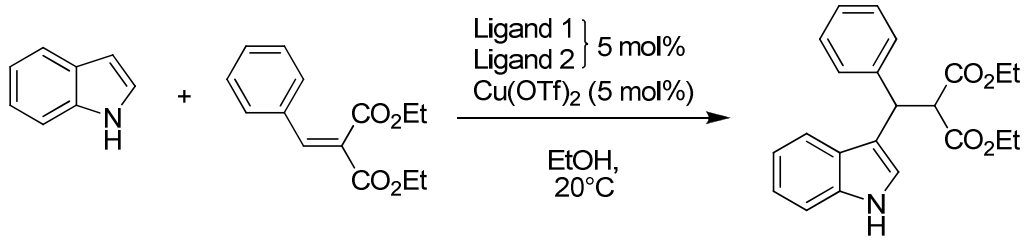
$$\nu_{rel} = \frac{X_2(ee_2 + ee_r)}{X_1(ee_1 - ee_r)}$$

X_1 and X_2 represent the amount of catalyst 1 and catalyst 2 respectively.

With this formula the relative reaction rates of two catalysts should be determinable in any proportion.

For these experiments the BOX ligand *ent*-**35a** and the AzaBOX ligand **80a** were employed. The use of ligand **80a** instead of **36a** is rationalized by the higher solubility of the corresponding copper complex because a precipitation of one of the complexes would alter the composition of active species. The results are shown in Table 26.

***Table 26*:** Assessment of relative reaction rates using uneven amounts of catalysts.[a]



196 **197** **198**

Entry	Amount 80a (%)	Amount *ent*-35a (%)	Yield (%)[b]	ee (%)[c]	ν_{rel}
1	0	100	93	-90	–
2	10	90	89	- 89	18,4
3	20	80	89	- 83	5,7
4	40	60	87	- 36	1,4
5	50	50	89	- 63	5,2
6	60	40	89	- 63	7,8
7	80	20	89	- 1	3,5
8	90	10	88	+ 31	0,29
9	100	0	84	+ 77	–

[a] Reagents and conditions: 1.2 mmol indole, 1.0 mmol malonate, 20°C, 16h, solvent: 4 mL EtOH. [b] Isolated yield; average of two runs. [c] Determined by chiral HPLC; average of two runs.

All experiments gave very good yields but, unfortunately, the obtained enantioselectivities and the thereof derived rate ratios did not represent the intended values. In principle all reactions should give the same value, the one of the 1/1 mixture of ligands (entry 5), apart from a certain inaccuracy in the measurements. But the ratios fluctuate in a huge range. In order to elucidate the results it was investigated if the reactions are influenced by non linear effects of the catalysts, because it is known for bis(oxazolines) that NLE's can occur.[12] Thus, the correlation between the ee of the product and the ee of the utilized ligand was explored. The results are visualized in Figure 22.

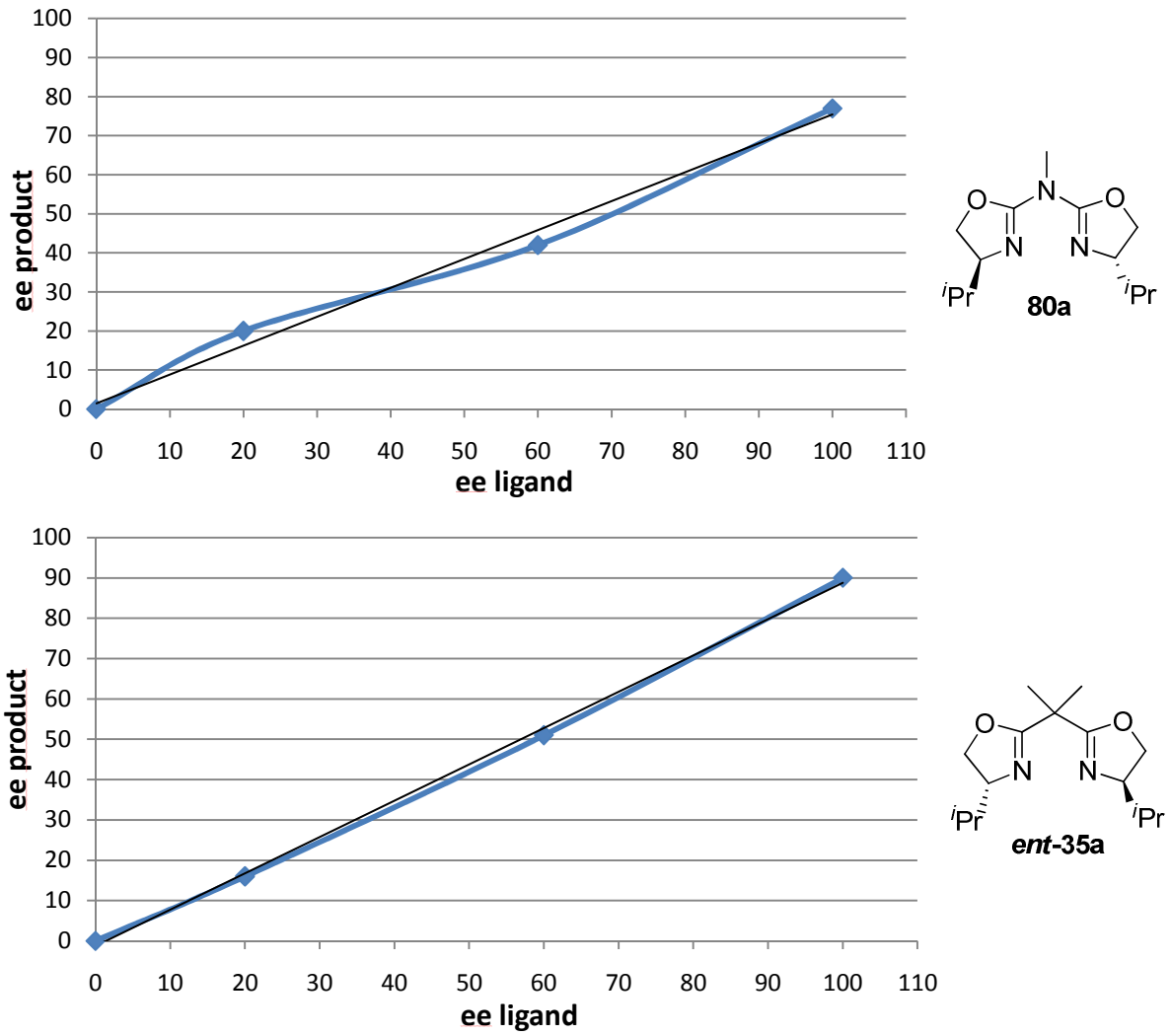
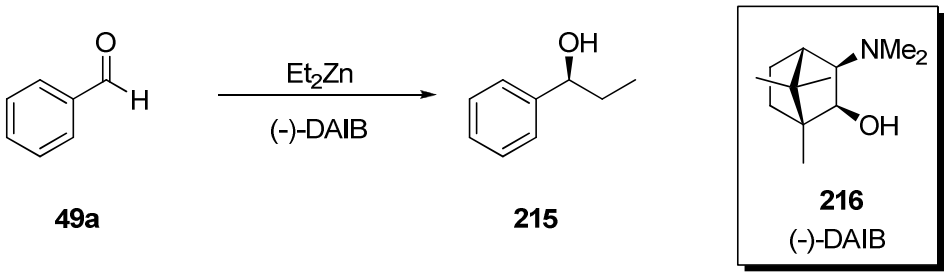


***Figure 22*:** Correlation of the product ee and the ligand ee.

The diagrams lead to the suggestion that no non linear effect is present under the employed reaction conditions. Nevertheless, these experiments only represent the situation for the application of only one pair of enantiomers. The actual conditions of the ligand comparison experiments are not displayed by these investigations. Non linear effects often are ascribed to the so called *Reservoir Effect*[13], this means that the formation of heterochiral dimeric complexes is favored due to a higher stability of these complexes compared to the homochiral ones, as the steric repulsion is reduced in these cases. Several examples of chiral amplifications are known and can be ascribed to this effect.[14] Probably the most prominent example of a chiral amplification was published by Noyori et al. with the diethylzinc addition to benzaldehyde using an aminoalcohol as chiral ligand (Scheme 52).



***Scheme 52*:** Diethylzinc addition to benzaldehyde by Noyori et al.[15]

For this reaction a ligand with only 14% ee was used and 98% ee were obtained due to the formation of heterochiral dimeric complexes which were catalytic inactive. As there are several examples of heterochiral dimeric complexes reported being more stable than their homochiral complements[16] we also tried to get an idea of the composition of complex species formed under the given conditions, therefore ESI-mass spectra were recorded. The spectra are depicted in Figure 23 and the most important peaks are labeled.

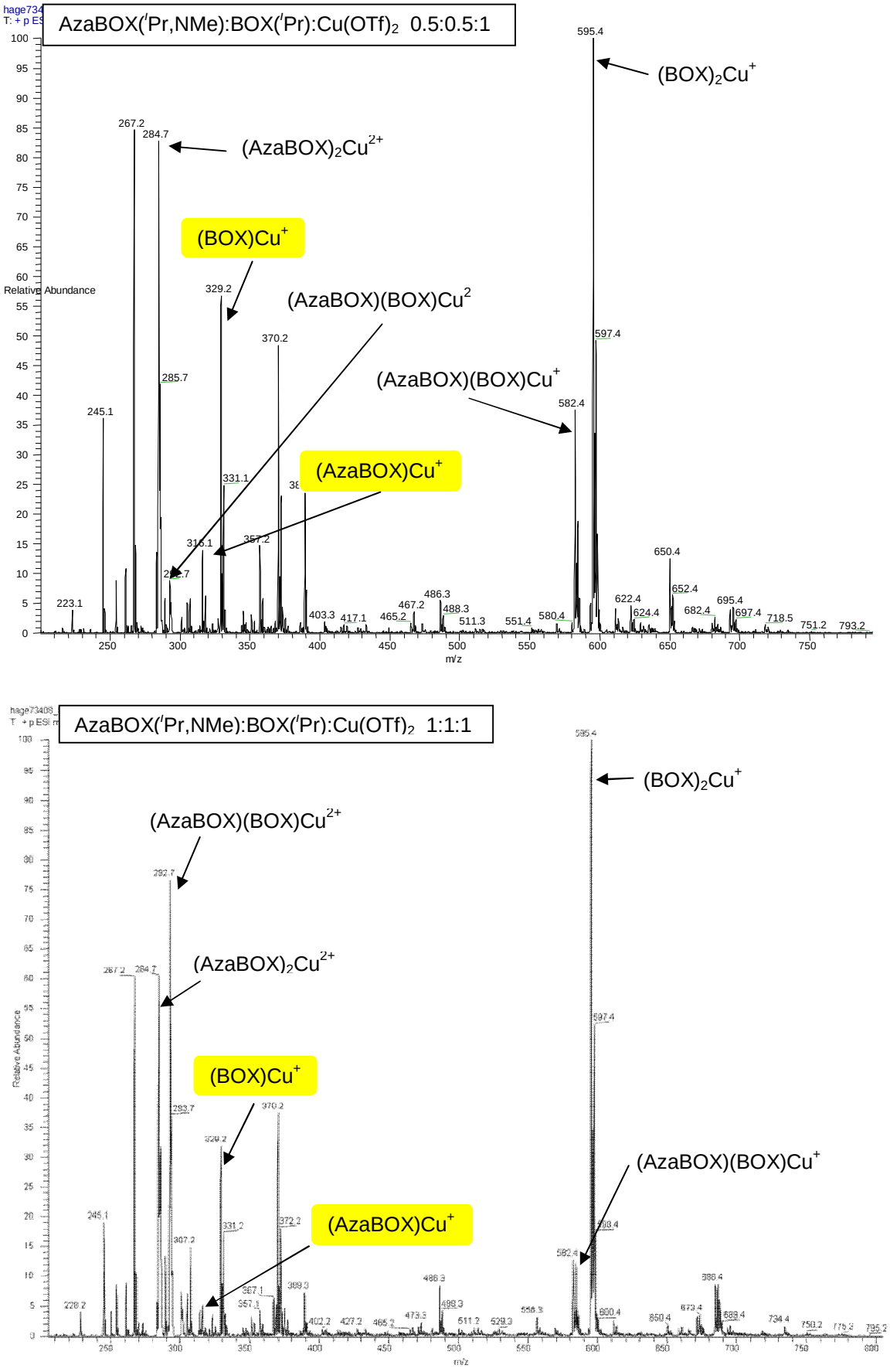
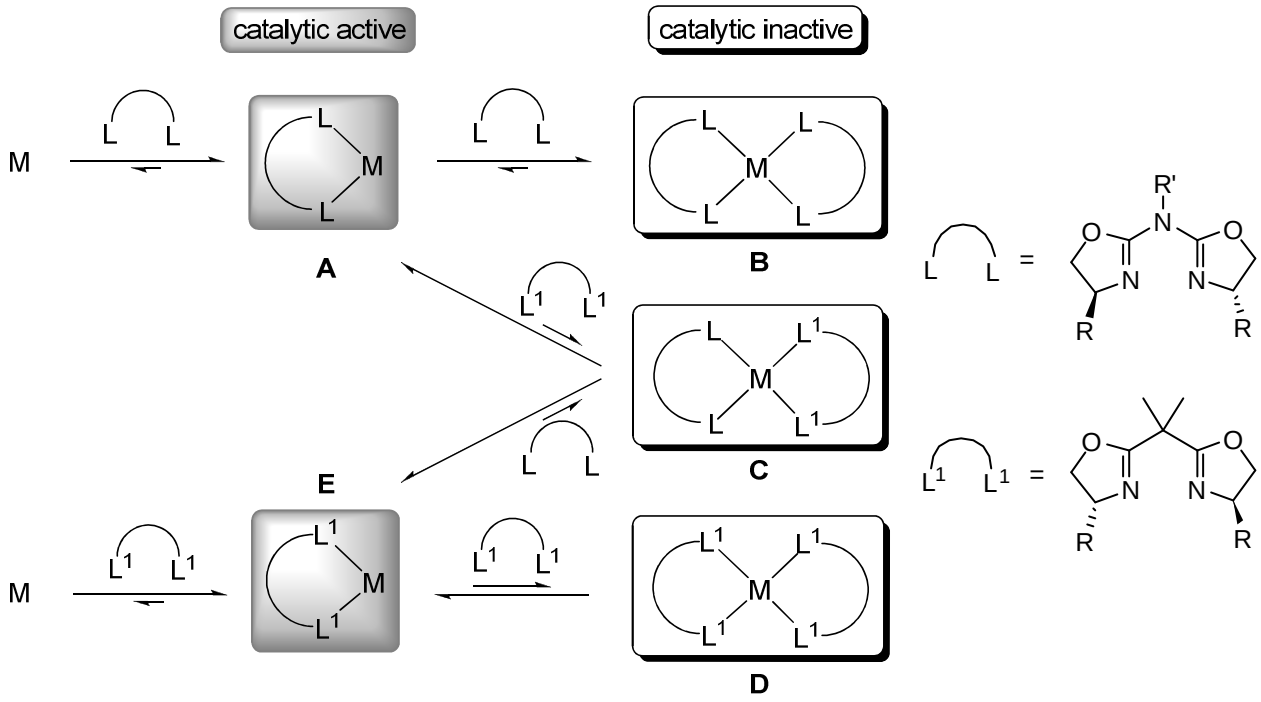


***Figure 23*:** ESI-spectra of ligand *ent*-**35a** and **80a** with copper(II)triflate.

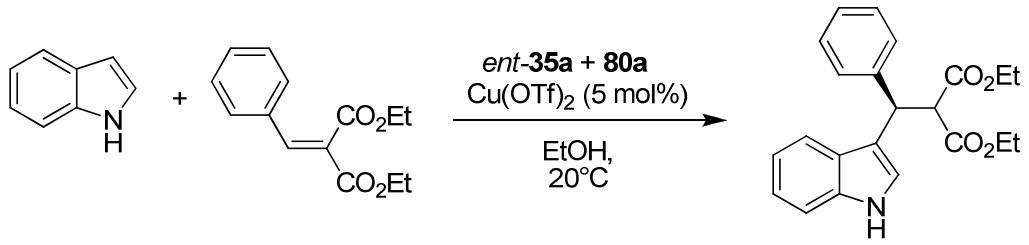
The spectra indicate that mainly complexes are formed, where the metal is coordinated by two ligand molecules. This is quite surprising, at least for the first spectra, because here the ligands are added in equimolar amounts referring to the metal source and 1/1 complexes would be suggestive, since otherwise free metal would be present and this principally should give rise to reduced enantioselectivities. The 2/1 species are catalytic inactive because in these cases the coordination of the malonate at the metal center is obviated. It can also be estimated, that in the present case it comes to the preferential formation of homochiral instead of heterochiral 2/1 complexes, which would be in contrast to the results by Chen et al. who used pseudo-enantiomeric bis(oxazoline) ligands for his investigations.[16] Furthermore, an interesting observation can be made for the catalytic active species, so the monomeric ligand-metal complex. If the quantity of ligands is incrased (Figure 23, lower spectra) the peak of the BOX•Cu^+ species is reduced but the signal for the AzaBOX•Cu^+ species vanishes almost completely, because now the equilibrium is ever further shifted towards the dimeric homochiral complex. As the latter complex is inactive in the catalysis this can be an explanation why the bis(oxazoline) ligand dominates the resulting ee even when the amount of azabis(oxazoline) is increased. These findings also support the hypothesis that the azabis(oxazolines) stronger bind to a metal center due to the different electronic properties compared with bis(oxazolines). Of course, these results only represent the situation in the gas phase, but together with the well known X-ray structures of 2/1 complexes, they can at least give a hint of the conditions in solution. The postulated situation that accounts for the results obtained with different ligand amounts is displayed in Scheme 53.



***Scheme 53*:** Schematic representation of the possible complexes.

If the metal is coordinated only by one ligand, BOX or AzaBOX, the catalytic active species **A** and **E** are formed because in that case free coordination sites are present for the substrate to bind to the metal. These two complexes are able to coordinate another ligand molecule, to form the agglomerates **B**, **C** and **D**, whereupon the heterochiral complex **C** is of insignificant importance. The two homochiral species can be seen as a resting state of the active catalyst. Probably due to the stronger binding of the azabis(oxazoline) to the metal the equilibrium is shifted strongly towards the side of the complex **B**, especially if the amount of AzaBOX is increased. This would lead to the suggestion that an increase in the concentration of ligand **80a**, compared to the metal salt, would not favor the formation of the (*S*)-enantiomer (coined by the azabis(oxazoline)), instead a suppression of the active species A would be the result. The conclusion would be that the stereochemical outcome of the reaction should be dominated by the BOX ligand with an increase of the ligand concentrations. For that reason the reaction was run with elevated amounts of ligand. The results are summarized in Table 27.

***Table 27*:** Influence of the ligand concentration.[a]



196 **197** **198**

Entry	Order of Addition	mol% of the ligands		Yield (%)[b]	ee (%)[c]
		80a	***ent*-35a**		
1	BOX was added first	5	5	88	- 84
2	AzaBOX was added first	5	5	88	- 78
3	ligands added simultaneously	5	5	90	- 84
4	BOX was added first	10	10	61	- 83
5	AzaBOX was added first	10	10	68	- 76
6	ligands added simultaneously	10	10	66	- 84

[a] Reagents and conditions: 0.6 mmol indole, 0.5 mmol malonate, 20℃, 16h, solvent: 2 mL EtOH. [b] Isolated yield; average of two runs. [c] Determined by chiral HPLC; average of two runs.

In order to verify if dynamic ligand exchange processes take place the order of ligand addition was varied. Therefore either one of the two ligands was stirred with the metal salt for a certain amount of time before the other ligand was added, or both ligands were added simultaneously as a solution in EtOH. The mixture then was stirred again for a while, so that the ligand exchange can take place. The results clearly show that the ligand molecules are exchanging because in all experiments the (-)-enantiomer is formed mainly, and this can be ascribed to the reaction catalyzed by ligand *ent*-**35a**. It can also be seen that the catalytic active species of the AzaBOX ligand is suppressed almost completely, even at a ligands to metal ratio of 2/1, as the resulting ee almost equals the value of the reaction catalyzed only by the BOX ligand (90% ee). If the concentration of the ligands is increased further to a ligands/metal ratio of 4/1 no change in selectivity is observable, but the isolated yields are diminished considerably (entries 4-6). Because of the high amounts of ligands these reactions were found to proceed sluggish, as the coordination of the benzylidene malonate to the copper is oppressed especially in the end, when only low concentrations of malonate are present.

In a further control experiment it should be investigated if the method is applicable when two azabis(oxazolines) are used in uneven molar amounts. Therefore the ligands *ent*-**36c** and **36d** were employed, because the only structural difference is the additional CH_2-group of the substituents in **36d**. Since the electronic properties of these two ligands are complementary only the different steric properties of these substituents should influence the formation of the distinct complexes.

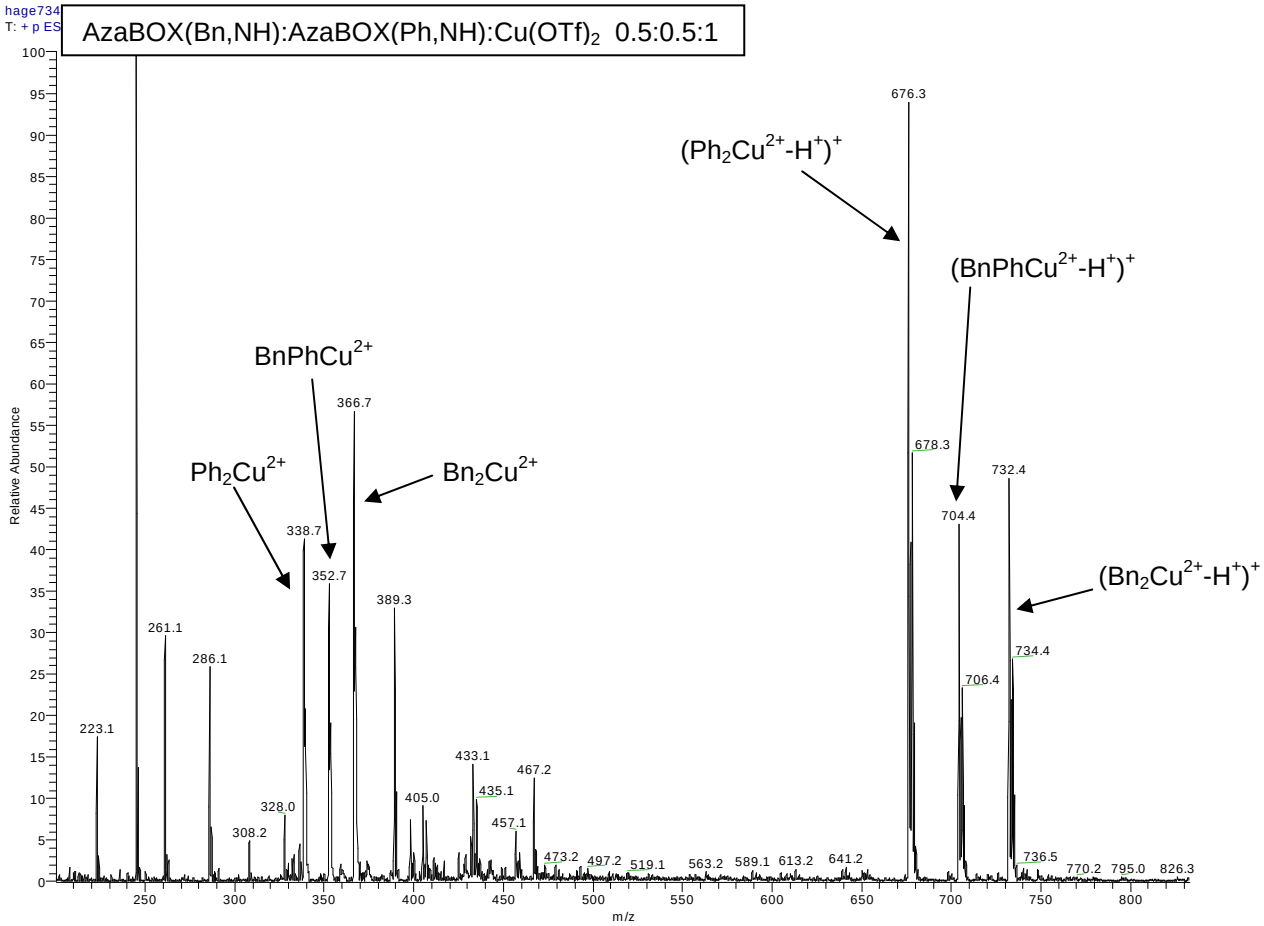
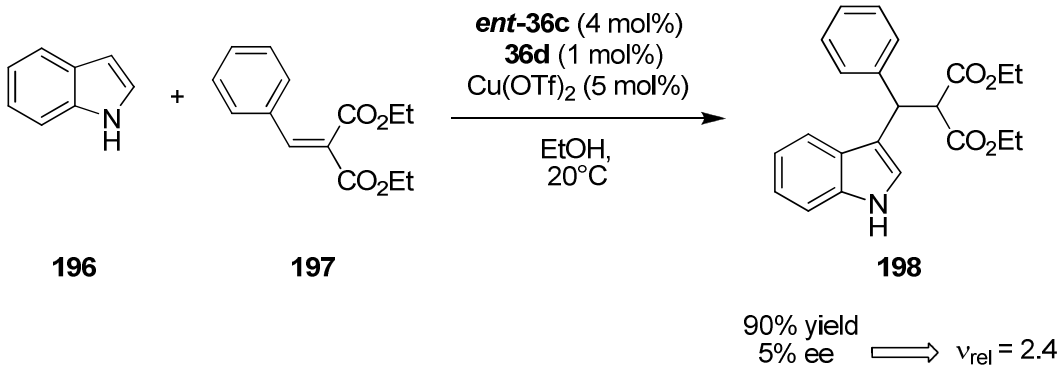


***Figure 24*:** ESI-mass spectrum of the ligands *ent*-**36c** and **36d** with copper(II)-triflate.

The spectrum shows all three possible dimeric agglomerates, the two homochiral and the heterochiral one. Furthermore, a set of peaks appears which can be ascribed to the deprotonation of the latter complexes.

The results of the experiments are shown in Scheme 54 and represent again the average of two runs with only negligible variations.



***Scheme 54*:** Michael-addition with uneven molar amounts of ligands *ent*-**36c** and **36d**.

The product was obtained in good yields and the cumulated enantiomeric excess was 5%. This leads to a relative reaction rate of 2.4 (in preference of the Bn-substituted ligand **36d**), which is quite in accordance to the obtained value of the experiment using equimolar amounts (3.2). The small aberrance can be explained by the relatively high inaccuracy of the method when it comes to very low ees. Nevertheless, it could be shown that the approach is applicable not only for the use of even catalyst amounts.

Finally, the reaction kinetics of the Michael addition of indole to benzylidene malonate catalyzed by the ligands *ent*-**35a** and **36a** was verified. Therefore, aliquots were taken from the reaction mixture after certain intervals of time and, after a small workup, were analyzed by HPLC. The reaction progress of the BOX catalyzed reaction is depicted in Figure 25.

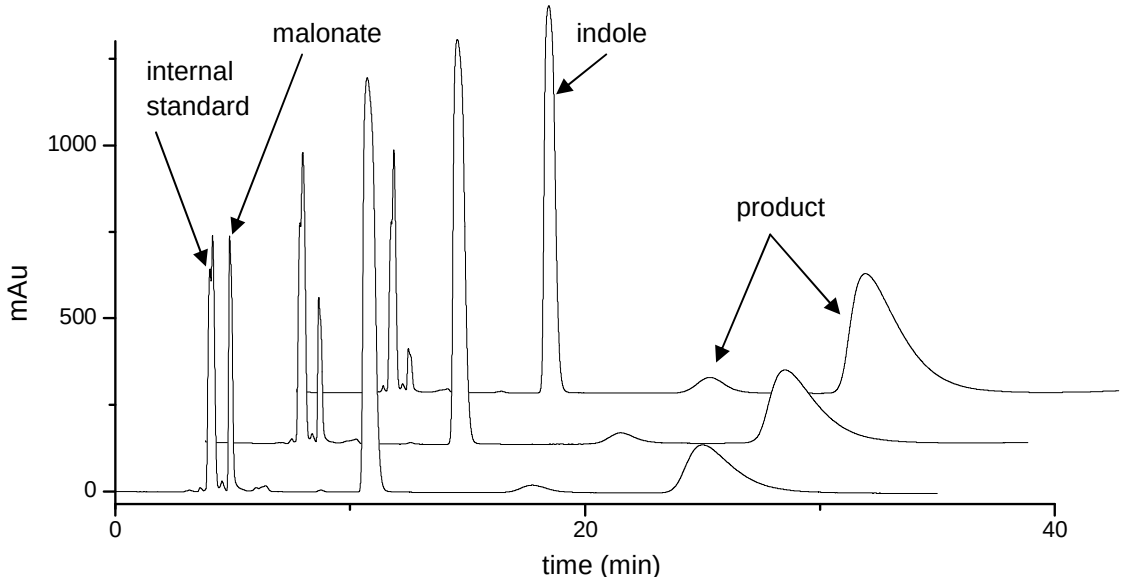


***Figure 25*:** Waterfall diagram of selected HPLC spectra to show the reaction progress; the displayed samples were taken after 15, 60 and 300 min.

The results of the kinetic measurements are shown in Figure 26. The clear tendency that was obtained before can also be seen in these data, the bis(oxazoline) ligand is able to perform the reaction with higher activity.

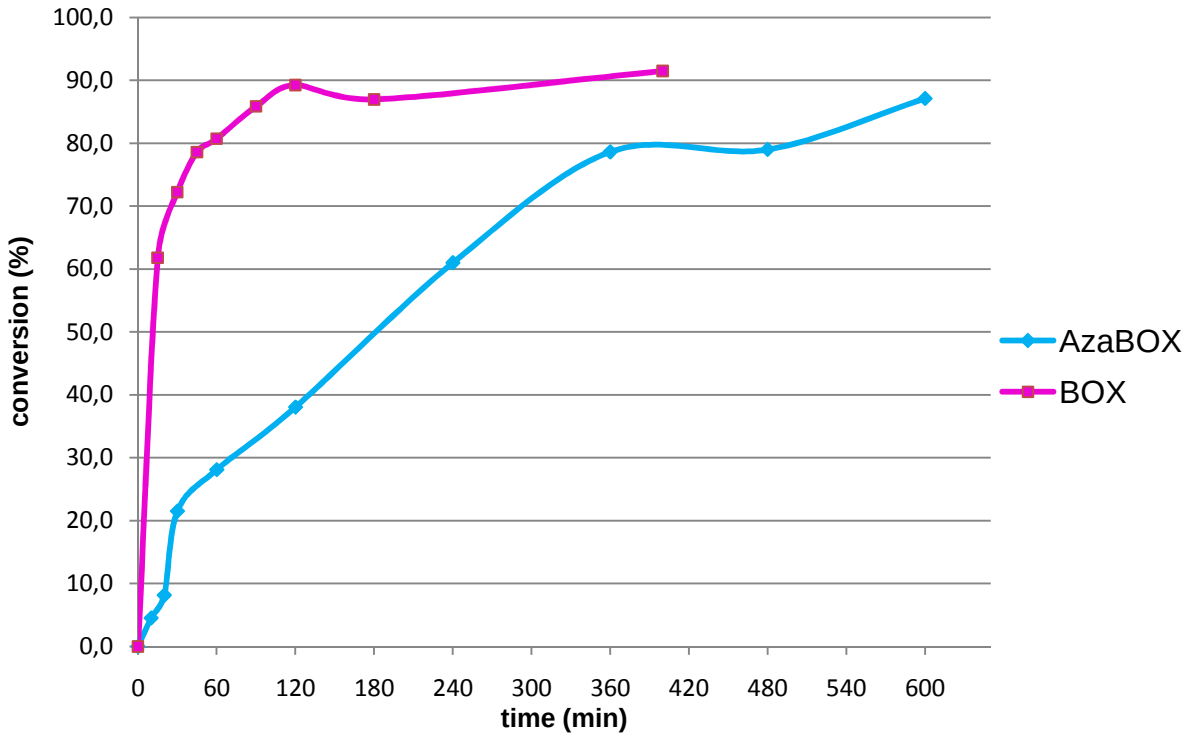
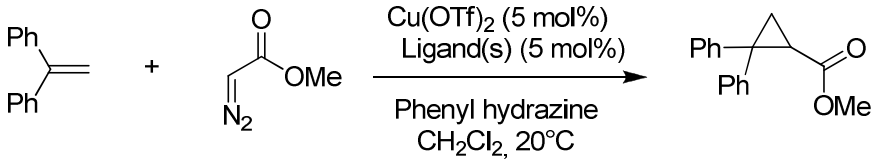


***Figure 26*:** Results of the kinetic measurements.

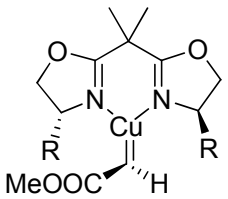
To further validate the established methodology other transformations were investigated. One of the first asymmetric catalytic reactions examined is the cyclopropanation of olefins. A plethora of catalytic systems was already applied for this type of transformation, including salen-,[17] bis(oxazoline)-[18] and semicorrin-ligands.[19] Also azabis(oxazolines) were already successfully applied in these processes,[20] therefore this kind of reaction would also be suitable for the employment in ligand comparison experiments. For the investigations the reaction between 1,1-diphenylethylene **217** and the diazo ester **218** was chosen (Scheme 55).



217 **218** **219**

***Scheme 55*:** Cyclopropanation of 1,1-diphenylethylene with methyl diazo ester.

The measurement of kinetics in these kinds of reactions is quite difficult, as one reagent (the diazo ester) is added slowly over a long period of time. The rate ratios in this process depend on two factors, the decomposition of the diazo ester to form the carbene intermediate **220** and the transmission of the carbene to the double bond.

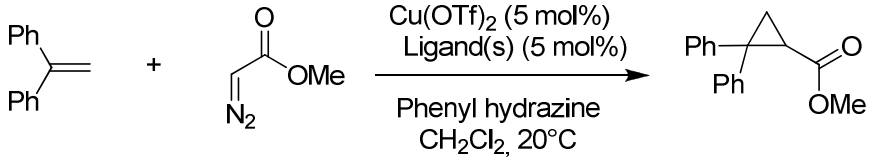


220

***Figure 27*:** Carbene intermediate formed during the cyclopropanation.

It is also known in literature, that the reaction rate of the cyclopropanation depends on the ligand/metal ratio.[21] A strong deactivation was observed, when two equivalents of ligand were used with regard to the metal, because the metal was complexed by two ligand molecules and no more free coordination site was present. The results of the conducted experiments are summarized in Table 28.

***Table 28*:** Results of the cyclopropanation.[a]



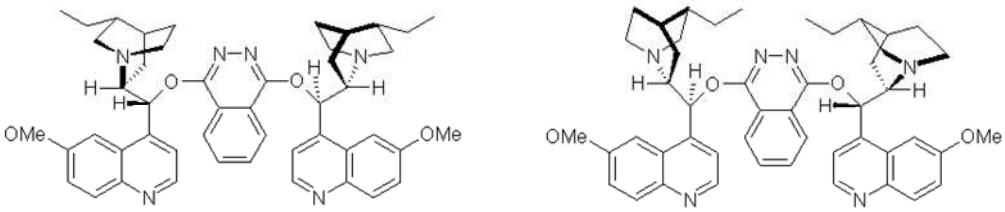
217 **218** **219**

Entry	Ligand *ent*-35a (mol%)	Ligand 80a (mol%)	Yield (%)[b]	ee (%)[c]	ν_{rel}
1	5	-	70	+ 53	-
2	-	5	86	- 57	-
3[d]	2.5	2.5	82	+ 7	1.4
4[d]	2	3	70	+ 25	4.4
5[d]	3	2	72	+ 34	3.2

[a] Reagents and conditions: 1.0 mmol 1,1-diphenylethylene, 2.0 mmol diazo ester, 1 drop phenyl hydrazine, 20℃, 16h, solvent: 2 mL DCM. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Average of two runs.

Both ligands, when used alone, give the product in good yields and with moderate enantioselectivities, which is known for these substrates. The azabis(oxazoline) is a little inferior in both, yield and selectivity, but without significant differences. In this case it can be seen that the used ligands show almost the same reaction rate, ligand *ent*-**35a** is only marginally faster. Furthermore, it was tested again if the amount of ligands can be varied. But once more the received values are not in accordance with the 1/1 experiment, most probably due to the already discussed reasons.

Another reaction that was examined is the dihydroxylation of olefins using the methodology of Sharpless.[22] In this process an alkene is reacted with osmium tetroxide in the presence of the chiral quinine ligands $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL (Figure 28).

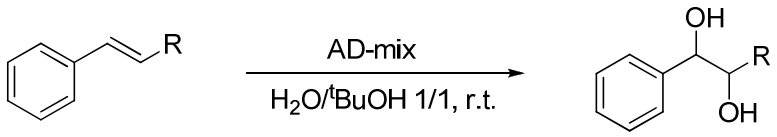


$(DHQ)_2$-PHAL (AD-mix-α) $(DHQD)_2$-PHAL (AD-mix-β)

***Figure 28*:** Ligands for the asymmetric dihydroxylation using AD-mixes.

The investigations took place with styrene and trans-stilbene as substrates; the results are listed in Table 29. For all reaction the commercially available AD-mixes were used, which contain 0.14% of the osmium source and 0.32% of the chiral ligand. The osmium tetroxide is regenerated during the reaction by a 1/1 mixture of potassium carbonate and potassium ferricyanide.

***Table 29*:** Results of the Sharpless asymmetric dihydroxylation.[a]



221: R=H
222: R=Ph

223: R=H
224: R=Ph

Entry	R	AD-mix	Yield (%)[b]	ee (%)[c]	ν_{rel}
1	H	α	27	+ 95	-
2	H	β	43	- 93	-
3	Ph	α	47	> - 99.9	-
4	Ph	β	54	> + 99.9	-
5[d]	H	α+β	28	+ 9	1.2
6[d]	Ph	α+β	52	+ 6	1.1

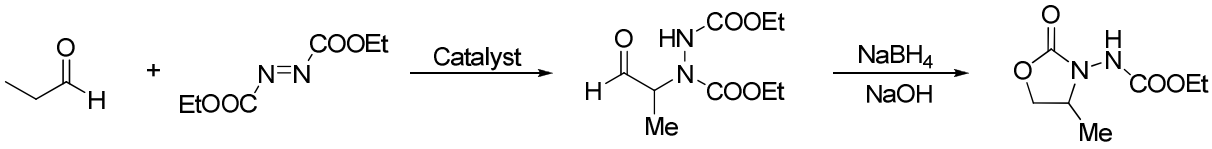
[a] Reagents and conditions: 1.0 mmol alkene, 3.0 mmol AD-mix (α, β, α+β), 20°C, 48h, solvent: 1 mL H_2O, 1 mL ^tBuOH. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Average of two runs.

The products were obtained with low to moderate yield after 48h, especially the styrene showed only low reactivity (27-43 % yield). The obtained selectivities using only one AD-mix are very good for styrene; the reaction of trans-stilbene gave a product that was enantiomerically pure. In the ligand comparison the intended results

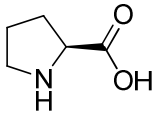
are obtained, the two AD-mixes can be regarded as equally fast, which is not surprising, since the chiral ligands are pseudo-enantiomers of one another.

To further explore the generality of the given method organocatalytic methods should be applied, the latter reactions were carried out by C. Padié. The reaction between propanal **225** and diethyl azodicarboxylate **226** was chosen as model reaction, which represents an electrophilic α-amination of carbonyl compounds. After the first direct, enantioselective α-amination of 2-keto esters by Jørgensen et al., [23] using copper(II)-bis(oxazolines), several organocatalytic approaches have been made successfully.[24] Especially proline and proline derived catalysts were able to perform this kind of transformation with high yield and selectivity. Hence, (*L*)-proline **229** and the Jørgensen-Hayashi catalyst **230** were used for the studies.

***Table 30*:** Results of the organocatalytic experiments.[a]

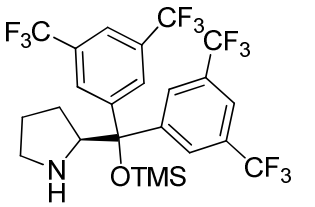


225 **226** **227** **228**



(*L*)-proline

229



Jørgensen-Hayashi catalyst

230

Entry	Catalyst	mol%	Yield (%)[b]	ee (%)[c]	ν_{rel}
1	proline	5	43	- 98	-
2	Jørgensen	5	48	+ 79	-
3[d]	proline + Jørgensen	5 + 5	45	+ 59	7.9
4[d]	proline + Jørgensen	2.5 + 2.5	67	+ 60	8.1

[a] Reagents and conditions: 1.5 mmol propanal, 1.0 mmol diethyl azodicarboxylate, addition of 1.3 mmol $NaBH_4$ after disappearance of the yellow color of the azodicarboxylate, 20℃, solvent: 2.5 mL DCM. [b] Isolated yield. [c] Determined by chiral GC. [d] Average of two runs.

A problem that occurs when the reaction is performed is that the enantiomeric excess of the product formed by the direct α-amination decreases slowly because of the acidity of the α-position. To circumvent this problem the compound **227** was in situ reduced by sodium borohydride, leading to the oxazolidinone **228** after basic treatment. It might be intuitive expectation that ligands within the same enantiomeric series coin the chiral information in the target molecule alike. However, the two utilized catalysts give rise to different enantiomers although they have the same stereochemistry. All reaction suffer from moderate yields, nevertheless, with proline very high enantioselectivities were obtained (entry 1). The Jørgensen-Hayashi catalyst paled in the comparison of selectivity and gave only 79% ee (entry 2). However, the mixture of catalysts **229** and **230** furnished the (*S*)-configured aminated product **228** with a conglomerated enantioselectivity of 59% and 60% respectively (entry 3 and 4). Therefore it appears that **230** is an eightfold faster promoter of that reaction. The reason for this big discrepancy in activity can be seen in the kinetic measurements carried out by UV-spectroscopy (Figure 29). Whereas the Jørgensen-Hayashi catalyst is active right in the beginning the (*L*)-proline shows an induction period in which only very low conversions are observable.

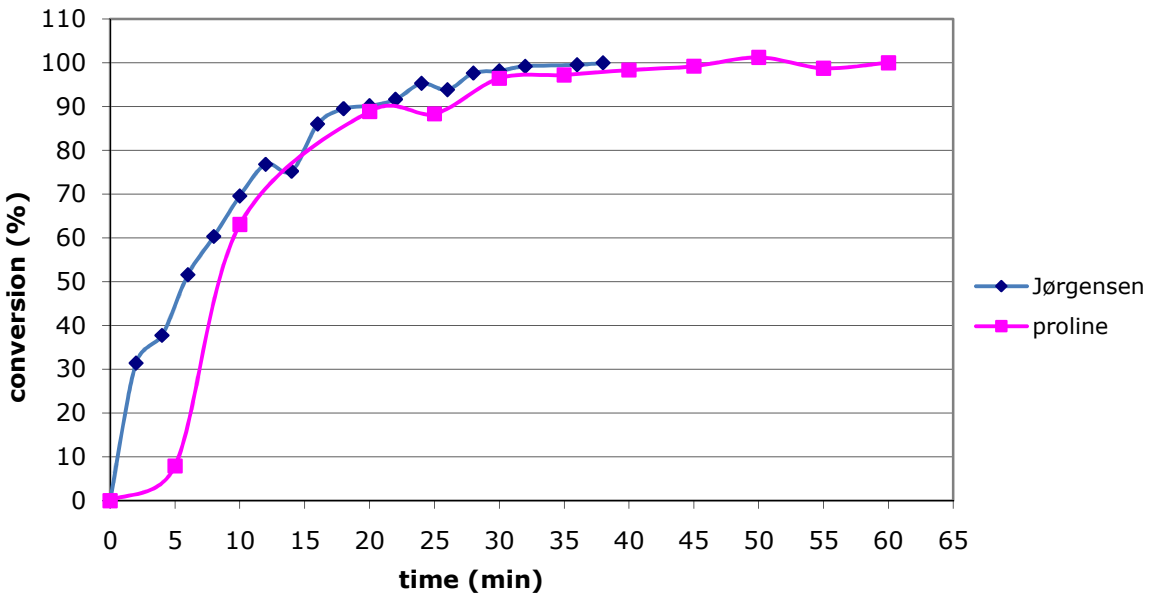
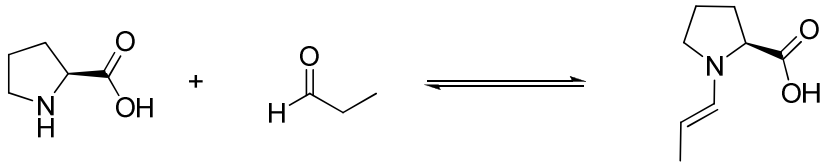


***Figure 29*:** Kinetic measurements of the α-amination reaction of propanal and diethyl azodicarboxylate.

This induction period can probably be ascribed to the relatively slow formation of the enamine **231** with the aldehyde, due to the low solubility of the catalyst.



229 **225** **231**

***Scheme 56*:** Formation of the enamin intermediate.

After approximately 5 min the activity is increased rapidly, but almost 50% of the starting material is already converted by catalyst **230**. This case clearly demonstrates that the present method only represents the determination of the situation at the end point of the reaction, a variation of catalyst activity during the process, caused by induction periods or maybe decomposition of a catalyst, cannot be determined.

In conclusion, a new methodology for the simple and rapid assessment of relative reaction rates has been established. The determination of enantiomeric excesses is sufficient for the evaluation of catalyst activities and no time consuming and tedious kinetics have to be measured. Furthermore, no special lab equipment besides normal HPLC and GC techniques is needed. Nevertheless, it has to be pointed out clearly, that the present method illustrates only the situation at the end point of the reaction and effects like induction periods cannot be determined.

The applicability of the new approach was shown in different reactions, i.e. Michael-addition, cyclopropanation, dihydroxylation and α-amination. Moreover, the scope of catalysts is not constricted to organometallic compounds only; in principle every catalyst is applicable, which was shown to some extent by the use of organocatalysts.

Besides the determination of reaction rates deeper insight into the formation and arrangement of ligand/metal complexes was gained. This can be of big relevance for further investigations and helpful for the design of new catalytic processes.

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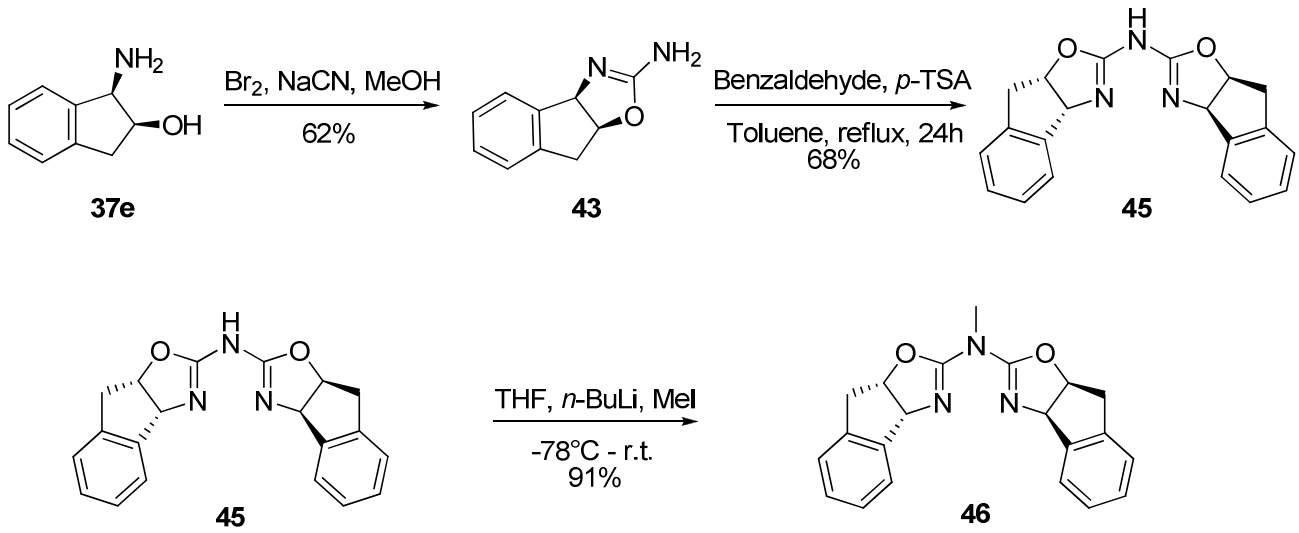
C. Summary

1. Ligand Synthesis

Chiral bis(oxazolines) represent one of the most useful ligand classes, due to their simple synthesis, starting from amino alcohols, and their ability of coordinating a large number of metals. The in our group developed azabis(oxazolines) show a close structural relation and could also prove their usefulness in a series of different transformations.[1] One aim of this work was to synthesize new azabis(oxazoline) ligands. Therefore the commercially available amino alcohol **37e** was chosen as starting point. In a short and straightforward synthesis, applying the protocol of Glos,[1] the new ligands **45** and **46** could be obtained in acceptable yield (Scheme 57).



37e **43** **45** **45** **46**

***Scheme 57*:** Synthesis of the new ligands **45** and **46**.

The catalytic activity of the new ligands was shown in the asymmetric Henry-reaction, but up to now no adequate, new transformation was found.

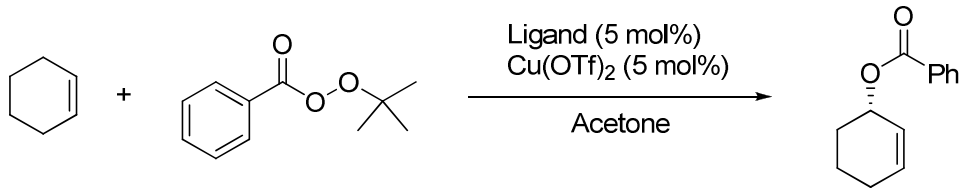
2. Catalysis

2.1 Kharasch-Sosnovsky-reaction

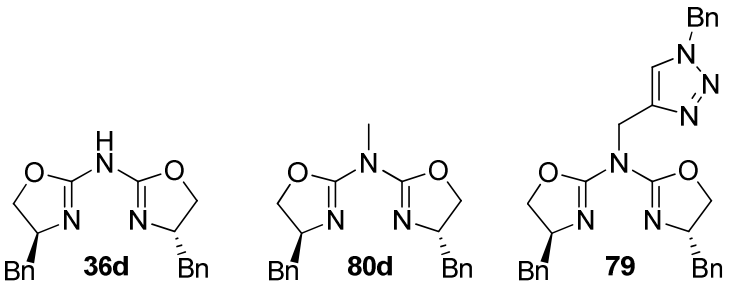
The main focus of this work was pointed towards the evaluation and optimization of catalytic processes. Therefore different reactions were investigated, starting with the Kharasch-Sosnovsky reaction. The allylic oxidation was fulfilled in acceptable

chemical yields and good enantioselectivities comparable to those known in literature (Table 31).

***Table 31*:** Selected results of the Kharasch-Sosnovsky-reaction.



81 **82** **83**



Entry	Ligand	Time	Temp.	$PhNHNH_2$	Yield (%)[b]	$[\alpha]_D^{20}$	ee (%)[c]
1[d]	**36d**	2 h	r.t.	yes	74	-168.0	75
2[d]	**36d**	16 h	0℃	yes	68	-161.1	74
3[d]	**79**	16 h	0℃	yes	74	-173.0	78
4	**80d**	16 h	r.t.	yes	54	-174.0	78

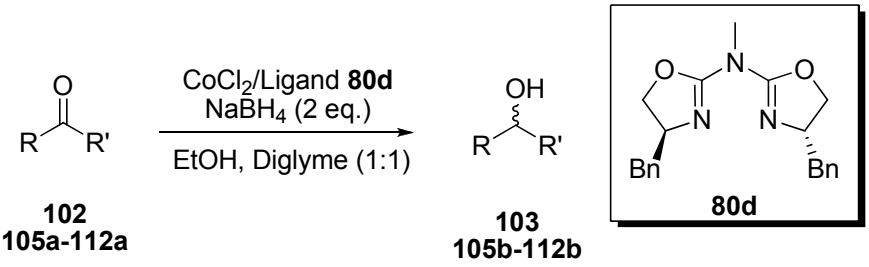
[a] Reagents and conditions: 10 mmol cyclohexene, 1 mmol *t*-butyl perbenzoate, 1 drop of phenyl hydrazine, 5 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Results of the diploma thesis.[2]

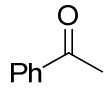
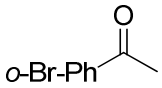
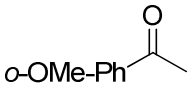
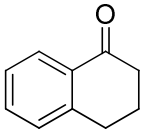
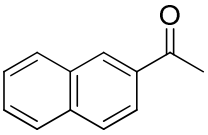
A remarkable fact is the relative short reaction time compared to literature values, indicating a reactive catalytic system. Unfortunately, the scope of substrates is restricted to olefins bearing no electron withdrawing groups. For that reason the applicability of the process is diminished.

2.2 Co(II)-AzaBOX catalyzed asymmetric reductions

On the basis of the results of C. Geiger[1j,3] investigations were carried out for the asymmetric reduction of carbonyl compounds using Co(II)-AzaBOX complexes in combination with $NaBH_4$. Nevertheless, these processes suffered from low yields and low ees (Table 32).

***Table 32*:** Selected results of the asymmetric reduction of carbonyl compounds.



Entry	Ketone		Temp. (°C)	Yield (%) [b]	ee (%)[c]	Conformation[d]
1		**102**	0	79	48	(*R*)
2		**106a**[e]	0	20	48	(*R*)
3		**107a**	0	66	52	(*R*)
4		**109a**	0	40	56	(*R*)
5		**110a**	rt	73	45	(*R*)

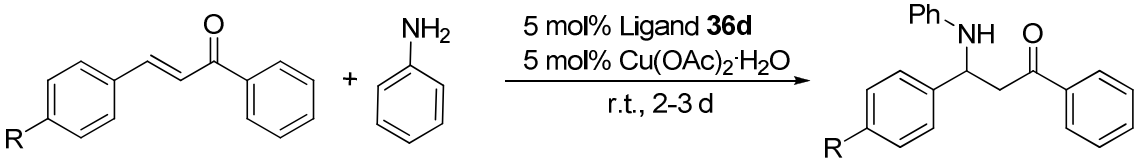
[a] Reagents and conditions: 0.5 mmol substrate, 1.0 mmol $NaBH_4$, 5 mol% ligand, 5 mol% $CoCl_2 \bullet 6H_2O$, 1 mL EtOH, 1 mL diglyme. [b] Isolated yield. [c] Determined by chiral GC or chiral HPLC. [d] The configuration was deduced by comparison of the optical rotation with literature values. [e] A partial dehalogenation occurred.

As the results obtained were not comparable to literature values[4] the efforts for this project were ceased.

2.3 Asymmetric aza-Michael reaction

Another process that was investigated during the course of this work was the asymmetric aza-Michael reaction between chalcones and anilines. The reaction of these simple substrates is, to the best of the author's knowledge, rather unexplored so far.[5] Some of the results are depicted in Table 33.

***Table 33*:** Selected results of the asymmetric aza-Michael addition.



132a: R=H
132f: R=CF_3

136

137a: R=H
137f: R=CF_3

Entry	R	Product	Solvent	Yield (%)[b]	ee (%)[c]
1	Ph (**132a**)	**137a**	Toluene	52	70
2	Ph (**132a**)	**137a**	CH_2Cl_2	19	73
3	CF_3 (**132f**)	**137f**	Toluene	49	55

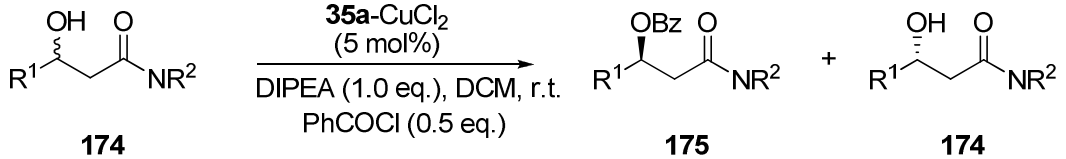
[a] Reagents and conditions: 0.5 mmol chalcone, 1.0 mmol aniline, 5 mol% ligand, 5 mol% $Cu(OAc)_2 \bullet H_2O$, 1 mL solvent, r.t. [b] Isolated yield. [c] Determined by chiral HPLC.

The results achieved for the product **137a** represent the highest enantioselectivities reported in literature, although the approach is facing the problem of low reactivity and the therefore obtained low to moderate chemical yields. Furthermore, only ligand **36d** was able to induce good selectivities, probably through an optimal π–π-interaction of substrate and catalyst.

2.4 Kinetic resolution of β-hydroxy amides

The kinetic resolution of alcohols represents one of the most prominent ways for gaining chiral products. Since this methodology was already applied successful using azabis(oxazolines),[1e,f,i,6] further studies were undertaken to broaden the scope of substrates. Therefore β-hydroxy amides were subjected to the asymmetric Cu(II)-catalyzed benzoylation.

***Table 34*:** Selected results of the kinetic resolution of β-hydroxy amides.



174
176a-h

175
177a-h

174
176a-h

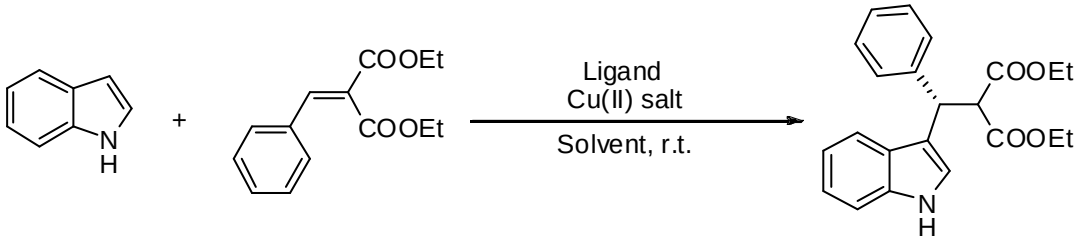
Entry	Substrate	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]
1	**174**	Ph	Me	**175**	48	83
2	**176a**	Ph	^{i}Pr	**177a**	49	78
3	**176c**	Ph	-$(CH_2)_5$-	**177c**	42	70
4	**176d**	*p*-OMe-Ph	Me	**177d**	39	73
5	**176e**	*p*-Cl-Ph	Me	**177e**	40	75
6	**176g**	cyclohexyl	Me	**177g**	38	72[d]
7	**176h**	^{n}Pr	Me	**177h**	47	73[d]

[a] Reaction conditions: Substrate (0.5 mmol), ligand-Cu-complex (5 mol%), base (0.5 mmol), benzoylchloride (0.25 mmol) in 3 mL of solvent at r.t. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by chiral GC after cleavage of the Bz-group.

It was shown for a variety of different substrates that azabis(oxazolines) are able to perform the kinetic resolution of β-hydroxy amides in good to excellent yields and with good ees.

3. Assessment of relative reaction rates

Besides the classical catalytic investigations a new approach for the assessment of catalyst activities was made. This method mainly focused on the well explored Michael-addition of benzylidene malonates to indoles (Scheme 58).[1k,7]



196 **197** **198**

***Scheme 58*:** Michael-addition of benzylidene malonate to indole.

In this approach only the enantioselectivity derived from the catalytic experiment was used for the deduction of relative reaction rates. For the calculation of the reaction rates the following formula was developed:

$$v_{rel} = \frac{ee_2 + ee_r}{ee_1 - ee_r}$$

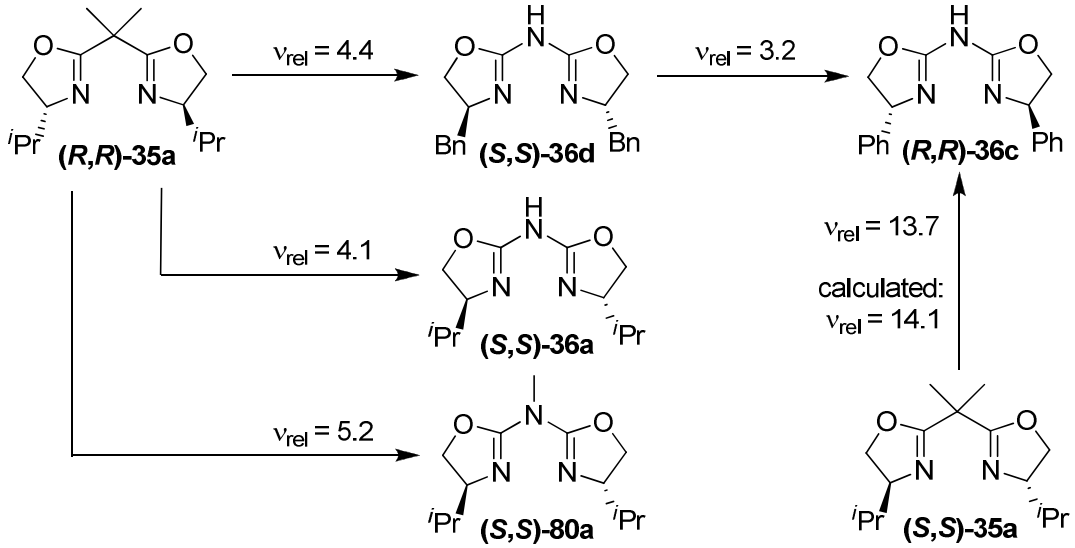
ν_{rel} = relative reaction rate

ee_1 = enantioselectivity of ligand 1

ee_2 = enantioselectivity of ligand 2

ee_r = resulting enantioselectivity using both ligands

According to this formula the relative reaction rates of different ligands were determined in competitive reactions using two different ligands at the same time. The results of the ligand comparison experiments are depicted in Scheme 59.



***Scheme 59*:** Schematic representation of the rate ratios of bis(oxazoline)- and different azabis(oxazoline)-ligands; arrows point towards the less active ligand.

It was shown that the results are reproducible, when a 1/1 mixture of ligands was used. Applying unequal amounts of ligands lead to unexpected results, which could be rationalized by the formation of different amounts of catalytic active species, due to the generation of inactive 2/1 ligand/Cu complexes.

Furthermore it was shown, that the method is applicable for different transformations, like cyclopropanations or dihydroxylations, and catalytic systems, e.g. organo-catalysts.

In summary, a novel methodology has been established for the rapid and simple determination of relative rate ratios of catalysts.

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3 C. Geiger, Dissertation **2006**, Universität Regensburg.

4 T. Nagata, K. Yorozu, T. Yamada, T. Mukaiyama, *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2145.

5 A. Scettri, A. Massa, L. Palombi, R. Villano, M. R. Acocella; *Tetrahedron: Asym*. **2008**, *19*, 2149.

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7 A. Schaetz, R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Chem. Eur. J*. **2008**, *14*, 7259.

D. Experimental

1. General comments:

All reactions were carried out in oven dried glassware under atmospheric conditions unless utherwise stated.Commercially available chemicals were used as received, without any further purification.

The following solvents and reagents were purified prior to use:

Dichloromethane (CH_2Cl_2) was distilled from calciumhydride. Ethanol (EtOH) and methanol (MeOH) were distilled from magnesium and stored over molecular sieves (3 Å). Tetrahydrofurane (THF) was distilled from sodium wire. Toluene and Xylene were dried with CaH_2, distilled and stored over sodium wire. Ethylacetate (EE) and hexanes (PE) for chromatographic separations were distilled prior to use.

Benzaldehyde, benzoylchloride, cyclohexene, styrene, trans-stilbene and N,N-diisopropylethylamine (DIPEA) were distilled prior to use.

Analytical thin layer chromatography was performed on Merck TLC aluminium sheets silica gel 60 F 254. Visualization was accomplished with UV light (254 nm) and vaniline solution followed by heating. Liquid chromatography was performed using Merck silica gel 60 (70-230 mesh ASTM).

^{1}H- and ^{13}C-NMR:

NMR-spectra were recorded on a FT-NMR-spectrometer of the type Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) at ambient temperature. Data are as follows: Chemical shift in ppm from internal $CHCl_3$ (7.26 ppm) as standard on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, dd = doublet of doublet and m = multiplet), integration and coupling constant (Hz). ^{13}C chemical shifts are reported in ppm from internal $CHCl_3$ (77 ppm) as standard on the δ scale. The ^{13}C signals were assigned with the help of DEPT 90 and DEPT 135 techniques.

Melting points:

The melting points were measured on a Büchi SMP-20 apparatus in a silicon oil bath or on a SRS MPA 100 OptiMelt. Values thus obtained were not corrected.

Mass spectrometry:

Mass spectrometry was performed using a Varian MAT 311A, Finnigan MAT 95 or Thermoquest Finnigan TSQ 7000 at the Central Analytical Laboratory (Universität Regensburg).

IR spectroscopy:

ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System.

Optical rotation:

The optical rotation was determined in a Perkin Elmer 241 polarimeter at 589 nm wavelength (sodium-d-line) in a 1.0 dm measuring cell of ca. 2 mL volume.

HPLC:

High performance liquid chromatography was carried out using a HPLC 335 detector on a 325 system by Kontron Instruments or a Varian 920-LC with DAD.
Chiralcel OD-H, OJ and AS respectively served as chiral stationary phase.

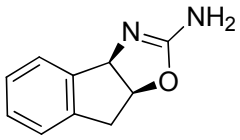
GC:

Gas chromatography was performed on a Fisons GC 8000.
CP-Chirasil-Dex CB (25m x 0.25mm D_i, 0.25µm Film) was used as chiral stationary phase.

2. Synthesis of literature-known compounds:

The following compounds were prepared according to literature synthesis: (S)-4-isopropyl-4,5-dihydrooxazol-2-amine (**38a**),[1] (R)-4-phenyl-4,5-dihydrooxazol-2-amine (*ent*-**38c**),[1] (S)-4-benzyl-4,5-dihydrooxazol-2-amine (**38d**),[2] (S)-4-isopropyloxazolidin-2-one (**42a**),[1] (R)-4-phenyloxazolidin-2-one (*ent*-**42c**),[1] (S)-4-benzyloxazolidin-2-one (**42d**),[2] (S)-2-ethoxy-4-isopropyl-4,5-dihydrooxazole (**39a**),[1] (R)-2-ethoxy-4-phenyl-4,5-dihydrooxazole (*ent*-**39c**),[1] (S)-4-benzyl-2-ethoxy-4,5-dihydrooxazole (**39d**),[2] (S)-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)amine (**36a**),[1] (R)-bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)amine (*ent*-**36c**),[1] (S)-bis((S)-4-benzyl-4,5-dihydrooxazol-2-yl)amine (**36d**),[2] (S)-4-isopropyl-N-((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-N-methyl-4,5-dihydrooxazol-2-amine (**80a**),[1] (R)-N-methyl-4-phenyl-N-((R)-4-phenyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-amine (*ent*-**80c**),[1] (S)-4-benzyl-N-((S)-4-benzyl-4,5-dihydrooxazol-2-yl)-N-methyl-4,5-dihydro-oxazol-2-amine (**80d**),[2] 4-(3-bromopropoxy)benzaldehyde (**61**),[3] (E)-4-methoxy-N-(1-phenylethylidene)aniline (**116**),[4] ethyl 3-hydroxy-3-phenylpropanoate (**169**),[5] 2-acetoxyacetic acid (**186**),[6] 2-chloro-2-oxoethyl acetate (**187**),[6] (E)-N-benzylidene-aniline (**188**),[7] diethyl 2-benzylidenemalonate (**197**),[8] diethyl 2-(4-methyl-benzylidene)malonate (**203**),[8] diethyl 2-(4-chlorobenzylidene)malonate (**204**),[8] diethyl 2-(4-methoxybenzylidene)malonate (**212**),[8]

3. Ligand synthesis:

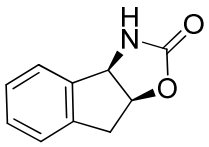


(3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-amine (43):

10 mL of MeOH were cooled to 0℃, bromine (190 µL, 3.69 mmol, 1.1 eq.) was added and NaCN (181 mg, 3.69 mmol, 1.1 eq.) was added in small portions. Afterwards the amino indanol **37e** (500 mg, 3.35 mmol, 1.0 eq.) was added as a solution in 10 mL of MeOH. The mixture was stirred for 30 min at 0℃ and 30 min at r.t., before an aqueous NH_3-solution (25 %) was added under ice cooling. The mixture was stirred again for 30 min and subsequently the MeOH was evaporated.

The residue was cooled to 0°C and NaOH (20 % in water) was added. After extraction with DCM the organic layer was dried over $MgSO_4$ and the solvent was removed. The crude product was recristallized from DCM/hexanes or toluene to yield 240 mg (62%) as a white solid.

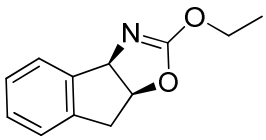
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.23 (dd, *J* = 1.3, 17.7 Hz, 1H), 3.37 (dd, *J* = 6.3, 17.8 Hz, 1H), 4,51 (bs, 2H), 5.27-5.35 (m, 1H), 5.41 (d, *J* = 7.4 Hz, 1H), 7.18-7.25 (m, 3H), 7.32-7.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 143.1, 139.4, 128.3, 127.5, 125.2, 84.0, 74.6, 39.2; IR: 3448, 3015, 1676, 1410, 1312, 1172, 1023, 945, 750, 716, 686 [cm^{-1}]; MS (EI-MS, 70 eV): m/z (%) = 174 (47), 131 (34), 130 (100), 104 (22), 103 (24), 77 (24), 44 (26); HRMS (PI-EIMS, m/z) [$M^{+\bullet}$]: calc.: 174.0793, found: 174.0793; mp: 148-153°C (decomposition).



(3aR,8aS)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one (42e):

77 mg sodium (3.35 mmol, 1.0 eq.) were dissolved in EtOH (15 mL), amino indanol **37e** and diethyl carbonate were added and the mixture stirred at r.t. for 1 h and refluxed for 3-4 h. After that the solvent was removed, the residue was taken up in DCM and sat. NH_4Cl-solution and the layers were separated. The aqueous layer was extracted 3x with DCM, the combined org. layers were dried over $MgSO_4$ and the solvent was evaporated, to obtain 571 mg (97%) as a pale brown solid.

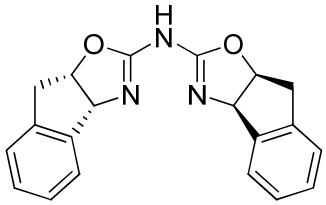
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.33 (dd, *J* = 2.2, 17.8 Hz, 1H), 3.42 (dd, *J* = 6.2, 17.8 Hz, 1H), 5.18 (d, *J* = 7.4 Hz, 1H), 5.38-5.47 (m, 1H), 6.34 (bs, 1H), 7.21-7.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 140.3, 139.8, 129.4, 127.9, 125.6, 124.8, 80.6, 61.2, 38.9; IR: 3240, 3142, 2923, 2841, 1744, 1700, 1392, 1233, 1204, 1107, 1050, 960, 749, 681, 601, 435 [cm^{-1}]; MS (EI-MS, 70 eV): m/z (%) = 175 ($M^{+\bullet}$, 100), 147 (17), 146 (25), 132 (35), 131 (93), 130 (79), 118 (19), 104 (87), 103 (45), 89 (17), 78 (30), 77 (43), 65 (33), 63 (17), 51 (27); HRMS (PI-EIMS, m/z) [$M^{+\bullet}$]: calc.: 175.0633, found: 175.0636.



(3aR,8aS)-2-ethoxy-8,8a-dihydro-3aH-indeno[1,2-d]oxazole (44):

The oxazolidinone **42e** (434 mg, 2.48 mmol, 1.0 eq.) was dissolved in 30-40 mL of DCM, cooled to 0℃ and a solution of Et_3OBF_4 (566 mg, 2.98 mmol, 1.2 eq.) in 5 mL of DCM was added dropwise. The mixture was stirred at r.t. overnight. Afterwards it was quenched with sat. Na_2CO_3-solution, the layers were separated and the aqueous layer was extracted twice with DCM. The combined org. layers were dried over $MgSO_4$ and the solvent was removed to gain 466 mg (92 %) as a pale brown solid.

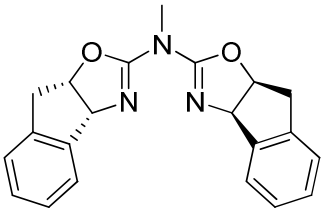
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3H), 3.30 (dd, *J* = 1.6, 17.8 Hz, 1H), 3.41 (dd, *J* = 6.3, 18.1 Hz, 1H), 4.13-4.31 (m, 2H), 5.37-5.43 (m, 1H), 5.46 (d, *J* = 7.4 Hz, 1H), 7.23-7.34 (m, 3H), 7.43-7.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 142.7, 139.6, 128.3, 127.5, 125.8, 125.5, 83.8, 73.6, 66.7, 39.2, 14.3; IR: 3044, 2985, 2948, 2902, 1650, 1381, 1349, 1293, 1242, 1006, 832, 750, 730 [cm^{-1}]; MS (EI-MS, 70 eV): m/z (%) = 203 ($M^{+\bullet}$, 30), 175 (100), 146 (83), 130 (73), 116 (37), 103 (31), 77 (23); HRMS (PI-EIMS, m/z) [$M^{+\bullet}$]: calc.: 203.0946, found: 203.0941.



(3aR,8aS)-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)amine (45):

Aminooxazoline **43** (500 mg, 2.87 mmol, 1.0 eq.), benzaldehyde (305 mg, 290 µL, 2.87 mmol, 1.0 eq.) and *p*-TSA (30 mg, 0.15 mmol, 5 mol%) were dissolved in toluene (50 mL) and the mixture was refluxed overnight, using a Dean-Stark apparatus. After that the mixture was stored for 2 days r.t. upon which the product precipitated. The solid was filtered off and dried in vacuum to obtain 222 mg (47 %) as a white solid. The filtrate was evaporated and the residue was purified by column chromatography (hexanes/EE: 25/75 followed by EE) to obtain 100 mg (21 %) of product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28-3.46 (m, 4H), 5.28-5.36 (m, 2H), 5.42 (d, *J* = 7.7 Hz, 2H), 7.22-7.33 (m, 6H), 7.41-7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =165.5, 141.5, 140.0, 128.9, 127.6, 125.5, 125.0, 81.6, 69.0, 39.2; IR: 2938, 2838, 1632, 1611, 1579, 1382, 1202, 1098, 1072, 1027, 748, 725, 679 [cm^{-1}]; MS (EI-MS, 70 eV): m/z (%) = 331 ($M^{+\bullet}$, 100), 302 (59), 201 (11), 158 (14), 131 (39), 115 (64), 104 (40), 44 (17); HRMS (PI-EIMS, m/z) [$M^{+\bullet}$]: calc.: 331.1321, found: 331.1320; $[\alpha]_D^{25}$ = + 445.5 (20.2 mg/2 mL $CHCl_3$); mp: 190-194℃ (decomposition).

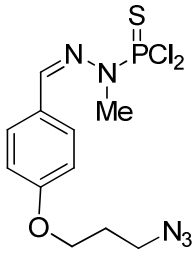


(3aR,8aS)-N-((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-N-methyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-amine (46):

Azabis(oxazoline) **45** (222 mg, 0.67 mmol, 1.0 eq.) was dissolved in THF (60 mL), cooled to -78℃ and *n*-BuLi (444 µL of a 1.6 M solution in hexane, 0.74 mmol 1.1 eq.) was added dropwise. The mixture was stirred for 5 min at this temperature and then MeI (208 µL, 3.35 mmol, 5.0 eq.) was added. Subsequently, the cooling was removed and the reaction mixture was stirred overnight at r.t. After that it was quenched with sat. $NaHCO_3$-solution and H_2O, the THF was removed in vacuum and the residue was extracted with DCM (3x). The org. layer was dried over $MgSO_4$ and the solvent was removed to obtain 211 mg (91 %) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 3H), 3.32 (dd, *J* = 1.9, 17.8 Hz, 2H), 3.41 (dd, *J* = 5.8, 18.1 Hz, 2H), 5.41-5.48 (m, 2H), 5.50 (d, *J* = 7.4 Hz, 2H), 7.20-7.28 (m, 6H), 7.44-7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 142.6, 139.5, 128.4, 127.5, 125.6, 125.2, 84.6, 74.2, 39.4, 37.1; IR: 3022, 2941, 2899, 1627, 1421, 1386, 1307, 1247, 1167, 1022, 1004, 970, 840, 753, 734, 695, 582, 441 [cm^{-1}]; MS (EI-MS, 70 eV): m/z (%) = 345 ($M^{+\bullet}$, 7), 189 (100), 188 (14), 157 (18), 132 (57), 115 (43), 103 (17); HRMS (PI-EIMS, m/z) [$M^{+\bullet}$]: calc.: 345.1477, found: 345.1474; mp: 190-195℃ (decomposition).

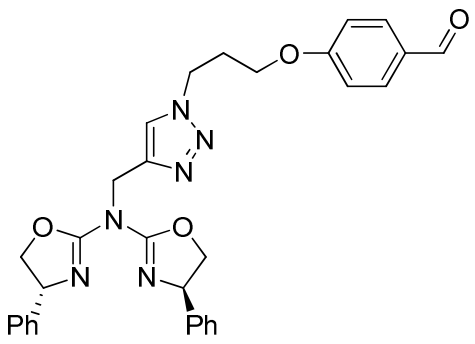
4. Dendron Synthesis:



(Z)-N'-(4-(3-azidopropoxy)benzylidene)-N-methylphosphorohydrazidothioic dichloride (69):

Aldehyde **62** (1.79 g, 8.7 mmol, 1.0 eq.) was dissolved in 2 mL of THF, cooled to 0℃ and a solution of hydrazine derivative **56** in $CHCl_3$ (40 mL, 0.24 mol/L, 9.6 mmol, 1.1 eq.) was added. 10 mL of THF were added to dissolve the built precipitate and the mixture was stirred overnight at r.t. Afterwards the solvent was removed partially (~ 7 mL remaining) and the solution was dropped into pentane. The precipitate was filtered off, redissolved in $CHCl_3$ and again dropped into pentane. The pentane was filtered off over a cannula and the product was dried in vacuum, to obtain 1.70 g (56 %) of a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (qt, *J* = 6.2 Hz, 2H), 3.50 (d, *J* = 14.5 Hz, 3H), 3.56 (t, *J* = 6.6 Hz, 2H), 4.11 (t, *J* = 5.9 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.67-7.73 (m, 3H); ^{31}P NMR (81 MHz, $CDCl_3$): δ = 63.4; IR: 2941, 2883, 2088, 1598, 1512, 1465, 1239, 1168, 1055, 950, 926, 833, 766, 695, 600, 490 [cm^{-1}].

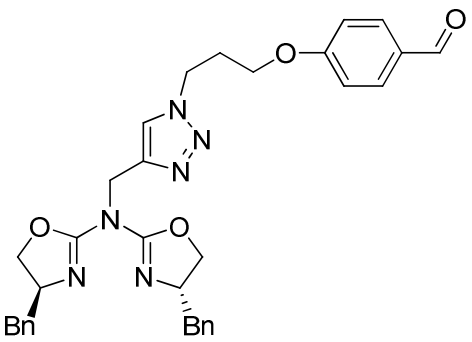


4-(3-(4-((bis((R)-4-phenyl-4,5-dihydrooxazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (*ent*-64b):

Propargylated azabis(oxazoline) *ent*-**63b** (484 mg, 1.4 mmol, 1.2 eq.) and azide **62** (240 mg, 1.2 mmol, 1.0 eq.) were dissolved in THF/TEA (20 mL, 4/1), the solution was degassed and CuI (23 mg, 0.12 mmol, 10 mol%) was added under Ar-

atmosphere. The mixture was stirred at r.t. for 16 h, afterwards the solvent was removed in vacuum, the residue was extracted several times with EDTA-solution (1% in H_2O) and the combined aqueous layers were re-extracted once with DCM. The combined org. layers were washed with sat. NH_4Cl-solution, dried over Na_2SO_4 and the solvent was removed. The crude product was furthermore dissolved in DCM and slowly dropped into hexane, whereupon the product precipitated. The solid was filtered and dried to get a pale brown solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (qt, *J* = 6.2 Hz, 2H), 3.98-4.12 (m, 2H), 4.28 (t, *J* = 7.8 Hz, 2H), 4.56 (t, *J* = 6.8 Hz, 2H), 4.83 (t, *J* = 9.0 Hz, 2H), 5.13-5.37 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.17-7.40 (m, 10 H), 7.70 (bs, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 9.89 (s, 1H).



4-(3-(4-((bis((S)-4-benzyl-4,5-dihydrooxazol-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (64a):

Propargylated azabis(oxazoline) **63a** (374 mg, 1.0 mmol, 1.2 eq.) and azide **62** (171 mg, 0.8 mmol, 1.0 eq.) were dissolved in THF/TEA (20 mL, 4/1), the solution was degassed and CuI (15 mg, 0.08 mmol, 10 mol%) was added under Ar-atmosphere. The mixture was stirred at r.t. for 16 h, afterwards the solvent was removed in vacuum, the residue was extracted several times with EDTA-solution (1% in H_2O) and the combined aqueous layers were re-extracted once with DCM. The combined org. layers were washed with sat. NH_4Cl-solution, dried over Na_2SO_4 and the solvent was removed. The crude product was furthermore dissolved in DCM and slowly dropped into hexane, whereupon the product precipitated. The solid was filtered and dried to get a pale brown solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (qt, *J* = 6.2 Hz, 2H), 2.61 (dd, *J* = 8.6, 13.7 Hz, 2H), 3.07 (dd, *J* = 4.2, 13.4 Hz, 2H), 4.04 (t, *J* = 5.7 Hz, 2H), 4.13 (t, *J* = 6.7 Hz, 2H),

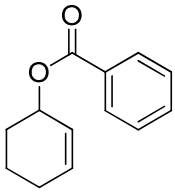
4.25-4.43, (m, 4H), 4.54 (t, *J* = 6.7 Hz, 2H), 5.10 (dd, *J* = 13.0, 15.5 Hz, 2H), 6.95, (d, *J* = 8.4 Hz, 2H), 7.10-7.33 (m, 10H), 7.55 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 9.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 41.9, 44.8, 46.8, 64.5, 65.5, 73.1, 114.7, 123.5, 126.5, 128.5, 129.2, 132.0, 137.8, 144.1, 157.2, 163.4, 190.7; IR: 3417, 3302, 3027, 2927, 2245, 1637, 1601, 1476, 1428, 1258, 1161, 911, 733, 703 [cm^{-1}]; MS (CI-MS): m/z (%) = 579 (100), 420 (26), 193 (20), 233 (11), 212 (19), 195 (31), 179 (16), 151 (8).

5. Catalysis:

5.1 Asymmetric Kharasch-Sosnovsky reaction:

General procedure (GP1) for the asymmetric Kharasch-Sosnovsky reaction:

$Cu(OTf)_2$ (18.1mg, 0.05mmol, 0.05 eq.) and ligand (0.05 mmol, 0.05 eq.) were dissolved in dry acetone (5 mL) and stirred for at least 1 h at r.t. Afterwards one drop of phenyl hydrazine was added, stirred again for 10 min and the alkene was added (10 mmol, 10 eq.). After 10 min the reaction was started by adding *t*-butyl perbenzoate (187 µL, 1.0 mmol, 1.0 eq.). After consumption of the oxidant (determined by TLC) the solvent was removed under reduced pressure and the residue was purified by column chromatography.

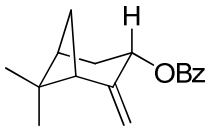


Cyclohex-2-enyl benzoate (83):

Prepared according to general procedure GP1. For the column chromatography hexanes/ethyl acetate 95/5 was used. The product was obtained as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62-2.22 (m, 6H), 5.48-5.55 (m, 1H), 5.80-5.88 (m, 1H), 7.38-7.46 (m, 2H), 7.50-7.58 (m, 1H), 8.02-8.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 132.9, 132.8, 130.8, 129.6, 128.3, 125.7, 68.6, 28.4, 25.0, 19.0; IR: 2942, 1712, 1269, 1111, 712, 632, 538, 499 [cm^{-1}]; MS (EI, 70 eV): m/z (%) = 202

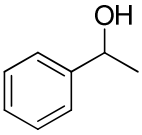
($M^{+\bullet}$, 13), 105 (100), 97 (14), 81 (33), 80 (23), 79 (44), 77 (55), 53 (10), 51 (25), 41 (16), 39 (15); HPLC analysis (Chiralcel OD-H, 0.1% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm): t_r (major) = 11.02 min, t_r (minor) = 11.93 min.



(1R,3S,5R)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl benzoate (93):
Prepared according to general procedure GP1. For the column chromatography hexanes/ethyl acetate 95/5 was used. The product was obtained as colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (s, 3H), 1.32 (s, 3H), 1.77 (d, *J* = 9.9 Hz, 1H), 1.90-2.10 (m, 2H), 2.42-2.55 (m, 2H), 2.59 (t, *J* = 5.5 Hz, 1H), 4.92 (bs, 1H), 5.15 (t, *J* = 1.2 Hz, 1H), 5.82 (d, *J* = 7.7 Hz, 1H), 7.39-7.48 (m, 2H), 7.51-7.59 (m, 1H), 8.01-8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 150.1, 132.8, 130.9, 129.6, 128.3, 114.5, 69.2, 50.8, 40.6, 39.6, 33.4, 28.0, 25.9, 22.0; IR: 2971, 2932, 1713, 1267, 1109, 711, 632, 537, 496 [cm^{-1}]; HPLC analysis (Chiralcel OJ, 1% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 8.16 min.

5.2 Asymmetric Co-catalyzed reduction:

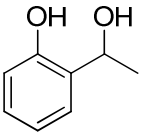
General procedure (GP2) for the asymmetric cobalt catalyzed reduction:
Ligand (5 mol%) and $CoCl_2$•$6H_2O$ (5 mol%) were dissolved in EtOH (1 mL) and stirred for 30 min at r.t. before diglyme (1 mL) or dioxane (1 mL) and carbonyl compound (0.5 mmol, 1.0 eq.) were added. After that the solution was cooled to 0℃ and $NaBH_4$ (47 mg, 1.25 mmol, 2.5 eq.) was added slowly. The mixture was stirred at r.t. until completion (monitored by TLC), quenched with H_2O and extracted with DCM (3x). The combined org. layers were washed once with H_2O, dried over $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography.



1-phenylethanol (103):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 80/20) to obtain the pure product as a colorless liquid.

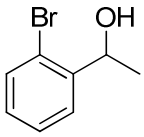
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.6 Hz, 3H), 1.88 (bs, 1H), 4.90 (q, *J* = 6.6 Hz, 1H), 7.24-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9, 128.5, 127.4, 125.5, 70.3, 25.2; IR: 3356, 2973, 1451, 1204, 1076, 898, 760, 700, 632, 535, 495, 422 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 110°C isothermal): t_r = 6.35 min, t_r = 6.96 min.



2-(1-hydroxyethyl)phenol (105b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 75/25) to obtain the pure product as a colorless liquid.

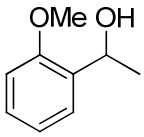
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 6.6 Hz, 3H), 2.59 (bs, 1H); 5.08 (q, *J* = 6.6 Hz, 1H), 6.80-6.91 (m, 2H), 6.96-7.02 (m, 1H), 7.13-7.21 (m, 1H), 7.96 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 129.5, 128.2, 126.3, 120.3, 117.2, 75.5, 22.3; IR: 3371, 2974, 2929, 1586, 1490, 1450, 1232, 1060, 751, 495 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 95°C isothermal, TMS-imidazole was added): t_r = 21.12 min, t_r = 21.69 min.



1-(2-bromophenyl)ethanol (106b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 75/25) to obtain the product as a colorless liquid (a partial dehalogenation was observed during the reaction).

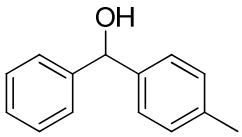
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.6 Hz, 3H), 2.13 (bs, 1H), 5.24 (q, *J* = 6.6 Hz, 1H), 7.08-7.17 (m, 1H), 7.30-7.40 (m, 1H), 7.48-7.54 (m, 1H), 7.56-7.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 132.7, 128.8, 127.9, 126.7, 69.2, 23.6; IR: 3404, 2974, 2925, 1441, 1200, 1090, 1024, 894, 756, 632, 541, 497 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 100℃ (12 min) to 140 ℃ (15℃/min)): t_r = 20.16 min, t_r = 22.78 min.



1-(2-methoxyphenyl)ethanol (107b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 75/25) to obtain the pure product as a colorless liquid.

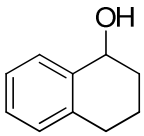
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.7 Hz, 3H), 2.65 (bs, 1H), 3.87 (s, 3H), 5.10 (q, *J* = 6.7 Hz, 1H), 6.86-6.91 (m, 1H), 6.93-7.00 (m, 1H), 7.21-7.29 (m, 1H), 7.32-7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 133.4, 128.3, 126.1, 120.8, 110.4, 66.6, 55.3, 22.8; IR: 3354, 2971, 2836, 1601, 1491, 1237, 1077, 1030, 754, 632, 540, 497 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 140℃ isothermal): t_r = 7.36 min, t_r = 7.86 min.



Phenyl(p-tolyl)methanol (108b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 80/20) to obtain the pure product as a colorless oil.

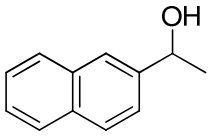
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (bs, 1H), 2.33 (s, 3H), 5.82 (d, *J* = 3.3Hz, 1H), 7.12-7.18 (m, 2H), 7.22-7.42 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 141.0, 137.3, 129.2, 128.5, 127.5, 126.6, 76.1, 21.1; IR: 1656, 1606, 1447, 1317, 1278, 1177, 732, 700, 632, 543, 494.



1,2,3,4-tetrahydronaphthalen-1-ol (109b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 75/25) to obtain the pure product as a colorless liquid.

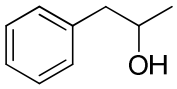
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70-2.08 (m, 4H), 2.59-2.90 (m, 2H), 4.78 (t, *J* = 4.7 Hz, 1H), 7.07-7.14 (m, 1H), 7.15-7.33 (m, 2H), 7.40-7.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 137.1, 129.0, 128.7, 127.6, 126.2, 68.1, 32.3, 29.3, 18.9; IR: 3351, 2932, 2865, 1743, 1665, 1489, 1454, 1065, 1037, 1001, 962, 773, 737, 615 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 120℃ isothermal): t_r = 18.24 min, t_r = 18.96 min.



1-(naphthalen-2-yl)ethanol (110b):

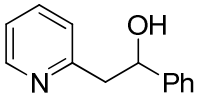
Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 90/10) to obtain the pure product as colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 6.6 Hz, 3H), 1.96 (d, *J* = 2.6 Hz, 1H), 5.07 (dq, *J* = 2.5, 6.6 Hz, 1H), 7.42-7.55 (m, 3H), 7.79-7.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.2, 133.3, 132.9, 128.3, 128.0, 127.7, 126.2, 125.8, 123.8, 70.6, 25.2; IR: 3256, 2973, 1600, 1507, 1365, 1275, 1124, 1074, 900, 860, 822, 742, 483 [cm^{-1}]; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 24.02 min, t_r = 25.73 min.



1-phenylpropan-2-ol (111b):

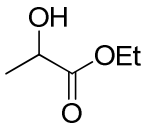
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.0 Hz, 3H), 2.70 (dd, *J* = 8.0, 13.4 Hz, 1H), 2.80 (dd, *J* = 4.9, 13.4 Hz, 1H), 3.95-4.10 (m, 1H), 7.15-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 129.4, 129.2, 128.6, 126.5, 68.9, 45.8, 22.8; IR: 3404, 2970, 2925, 1661, 1453, 1079, 940, 742, 699, 503 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 100℃ isothermal): t_r = 11.43 min, t_r = 11.87 min.



1-phenyl-2-(pyridin-2-yl)ethanol (112b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 80/20) to obtain the pure product as a pale brown solid.

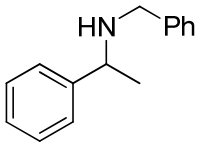
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97-3.21 (m, 2H), 5.17 (dd, *J* = 4.4, 7.7 Hz, 1H), 5.72 (bs, 1H), 7.08-7.14 (m, 1H), 7.15-7.22 (m, 1H), 7.23-7.30 (m, 1H), 7.31-7.39 (m, 2H), 7.40-7.47 (m, 2H), 7.58-7.66 (m, 1H), 8.51-8.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 148.6, 144.1, 136.9, 128.3, 127.3, 125.9, 123.8, 121.8, 73.4, 45.7; IR: 3183, 3063, 2936, 1594, 1568, 1439, 1306, 1048, 756, 694, 540 [cm^{-1}]; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r (major) = 21.36 min, t_r (minor) = 33.19 min.



ethyl 2-hydroxypropanoate (113b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 50/50) to obtain the pure product as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3H), 2.36 (d, *J* = 6.9 Hz, 3H), 3.10 (bs, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 66.7, 61.5, 20.3, 14.1; IR: 3466, 2985, 1732, 1211, 1128, 632, 536, 498 [cm^{-1}]; GC analysis (CP-Chirasil-Dex CB, 60℃ isothermal): t_r = 8.63 min, t_r = 9.95 min.



N-benzyl-1-phenylethanamine (114b):

Prepared according to the general procedure GP1 and purified by column chromatography (performed with hexanes/ethyl acetate 90/10 followed by 80/20) to obtain the pure product as a pale yellow liquid.

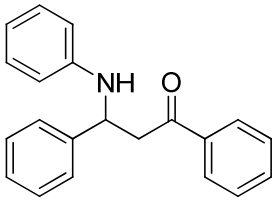
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.6 Hz, 3H), 1.61 (bs, 1H), 3.63 (dd, *J* = 13.2, 21.0 Hz, 2H), 3.82 (q, *J* = 6.6 Hz, 1H), 7.20-7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6, 140.7, 128.5, 128.4, 128.2, 127.0, 126.9, 126.7, 57.5, 51.7, 24.5; IR: 3027, 2962, 1493, 1452, 1128, 700, 632, 535, 501 [cm^{-1}]; HPLC analysis (Chiralcel OD-H, *n*-heptane, 0.5 mL/min, 254 nm): t_r = 20.41 min, t_r = 24.23 min.

5.3 Asymmetric aza-Michael addition:

General procedure (GP3) for the asymmetric aza-Michael addition:

Azabis(oxazoline) (5 mol%) and $Cu(OAc)_2$•H_2O (5 mol%) were dissolved in toluene (2 mL) and stirred for at least 1 h at r.t. After that the chalcone (0.5 mmol, 1.0 eq.) and aniline (1.0 mmol, 2.0 eq.) were added and the reaction mixture was stirred at r.t.

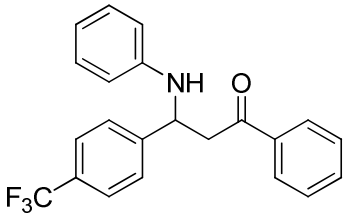
for 1-3 d. Afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography.



1,3-diphenyl-3-(phenylamino)propan-1-one (137a):

According to general procedure GP3 104 mg of chalcone and 91 µL of aniline were reacted to obtain the product as a white solid. The column chromatography was performed using hexanes/ethyl acetate 95/5 followed by 90/10.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (dd, *J* = 7.7, 16.2 Hz, 1H), 3.52 (dd, *J* = 5.5, 16.0 Hz, 1H), 4.56 (bs, 1H), 5.01 (dd, *J* = 5.2, 7.4 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 2H), 6.67 (t, *J* = 7.4 Hz, 1H), 7.03-7.13 (m, 2H), 7.20-7.28 (m, 1H), 7.29-7.37 (m, 2H), 7.41-7.49 (m, 4H), 7.52-7.61 (m, 1H), 7.88-7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 147.0, 143.0, 136.7, 133.5, 129.1, 128.9, 128.7, 128.5, 128.2, 127.4, 126.4, 117.8, 113.8, 54.8, 46.3; IR: 3377, 1666, 1601, 1509, 1448, 1372, 1286, 1174, 1028, 994, 746, 683, 510 [cm^{-1}]; MS (ESI-MS): m/z (%) = 343 (16), 302 (MH^+, 100); mp: 135-141°C; HPLC analysis (Chiralcel OD-H, 5% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r (major) = 47.10 min, t_r (minor) = 51.75 min.

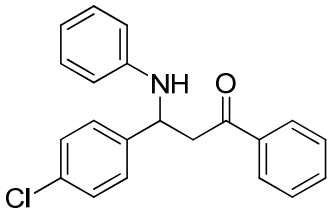


1-phenyl-3-(phenylamino)-3-(4-(trifluoromethyl)phenyl)propan-1-one (137f):

According to general procedure GP3 138 mg of chalcone and 91 µL of aniline were reacted to obtain the product as a white solid. The column chromatography was performed using hexanes/ethyl acetate 90/10.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (dd, *J* = 6.8, 16.5 Hz, 1H), 3.52 (dd, *J* = 5.5, 16.5 Hz, 1H), 4.62 (bs, 1H), 5.06 (dd, *J* = 5.8, 6.6 Hz, 1H), 6.50-6.57 (m, 2H), 6.65-

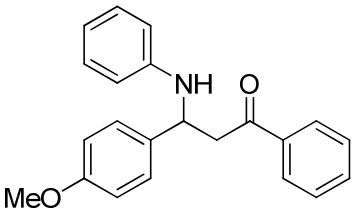
6.73 (m, 1H), 7.06-7.15 (m, 2H), 7.42-7.50 (m, 2H), 7.54-7.62 (m, 5H), 7.87-7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =197.7, 147.2, 146.6, 136.5, 11.7, 130.3, 129.8, 129.4, 129.3, 128.8, 128.2, 126.9, 125.9, 125.9, 125.8, 125.7, 122.3, 118.2, 113.9, 54.4, 46.0; IR: 3402, 1678,1605, 1515, 1327, 1295, 1163, 1117, 1064, 841, 734, 689, 623, 508 [cm^{-1}]; MS (ESI-MS): m/z (%) = 411 (44), 370 (MH^+, 100); mp: 128-134℃; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r (major) = 37.56 min, t_r (minor) = 50.45 min.



3-(4-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (137e):

According to general procedure GP3 121 mg of chalcone and 91 µL of aniline were reacted to obtain the product as a white solid. The column chromatography was performed using hexanes/ethyl acetate 90/10.

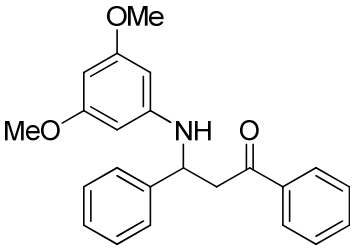
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (dd, *J* = 7.1, 16.2 Hz, 1H), 3.48 (dd, *J* = 5.5, 16.2 Hz, 1H), 4.57 (bs, 1H), 4.97 (dd, *J* = 5.6, 7.1 Hz, 1H), 6.50-6.57 (m, 2H), 6.64-6.72 (m, 1H), 7.05-7.14 (m, 2H), 7.24-7.32 (m, 2H), 7.35-7.50 (m, 4H), 7.53-7.62 (m, 1H), 7.87-7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 146.7, 141.6, 136.6, 133.6, 133.0, 129.6, 129.3, 129.2, 129.0, 128.8, 128.6, 128.2, 127.9, 118.1, 113.9, 54.1, 46.1; IR: 3378, 1666, 1600, 1511, 1489, 1291, 1218, 1179, 992, 746, 688, 508 [cm^{-1}]; MS (ESI-MS): m/z (%) = 377 (25), 336 (MH^+, 100); mp: 108-112℃; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r (major) = 36.23 min, t_r (minor) = 46.29 min.



3-(4-methoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (137d):

According to general procedure GP3 119 mg of chalcone and 91 µL of aniline were reacted to obtain the product as a pale yellow solid. The column chromatography was performed using hexanes/ethyl acetate 90/10.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40 (dd, *J* = 7.4, 16.2 Hz, 1H), 3.50 (dd, *J* = 5.5, 16.2 Hz, 1H), 3.77 (s, 3H), 4.51 (bs, 1H), 4.96 (dd, *J* = 5.7, 7.2 Hz, 1H), 6.52-6.59 (m, 2H), 6.62-6.70 (m, 1H), 6.81-6.88 (m, 2H), 7.04-7.14 (m, 2H), 7.31-7.38 (m, 2H), 7.40-7.49 (m, 2H), 7.52-7.59 (m, 1H), 7.87-7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 158.8, 147.1, 136.8, 135.0, 133.4, 129.1, 128.7, 128.2, 127.5, 117.7, 114.2, 113.8, 55.3, 54.2, 46.4; IR: 3375, 1665, 1602, 1509, 1285, 1247, 1220, 1174, 1028, 995, 747, 683, 511 [cm^{-1}]; MS (ESI-MS): m/z (%) = 373 (6), 332 (MH^+, 100); mp: 140-145°C; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r (major) = 43.78 min, t_r (minor) = 48.94 min.



3-(3,5-dimethoxyphenylamino)-1,3-diphenylpropan-1-one (146a):

According to general procedure GP3 138 mg of chalcone and 91 µL of aniline were reacted to obtain the product as a dark brown solid. The column chromatography was performed using hexanes/ethyl acetate 90/10 followed by 85/15.

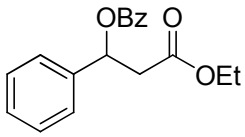
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40 (dd, *J* = 7.4, 16.2 Hz, 1H), 3.51 (dd, *J* = 5.2, 16.2 Hz, 1H), 3.66 (s, 6H), 4.63 (bs, 1H), 4.98 (dd, *J* = 5.2, 7.4 Hz, 1H), 5.76 (d, *J* = 2.2 Hz, 2H), 5.84 (t, *J* = 2.2 Hz, 1H), 7.19-7.27 (m, 1H), 7.28-7.36 (m, 2H), 7.40-7.48 (m, 4H), 7.52-7.60 (m, 1H), 7.87-7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 161.5, 149.0, 144.9, 142.9, 136.6, 133.5, 132.9, 130.6, 129.0, 128.9, 128.7, 128.6,

128.5, 128.5, 128.2, 127.4, 126.3, 122.1, 93.8, 92.6, 90.3, 55.2, 55.1, 54.8, 46.2; IR: 3397, 2935, 1683, 1594, 1448, 1201, 1148, 1068, 810, 730, 688, 535 [cm^{-1}]; MS (ESI-MS): m/z (%) = 362 (MH^+, 100); mp: 99-103°C; HPLC analysis (Chiralcel OD-H , 30% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 215 nm): t_r = 11.72 min, t_r = 13.28 min.

5.4 Kinetic resolution of β-hydroxy amides

General procedure (GP4) for the asymmetric benzoylation:

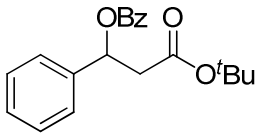
Substrate (0.5 mmol, 1.0 eq.) and ligand•$CuCl_2$-complex (5 mol%) were dissolved in 3 mL of DCM and stirred at r.t. for some minutes. After addition of DIPEA (85 µL, 0.5 mmol, 1.0 eq.) benzoylchloride (28 µL, 0.25 mmol, 0.5 eq.) was added and the mixture was stirred overnight at r.t. Afterwards, the solvent was removed in vacuum and the residue was purified by column chromatography on silica gel.



3-ethoxy-3-oxo-1-phenylpropyl benzoate (172):

According to general procedure GP4 97 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 85/15.

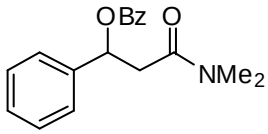
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 3H), 2.89 (dd, *J* = 5.2, 15.6 Hz, 1H), 3.13 (dd, *J* = 9.0, 15.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 6.42 (dd, *J* = 4.9, 9.0 Hz, 1H), 7.27-7.49 (m, 7H), 7.52-7.60 (m, 1H), 8.03-8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 165.4, 139.3, 133.1, 130.1, 129.7, 128.7, 128.4, 128.3, 126.5, 72.9, 60.9, 41.9, 14.1; MS (CI-MS): m/z (%) = 316 (MNH_4^+, 100), 299 (MH^+, 10), 244 (12), 194 (25), 177 (6); HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 14.60 min, t_r = 17.01 min.



3-tert-butoxy-3-oxo-1-phenylpropyl benzoate (173):

According to general procedure GP4 111 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 95/5 followed by 90/10.

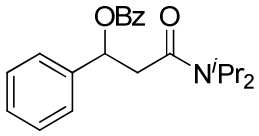
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9H), 2.82 (dd, *J* = 5.2, 15.4 Hz, 1H), 3.04 (dd, *J* = 9.1, 15.4 Hz, 1H), 6.37 (dd, *J* = 5.5, 9.1 Hz, 1H), 7.28-7.48 (m, 7H), 7.52-7.59 (m, 1H), 8.03-8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 139.4, 133.1, 130.1, 129.7, 128.6, 128.4, 126.6, 81.2, 73.1, 43.1, 27.9; MS (EI, 70 eV): m/z (%) = 270 (M-$C_4H_8^{+\bullet}$, 24), 253 (5), 165 (90), 131 (19), 105 (100), 77 (24), 57 (25); HPLC analysis (Chiralcel OD-H, 5% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 12.71 min, t_r = 13.77 min.



3-(dimethylamino)-3-oxo-1-phenylpropyl benzoate (175):

According to general procedure GP4 97 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 25/75.

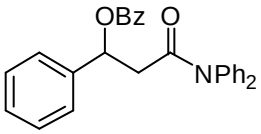
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.86 (dd, *J* = 5.6, 15.8 Hz, 1H), 2.89 (s, 3H), 2.98 (s, 3H), 3.18 (dd, *J* = 7.7, 15.4 Hz, 1H), 6.49 (dd, *J* = 6.0, 7.4 Hz, 1H), 7.23-7.59 (m, 8H), 7.99-8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 165.4, 140.3, 133.0, 130.3, 129.7, 128.6, 128.4, 128.2, 126.5, 73.6, 40.4, 37.3, 35.5; IR: 2927, 1707, 1639, 1451, 1414, 1349, 1272, 1139, 1110, 1067, 994, 761, 701, 602, 562 [cm^{-1}]; MS (CI-MS): m/z (%) = 315 (9), 298 (MH^+, 100), 192 (4), 176 (32); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 297.1365, found: 297.1368; HPLC analysis (Chiralcel AS, 15% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 48.41 min, t_r = 62.16 min.



3-(diisopropylamino)-3-oxo-1-phenylpropyl benzoate (177a):

According to general procedure GP4 125 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 90/10 followed by 80/20.

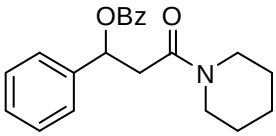
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (dd, *J* = 6.6, 24.7 Hz, 6H), 1.29 (dd, *J* = 4.9, 6.6 Hz, 6H), 2.85 (dd, *J* = 5.8, 15.1 Hz, 1H), 3.13 (dd, *J* = 8.2, 14.8 Hz, 1H), 3.40-3.60 (m, 1H), 3.98 (st, *J* = 6.7 Hz, 1H), 6.51 (dd, *J* = 5.8, 8.0 Hz, 1H), 7.21-7.57 (m, 8H), 8.01-8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 165.4, 140.3, 132.9, 130.4, 129.7, 128.5, 128.3, 128.1, 126.5, 73.9, 45.9, 42.1, 21.2, 21.0, 20.5; IR: 2970, 1720, 1623, 1450, 1316, 1266, 1111, 892, 737, 631, 536 [cm^{-1}]; MS (CI-MS): m/z (%) = 354 (MH^+, 100), 250 (9), 234 (4), 232 (21); HPLC analysis (Chiralcel AS, 5% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 18.24 min, t_r = 22.04 min.



3-(diphenylamino)-3-oxo-1-phenylpropyl benzoate (177b):

According to general procedure GP4 159 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 70/30.

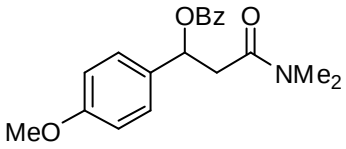
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (dd, *J* = 6.0, 15.1 Hz, 1H), 3.12 (dd, *J* = 8.0, 15.1 Hz, 1H), 6.53 (dd, *J* = 6.2, 7.9 Hz, 1H), 7.03-7.66 (m, 18H), 8.02-8.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 165.4, 142.5, 139.8, 133.0, 130.3, 129.7, 128.6, 128.3, 128.2, 126.6, 73.9, 42.2, 20.8; IR: 3062, 3034, 1715, 1646, 1400, 1273, 1153, 1112, 713, 631, 536 [cm^{-1}]; MS (CI-MS): m/z (%) = 439 (MNH_4^+, 10), 422 (MH^+, 100), 319 (10), 300 (74), 170 (24); HPLC analysis (Chiralcel OD-H, 15% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 27.79 min, t_r = 40.46 min.



3-oxo-1-phenyl-3-(piperidin-1-yl)propyl benzoate (177c):

According to general procedure GP4 97 mg of substrate were reacted to obtain the product as a colorless oil. The column chromatography was performed using hexanes/ethyl acetate 25/75.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37-1.66 (m, 6H), 2.89 (dd, *J* = 5.8, 15.4 Hz, 1H), 3.18 (dd, *J* = 7.7, 15.1 Hz, 1H), 3.34-3.63 (m, 4H), 6.47 (dd, *J* = 5.8, 7.7 Hz, 1H), 7.27-7.59 (m, 8H), 8.02-8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 165.4, 140.2, 132.9, 130.3, 129.7, 128.6, 128.3, 128.2, 126.6, 73.7, 46.9, 42.8, 40.3, 26.4, 25.5, 24.5; IR: 2937, 2856, 1718, 1638, 1451, 1354, 1270, 1110, 1070, 1026, 752, 713, 632, 535 [cm^{-1}]; MS (CI-MS): m/z (%) = 355 (2), 338 (MH^+, 100), 232 (4), 216 (18); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 337.1678, found: 337.1670; HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 38.63 min, t_r = 42.77 min.

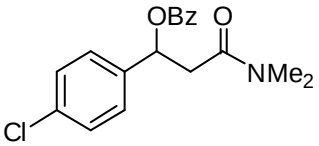


3-(dimethylamino)-1-(4-methoxyphenyl)-3-oxopropyl benzoate (177d):

According to general procedure GP4 112 mg of substrate were reacted to obtain the product as colorless solid. The column chromatography was performed using hexanes/ethyl acetate 25/75.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (dd, *J* = 9.3, 15.4 Hz, 1H), 2.90 (s, 3H), 3.02 (s, 3H), 3.19 (dd, *J* = 7.7, 15.3 Hz, 1H), 3.79 (s, 3H), 6.44 (dd, *J* = 6.3, 7.4 Hz, 1H), 6.84-6.92 (m, 2H), 7.37-7.47 (m, 4H), 7.49-7.58 (m, 1H), 8.00-8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 165.4, 159.4, 132.9, 132.3, 130.4, 129.7, 128.3, 1208.0, 113.9, 73.3, 55.3, 40.3, 37.4, 35.4; IR: 3056, 2936, 1706, 1643, 1513, 1397, 1314, 1276, 1243, 1177, 1141, 1110, 1069, 1028, 1000, 874, 829, 756, 713, 621, 577, 543 [cm^{-1}]; MS (CI-MS): m/z (%) = 328 (MH^+, 3), 223 (60), 206 (100), 191 (5); HPLC

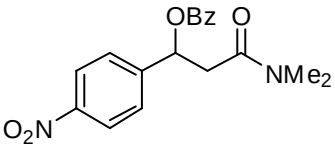
analysis (Chiralcel AS, 15% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 71.24 min, t_r = 92.02 min.



1-(4-chlorophenyl)-3-(dimethylamino)-3-oxopropyl benzoate (177e):

According to general procedure GP4 114 mg of substrate were reacted to obtain the product as colorless solid. The column chromatography was performed using hexanes/ethyl acetate 25/75.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.86 (dd, *J* = 6.3, 15.6 Hz, 1H), 2.91 (s, 3H), 3.00 (s, 3H), 3.17 (dd, *J* = 7.3, 15.5 Hz, 1H), 6.45 (t, *J* = 6.7 Hz, 1H), 7.29-7.35 (m, 2H), 7.39-7.47 (m, 4H), 7.51-7.59 (m, 1H), 7.99-8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 165.3, 138.8, 134.0, 133.1, 130.1, 129.7, 128.8, 128.4, 128.1, 72.9, 40.2, 37.3, 35.5; IR: 2918, 1716, 1647, 1489, 1401, 1352, 1273, 1175, 1119, 1009, 875, 837, 710, 611, 564 [cm^{-1}]; MS (CI-MS): m/z (%) = 349 (MNH_4^+, 13), 332 (MH^+, 100), 226 (6), 210 (54); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 331.0975, found: 331.0967; HPLC analysis (Chiralcel AS, 15% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 47.12 min, t_r = 56.41 min.

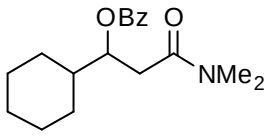


3-(dimethylamino)-1-(4-nitrophenyl)-3-oxopropyl benzoate (177f):

According to general procedure GP4 119 mg of substrate were reacted to obtain the product as pale yellow solid. The column chromatography was performed using hexanes/ethyl acetate 25/75.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (dd, *J* = 6.6, 15.9 Hz, 1H), 2.92 (s, 3H), 3.02 (s, 3H), 3.21 (dd, *J* = 6.7, 15.9 Hz, 1H), 6.55 (t, *J* = 6.7 Hz, 1H), 7.40-7.50 (m, 2H), 7.54-7.62 (m, 1H), 7.65-7.72 (m, 2H), 8.00-8.07 (m, 2H), 8.18-8.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 165.2, 147.6, 133.4, 129.7, 129.6, 128.5, 127.6, 123.9, 72.6,

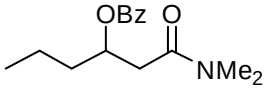
40.0, 37.3, 25.5; IR: 2929, 1709, 1651, 1519, 1402, 1348, 1272, 1138, 1106, 1068, 1009, 848, 781, 754, 712, 609, 555 [cm^{-1}]; MS (CI-MS): m/z (%) = 360 (MNH_4^+, 21), 343 (MH^+, 100), 238 (5), 221 (15), 191 (79); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 342.1216, found: 342.1208; HPLC analysis (Chiralcel OD-H, 20% ^{i}PrOH/*n*-heptane, 0.5 mL/min, 254 nm): t_r = 27.79 min, t_r = 33.91 min.



1-cyclohexyl-3-(dimethylamino)-3-oxopropyl benzoate (177g):

According to general procedure GP4 99 mg of substrate were reacted to obtain the product as colorless oil. The column chromatography was performed using hexanes/ethyl acetate 25/75. For the determination of the ee the product was dissolved in MeOH, Mg was added and the mixture was stirred overnight at r.t. Afterwards the solvent was removed and the residue was purified by column chromatography (hexanes/ethyl acetate 25/75).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05-1.35 (m, 5H), 1.61-1.90 (m, 6H), 2.66 (dd, *J* = 5.9, 15.0 Hz, 1H), 2.79 (dd, *J* = 7.4, 15.1 Hz, 1H), 2.89 (s, 3H), 3.03 (s, 3H), 5.36-5.45 (m, 1H), 7.38-7.46 (m, 2H), 7.50-7.58 (m, 1H), 7.99-8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 165.9, 132.8, 130.6, 129.6, 128.3, 75.4, 41.2, 37.6, 35.5, 35.3, 29.4, 27.6, 26.4, 26.1, 26.0; IR: 2922, 2851, 1622, 1498, 1449, 1398, 1262, 1147, 1045, 892, 606 [cm^{-1}]; MS (CI-MS): m/z (%) = 305 (19), 304 (MH^+, 100), 182 (6); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 303.1834, found: 303.1828; GC analysis (CP-Chirasil-Dex CB, 130℃(10 min) to 175℃ (3℃/min), 1 drop of TMS-imidazole was added): t_r = 20.26 min, t_r = 20.52 min.

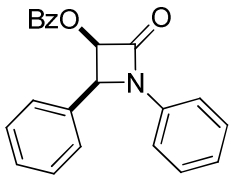


1-(dimethylamino)-1-oxohexan-3-yl benzoate (177h):

According to general procedure GP4 80 mg of substrate were reacted to obtain the product as colorless oil. The column chromatography was performed using

hexanes/ethyl acetate 25/75. For the determination of the ee the product was dissolved in MeOH, Mg was added and the mixture was stirred overnight at r.t. Afterwards the solvent was removed and the residue was purified by column chromatography (hexanes/ethyl acetate 25/75).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95(t, *J* = 7.3 Hz, 3H), 1.35-1.54 (m, 2H), 1.73-1.87 (m, 2H), 2.59 (dd, *J* = 7.3, 14.8 Hz, 1H), 2.88 (dd, *J* = 5.9, 14.9 Hz, 1H), 2.92 (s, 3H), 3.05 (s, 3H), 5.41-5.53 (m, 1H), 7.38-7.48 (m, 2H), 7.51-7.60 (m, 1H), 7.98-8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 166.0, 132.9, 130.5, 129.5, 128.3, 72.0, 38.3, 37.5, 36.4, 35.4, 18.7, 13.9; IR: 2959, 2936, 1718, 1665, 1595, 1491, 1451, 1377, 1314, 1266, 1177, 1108, 1070, 1026, 1000, 758, 699, 633, 544 [cm^{-1}]; MS (CI-MS): m/z (%) = 281 (8), 264 (MH^+, 100), 142 (4); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 263.1521, found: 263.1525; GC analysis (CP-Chirasil-Dex CB, 105°C isothermal): t_r = 22.57 min, t_r = 23.51 min.



2-oxo-1,4-diphenylazetidin-3-yl benzoate (195):

According to general procedure GP4 120 mg of substrate were reacted to obtain the product as colorless solid. The column chromatography was performed using hexanes/ethyl acetate 80/20.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.50 (d, *J* = 5.0 Hz, 1H), 6.27 (d, *J* = 5.0 Hz, 1H), 7.08-7.15 (m, 1H), 7.18-7.42 (m, 12H), 7.44-7.52 (m, 1H), 7.64-7.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 162.1, 136.9, 133.5, 132.3, 129.6, 129.3, 128.8, 128.6, 128.3, 128.2, 127.7, 124.8, 117.6, 76.4, 61.5; IR: 1755, 1722, 1495, 1396, 1262, 1114, 1057, 753, 546; MS (EI, 70 eV): m/z (%) = 343 ($M^{+\bullet}$, 9), 224 (9), 221 (8), 181 (11), 105 (100), 77 (37), 51 (6); HRMS (EI-MS, m/z) [$M^{+\bullet}$]: calc.: 343.1208, found: 343.1207; mp: 180-184°C; HPLC analysis (Chir alcel OD-H, 20% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm): t_r = 6.97 min, t_r = 13.00 min.

5.5 Assessment of relative reaction rates

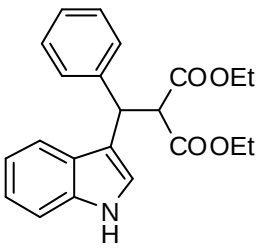
General Procedure (GP5) for the asymmetric Michael additions:

Reaction using one ligand (GP5.1):

To a Schlenk tube ligand (0.05 mmol) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) were added under air atmosphere. Ethanol (2 mL) was added and the mixture was stirred for 1h at room temperature (20-25℃). To the result ing blue-green solution malonate (1.0 mmol, 1.0 eq.) in EtOH (2 mL) was added and stirring was continued for 20 min before the indole (141 mg, 1.2 mmol, 1.2 eq.) was added. After the stirring for overnight at room temperature, the red colored solution was concentrated under reduced pressure. The crude product was purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM).

Reaction using two ligands (GP5.2):

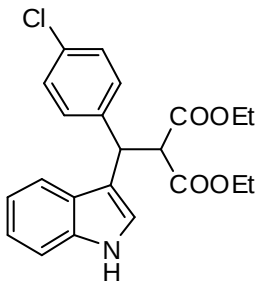
To a Schlenk tube both ligands (0.025 mmol of each) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) were added under air atmosphere. Ethanol (2 mL) was added and the mixture was stirred for 1h at room temperature (20-25℃). To the resulting blue-green solution malonate (1.0 mmol, 1.0 eq.) in EtOH (2 mL) was added and stirring was continued for 20 min before the indole (141 mg, 1.2 mmol, 1.2 eq.) was added. After the stirring for overnight at room temperature, the red colored solution was concentrated under reduced pressure. The crude product was purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM).



Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate (198):

Prepared according to the general procedure GP5.1 or GP5.2 and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

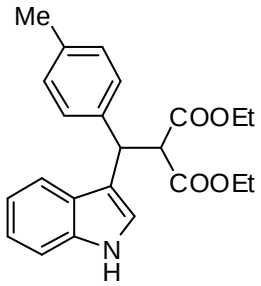
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93-1.06 (m, 6 H), 3.93-4.06 (m, 4 H), 4.30 (d, *J* = 11.8 Hz, 1 H), 5.09 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.09-7.31 (m, 6 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 8.07 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.9, 141.4, 136.2, 128.4, 128.2, 126.8, 126.7, 122.3, 120.9, 119.5, 119.4, 117.0, 111.0, 61.5, 61.4, 58.4, 42.9, 13.8, 13.8; MS (CI): m/z (%) = 383 (MNH_4^+, 89), 366 (MH^+, 3), 206 (100), 178 (5); mp 174-176°C; HPLC analysis (Chiralcel OJ-H, 30% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*S*) = 19.46 min, t_r (*R*) = 25.95 min).



Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-chlorophenyl) propanoate (208):

Prepared according to the general procedure GP5.1 or GP5.2 and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

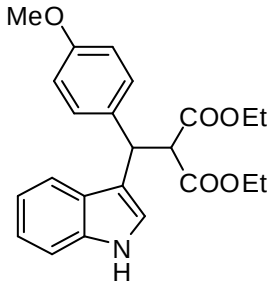
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 3.96-4.06 (m, 4 H), 4.24 (d, *J* = 11.8 Hz, 1 H), 5.06 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.10-7.23 (m, 4 H), 7.27-7.34 (m, 3 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 8.05 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 167.8, 140.1, 136.3, 132.5, 129.6, 128.5, 126.5, 122.4, 121.0, 119.7, 119.2, 116.4, 111.1, 61.6, 58.2, 42.3, 13.9, 13.8; MS (CI): m/z (%) = 417 (MNH_4^+, 100), 399 (3), 242 (30), 240 (67), 206 (2), 178 (8); mp 157-158°C; HPLC analysis (Chiralcel OJ-H, 20% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R*) = 15.22 min, t_r (*S*) = 19.03 min).



Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-methylphenyl) propanoate (207):

Prepared according to the general procedure GP5.1 or GP5.2 and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.1 Hz, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H), 2.24 (s, 3 H), 3.94-4.05 (m, 4 H), 4.27 (d, *J* = 11.8 Hz, 1 H), 5.04 (d, *J* = 11.8 Hz, 1 H), 6.99-7.06 (m, 3 H), 7.08-7.18 (m, 2 H), 7.22-7.31 (m, 3 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.99 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.9, 138.4, 136.2, 136.2, 129.0, 128.0, 126.7, 122.2, 120.8, 119.5, 119.5, 117.3, 110.9, 61.4, 61.4, 58.4, 42.4, 21.0, 13.8, 13.8; MS (CI): m/z (%) = 397 (MNH_4^+, 73), 379 (2), 220 (100), 178 (7); mp 140-142℃; HPLC analysis (Chiralcel OJ-H, 30% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R*) = 12.23 min, t_r (*S*) = 24.87 min).



Diethyl 2-((1H-indol-3-yl)(4-methoxyphenyl)methyl)malonate (213):

Prepared according to the general procedure GP5.1 or GP5.2, but the reaction was only stirred for ca. 5h and then purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97-1.07 (m, 6H), 3.73 (s, 3H), 3.95-4.04 (m, 4H), 4.23 (d, *J* = 11.7 Hz, 1H), 5.03 (d, *J* = 11.8 Hz, 1H), 6.73-6.78 (m, 2H), 6.98-7.31 (m, 6H), 7.52 (d, *J* = 7.8 Hz, 1H), 8.01 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 158.3, 136.3, 133.5, 129.2, 126.7, 122.3, 120.7, 119.5, 117.4, 113.7, 110.9, 61.4,

58.6, 55.3, 42.1, 13.8; MS (CI): m/z (%) = 413 (MNH_4^+, 71), 396 (MH^+, 3), 236 (100), 178 (13); mp 146-148℃; HPLC analysis (Phenomenex Lux Cellulose-1, 10% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R*) = 19.34 min, t_r (*S*) = 21.70 min).

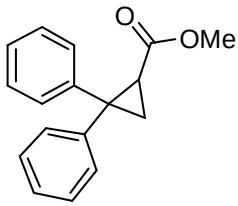
General Procedure (GP6) for the asymmetric cyclopropanation:

Reaction using one ligand (GP6.1):

To a Schlenk tube ligand (0.05 mmol) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) were added under N_2-atmosphere. DCM (2 mL) was added and the mixture was stirred for at least 1h at room temperature (20-25℃). Then one drop of phenyl hydrazine was added, the mixture was stirred for another 10 min before the alkene (1 mmol, 1 eq.) was added. The diazo ester was then added via syringe pump (~0.5 mL/h) as a solution in DCM (~10%, m/v, 2.0 g, 2.0 eq.). The mixture was stirred overnight at r.t., afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography.

Reaction using two ligands (GP6.2):

To a Schlenk tube both ligands (0.025 mmol of each) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) were added under N_2-atmosphere. DCM (2 mL) was added and the mixture was stirred for at least 1h at room temperature (20-25℃). Then one drop of phenyl hydrazine was added, the mixture was stirred for another 10 min before the alkene (1.0 mmol, 1 eq.) was added. The diazo ester was then added via syringe pump (~0.5 mL/h) as a solution in DCM (~10%, m/v, 2.0 g, 2 eq.). The mixture was stirred overnight at r.t., afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography.



Methyl 2,2-diphenylcyclopropanecarboxylate (219):

Prepared according to the general procedure GP6.1 or GP6.2 and purified by column chromatography (performed with hexanes, followed by hexanes/ethyl acetate 95:5) to obtain the pure product as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (dd, *J* = 4.8, 8.1 Hz, 1H), 2.17 (dd, *J* = 4.9, 5.8 Hz, 1H), 2.56 (dd, *J* = 5.9, 8.1 Hz, 1H), 3.48 (s, 3H), 7.13-7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 144.8, 140.2, 129.6, 128.5, 128.4, 127.6, 127.0, 126.6, 51.7, 40.0, 28.8, 20.2; MS (EI): m/z (%) = 252 ($M^{+\bullet}$, 3), 193 (59), 192 (100), 191 (31), 178 (21), 165 (21), 115 (47), 91 (14); HPLC analysis (Chiralcel OJ-H, 30% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R*) = 15.31 min, t_r (*S*) = 23.71 min).

General Procedure (GP7) for the asymmetric dihydroxylation:

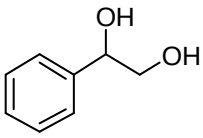
Reaction using AD-α-Mix or AD-β-Mix (GP7.1):

To a 10mL round bottom flask was added AD-Mix (700 mg, 3.0 mmol, 3.0 eq.), alkene (1.0 mmol, 1.0 eq.), 1 mL H_2O and 1 mL ^{t}BuOH. The mixture was vigorously stirred for the indicated period of time, then a sat. Na_2SO_3 solution was added for quenching. The mixture was extracted thrice with DCM, the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography.

Reaction using AD-α-Mix and AD-β-Mix (GP7.2):

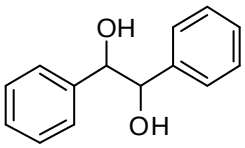
To a 10mL round bottom flask was added AD-α-Mix (350 mg, 1.5 mmol, 1.5 eq.), AD-β-Mix (350 mg, 1.5 mmol, 1.5 eq.), alkene (1.0 mmol, 1.0 eq.), 1 mL H_2O and 1 mL ^{t}BuOH. The mixture was vigorously stirred for the indicated period of time, then a sat. Na_2SO_3 solution was added for quenching. The mixture was extracted thrice with DCM, the combined organic layers were dried over $MgSO_4$, and the solvent was

removed under reduced pressure. The residue was purified by column chromatography.



1-phenylethane-1,2-diol (223):

Prepared according to the general procedure GP7.1 or 7.2, the reaction mixture was stirred for 2 days. The column chromatography was done using hexanes/ethyl acetate (50:50), to obtain the product as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (bs, 1H), 3.53-3.74 (m, 2H), 3.80 (bs, 1H), 4.75 (dd, *J* = 3.3, 8.2 Hz, 1H), 7.24-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 128.5, 128.0, 126.1, 74.8, 68.0; MS (CI): m/z (%) = 173 (MNH_4^++NH_3, 3), 157 (8), 156 (MNH_4^+, 100), 138 (4); HPLC analysis (Chiralcel OD-H, 5% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R*) = 17.44 min, t_r (*S*) = 19.13 min).



1,2-diphenylethane-1,2-diol (224):

Prepared according to the general procedure GP7.1 or 7.2, the reaction mixture was stirred for 4 days. The column chromatography was done using hexanes/ethyl acetate (80:20) followed by hexanes/ethyl acetate (50:50), to obtain the product as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (s, 2H), 4.71 (s, 2H), 7.08-7.17 (m, 4H), 7.20-7.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8, 128.2, 128.0, 127.0, 79.1; MS (CI): m/z (%) = 233 (14), 232 (MNH_4^+, 100), 214 (12); HPLC analysis (Chiralcel OJ-H, 10% ^{i}PrOH/*n*-heptane, 1.0 mL/min, 254 nm; t_r (*R,R*) = 13.24 min, t_r (*S,S*) = 14.78 min).

5.6 Mathematic derivation of the formula:

The selectivity of two catalysts is constituted by their ee-values ee_1 and ee_2. Furthermore, the resulting ee-value of the mixture of both catalysts is denoted by ee_r. In the following the rate ratio $v_{rel} = \frac{R_1 + S_1}{R_2 + S_2}$ of the two catalysts will be derivated by means of the aforementioned values.

According to the definition of the ee-value it is deemed to be:

$$ee_1 = \frac{R_1 - S_1}{R_1 + S_1} \qquad (1)$$

$$ee_2 = \frac{R_2 - S_2}{R_2 + S_2} \qquad (2)$$

$$ee_r = \frac{R_r - S_r}{R_r + S_r} = \frac{(R_1 + R_2) - (S_1 + S_2)}{(R_1 + R_2) + (S_1 + S_2)} \qquad (3)$$

By variables substitution one can simplify the problem.

$$p = R_1 + S_1 \qquad (4)$$

$$\hat{p} = R_1 - S_1 \qquad (5)$$

$$q = R_2 + S_2 \qquad (6)$$

$$\hat{q} = R_2 - S_2 \qquad (7)$$

From the last formulas ensues:

$$ee_1 = \frac{\hat{p}}{p} \qquad (8)$$

$$ee_2 = \frac{\hat{q}}{q} \qquad (9)$$

$$ee_r = \frac{\hat{p} + \hat{q}}{p + q} \qquad (10)$$

With the variable order ($\hat{p}$; p; $\hat{q}$; q) we get the following homogeneous system of equations (row order (10,9,8)):

$$\begin{pmatrix} \hat{q} \\ q \\ \hat{p} \\ p \end{pmatrix} = \lambda \begin{pmatrix} \frac{ee_1 ee_r - {ee_r}^2}{ee_r - ee_2} - ee_1 + ee_r \\ \frac{ee_1 - ee_r}{ee_r - ee_2} \\ ee_1 \\ 1 \end{pmatrix}$$

$$v_{rel} = \frac{R_1 + S_1}{R_2 + S_2} = \frac{p}{q} = \frac{\lambda \cdot 1}{\lambda \cdot \frac{ee_1 - ee_r}{ee_r - ee_2}} = \frac{ee_r - ee_2}{ee_1 - ee_r}$$

The sought formula is:

$$v_{rel} = \frac{ee_r - ee_2}{ee_1 - ee_r}$$

For the utilization of this formula one has to convert all values to either the (*R*) or (*S*) enantiomer:

$$ee_x(R) = -ee_x(S); x \in \{1,2,r\}$$

Hence, the final formula for a 1:1 ratio of the 2 catalysts is:

$$v_{rel} = \frac{ee_2 + ee_r}{ee_1 - ee_r}$$

For the general formula:

$$v_{rel} = \frac{X_2(R_1 + S_1)}{X_1(R_2 + S_2)}$$

X_1 and X_2 are the ratios of Catalyst 1 and Catalyst 2 respectively.

As stated above:

$$v_{rel} = \frac{X_2(R_1 + S_1)}{X_1(R_2 + S_2)} = \frac{X_2 \cdot p}{X_1 \cdot q} = \frac{X_2 \cdot \lambda \cdot 1}{X_1 \cdot \lambda \cdot \frac{ee_1 - ee_r}{ee_r - ee_2}} = \frac{X_2(ee_2 - ee_r)}{X_1(ee_1 - ee_r)}$$

$$ee_x(R) = -ee_x(S); x \in \{1,2,r\}$$

$$v_{rel} = \frac{X_2(ee_2 + ee_r)}{X_1(ee_1 - ee_r)}$$

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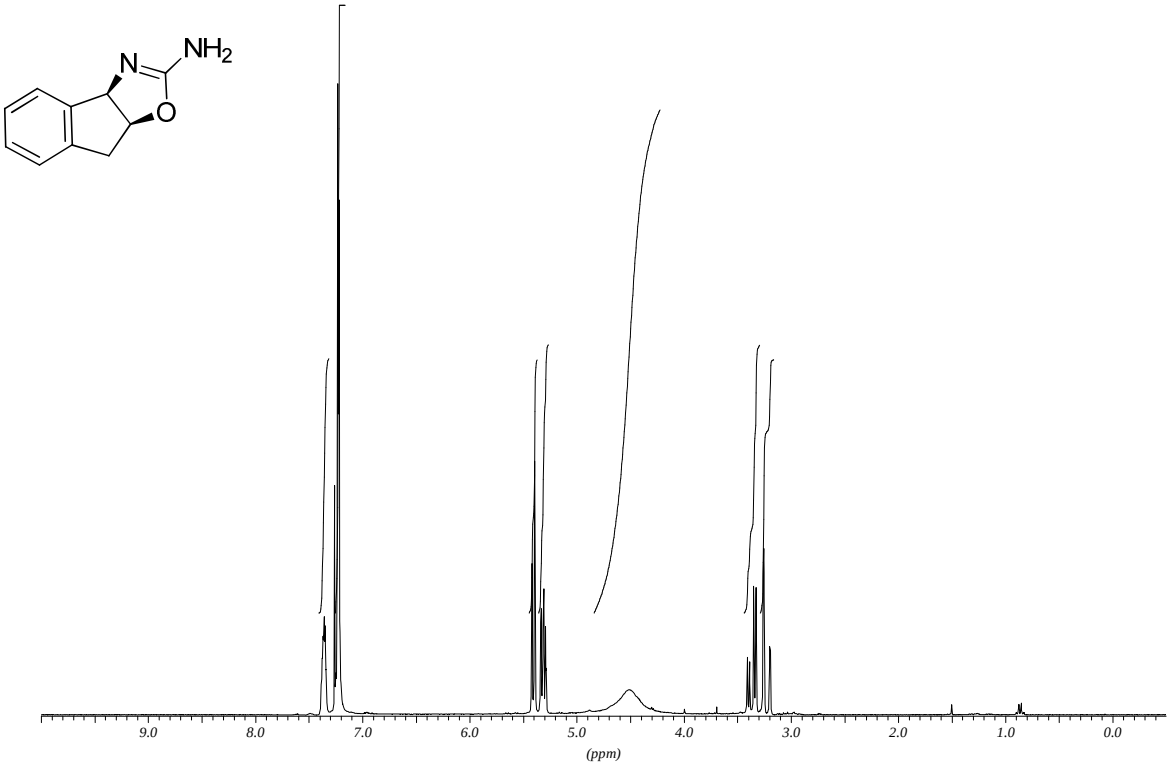
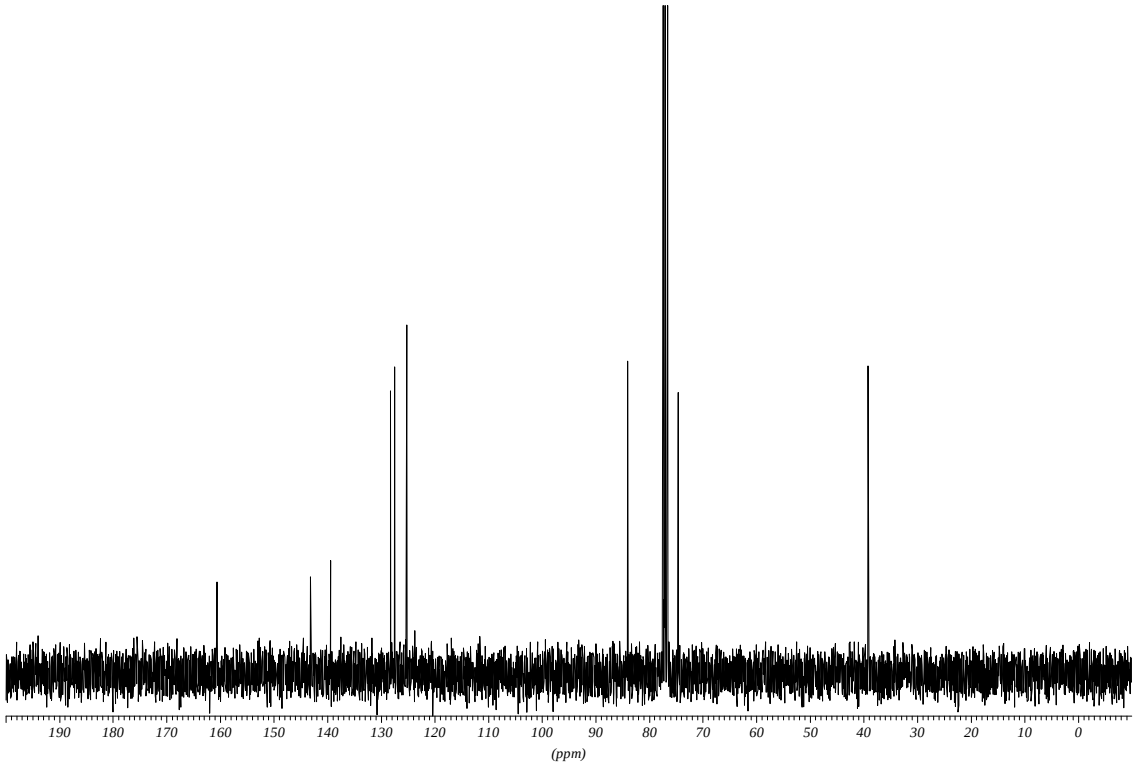
E. Appendix

1. NMR Spectra

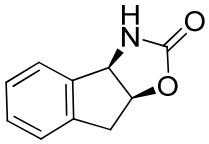
^{1}H-NMR (300 MHz):	upper image
^{13}C-NMR (75 MHz):	lower image
Solvent (if not stated otherwise):	$CDCl_3$

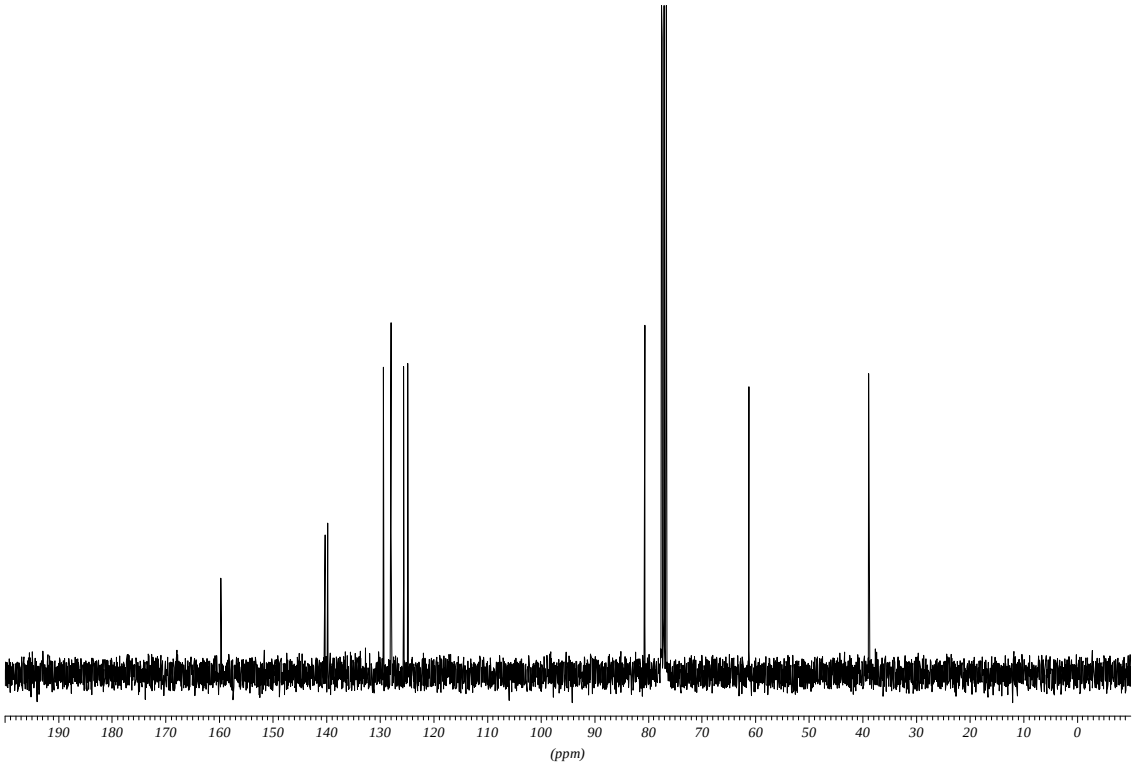
(3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-amine (43)



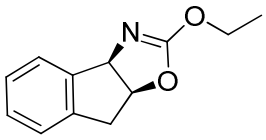


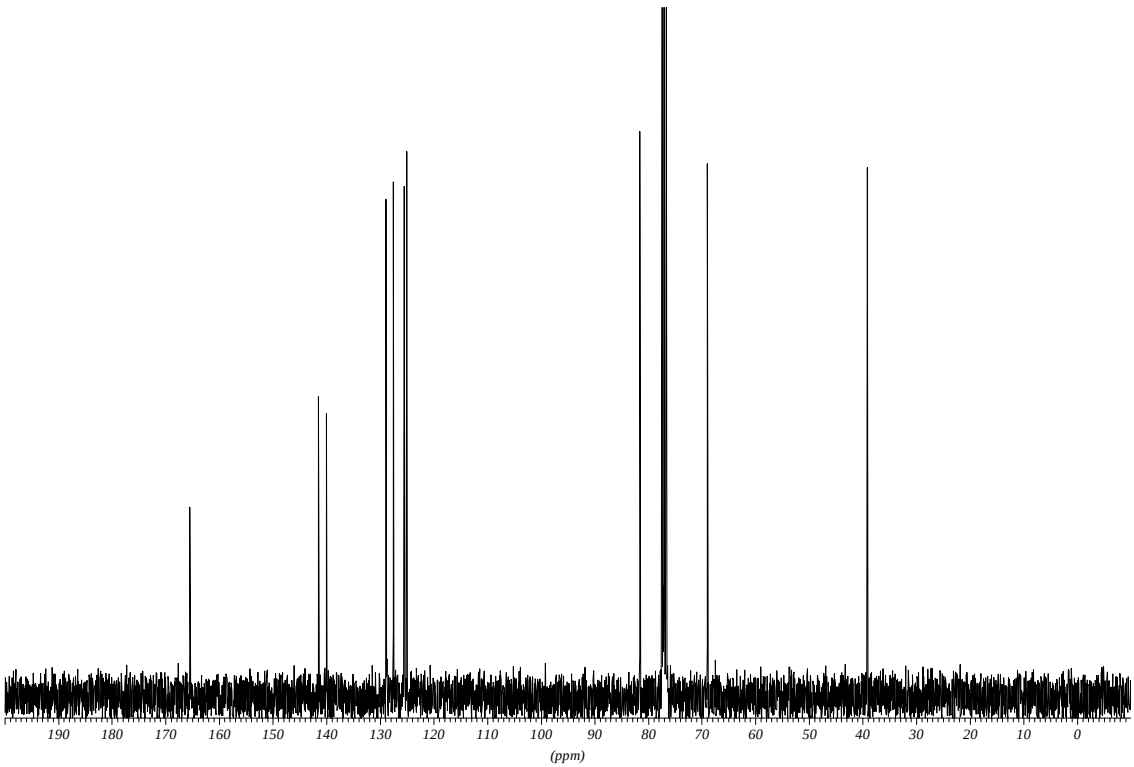
(3aR,8aS)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one (42e)



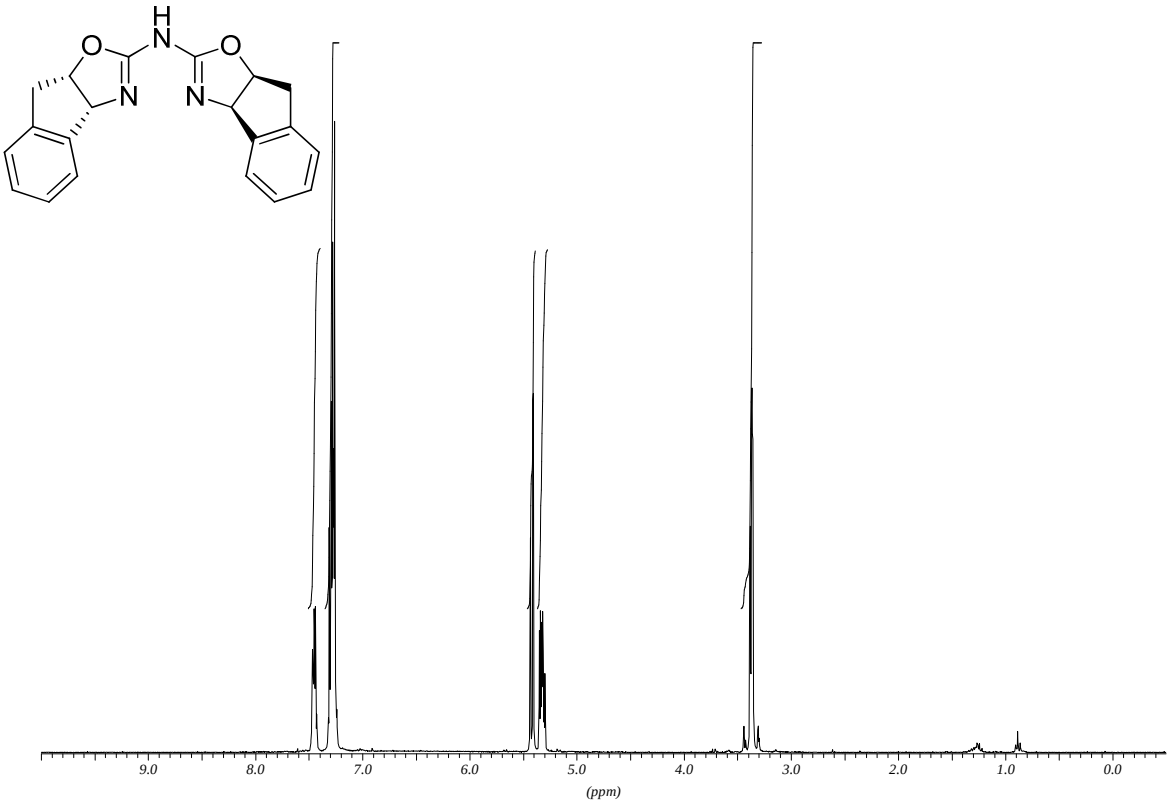


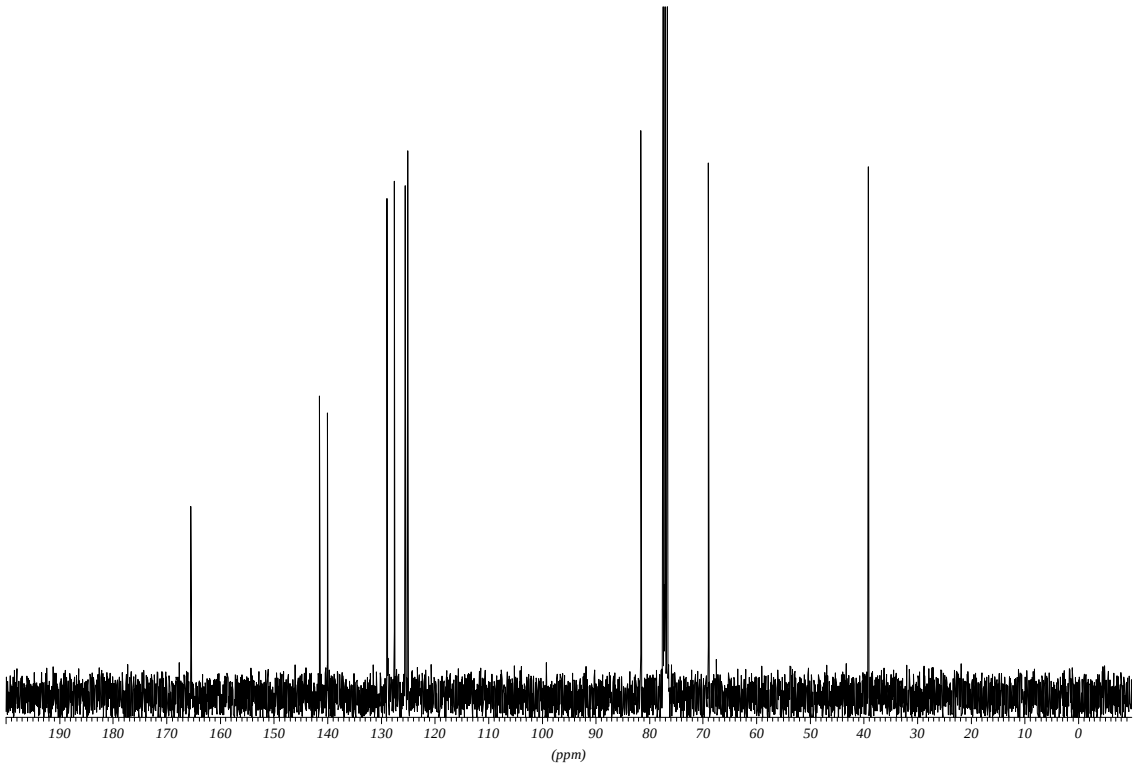
(3aR,8aS)-2-ethoxy-8,8a-dihydro-3aH-indeno[1,2-d]oxazole (44)



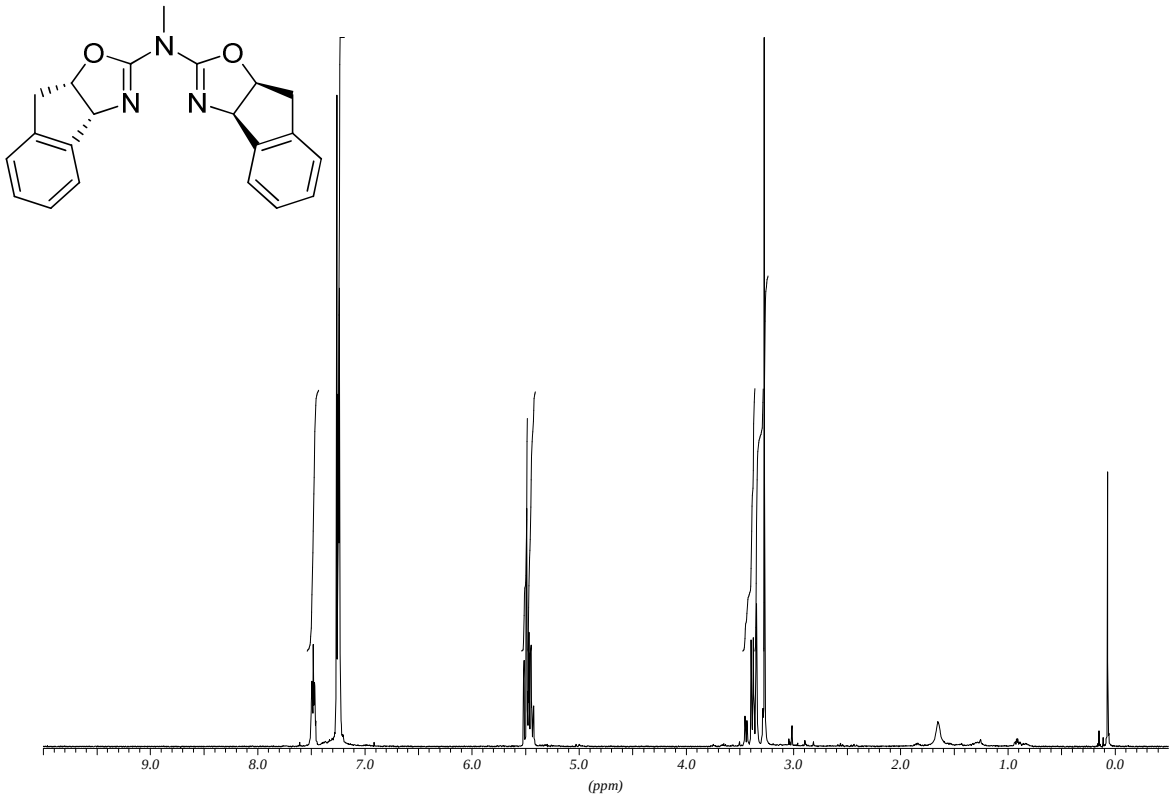


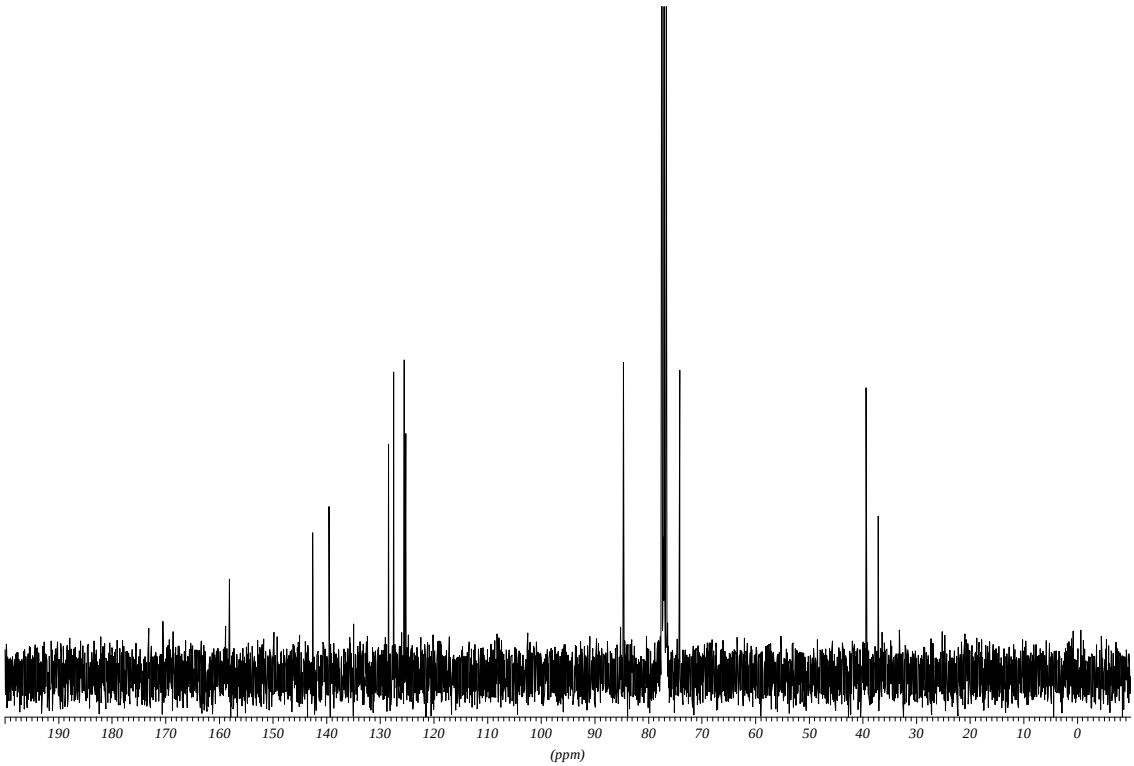
(3aR,8aS)-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)amine (45)



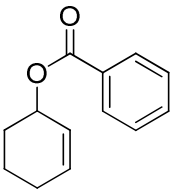


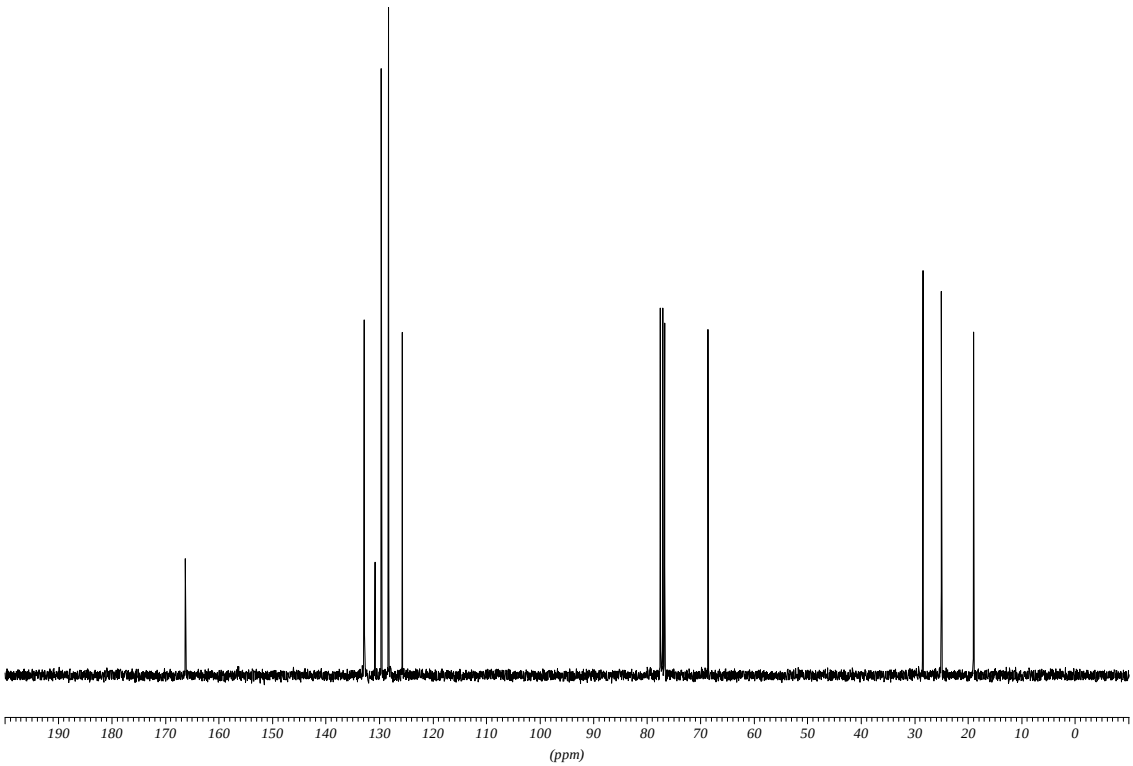
(3aR,8aS)-N-((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-N-methyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-amine (46)



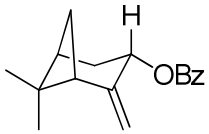


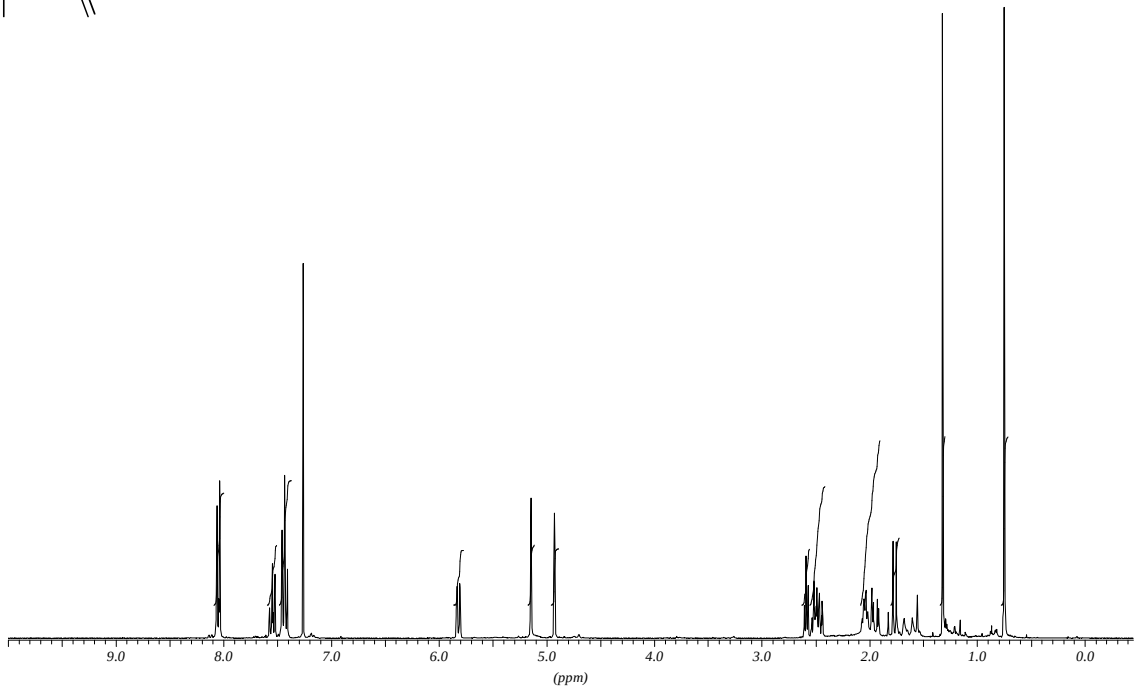
Cyclohex-2-enyl benzoate (83)

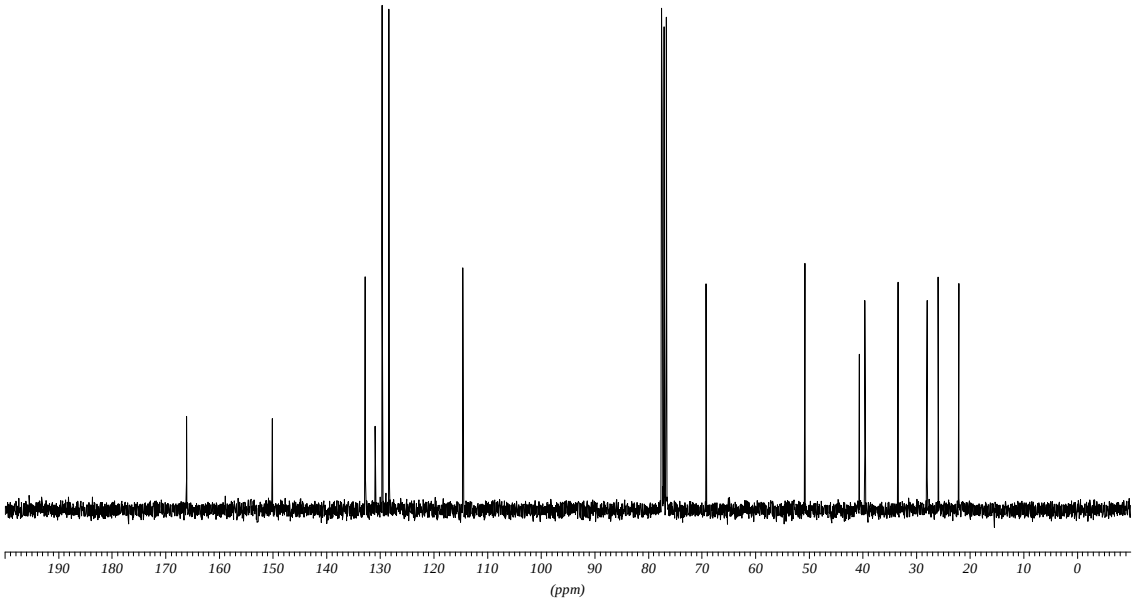




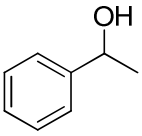
(1R,3S,5R)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl benzoate (93)

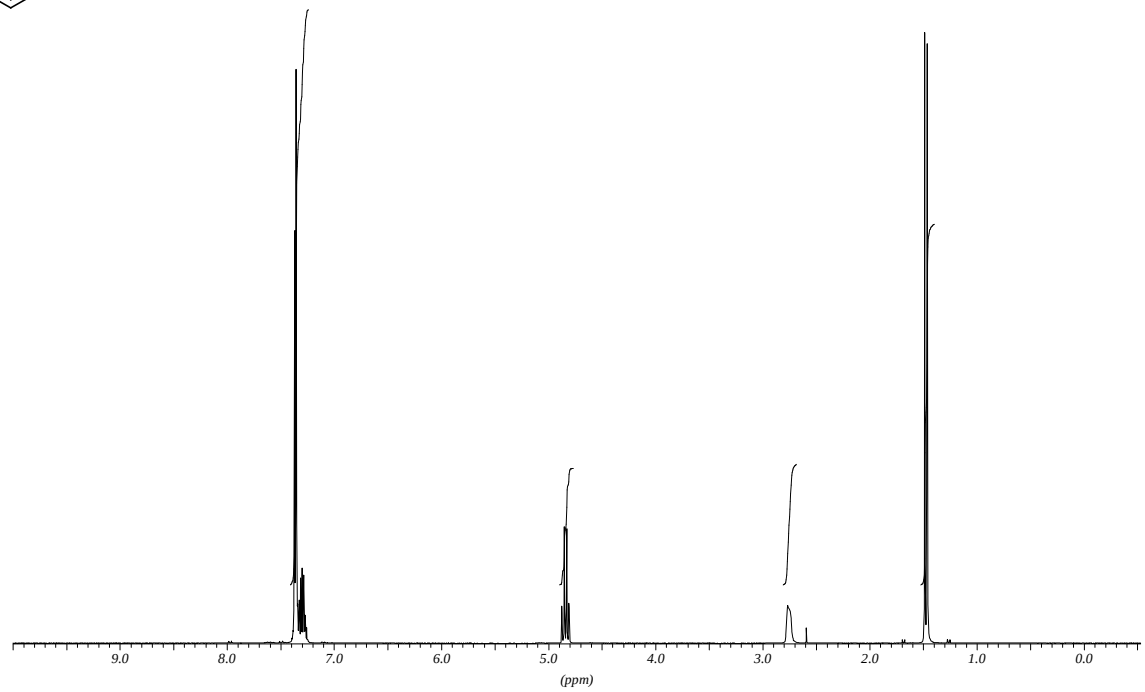


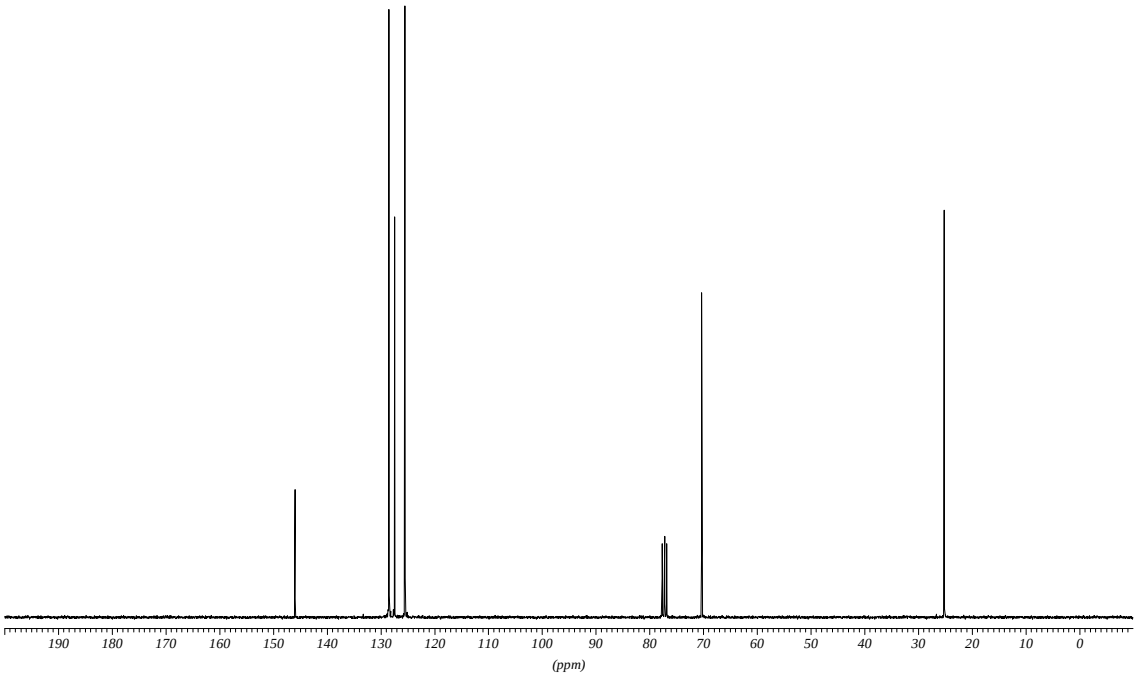




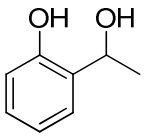
1-phenylethanol (103)

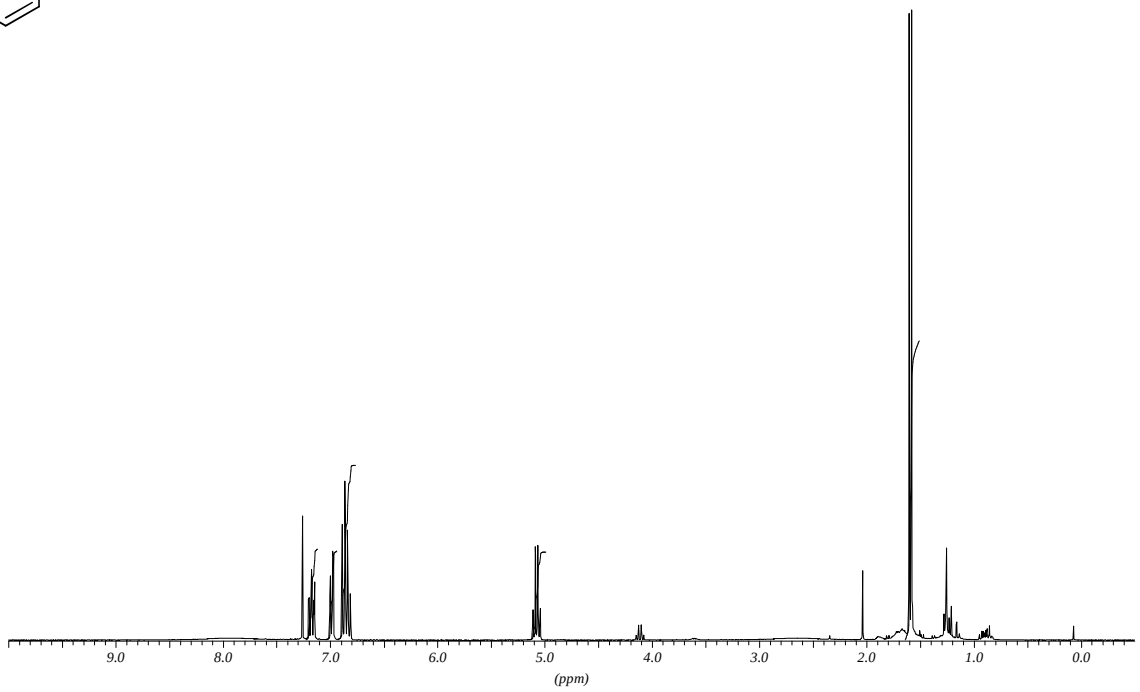


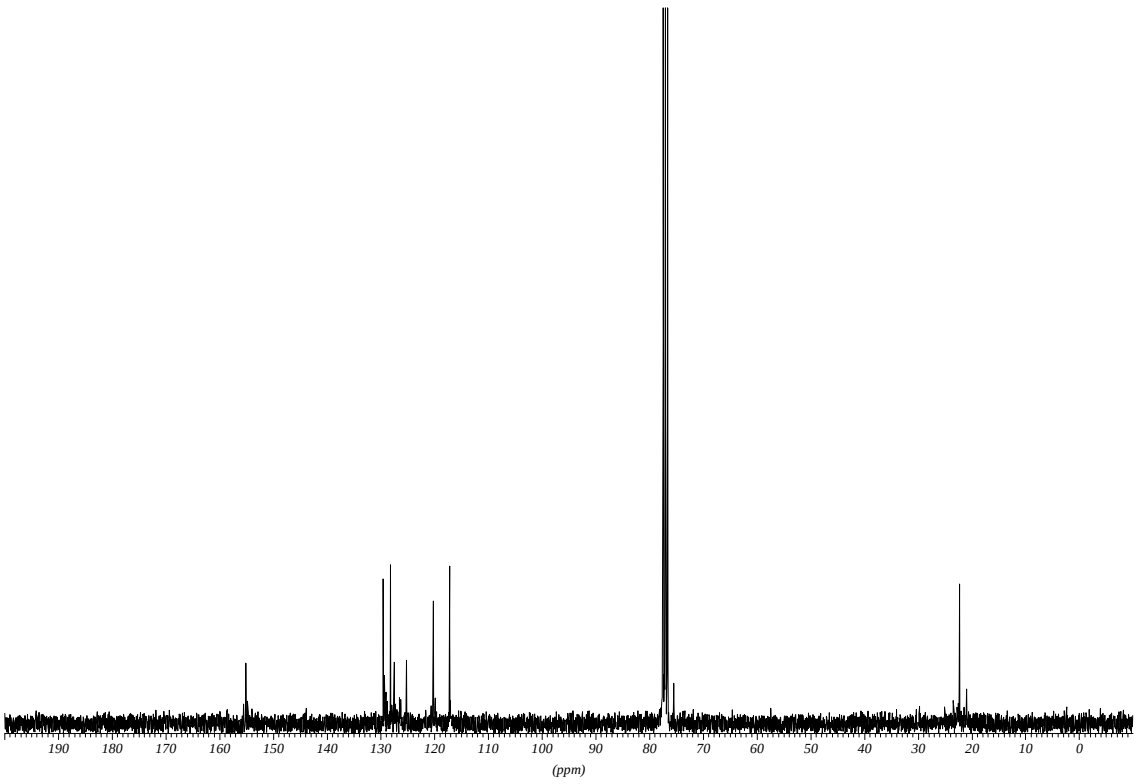




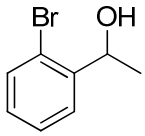
2-(1-hydroxyethyl)phenol (105b)

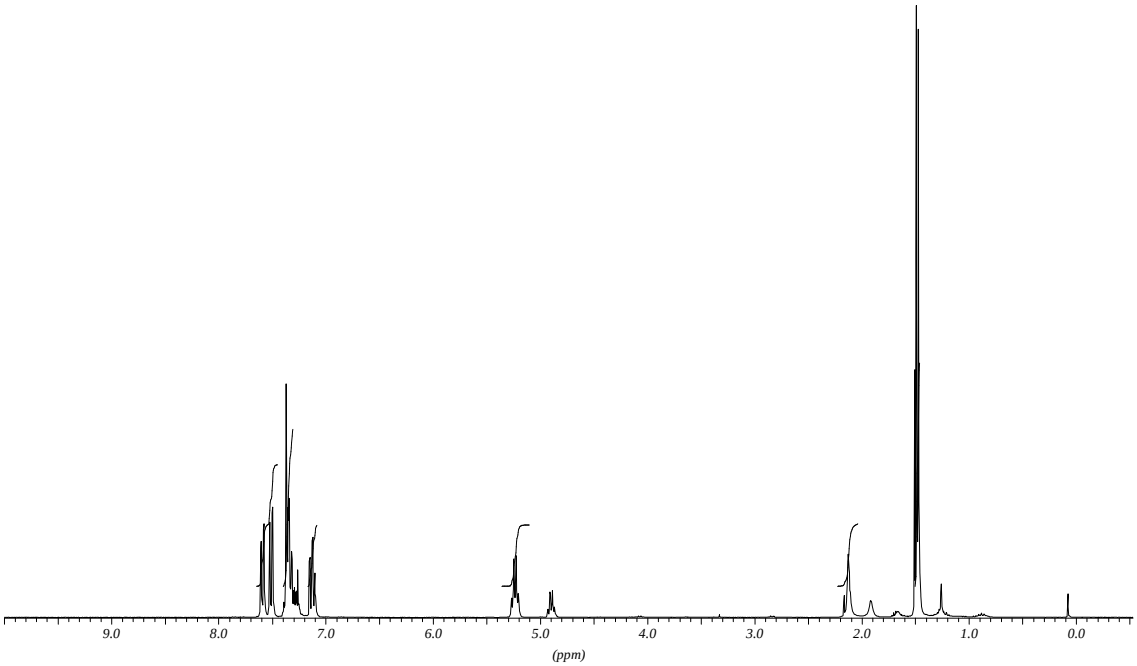


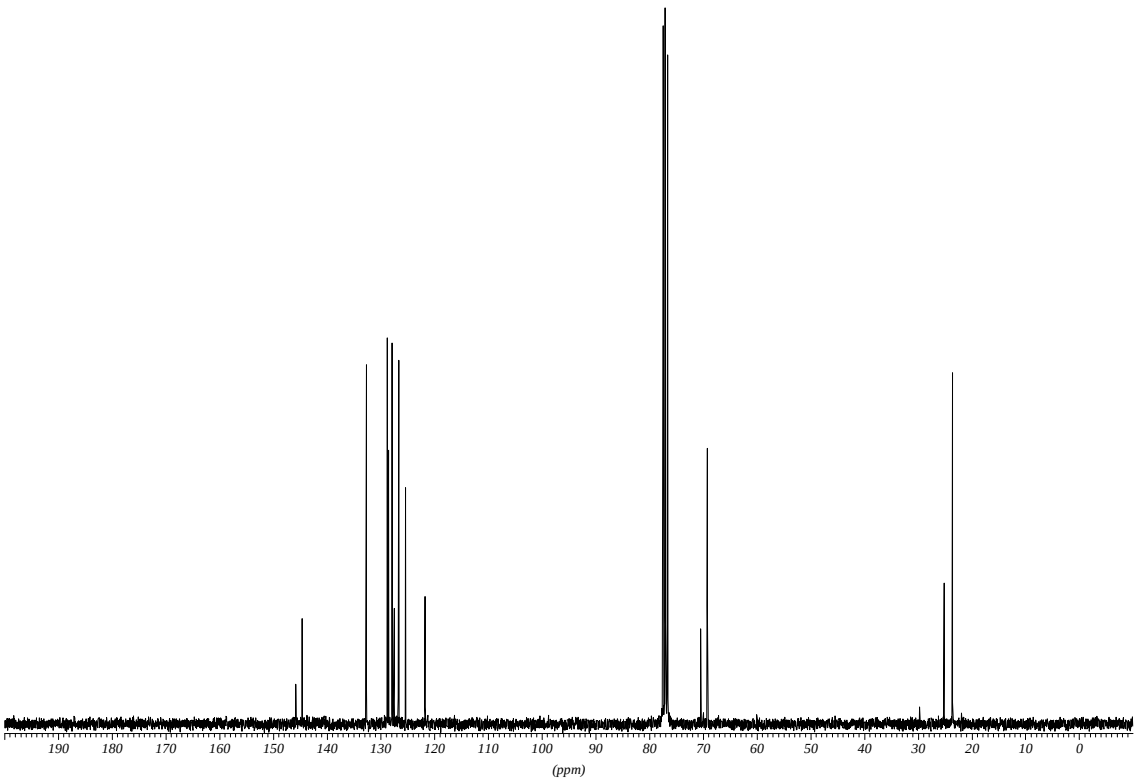




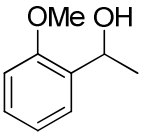
1-(2-bromophenyl)ethanol (106b)

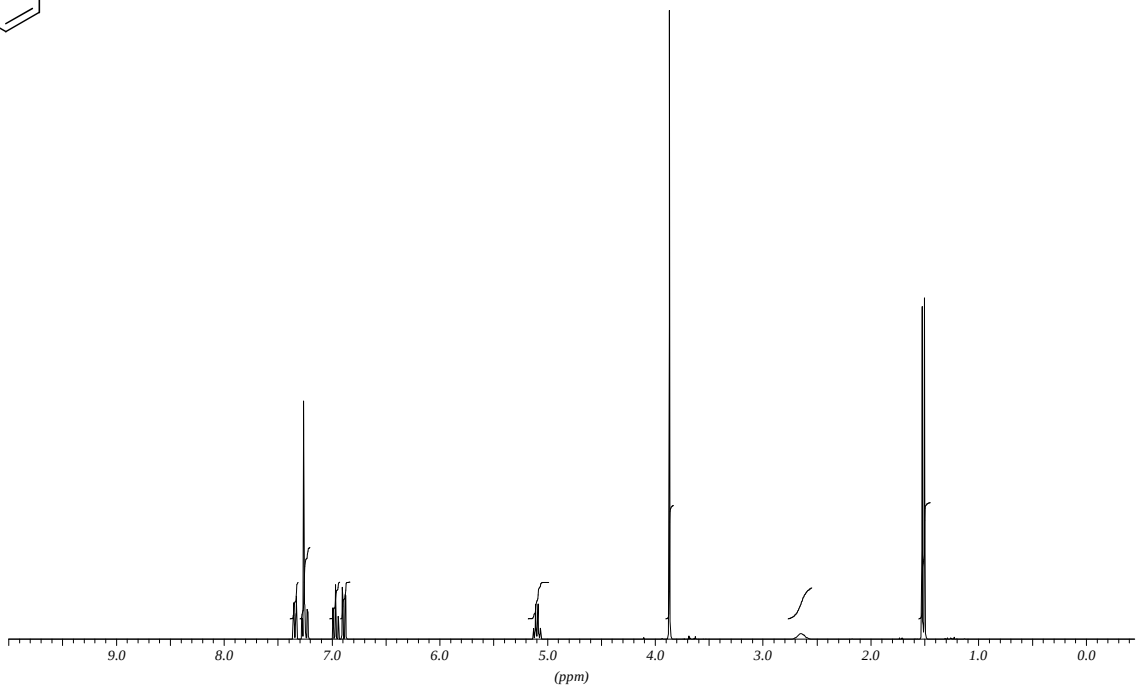


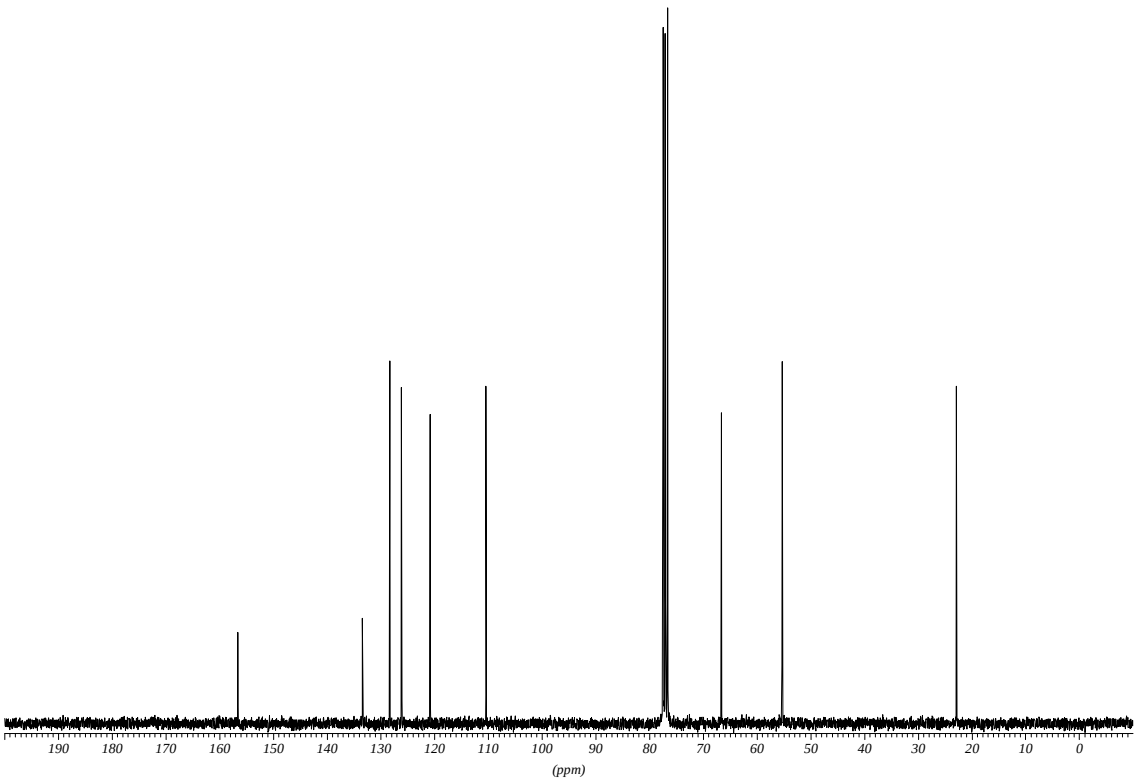




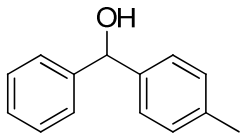
1-(2-methoxyphenyl)ethanol (107b)

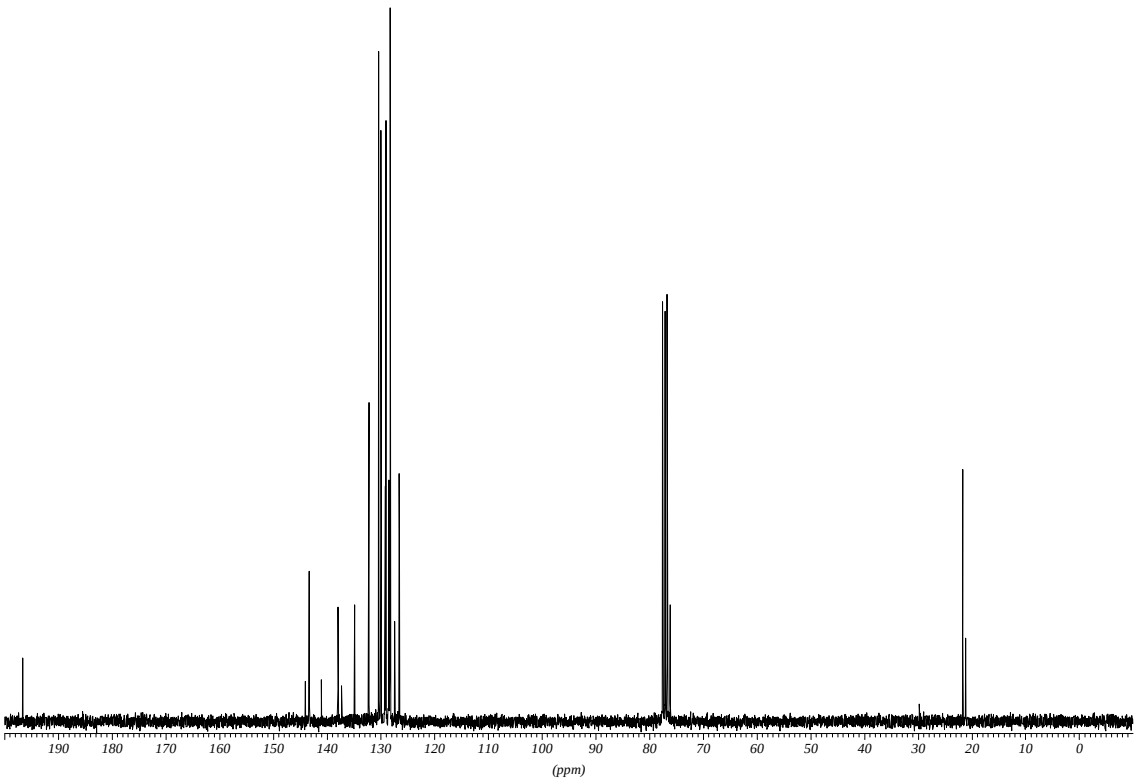




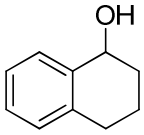


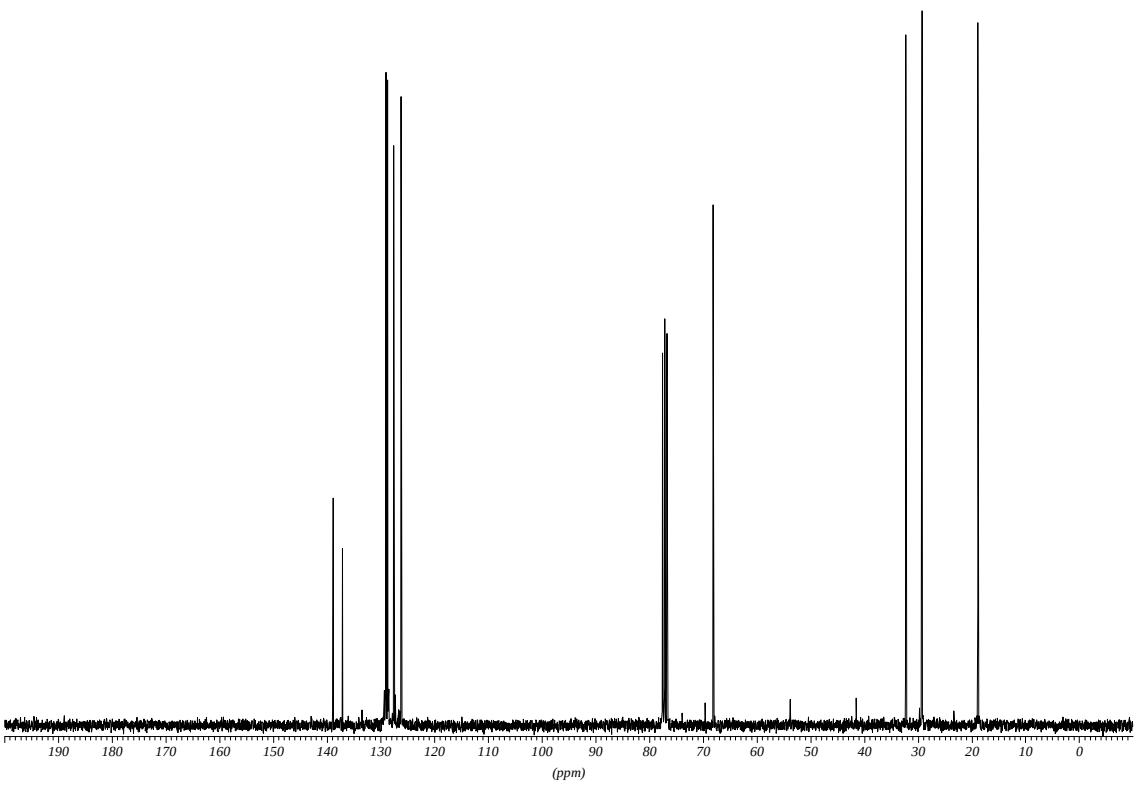
Phenyl(p-tolyl)methanol (108b)



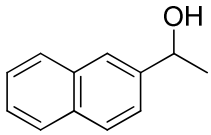


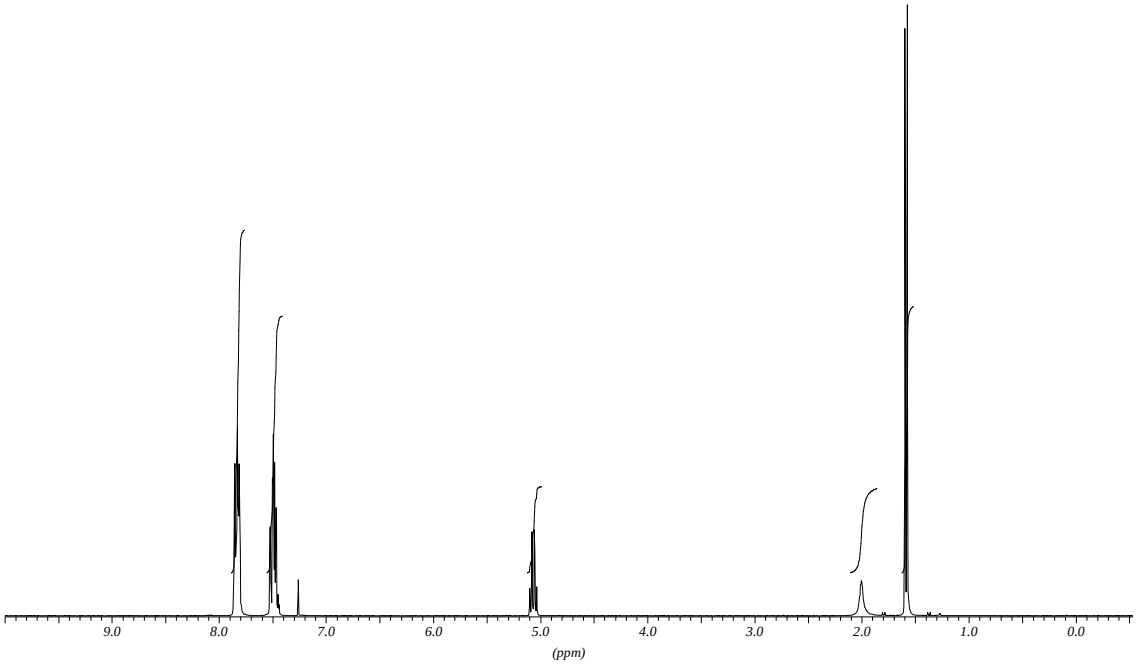
1,2,3,4-tetrahydronaphthalen-1-ol (109b)

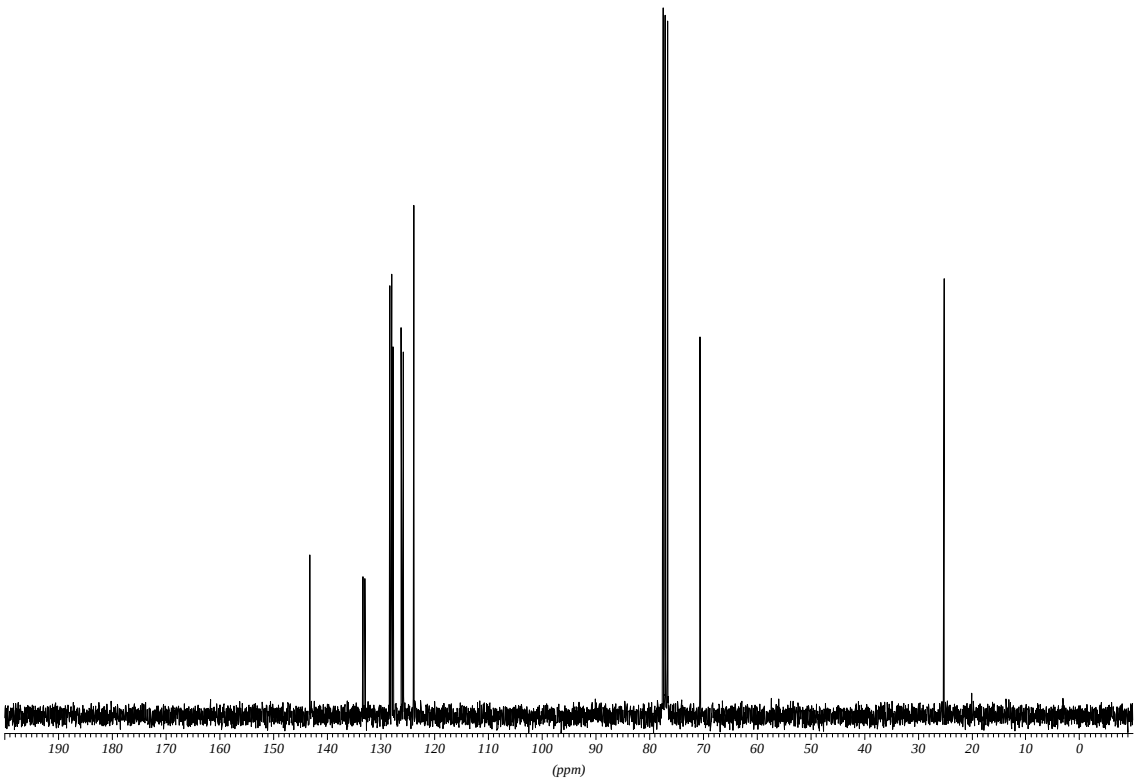




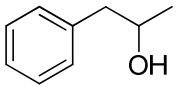
1-(naphthalen-2-yl)ethanol (110b)

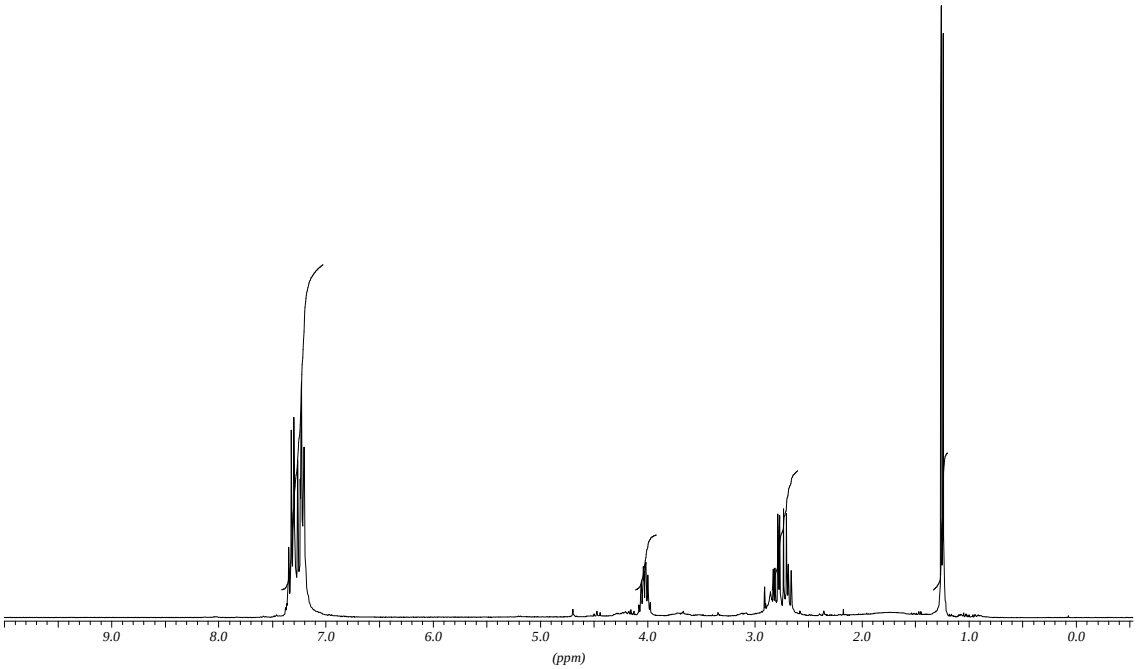


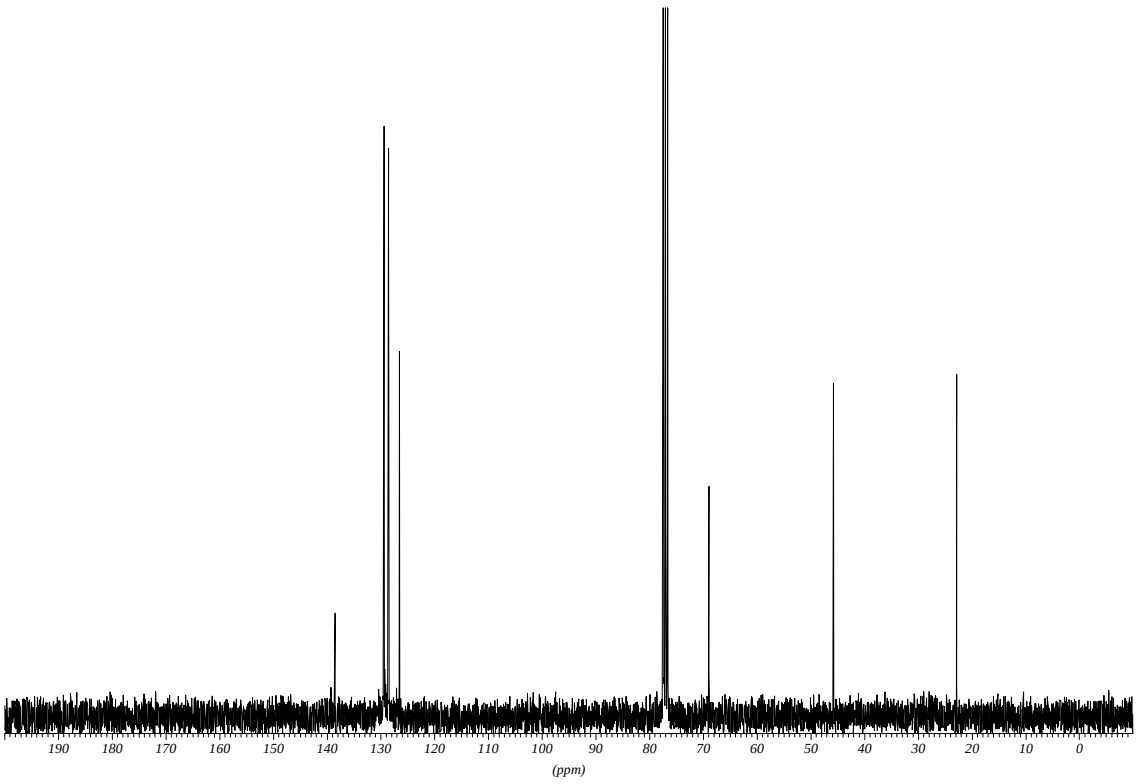




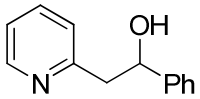
1-phenylpropan-2-ol (111b)

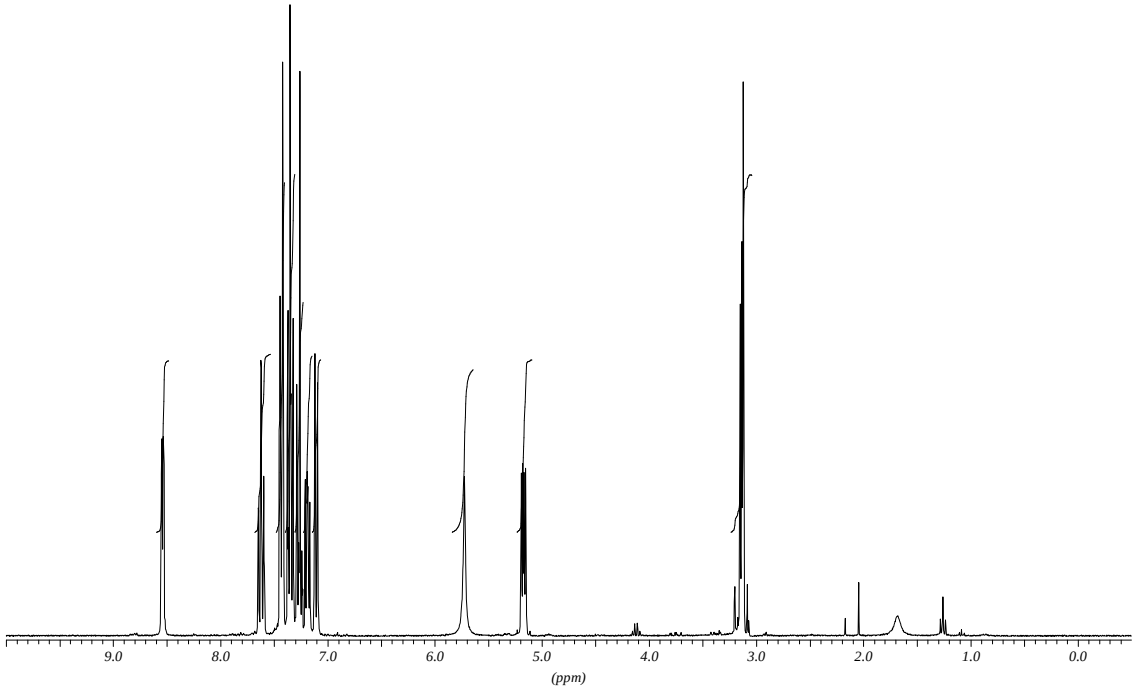


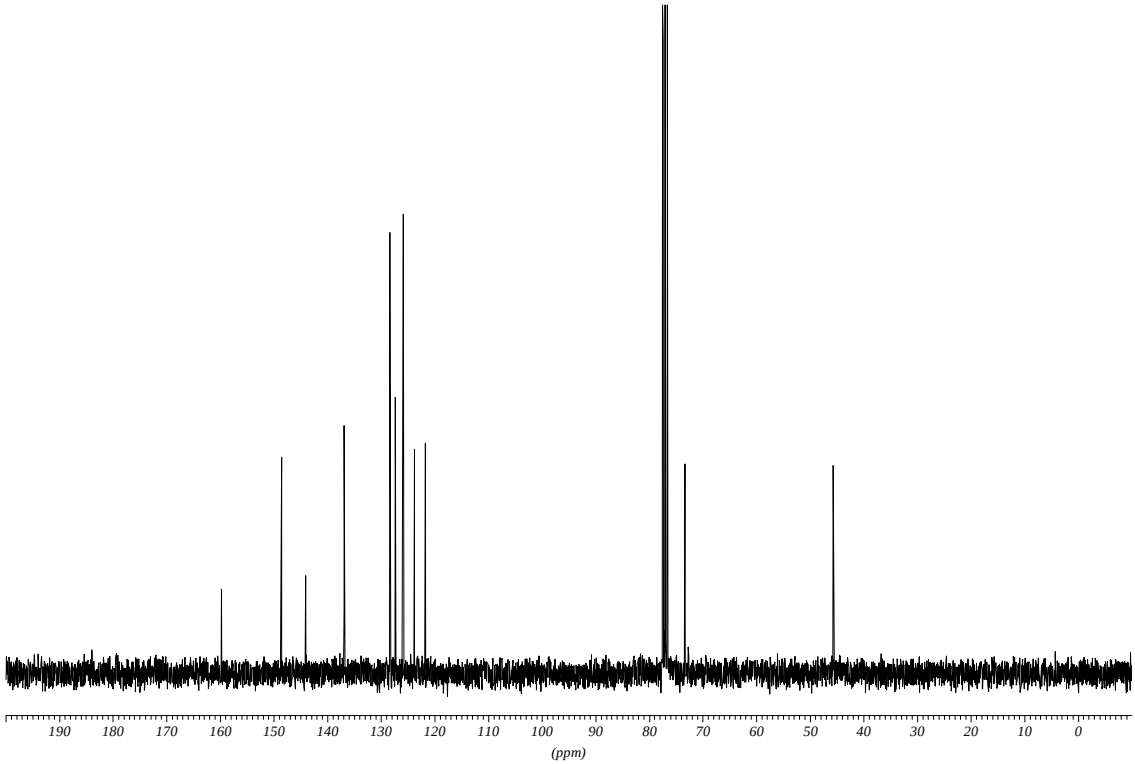




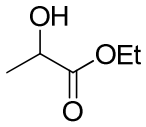
1-phenyl-2-(pyridin-2-yl)ethanol (112b)

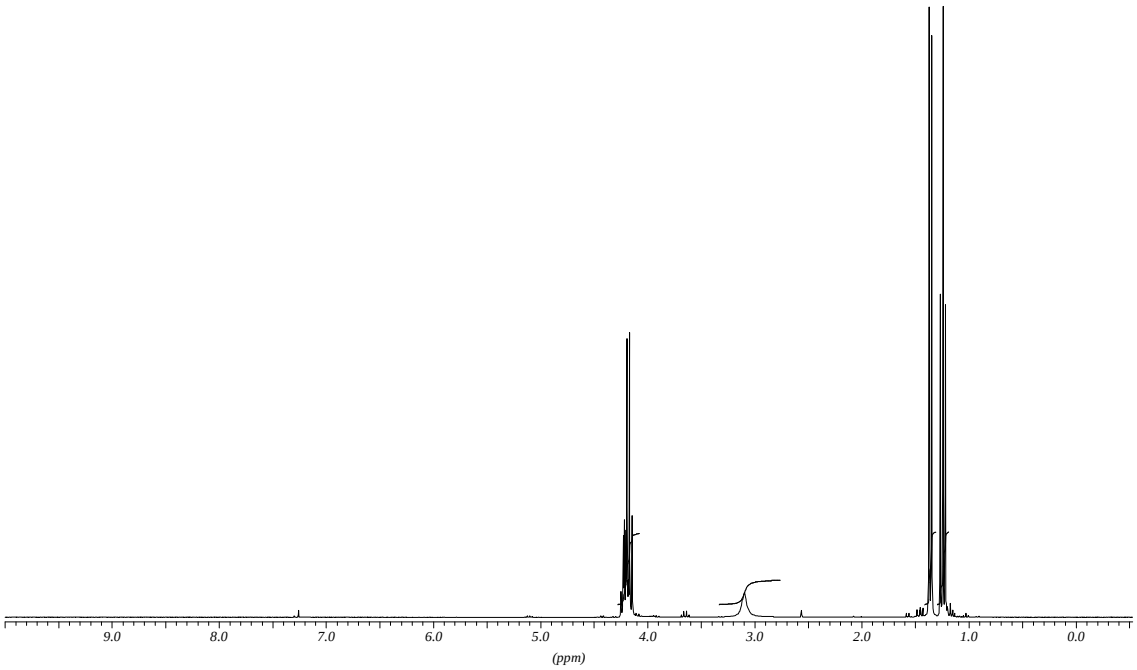


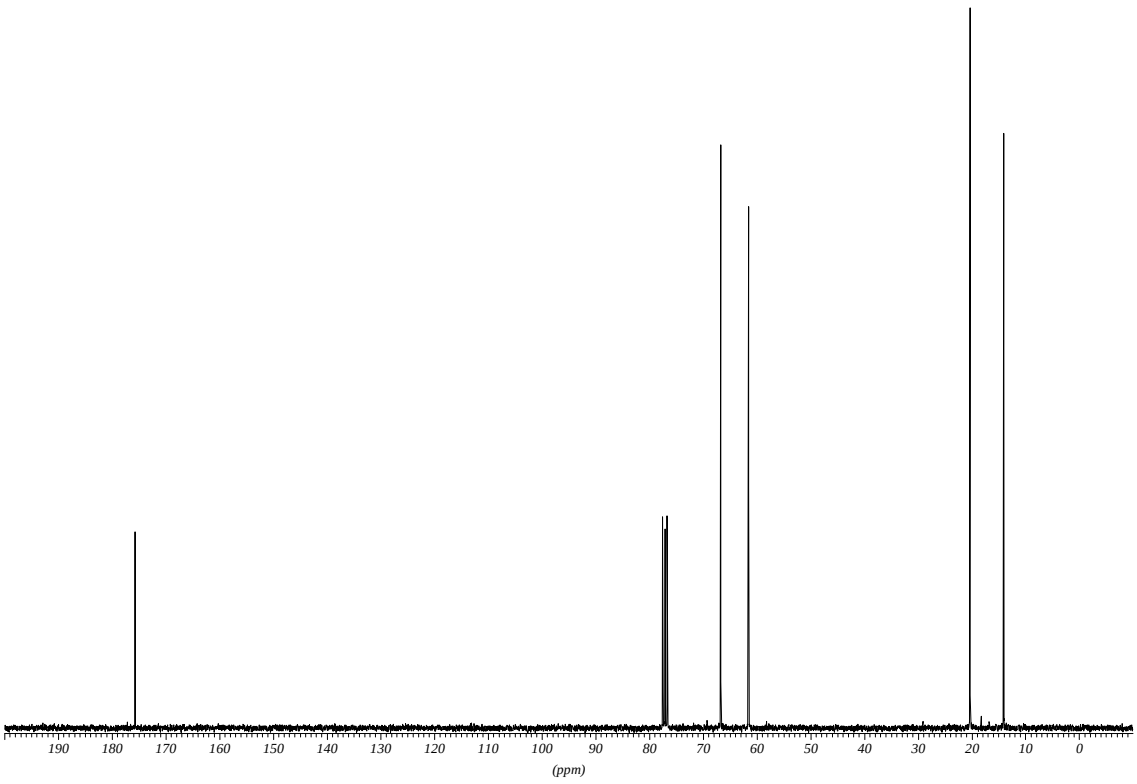




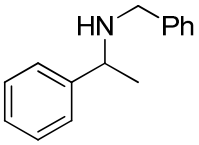
Ethyl 2-hydroxypropanoate (113b)

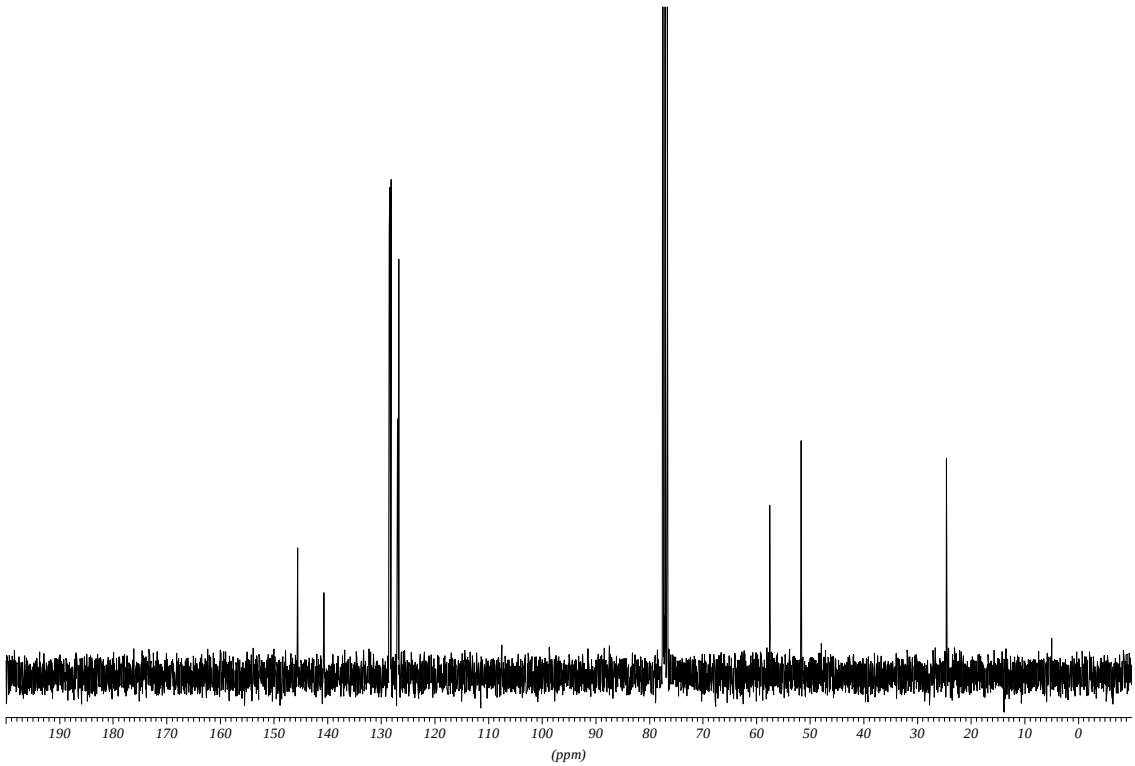




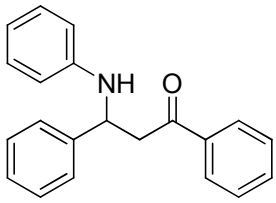


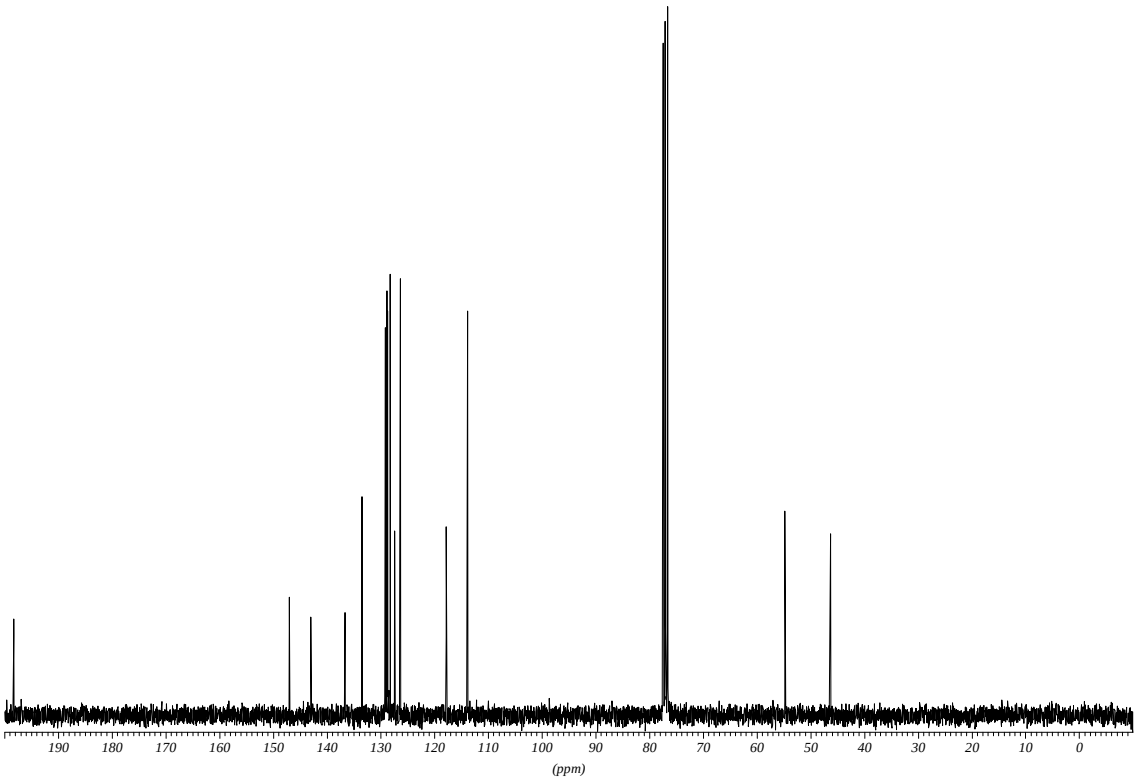
N-benzyl-1-phenylethanamine (114b)



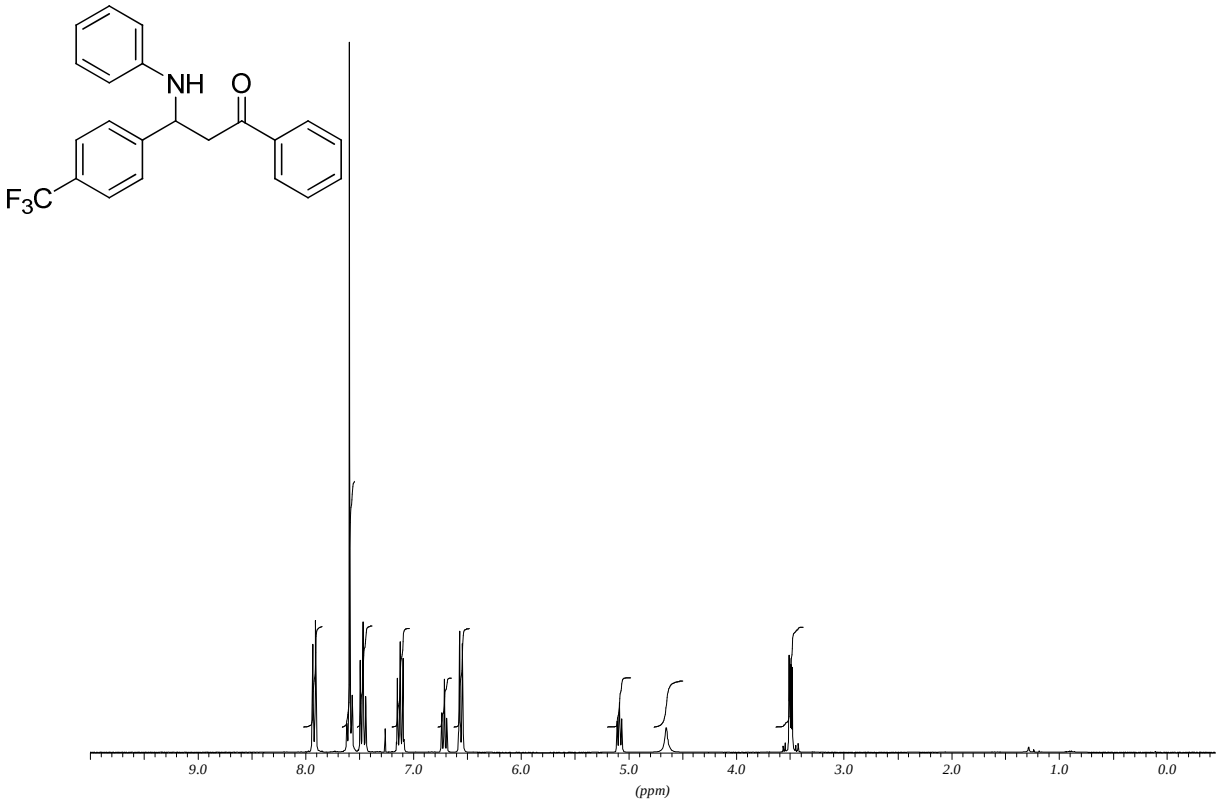


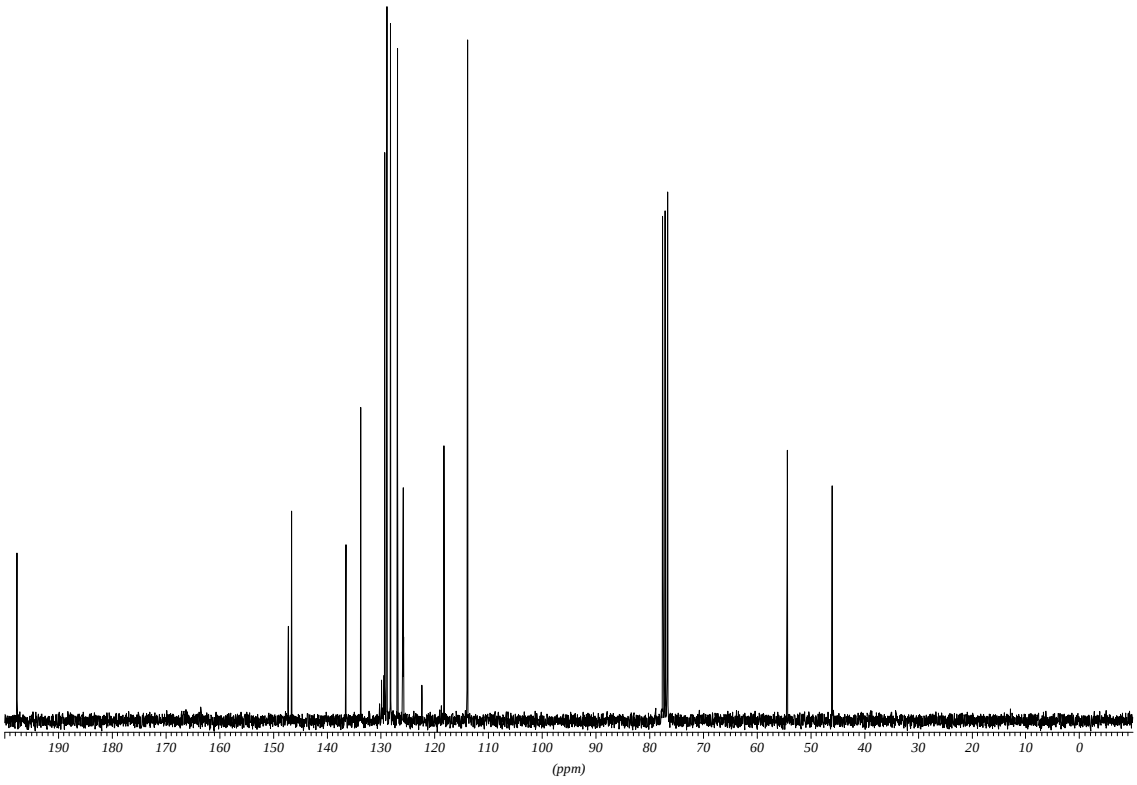
1,3-diphenyl-3-(phenylamino)propan-1-one (137a)



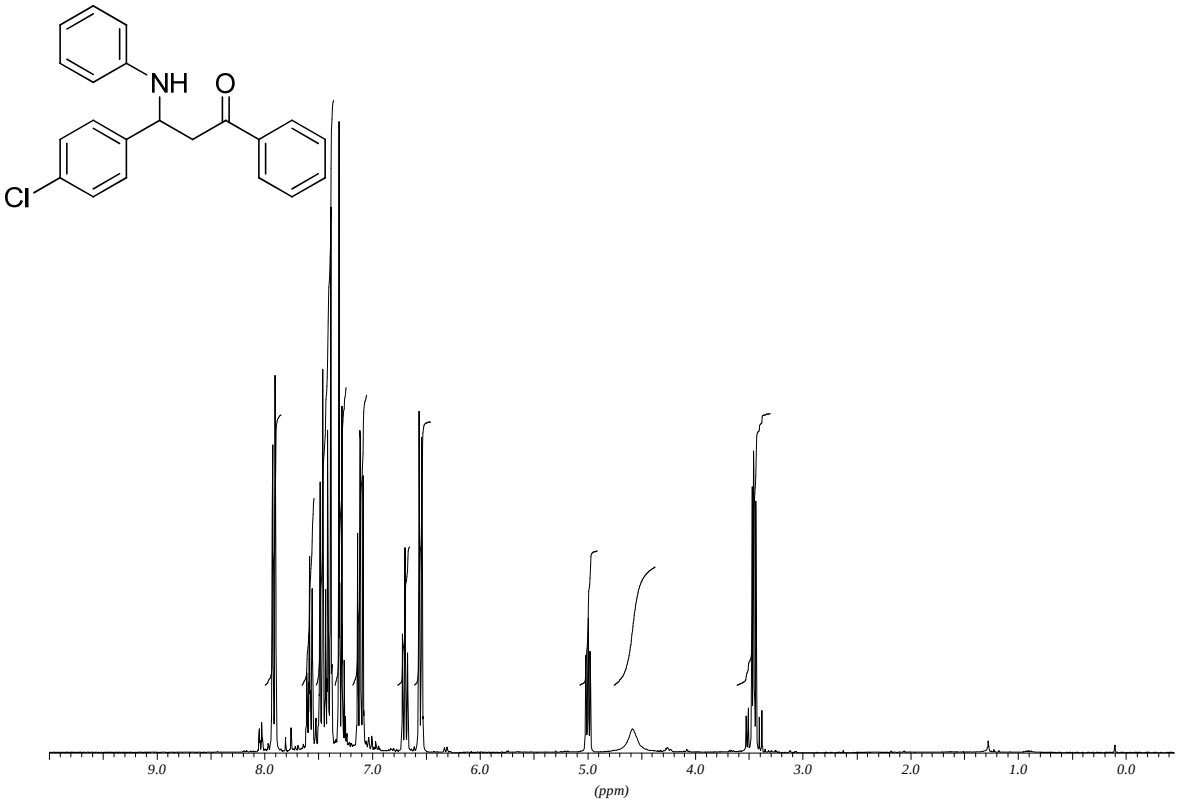


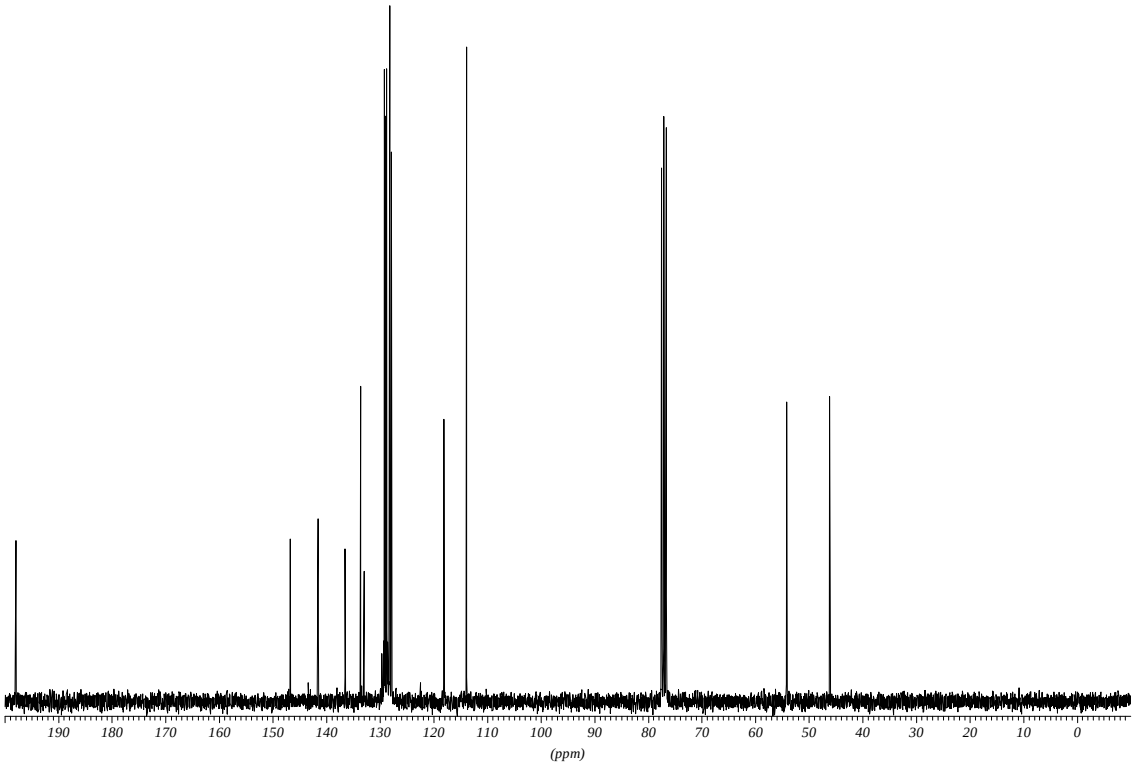
1-phenyl-3-(phenylamino)-3-(4-(trifluoromethyl)phenyl)propan-1-one (137f)



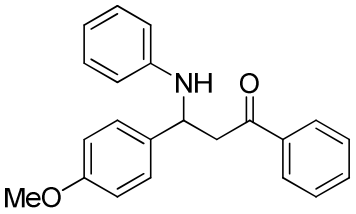


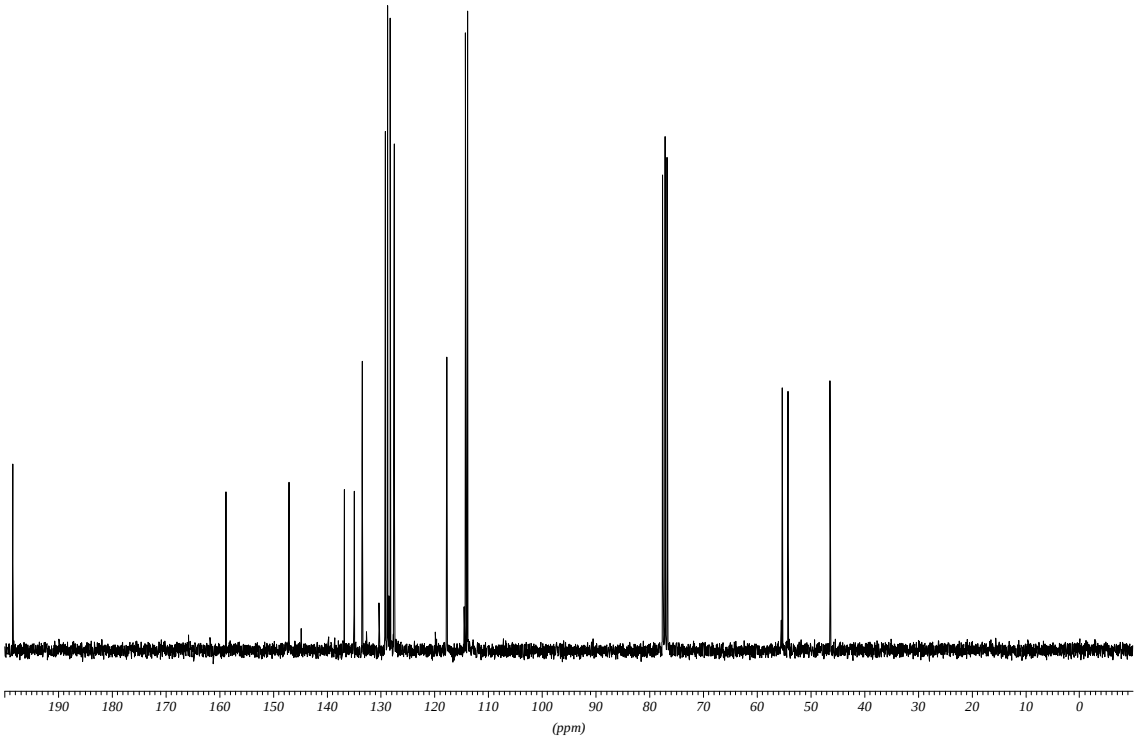
3-(4-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (137e)



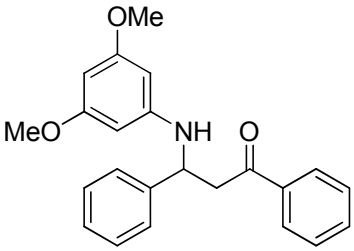


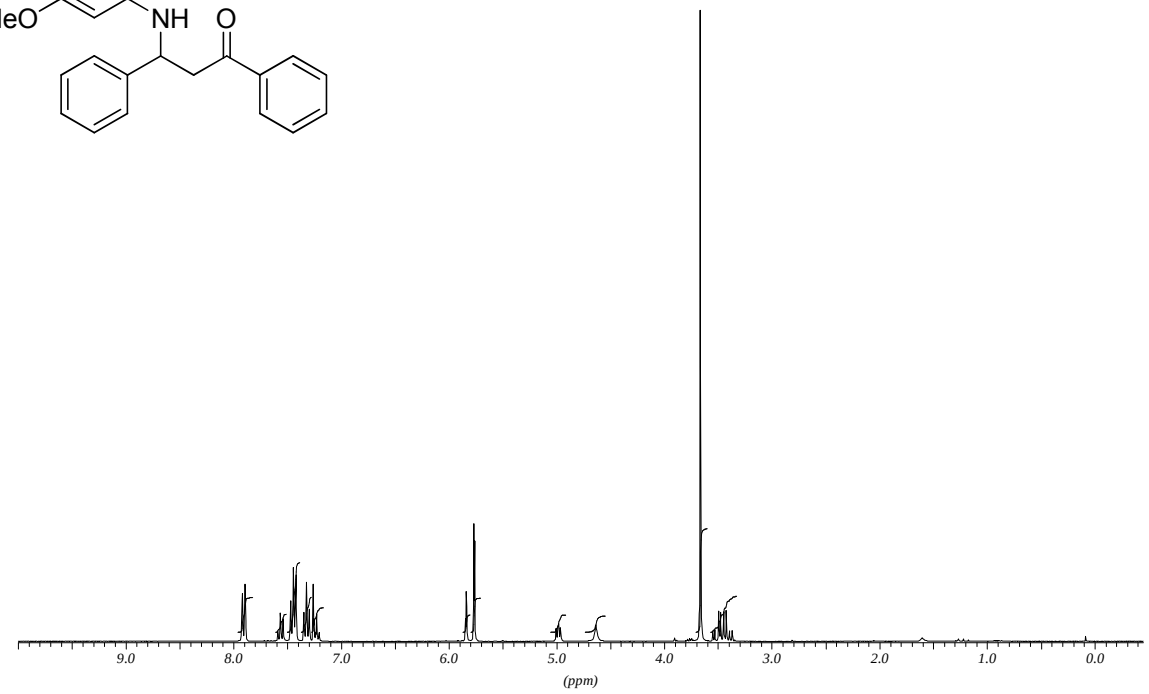
3-(4-methoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (137d)

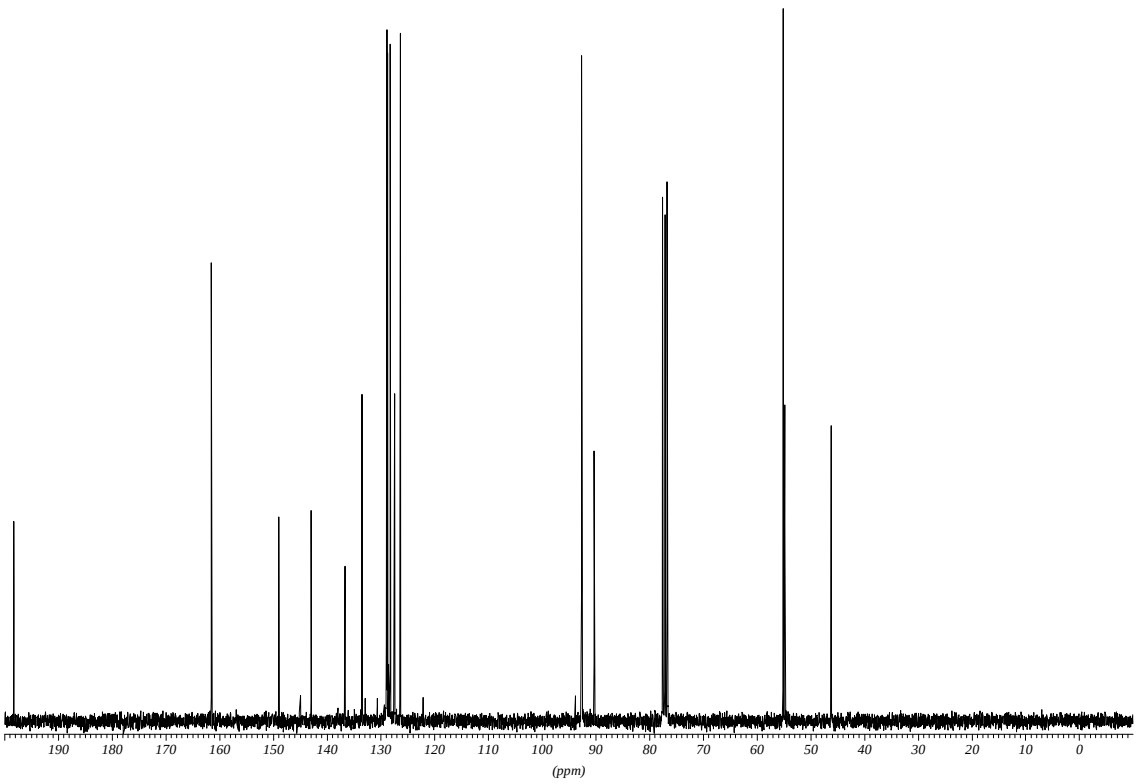




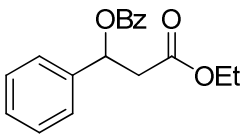
3-(3,5-dimethoxyphenylamino)-1,3-diphenylpropan-1-one (146a)

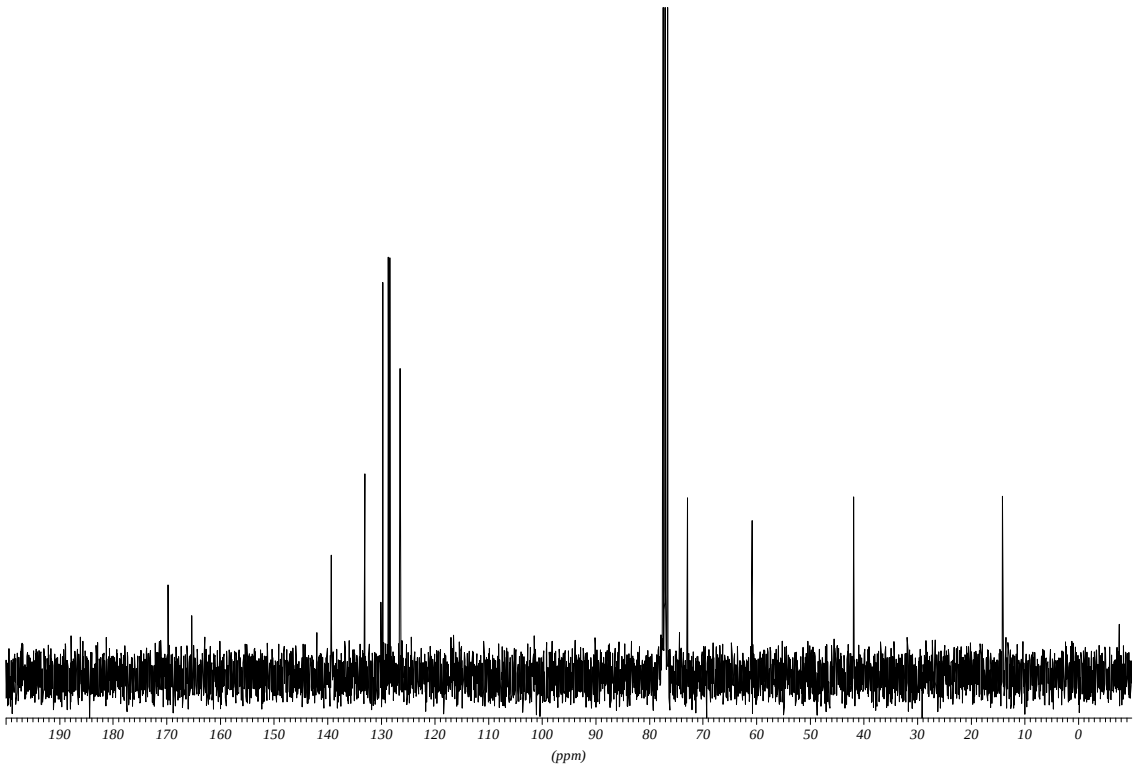




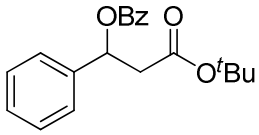


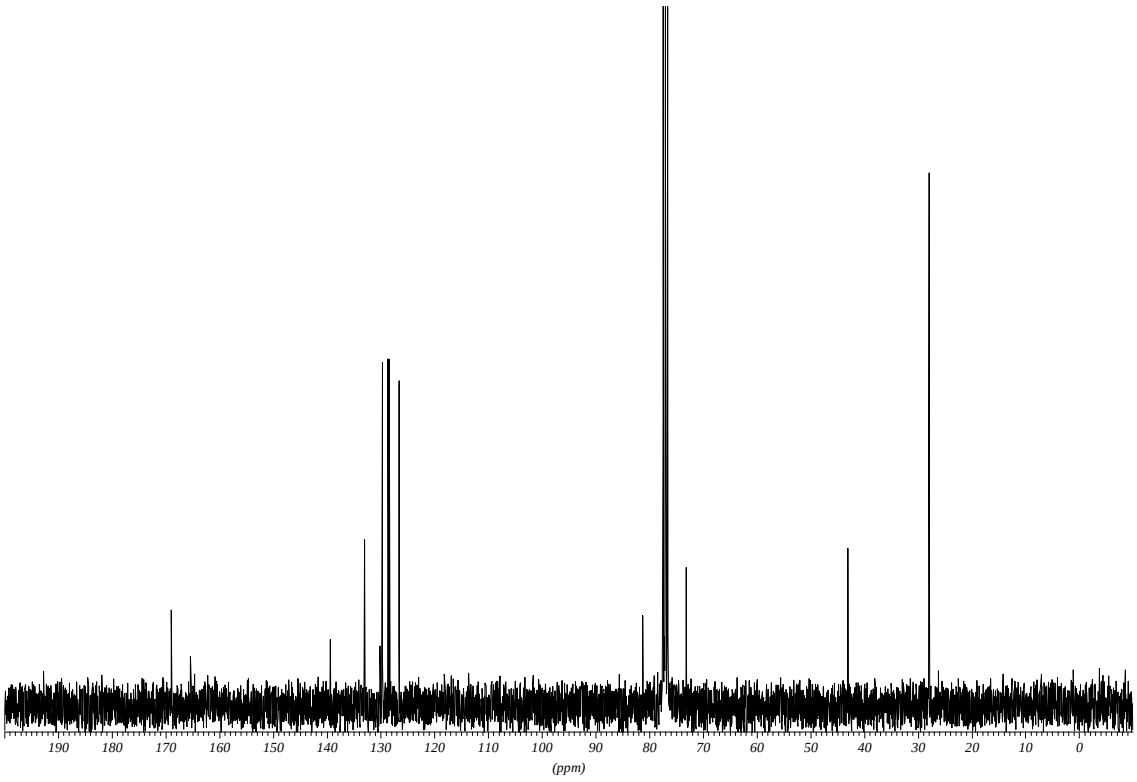
3-ethoxy-3-oxo-1-phenylpropyl benzoate (172)



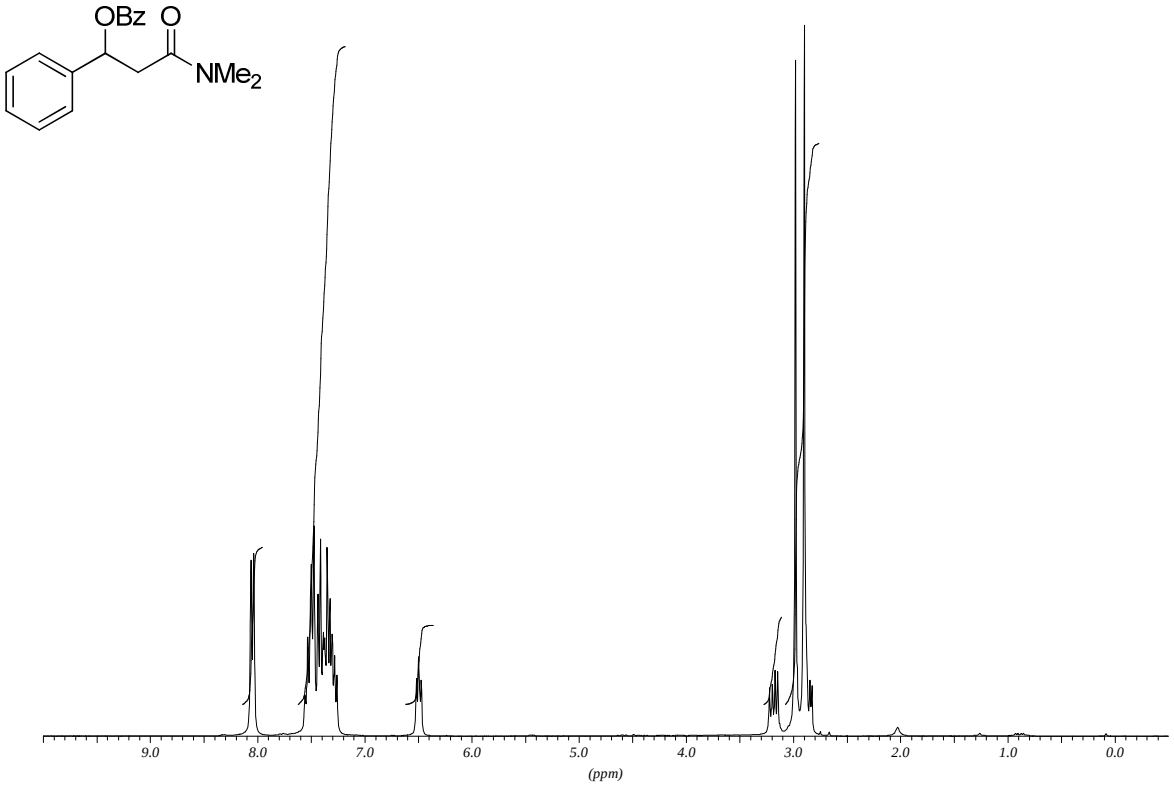


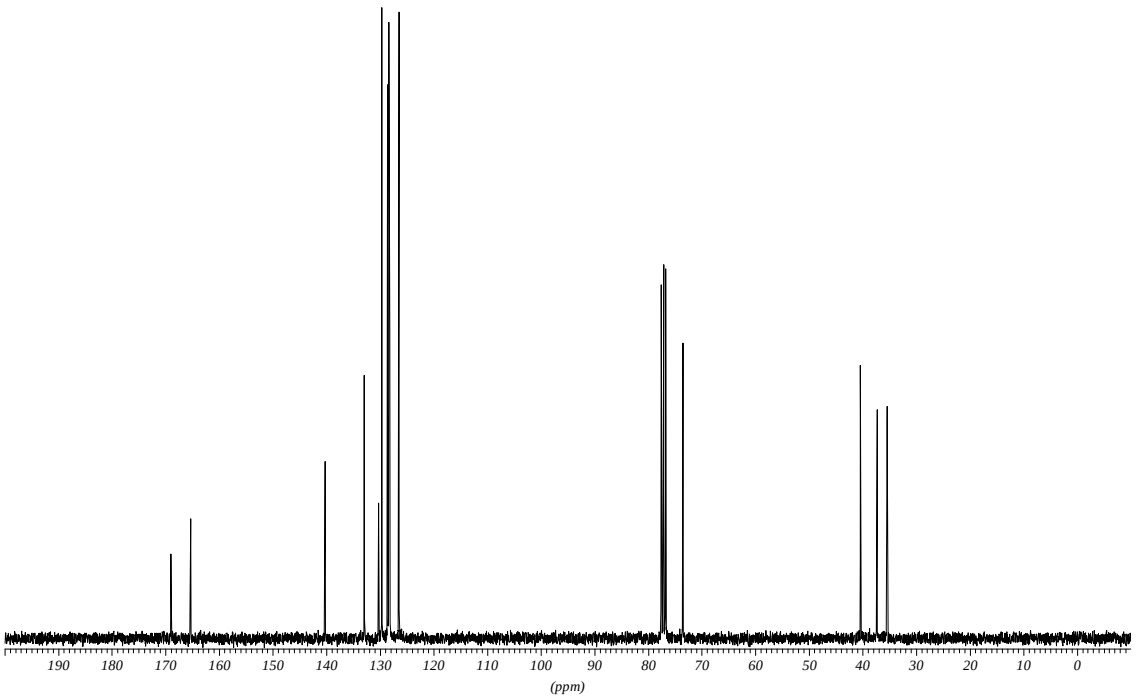
3-tert-butoxy-3-oxo-1-phenylpropyl benzoate (173)



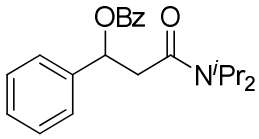


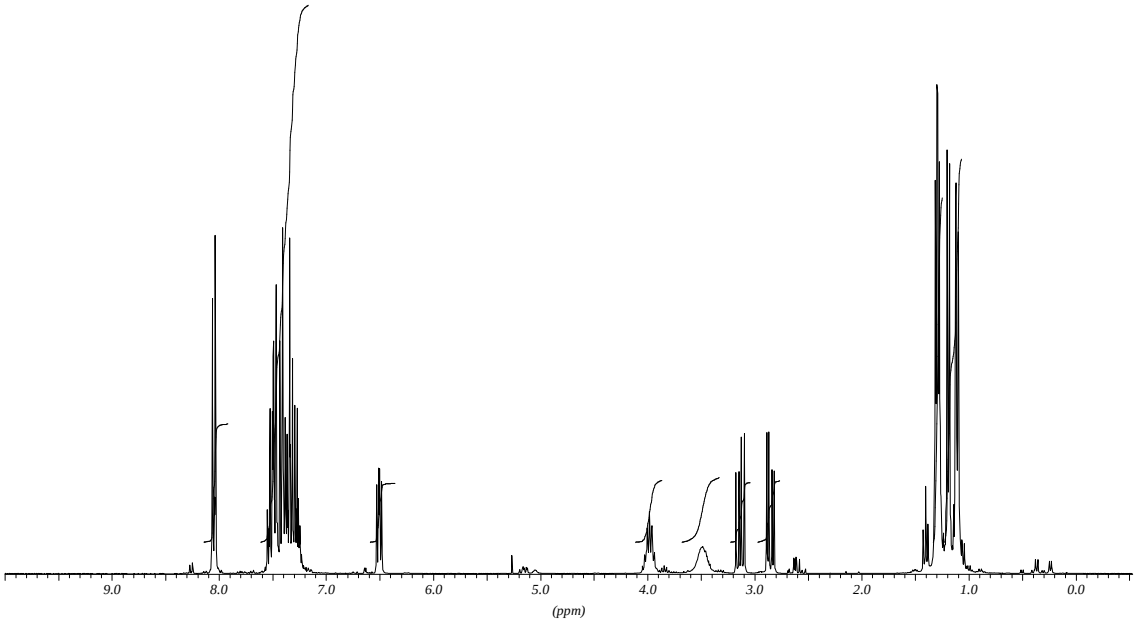
3-(dimethylamino)-3-oxo-1-phenylpropyl benzoate (175)

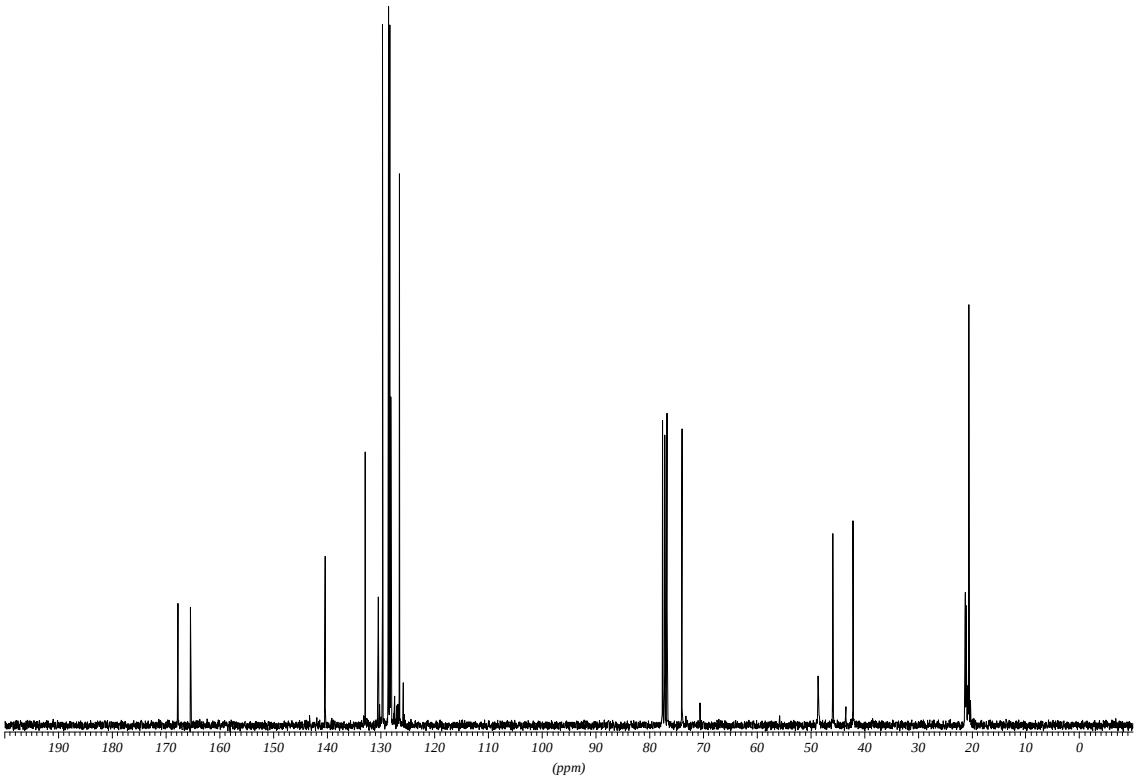




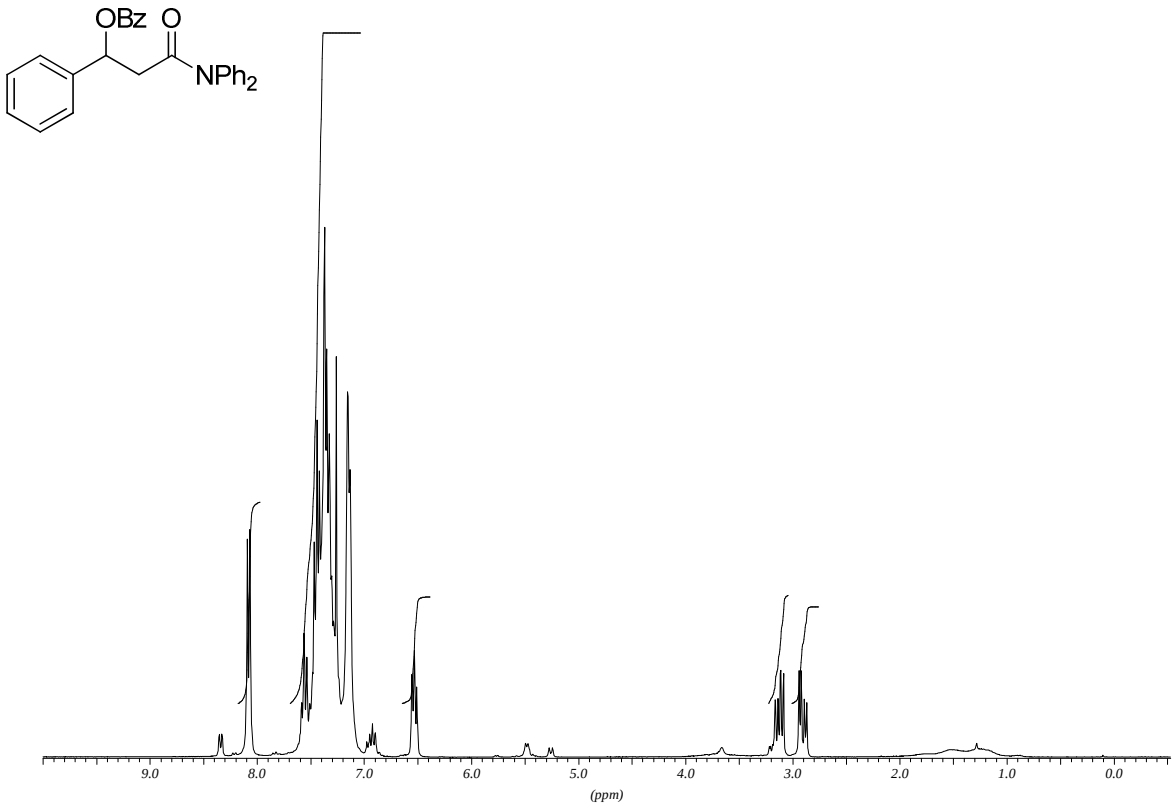
3-(diisopropylamino)-3-oxo-1-phenylpropyl benzoate (176a)

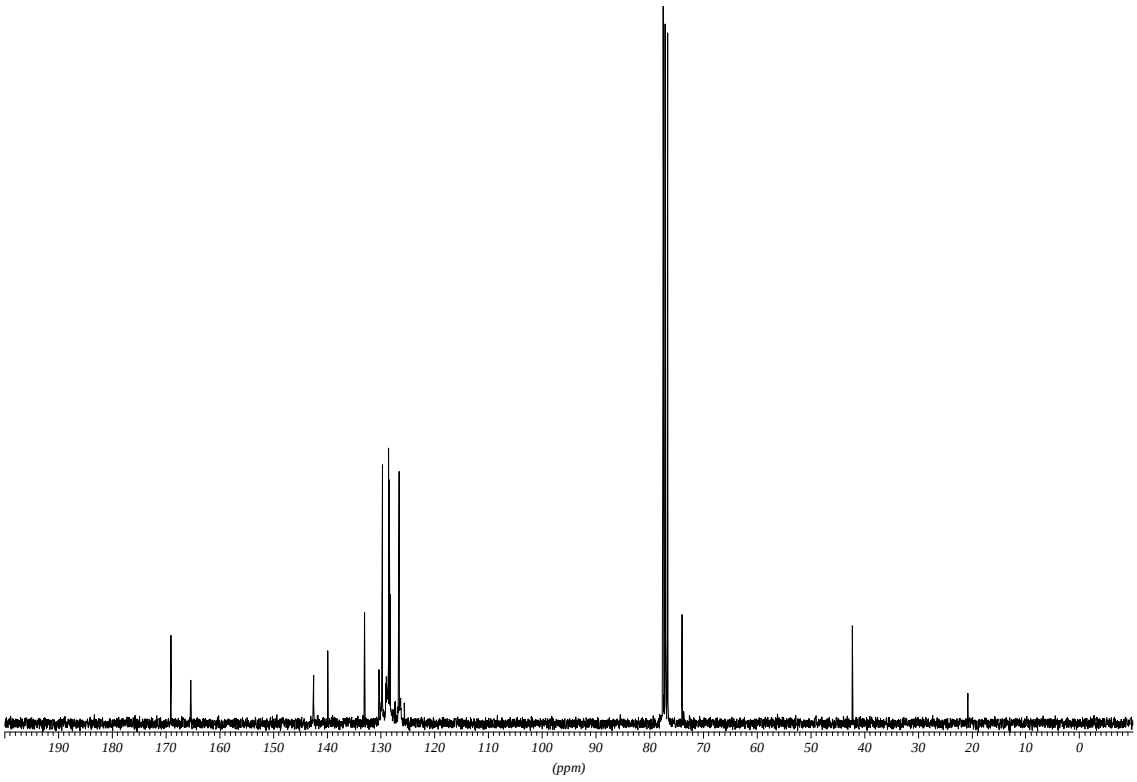




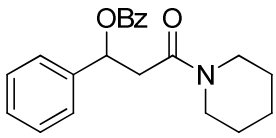


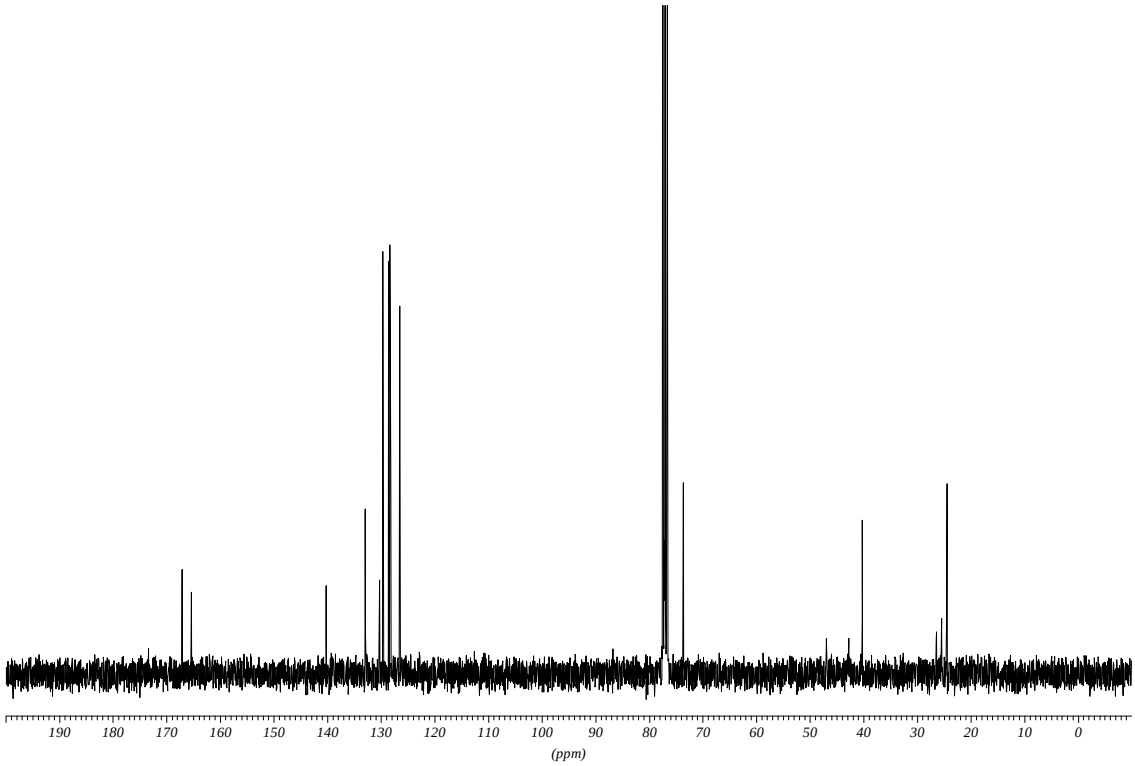
3-(diphenylamino)-3-oxo-1-phenylpropyl benzoate (176b)



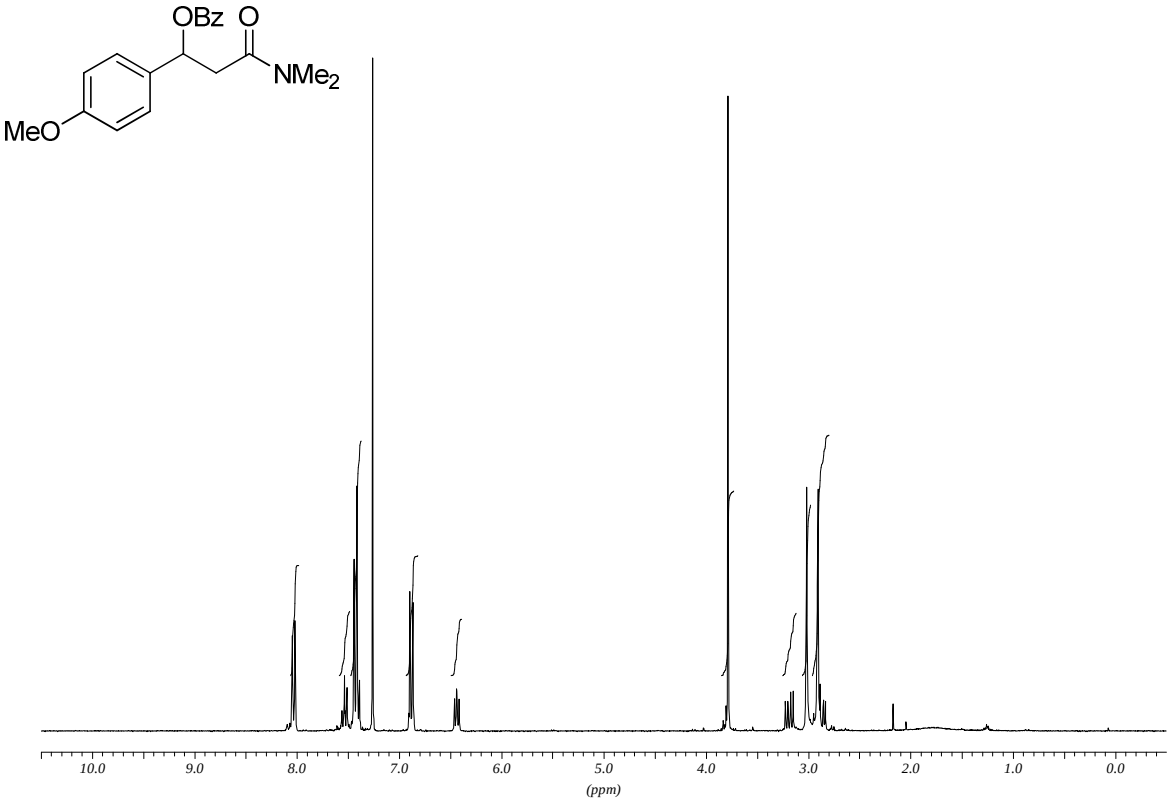


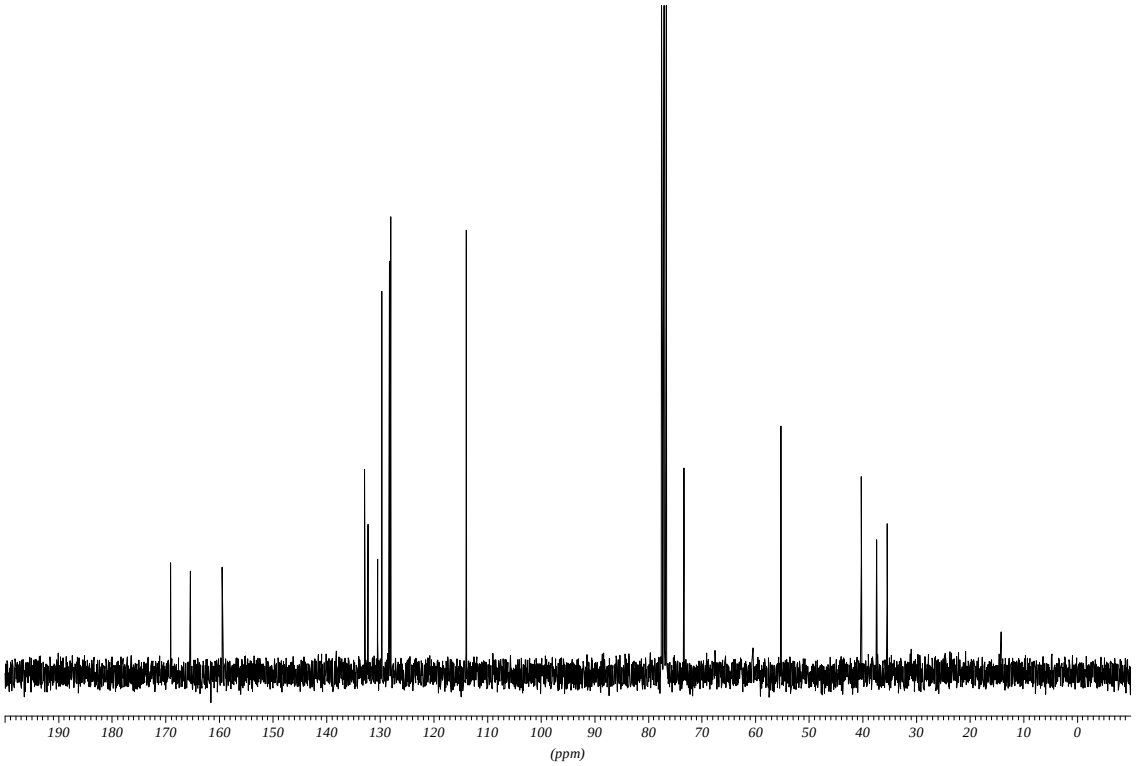
3-oxo-1-phenyl-3-(piperidin-1-yl)propyl benzoate (176c)



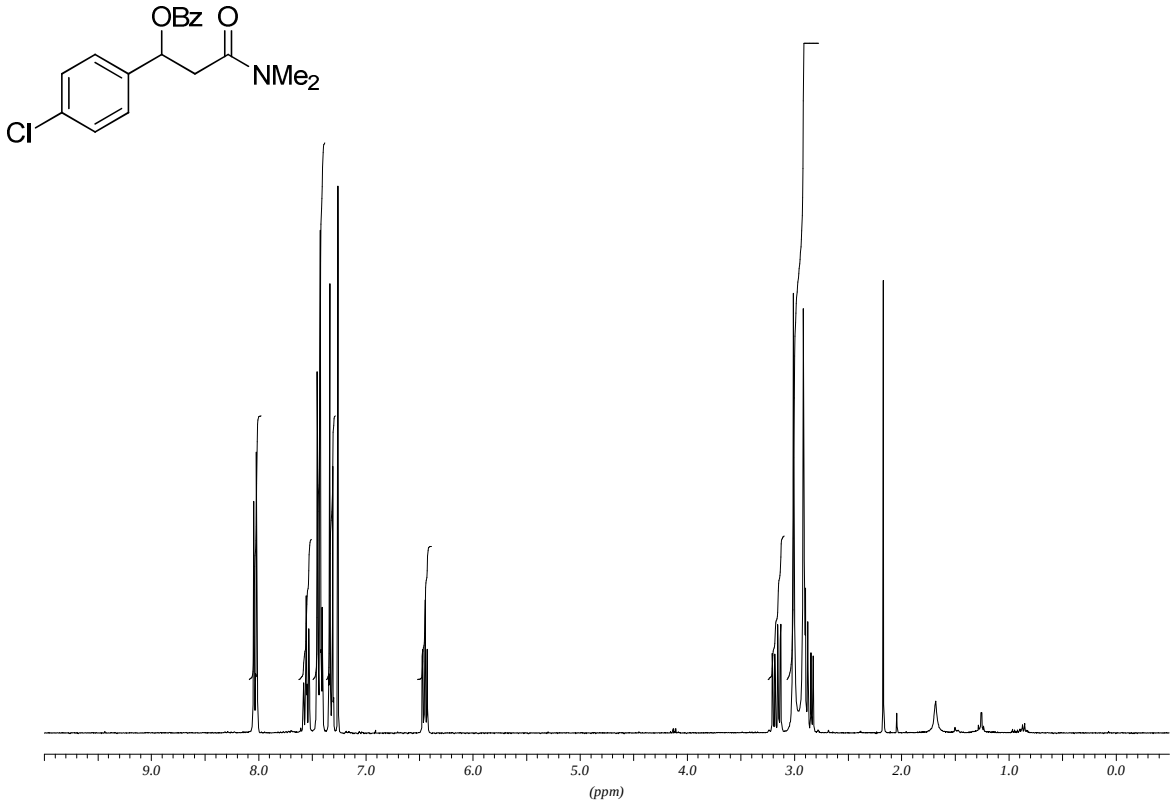


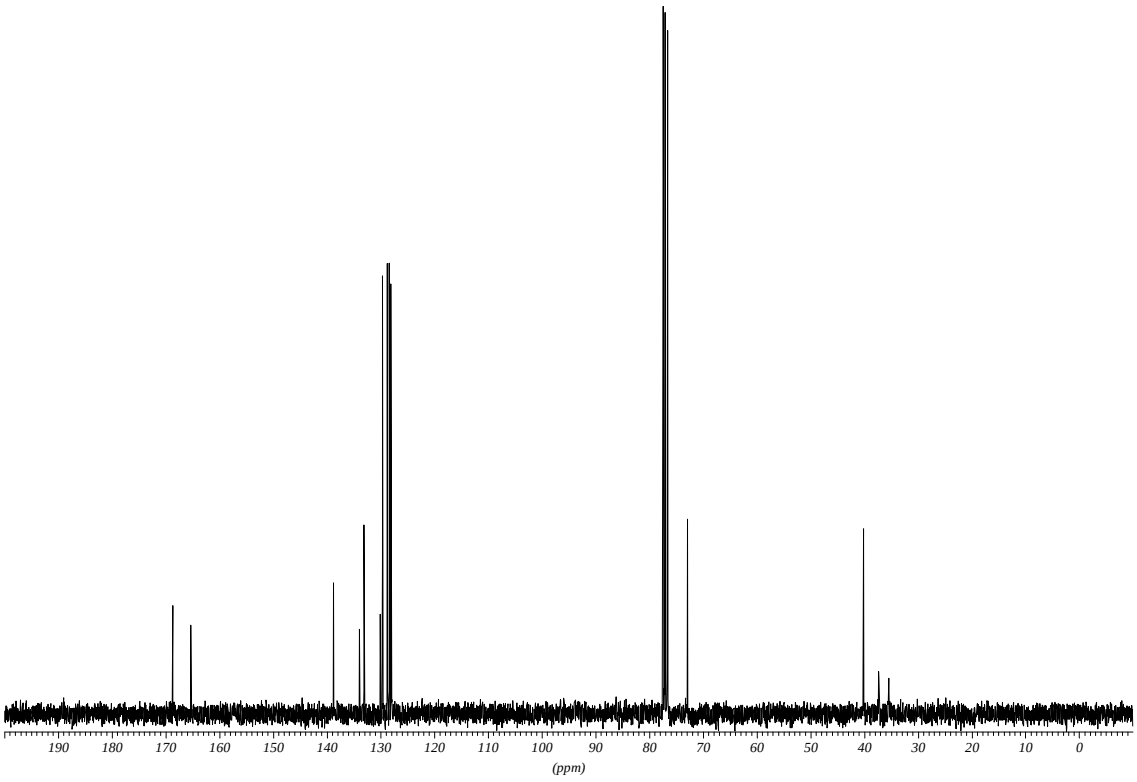
3-(dimethylamino)-1-(4-methoxyphenyl)-3-oxopropyl benzoate (176d)



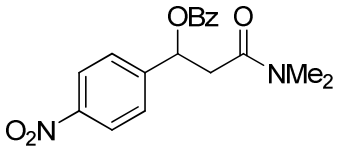


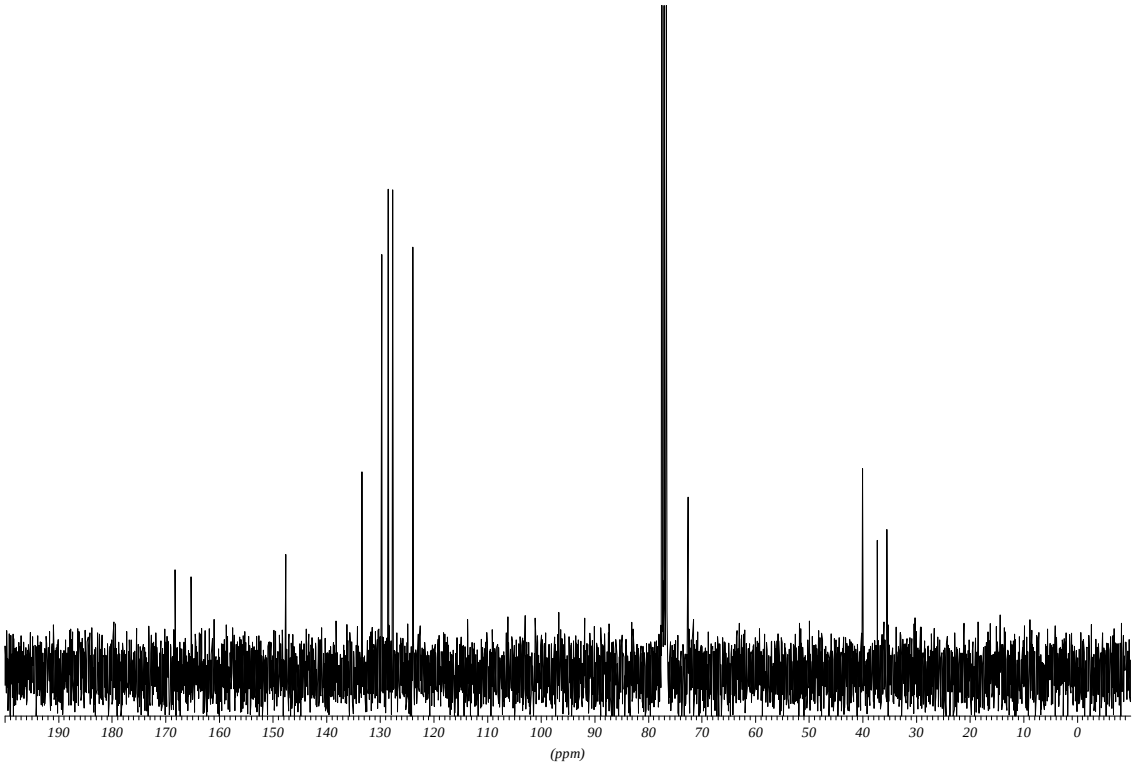
1-(4-chlorophenyl)-3-(dimethylamino)-3-oxopropyl benzoate (176e)



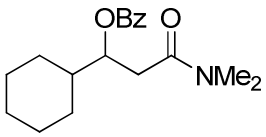


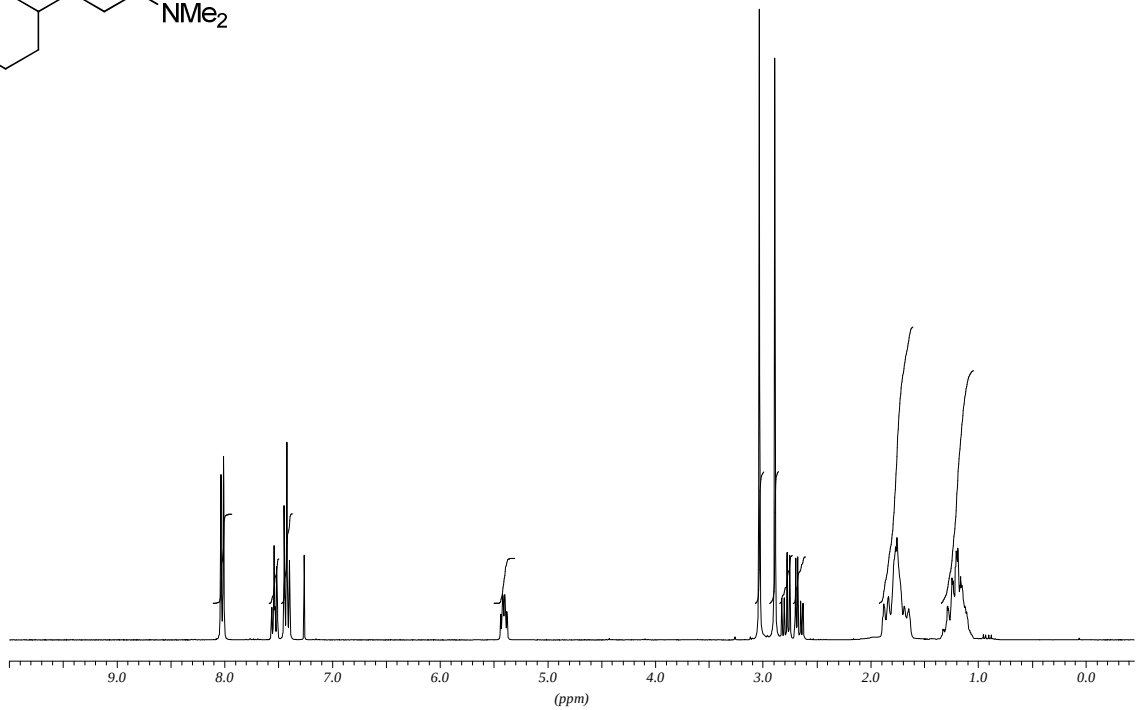
3-(dimethylamino)-1-(4-nitrophenyl)-3-oxopropyl benzoate (176f)

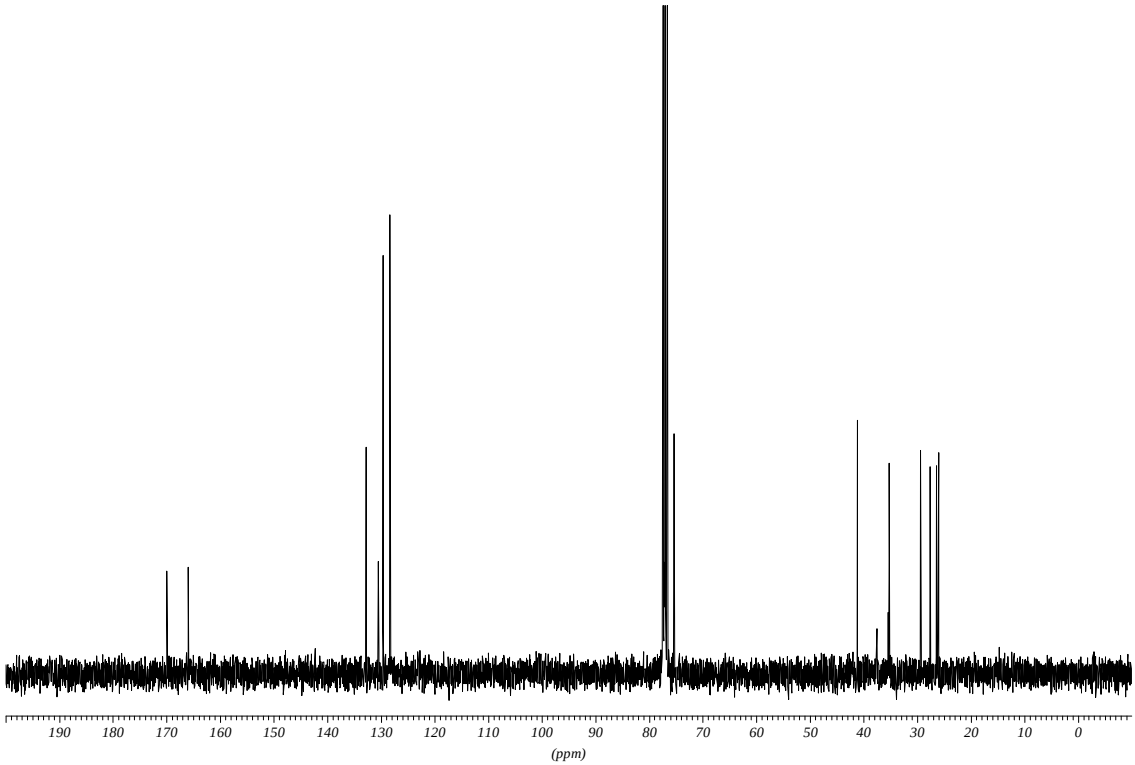




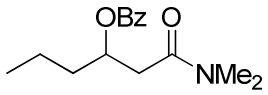
1-cyclohexyl-3-(dimethylamino)-3-oxopropyl benzoate (176g)

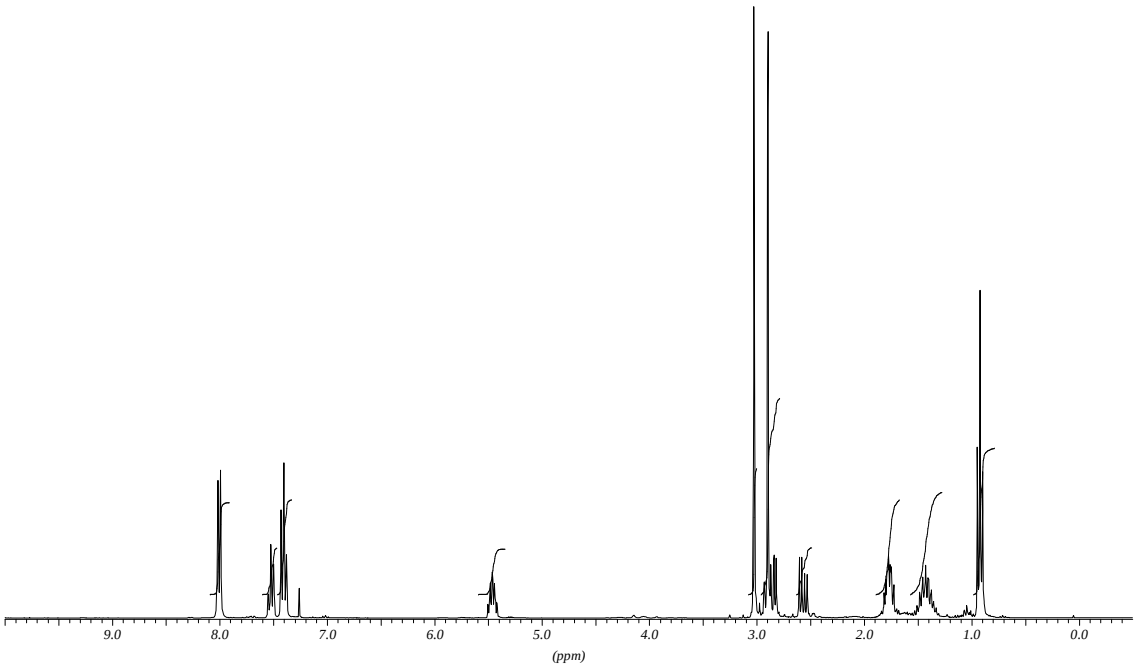


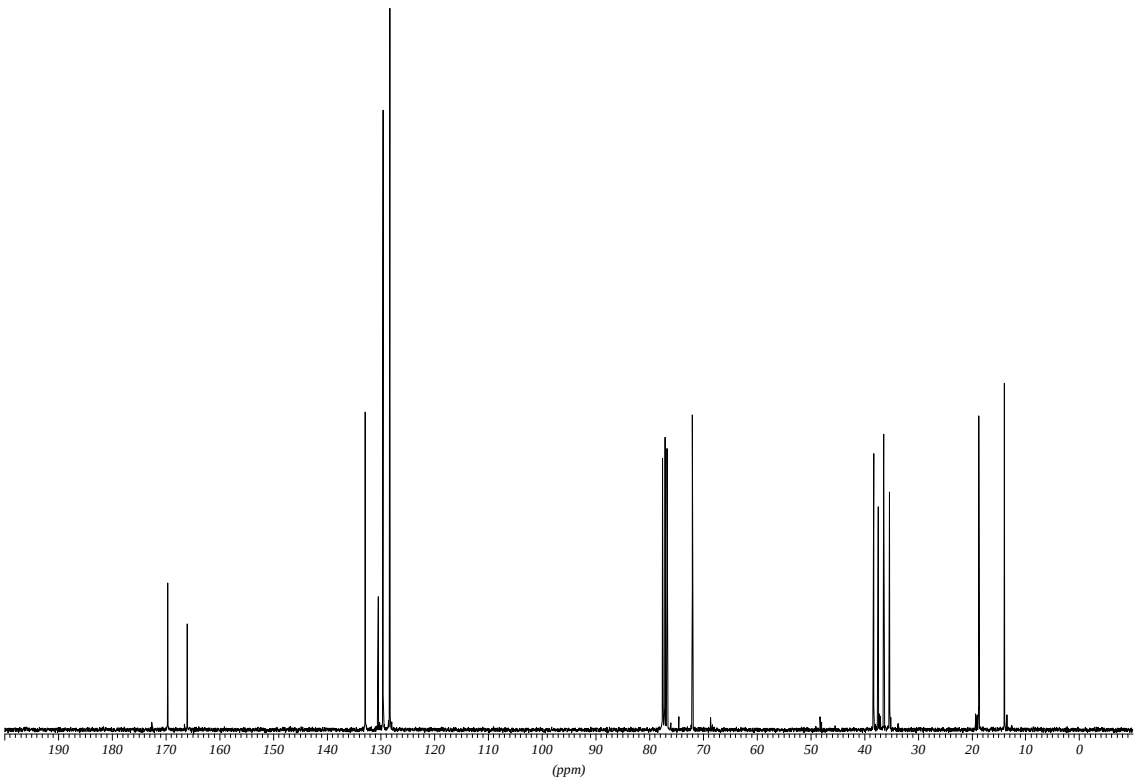




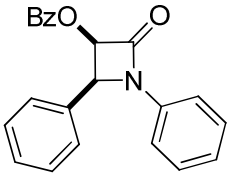
1-(dimethylamino)-1-oxohexan-3-yl benzoate (176h)

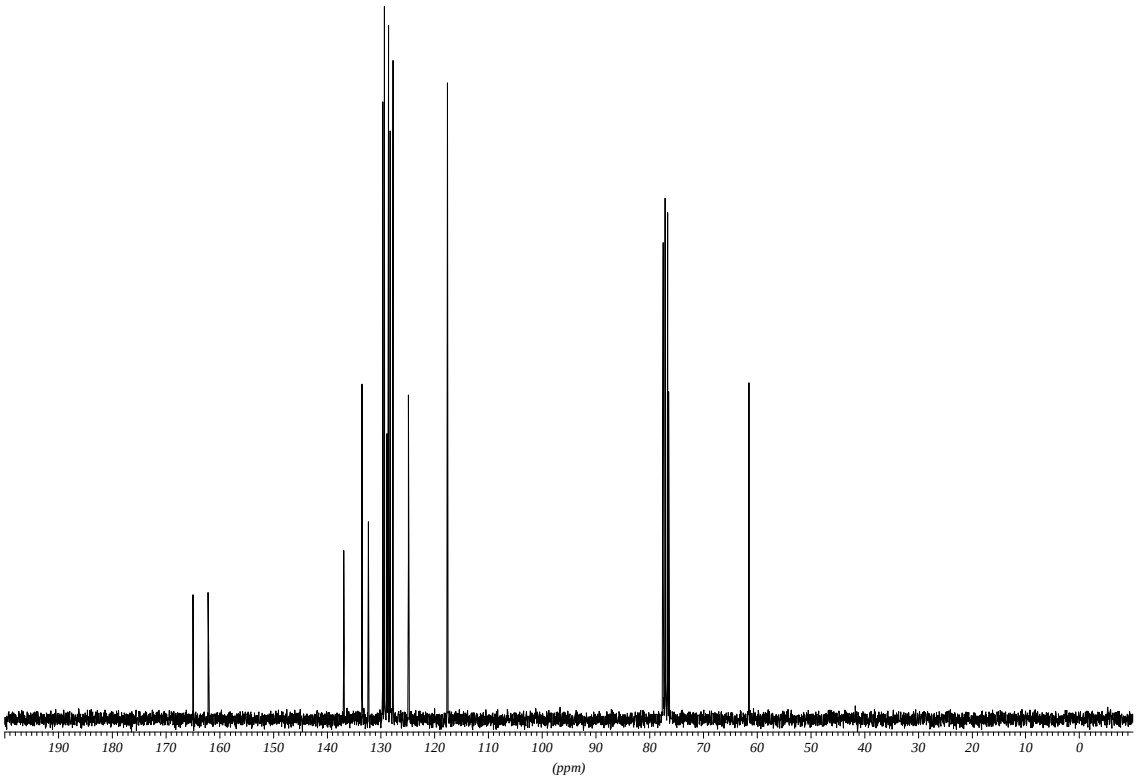




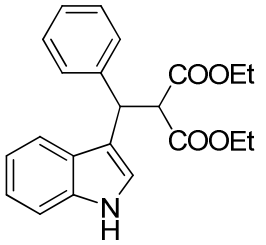


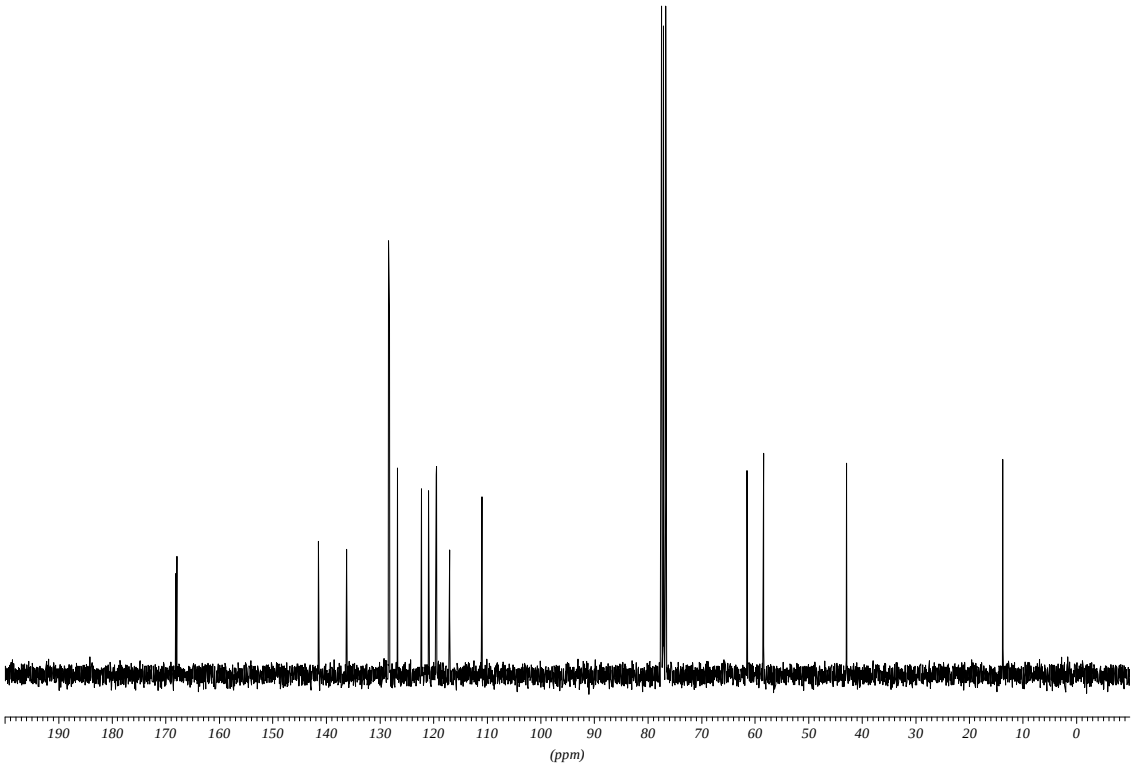
2-oxo-1,4-diphenylazetidin-3-yl benzoate (195)



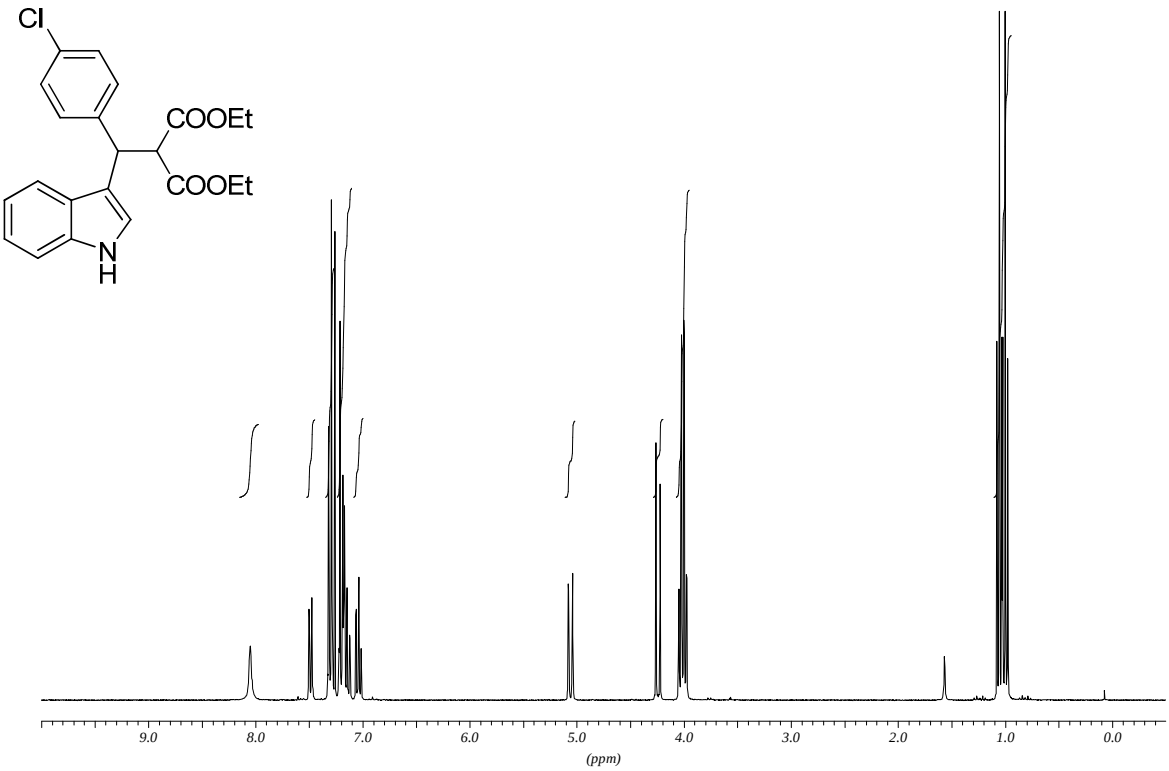


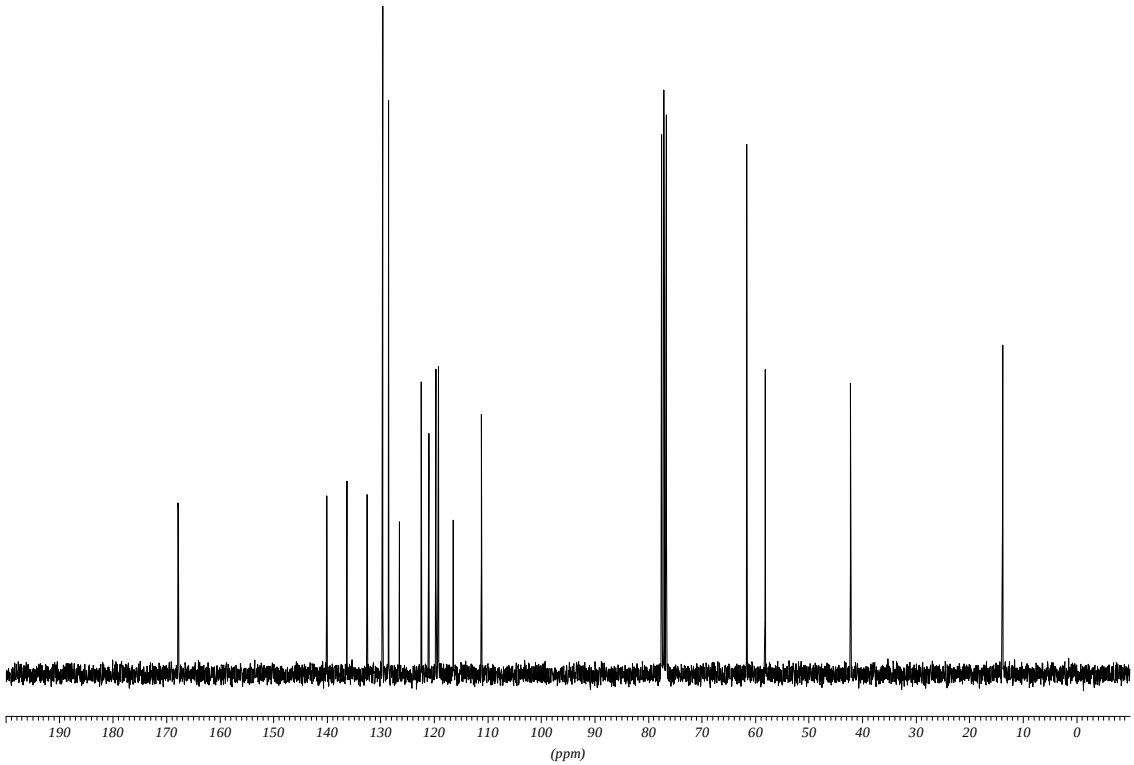
Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate (198)



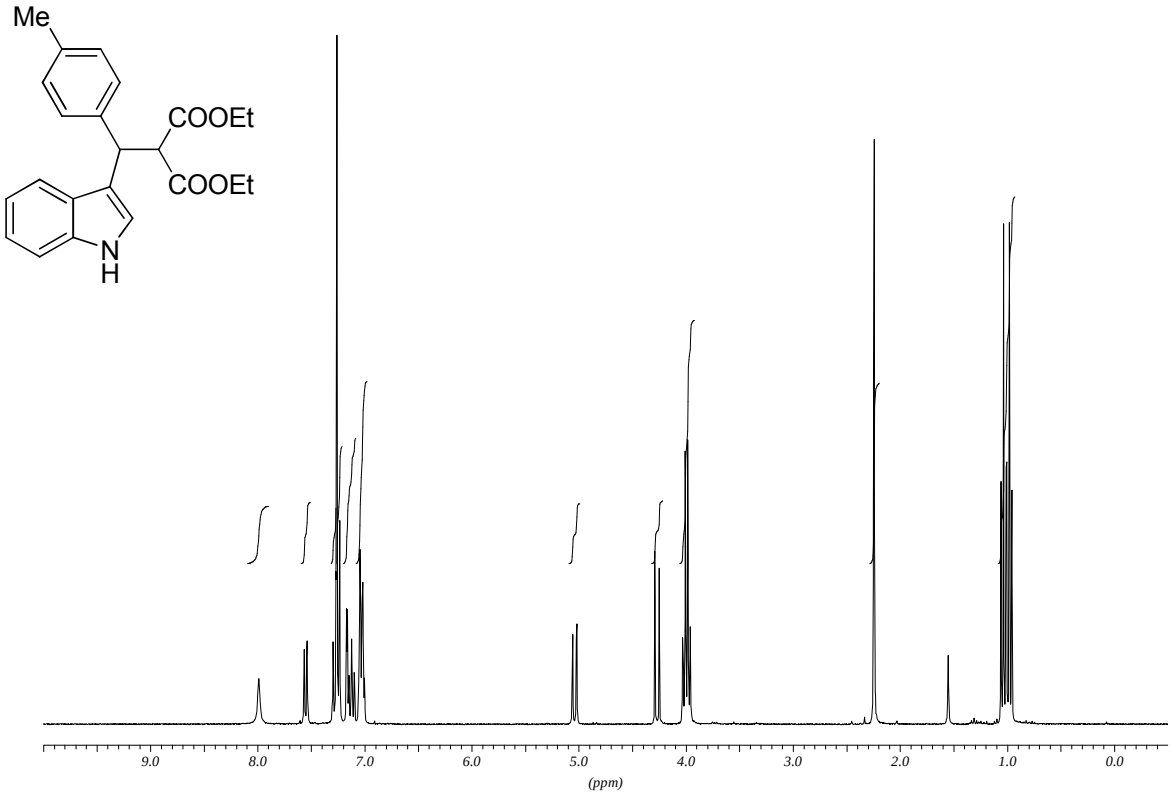


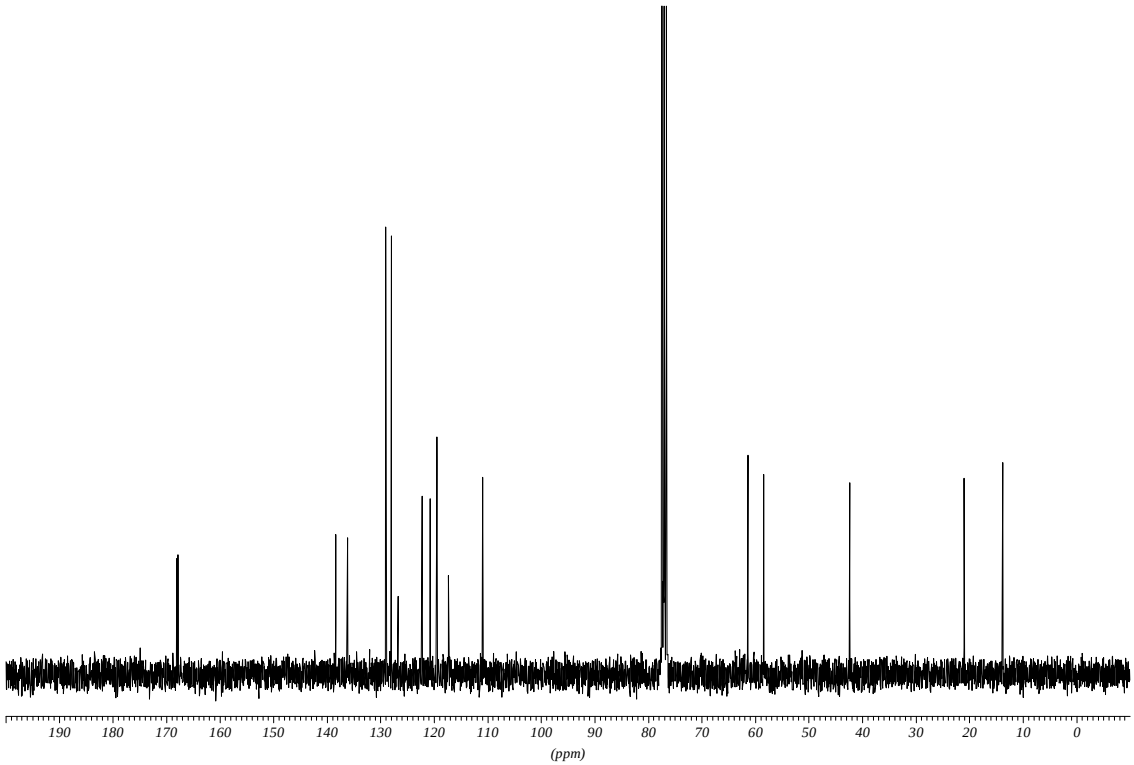
Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-chlorophenyl) propanoate (208)



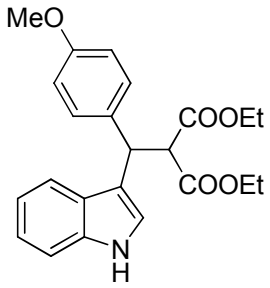


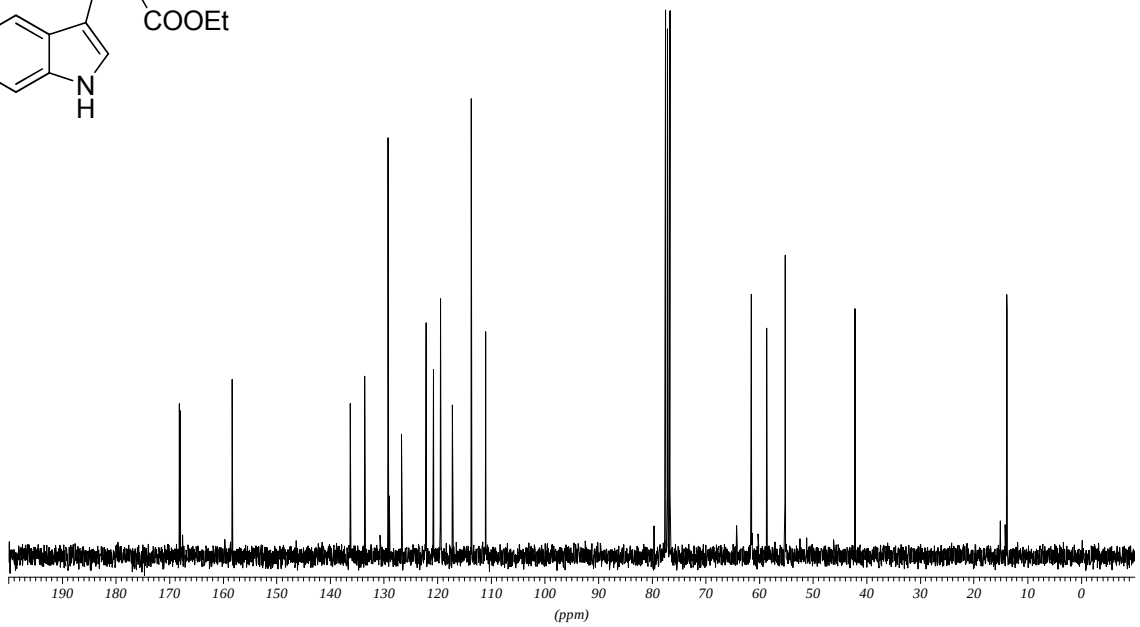
Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(p-methylphenyl) propanoate (207)

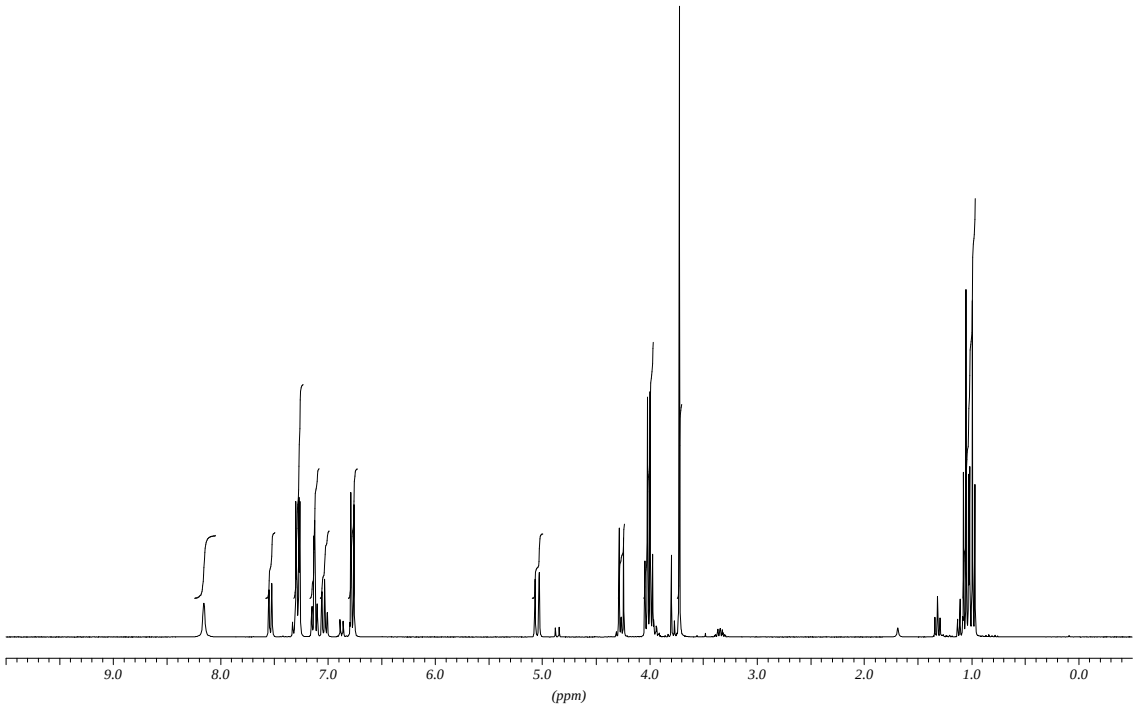




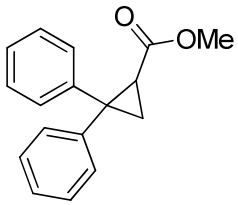
Diethyl 2-((1H-indol-3-yl)(4-methoxyphenyl)methyl)malonate (213)

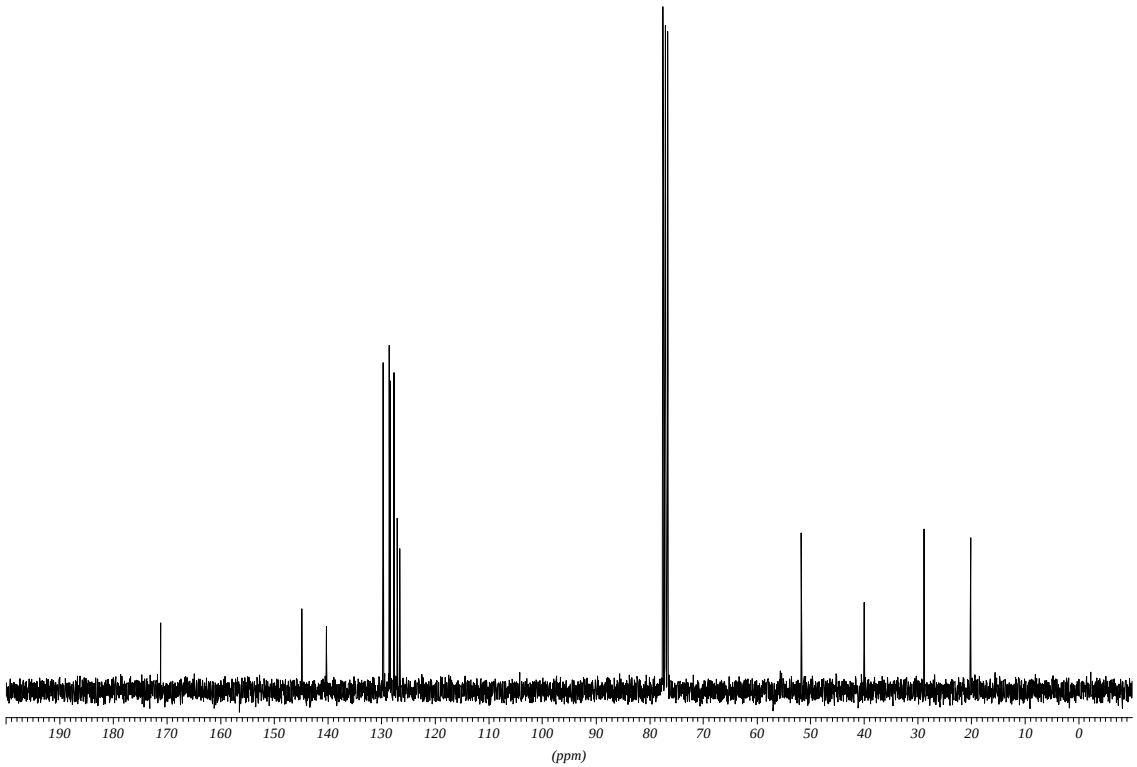




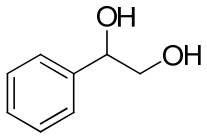


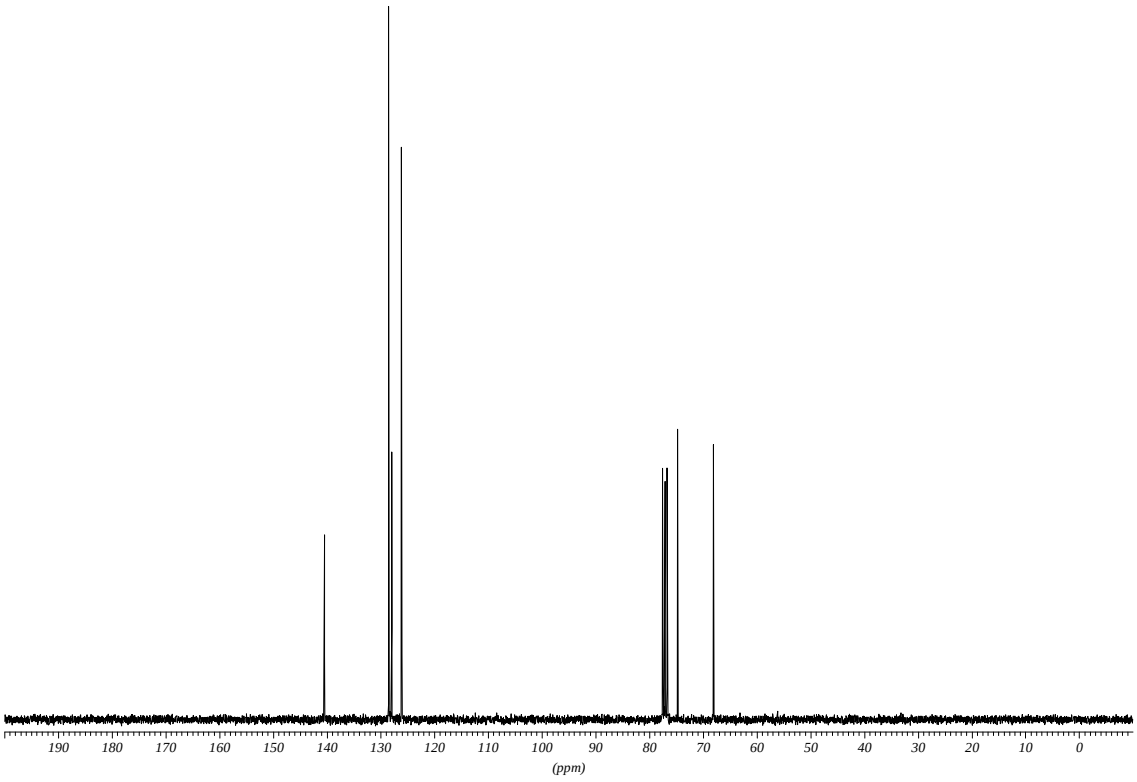
Methyl 2,2-diphenylcyclopropanecarboxylate (219)



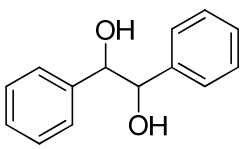


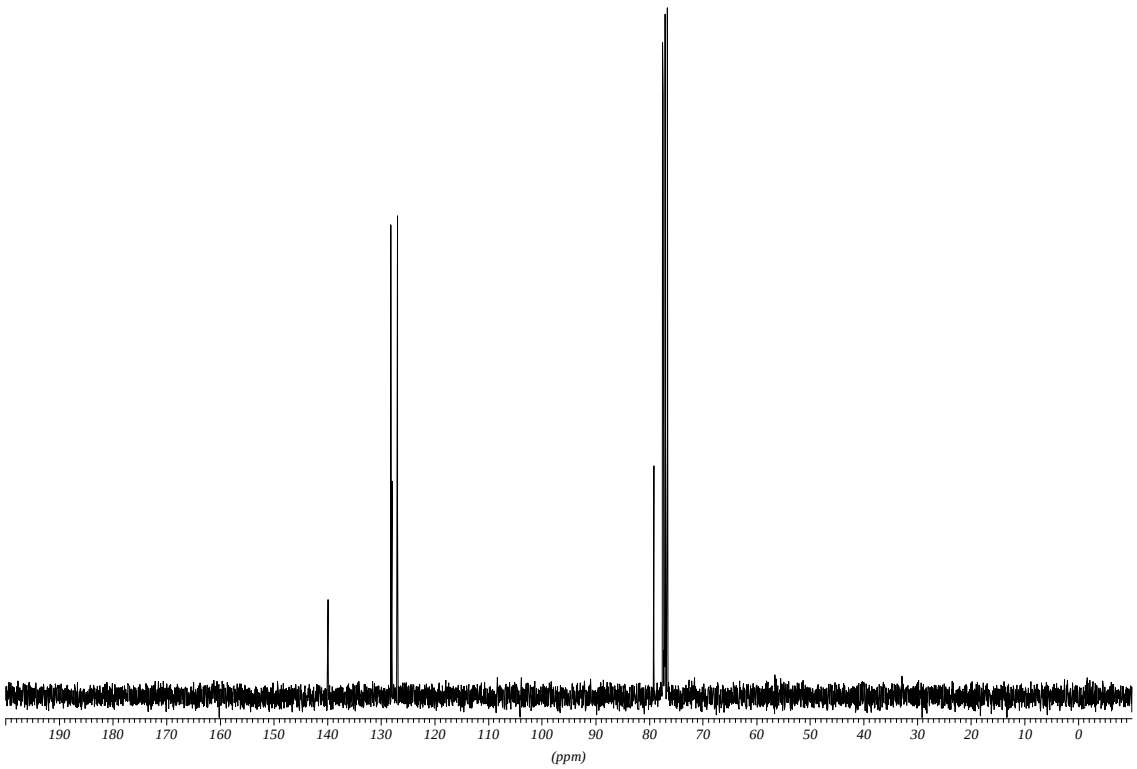
1-phenylethane-1,2-diol (223)





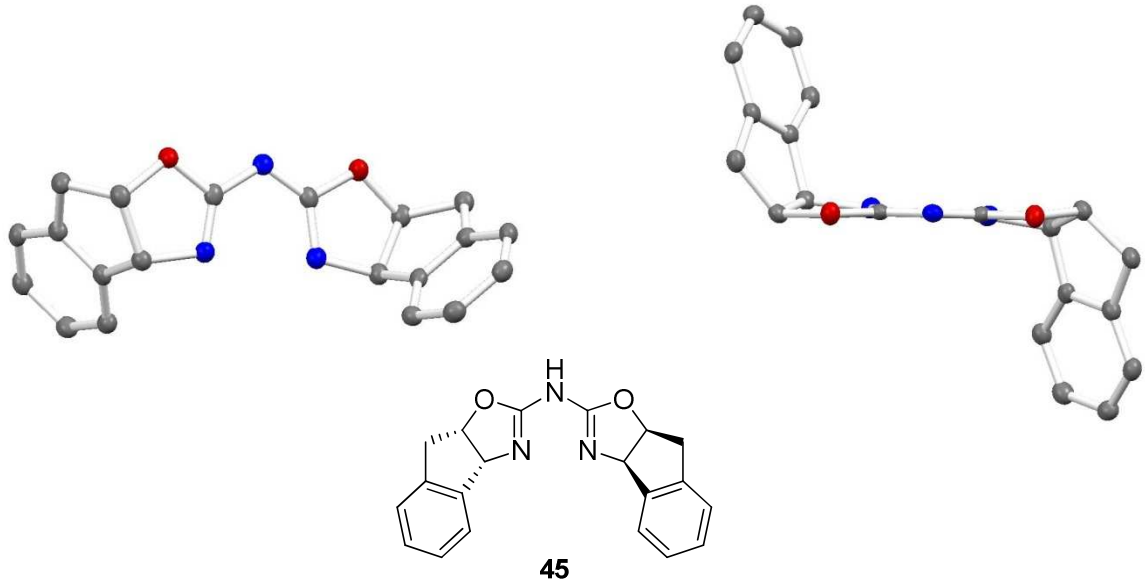
1,2-diphenylethane-1,2-diol (224)





2. X-ray crystallographic data

(3aR,8aS)-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)amine (45)



45

***Table 1*:** Crystal data and structure refinement for **45**.

Crystal Data	
Empirical formula	C20 H17 N3 O2
Formula weight	331.37
Crystal size	0.190 x 0.120 x 0.050 mm
Crystal description	rod
Crystal colour	colourless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.07650(10) A alpha = 90 deg.
	b = 11.0849(3) A beta = 90 deg.
	c = 27.5100(7) A gamma = 90 deg.
Volume	1548.06(7) A^3
Z, Calculated density	4, 1.422 Mg/m^3
Absorption coefficient	0.759 mm^-1
F(000)	696
Data Collection	
Measurement device type	Oxford Diffraction Gemini Ultra
Measuremnet method	omega-scan
Temperature	123 K
Wavelength	1.54184 A
Monochromator	graphite
Theta range for data collection	3.21 to 66.66 deg.
Index ranges	=-4<=h<=5 -12<=k<=12 -28<=l<=32
Reflections collected / unique	5227 / 2657 [R(int) = 0.0168]
Reflections greater I>2\s(I)	2466

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.82211

Refinement

Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	2657 / 1 / 229
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0346, wR2 = 0.0937
R indices (all data)	R1 = 0.0377, wR2 = 0.0957
Absolute structure parameter	-0.2(2)
Largest diff. peak and hole	0.393 and -0.454 e.A^-3

***Table 2*:** Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **45**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	-6930(2)	-1955(1)	-2018(1)	24(1)
O(2)	-13434(2)	-2002(1)	-3157(1)	24(1)
N(1)	-10122(3)	-1986(1)	-2596(1)	22(1)
N(2)	-8217(3)	-3773(1)	-2251(1)	24(1)
N(3)	-11763(3)	-3820(1)	-2942(1)	23(1)
C(1)	-8533(3)	-2584(1)	-2313(1)	20(1)
C(2)	-5127(3)	-2793(1)	-1776(1)	24(1)
C(3)	-6499(3)	-4019(1)	-1838(1)	23(1)
C(4)	-7949(3)	-4172(1)	-1358(1)	21(1)
C(5)	-7105(3)	-3316(1)	-1021(1)	22(1)
C(6)	-5007(3)	-2516(2)	-1233(1)	23(1)
C(7)	-8191(4)	-3292(1)	-556(1)	24(1)
C(8)	-10098(4)	-4130(1)	-433(1)	25(1)
C(9)	-10935(4)	-4984(2)	-772(1)	27(1)
C(10)	-9874(3)	-5014(1)	-1237(1)	23(1)
C(11)	-11721(3)	-2671(1)	-2886(1)	21(1)
C(12)	-15025(3)	-2848(1)	-3434(1)	23(1)
C(13)	-13601(3)	-4065(1)	-3343(1)	22(1)
C(14)	-12132(3)	-4289(1)	-3815(1)	21(1)
C(15)	-12804(3)	-3439(1)	-4165(1)	21(1)
C(16)	-14859(4)	-2573(1)	-3978(1)	24(1)
C(17)	-11610(4)	-3461(1)	-4622(1)	24(1)
C(18)	-9749(4)	-4344(2)	-4721(1)	25(1)
C(19)	-9084(3)	-5194(2)	-4367(1)	25(1)
C(20)	-10262(3)	-5169(2)	-3912(1)	23(1)

***Table 3*:** Bond lengths [Å] and angles [deg] for **45**.

O(1)-C(1)	1.3441(18)	C(4)-C(5)-C(7)	120.15(15)
O(1)-C(2)	1.4643(19)	C(6)-C(5)-C(7)	128.72(15)
O(2)-C(11)	1.3636(18)	C(4)-C(5)-C(6)	111.13(14)
O(2)-C(12)	1.4538(19)	C(2)-C(6)-C(5)	103.50(13)
N(1)-C(1)	1.303(2)	C(5)-C(7)-C(8)	119.14(15)
N(1)-C(11)	1.368(2)	C(7)-C(8)-C(9)	120.47(16)
N(2)-C(1)	1.339(2)	C(8)-C(9)-C(10)	120.87(17)
N(2)-C(3)	1.457(2)	C(4)-C(10)-C(9)	118.46(15)
N(3)-C(11)	1.283(2)	O(2)-C(11)-N(3)	117.64(13)
N(3)-C(13)	1.471(2)	O(2)-C(11)-N(1)	113.29(13)
N(1)-H(1N)	0.955(16)	N(1)-C(11)-N(3)	129.04(15)
C(2)-C(3)	1.537(2)	O(2)-C(12)-C(16)	110.72(13)
C(2)-C(6)	1.526(2)	O(2)-C(12)-C(13)	102.61(12)
C(3)-C(4)	1.523(2)	C(13)-C(12)-C(16)	107.74(13)
C(4)-C(5)	1.394(2)	C(12)-C(13)-C(14)	103.55(13)
C(4)-C(10)	1.391(2)	N(3)-C(13)-C(14)	111.15(13)
C(5)-C(7)	1.394(2)	N(3)-C(13)-C(12)	104.80(12)
C(5)-C(6)	1.505(2)	C(13)-C(14)-C(15)	111.17(13)
C(7)-C(8)	1.384(3)	C(13)-C(14)-C(20)	128.01(14)
C(8)-C(9)	1.394(2)	C(15)-C(14)-C(20)	120.78(14)
C(9)-C(10)	1.389(2)	C(14)-C(15)-C(16)	111.43(14)
C(12)-C(16)	1.531(2)	C(16)-C(15)-C(17)	128.22(15)
C(12)-C(13)	1.550(2)	C(14)-C(15)-C(17)	120.35(14)
C(13)-C(14)	1.518(2)	C(12)-C(16)-C(15)	104.16(13)
C(14)-C(20)	1.387(2)	C(15)-C(17)-C(18)	119.04(15)
C(14)-C(15)	1.389(2)	C(17)-C(18)-C(19)	120.17(16)
C(15)-C(16)	1.508(2)	C(18)-C(19)-C(20)	120.79(15)
C(15)-C(17)	1.395(2)	C(14)-C(20)-C(19)	118.86(15)
C(17)-C(18)	1.388(3)	O(1)-C(2)-H(2)	112.00
C(18)-C(19)	1.397(2)	C(3)-C(2)-H(2)	112.00
C(19)-C(20)	1.387(2)	C(6)-C(2)-H(2)	112.00
C(2)-H(2)	10.000	N(2)-C(3)-H(3)	113.00
C(3)-H(3)	10.000	C(2)-C(3)-H(3)	113.00
C(6)-H(6A)	0.9900	C(4)-C(3)-H(3)	113.00
C(6)-H(6B)	0.9900	C(2)-C(6)-H(6A)	111.00
C(7)-H(7)	0.9500	C(2)-C(6)-H(6B)	111.00
C(8)-H(8)	0.9500	C(5)-C(6)-H(6A)	111.00
C(9)-H(9)	0.9500	C(5)-C(6)-H(6B)	111.00
C(10)-H(10)	0.9500	H(6A)-C(6)-H(6B)	109.00
C(12)-H(12)	10.000	C(5)-C(7)-H(7)	120.00
C(13)-H(13)	10.000	C(8)-C(7)-H(7)	120.00
C(16)-H(16A)	0.9900	C(7)-C(8)-H(8)	120.00
C(16)-H(16B)	0.9900	C(9)-C(8)-H(8)	120.00
C(17)-H(17)	0.9500	C(8)-C(9)-H(9)	120.00
C(18)-H(18)	0.9500	C(10)-C(9)-H(9)	120.00
C(19)-H(19)	0.9500	C(4)-C(10)-H(10)	121.00
C(20)-H(20)	0.9500	C(9)-C(10)-H(10)	121.00
C(1)-O(1)-C(2)	108.84(12)	O(2)-C(12)-H(12)	112.00

C(11)-O(2)-C(12)	106.83(11)	C(13)-C(12)-H(12)	112.00
C(1)-N(1)-C(11)	115.77(14)	C(16)-C(12)-H(12)	112.00
C(1)-N(2)-C(3)	110.81(13)	N(3)-C(13)-H(13)	112.00
C(11)-N(3)-C(13)	106.48(13)	C(12)-C(13)-H(13)	112.00
C(11)-N(1)-H(1N)	91.0(10)	C(14)-C(13)-H(13)	112.00
C(1)-N(1)-H(1N)	123.5(10)	C(12)-C(16)-H(16A)	111.00
O(1)-C(1)-N(2)	111.21(13)	C(12)-C(16)-H(16B)	111.00
O(1)-C(1)-N(1)	118.16(14)	C(15)-C(16)-H(16A)	111.00
N(1)-C(1)-N(2)	130.62(15)	C(15)-C(16)-H(16B)	111.00
O(1)-C(2)-C(6)	109.96(12)	H(16A)-C(16)-H(16B)	109.00
C(3)-C(2)-C(6)	107.76(13)	C(15)-C(17)-H(17)	120.00
O(1)-C(2)-C(3)	103.17(12)	C(18)-C(17)-H(17)	121.00
C(2)-C(3)-C(4)	102.79(13)	C(17)-C(18)-H(18)	120.00
N(2)-C(3)-C(2)	101.08(12)	C(19)-C(18)-H(18)	120.00
N(2)-C(3)-C(4)	114.07(13)	C(18)-C(19)-H(19)	120.00
C(5)-C(4)-C(10)	120.91(15)	C(20)-C(19)-H(19)	120.00
C(3)-C(4)-C(10)	128.43(14)	C(14)-C(20)-H(20)	121.00
C(3)-C(4)-C(5)	110.66(13)	C(19)-C(20)-H(20)	121.00

***Table 4*:** Anisotropic displacement parameters (A^2 x 10^3) for h262. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + .. + 2 h k a*b*U12]

Atom	U11	U22	U33	U23	U13	U12
O(1)	23(1)	25(1)	24(1)	1(1)	-4(1)	-4(1)
O(2)	25(1)	23(1)	25(1)	-2(1)	-4(1)	2(1)
N(1)	20(1)	25(1)	21(1)	-1(1)	3(1)	1(1)
N(2)	25(1)	26(1)	21(1)	-1(1)	0(1)	2(1)
N(3)	25(1)	23(1)	21(1)	2(1)	-1(1)	-2(1)
C(1)	18(1)	26(1)	17(1)	-2(1)	3(1)	-2(1)
C(2)	17(1)	29(1)	24(1)	1(1)	-1(1)	0(1)
C(3)	21(1)	25(1)	23(1)	-1(1)	-1(1)	1(1)
C(4)	19(1)	23(1)	20(1)	0(1)	-3(1)	4(1)
C(5)	19(1)	21(1)	24(1)	2(1)	-2(1)	1(1)
C(6)	18(1)	26(1)	25(1)	1(1)	-3(1)	-2(1)
C(7)	26(1)	25(1)	22(1)	-2(1)	-5(1)	1(1)
C(8)	25(1)	27(1)	22(1)	3(1)	2(1)	3(1)
C(9)	24(1)	25(1)	31(1)	3(1)	-1(1)	-1(1)
C(10)	21(1)	22(1)	26(1)	-2(1)	-2(1)	1(1)
C(11)	17(1)	28(1)	17(1)	0(1)	3(1)	0(1)
C(12)	17(1)	28(1)	24(1)	-2(1)	0(1)	-3(1)
C(13)	19(1)	23(1)	23(1)	-1(1)	0(1)	-2(1)
C(14)	18(1)	23(1)	21(1)	-3(1)	-2(1)	-4(1)
C(15)	16(1)	23(1)	24(1)	-2(1)	-3(1)	-1(1)
C(16)	21(1)	25(1)	25(1)	-1(1)	-4(1)	3(1)
C(17)	24(1)	28(1)	20(1)	2(1)	-4(1)	-2(1)
C(18)	24(1)	30(1)	22(1)	-3(1)	1(1)	-3(1)
C(19)	23(1)	26(1)	28(1)	-3(1)	0(1)	2(1)
C(20)	21(1)	23(1)	25(1)	1(1)	-4(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **45**.

Atom	x	y	z	U(eq)
H(1N)	-11600(30)	-1537(15)	-2480(6)	26
H(2)	-3338	-2786	-1928	28
H(3)	-5229	-4690	-1903	27
H(6A)	-3253	-2714	-1098	28
H(6B)	-5395	-1655	-1170	28
H(7)	-7628	-2707	-325	29
H(8)	-10843	-4123	-117	30
H(9)	-12247	-5554	-683	32
H(10)	-10451	-5595	-1467	27
H(12)	-16890	-2868	-3317	28
H(13)	-14859	-4731	-3265	26
H(16A)	-16577	-2713	-4139	28
H(16B)	-14315	-1726	-4035	28
H(17)	-12065	-2879	-4861	29
H(18)	-8925	-4371	-5031	30
H(19)	-7810	-5796	-4438	30
H(20)	-9797	-5745	-3672	28

***Table 6*:** Torsion angles [deg] for **45**.

C(2)-O(1)-C(1)-N(1)	-173.62(13)	C(5)-C(4)-C(10)-C(9)	-0.2(2)
C(2)-O(1)-C(1)-N(2)	7.60(16)	C(10)-C(4)-C(5)-C(7)	-0.1(2)
C(1)-O(1)-C(2)-C(3)	-18.49(15)	C(3)-C(4)-C(10)-C(9)	-179.96(15)
C(1)-O(1)-C(2)-C(6)	-133.21(13)	C(4)-C(5)-C(7)-C(8)	0.4(3)
C(12)-O(2)-C(11)-N(1)	-178.61(12)	C(4)-C(5)-C(6)-C(2)	12.83(17)
C(11)-O(2)-C(12)-C(13)	-9.58(15)	C(7)-C(5)-C(6)-C(2)	-167.53(16)
C(12)-O(2)-C(11)-N(3)	2.95(18)	C(6)-C(5)-C(7)-C(8)	-179.23(16)
C(11)-O(2)-C(12)-C(16)	-124.31(13)	C(5)-C(7)-C(8)-C(9)	-0.4(3)
C(1)-N(1)-C(11)-O(2)	176.86(13)	C(7)-C(8)-C(9)-C(10)	0.1(3)
C(1)-N(1)-C(11)-N(3)	-4.9(2)	C(8)-C(9)-C(10)-C(4)	0.2(3)
C(11)-N(1)-C(1)-O(1)	-179.63(13)	O(2)-C(12)-C(13)-C(14)	-104.03(13)
C(11)-N(1)-C(1)-N(2)	-1.1(2)	C(16)-C(12)-C(13)-N(3)	129.43(14)
C(3)-N(2)-C(1)-O(1)	7.70(18)	O(2)-C(12)-C(16)-C(15)	97.52(14)
C(1)-N(2)-C(3)-C(2)	-18.37(16)	C(13)-C(12)-C(16)-C(15)	-13.95(17)
C(1)-N(2)-C(3)-C(4)	91.17(16)	C(16)-C(12)-C(13)-C(14)	12.85(16)
C(3)-N(2)-C(1)-N(1)	-170.88(16)	O(2)-C(12)-C(13)-N(3)	12.55(15)
C(11)-N(3)-C(13)-C(14)	99.92(15)	N(3)-C(13)-C(14)-C(15)	-118.89(14)
C(11)-N(3)-C(13)-C(12)	-11.30(16)	N(3)-C(13)-C(14)-C(20)	58.7(2)
C(13)-N(3)-C(11)-N(1)	-172.42(15)	C(12)-C(13)-C(14)-C(15)	-6.88(17)
C(13)-N(3)-C(11)-O(2)	5.73(18)	C(12)-C(13)-C(14)-C(20)	170.71(15)
C(6)-C(2)-C(3)-N(2)	137.57(13)	C(13)-C(14)-C(15)-C(16)	-1.94(19)
C(6)-C(2)-C(3)-C(4)	19.50(15)	C(13)-C(14)-C(15)-C(17)	178.03(15)
O(1)-C(2)-C(6)-C(5)	91.81(14)	C(20)-C(14)-C(15)-C(16)	-179.72(15)
C(3)-C(2)-C(6)-C(5)	-19.96(16)	C(20)-C(14)-C(15)-C(17)	0.3(2)

O(1)-C(2)-C(3)-N(2)	21.27(15)	C(13)-C(14)-C(20)-C(19)	-177.89(15)
O(1)-C(2)-C(3)-C(4)	-96.80(13)	C(15)-C(14)-C(20)-C(19)	-0.5(2)
C(2)-C(3)-C(4)-C(5)	-11.77(17)	C(14)-C(15)-C(16)-C(12)	10.00(18)
C(2)-C(3)-C(4)-C(10)	168.05(16)	C(17)-C(15)-C(16)-C(12)	-169.96(16)
N(2)-C(3)-C(4)-C(10)	59.6(2)	C(14)-C(15)-C(17)-C(18)	0.1(3)
N(2)-C(3)-C(4)-C(5)	-120.26(15)	C(16)-C(15)-C(17)-C(18)	-179.92(16)
C(10)-C(4)-C(5)-C(6)	179.56(14)	C(15)-C(17)-C(18)-C(19)	-0.2(3)
C(3)-C(4)-C(5)-C(6)	-0.61(18)	C(17)-C(18)-C(19)-C(20)	-0.1(3)
C(3)-C(4)-C(5)-C(7)	179.72(15)	C(18)-C(19)-C(20)-C(14)	0.4(2)

Table 7: Hydrogen-bonds for **45** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2)...N(1)#1	10.000	26.100	3.513(2)	150.00

X-ray structure of complex **47**

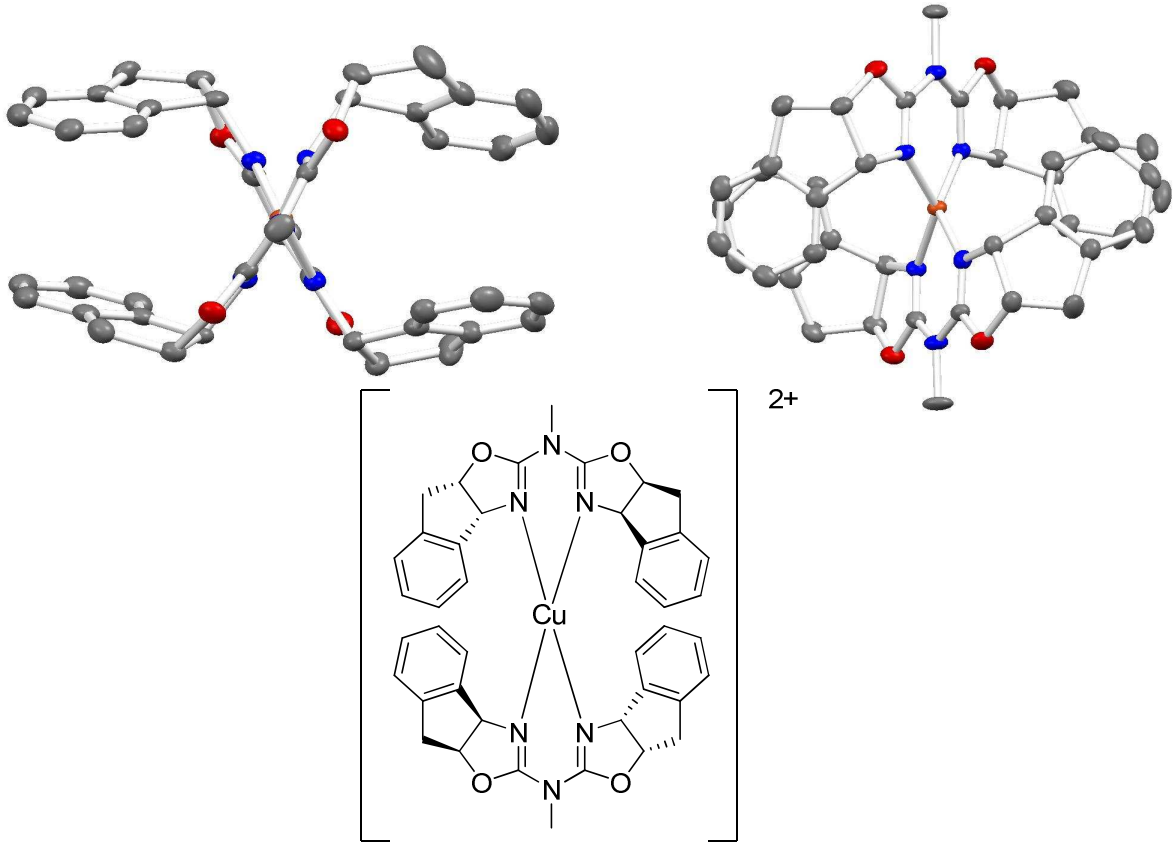


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***Table 1*:** Crystal data and structure refinement for **47**.

Crystal Data	
Empirical formula	C42 H38 Cu N6 O4, 2(Cl O4)
Formula weight	952.99
Crystal size	0.262 x 0.214 x 0.170 mm
Crystal description	prism
Crystal colour	smaragd green
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 11.2373(2) A alpha = 90 deg.
	b = 14.6525(2) A beta = 90 deg.
	c = 24.0956(4) A gamma = 90 deg.
Volume	3967.45(11) A^3
Z, Calculated density	4, 1.595 Mg/m^3
Absorption coefficient	2.665 mm^-1
F(000)	1963
Data Collection	
Measurement device type	Goniometer Xcalibur, detector: Ruby (Gemini ultra Mo)
Measuremnet method	\w scans

Temperature	123 K
Wavelength	1.54184 A
Monochromator	graphite
Theta range for data collection	3.53 to 66.65 deg.
Index ranges	=-13<=h<=11 -17<=k<=17 -28<=l<=26
Reflections collected / unique	18468 / 6900 [R(int) = 0.0243]
Reflections greater I>2\s(I)	6782
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90883
Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	6900 / 12 / 571
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0888
R indices (all data)	R1 = 0.0344, wR2 = 0.0894
Absolute structure parameter	-0.011(13)
Largest diff. peak and hole	0.654 and -0.853 e.A^-3

***Table 2*:** Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **47**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z
Cu(1)	5361(1)	10102(1)	8818(1)
O(1)	3226(2)	12217(1)	9340(1)
O(2)	1882(2)	9884(1)	8298(1)
O(3)	7656(2)	8109(1)	9371(1)
O(4)	8861(2)	10552(1)	8378(1)
N(1)	4666(2)	11233(1)	9100(1)
N(2)	2683(2)	11063(2)	8766(1)
N(3)	3785(2)	9709(1)	8569(1)
N(4)	6127(2)	8982(1)	9080(1)
N(5)	8148(2)	9368(2)	8884(1)
N(6)	6894(2)	10550(2)	8556(1)
C(1)	5274(2)	11891(2)	9479(1)
C(2)	5777(2)	11455(2)	9997(1)
C(3)	6803(3)	10933(2)	10052(1)
C(4)	7098(3)	10595(2)	10571(1)
C(5)	6382(3)	10786(2)	11027(1)
C(6)	5369(3)	11309(2)	10974(1)
C(7)	5064(2)	11640(2)	10456(1)
C(8)	4014(3)	12243(2)	10300(1)
C(9)	4232(2)	12487(2)	9691(1)
C(10)	3570(2)	11479(2)	9067(1)
C(11)	1486(2)	11498(2)	8744(1)
C(12)	2845(2)	10213(2)	8553(1)

C(13)	2158(3)	8945(2)	8127(1)
C(14)	1941(3)	8832(3)	7511(1)
C(15)	3163(3)	8907(2)	7257(1)
C(16)	3471(4)	8951(2)	6695(1)
C(17)	4661(4)	8977(2)	6556(1)
C(18)	5534(3)	8963(2)	6955(1)
C(19)	5235(3)	8928(2)	7518(1)
C(20)	4048(3)	8910(2)	7659(1)
C(21)	3511(2)	8875(2)	8232(1)
C(31)	5561(2)	8230(2)	9407(1)
C(32)	5064(2)	8533(2)	9958(1)
C(33)	4113(2)	9116(2)	10059(1)
C(34)	3776(3)	9284(2)	10604(1)
C(35)	4376(3)	8869(2)	11042(1)
C(36)	5327(3)	8287(2)	10940(1)
C(37)	5678(3)	8118(2)	10397(1)
C(38)	6642(3)	7498(2)	10191(1)
C(39)	6614(2)	7599(2)	9561(1)
C(40)	7261(2)	8836(2)	9101(1)
C(41)	9387(2)	8997(2)	8894(2)
C(42)	7914(2)	10154(2)	8606(1)
C(43)	8407(3)	11306(2)	8041(1)
C(44)	8451(3)	11071(3)	7422(1)
C(45)	7188(3)	11213(2)	7229(1)
C(46)	6753(3)	11176(2)	6686(1)
C(47)	5542(3)	11311(2)	6599(1)
C(48)	4787(3)	11494(2)	7039(1)
C(49)	5216(3)	11538(2)	7580(1)
C(50)	6419(2)	11385(2)	7671(1)
C(51)	7086(2)	11391(2)	8211(1)
Cl(2)	8273(1)	7846(1)	7619(1)
O(9)	7787(4)	7642(3)	8157(2)
O(10)	7441(3)	7471(2)	7209(1)
O(11)	9353(3)	7529(2)	7556(2)
O(12)	8226(3)	8847(2)	7559(1)
O(13)	9755(11)	7645(10)	7885(4)
O(14)	8706(11)	8259(9)	7152(4)
O(15)	8299(13)	6825(9)	7512(4)
O(16)	7797(12)	7996(10)	8112(6)
Cl(1)	808(1)	10197(1)	10014(1)
O(5)	565(3)	9505(2)	10418(1)
O(6)	-294(2)	10509(2)	9769(1)
O(7)	1392(2)	10962(2)	10269(1)
O(8)	1565(2)	9823(1)	9587(1)

***Table 3*:** Bond lengths [Å] and angles [deg] for **47**.

Cu(1)-N(1)	1.954(2)	C(3)-C(2)-C(7)	C(3)-C(2)-C(7)
Cu(1)-N(3)	1.957(2)	C(2)-C(3)-C(4)	C(2)-C(3)-C(4)
Cu(1)-N(4)	1.959(2)	C(3)-C(4)-C(5)	C(3)-C(4)-C(5)
Cu(1)-N(6)	1.949(2)	C(4)-C(5)-C(6)	C(4)-C(5)-C(6)
Cl(2)-O(10)	1.467(3)	C(5)-C(6)-C(7)	C(5)-C(6)-C(7)
Cl(2)-O(11)	1.309(3)	C(6)-C(7)-C(8)	C(6)-C(7)-C(8)
Cl(2)-O(12)	1.475(3)	C(2)-C(7)-C(6)	C(2)-C(7)-C(6)
Cl(2)-O(13)	1.809(12)	C(2)-C(7)-C(8)	C(2)-C(7)-C(8)
Cl(2)-O(14)	1.367(11)	C(7)-C(8)-C(9)	C(7)-C(8)-C(9)
Cl(2)-O(15)	1.519(13)	C(1)-C(9)-C(8)	C(1)-C(9)-C(8)
Cl(2)-O(9)	1.438(4)	O(1)-C(9)-C(1)	O(1)-C(9)-C(1)
Cl(2)-O(16)	1.322(14)	O(1)-C(9)-C(8)	O(1)-C(9)-C(8)
Cl(1)-O(7)	1.437(3)	N(1)-C(10)-N(2)	N(1)-C(10)-N(2)
Cl(1)-O(8)	1.444(2)	O(1)-C(10)-N(1)	O(1)-C(10)-N(1)
Cl(1)-O(6)	1.445(2)	O(1)-C(10)-N(2)	O(1)-C(10)-N(2)
Cl(1)-O(5)	1.432(3)	N(2)-C(12)-N(3)	N(2)-C(12)-N(3)
O(1)-C(9)	1.467(3)	O(2)-C(12)-N(2)	O(2)-C(12)-N(2)
O(1)-C(10)	1.323(3)	O(2)-C(12)-N(3)	O(2)-C(12)-N(3)
O(2)-C(12)	1.334(3)	C(14)-C(13)-C(21)	C(14)-C(13)-C(21)
O(2)-C(13)	1.469(4)	O(2)-C(13)-C(14)	O(2)-C(13)-C(14)
O(3)-C(40)	1.325(3)	O(2)-C(13)-C(21)	O(2)-C(13)-C(21)
O(3)-C(39)	1.463(3)	C(13)-C(14)-C(15)	C(13)-C(14)-C(15)
O(4)-C(42)	1.332(3)	C(14)-C(15)-C(16)	C(14)-C(15)-C(16)
O(4)-C(43)	1.463(4)	C(14)-C(15)-C(20)	C(14)-C(15)-C(20)
N(1)-C(10)	1.286(3)	C(16)-C(15)-C(20)	C(16)-C(15)-C(20)
N(1)-C(1)	1.493(3)	C(15)-C(16)-C(17)	C(15)-C(16)-C(17)
N(2)-C(10)	1.374(3)	C(16)-C(17)-C(18)	C(16)-C(17)-C(18)
N(2)-C(11)	1.490(3)	C(17)-C(18)-C(19)	C(17)-C(18)-C(19)
N(2)-C(12)	1.361(3)	C(18)-C(19)-C(20)	C(18)-C(19)-C(20)
N(3)-C(12)	1.289(3)	C(15)-C(20)-C(19)	C(15)-C(20)-C(19)
N(3)-C(21)	1.498(3)	C(15)-C(20)-C(21)	C(15)-C(20)-C(21)
N(4)-C(40)	1.293(3)	C(19)-C(20)-C(21)	C(19)-C(20)-C(21)
N(4)-C(31)	1.496(3)	N(3)-C(21)-C(13)	N(3)-C(21)-C(13)
N(5)-C(42)	1.359(3)	N(3)-C(21)-C(20)	N(3)-C(21)-C(20)
N(5)-C(40)	1.368(3)	C(13)-C(21)-C(20)	C(13)-C(21)-C(20)
N(5)-C(41)	1.495(3)	N(4)-C(31)-C(32)	N(4)-C(31)-C(32)
N(6)-C(51)	1.502(3)	N(4)-C(31)-C(39)	N(4)-C(31)-C(39)
N(6)-C(42)	1.290(3)	C(32)-C(31)-C(39)	C(32)-C(31)-C(39)
C(1)-C(2)	1.513(4)	C(31)-C(32)-C(33)	C(31)-C(32)-C(33)
C(1)-C(9)	1.548(3)	C(33)-C(32)-C(37)	C(33)-C(32)-C(37)
C(2)-C(3)	1.390(4)	C(31)-C(32)-C(37)	C(31)-C(32)-C(37)
C(2)-C(7)	1.391(4)	C(32)-C(33)-C(34)	C(32)-C(33)-C(34)
C(3)-C(4)	1.385(4)	C(33)-C(34)-C(35)	C(33)-C(34)-C(35)
C(4)-C(5)	1.389(5)	C(34)-C(35)-C(36)	C(34)-C(35)-C(36)
C(5)-C(6)	1.378(5)	C(35)-C(36)-C(37)	C(35)-C(36)-C(37)
C(6)-C(7)	1.384(4)	C(32)-C(37)-C(36)	C(32)-C(37)-C(36)
C(7)-C(8)	1.521(4)	C(36)-C(37)-C(38)	C(36)-C(37)-C(38)

C(8)-C(9)	1.530(4)	C(32)-C(37)-C(38)	C(32)-C(37)-C(38)
C(13)-C(21)	1.545(4)	C(37)-C(38)-C(39)	C(37)-C(38)-C(39)
C(13)-C(14)	1.515(5)	O(3)-C(39)-C(31)	O(3)-C(39)-C(31)
C(14)-C(15)	1.507(5)	O(3)-C(39)-C(38)	O(3)-C(39)-C(38)
C(15)-C(20)	1.389(5)	C(31)-C(39)-C(38)	C(31)-C(39)-C(38)
C(15)-C(16)	1.399(5)	O(3)-C(40)-N(5)	O(3)-C(40)-N(5)
C(16)-C(17)	1.379(6)	O(3)-C(40)-N(4)	O(3)-C(40)-N(4)
C(17)-C(18)	1.373(5)	N(4)-C(40)-N(5)	N(4)-C(40)-N(5)
C(18)-C(19)	1.399(4)	O(4)-C(42)-N(5)	O(4)-C(42)-N(5)
C(19)-C(20)	1.377(5)	O(4)-C(42)-N(6)	O(4)-C(42)-N(6)
C(20)-C(21)	1.509(4)	N(5)-C(42)-N(6)	N(5)-C(42)-N(6)
C(31)-C(39)	1.547(3)	O(4)-C(43)-C(44)	O(4)-C(43)-C(44)
C(31)-C(32)	1.507(4)	O(4)-C(43)-C(51)	O(4)-C(43)-C(51)
C(32)-C(37)	1.402(4)	C(44)-C(43)-C(51)	C(44)-C(43)-C(51)
C(32)-C(33)	1.389(3)	C(43)-C(44)-C(45)	C(43)-C(44)-C(45)
C(33)-C(34)	1.388(4)	C(44)-C(45)-C(46)	C(44)-C(45)-C(46)
C(34)-C(35)	1.392(4)	C(44)-C(45)-C(50)	C(44)-C(45)-C(50)
C(35)-C(36)	1.389(4)	C(46)-C(45)-C(50)	C(46)-C(45)-C(50)
C(36)-C(37)	1.390(4)	C(45)-C(46)-C(47)	C(45)-C(46)-C(47)
C(37)-C(38)	1.498(4)	C(46)-C(47)-C(48)	C(46)-C(47)-C(48)
C(38)-C(39)	1.524(4)	C(47)-C(48)-C(49)	C(47)-C(48)-C(49)
C(43)-C(51)	1.545(4)	C(48)-C(49)-C(50)	C(48)-C(49)-C(50)
C(43)-C(44)	1.532(4)	C(49)-C(50)-C(51)	C(49)-C(50)-C(51)
C(44)-C(45)	1.508(5)	C(45)-C(50)-C(49)	C(45)-C(50)-C(49)
C(45)-C(46)	1.396(4)	C(45)-C(50)-C(51)	C(45)-C(50)-C(51)
C(45)-C(50)	1.395(4)	C(43)-C(51)-C(50)	C(43)-C(51)-C(50)
C(46)-C(47)	1.391(5)	N(6)-C(51)-C(43)	N(6)-C(51)-C(43)
C(47)-C(48)	1.383(5)	N(6)-C(51)-C(50)	N(6)-C(51)-C(50)
C(48)-C(49)	1.391(5)	N(1)-C(1)-H(1)	N(1)-C(1)-H(1)
C(49)-C(50)	1.388(4)	C(2)-C(1)-H(1)	C(2)-C(1)-H(1)
C(50)-C(51)	1.503(4)	C(9)-C(1)-H(1)	C(9)-C(1)-H(1)
C(1)-H(1)	10.000	C(2)-C(3)-H(3)	C(2)-C(3)-H(3)
C(3)-H(3)	0.9500	C(4)-C(3)-H(3)	C(4)-C(3)-H(3)
C(4)-H(4)	0.9500	C(5)-C(4)-H(4)	C(5)-C(4)-H(4)
C(5)-H(5)	0.9500	C(3)-C(4)-H(4)	C(3)-C(4)-H(4)
C(6)-H(6)	0.9500	C(6)-C(5)-H(5)	C(6)-C(5)-H(5)
C(8)-H(8B)	0.9900	C(4)-C(5)-H(5)	C(4)-C(5)-H(5)
C(8)-H(8A)	0.9900	C(5)-C(6)-H(6)	C(5)-C(6)-H(6)
C(9)-H(9)	10.000	C(7)-C(6)-H(6)	C(7)-C(6)-H(6)
C(11)-H(11C)	0.9800	C(7)-C(8)-H(8A)	C(7)-C(8)-H(8A)
C(11)-H(11A)	0.9800	C(7)-C(8)-H(8B)	C(7)-C(8)-H(8B)
C(11)-H(11B)	0.9800	C(9)-C(8)-H(8A)	C(9)-C(8)-H(8A)
C(13)-H(13)	10.000	C(9)-C(8)-H(8B)	C(9)-C(8)-H(8B)
C(14)-H(14A)	0.9900	H(8A)-C(8)-H(8B)	H(8A)-C(8)-H(8B)
C(14)-H(14B)	0.9900	O(1)-C(9)-H(9)	O(1)-C(9)-H(9)
C(16)-H(16)	0.9500	C(1)-C(9)-H(9)	C(1)-C(9)-H(9)
C(17)-H(17)	0.9500	C(8)-C(9)-H(9)	C(8)-C(9)-H(9)
C(18)-H(18)	0.9500	N(2)-C(11)-H(11A)	N(2)-C(11)-H(11A)

C(19)-H(19)	0.9500	N(2)-C(11)-H(11B)	N(2)-C(11)-H(11B)
C(21)-H(21)	10.000	N(2)-C(11)-H(11C)	N(2)-C(11)-H(11C)
C(31)-H(31)	10.000	H(11A)-C(11)-H(11B)	H(11A)-C(11)-H(11B)
C(33)-H(33)	0.9500	H(11A)-C(11)-H(11C)	H(11A)-C(11)-H(11C)
C(34)-H(34)	0.9500	H(11B)-C(11)-H(11C)	H(11B)-C(11)-H(11C)
C(35)-H(35)	0.9500	C(14)-C(13)-H(13)	C(14)-C(13)-H(13)
C(36)-H(36)	0.9500	C(21)-C(13)-H(13)	C(21)-C(13)-H(13)
C(38)-H(38A)	0.9900	O(2)-C(13)-H(13)	O(2)-C(13)-H(13)
C(38)-H(38B)	0.9900	C(15)-C(14)-H(14A)	C(15)-C(14)-H(14A)
C(39)-H(39)	10.000	C(15)-C(14)-H(14B)	C(15)-C(14)-H(14B)
C(41)-H(41B)	0.9800	C(13)-C(14)-H(14A)	C(13)-C(14)-H(14A)
C(41)-H(41C)	0.9800	C(13)-C(14)-H(14B)	C(13)-C(14)-H(14B)
C(41)-H(41A)	0.9800	H(14A)-C(14)-H(14B)	H(14A)-C(14)-H(14B)
C(43)-H(43)	10.000	C(15)-C(16)-H(16)	C(15)-C(16)-H(16)
C(44)-H(44A)	0.9900	C(17)-C(16)-H(16)	C(17)-C(16)-H(16)
C(44)-H(44B)	0.9900	C(18)-C(17)-H(17)	C(18)-C(17)-H(17)
C(46)-H(46)	0.9500	C(16)-C(17)-H(17)	C(16)-C(17)-H(17)
C(47)-H(47)	0.9500	C(17)-C(18)-H(18)	C(17)-C(18)-H(18)
C(48)-H(48)	0.9500	C(19)-C(18)-H(18)	C(19)-C(18)-H(18)
C(49)-H(49)	0.9500	C(18)-C(19)-H(19)	C(18)-C(19)-H(19)
C(51)-H(51)	10.000	C(20)-C(19)-H(19)	C(20)-C(19)-H(19)
N(1)-Cu(1)-N(3)	89.73(9)	N(3)-C(21)-H(21)	N(3)-C(21)-H(21)
N(1)-Cu(1)-N(4)	140.72(9)	C(13)-C(21)-H(21)	C(13)-C(21)-H(21)
N(1)-Cu(1)-N(6)	100.38(9)	C(20)-C(21)-H(21)	C(20)-C(21)-H(21)
N(3)-Cu(1)-N(4)	104.49(9)	N(4)-C(31)-H(31)	N(4)-C(31)-H(31)
N(3)-Cu(1)-N(6)	143.10(9)	C(32)-C(31)-H(31)	C(32)-C(31)-H(31)
N(4)-Cu(1)-N(6)	89.89(9)	C(39)-C(31)-H(31)	C(39)-C(31)-H(31)
O(9)-Cl(2)-O(10)	106.7(2)	C(32)-C(33)-H(33)	C(32)-C(33)-H(33)
O(9)-Cl(2)-O(11)	112.6(2)	C(34)-C(33)-H(33)	C(34)-C(33)-H(33)
O(9)-Cl(2)-O(12)	106.4(2)	C(33)-C(34)-H(34)	C(33)-C(34)-H(34)
O(10)-Cl(2)-O(11)	112.3(2)	C(35)-C(34)-H(34)	C(35)-C(34)-H(34)
O(10)-Cl(2)-O(12)	106.49(19)	C(34)-C(35)-H(35)	C(34)-C(35)-H(35)
O(11)-Cl(2)-O(12)	112.0(2)	C(36)-C(35)-H(35)	C(36)-C(35)-H(35)
O(14)-Cl(2)-O(15)	106.8(7)	C(35)-C(36)-H(36)	C(35)-C(36)-H(36)
O(14)-Cl(2)-O(16)	144.2(8)	C(37)-C(36)-H(36)	C(37)-C(36)-H(36)
O(15)-Cl(2)-O(16)	108.9(8)	C(37)-C(38)-H(38A)	C(37)-C(38)-H(38A)
O(5)-Cl(1)-O(6)	109.75(17)	C(37)-C(38)-H(38B)	C(37)-C(38)-H(38B)
O(5)-Cl(1)-O(7)	110.37(15)	H(38A)-C(38)-H(38B)	H(38A)-C(38)-H(38B)
O(5)-Cl(1)-O(8)	109.16(14)	C(39)-C(38)-H(38A)	C(39)-C(38)-H(38A)
O(6)-Cl(1)-O(7)	108.68(13)	C(39)-C(38)-H(38B)	C(39)-C(38)-H(38B)
O(6)-Cl(1)-O(8)	109.50(13)	C(38)-C(39)-H(39)	C(38)-C(39)-H(39)
O(7)-Cl(1)-O(8)	109.38(13)	O(3)-C(39)-H(39)	O(3)-C(39)-H(39)
C(9)-O(1)-C(10)	106.43(19)	C(31)-C(39)-H(39)	C(31)-C(39)-H(39)
C(12)-O(2)-C(13)	107.2(2)	N(5)-C(41)-H(41A)	N(5)-C(41)-H(41A)
C(39)-O(3)-C(40)	107.29(19)	H(41A)-C(41)-H(41B)	H(41A)-C(41)-H(41B)
C(42)-O(4)-C(43)	106.4(2)	N(5)-C(41)-H(41B)	N(5)-C(41)-H(41B)
Cu(1)-N(1)-C(10)	126.76(18)	N(5)-C(41)-H(41C)	N(5)-C(41)-H(41C)
C(1)-N(1)-C(10)	107.2(2)	H(41A)-C(41)-H(41C)	H(41A)-C(41)-H(41C)

Cu(1)-N(1)-C(1)	125.28(16)	H(41B)-C(41)-H(41C)	H(41B)-C(41)-H(41C)
C(10)-N(2)-C(12)	120.6(2)	C(51)-C(43)-H(43)	C(51)-C(43)-H(43)
C(11)-N(2)-C(12)	119.9(2)	O(4)-C(43)-H(43)	O(4)-C(43)-H(43)
C(10)-N(2)-C(11)	119.0(2)	C(44)-C(43)-H(43)	C(44)-C(43)-H(43)
C(12)-N(3)-C(21)	106.4(2)	C(43)-C(44)-H(44A)	C(43)-C(44)-H(44A)
Cu(1)-N(3)-C(12)	125.57(18)	C(43)-C(44)-H(44B)	C(43)-C(44)-H(44B)
Cu(1)-N(3)-C(21)	126.31(15)	C(45)-C(44)-H(44A)	C(45)-C(44)-H(44A)
Cu(1)-N(4)-C(40)	125.72(18)	C(45)-C(44)-H(44B)	C(45)-C(44)-H(44B)
C(31)-N(4)-C(40)	106.1(2)	H(44A)-C(44)-H(44B)	H(44A)-C(44)-H(44B)
Cu(1)-N(4)-C(31)	126.89(16)	C(45)-C(46)-H(46)	C(45)-C(46)-H(46)
C(40)-N(5)-C(41)	117.8(2)	C(47)-C(46)-H(46)	C(47)-C(46)-H(46)
C(40)-N(5)-C(42)	122.0(2)	C(46)-C(47)-H(47)	C(46)-C(47)-H(47)
C(41)-N(5)-C(42)	119.7(2)	C(48)-C(47)-H(47)	C(48)-C(47)-H(47)
Cu(1)-N(6)-C(42)	127.11(19)	C(47)-C(48)-H(48)	C(47)-C(48)-H(48)
Cu(1)-N(6)-C(51)	125.64(16)	C(49)-C(48)-H(48)	C(49)-C(48)-H(48)
C(42)-N(6)-C(51)	107.1(2)	C(48)-C(49)-H(49)	C(48)-C(49)-H(49)
N(1)-C(1)-C(2)	113.8(2)	C(50)-C(49)-H(49)	C(50)-C(49)-H(49)
N(1)-C(1)-C(9)	102.72(18)	N(6)-C(51)-H(51)	N(6)-C(51)-H(51)
C(2)-C(1)-C(9)	104.4(2)	C(43)-C(51)-H(51)	C(43)-C(51)-H(51)
C(1)-C(2)-C(3)	128.4(3)	C(50)-C(51)-H(51)	C(50)-C(51)-H(51)
C(1)-C(2)-C(7)	C(1)-C(2)-C(7)		

Table 4: Anisotropic displacement parameters (A^2 x 10^3) for **47**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Cu(1)	15(1)	15(1)	26(1)	-1(1)	1(1)	0(1)
O(1)	25(1)	18(1)	35(1)	-4(1)	2(1)	5(1)
O(2)	16(1)	27(1)	31(1)	-2(1)	-3(1)	-2(1)
O(3)	24(1)	22(1)	38(1)	4(1)	-3(1)	4(1)
O(4)	16(1)	30(1)	35(1)	2(1)	2(1)	-4(1)
N(1)	19(1)	17(1)	29(1)	-1(1)	2(1)	2(1)
N(2)	17(1)	21(1)	28(1)	1(1)	0(1)	3(1)
N(3)	19(1)	18(1)	23(1)	-1(1)	0(1)	-2(1)
N(4)	19(1)	17(1)	28(1)	0(1)	-1(1)	1(1)
N(5)	16(1)	20(1)	38(1)	-1(1)	1(1)	2(1)
N(6)	22(1)	20(1)	23(1)	0(1)	2(1)	-4(1)
C(1)	23(1)	16(1)	31(1)	-3(1)	2(1)	-3(1)
C(2)	27(1)	17(1)	34(1)	-3(1)	-2(1)	-7(1)
C(3)	24(1)	26(1)	38(2)	-6(1)	-1(1)	-3(1)
C(4)	33(2)	23(1)	44(2)	-1(1)	-9(1)	-1(1)
C(5)	40(2)	27(1)	37(2)	3(1)	-8(1)	-11(1)
C(6)	39(2)	27(1)	33(2)	-2(1)	4(1)	-10(1)
C(7)	29(2)	19(1)	35(2)	-5(1)	2(1)	-7(1)
C(8)	28(2)	29(1)	35(2)	-7(1)	4(1)	-1(1)
C(9)	22(1)	19(1)	34(1)	-4(1)	3(1)	-1(1)
C(10)	21(1)	16(1)	27(1)	3(1)	5(1)	0(1)

C(11)	18(1)	31(2)	41(2)	9(1)	3(1)	9(1)
C(12)	19(1)	21(1)	22(1)	4(1)	2(1)	-1(1)
C(13)	24(1)	26(1)	40(2)	-6(1)	0(1)	-5(1)
C(14)	32(2)	50(2)	49(2)	-20(2)	-13(1)	6(2)
C(15)	41(2)	26(1)	33(2)	-7(1)	-7(1)	-1(1)
C(16)	64(2)	30(2)	32(2)	-4(1)	-9(2)	7(2)
C(17)	77(3)	31(2)	25(2)	-3(1)	7(2)	-1(2)
C(18)	52(2)	33(2)	37(2)	-5(1)	18(2)	-7(2)
C(19)	30(2)	23(1)	33(2)	-4(1)	4(1)	-5(1)
C(20)	32(2)	16(1)	28(1)	-2(1)	2(1)	-1(1)
C(21)	19(1)	18(1)	30(1)	-1(1)	0(1)	-4(1)
C(31)	23(1)	15(1)	32(1)	2(1)	-3(1)	-5(1)
C(32)	26(1)	19(1)	29(1)	2(1)	0(1)	-8(1)
C(33)	22(1)	25(1)	33(1)	5(1)	-2(1)	-2(1)
C(34)	31(2)	27(1)	38(2)	2(1)	7(1)	-5(1)
C(35)	45(2)	30(2)	31(2)	-2(1)	3(1)	-11(1)
C(36)	38(2)	25(1)	29(1)	5(1)	-6(1)	-9(1)
C(37)	31(2)	17(1)	36(2)	3(1)	-4(1)	-8(1)
C(38)	36(2)	24(1)	37(2)	10(1)	-6(1)	3(1)
C(39)	24(1)	16(1)	38(2)	2(1)	-3(1)	-2(1)
C(40)	23(1)	18(1)	28(1)	-2(1)	-2(1)	2(1)
C(41)	12(1)	31(2)	64(2)	-5(2)	-3(1)	5(1)
C(42)	17(1)	23(1)	25(1)	-4(1)	1(1)	-1(1)
C(43)	25(1)	31(1)	28(1)	1(1)	2(1)	-6(1)
C(44)	26(2)	58(2)	30(2)	1(1)	6(1)	-8(1)
C(45)	30(2)	25(1)	29(1)	-2(1)	2(1)	-3(1)
C(46)	47(2)	25(2)	29(2)	-2(1)	-4(1)	-5(1)
C(47)	48(2)	22(1)	33(2)	1(1)	-14(1)	-2(1)
C(48)	34(2)	26(2)	51(2)	6(1)	-14(2)	5(1)
C(49)	32(2)	23(1)	35(2)	2(1)	-1(1)	4(1)
C(50)	25(1)	17(1)	31(1)	1(1)	0(1)	-3(1)
C(51)	24(1)	20(1)	25(1)	1(1)	1(1)	-3(1)
Cl(2)	55(1)	46(1)	41(1)	-12(1)	6(1)	-12(1)
O(9)	51(1)	52(1)	55(1)	-11(1)	-9(1)	-9(1)
O(10)	51(1)	52(1)	55(1)	-11(1)	-9(1)	-9(1)
O(11)	51(1)	52(1)	55(1)	-11(1)	-9(1)	-9(1)
O(12)	51(1)	52(1)	55(1)	-11(1)	-9(1)	-9(1)
O(13)	68(4)	86(5)	39(3)	-14(3)	2(3)	-9(4)
O(14)	68(4)	86(5)	39(3)	-14(3)	2(3)	-9(4)
O(15)	68(4)	86(5)	39(3)	-14(3)	2(3)	-9(4)
O(16)	68(4)	86(5)	39(3)	-14(3)	2(3)	-9(4)
Cl(1)	29(1)	25(1)	29(1)	1(1)	6(1)	2(1)
O(5)	75(2)	36(1)	46(1)	14(1)	28(1)	4(1)
O(6)	25(1)	38(1)	53(1)	-10(1)	3(1)	8(1)
O(7)	42(1)	39(1)	51(1)	-10(1)	-3(1)	-6(1)
O(8)	26(1)	35(1)	31(1)	3(1)	6(1)	8(1)

Table 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **47**.

	x	y	z	U(eq)
H(1)	5885	12263	9279	28
H(3)	7292	10810	9740	35
H(4)	7791	10231	10616	40
H(5)	6596	10553	11381	41
H(6)	4888	11439	11289	40
H(8A)	3994	12799	10533	36
H(8B)	3254	11910	10344	36
H(9)	4413	13152	9648	30
H(11A)	987	11251	9041	45
H(11B)	1116	11370	8384	45
H(11C)	1569	12159	8792	45
H(13)	1703	8487	8350	36
H(14A)	1580	8231	7429	52
H(14B)	1409	9318	7369	52
H(16)	2874	8964	6415	51
H(17)	4883	9005	6176	53
H(18)	6347	8977	6848	49
H(19)	5834	8917	7796	34
H(21)	3727	8301	8433	27
H(31)	4950	7898	9182	28
H(33)	3700	9395	9760	32
H(34)	3131	9685	10678	38
H(35)	4133	8985	11413	42
H(36)	5735	8007	11240	37
H(38A)	6484	6858	10301	39
H(38B)	7426	7684	10341	39
H(39)	6552	6993	9373	31
H(41A)	9459	8506	8620	54
H(41B)	9565	8758	9264	54
H(41C)	9950	9486	8803	54
H(43)	8850	11883	8120	33
H(44A)	9005	11481	7222	46
H(44B)	8704	10431	7364	46
H(46)	7272	11061	6383	40
H(47)	5229	11276	6234	41
H(48)	3964	11591	6970	44
H(49)	4696	11670	7880	36
H(51)	6932	11961	8428	27

***Table 6*:** Torsion angles [deg] for **47**.

N(3)-Cu(1)-N(1)-C(1)	166.8(2)	N(1)-C(1)-C(9)-O(1)	-9.9(2)
N(4)-Cu(1)-N(1)-C(1)	53.9(3)	N(1)-C(1)-C(9)-C(8)	108.5(2)
N(6)-Cu(1)-N(1)-C(1)	-48.9(2)	C(9)-C(1)-C(2)-C(3)	-172.4(3)
N(3)-Cu(1)-N(1)-C(10)	-1.9(2)	C(2)-C(1)-C(9)-C(8)	-10.5(3)
N(4)-Cu(1)-N(1)-C(10)	-114.8(2)	C(2)-C(1)-C(9)-O(1)	-128.9(2)
N(6)-Cu(1)-N(1)-C(10)	142.4(2)	N(1)-C(1)-C(2)-C(7)	-103.8(2)
N(1)-Cu(1)-N(3)-C(12)	10.5(2)	C(3)-C(2)-C(7)-C(6)	0.3(4)
N(4)-Cu(1)-N(3)-C(12)	153.4(2)	C(1)-C(2)-C(7)-C(8)	-1.4(3)
N(6)-Cu(1)-N(3)-C(12)	-96.6(2)	C(7)-C(2)-C(3)-C(4)	0.4(4)
N(1)-Cu(1)-N(3)-C(21)	173.6(2)	C(3)-C(2)-C(7)-C(8)	178.4(2)
N(4)-Cu(1)-N(3)-C(21)	-43.4(2)	C(1)-C(2)-C(7)-C(6)	-179.5(2)
N(6)-Cu(1)-N(3)-C(21)	66.5(3)	C(1)-C(2)-C(3)-C(4)	-179.8(3)
N(1)-Cu(1)-N(4)-C(31)	67.7(3)	C(2)-C(3)-C(4)-C(5)	-0.6(4)
N(3)-Cu(1)-N(4)-C(31)	-40.3(2)	C(3)-C(4)-C(5)-C(6)	0.2(5)
N(6)-Cu(1)-N(4)-C(31)	174.1(2)	C(4)-C(5)-C(6)-C(7)	0.5(5)
N(1)-Cu(1)-N(4)-C(40)	-97.6(2)	C(5)-C(6)-C(7)-C(8)	-178.5(3)
N(3)-Cu(1)-N(4)-C(40)	154.4(2)	C(5)-C(6)-C(7)-C(2)	-0.7(4)
N(6)-Cu(1)-N(4)-C(40)	8.8(2)	C(2)-C(7)-C(8)-C(9)	-5.3(3)
N(1)-Cu(1)-N(6)-C(42)	139.2(2)	C(6)-C(7)-C(8)-C(9)	172.7(3)
N(3)-Cu(1)-N(6)-C(42)	-117.1(2)	C(7)-C(8)-C(9)-C(1)	9.7(3)
N(4)-Cu(1)-N(6)-C(42)	-2.6(2)	C(7)-C(8)-C(9)-O(1)	123.1(2)
N(1)-Cu(1)-N(6)-C(51)	-46.4(2)	C(21)-C(13)-C(14)-C(15)	-12.0(4)
N(3)-Cu(1)-N(6)-C(51)	57.3(3)	C(14)-C(13)-C(21)-C(20)	10.9(3)
N(4)-Cu(1)-N(6)-C(51)	171.8(2)	O(2)-C(13)-C(14)-C(15)	99.7(3)
C(9)-O(1)-C(10)-N(2)	172.4(2)	C(14)-C(13)-C(21)-N(3)	128.9(3)
C(9)-O(1)-C(10)-N(1)	-8.5(3)	O(2)-C(13)-C(21)-N(3)	12.4(3)
C(10)-O(1)-C(9)-C(1)	11.0(3)	O(2)-C(13)-C(21)-C(20)	-105.6(2)
C(10)-O(1)-C(9)-C(8)	-104.9(2)	C(13)-C(14)-C(15)-C(16)	-172.4(3)
C(13)-O(2)-C(12)-N(2)	-175.9(2)	C(13)-C(14)-C(15)-C(20)	9.0(4)
C(13)-O(2)-C(12)-N(3)	4.1(3)	C(14)-C(15)-C(20)-C(21)	-2.3(4)
C(12)-O(2)-C(13)-C(14)	-125.4(3)	C(16)-C(15)-C(20)-C(21)	179.0(3)
C(12)-O(2)-C(13)-C(21)	-10.3(3)	C(14)-C(15)-C(20)-C(19)	176.8(3)
C(39)-O(3)-C(40)-N(5)	-178.3(2)	C(14)-C(15)-C(16)-C(17)	-177.1(3)
C(40)-O(3)-C(39)-C(38)	-121.7(2)	C(20)-C(15)-C(16)-C(17)	1.4(4)
C(40)-O(3)-C(39)-C(31)	-6.2(3)	C(16)-C(15)-C(20)-C(19)	-2.0(4)
C(39)-O(3)-C(40)-N(4)	3.4(3)	C(15)-C(16)-C(17)-C(18)	-0.2(4)
C(43)-O(4)-C(42)-N(5)	172.6(2)	C(16)-C(17)-C(18)-C(19)	-0.5(4)
C(42)-O(4)-C(43)-C(51)	11.2(3)	C(17)-C(18)-C(19)-C(20)	-0.1(4)
C(43)-O(4)-C(42)-N(6)	-8.9(3)	C(18)-C(19)-C(20)-C(15)	1.3(4)
C(42)-O(4)-C(43)-C(44)	-104.8(3)	C(18)-C(19)-C(20)-C(21)	-179.8(3)
C(10)-N(1)-C(1)-C(2)	117.9(2)	C(15)-C(20)-C(21)-N(3)	-116.9(2)
C(1)-N(1)-C(10)-O(1)	1.5(3)	C(15)-C(20)-C(21)-C(13)	-5.3(3)
C(10)-N(1)-C(1)-C(9)	5.7(3)	C(19)-C(20)-C(21)-N(3)	64.1(3)
Cu(1)-N(1)-C(1)-C(9)	-164.84(16)	C(19)-C(20)-C(21)-C(13)	175.7(3)
Cu(1)-N(1)-C(1)-C(2)	-52.7(3)	N(4)-C(31)-C(39)-C(38)	123.6(2)
C(1)-N(1)-C(10)-N(2)	-179.5(2)	C(32)-C(31)-C(39)-O(3)	-112.8(2)
Cu(1)-N(1)-C(10)-O(1)	171.84(17)	N(4)-C(31)-C(32)-C(33)	66.7(3)

Cu(1)-N(1)-C(10)-N(2)	-9.2(4)	N(4)-C(31)-C(32)-C(37)	-115.2(2)
C(12)-N(2)-C(10)-N(1)	13.5(4)	C(39)-C(31)-C(32)-C(33)	179.3(2)
C(10)-N(2)-C(12)-O(2)	176.6(2)	C(39)-C(31)-C(32)-C(37)	-2.6(3)
C(11)-N(2)-C(10)-O(1)	4.1(3)	N(4)-C(31)-C(39)-O(3)	6.7(3)
C(11)-N(2)-C(10)-N(1)	-175.0(3)	C(32)-C(31)-C(39)-C(38)	4.1(3)
C(12)-N(2)-C(10)-O(1)	-167.5(2)	C(33)-C(32)-C(37)-C(36)	0.4(4)
C(11)-N(2)-C(12)-O(2)	5.2(3)	C(33)-C(32)-C(37)-C(38)	178.3(2)
C(11)-N(2)-C(12)-N(3)	-174.8(3)	C(31)-C(32)-C(37)-C(38)	0.0(3)
C(10)-N(2)-C(12)-N(3)	-3.3(4)	C(31)-C(32)-C(33)-C(34)	178.0(3)
Cu(1)-N(3)-C(12)-O(2)	170.45(16)	C(37)-C(32)-C(33)-C(34)	0.1(4)
C(12)-N(3)-C(21)-C(20)	101.2(2)	C(31)-C(32)-C(37)-C(36)	-177.9(2)
C(21)-N(3)-C(12)-N(2)	-175.5(2)	C(32)-C(33)-C(34)-C(35)	-0.5(4)
Cu(1)-N(3)-C(21)-C(13)	-176.33(17)	C(33)-C(34)-C(35)-C(36)	0.6(5)
Cu(1)-N(3)-C(21)-C(20)	-64.6(3)	C(34)-C(35)-C(36)-C(37)	-0.2(5)
Cu(1)-N(3)-C(12)-N(2)	-9.6(4)	C(35)-C(36)-C(37)-C(38)	-177.8(3)
C(21)-N(3)-C(12)-O(2)	4.6(3)	C(35)-C(36)-C(37)-C(32)	-0.3(4)
C(12)-N(3)-C(21)-C(13)	-10.6(3)	C(32)-C(37)-C(38)-C(39)	2.6(3)
C(40)-N(4)-C(31)-C(32)	107.8(2)	C(36)-C(37)-C(38)-C(39)	-179.7(3)
Cu(1)-N(4)-C(31)-C(39)	-172.70(17)	C(37)-C(38)-C(39)-O(3)	108.3(2)
Cu(1)-N(4)-C(40)-N(5)	-8.9(4)	C(37)-C(38)-C(39)-C(31)	-4.1(3)
C(40)-N(4)-C(31)-C(39)	-5.1(3)	O(4)-C(43)-C(44)-C(45)	124.8(3)
C(31)-N(4)-C(40)-O(3)	1.3(3)	C(44)-C(43)-C(51)-C(50)	-10.6(3)
C(31)-N(4)-C(40)-N(5)	-176.7(3)	O(4)-C(43)-C(51)-N(6)	-9.9(3)
Cu(1)-N(4)-C(40)-O(3)	169.10(18)	O(4)-C(43)-C(51)-C(50)	-128.8(2)
Cu(1)-N(4)-C(31)-C(32)	-59.9(3)	C(51)-C(43)-C(44)-C(45)	11.0(3)
C(41)-N(5)-C(42)-O(4)	-2.5(4)	C(44)-C(43)-C(51)-N(6)	108.3(3)
C(40)-N(5)-C(42)-O(4)	-174.2(2)	C(43)-C(44)-C(45)-C(46)	173.6(3)
C(42)-N(5)-C(40)-N(4)	-0.1(4)	C(43)-C(44)-C(45)-C(50)	-7.5(4)
C(40)-N(5)-C(42)-N(6)	7.4(4)	C(46)-C(45)-C(50)-C(49)	-1.2(4)
C(42)-N(5)-C(40)-O(3)	-178.3(2)	C(46)-C(45)-C(50)-C(51)	179.9(2)
C(41)-N(5)-C(42)-N(6)	179.1(3)	C(50)-C(45)-C(46)-C(47)	-0.2(4)
C(41)-N(5)-C(40)-O(3)	9.9(4)	C(44)-C(45)-C(50)-C(49)	179.8(3)
C(41)-N(5)-C(40)-N(4)	-172.0(3)	C(44)-C(45)-C(46)-C(47)	178.7(3)
Cu(1)-N(6)-C(51)-C(43)	-169.93(17)	C(44)-C(45)-C(50)-C(51)	0.9(3)
Cu(1)-N(6)-C(42)-O(4)	177.18(17)	C(45)-C(46)-C(47)-C(48)	1.1(4)
C(42)-N(6)-C(51)-C(43)	5.4(3)	C(46)-C(47)-C(48)-C(49)	-0.7(4)
C(51)-N(6)-C(42)-O(4)	1.9(3)	C(47)-C(48)-C(49)-C(50)	-0.7(4)
Cu(1)-N(6)-C(42)-N(5)	-4.5(4)	C(48)-C(49)-C(50)-C(45)	1.6(4)
Cu(1)-N(6)-C(51)-C(50)	-57.8(3)	C(48)-C(49)-C(50)-C(51)	-179.7(3)
C(51)-N(6)-C(42)-N(5)	-179.7(2)	C(45)-C(50)-C(51)-C(43)	6.1(3)
C(42)-N(6)-C(51)-C(50)	117.5(2)	C(49)-C(50)-C(51)-N(6)	76.3(3)
C(9)-C(1)-C(2)-C(7)	7.4(3)	C(49)-C(50)-C(51)-C(43)	-172.7(3)
N(1)-C(1)-C(2)-C(3)	76.5(3)	C(45)-C(50)-C(51)-N(6)	-104.9(3)

***Table 7*:** Hydrogen-bonds for **47** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(8)-H(8B)...O(7)	0.9900	25.200	3.494(4)	169.00
C(9)-H(9)...O(6)#1	10.000	24.400	3.255(3)	139.00
C(9)-H(9)...O(7)#1	10.000	25.800	3.326(3)	131.00
C(11)-H(11A)...O(6)	0.9800	25.200	3.494(4)	176.00
C(11)-H(11A)...O(8)	0.9800	25.600	3.187(4)	122.00
C(11)-H(11C)...O(1)	0.9800	22.800	2.645(3)	101.00
C(33)-H(33)...O(8)	0.9500	25.100	3.251(3)	134.00
C(38)-H(38A)...O(8)#2	0.9900	24.800	3.444(4)	164.00
C(39)-H(39)...O(5)#2	10.000	25.100	3.301(4)	136.00
C(41)-H(41A)...O(9)	0.9800	25.300	3.214(5)	127.00
C(41)-H(41C)...O(2)#3	0.9800	25.600	3.408(3)	145.00
C(41)-H(41C)...O(4)	0.9800	22.300	2.662(4)	105.00
C(44)-H(44A)...O(11)#4	0.9900	24.600	3.264(5)	138.00
C(44)-H(44B)...O(12)	0.9900	24.300	3.285(5)	145.00
C(47)-H(47)...O(5)#5	0.9500	24.400	3.328(4)	155.00
C(48)-H(48)...O(9)#6	0.9500	25.200	3.379(6)	151.00

3. List of Publications

1) ***Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate Using Simple Bis(oxazoline) Ligands: Importance of Metal/Ligand Ratio***
   Ramesh Rasappan, Markus Hager, Anja Gissibl, Oliver Reiser,
   Org. Lett. **2006**, *8*, 6099-6102.

2) ***Synthesis and Application of Phosphorus Dendrimer Immobilized Aza-bis(oxazolines)***
   Anja Gissibl, Clément Padié, Markus Hager, Florian Jaroschik, Ramesh Rasappan, Erick Cuevas-Yañez, Cédric-Olivier Turrin, Anne-Marie Caminade, Jean-Pierre Majoral, Oliver Reiser
   Org. Lett. **2007**, *9*, 2895-2898.

3) ***Dependence of Enantioselectivity on the Ligand/Metal Ratio in the Asymmetric Michael Addition of Indole to Benzylidene Malonates: Electronic Influence of Substrates***
   Alexander Schätz, Ramesh Rasappan, Markus Hager, Anja Gissibl, Oliver Reiser
   Chem. Eur. J. **2008***, 14,* 7259-7265.

4) ***Cu(II)-Azabis(oxazoline)-Complexes Immobilized on Superparamagnetic Magnetite@Silica-Nanoparticles: A Highly Selective and Recyclable Catalyst for the Kinetic Resolution of 1,2-Diols***
   Alexander Schätz, Markus Hager, Oliver Reiser
   Adv. Funct. Mater. **2009**, *19*, 2109-2115.

5) **Estradiol inhibits chondrogenic differentiation of mesenchymal stem cells via non-classical signalling**
   Z. Jenei-Lanzl, R. H. Straub, T. Dienstknecht, M. Huber, M. Hager, S. Grässel, R. Kujat, M. K. Angele, M. Nerlich, P. Angele
   Arthritis & Rheumatism **2009**, accepted.

4. Poster presentations and scientific meetings

1) *Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany,* ***2007****.*
   Poster presentation:
   Asymmetric Reactions Catalyzed by Native and Immobilized Azabis(oxazoline) Ligands
   Ramesh Rasappan, Markus Hager, Anja Gissibl, Clément Padié, Jean-Pierre Majoral, Oliver Reiser

2) *Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany,* ***2009****.*

5. Curriculum Vitae

Personal Data

Name:	Markus Hager
Date of birth:	29.05.1981 in Rotthalmünster, Germany
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Education

10/2006-03/2010	**PhD thesis** at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser *"Synthesis and Applications of Azabis(oxazoline)-Ligands"*
10/2006-12/2006	**Research project** at the LCC du CNRS in Toulouse (France) under the supervision of Prof. Jean-Pierre Majoral *"Synthesis of water-soluble dendrons for asymmetric catalysis"*
09/2006	**Graduation**: Diplom-Chemiker (diploma in chemistry, Master of Science equivalent)
01/2006-09/2006	**Diploma thesis** at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser *„Synthese und Immobilisierung von Azabis-(oxazolinen) und deren Anwendung in der asymmetrischen Katalyse"*
10/2001-09/2006	**Studies in Chemistry**, University of Regensburg, Germany
08/2000-07/2001	Zivildienst (Civil service)
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1989-1991	Primary school Aigen am Inn
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German (native)

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