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STUDIES ON BASE-CATALYZED CONDENSATION OF BENZALDEHYDE AND BOROXAZOLIDONES

Master of Science Thesis

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ABSTRACT

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The formation of imines is one of the most important reactions in organic synthesis, as imines are used as highly versatile and exquisite precursors in numerous synthetic processes. In addition, these have proven to possess a wide selection of biological activities, such as antibacterial, antifungal, antiviral and anticancer properties. Even though several methods for imine preparation have been reported, most of the techniques require harsh conditions, expensive catalysts or they are effective only with a limited selection of starting materials.

The most common way to produce imines utilizes condensation reaction between amines and carbonyl compounds. Such reaction between *L*-valine derived boroxazolidone and benzaldehyde had already been studied in synthesis laboratory to synthesize highly functional imines, which could be further employed in challenging α-amino acid functionalization. As the reaction resulted in formation of tautomeric isomers, the aim of the study, which was adopted as the aim of this Master's thesis, was to optimize the reaction conditions towards selective formation of only one of the regioisomers. Through screening of different reaction parameters in the abovementioned reaction, the base catalysis was found to be effective in controlling the interconversion of the isomers. Depending on the activating nature of the base catalyst, the reaction could be directed towards either the aldimine formation or the ketimine formation, and in most cases, only one isomer could be obtained. The highest aldimine conversion, 14 %, was obtained with 1,2-bis(diphenylphosphino)ethane (DPPE), as the reaction with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) gave the highest ketimine yield, 27 %.

In addition, not only the choice of base, but also reaction temperature, reaction time, choice of solvent and reagent ratio were noticed to have an effect in the outcome. After these parameters were optimized in DBU-catalyzed reactions, the obtained yield of ketimine was increased to 62 %. When applying the optimized conditions to condensation reactions between benzaldehyde and two other boroxazolidones, the corresponding ketimines were obtained in 64 % and 44 % yields, respectively.

TIIVISTELMÄ

MANNOJA, JENNA: Emäskatalysoitu bentsaldehydin ja boroksatsolidonien kondensaatio

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Imiinit ovat monipuolisia ja ainutlaatuisia yhdisteitä, joita hyödynnetään lukemattomissa synteeseissä. Tästä johtuen imiinisynteesiä voidaan pitää yhtenä keskeisimmistä ja tärkeimmistä synteettisen orgaanisen kemian reaktioista. Sen lisäksi, että imiinit toimivat prekursoreina reaktioissa, niillä on havaittu sieni-, bakteeri- ja virusinfektioita hoitavia sekä syöpäsoluja tuhoavia ominaisuuksia. Siitä huolimatta, että imiinien valmistamiseksi on kehitetty useita synteesireittejä, monet näistä metodeista vaativat rankat reaktio-olosuhteet sekä kalliiden katalyyttien hyödyntämisen, tai ne toimivat vain tiettyjen lähtöaineiden kanssa.

Imiinejä valmistetaan tavallisimmin amiinien ja karbonyyliyhdisteiden välisellä kondensaatioreaktiolla. Synteesilaboratoriossamme on ennen tätä diplomityötä tutkittu vastaavanlaista reaktiota *L*-valiinista johdetun boroksatsolidonin ja bentsaldehydin välillä. Kyseisen projektin tarkoituksena oli valmistaa monitoiminnallisia imiinejä, joita voitaisiin hyödyntää erityisen haastavissa α-aminohappojen funktionalisoinneissa. Projektin aikana kuitenkin ilmeni, että kyseisessä reaktiossa syntyy kahta isomeeriä tautomerisaation seurauksena. Tutkimuksen tavoitteeksi tulikin löytää ne reaktio-olosuhteet, jossa tasapainoreaktiota näiden isomeerien välillä voitaisiin ohjata haluttuun suuntaan. Tämän pohjalta syntyi tämän diplomityön päätavoite eli yllämainitun reaktion olosuhteiden optimointi niin, että tautomerisaatiota pystyttäisiin hallitsemaan.

Hyödyntämällä erityyppisiä katalyyttejä reaktiossa havaittiin, että tautomerisaatiota oli mahdollista kontrolloida. Emäskatalysoiduissa reaktioissa, riippuen käytetyn katalyytin ominaisuuksista, tasapainoa voitiin ohjata joko aldimiinin tai ketimiinin muodostumisen suuntaan ja monessa tapauksessa täysin selektiivinen kontrollointi onnistui. Suurin aldimiinin konversio, 14 %, saavutettiin 1,2-bis(difenyylifosfiini)etaani- eli DPPE-katalysoidulla reaktiolla, kun taas 1,8-diatsabisyklo[5.4.0]undek-7-eeni- eli DBU-katalysoitu reaktio tuotti ketimiiniä 27 % saannolla.

Reaktiossa käytetyn emäskatalyytin lisäksi reaktiolämpötilan, reaktioajan, liuottimen sekä lähtöaineiden keskinäisen suhteen havaittiin vaikuttavan reaktion lopputulokseen. Reaktio-olosuhteiden optimoinnin myötä DBU-katalysoidulla reaktiolla onnistuttiin tuottamaan ketimiiniä 62 % saannolla. Lisäksi optimoituja olosuhteita testattiin kahden muun boroksatsolidonin ja bentsaldehydin välisessä reaktiossa, jolloin ketimiiniä saatiin 64 % ja 44 % saannoilla.

PREFACE

The experimental part of this thesis was performed in the synthesis laboratory of the Department of Chemistry and Bioengineering in Tampere University of Technology during November 2014 - September 2015.

First, I'm sincerely thankful to my supervisor Professor Robert Franzén for introducing me to the field of organic synthesis, for giving me an opportunity to work with such interesting research topic and for offering all the resources and support during this project. I'm also deeply grateful to my second supervisor Docent Nuno R. Candeias for the numerous practical advices and his endless patience and flexibility. Most importantly, I'm especially thankful for all the motivation and support he has provided me during this Master's thesis project. In addition, I would like to thank Dr. Alexander Efimov of his advice with the NMR equipment and measurements.

I would also like to thank my dear friends and colleagues Jenni and Hanna for the relaxed and warm atmosphere in the office, for all the long talks over a cup of coffee, and just for being there in both happy and hard moments during this project.

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ABBREVIATIONS AND NOTATIONS

^{13}C	carbon-13
^{1}H	proton
br	broad (NMR)
δ	chemical shift, ppm (NMR)
d	doublet (NMR)
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	diisopropylethylamine, Hünig's base
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
eq	molar equivalent
EtOAc	ethylacetate
HMPA	hexamethylphosphoramide
J	coupling constant (NMR)
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
LA	Lewis acid
LB	Lewis base
m	multiplet (NMR)
MeOH	methanol
NMR	nuclear magnetic resonance
ODH	oxidative dehydrogenation
OP(*n*-Bu)$_3$	tributylphosphine oxide
Ph	phenyl group
PPh$_3$	triphenylphosphine
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
wt%	weight percent

1. INTRODUCTION

Behind every research there are previously performed studies, which have inspired the researcher to start investigating an issue in more detail. The origins of this thesis study go back to the studies of organoboron compounds performed by Kuuloja [1] in years 2006−2011. During her Ph.D. work, a mild and an effective route to prepare boron containing amino acid derivatives, boroxazolidones, from tetraphenylborates was developed.

The studies for utilizing boroxazolidones continued, as it was envisioned, that applying boroxazolidones in imine synthesis could provide highly functionalized products to be used as tools for amino acid functionalization. As the studied condensation reaction between *L*-valine based boroxazolidone and benzaldehyde resulted in tautomerization, and chirality in α-position was lost during this process, the need to find ways to control the outcome was arisen, which resulted in initiating this Master's thesis project.

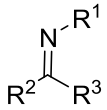
The aim of this thesis study is to find the optimized reaction conditions for the condensation reaction between *L*-valinatodiphenylboron and benzaldehyde, so that the interconversion between the two imine products could be selectively directed. Through screening of different reaction parameters, such as catalysts, solvents, temperatures and ratios of reactants, it was predicted that it could be possible to control the equilibrium between the isomeric products in a way that only one isomer with high yield could be obtained.

The overall structure of the study takes the form of six chapters, which are divided between literature survey and experimental research. The literature survey in this thesis has been divided into two main sections. Chapter 2 focuses on imines, also known as Schiff bases, and especially on the procedures, which are used to prepare these versatile compounds. To demonstrate the wide applicability and important role of imines, short descriptions of imines in synthesis, bio-processes and medicinal chemistry are given. Chapter 3 begins with a brief presentation of the characteristics of boron and its organic derivatives and continues to giving examples of the synthesis and applications of organoboron compounds. The rest of this chapter is focused on the main subjects of this thesis, as nitrogen-boron (N-B) bond and N-B bond containing organoboron heterocycles, boroxazolidones, are introduced in detail. At the end of this chapter, a short description of Lewis acid-Lewis base interactions is given. It also opens up the reasoning behind the hypotheses and conclusions made in the experimental section.

The last three chapters describe the experimental work performed during this project. The results obtained from the experimental work are collected to and discussed in Chapter 4. The effects of changing the reaction parameters on the reaction are presented and analyzed through comparison and explained in terms of the hypothesized reaction mechanisms. In addition, the results obtained from applying the optimized conditions into reactions with different boroxazolidones are presented and discussed. The detailed descriptions of the performed syntheses, work-up procedures and the structural data acquired from NMR spectroscopy measurements are collected to Chapter 6.

2. IMINES – SYNTHESIS & APPLICATIONS

Imines, also known as azomethines or Schiff bases, were discovered by a German scientist Hugo Schiff in 1864. By structure imine **1** is a nitrogen analogue of an aldehyde or a ketone, in which the oxygen has been replaced with a N-R^1-group. If R^1 is hydrogen, the compound is called a primary imine and if R^1 is a hydrocarbyl group, the substance is called a secondary imine. When R^1 is OH group, the imine is called an oxime and a hydrazine if R^1 is NH_2 (Scheme 1). [2-4]



1

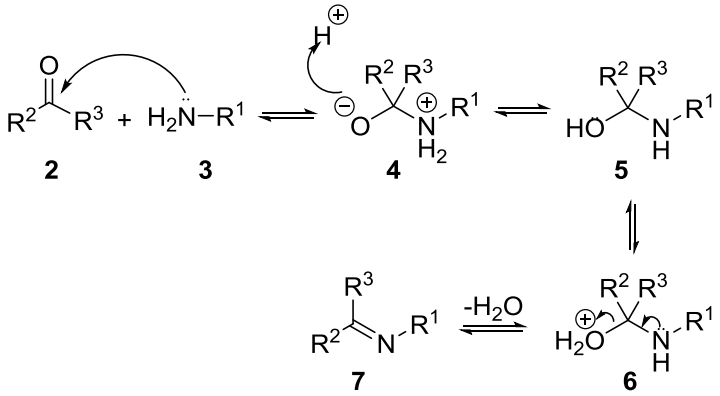
Scheme 1: *The general structure of an imine **1**.*

2.1 Synthetic Methods for Preparation of Imines

Several different methods for preparation of imines have been reported since the discovery of these compounds. Nevertheless, the most common way is based on the reaction originally reported by Schiff in 1864. In his studies, the reaction of aniline with different aldehydes was studied and as a result, the new species of compounds, imines, were discovered. [4; 5]

2.1.1 Reaction of Aldehydes and Ketones with Amines

The synthesis of imines can be achieved by letting any primary amine **3** react with an aldehyde or a ketone **2**. Such reaction proceeds by nucleophilic attack by the amine at the carbonyl carbon to give a hemiaminal intermediate **5**. In the last step elimination of water molecule gives the corresponding imine **7** (Scheme 2). [2-4]



2 **3** **4** **5** **7** **6**

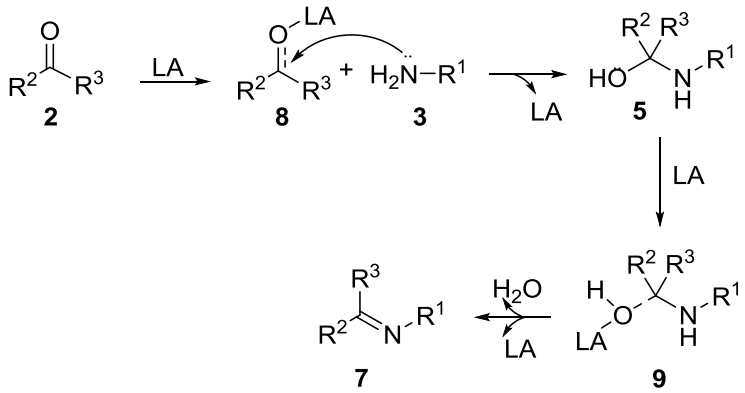
Scheme 2*: Synthesis of an imine **7** from a primary amine **3** and an aldehyde or a ketone **2**. [2]*

Usually imine formation can be accelerated with an acid catalyst, which is needed in the elimination step. Still it is important to acknowledge that the lower the pH decreases, the more amine gets protonated which slows down the rate of the addition step. On the other hand, at high pH, the low proton concentration prevents protonation of the leaving group OH in the elimination step. The imine formation is in fact fastest around pH 4−6. [2]

Another important factor which affects to the equilibrium of the reaction is the rate of removal of water in the dehydration step. Imines are usually unstable and easily hydrolyzed back to the carbonyl compound and amine. Due to this, it is necessary to use azeotropic distillation with Dean-Stark apparatus or dehydrating agents such as molecular sieves [6], trimethyl orthoformate [7] or tetramethyl orthosilicate [8] to push the reaction forward. Moreover, the reaction is usually performed using a superstoichiometric amount of amine to drive the reaction equilibrium towards the product. Other factors which have an influence to the reaction equilibrium are concentration, temperature, solvents and steric and electronic effects. [2; 3]

2.1.2 Lewis Acid Catalysis

As an alternative method, imine synthesis can be carried out in the presence of a Lewis acid (LA). Lewis acids have a twofold function in the reaction. First they catalyze the reaction by attaching to a nucleophilic site of the carbonyl compound **2** and this way they activate the molecule for the nucleophilic attack by the amine **3**. Secondly they act as dehydrating agents through irreversible binding with water and this way promote the removal of water in the dehydration step (Scheme 3). [2; 9]



Scheme 3: *Imine **7** synthesis with Lewis acid (LA) catalysis. [9]*

Numerous different Lewis acids have been successfully included in the reaction between carbonyl compounds and amines, such as $TiCl_4$, $MgSO_4$, $CuSO_4$, $Ti(OR)_4$, $ZnCl_2$, $Cu(NO_3)_2$, P_2O_5 supported on Al_2O_3 or SiO_2, $CeCl_3 \cdot H_2O$ and $Mg(ClO_4)_2$. [3]

There are some disadvantages with these traditional methods reported. In some cases, especially when imines are prepared from amines that have an alkyl group in the

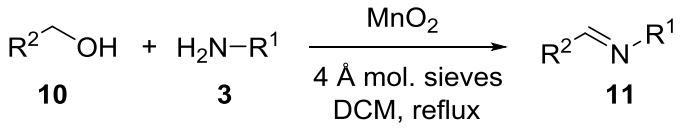
structure, reaction products have been noticed to decompose rapidly or instead they polymerize. This can be prevented by having at least one aryl group attached to the nitrogen or the carbon atom. When compared to aldehydes, ketones' reactions with amines proceed more slowly and usually the conversion into imine requires harsh conditions. All in all these procedures require long reaction times, high reaction temperatures, an excess of dehydrating agents and tedious workup. In addition, the efficiency of these methods seems to have limitation to reactions between strongly nucleophilic amines and highly electrophilic carbonyl compounds.

Due to these drawbacks, researchers have been working hard with developing more efficient and sustainable methods for imine synthesis with a broad scope of products. Following the principles of Green chemistry, methods with more sustainable energy sources, catalysts, solvents and even solvent-free conditions have been developed. [3; 4; 9]

2.1.3 Other Catalytic Methods

While the classical methods are still the most used procedures for imine synthesis, simultaneously various new techniques are being developed to conquer the harsh conditions required in traditional ways. However, much of the knowledge already obtained from the new methodologies, as the information concerning chemistry of imines in general, is scattered throughout the literature. In 2013 Patil [3] compiled the most pivotal research in his review article on catalytic methods for imine synthesis. In accordance with Patil's review and keeping to his classification of methods, the most important examples were chosen from high impact journals and will be introduced in this section. First, imine synthesis through oxidative coupling of alcohols and amines will be presented. Next, examples of transition metal catalyzed, biomimetical and photocatalyzed approaches utilizing oxidative dehydrogenation (ODH) of amines are given. Finally, hydroamination of alkynes with amines is introduced. In addition, some methods that do not fall under these categories are listed in the end of this section.

One of the commonly used methods utilizes tandem oxidative process, where imine is prepared from an alcohol and an amine in the presence of oxidizing agent. This method is highly desirable, because of the use of alcohols as starting material. As an example of such reaction, Blackburn and Taylor [10] reported in 2001 the direct conversion of activated alcohols (allylic, benzylic and propargylic) **10** to imines **11** by using MnO_2 as oxidizing agent (Scheme 4).

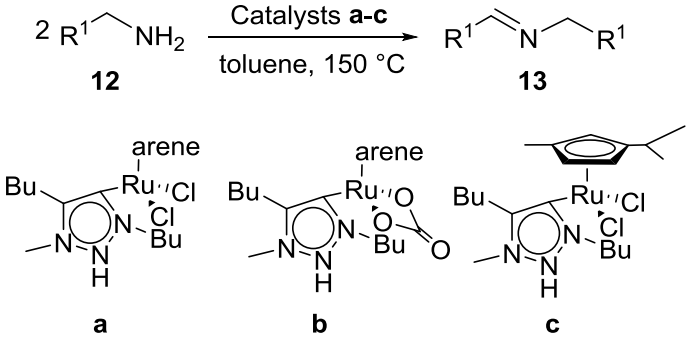


Scheme 4: *Oxidative imine **11** formation with manganese dioxide as in situ oxidant by Blackburn & Taylor. [10]*

The suggested mechanism of this reaction starts with a radical formation: first a manganate ester is formed, which, through a hydrogen atom transfer, gives a stable radical. Subsequently by an intramolecular electron transfer, an aldehyde is formed, which can then react with the amine **3**. Even though the yields were excellent and the process was overall straightforward with less tedious work-up, the excess amount of MnO_2 needed and method's efficiency only to activated alcohols became drawbacks of this method. [10]

In addition, one of the ground-laying methods to produce imines is through oxidative dehydrogenation (ODH) of primary or secondary amines. When ODH of primary amines is used, a selective catalytic system is required, since the oxidation of primary amines generally leads to a variety of other nitrogen containing compounds, such as nitriles. The methods are divided to three categories which are introduced next: ODH through 1) transition metal catalysis, 2) biomimetical approach and 3) photocatalysis. [3]

Transition-metal-catalyzed ODHs of amines are well known for their selectivity. In 2011, Prades et al. [11] reported ruthenium (Ru)-catalyzed homocoupling of primary amines by using three different "(η^6-arene)Ru-(NHC)" complexes (arene = p-cymene or C_6Me_6, NHC = N-heterocyclic carbene) as catalysts (Scheme 5).



Scheme 5: *Ruthenium-catalyzed oxidative dehydrogenation of amines by Prades et al. [11]*

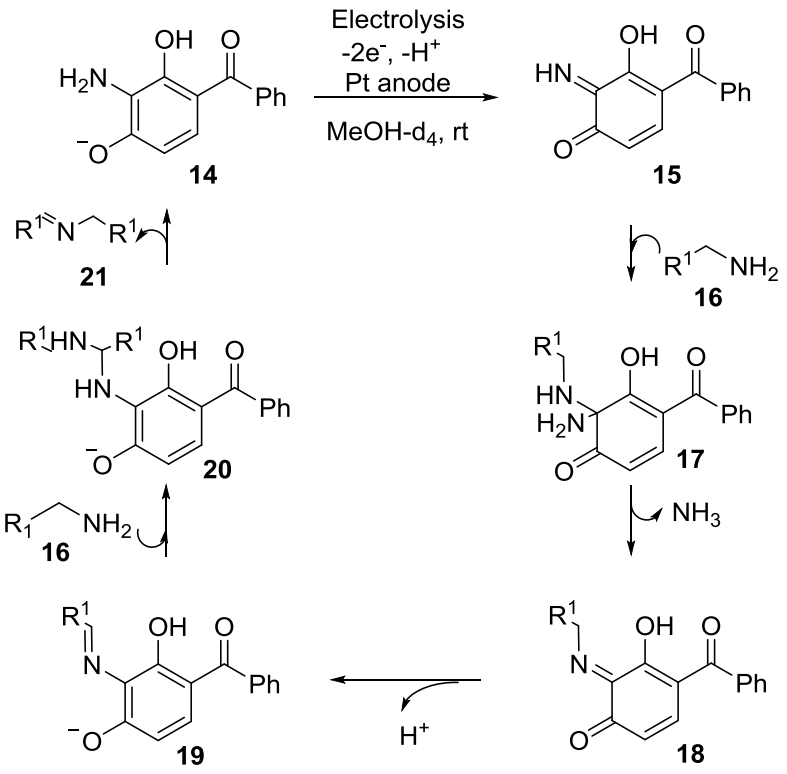
The reaction took place at 150 °C, in oxidant- and base-free conditions and with only 5 mol-% loading of the catalyst. It was noticed, when the regular NHC-complex catalyst **c**

was used, that full conversion was achieved only in 12 hours. Catalyst **a** was less active and the full conversion took 20 hours. Catalyst **b** with carbonyl group proved to be inactive, why it was proposed, that the carbonate ligand exchange by the amine is thermodynamically disfavored. Through this method both aromatic and aliphatic amines were oxidized successfully, even though the latter with slower reaction rates and mediate yields. [11]

Another widely studied transition metal for ODH of amines is gold (Au). The major advantage with gold catalyzed oxidation, when compared to ruthenium-catalyzed reaction, is that the reaction products are usually predominantly imines. With ruthenium, controlling the subsequent reaction leading to the formation of nitriles is more difficult than with Au-catalysts, even though both are thought to proceed with the same mechanism. The explicit explanation for this behavior remains to be discovered. [3] Besides Ru- and Au-based catalysts, examples of ODH of amines with other transition metal based catalysts, such as vanadium, copper, manganese, cobalt, palladium, nickel, iridium, zinc and mercury have been recently reported. [3]

Despite of its advantages, such as the high selectivity, transition metal catalysis normally requires harsh reaction conditions and, in addition, the availability of these catalysts is limited and the prices are high. This has driven researchers to find other, more sustainable and affordable methods: for example nature's own processes have been intensively studied and numerous attempts have been carried out to make the mechanisms behind these naturally occurring processes synthetically possible.

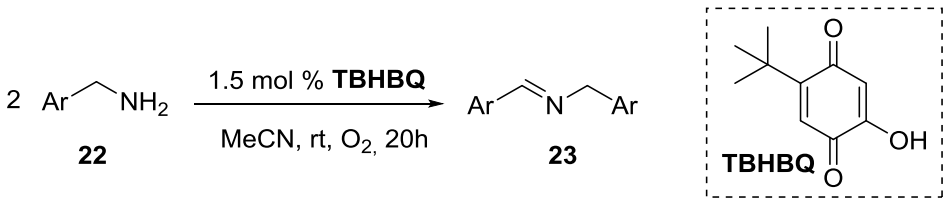
In nature, amines do not dehydrogenate. Instead, they react with quinone cofactors to form imine intermediates, which are further hydrolyzed to corresponding aldehydes and aminophenol products. Subsequently, aminophenol oxidizes and quinone cofactor regenerates and new loop in the cycle can start. In water-free conditions, it is possible for the imine intermediate to go through transamination, which leads to formation of an imine instead of an aldehyde. Various methods which mimic these catalytic cycles have been reported and one of the most elegant biomimetic approaches was reported by Largeron and Fleury (Scheme 6). [3; 12]



Scheme 6: *Autorecycling oxidation of primary aliphatic amines mediated by electrogenerated o-iminoquinone cofactor* ***15****. [12]*

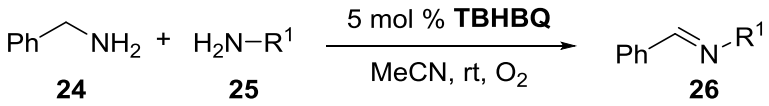
The 3,4-iminoquinone (IQ) **15** works as a biomimetic catalyst for the oxidation of primary aliphatic amines. First the unstable IQ is generated from its precursor o-aminophenol derivative **14** (2 mol-%) through anodic-controlled potential electrolysis at a platinum-anode in deuterated methanol with an excess of amine **16**. The formation of highly reactive imine intermediate **19** allows the activation of the imine function for further nucleophilic attack by the amine, leading to formation of imine **21** and regeneration of IQ's precursor **14**. [12]

Another example of bioinspired method has been reported by Wendlandt & Stahl [13] in 2012. In their study, chemoselective homocoupled ODH of benzylic amines **22** was accomplished with a quinone species, TBHBQ (4-tert-butyl-2-hydroxybenzoquinone), as a catalyst and oxygen as the oxidant in room temperature (Scheme 7). [13]



Scheme 7: *Organocatalyzed oxidative dehydrogenation of benzylic amines. [13]*

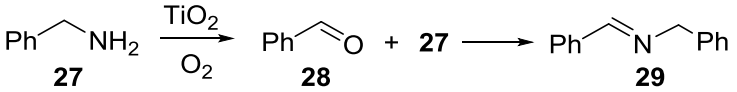
With electron-rich amines, such as *p*-methoxybenzylamine and piperonylamine, the yields exceeded 90 % and the complete conversion took only 20h. With aliphatic primary amines and with given reaction conditions, the reaction did not proceed at all. Due to the excellent selectivity with benzylic amines, it was envisioned that heterocoupled ODH could be possible when benzylic amine **24** and a less easily oxidized amine **25** were combined. As a result, Wendlandt & Stahl reported that ODH through cross-coupling of primary amines was achieved with high yields (76−92 %) of imine **26**, when the quinone catalyst loading was increased to 5 mol-% (Scheme 8). [13]



Scheme 8: *Organocatalyzed oxidative cross-coupling of primary amines. [13]*

The most used oxidant in ODH is molecular oxygen and even though it is widely available, its unpredictable reactivity with organic compounds brings some difficulties in the ODH reactions: normally the reactions require harsh conditions and have poor selectivity. Due to this, photocatalysis and especially TiO_2-based photocatalyzed systems have been given much attention in recent years. TiO_2 is an attractive material for photocatalysis because it is inexpensive and has excellent stability towards chemical reactions, but the drawback is that most photocatalytic reactions with TiO_2 proceed only under UV radiation. Visible light photocatalysis requires doping the TiO_2 surface with additional noble metal complexes or nanoparticles. [3; 14]

Lang et al. [14] have reported on selective formation of imines by photocatalytic ODH of amines on TiO_2 with both UV and visible light irradiation using 1 atm of air as the oxidant (Scheme 9).



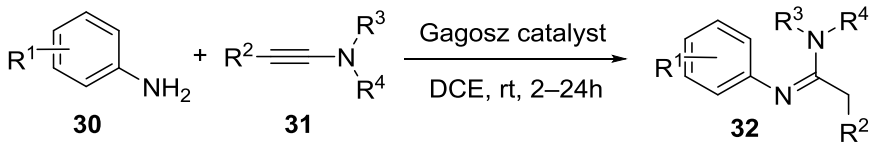
Scheme 9: *Formation of imines through photocatalytic oxidation by TiO_2 surface. [14]*

The formation of imines begins with highly selective oxidation of amines **27** to aldehydes **28**. The reaction proceeds with condensation reaction between the aldehyde and the unreacted or in-situ generated amine **27** and the corresponding imine **29** is formed. The method was effective with both primary and secondary amines and measured conversions in most entries exceeded 90 %. [3; 14]

Along with ODH and oxidative coupling of alcohols and amines, imine synthesis can be performed through hydroamination of alkynes with amines. The direct addition of

amines to alkynes catalyzed by transition metal catalysts is a highly efficient way for synthesizing imines, even though the use of transition metal catalysts brings some drawbacks such as the need for higher temperatures and longer reaction times.

In 2009, Kramer et al. [15] discovered a highly regioselective method for hydroamination of electron-rich non-symmetrical alkynes **31** with anilines **30**. Reaction was catalyzed with Gagosz catalyst ($(PPh_3)AuNTf_2$) and proceeded at room temperature with excellent yields (80−98 %) (Scheme 10).



Scheme 10: *Hydroamination of alkyne **31** with aniline **30** by Kramer et al. [15]*

In addition, a wide selection of other synthetic methods for imine formation has been reported. Other oxidative methods besides the ones mentioned above include nitrosobenzene-mediated oxidative decarboxylation of esters and oxidative imination of toluenes. Furthermore, imines have been synthesized through addition of Grignard and organolithium reagents to nitriles or to *N*-substituted formamides, by arylation of nitriles, reaction of aldimines with boronates or iminocarbonylative cross-coupling between isocyanides, aryl halides and 9-alkyl-9-BBN-derivatives. [3; 4]

Regarding reductive processes, imines can be also prepared by reductive imination of nitroarenes with aldehydes or by reduction of secondary amides. Other miscellaneous methods include insertion of isocyanides into electron-rich aromatic compounds, coupling of aldehydes and ammonia with epoxides or bromides, reaction between primary amines and *gem*-dibromomethylaryl compounds, coupling of amines and vinyl bromides. One of the most recently reported methods to synthesize imines utilizes a reaction between diazocarbonyl compounds and azides. [3; 4; 16]

2.2 Applications

The importance of imines in chemistry cannot be emphasized enough: the enormous number of publications and different applications concerning imines in organic synthesis and bioorganic and medicinal chemistry implicates that imines are one of the most widely studied and used organic compounds.

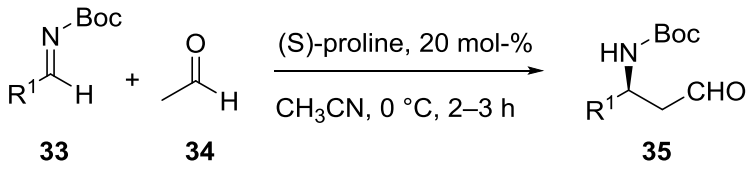
2.2.1 Imines in Organic Synthesis

Organic molecules, which contain nitrogen atoms substituted with carbon stereogenic centers, represent the majority of bioactive compounds, such as amino acids. Due to the

various application possibilities, the development of efficient methods to construct chiral amines has attracted the interest of researchers and has dominated the studies in the field of synthetic organic chemistry.

Imines work as a versatile precursors in organic synthesis, especially for the synthesis of nitrogen-containing compounds. The carbon-nitrogen (C=N) bond in imines makes them one of the most important functional groups in organic chemistry: because of the imine's electrophilic nature, it reacts easily with carbon nucleophiles leading to formation of new carbon-carbon bonds. Imines are able to act as electrophiles in reductions, additions, condensations and cycloaddition reactions. [4; 17]

One of the most important methods for generating chiral amines is the addition reaction to C=N-systems. An example of such reaction was performed by Yang et al. [18] in 2008, where an excess of acetaldehyde **34** (5−10 eq.) was treated with alkyl and aryl *N-tert*-butoxycarbonyl (*N*-Boc)-imines **33** in proline-catalyzed Mannich reaction (Scheme 11).



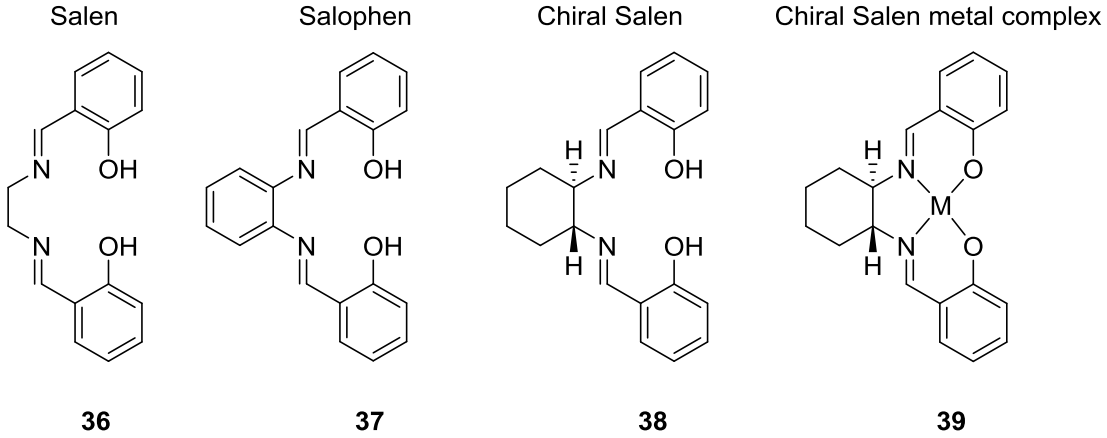
Scheme 11: *Highly enantioselective proline-catalyzed Mannich reaction of N-Boc-imine and aldehyde by Yang et al. [18]*

These reactions afforded *β*-amino aldehydes **35** with exceptional enantioselectivities (≥ 98:2 enantiomeric ratio) and moderate yields from 30 % to 58 %. The value of the reaction and the applicability of the products were demonstrated by several transformations of one of the products **35a** (R^1=Ph). For instance, oxidation of the **35a** with sodium chlorite resulted in formation of the corresponding *β*-amino acid. Latter reduced to the corresponding alcohol and reductive amination of **35a** provided a piperidine derivative. [18]

Due to the lone pair of electrons on imine's nitrogen atom, the imine is also able to coordinate to metals and form coordination complexes. Usually imines are coupled with aldehydes and the condensation reaction products are called Schiff base ligands. In Schiff base metal complexes, imines are thought to enhance metal's catalytic abilities by stabilizing the multiple oxidation states of the metal. In addition, Schiff base ligands are called "privileged catalysts" because they are enantioselective towards a wide selection of reactions. The chiral information can be transmitted when chiral amines or chiral imines are used to prepare the Schiff base ligand. [19; 20]

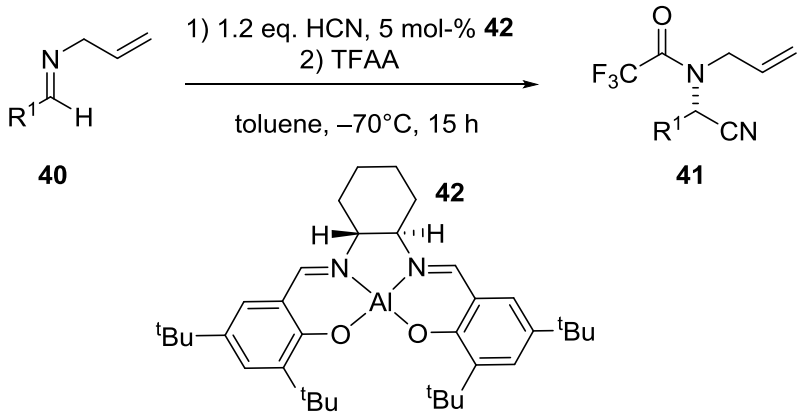
When diamine is coupled with two equivalents of salicylaldehyde, a special type of Schiff base ligands, Salen ligands, with tetradentate binding site are formed. Some

examples of the Salen-type ligands and Salen metal complexes are given in Scheme 12. The most common metals (M) used in these compounds include Ti, Zr, Al, Ga, In, Mn and Cu. [19]



Scheme 12: *Examples of different Salen-type ligands* ***36-38*** *and a Salen metal complex* ***39****. [19]*

In 1998, Sigman & Jacobsen [21] reported the first enantioselective Strecker reaction catalyzed with a chiral (Salen)Al(III) complex **42** (Scheme 13). In their study, the addition of HCN to various *N*-allyl imines **40** resulted in corresponding trifluoroacetamides **41** with good yields varying from 69−99 % and moderate-to-excellent enantioselectivities (37−95 % ee.). The authors noticed that the best results were achieved with aryl substituted imines.



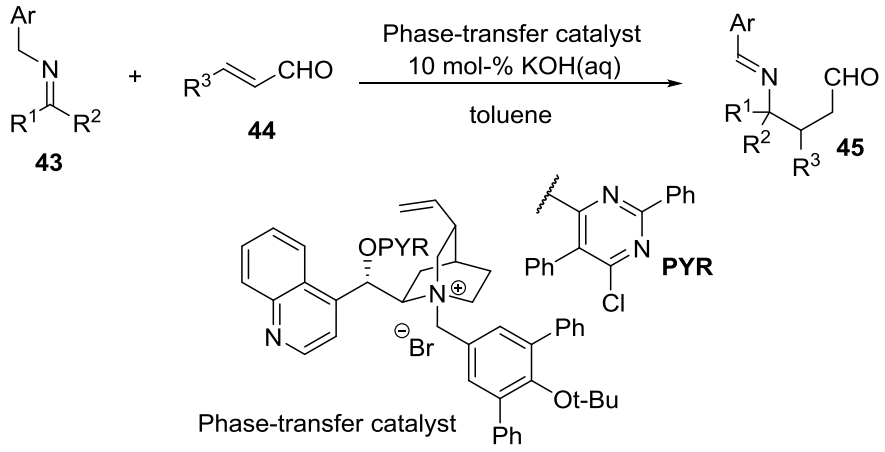
Scheme 13: *Enantioselective, (Salen)Al(III)-complex catalyzed Strecker reaction by Sigman & Jacobsen. [21]*

This reaction by Sigman & Jacobsen actually combines two different imine applications: 1) already presented chiral Salen metal complex catalysis and 2) asymmetric Strecker reaction. Even though the first Strecker reaction, addition of cyanide to imines, was reported over 150 years ago, the modern version of this reaction which provides a direct and sustainable access to various enantioenriched α-amino acids

remains highly investigated. [21] In addition, other important imine applications, such as Staudinger reaction with ketenes leading to formation of *β*-lactams and Hetero Diels-Alder reactions that produce functionalized heterocyclic rings, are among the key reactions in the synthesis of complex natural and unnatural compounds. [4]

Due to the electrophilic nature of imines and their important role in reactions where new carbon-carbon (C-C) bonds are formed, they are one of the most used precursors for amine synthesis. It has been envisioned, that the natural electrostatic polarization of the imine functionality could be transformed somehow, so that instead acting as an electrophile imine would act as a nucleophile. These types of umpolung reactions would create countless new prospects not only for amine synthesis but for the whole field of organic synthesis.

According to the most recent studies, successful umpolung reactions of imines have already been achieved. In 2015 Wu et al. [22] developed a new class of chiral phase transfer catalysts, which promoted asymmetric umpolung reactions of imines **43** with electrophilic *α,β*-unsaturated aldehydes **44** (Scheme 14) and provided a direct route to chiral amines. Even though the reaction originally afforded different products than the authors intended, it was found that by manipulating the cinchonine-derived phase-transfer catalyst by changing the groups attached to the quaternary nitrogen atom, the reaction could be directed towards the desired product.

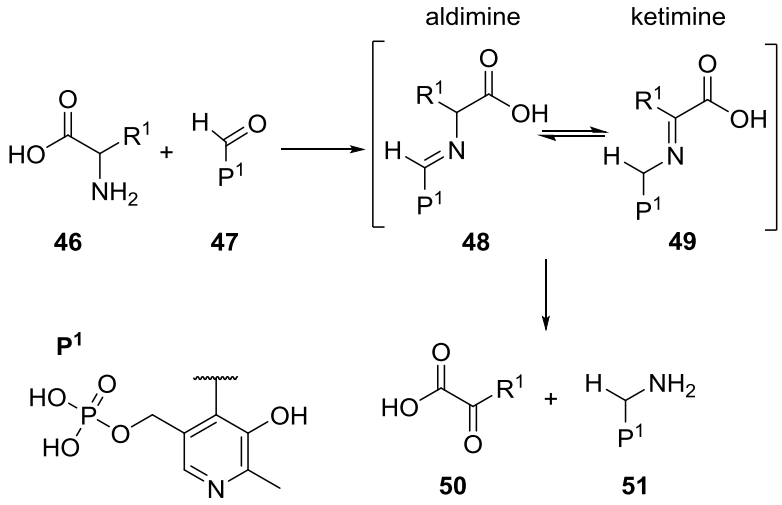


Scheme 14: *Catalytic umpolung reaction of aryl imines **43** with enals **44**, where Ar=4-nitrophenyl. [22]*

2.2.2 Imines in Bio-Processes

In nature, imines are pivotal intermediates in several bio-processes. The most vital must be the role of the imine in enzyme catalyzed transamination reaction in catabolic process of proteins. In transamination, amino acids are modified to products which can be used in citric acid cycle. As shown in Scheme 15, the α-amino acid **46** reacts with pyridoxal phosphate **47** through nucleophilic addition to give aldimine **48.** Internal

proton transfer results in aldimine-ketimine (**48-49**) tautomerization. In the last step imine hydrolyzes to give the transamination products; an α-keto acid **50** and pyridoxamine phosphate **51**. [4; 23]

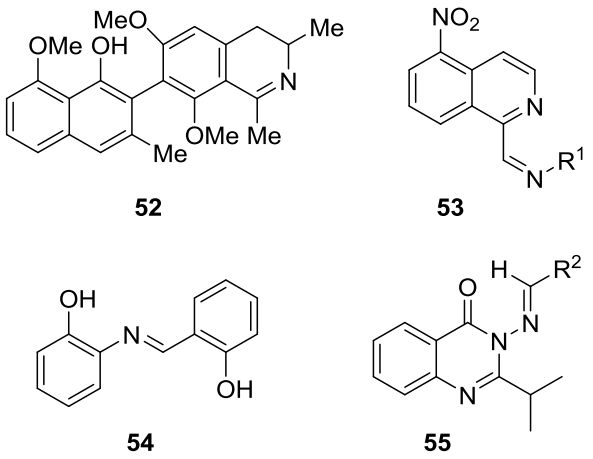


Scheme 15: *Imine-intermediated transamination reaction of α-aminoacids to α-keto acids.[4]*

2.2.3 Imines as Active Pharmaceutical Ingredients

Even though imines are primarily recognized as precursors in various syntheses, they are also present in numerous natural and synthetic bioactive compounds. Imines have been shown to be important active pharmaceutical ingredients, APIs, due to the variety of different biological activities they possess, such as antibacterial, antifungal, antiviral and anticancer properties.

In the treatment of malaria, imines have demonstrated to have an important function. For example, naturally occurring ancistrocladidine **52** (Scheme 16) has proven to be active against *P. falciparum* K1 and 3D7. In addition, Rathelot et al. [24] prepared imine containing isoquinoline derivatives **53** (Scheme 16), which exhibited *in vitro* activity against drug-resistant *P. falciparum* strain. The search for effective antimycobacterial drugs began after the drug-resistant strain of tuberculosis, *Mycobacterium tuberculosis*, emerged and caused steep increase in the mortality rate caused by infectious diseases. The antibacterial activity towards *Mycobacterium tuberculosis* of *N*-(salicylidene)-2-hydroxyaniline **54** (Scheme 16) was studied and was shown to be effective and highly selective. In 2013, Karakaya et al. [25] synthesized novel quinazolinone-based imines **55** (Scheme 16), which showed antifungal activity by inhibiting the growth of different fungi, such as *F. proliferatum*, *A. parasiticus*, *A. niger* and *T. reseii*. [4]



Scheme 16: *Examples of bioactive imines used as APIs. [4; 24; 25]*

3. BORON COMPLEXES OF AMINO ACIDS

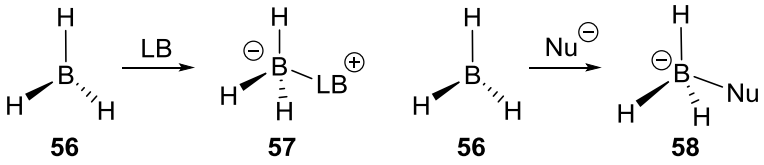
3.1 Background of Organoboron Chemistry

In the past, before elemental boron was even discovered, boron containing compounds had already various applications. For example, naturally-occurring borax was used to prepare borosilicate glass. In the beginning of 19th century, boron was first discovered and isolated from Borax in its impure form by Sir Humphry Davy, J.L. Gay-Lussac and L.J. Thenard. It took nearly a century before almost pure (95−98 %) samples of elemental boron were obtained by H. Moisson in 1892. His route to elemental boron involved reducing boric oxide with magnesium. [26]

The beginning of the research of boron derivatives is usually dated to year 1860 when Frankland was the first to report on preparation and isolation of a boronic acid. Since, the interest in organoboron compounds has been increasingly growing and nowadays they play crucial roles in the field of chemistry due to their impact in synthesis. The importance and success of this area can be indicated with the fact that the contributions in this particular field have been awarded twice with the Nobel Prize in Chemistry: H. C. Brown with G. Wittig in 1979 and most recently, A. Suzuki together with R.F. Heck and E. Negishi in 2010. [27; 28]

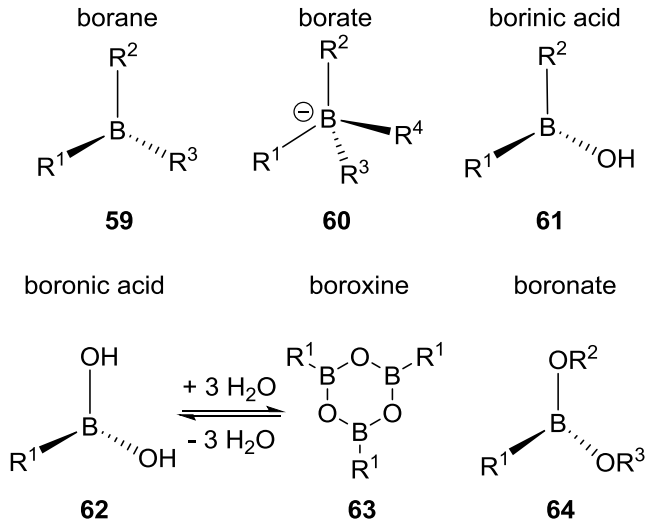
3.2 Boron and Boron Derivatives

Elemental boron, with chemical symbol B, is positioned in group 13 in the periodic table of elements. Boron is the only non-metal in this group and it is classified as a metalloid. In nature, boron has two stable isotopes, ^{10}B and ^{11}B, the latter being about 80 % abundant. Both isotopes have a nonzero spin, so boron containing compounds can be effectively detected with boron NMR spectroscopy. Chemically boron reminds its neighboring elements carbon and silica with its tendency to form covalent bonds. However, with the electron configuration [He]2s^{2}2p^1, boron has only three valence electrons thus resulting in a trigonal planar geometry with three covalent bonds to other atoms, leaving one vacant 2p-orbital orthogonal to the plane. This empty orbital controls the reactivity and other properties by making borane and its derivatives electron deficient and enables them to work in two ways: 1) as Lewis acids by accepting a lone pair from electron-rich Lewis bases resulting neutral species or 2) combining with a nucleophile and generating anionic tetravalent boron compound, which can behave as a nucleophilic molecule (Scheme 17). [2; 28]



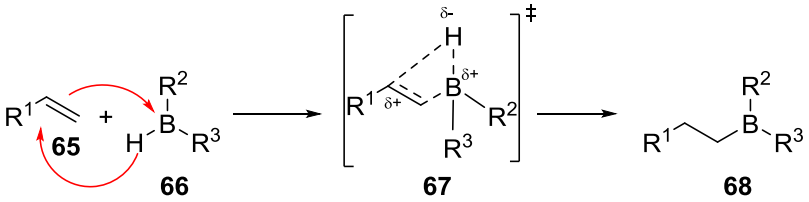
Scheme 17: *Electron deficient borane **56**.*

Due to boron's unique electronic nature and its ability to form covalent bonds with various elements (such as H, C, N, O, F, and Cl), it can be easily incorporated in molecules. Consequently organoboron compounds have received much attention in research. The most common organoboron compound structures and their nomenclature are illustrated in Scheme 18. [27]



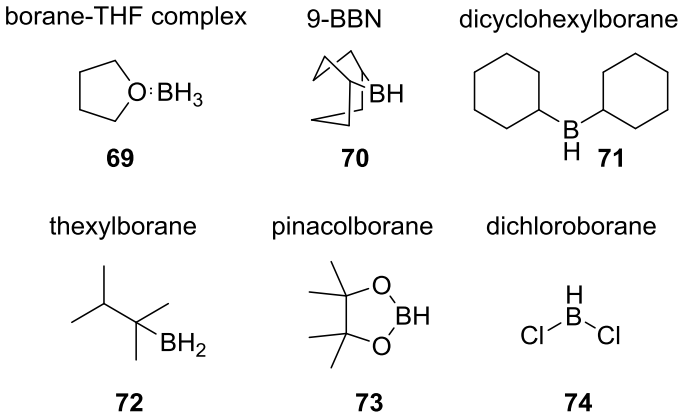
Scheme 18: *Nomenclature for organoboron compounds. [27]*

The most central route to organoboron compounds is the hydroboration of alkenes and alkynes. For example, in the reaction of hydroboration of alkenes, boranes **66** react with alkenes **65** through stereoselective *syn* addition reaction which results a boron compound **68**, where one of original hydrogen atoms in boron is replaced with an alkyl. Instead of proceeding in a stepwise manner via carbocation formation, hydroboration is thought to proceed through a concerted mechanism via a cyclic transition state. The new bonds form at the same time as the π-bond breaks. The reaction is formally a violation of Markovnikoff's rule, because of the nucleophilic character of the hydrogen. In the transition state **67** the partially negative hydrogen atom forms a bond with the partially positive carbon atom, preferentially the most substituted carbon. [2]



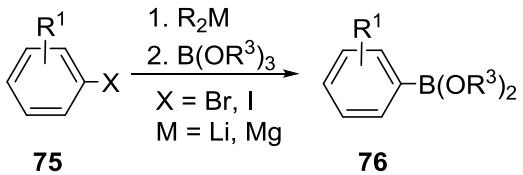
Scheme 19: *Mechanism of hydroboration. [2]*

Since Brown et al. discovered hydroboration reaction in 1956, and were awarded with Nobel award in 1959, hydroboration chemistry has been under intensive studies and different variations of hydroboration have been reported. A wide variety of hydroboration reagents are nowadays commercially available and the most common ones are illustrated in Scheme 20. [27; 29]



Scheme 20: *Examples of hydroboration agents.*

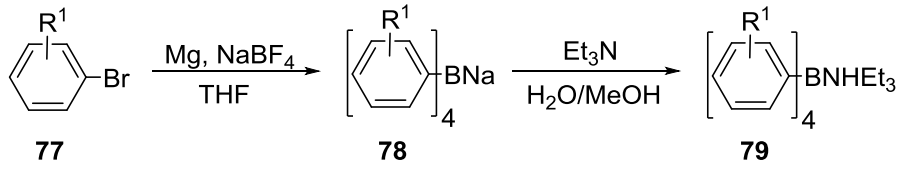
However, hydroboration is effective only for preparation of alkyl- and alkenylboron compounds. Due to this limitation, several other methods have been extensively studied. One of the most studied methods for synthesizing organoboron compounds involves metal-halogen exchange with aryl halides **75** and a subsequent reaction with boron reagents, such as trialkylborates (Scheme 21). If the aryl halide is compatible with its transformation into a strongly nucleophilic compound, a variety of aryl-, alkenyl- and even alkylboron compounds can be obtained with this method. [27]



Scheme 21: *Preparation of organoboron compounds from a sequence of metal-halogen exchange and electrophilic trapping with boron reagents. [27]*

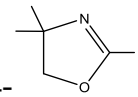
Recently, Kuuloja et al. [30] reported on preparation of substituted tetra-arylborates with a similar method to above mentioned traditional metal-halogen reaction. In their

method the Grignard reagent was prepared *in situ* in the presence of the boron source, $NaBF_4$, which reduced the synthetic steps when compared to the traditional methods. Through cation exchange, triethylammonium substituted tetra-arylborates (TEATABs) **79** were obtained as stable solids from moderate to high yields and were found to be easier to prepare and purify than their corresponding sodium salts **78** (Scheme 22)**.** The reaction method proved to be suitable for all six TEATABs prepared. The Scheme 22 shows the general reaction procedure for this synthesis and the yields given by different substituents R^1 are collected in Table 1. In addition, the prepared TEATABs were found to be valuable coupling partners in the Suzuki-Miyaura reaction (Scheme 23).



Scheme 22: *Preparation of triethylammonium tetra-arylborates (TEATABs) by Kuuloja et al. [30]*

Table 1: *Prepared TEATABs and gained yields by Kuuloja et al. [30]*

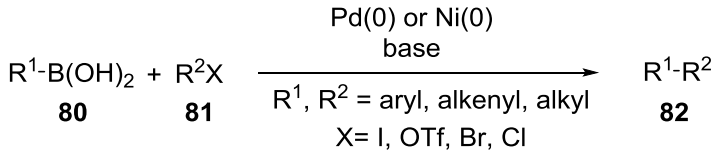
Entry	Compound	R^1	Yield (%)[a]
1	**79a**	H	75[b]
2	**79b**	4-Cl	81
3	**79c**	3-Cl	86
4	**79d**	3,5-di-Cl	44
5	**79e**	4-OMe	53
6	**79f**	4- 	50

[a]Isolated yield after recrystallization, [b]Prepared straight from commercially available Ph_4BNa through cation exchange.

From the large family of organoboron compounds, truly attractive for synthetic organic chemistry is the group of boronic acids **62** and their derivatives. This can be attributed to the reactivity of boronic acid as a mild Lewis acid, to its stability and unproblematic handling in synthesis combined with low toxicity and eventual oxidative degradation to boric acid. Boronic acids can be easily formed straight from boranes from twofold oxidation, and their characteristics, such as reactivity, are highly dependent on the hydrocarbon group directly bonded to boron atom. They tend to exist as mixtures of six-membered heterocycles called boroxines **63**, hence the corresponding boronates

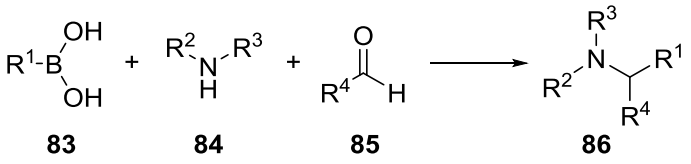
(boronic esters) **64**, where the two hydroxyl groups are masked, are often preferred as key intermediates in synthesis. [27]

Boronic acid and its derivatives have proven to be highly important in various organic syntheses. They are especially effective in reactions, where new carbon-carbon or carbon-heteroatom bonds are created. In their studies in the end of the 1970's, which revolutionized organoboron chemistry, Suzuki and Miyaura developed a palladium(0)-catalyzed method where arylated alkenes **82** were attained in high yields by coupling boronic acids **80** with aryl halides **81** in the presence of a base. Since then, the Suzuki-Miyaura cross-coupling reaction has been under continuous investigation and countless reaction variations with diverse options for coupling compounds, bases, catalysts and solvents have been reported. The method has provided an efficient way to such compounds as arylated alkenes, biaryls and polyolefins (Scheme 23). [27; 31]



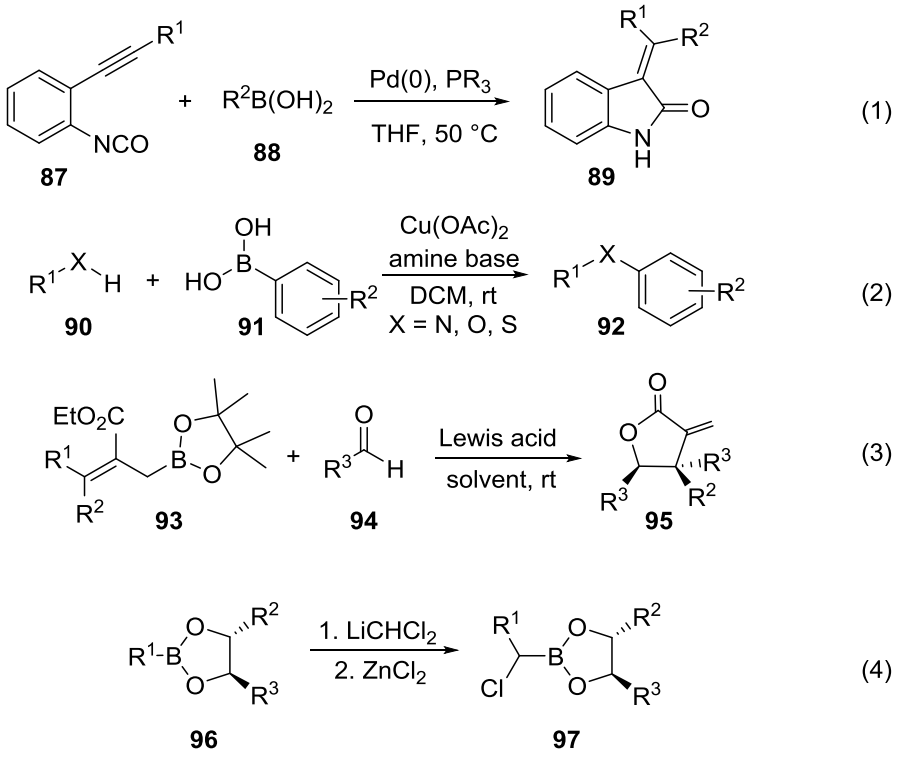
***Scheme 23**: Suzuki-Miyaura cross-coupling reaction.*

Another method, in which boronic acids and boronates have been successfully employed, is the Petasis borono-Mannich reaction (Scheme 24). The method includes a multicomponent reaction between a boronic acid **83**, an amine **84** and an aldehyde **85**. The reaction has led to a wide selection of small organic products, when differently substituted starting materials have been employed. As one of the most important applications of such transformation, the Petasis borono-Mannich reaction has provided a novel synthetic route to α-amino acids. [27; 32]



***Scheme 24:** The Petasis borono-Mannich reaction.*

In addition, organoboron reagents have been used in many other applications and some examples are illustrated in Scheme 25: rhodium- and other transition metal-catalyzed additions to carbonyl compounds and alkenes (Equation **1**), copper(II)-catalyzed heteroatom couplings (Chan-Lam coupling, Equation **2**), allylboration (Equation **3**), and Matteson-type homologation of boronic esters (Equation **4**). [27]



Scheme 25: *Examples of organoboron reagents in synthesis.*

As already demonstrated in previous examples, boron compounds have become extremely important and powerful tools for synthetic chemists with countless applications in catalysis and in other organic transformations of highly functionalized and complex molecules. Due to their exclusive properties, excellent selectivities, mild reaction conditions, high yields and wide availability, these compounds have also found their way into a variety of industrial, pharmacological and medical applications.

Since boron's role as a vital element in higher plants was discovered in the beginning of 20th century, in addition to its exceptional chemical properties, its unique biological characteristics and functions have also gained wide attention. A discovery, which later inspired organic chemists to begin investigating boron containing natural products, happened in 1967, when the first boron containing biomolecule boromycin was isolated. Its ability to act as an antibacterial agent was quickly discovered, and more recent studies have suggested it to have promising antiviral activity towards HIV as well. During these past 50 years, the biological activity on natural and synthetic organoboron compounds have been studied and they have become essential when treating human diseases. [33]

The current status of these studies can be much attributed to the search of anticancer agents for boron neutron capture therapy (BNCT). The core BNCT research is focused on the synthesis of boron derivatives of biomolecules, such as amino acids, peptides, nucleosides, porphyrins and sugars. The principle idea in BNCT is to deliver a substance carrying ^{10}B atoms to a tumor, irradiate the area with neutrons and utilize the

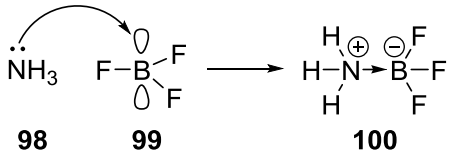
ability of boron-10 to undergo a neutron capture event and release high-energy particles to destroy the tumor cells. It is important, that the designed boron containing cytotoxins are able to penetrate the blood-brain barrier and, most importantly, have a low overall toxicity. Thus, the key challenge of this potential cancer treatment is how to selectively incorporate the substance with ^{10}B into tumor cells rather than into healthy cells. In addition, during these BNCT studies unexpected pharmacological activities of the studied molecules were discovered: several organoboron compounds were found to have hypolipidemic, antineoplastic, anti-inflammatory, antiosteoporotic and antiobesity activities. [34; 35]

Especially the nitrogen-boron (N-B) bond containing boron heterocycles derived from amino acids have shown their potential as cytotoxins and as other pharmacological agents. One of the most important classes of these heterocycles is the family of boroxazolidones, which will be introduced in more detail in Section 3.4. To give an illustration of the growing interest towards boroxazolidones and to present one of the many potential applications, the study of González et al. [36] is described. The aim of their studies was to synthesize boron carriers with enhanced properties compared to the compounds already used clinically. As a result, in 1998 González et al. reported of the synthesis of six boroxazolidones derived from L-cysteine. According to González et al., boroxazolidones are particularly attractive for further studies, due to their potential multipurpose use. They envision that in addition to the important function of the boron moiety in BNCT, the amino acid portion of the compound could be used in protein synthesis or it could act as an active carrier of bioactive molecules, such as pharmaceutical drugs. [36]

3.3 The Nitrogen-Boron Bond

Even though organoboron compounds are widely used in synthetic applications, they are rarely a part of the target molecule. A promising approach for including boron in organic compounds is to introduce a dative N-B bond into the structure.

The N-B bond is called dative covalent or coordinative and sometimes indicated with an arrow pointing from nitrogen to boron, which means that the shared pair of electrons has come from the nitrogen atom. This reaction forms donor-acceptor or Lewis acid-Lewis base adducts, ate-complexes, in which bond-forming atoms become electronically saturated: nitrogen takes a positive charge by donating electrons and boron takes on a negative charge by accepting the electrons. For example, reaction between ammonia **98** and boron trifluoride **99** (illustrated in Scheme 26) results a formation of a dative N-B bond in compound **100**. [2]



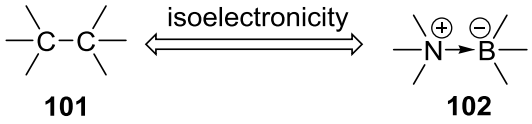
Scheme 26: *The dative bond formation between ammonia* ***98*** *and boron trifluoride* ***99****.*

Since G.N. Lewis published his revolutionary theory in 1923, compounds with Lewis acid-Lewis base interactions have been under intensive research. There has been much interest in understanding the factors that control the molecular interactions. Combined with physical studies, various analytical methods for the study and quantification of N-B bonds have been applied, such as X-ray crystallography, computational modelling, theoretical calculations, mass spectrometric studies, and boron-, nitrogen- and dynamic NMR studies. As a result, some understanding of the characteristics of N-B bonds has already been attained. For example, Höpfl and coworkers have been intensively studying numerous boron complexes with a coordinative N-B bond and have come to a conclusion that the substituents in both nitrogen and boron atoms have a strong influence to the strength of this dative bond. When electron withdrawing groups are introduced into the boron atom, the Lewis acidity of boron increases and, in addition, the Lewis basicity of the nitrogen atom can be increased with introduction of electron-rich alkyl groups. Nevertheless, it has also been observed, that when integrating these substituents, steric factors can have a significant effect on these interactions. [37; 38] Moreover, more recent studies done by Collins et al. [39] have shown that the N-B interactions can be dependent of the chosen solvent.

Due to its unique properties, the dynamic N-B bond has already been included in various applications in a myriad of areas, such as protein modification, self-assembled nanostructures, crystal engineering and production of polymeric materials and molecular sensors. More recently, in the field of synthetic organic chemistry, the isosteric and isoelectric relationship between C-C bonds and N-B bonds has been exploited to modify the structures of organic compounds and, specially, the structures of widely available bioactive natural products. Through alteration of these structures, novel bioactive compounds with enhanced properties can be synthesized and utilized for example in pharmacological purposes. However, the synthetic methods to prepare these compounds are extremely demanding, complex and usually compound specific, so that the same methods are not applicable when synthesizing different molecules. To find highly efficient and more general method to produce these natural product derivatives is of significant importance and is the objective for many researchers doing synthesis. [40; 41]

A quite new approach to create novel bioactive structures is to replace the carbon-carbon bond in natural product with isoelectronic N-B motif. The isoelectronic relationship between C-C and N-B bonds is illustrated in Scheme 27. As boron has 3

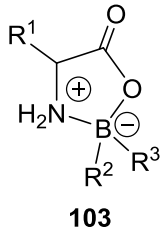
valence electrons and nitrogen has five, the overall electron count in N-B bond is the same as in C-C bond, where each of the carbon atoms has 4 valence electrons. Even though these motifs are isoelectronic, the dipolar nature of the N-B bond is behind the different chemical properties of the molecules. [42]



Scheme 27: *Isoelectronic C-C and N-B motifs. [42]*

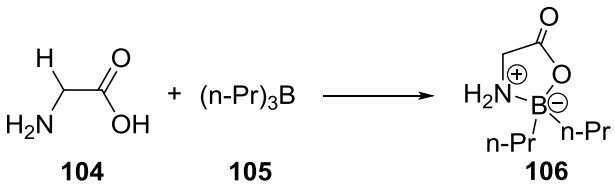
3.4 Boroxazolidones

Scheme 28 illustrates the structure of an essential class of five-membered heterocycles **103** containing a coordinative N-B bond. Compounds with this structure go by different names in literature, such as esters or mixed anhydrides of amino acids and di-alkyl or diaryl boronic acids and amino acid boron chelates, but in this context, the concise term boroxazolidones will be used.



Scheme 28: *General structure of a boroxazolidone.*

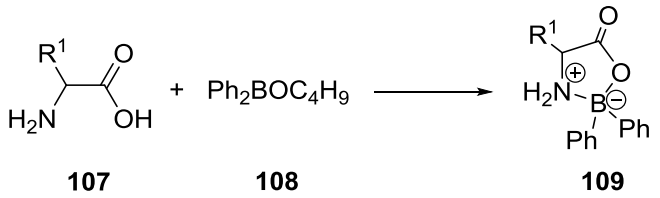
This nowadays quite forgotten family of boron containing amino acid derivatives was discovered already 60 years ago by Lang [43] et al. by reaction of glycine with tri-*n*-propylborane involving a carbon-boron bond cleavage in refluxing xylene (Scheme 29). Even though this method was satisfactory with glycine, it wasn't applicable with tyrosine and histidine as starting materials. Another limiting factor of this route to boroxazolidones is that the triphenylborane is highly unstable towards oxidation. [44]



Scheme 29: *Boroxazolidone **106** synthesis by Lang et al. [43]*

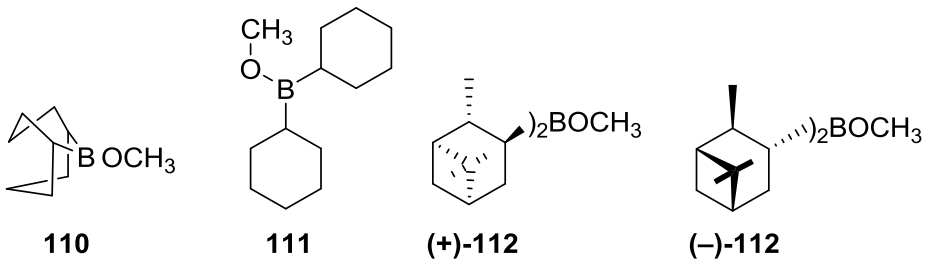
A different route to boroxazolidones was reported by Skoog [45] in 1963, where glycine, alanine and leucine (R^1=H, CH_3, $CH_2CH(CH_3)_2$, respectively) were coupled

with *n*-butyldiphenylborinate, illustrated in Scheme 30. Similar method was also described by Tung et al. in 1967 with a wider selection of α-amino acids (R^1 = CH_2OH, CH_2SH, CH(Me)OH, *i*-Pr, *n*-Pr, *n*-Bu, 3-imidazolylmethyl, 3-indolylmethyl). The drawback of this method lies also in the characteristics of the boron compound: the butyl diphenylborinate is an oxidatively unstable compound, which requires prior preparation. [44; 46]



Scheme 30: *Reaction of α-amino acids with n-butyl diphenylborinate by Skoog. [45]*

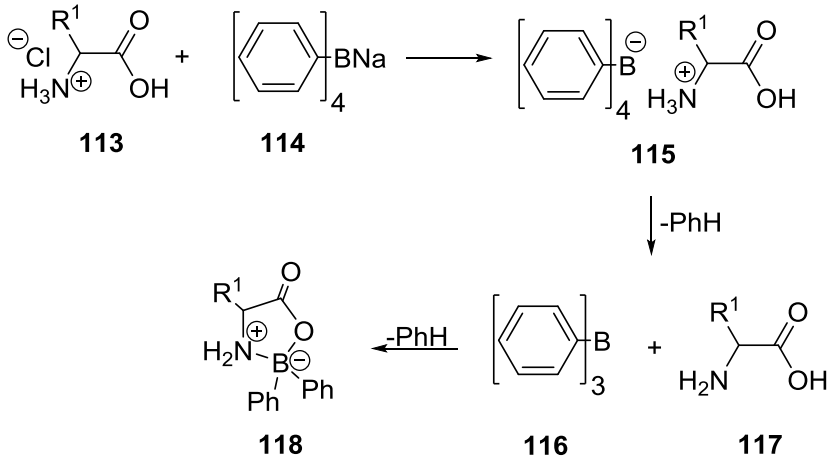
With a similar chelation reaction, but by utilizing different borinates **110**−**112** (Scheme 31) Brown & Gupta [47] were able to synthesize a variety of boroxazolidones from glycine, *N*-methylglycine, *N*,*N*-dimethylglycine, alanine, valine, phenylglycine, phenylalanine and *L*-proline. In most cases the chelation reaction was successful and produced white crystalline boroxazolidones. However, in some cases the reaction between borinates and amino acids produced viscous liquids, which were recognized as transesterification products. This was explained by the steric hindrance: as the steric bulk around both boron and nitrogen increases, the harder it is for the chelation reaction to proceed.



Scheme 31: *Borinates utilized in boroxazolidone synthesis by Brown & Gupta. [47]*

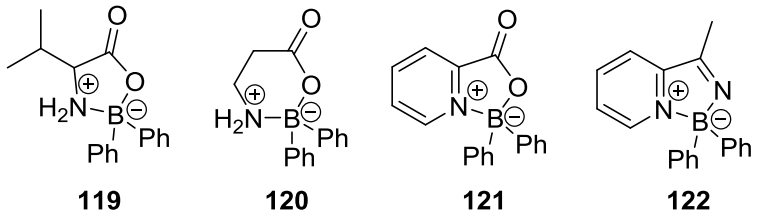
Due to the stability problems with these borinates, more stable and readily available organoboron compounds were searched for boroxazolidone synthesis. A few years later Baum successfully utilized commercially available sodium tetraphenylborate with amino acid and hydrochloric acid in refluxing aqueous solution for the preparation of boroxazolidones (Scheme 32). The reaction mechanism was proposed to proceed through three steps: first the tetraphenylborate salt of the amino acid chlorohydrate **115** is attained, after which the salt decomposes to triphenylborane **116**, benzene and amino acid **117**. In the following and final step, the triphenylborane and the amino acid react to produce boroxazolidone **118** with a reaction similar to one presented in Scheme 29. In

this manner, derivatives of glycine, alanine, phenylalanine, proline, cysteine and tyrosine were obtained. [44]



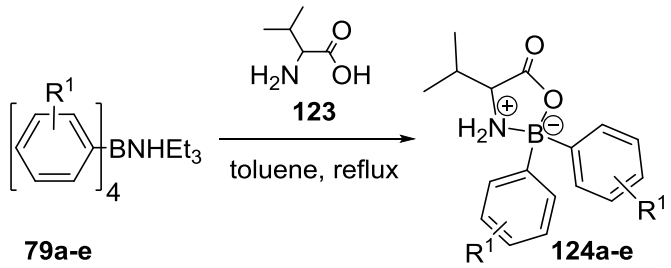
Scheme 32: *Boroxazolidone synthesis from reaction between sodium tetraphenylborate and amino acid chlorohydrate by Baum. [44]*

More recently, Bessler et al. [48] prepared diaryl species of boroxazolidones and other boron containing five and six-membered heterocycles in a way, which resembled Baum's method above. Instead forming the amino acid hydrochloride salt in the beginning, they utilized ammonium tetraphenylborate, which reacts straight with the amino acids and other chelating agents in solution. A few examples of the prepared compounds are presented in Scheme 33.



Scheme 33: *Diphenyl chelates obtained by Bessler et al. [48]*

To emphasize the efficiency of tetraphenylborates in boroxazolidone synthesis, unpublished work from Kuuloja [1] is presented. As a continuation of their studies with TEATABs [30], Kuuloja et al. applied the prepared TEATABs **79a−e** into boroxazolidone synthesis by letting them react with *L*-valine **123** according to the Scheme 34. TEATABs were found to be suitable boron containing reagents in the reaction, affording boroxazolidones **124a−e** with good yields. The results of their work are presented in Table 2.



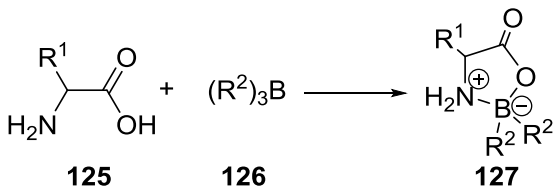
Scheme 34: *Boroxazolidone **124a-e** synthesis through reaction between TEATABs **79a-e** and L-valine **123**. [1]*

Table 2: *Gained yields in the preparation of boroxazolidones by Kuuloja et al. [1]*

Entry	Compound	R^1	Yield (%)
1	**124a**	H	96
2	**124b**	4-Cl	70
3	**124c**	3-Cl	77
4	**124d**	3,5-di-Cl	-
5	**124e**	4-OMe	52

In the beginning of boroxazolidone research when the first of these compounds were synthesized, the stability of boroxazolidones surprised the researchers, because practically all previously prepared boron compounds were sensitive to air and moisture. Thus, before the discovery of boroxazolidones, not much information was attained from organoboron compounds. The stability in boroxazolidones is highly attributed to the formation of a dative N-B bond, which, as mentioned in the previous section, can be described as an intramolecular Lewis acid-Lewis base interaction and additional stability is achieved by the five-membered ring formation. [43; 49; 50]

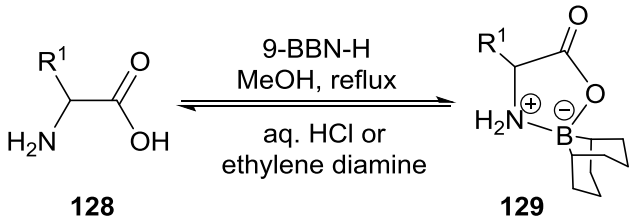
Even though various boroxazolidones have already been prepared, the studies of their chemical properties have not received much attention and little is known about their reactivity. For many decades, boroxazolidones have been primarily recognized as dual protecting groups of the amine and carboxylic acid groups in α-amino acids to control efficiently the functional groups in the side chain. Nefkens & Zwanenburg were the first to acknowledge this potential utility of these compounds. They prepared boroxazolidones by reaction between several α-amino acids **125** and triethyl- and triphenylboranes (R^2 = Et, Ph) **126** and studied their synthetic utility in amino acid protection (Scheme 35).



Scheme 35: *Preparation of boroxazolidones from reaction between α-amino acids and triethyl- and triphenylboranes. [46]*

In their study, Nefkens & Zwanenburg were able to reconvert the prepared boroxazolidones into corresponding *α*-amino acids by using mild acidic reagents, such as gaseous HCl. By this method, aspartic acid was successfully converted into *β*-benzyl aspartate and glutamic acid into *γ*-benzyl glutamate. As an interesting detail of their study, it was noticed that the diphenyl derivatives were more stable towards hydrolysis than the diethyl analogues, which made the aromatic derivatives less useful for the dual protection purpose. Another noteworthy result was that when the glycine-derived boroxazolidone was heated together with benzylamine in refluxing toluene, the starting material was recovered almost quantitatively. [46]

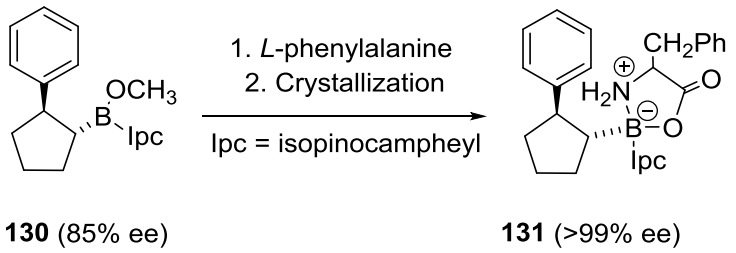
In 2001, inspired by the initial work of Nefkens and Zwanenburg, Dent III et al. [51] utilized 9-borabicyclononane (9-BBN) to protect functionalized amino acids for side chain manipulation (Scheme 36). In their procedure, a small excess of commercially available 9-BBN dimer was dissolved in refluxing methanol after which amino acid **128** was added. By using different amino acids, this reaction afforded 9-BBN containing boroxazolidones **129** with good yields (50−98 %). Only with histidine, a stable complex couldn't be obtained. The protecting group could be easily removed under mild conditions by treatment with either dilute HCl or by exchange with an excess of ethylene diamine in methanol.



Scheme 36: *Preparation of 9-BBN derived boroxazolidones **129** by Dent III et al. [51]*

Moreover, Dent III et al. had a few occasions during their studies to test the reactivity of compounds **129,** but a comprehensive study was not performed. Nevertheless, these compounds were found to be tolerant towards a wide collection of reaction conditions without any reaction at the amine or cleavage of the boroxazolidone, which illustrates the strength of the N-B motif and its importance to the stability of these structures. [51]

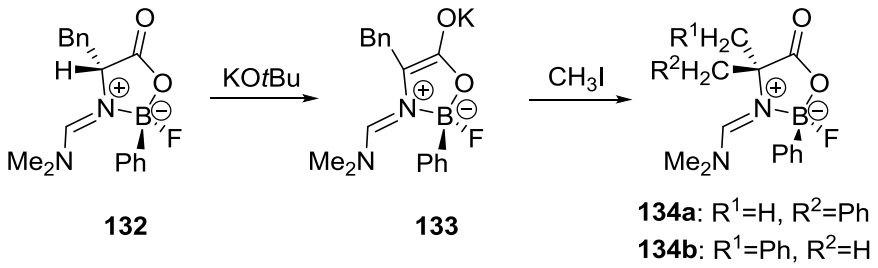
As another application of boroxazolidones, their synthesis has been employed to upgrade the optical purities of borinates and boronates. In the previously mentioned study of Brown & Gupta [47], methyl *trans*-2-phenylcyclopentyl-isopinocampheylborinate of 85 % ee **131** was prepared through hydroboration of 1-phenylcyclopentene with monoisopinocampheylborane, (−)-IpcBH$_2$, followed by transesterification with methanol. After treating the borinate **130** with *L*-phenylalanine, crystallizing the crude product from DMSO the corresponding boroxazolidone **131** was obtained with exceptionally high enantiomeric excess, > 99 % ee (Scheme 37).



130 (85% ee) **131** (>99% ee)

Scheme 37: *Upgrading the optical purity of borinates through boroxazolidone formation. [47]*

Chiral boron containing compounds are multipurpose reagents widely used in asymmetric synthesis. However, in most of these compounds, the chirality is usually contained in groups attached to boron. As an alternative, Vedejs et al. were the first ones to utilize boroxazolidones in asymmetric transformation reactions, where the asymmetric memory is imparted by a stereogenic boron atom. These boroxazolidone structures were found to be capable of asymmetric transformation through crystallization under the conditions of diastereomer interconversion, thus they could be obtained as single diastereomers with extraordinary selectivities. The asymmetric memory could be maintained throughout the synthesis of disubstituted amino acids derived from these diastereomers via the intermediate enolates. An example of such asymmetric transformation is given in Scheme 38, where phenylalanine-derived boroxazolidonine **132** is treated with potassium *t*-butoxide, KO*t*Bu, followed by addition of methyl iodide, producing a mixture of the isomeric products **134a** and **134b** in 5.5:1 ratio and with ≥ 99.5 % ee and combined yield of 70 %. Similar results were obtained by using different boroxazolidones derived from other amino acids and different halides. In addition, the conversion of boroxazolidones to amino acids was achieved in moderately mild conditions and the efficiency was found to be comparable to other methods based on enolate alkylations. [52]

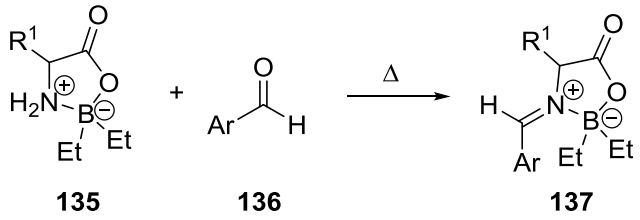


132 **133**

134a: R^1=H, R^2=Ph
134b: R^1=Ph, R^2=H

Scheme 38: *Alkylation of boroxazolidone **132** by Vedejs et al.* [52]

Even though mostly less-studied, the utilization of boroxazolidones in imine synthesis must be the most intriguing application. By introducing the imine function into boroxazolidones, a highly functional compound with a broad scope of applications can be obtained. During their boroxazolidone studies, Nefkens & Zwanenburg became interested in the reactivity of the compound and wondered if the strongly coordinated nitrogen could still have properties to allow it to act as a nucleophile. In 1984 they reported on such synthesis [53], where a condensation reaction between boroxazolidones **135** and aromatic aldehydes **136** in reflux and with azeotropic removal of water produced corresponding imines **137**, as shown in Scheme 39. As an important result of their study, this showed that even though a strong intramolecular interaction exists between nitrogen and boron, the nitrogen is still able to work as a nucleophile and attack the carbonyl group in the aldehyde. Four different aromatic aldehydes were tested and with benzaldehyde, *o*-carboxybenzaldehyde and *o*-phtalaldehyde the reaction was successful, producing corresponding imines in good yields. However, the reaction with salicylaldehyde did not produce an imine, but instead a polymeric material was obtained.



135 **136** **137**

Scheme 39: *Reaction of boroxazolidones with aromatic aldehydes. [53]*

3.5 Lewis Base-Lewis Acid Interactions

As seen in the studies of Nefkens & Zwanenburg, even though the nitrogen in the boroxazolidone is bonded with the boron by sharing its valence electrons, the nitrogen moiety can still behave as a nucleophile and attack electrophilic species. To be able to understand the interactions in the N-B motif and the overall reactivity of boroxazolidones, a closer look to these interactions is presented.

The modern understanding of acid-base reactions was born as a result of the pioneering work performed by G. N. Lewis in the early 20th century. As an outcome of his studies, Lewis was able to unify the preceding and complex theories of the chemical bonding and reactivity by defining the acid-base interactions merely as electron-pair transport between an electron-pair acceptor and electron-pair donor, Lewis acid and Lewis base, respectively. The driving force behind these interactions lies in the need of the atoms to satisfy the octet rule and this way to obtain the most stable state. Nevertheless, while some exceptions to the octet rule exist, so do exceptions to the Lewis acid-Lewis base interactions leading to reduced reactivity. Various examples of acid-base adducts with enhanced reactivity can be found in the literature. [54]

For several years, the use of Lewis acids as reagents and catalyzing agents has been dominating the field of organic chemistry. During the recent years, the potential of Lewis bases as promoters of different reactions has been also recognized. Even though Lewis basic co-catalysts are nowadays widely used as ligands in transition metal catalysis, non-metallic Lewis base catalysts remain less investigated catalyzing agents. This has been explained by the lack of target Lewis acid moieties in most commonly used organic molecules and the scarce chances for valence expansion at carbon centers. The interest towards Lewis base catalysis was initiated by the experiments, which showed that Lewis bases do not only work as electronical counterparts of Lewis acids but they are able to enhance both the electrophilic and nucleophilic nature of the bonding molecule. This feature of Lewis base catalysis has led to a remarkable variety of uses in numerous reactions. [54]

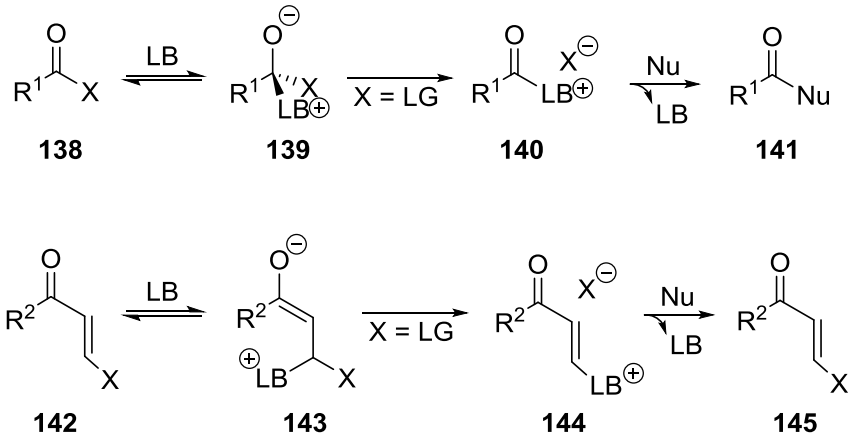
As the Lewis base catalysis is defined by the interaction of an electron-pair donating catalyst and an electron-pair accepting substrate or reagent, the enhancing effect is based on to the transfer of electron density to the acceptor subunit of the newly formed adduct, which usually translates to enhanced nucleophilicity of this subunit. Even though how illogical it sounds, the binding of a Lewis base can also improve the electrophilicity of the acceptor. It is the distribution of the electron density among the constituent atoms that need to be taken in consideration when trying to explain the effect of Lewis base catalysis, thus by investigating the nature of the newly formed coordinative bond some rationalization can be done. [54]

Jensen has divided the Lewis acid-Lewis base interactions into nine different categories in his analysis of molecular interactions (Table 3). These categories of interactions are formed by combining three kinds of non-bonding acceptor orbitals with three kinds of bonding donor orbitals, so that nine different categories are formed. Even though in theory all of these interactions are possible, in practice three of them are significant in catalysis: interactions of nonbonding electron pairs with π*-orbitals (n-π* interactions), σ*-orbitals (n-σ* interactions) or vacant nonbonding orbitals (n-n* interactions). [54]

Table 3: *Jensen's orbital analysis of molecular interactions. [54]*

Donor	**Acceptor**		
	n*	**σ***	**π***
n	n-n*	n-σ*	n-π*
σ	σ-n*	σ-σ*	σ-π*
π	π-n*	π-σ*	π-π*

The most recognized form of Lewis base catalysis includes the n-π* interactions. These Lewis base catalyzed reactions (Scheme 40) are analogous to those observed in the nucleophilic 1,2-additions to carbonyl groups and nucleophilic 1,4-additions to *α,β*-unsaturated compounds. In the former case, the attack of the Lewis base (LB) to carbonyl group leads to the formation of tetrahedral zwitterion with increased nucleophilicity. In the latter case with unsaturated compounds, the conjugation addition of Lewis base produces a zwitterionic enolate with enhanced nucleophilic character. If the zwitterionic molecules possess good leaving groups (LGs), they can collapse through elimination reaction and in both cases species with enhanced electrophilic character will be formed. In addition, a subsequent proton transfer might lead into new forms of reactivity. [54]



Scheme 40: *Lewis base catalysis based on n-π* interactions. [54]*

Even though n-σ* and n-n* interactions are less studied, they offer as various pathways as n-π* interactions for Lewis base catalysis. As the σ* symbol is used to generally describe the acceptor orbital in these organometallic reagents consisting of a variety of main-group elements, the n* symbol signifies a specific group of Lewis acid acceptors containing Group 13 elements, such as boron compounds. The common characteristic and an important requirement to these species is that they can achieve a hypervalent state, meaning that the acceptor can expand its coordination scope and bear more than

eight electrons in its valence shell. The adduct formation allows coincident enhancement of both nucleophilic and electrophilic fragments, depending on the polarizability of the bond. The behavior of these hypervalent species, and the reason why these interactions lead to novel forms of reactivity, has been explained by Gutmann. In his analysis, Gutmann observed that even though the overall electron density of the acceptor moiety increases in the adduct formation, the electron density is distributed unevenly among the atoms, which have obvious consequences to the bond lengths and strengths, thus to the reactivity of the compound. [54]

Similar n-n* interactions are present in the N-B motifs of the boroxazolidones, in which the polarization along the dative bond allows the nitrogen moiety to work as a Lewis base and the boron moiety as a Lewis acid. Due to this, it might be possible to effect to the reactivity of boroxazolidones by bringing competing Lewis acids or bases into the system, which could enhance the nucleophilic character of nitrogen or the electrophilic character of boron.

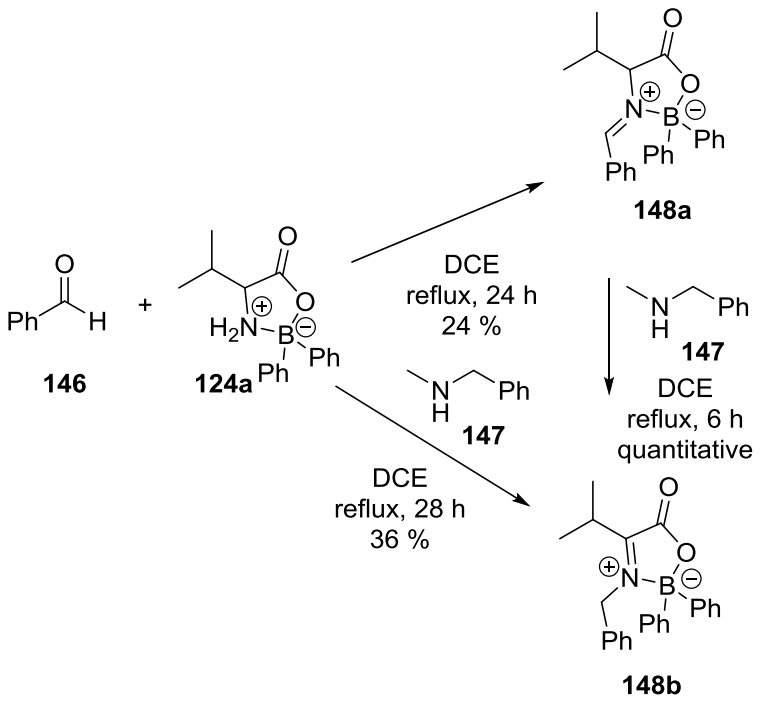
4. RESULTS AND DISCUSSION

The experimental part of this thesis was performed in the synthesis laboratory of the Department of Chemistry and Bioengineering in Tampere University of Technology during November 2014−September 2015. This section contains introducing the background and motivation for this thesis, the results and discussion of the syntheses done. The detailed descriptions of the syntheses of the prepared compounds have been collected under the experimental section of this thesis.

4.1 Background and Motivation for the Study

Taking the previous reports on the preparation of amine derived boroxazolidones and the possibility to prepare imines from the same compounds, it was envisioned that the highly functionalized imines could be explored as a tool for functionalization of amino acids. Hence, taking the condensation reaction between *L*-valine derived boroxazolidones and benzaldehyde, Candeias [55] tested several reaction conditions in which the use of harsh conditions reported by Nefkens & Zwanenburg could be avoided. [53]

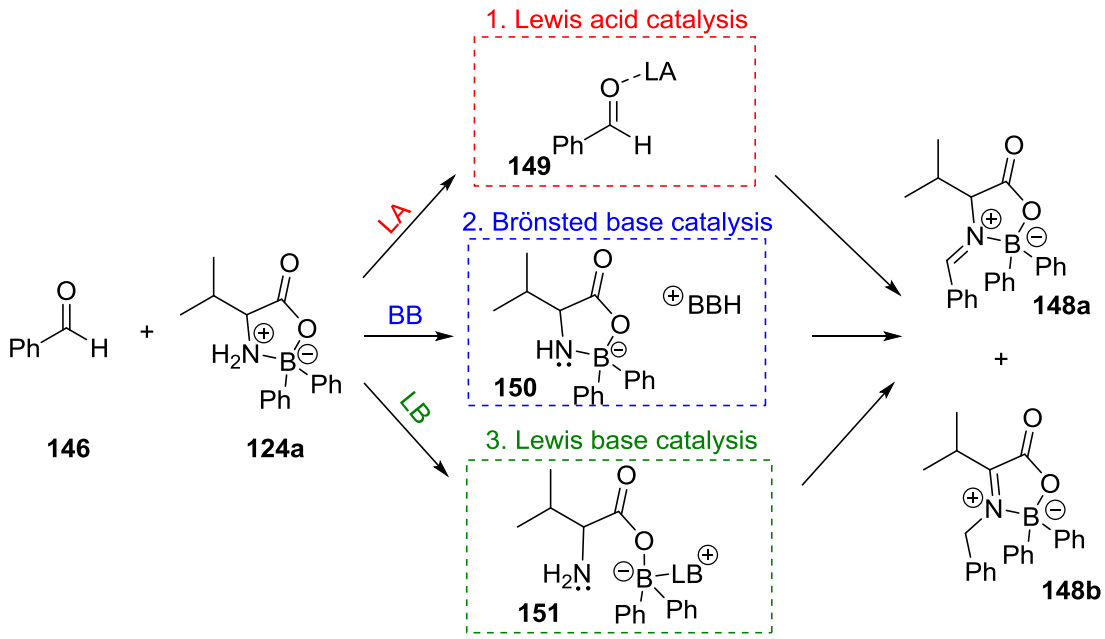
One of the approaches included utilizing base catalysis in the reaction. When *N*-benzylmethylamine **147** was introduced in the condensation reaction between *L*-valinatodiphenylboron **124a** and benzaldehyde **146**, the interconversion of the aldimine **148a** to ketimine **148b** was observed according to the results presented in Scheme 41. Similar tautomeric relationship, where both isomers exist in equilibrium, was observed in transamination of amino acids (Scheme 15), where the interconversion resulted from migration of hydrogen.



Scheme 41: *Base-catalyzed condensation reaction between boroxazolidone **124a** and benzaldehyde **146** resulting in aldimine **148a**-ketimine **148b** tautomerization*.

Due to the tautomerization between **148a** and **148b**, the main focus of the research was changed. The goal was now to find the conditions, which could be suitable for selective control of the interconversion of the isomers, so that the built-in chirality of the α-carbon could be preserved. With this goal in mind, this Master's thesis project was launched, aiming to find the conditions so that the equilibrium between aldimine **148a** and ketimine **148b** could be pushed towards desired direction.

As the dative N-B bond in boroxazolidones is formed between the Lewis acidic boron and Lewis basic nitrogen, it should be possible to manipulate this interaction by introducing different bases and acids to the system and in this way enhance the nucleophilicity of the nitrogen or the electrophilicity of the carbon in carbonyl compound. Three different routes were planned and they are presented in Scheme 42. First, it was assumed, that because Lewis acids are widely used to enhance reactions between amines and carbonyl compounds, they also might be suitable for the studied reaction. The hypothesis is that the Lewis acid (LA) activates the benzaldehyde for nucleophilic attack by attaching to the nucleophilic site in benzaldehyde and forming intermediate **149**. Secondly, it is envisioned, that by addition of Brönsted base (BB) in the reaction, the base could deprotonate the amine in boroxazolidone, which results in formation of more nucleophilic intermediate **150.** The third hypothesis is that the Lewis base could attach itself to the boron, making the amine in boroxazolidone more available to react with the carbonyl compound.



Scheme 42: *The suggested routes for imine synthesis from boroxazolidones by using different catalysts.*

4.2 Preparation of the Starting Material

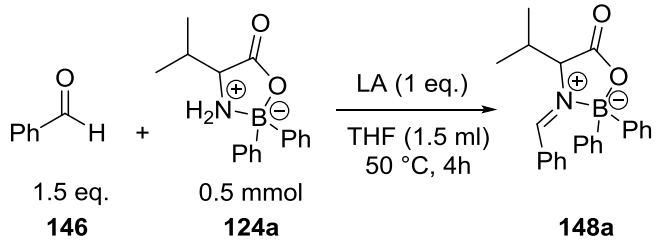
Before the experimental studies on imine synthesis were started, boroxazolidone **124a** was prepared, according to the developed procedure by Kuuloja [30]. First, the triethylammonium tetra-arylborate was prepared as presented in Scheme 22. This was followed by a subsequent reaction with *L*-valine, as presented in Scheme 34, providing *L*-valinatodiphenylboron, which was used as a model molecule in the studies on boroxazolidones. The reaction sequence provided the product in high yield, 98 %, without impurities. To choose a suitable solvent for further studies, solubility tests for boroxazolidone were performed. It was found that at room temperature the solubility of the material was quite poor in every screened solvent: THF, DCM and DCE. After heating to 50 °C, THF was the only solvent in which the compound dissolved.

4.3 The Optimization of Reaction Conditions

For obtaining more information on the Lewis acid-Lewis base interactions on boroxazolidone and to find the optimized reaction conditions for controlling the tautomerization, the studies performed by Candeias were continued as the experimental part of this Master's Thesis. In the beginning of these studies, a wide selection of Lewis acids and bases were introduced in the reaction in order to see how different catalysts would affect in the outcome of the imine formation. If not otherwise stated, all reactions were carried out under inert argon gas.

4.3.1 The Effect of Lewis Acids

As reported in the literature [3], several Lewis acids promote successfully the imine formation in numerous condensation reactions between amines and aldehydes by enhancing the electrophilicity of the aldehyde and simultaneously working as a drying agent. It was envisioned that the Lewis acid catalysis could also be incorporated in the studied reaction and result with high yields of product. The screening of the reaction conditions was started by testing a variety of different Lewis acids according to the reaction presented in Scheme 43, and the product formation was assessed by TLC. The tested Lewis acids and the results acquired are collected in Table 4.



Scheme 43: *The reaction scheme for testing different Lewis acids as catalysts.*

Table 4: *Results obtained from the acid-catalyzed reactions.*

Entry	Lewis Acid, LA	Outcome judged by TLC
1	$CuSO_4$[a]	n.r.[b]
2	$ZnCl_2$	traces[c]
3	$ZnBr_2$	traces
4	$AlCl_3$[d]	n.r.
5	Cu(I)Br	n.r.
6	Cu(II)Br	n.r.
7	Fe(II)Cl_2	n.r.
8	$TiCl_4$[e]	n.r.
9	BF_3	n.r.

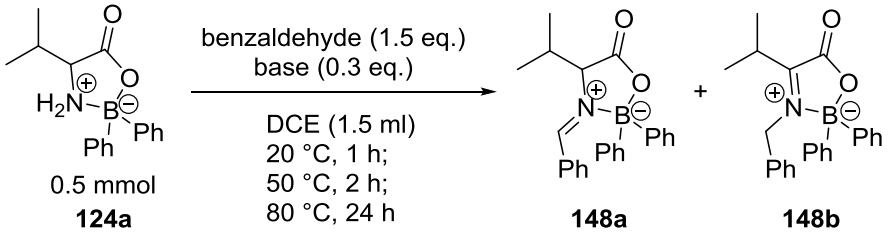
[a] Both hydrated and anhydrous $CuSO_4$ were screened. [b] n.r. = no reaction. [c] A faint trace of product was observed on TLC plate. [d] Both hydrated and anhydrous $AlCl_3$ were screened. [e] Reaction performed in toluene.

Although more experiments are needed, it seems that the nitrogen part in boroxazolidone is not nucleophilic enough to react with the benzaldehyde, even though

the electrophilicity of the benzaldehyde is enhanced by the Lewis acid. On the other hand, instead of enhancing the imine forming condensation reaction, it might be that the Lewis acid replaces boron in the boroxazolidone structure, and this way prevents the nucleophilic attack to the carbonyl of the benzaldehyde. This option is also supported by the fact that when using a milder Lewis acid, such as $ZnCl_2$ and $ZnBr_2$, a faint trace of product could be observed on the TLC plates. However, in these cases the yield was considered too low to be worth of performing any separation.

4.3.2 The Effect of Bases

As the results obtained from the Lewis acid-catalyzed reactions were highly disappointing, the studies were directed towards base catalysis. The first hypothesis was that the electron-rich Lewis base would attach to the electron-deficient boron with a dative bond and make the amine more nucleophilic. Other hypothesis was that if the base used works as a Brönsted base, it would protonate the amine in boroxazolidone. This would make the amine moiety more available to react with the carbonyl group of benzaldehyde. These assumptions were tested by conducting a series of base catalyzed reactions according to Scheme 44.



Scheme 44: *The reaction scheme for base screening.*

Simultaneously while investigating different bases in the reaction, different reaction temperatures were examined by letting the reaction to run in room temperature for an hour, after which the temperature was raised to 50 °C for 2 hours and finally to 80 °C for 24 hours. Before every temperature ascent, reactions were monitored by TLC. With the lower reaction temperatures, 20 °C and 50 °C, the TLCs showed no or only faint traces of the products **148a** and **148b**. To improve the outcome, it was decided to change the solvent from THF to DCE, so that higher temperatures could be reached. When the temperature was raised to 80 °C, stronger product spots in TLC plates could be observed. The selection of screened bases and the obtained conversions after 24 hours in 80 °C are given in Table 5.

Table 5: *Results obtained from the base-catalyzed reactions.*

Entry	Base	Conversion[a] (%) 148a	148b
1	DMF[b]	< 1	-
2	DMAP	12	6
3	Pyridine *N*-Oxide	7	-
4	Pyridine	6	-
5	HMPA	9	-
6	OP-(*n*-Bu)$_3$	9	3
7	TEA	3	25
8	DABCO	6	6
9	TMEDA	5	21
10	DBU	-	27[c]
11	DIPEA	2	20
12	PPh_3	13	-
13	Pyrrolidine	2	16
14	DPPE	14	-
15	JohnPhos	12	-

[a] Determined from the ^{1}H NMR measurements. [b] DMF used as a solvent, total amount 1.5 ml. [c] Isolated yield after column chromatography.

As the results show, the conversion to aldimine **148a** remains quite poor regardless of the choice of the base. The best results for synthesizing the aldimine product were obtained with bulky phosphine derived Lewis bases, such as PPh_3, DPPE and JohnPhos. These results obtained with the phosphine containing Lewis bases highly support the hypothesized reaction mechanism, where the attack of a Lewis base on the boron generates more reactive amine moiety.

With conversion to ketimine **148b**, it seems that nitrogen containing acyclic Lewis bases, such as TEA, TMEDA and DIPEA, give the best results even though the highest yield was surprisingly obtained with bicyclic DBU. Because the amine derived Lewis bases can also work as Brönsted bases and the reaction produced ketimine instead of aldimine, it might be that the bases in question instead of reacting as Lewis bases with the boron, they activate the nitrogen moiety by deprotonating the amine.

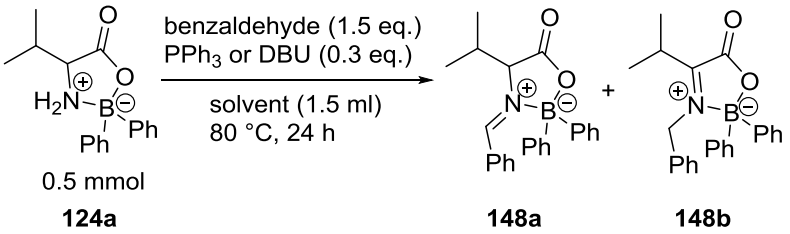
The important observation is that the interconversion between aldimine and ketimine is most likely mediated by Brönsted bases and, most importantly, that the tautomerization can be controlled selectively by changing the base in the reaction.

To be able to interpret the obtained results through comparison, a reaction between benzaldehyde and boroxazolidone at 80 °C DCE without any catalyst was also studied. This resulted in aldimine **148a** with 6 % conversion.

4.4 The Optimization of Other Reaction Conditions

After intensive studies on the effect of different Lewis acids and bases, other reaction conditions, such as different solvents, reaction temperatures, reaction times and ratios of starting materials were also screened for the studied reaction. While most methods available for imine preparation require the use of superstoichiometric amounts of amine, in the present case the starting amine, boroxazolidone, is more valuable than the commercially available aldehyde. Due to this, the boroxazolidone was always used as the limiting agent in the optimization studies.

For testing the solvent effect in imine formation, PPh_3 and DBU were chosen as the catalysts, as they provided good results in aldimine and ketimine formation, respectively. Reaction conditions for solvent screening are presented in Scheme 45 and achieved yields are gathered in Table 6. As it became possible to raise the reaction temperature with toluene, the last entry was performed in reflux (110 °C).



Scheme 45: *The screening of different solvents.*

Table 6: *The effect of solvent in PPh_3- and DBU-catalyzed reactions.*

		Conversion[a] with PPh_3 (%)		Yield[b] with DBU (%)	
Entry	**Solvent**	**148a**	**148b**	**148a**	**148b**
1	acetonitrile	3	-	-	12
2	DME	5	-	-	8
3	dioxane	-	-	-	15
4	DMF	-	6	-	5
5	THF	8	-	-	15
6	toluene[c]	12	7	7[d]	21

[a] Determined from 1H NMR-measurements. [b] Isolated yield after purification by column chromatography. [c] Performed under reflux. [d] Conversion determined from NMR-measurements.

Even though the obtained conversions and yields in the solvent screening were lower than with DCE as the solvent, the results show that along with the choice of the base, the tautomerization between aldimine and ketimine can be controlled also with the choice of the solvent.

In addition, other reaction conditions were investigated, according to Table 7, to see if these changes would also have an impact on the outcome.

Table 7: *The results obtained from miscellaneous reaction conditions.*

Entry	Catalyst	Catalyst loading (eq.)	Reaction conditions	Conversion (%) 148a	148b
1	PPh_3	0.3	80 °C, 72 h, DCE	12	-
2	DBU	0.3	80 °C, 72 h, DCE	-	37[a]
3	PPh_3	1	80 °C, 24 h, DCE	10	-
4	methanol	1	80 °C, 24 h, DCE	4	-
5	thiophenol	1	80 °C, 24 h, DCE	8	-
6	DMSO	1	80 °C, 24 h, DCE	2	-
7	DBU	0.3	80 °C, 24 h, water, air	-	-
8	DBU	0.3	80 °C, 24 h, DCE, molecular sieves 4 Å	-	25[a]
9[b]	DBU	1	80 °C, 24 h, DCE	-	11[a]
10	DBU	0.3	reflux, 24 h, DCE	-	44[a]

[a] Isolated yield after column chromatography. [b] Benzaldehyde added not until after 2h.

Neither prolonging the reaction time from 24 hours to 72 hours nor increasing the catalyst loading with triphenyl phosphine (Entries 1 and 3) did cause any remarkable changes in the conversion. Quite poor results were also obtained from introducing other nucleophiles that could compete for boron, such as methanol, thiophenol and DMSO into the reaction (Entries 4−6). Because of the lowered conversions, it is most likely that these compounds do not replace the nitrogen in the dative bond as was hypothized.

Different results were achieved when using DBU as the catalyst. When the DBU-catalyzed reaction was continued for a longer time, the reaction gave isolated yield of 37 % after 72 hours, which was already a fine development to the 27 % yield obtained after 24 hour reaction time.

In various imine syntheses in literature [3], molecular sieves have been utilized for trapping the forming water to improve the yield. This method was applied in Entry 8, where molecular sieves were employed to the DBU-catalyzed reaction, but according to the results they had no effect on the reaction. Moreover, some contradictory results have been reported in the literature [56] about reactions utilizing water as a solvent in imine formation. Some of these studies have shown excellent yields, while the rest report ineffective reactions. When water was introduced as a solvent in the studied reaction (Entry 7), no product was attained. This is probably due to the extremely low solubility of the studied boroxazolidone in water. When both the amine and the aldehyde are water soluble and the product is not, the product is basically removed from the aqueous

layer after formation and this is probably what drives the reaction to completion and leads to formation of imines with high yields. Otherwise, as in this entry, the water prevents any product formation.

It was also suggested that it could be possible to improve the yield by letting the DBU react with the boroxazolidone for 2 hours before adding the benzaldehyde to ensure the proper activation of the nucleophilic part of the molecule (Entry 9). As seen from the results, this entry gave lower yield than the regular reaction method. This result is another strong indication that the DBU works most likely as a Brönsted base in the reaction. In addition, a significant improvement of yield was observed, when the system was heated to reflux in the last entry (Entry 10).

Due to the progress achieved with the DBU-catalyzed reactions and to limit the scope of this study, the remaining research of this thesis was focused on the ketimine forming reactions.

Finally, different ratios of starting materials were tested to obtain the optimal benzaldehyde-boroxazolidone ratio. Each reaction was run for 24 hours in refluxing DCE. The ratios of the starting materials and the isolated yields of compound **148b** are given in Table 8:

Table 8: *The screening of different ratios of starting materials.*

Entry	Benzaldehyde (eq.)	Boroxazolidone (eq.)	Isolated Yield (%)
1	1	1.5	18
2	2	1	36
3	1	2	21
4	5	1	62

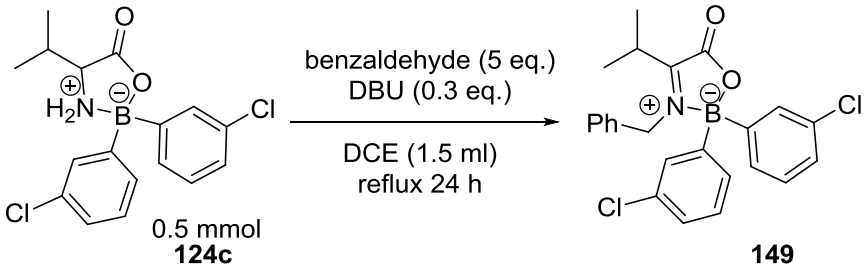
As seen from the table, the highest yields were acquired with an excess of benzaldehyde and the best result was achieved with 5:1 ratio of starting materials. This is quite surprising result, because usually imine formation requires superstoichiometric amounts of the amine to push the reaction forwards. However, this again tells us the different nature of the amine in boroxazolidones when compared to “regular” ones presented in Chapter 2.

4.5 Reactions with Different Boroxazolidones

The studies on base-catalyzed condensation reactions between boroxazolidones and benzaldehyde were continued with applying the obtained optimized reaction conditions to two new reactions. As two boroxazolidones with differently substituted boron atoms,

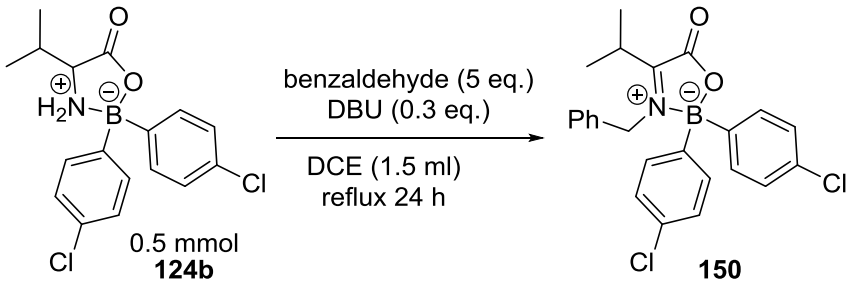
124b and **124c** were already prepared and available from previous work of Kuuloja [1], these were chosen for the studies.

At first, the *L*-valinatodi(3-chlorophenyl)boron **124c** was coupled with benzaldehyde to produce the corresponding imine **149** according to the Scheme 46. The ketimine product was obtained with a good yield, 64 %.



Scheme 46: *DBU-catalyzed reaction between L-valinatodi(3-chlorophenyl)boron* ***124c*** *and benzaldehyde.*

In the second entry, a reaction between *L*-valinatodi(4-chlorophenyl)boron **124b** and benzaldehyde was investigated. This reaction is illustrated in Scheme 47. While running the column chromatography, a new spot indicating an unknown side product **151** appeared into TLC-plates. Because of the poor separation of this side product and the compound **150** during the column chromatography, some amount of the imine was lost and the yield of the isolated product was decreased to 44 %.



Scheme 47: *DBU-catalyzed reaction between L-valinatodi(4-chlorophenyl)boron* ***124b*** *and benzaldehyde.*

The side product **151** was analyzed with ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR techniques. Due to the overlapping of the peaks between the compounds **150** and **151** and also the complexity of the compound, the absolute structure was found difficult to be interpreted and further analysis is left beyond the scope of this thesis. However, the most interesting observation is that the peak indicating ester structure around 170 ppm, as seen in boroxazolidones NMR spectra, has disappeared. Instead a peak in 204 ppm indicating ketone structure has appeared. This suggests that the normally stable boroxazolidone ring has been cleaved from the carboxylic acid moiety.

5. CONCLUSIONS AND FUTURE PLANS

The condensation reaction between boroxazolidones and carbonyl compounds results in an aldimine-ketimine tautomerization, where both of the isomers exist in equilibrium. Such process has been succesfully achieved as a part of this Master's thesis project with a reaction between *L*-valine derived boroxazolidones and benzaldehyde. By utilizing different base catalysts in the condensation reaction, it was noticed that the interconversion of aldimines and ketimines could be controlled selectively. Moreover, not only the choice of the base, but as well the modification of other reaction conditions was observed to have an influence on the outcome of the reaction. Most importantly, only one isomer could be obtained and isolated by optimizing the reaction conditions.

A wide range of reaction conditions, such as different catalysts, solvents, reaction times and temperatures as well as ratios of the starting materials were applied to the reaction in question and they were all found to have a significant effect on the results.

As the acid catalysis is one of the most wielded and effective method to produce imines from "regular" amines and carbonyl compounds according to the literature [3], the observation of Lewis acids being ineffective with the studied reaction indicated different nature of the amine moiety in boroxazolidones. A diverse approach with base catalysis succesfully resulted in acquiring products, either just one isomer or both, depending on the choice of the base. When phosphine-based Lewis bases were used, only aldimine could be obtained and the best result with 14 % conversion was achieved with DPPE. When nitrogen-derived bases were introduced into the reaction, the equilibrium turned towards ketimine formation and the highest yield of ketimine, 27 %, was achieved with DBU-catalyzed before screening of other reaction conditions.

In addition, through modification of the other reaction conditions it was found possible to control the outcome of the reaction. By 1) increasing the temperature, 2) changing the solvent, 3) lengthening the reaction times and 4) modifying the ratio of starting materials, the yield could be improved considerably from the non-catalyzed reaction yield of 6 %. With the optimized reaction conditions, the reaction of *L*-valinatodiphenylboron with benzaldehyde gave the corresponding ketimine with a good yield of 62 %. These conditions were also applied for reactions of benzaldehyde with di(3-chlorophenyl)- and di(4-chlorophenyl)-substituted boroxazolidones, resulting ketimines with 64 % and 44 % yields, respectively. Even though the substituents in the boron atom did not differ much, some effects on the reactivity of the boroxazolidones could already be detected in the scope of this study. For its part, this observation

demonstrates the important role of the dative N-B bond for bestowing distinct reactivity to these amino acid derivatives.

To be able to achieve deeper understanding of the reactivity and other characteristics of boroxazolidones, it would be important to perform further and more comprehensive studies on these amino acid derivatives. By expanding the substrate scope by introducing different functionalities in both the nitrogen and the boron atoms, the nature of the N-B bond and consequently the reactivity of the boroxazolidones could be modified to respond in the needs of various applications. For example, different aldehydes and other carbonyl compounds, such as ketones, could be introduced in the reaction. After characterization of the N-B bond by tuning the boron and nitrogen moieties in boroxazolidones, it would be very interesting to investigate, if this method could be applied to reactions with boroxazolidones derived from other natural α-amino acids.

6. EXPERIMENTAL

The reagents and solvents used were obtained from Sigma-Aldrich, Fluka and Merck and they were used as obtained unless otherwise stated.

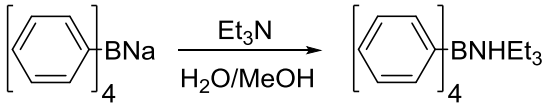
Thin-layer chromatography (TLC) was performed on precoated aluminium plates (Merck TLC silica gel 60 F_{254}), the detection was done in UV light and if staining was needed it was done with cerium molybdate solution. Flash column chromatography was performed on Merck silica gel 60 (0.040−0.063 mm).

^{1}H, ^{13}C NMR, COSY, HSQC and HMBC were measured using Varian Mercury 300 MHz spectrometer using $CDCl_3$, DMSO-d_6 and acetone-d_6 as solvents. The chemical shifts were reported as δ (ppm) values referenced to internal standard TMS. Solvent residues in NMR samples were identified from spectra using article from Gottlieb *et al.* [57]

The conversions were determined from the proton NMR spectra by first choosing one peak from each compound that did not overlap with other peaks and it was integrated to get the integration value. These peaks were boroxazolidone's α-hydrogen singlet at 3.38 ppm, aldimine's imine hydrogen singlet at 8.49 ppm and ketimine's doublet at 6.50 ppm which designated the hydrogens at *o*-positions in phenyl group that originated from benzaldehyde. The absolute integration value for ketimine was obtained by dividing it by 2, because the original integration value represented two hydrogens. These absolute integration values were then summed up to get the total value. To obtain the conversion (%) for a compound, the absolute integration value of this compound was divided with the total value and multiplied by 100. In DBU-catalyzed reactions, due to the overlapping of the DBU and boroxazolidone peaks, the calculated conversions contain a systematic error so that the actual conversions of the ketimines were slightly higher than the calculated ones. Due to this, the products produced in DBU-catalyzed reactions were purified via flash chromatography to obtain the isolated yields.

6.1 Preparation of Boroxazolidone

6.1.1 Triethylammonium Tetraphenylborate

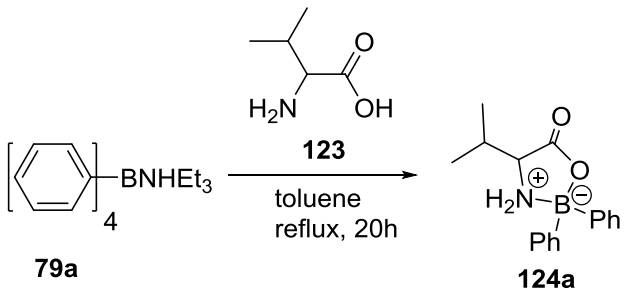


78a **79a**

Scheme 48: *The synthesis of triethylamine tetraphenylborate* ***79a****.*

Sodium tetraphenylborate **78a** (5.5 g, 16 mmol, 1.0 eq.) was dissolved in 50 ml of MeOH/water (1:1). 100 ml of 2.5 wt% solution of triethylamine was added through a dropping funnel to the reaction mixture. Upon addition white solid was formed. The reaction mixture was left to stir for 3 hours at room temperature. The crude product was filtered, washed three times with minimum amount of water and dried in vacuum. White solid (6.652 g, 98% yield); ^{1}H NMR (300 MHz, *acetone-d*$_6$) δ (ppm): 7.34 (dddt, *J*=6.68, 5.33, 2.64, 1.32, 1.32 Hz, 8 H), 6.94 (t, *J*=7.32 Hz, 8 H), 6.71 - 6.87 (m, 4 H), 3.28 (d, *J*=7.32 Hz, 5 H), 3.13 - 3.42 (m, 2 H), 1.29 (t, *J*=7.32 Hz, 9 H); ^{13}C NMR (75 MHz, *acetone-d*$_6$) δ ppm 206.33 (d, *J*=1.11 Hz), 163.86 - 165.94 (m), 136.69 - 137.15 (m), 126.06 (dd, *J*=5.53, 2.76 Hz), 122.32 (s), 48.11 (s), 29.00 - 30.80 (m), 9.40 (s). Appendices 1 and 2. NMR in accordance with Kuuloja et al. [30]

6.1.2 *L*-valinatodiphenylboron



79a **124a**

Scheme 49: *The synthesis of L-valinatodiphenylboron* ***124a****.*

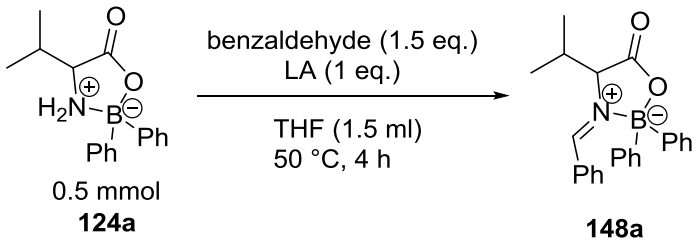
Triethylamine tetraphenylborate **79a** (4.217 g, 10 mmol, 1 eq.) was placed with 240 ml of toluene in a round bottom flask while stirring. *L*-valine **123** (1.173 g, 10 mmol, 1 eq.) was added and reaction mixture was heated to reflux. After 20 h the crude product was filtered and washed three times with 5 ml of water and twice with 5 ml of toluene and was dried in vacuum. White solid (2.674 g, 98% yield). ^{1}H NMR (300 MHz, *CDCl*$_3$ + drops of *DMSO*) δ ppm 7.31 - 7.48 (m, 4 H), 6.99 - 7.21 (m, 6 H), 6.92 (br. s., 1 H), 4.76 (br. s., 1 H), 3.38 (td, *J*=7.98, 5.13 Hz, 1 H), 2.07 - 2.32 (m, 1 H), 0.91 (d, *J*=6.74 Hz, 3 H), 0.80 (d, *J*=6.74 Hz, 3 H); ^{13}C NMR (75 MHz, *DMSO-d*$_6$) δ ppm 174.09 (s),

131.89 (s), 131.85 (s), 127.71 (s), 127.64 (s), 126.66 (s), 126.62 (s), 61.04 (s), 29.13 (s), 19.46 (s), 19.02 (s) Appendices 3 and 4.

6.2 Preparation of Imines

First, the general procedures for Lewis acid and base screening are described. Next, two examples of the base catalyzed condensation reaction procedures are explained in detail. In these two examples, only aldimine **148a** or ketimine **148b** was produced. With some of the screened bases, both isomeric products were obtained. The conversions and yields were determined as described above. The reactions were carried out in oven-dried glassware and under argon atmosphere.

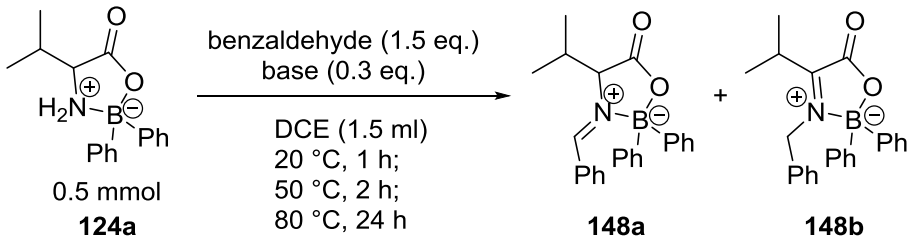
6.2.1 General Procedure for the Lewis Acid Screening



Scheme 50: *The general procedure for the screening of Lewis acids.*

Before Lewis acid screening, the solvent, THF, was dried by the use of still apparatus. Lewis acid (0.5 mmol, 1.0 eq.) was measured in a dry round bottom flask, after which benzaldehyde (0.076 ml, 0.75 mmol, 1.5 eq.) and THF (1.5 ml) were added while flushing the system with argon. Boroxazolidone **124a** (140 mg, 0.5 mmol, 1 eq.) was added, system was flushed again with argon and heated to 50 °C. Within the 4 hours, TLC was performed several times to monitor the reaction.

6.2.2 General Procedure for the Base Screening

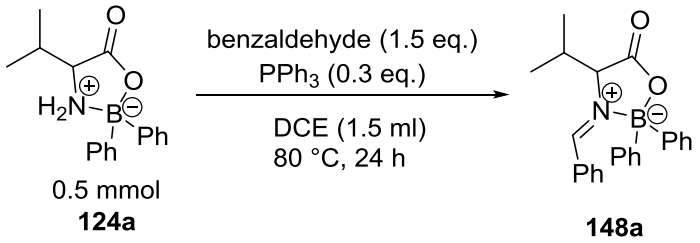


Scheme 51: *The general scheme for the screening of bases.*

Boroxazolidone **124a** (140 mg, 0.5 mmol, 1 eq.) was measured in an oven-dried round bottom flask with 1,2-dichloroethane (1.5 ml) and benzaldehyde (0.076 ml, 0.75 mmol, 1.5 eq.). Lewis base (0.15 mmol, 0.3 eq.) was added and system flushed with argon.

Mixture was stirred at room temperature for 1 hour, at 50 °C for 2 hours and at 80 °C for 24 hours. Before every ascent and after stopping the reaction, TLC was performed to monitor the reaction. During the work-up, the excess solvent was removed by evaporation and the crude product was dried in vacuum. Conversion was determined via NMR measurements and spectral analysis. With DBU-catalyzed reactions, the product was purified by column chromatography.

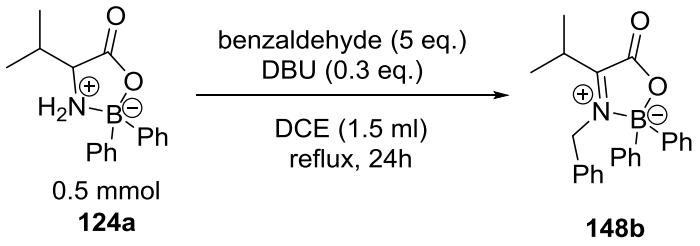
6.2.3 3-Benzylidene-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborolidin-5-one



Scheme 50: *The synthesis of aldimine **139a**.*

Triphenylphosphine (39 mg, 0.15 mmol, 0.3 eq.) was measured in an oven-dried round bottom flask. 1,2-Dichloroethane (1.5 ml), benzaldehyde (0.076 ml, 0.75 mmol, 1.5 eq.) and boroxazolidone **124a** (140 mg, 0.5 mmol, 1 eq.) were added under argon atmosphere while stirring and mixture was heated to 80 °C. After 24 hours, mixture was cooled down to room temperature and TLC showed a clear spots of product **148a** and starting material **124a**. The excess solvent was evaporated with rotavapor and the crude product was dried in vacuum. Cream colored solid, 12 % conversion. Appendix 5.

6.2.4 3-Benzyl-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborol-5(2*H*)-one

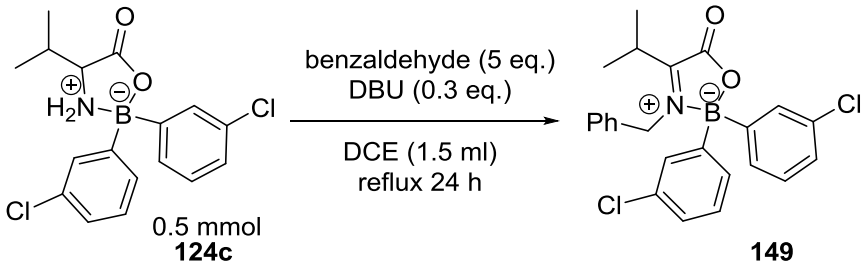


Scheme 51: *The synthesis of ketimine **148b.***

Boroxazolidone **124a** (140 mg, 0.5 mmol, 1 eq.) was measured in an oven-dried round bottom flask. 1.5 ml 1,2-dichloroethane was added while stirring under argon. Benzaldehyde (255 µl, 2.5 mmol, 5 eq.) and DBU (22 µl, 0.15 mmol, 0.3 eq.) were added dropwise through rubber septum and mixture was heated to reflux. After 24 hours, reaction was cooled down to room temperature and TLC showed strong spot of product **148b**. Excess solvent was evaporated with rotavapor and crude product was left

to dry in vacuum. The product was purified by column chromatography using ethyl acetate/hexane (2:8) as eluent. Cream colored solid (114.0 mg, 62 % yield); ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 7.40 - 7.52 (m, 4 H), 7.28 - 7.40 (m, 7 H), 7.05 - 7.22 (m, 3 H), 6.49 (d, *J*=7.03 Hz, 2 H), 5.00 (s, 2 H), 2.98 (quin, *J*=6.88 Hz, 1 H), 1.25 (d, *J*=6.74 Hz, 6 H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ ppm 175.78 (s), 162.77 (s), 133.84 (s), 133.09 (s), 129.20 (s), 128.60 (s), 128.24 (s), 128.01 (s), 127.28 (s), 52.08 (s), 30.20 (s), 17.94 (s). Appendix 6 and 7.

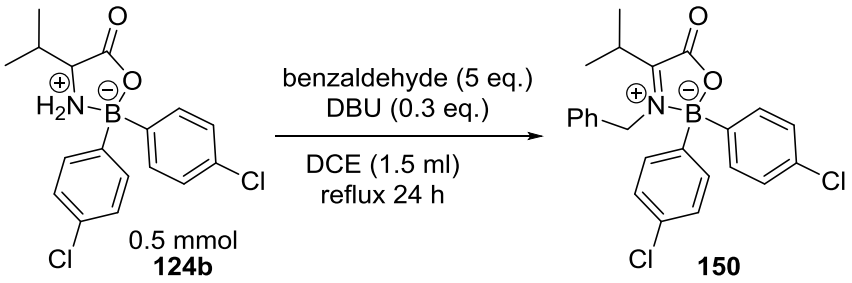
6.2.5 3-benzyl-2,2-bis(3-chlorophenyl)-4-isopropyl-1,3λ^4,2λ^4-oxazaborol-5(2*H*)-one



Scheme 52: *Preparation of ketimine **149**.*

Boroxazolidone **124c** (175 mg, 0.5 mmol, 1 eq.) was measured in an oven-dried round bottom flask. 1.5 ml 1,2-dichloroethane was added while stirring under argon. Benzaldehyde (255 µl, 2.5 mmol, 5 eq.) and DBU (22 µl, 0.15 mmol, 0.3 eq.) were added and the mixture was heated to reflux. After 24 hours, after cooling down, TLC was performed. A clear spot of product **149** was observed in the TLC plate. Excess solvent was evaporated with rotavapor and crude product was left to dry in vacuum. The product was purified by column chromatography using ethyl acetate/hexane (2:8) as eluent. Cream colored solid (139.6 mg, 64 % yield); ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 7.05 - 7.37 (m, 12 H (correct 11 H, peak overlapping with $CDCl_3$)), 6.51 (d, *J*=7.32 Hz, 2 H), 4.97 (s, 2 H), 2.98 (dt, *J*=13.62, 6.66 Hz, 1 H), 1.15 - 1.34 (m, 6 H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ ppm 176.71 (s), 162.18 (s), 134.36 (s), 133.09 (s), 132.57 (s), 130.85 (s), 129.67 (s), 129.22 (s), 128.73 (s), 128.15 (s), 127.00 (s), 52.00 (s), 30.12 (s), 17.97 (s). Appendices 8 and 9.

6.2.6 3-benzyl-2,2-bis(4-chlorophenyl)-4-isopropyl-1,3λ^4,2λ^4-oxazaborol-5(2*H*)-one



Scheme 53: *Preparation of ketimine* ***150****.*

Boroxazolidone **124b** (175 mg, 0.5 mmol, 1 eq.) was measured in an oven-dried round bottom flask and system was put under argon atmosphere. 1.5 ml 1,2-dichloroethane was added while stirring. Benzaldehyde (255 µl, 2.5 mmol, 5 eq.) and DBU (22 µl, 0.15 mmol, 0.3 eq.) were added dropwise through rubber septum and mixture was heated to reflux. After 24 hours, reaction was cooled down to room temperature and TLC showed clear spot of product **150** and a faint trace of other unknown product **151**. Excess solvent was evaporated with rotavapor and crude product was left drying in vacuum. The product was purified by column chromatography using ethyl acetate/hexane (2:8) as eluent. Two compounds were isolated: **150**: Cream colored solid (95.5 mg, 44 % yield); ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 7.13 (d, *J*=3.81 Hz, 6 H), 7.08 - 7.24 (m, 2 H), 6.93 - 7.08 (m, 3 H), 6.40 (d, *J*=7.03 Hz, 2 H), 4.85 (s, 2 H), 2.87 (quin, *J*=6.81 Hz, 1 H), 1.11 (d, *J*=6.74 Hz, 6 H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ ppm 176.50 (s, 1 C), 162.35 (s, 1 C), 134.33 (s, 1 C), 134.28 (s, 1 C), 133.24 (s, 1 C), 129.37 (s, 1 C), 128.84 (s, 1 C), 128.43 (s, 1 C), 127.03 (s, 1 C), 52.04 (s, 1 C), 30.26 (s, 1 C), 18.01 (s, 1 C) Appendices 10 and 11. **151**: viscous material (14.7 mg, 7 % yield) ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 7.32 - 7.42 (m, 3 H), 7.19 - 7.32 (m, 6 H), 7.09 (dd, *J*=6.44, 2.93 Hz, 2 H), 6.84 - 7.03 (m, 2 H), 5.36 (d, *J*=14.06 Hz, 1 H), 4.21 (s, 1 H), 3.67 (d, *J*=14.35 Hz, 1 H), 2.11 (s, 4 H), 1.23 (d, *J*=7.03 Hz, 1 H), 1.14 (s, 3 H), 0.66 (s, 3 H); ^{13}C NMR (75 MHz, *CDCl$_3$*) δ ppm 203.89 (s, 1 C), 159.84 (s, 1 C), 135.83 (s, 1 C), 134.61 (s, 1 C), 134.33 (s, 1 C), 134.01 (s, 1 C), 133.09 (s, 1 C), 129.52 (s, 1 C), 129.37 (s, 1 C), 129.20 (s, 1 C), 129.12 (s, 1 C), 128.59 (s, 1 C), 128.48 (s, 1 C), 128.42 (s, 1 C), 128.35 (s, 1 C), 127.77 (s, 1 C), 127.03 (s, 1 C), 126.62 (s, 1 C), 68.01 (s, 1 C), 46.27 (s, 1 C), 45.83 (s, 1 C), 26.38 (s, 1 C), 20.15 (s, 1 C), 18.00 (s, 1 C). Appendices 12−16.

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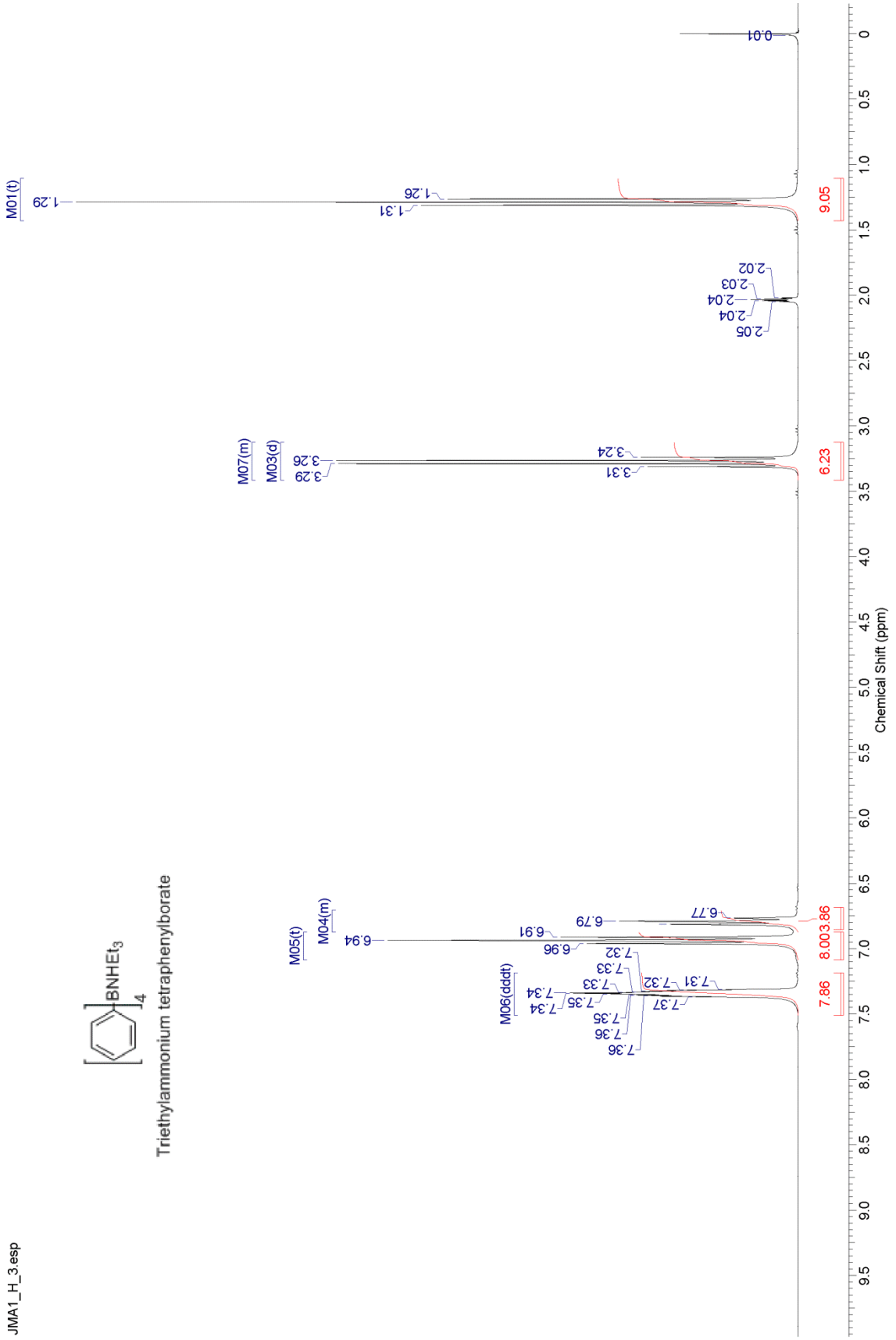
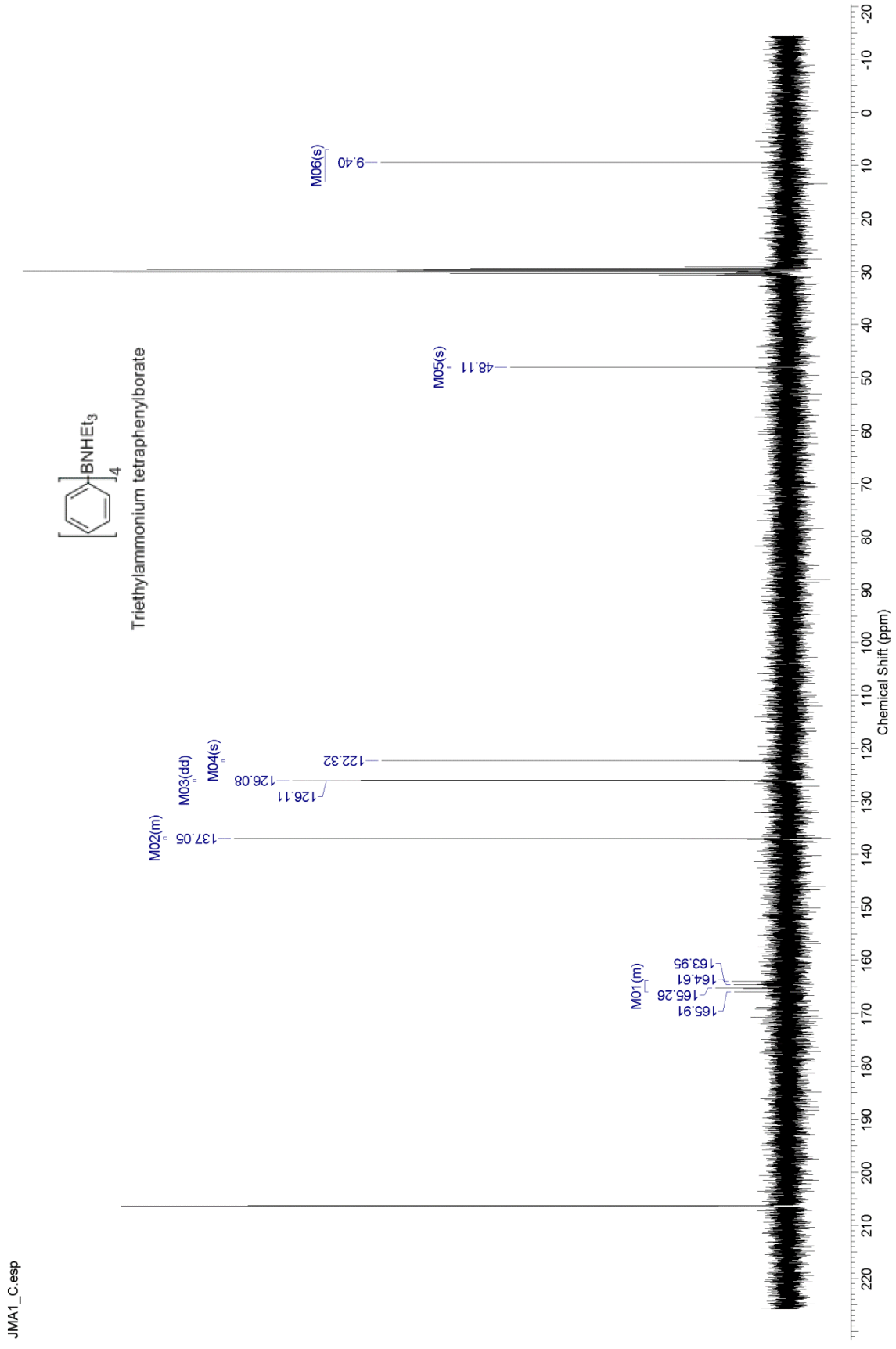
APPENDICES

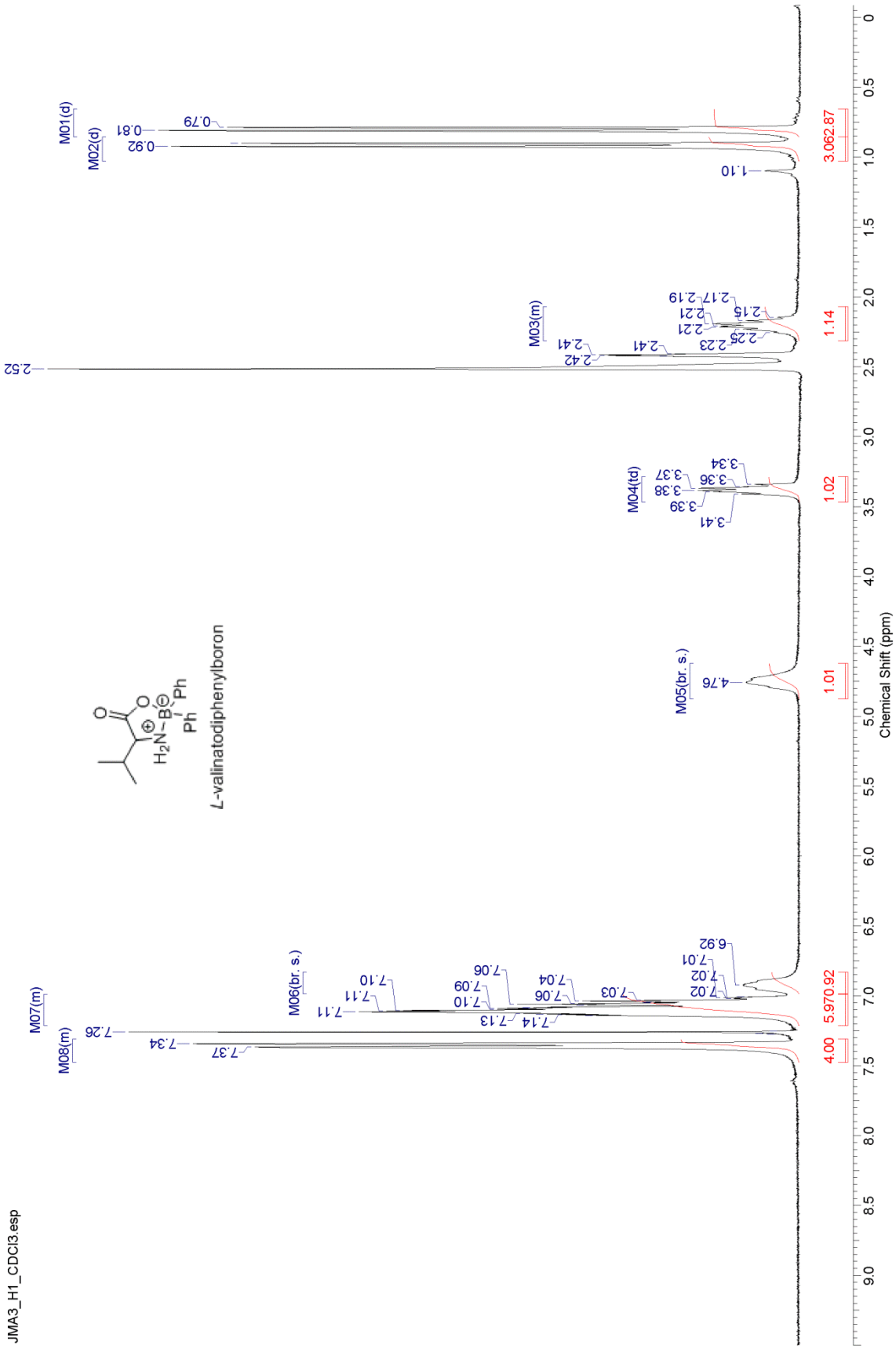
Appendix 1. ^{1}H NMR for compound 79a



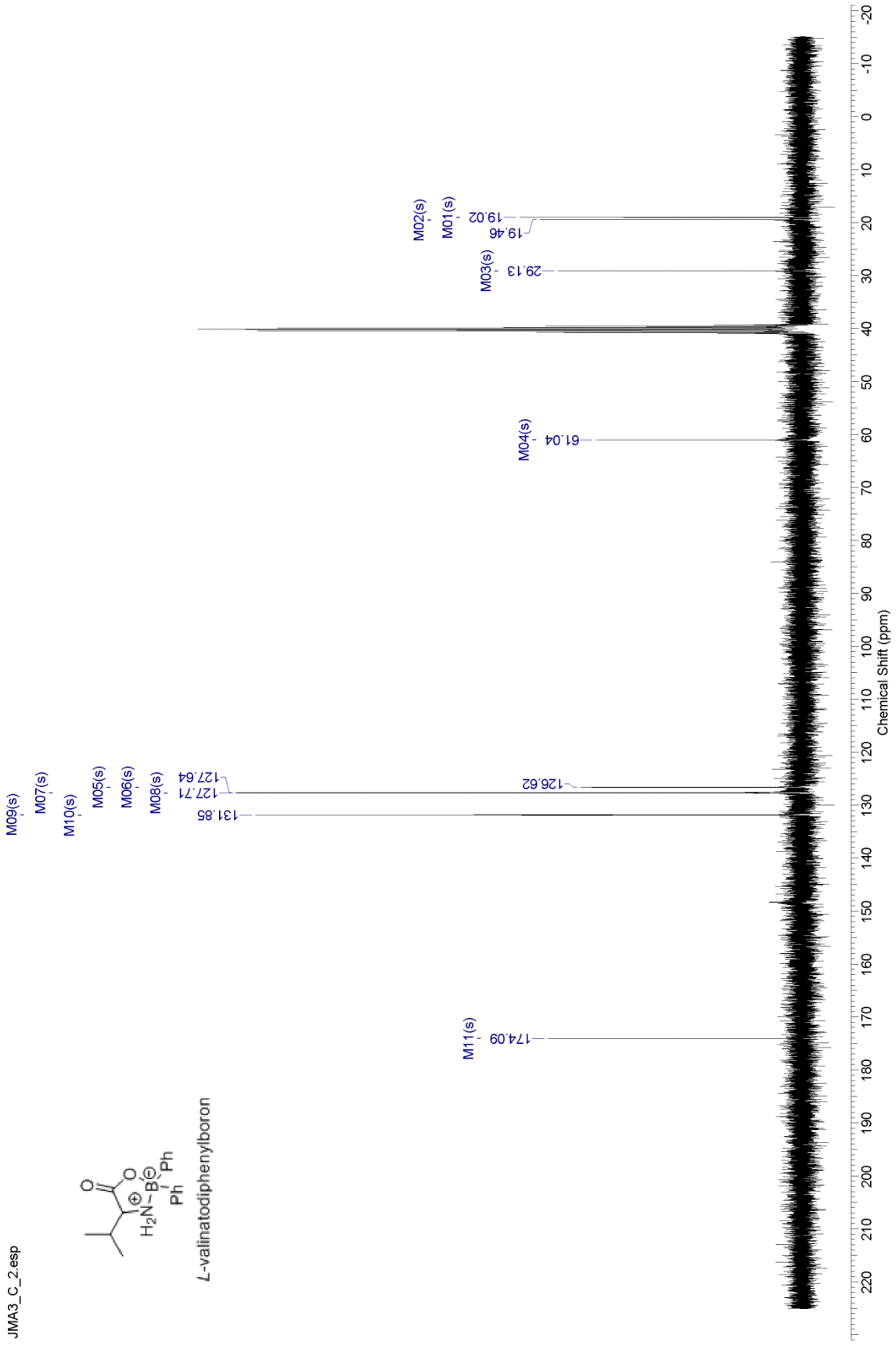
Appendix 2. ^{13}C NMR for compound 79a



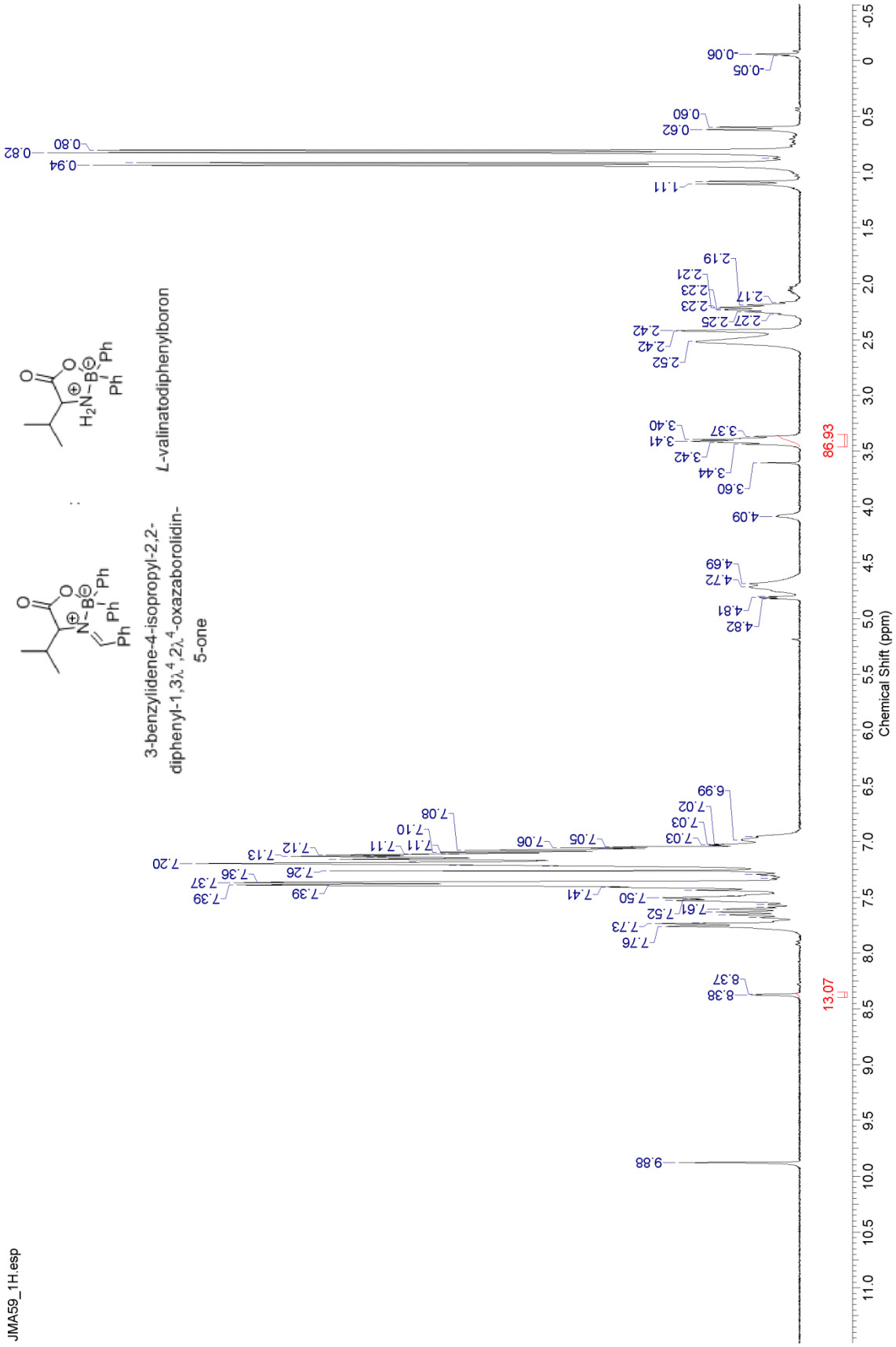
Appendix 3. ^{1}H NMR for compound 124a



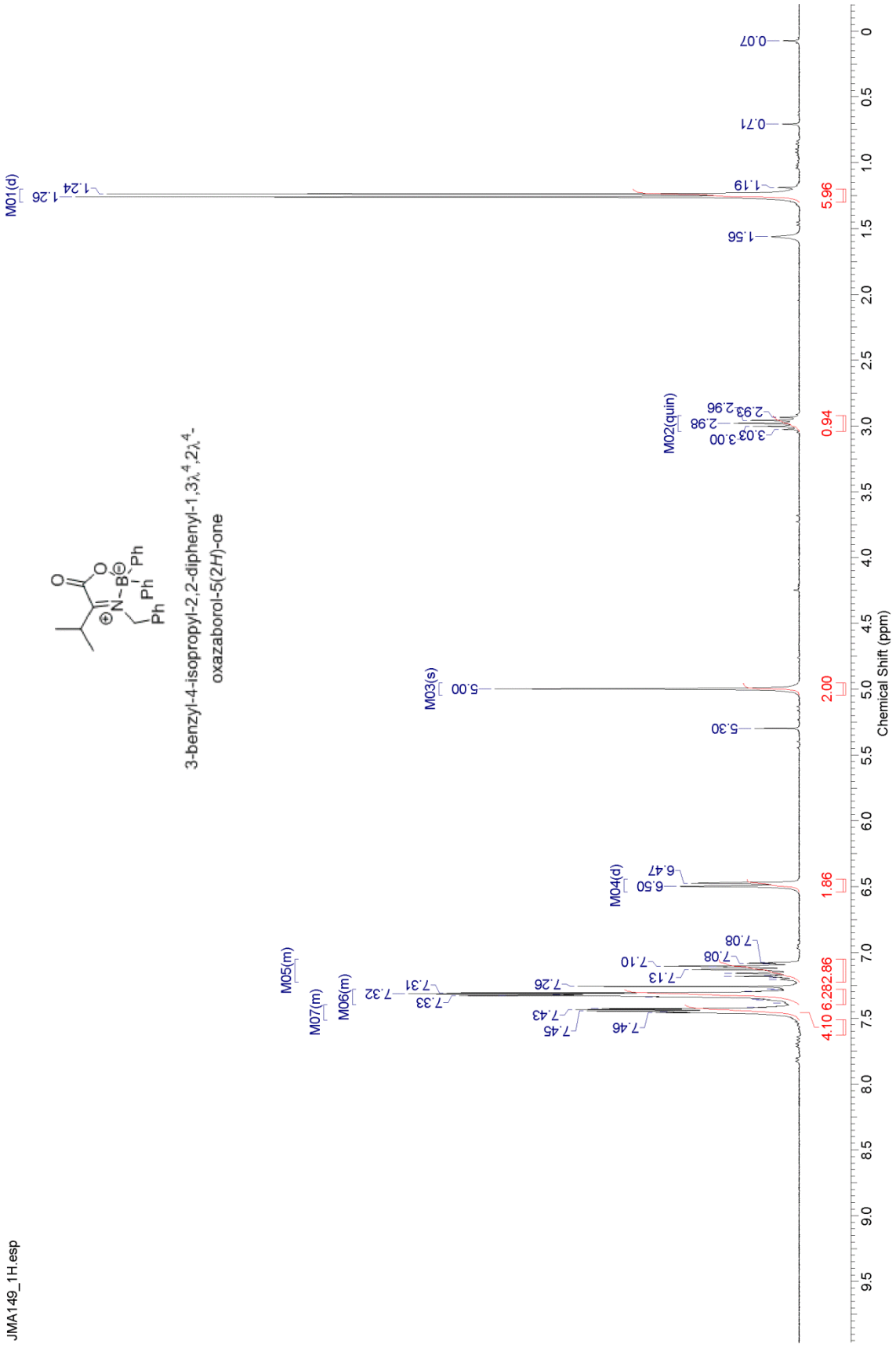
Appendix 4. ^{13}C NMR for compound 124a



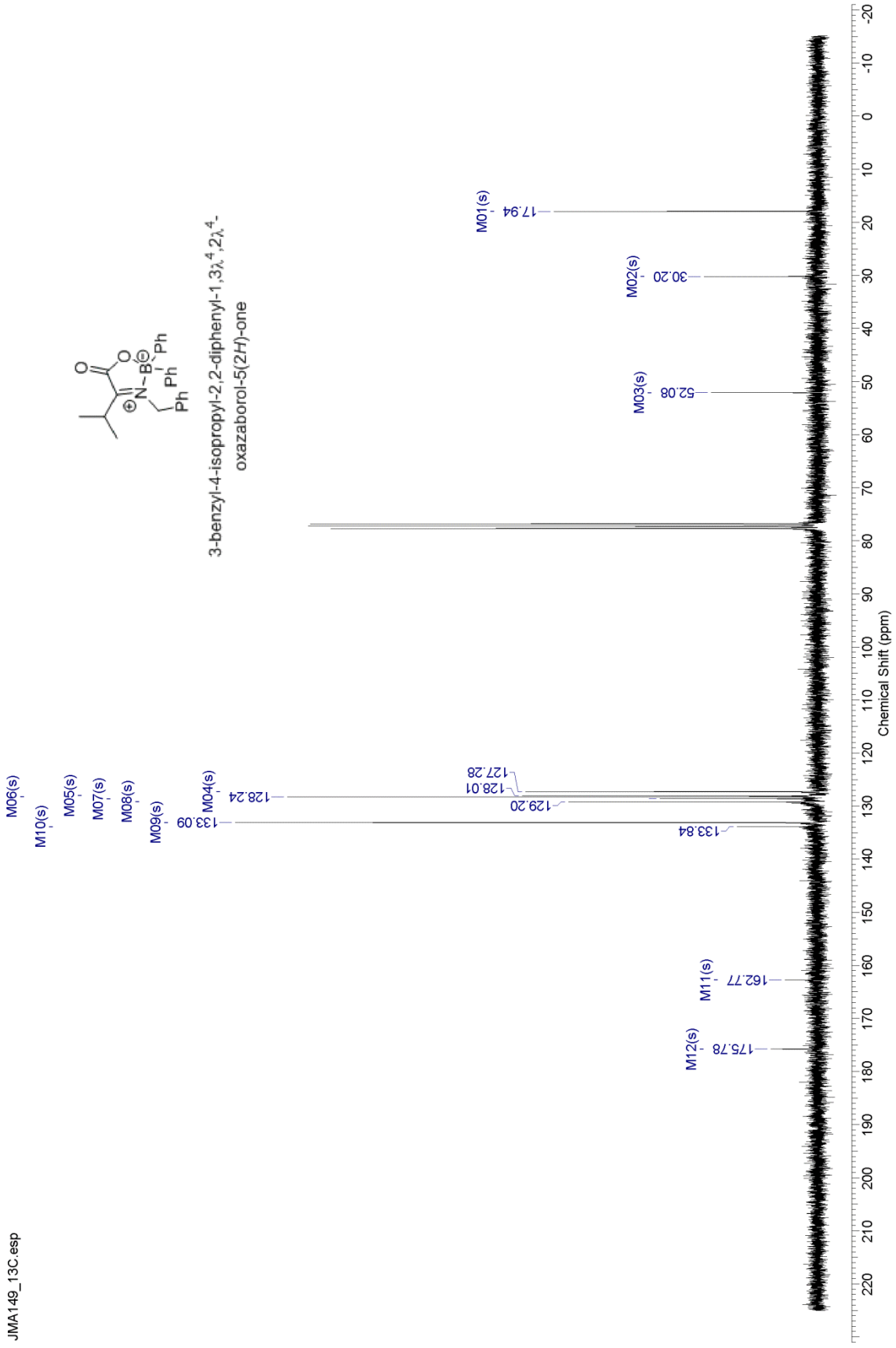
Appendix 5. ^{1}H NMR for crude product 148a:124a



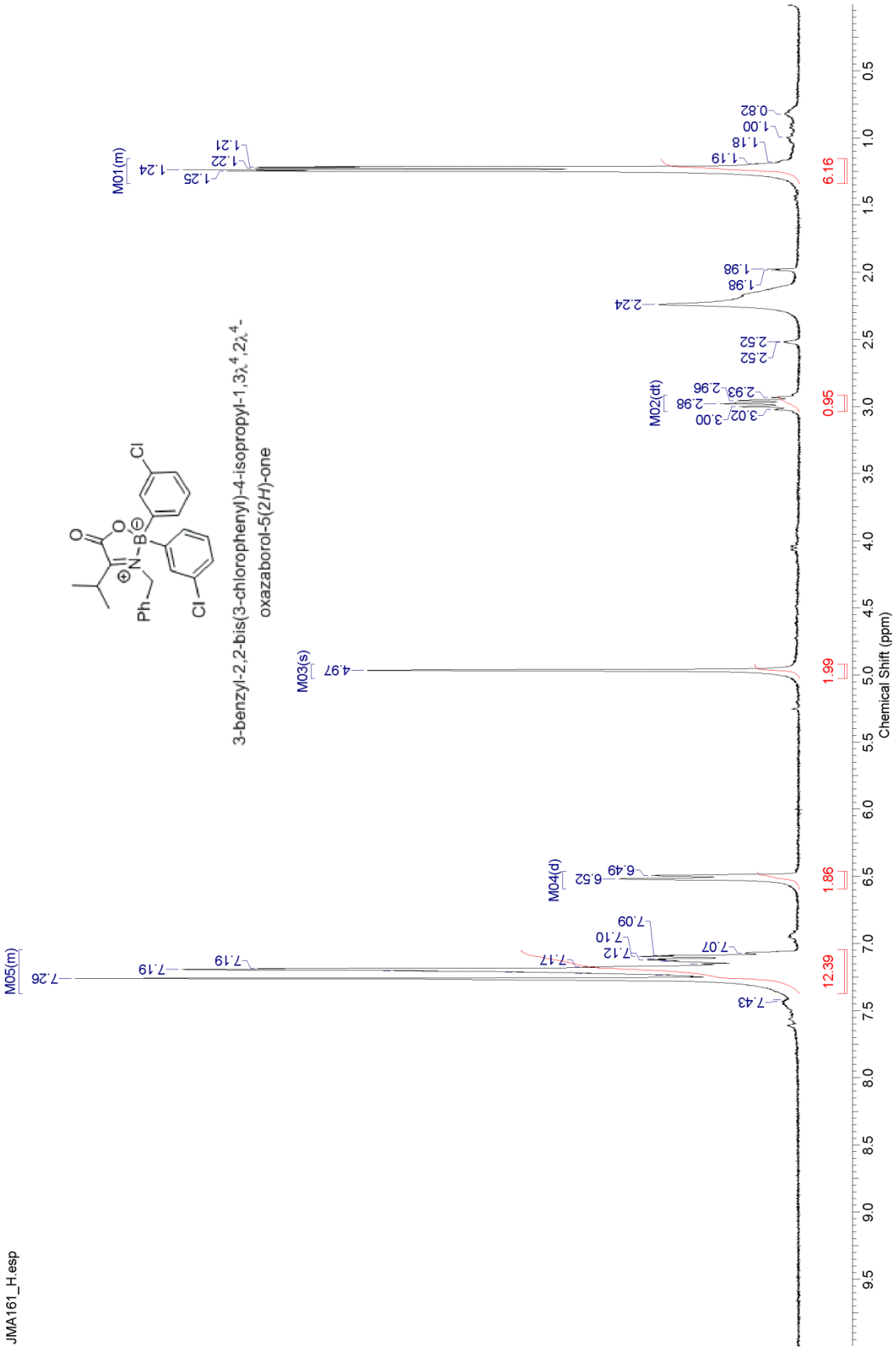
Appendix 6. ^{1}H NMR for compound 148b



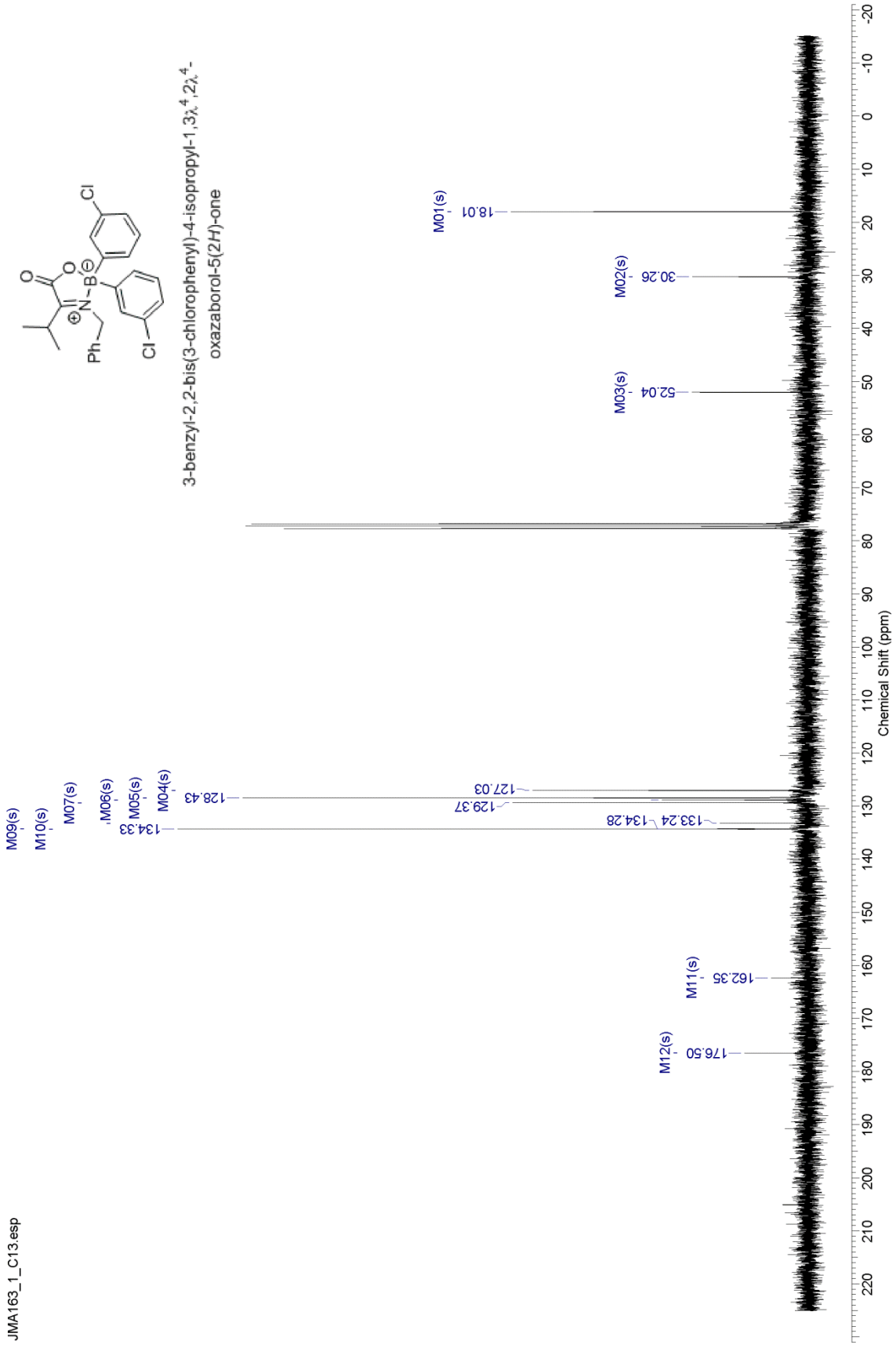
Appendix 7. ^{13}C NMR for compound 148b



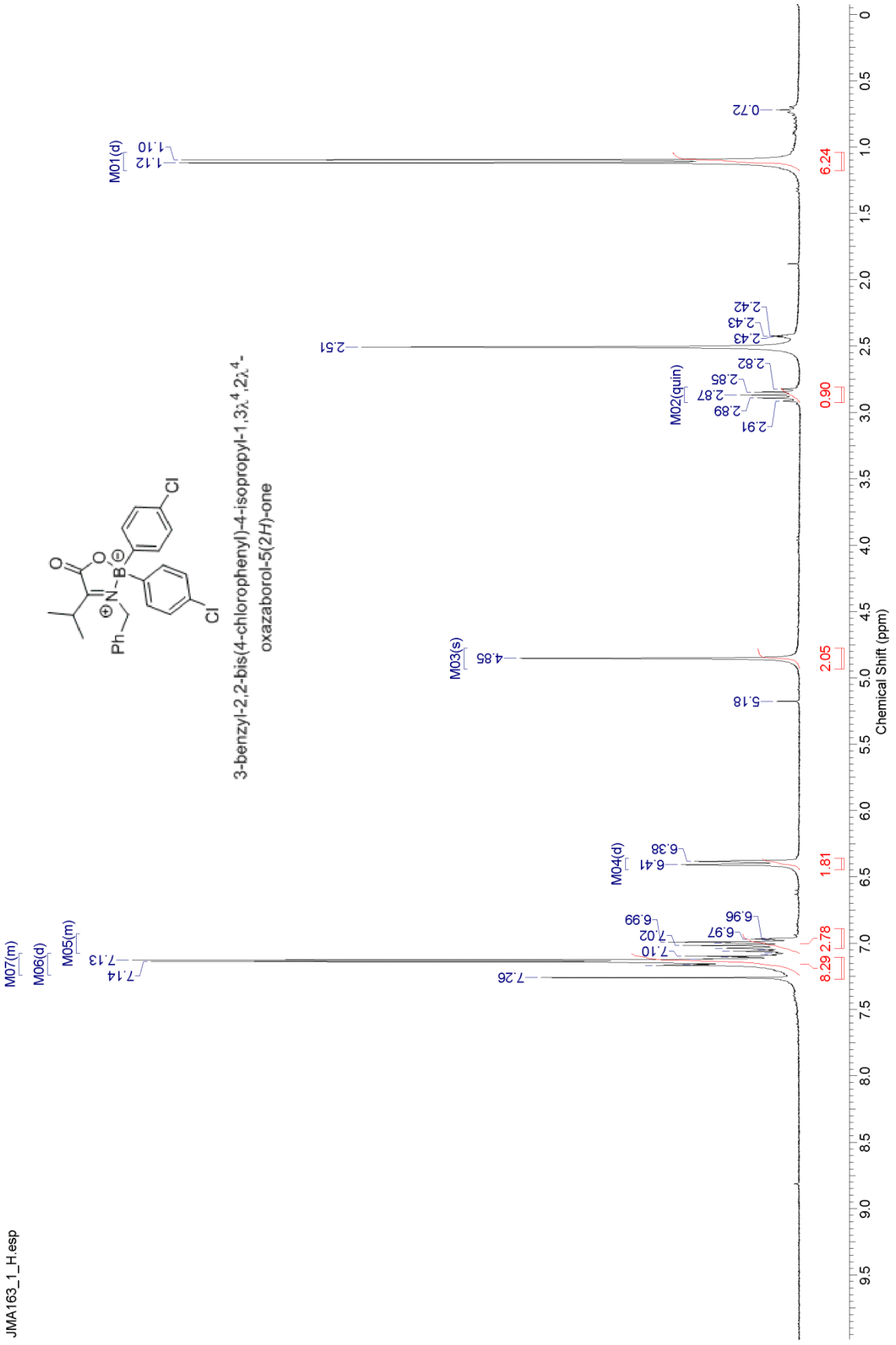
Appendix 8. ^{1}H NMR for compound 149



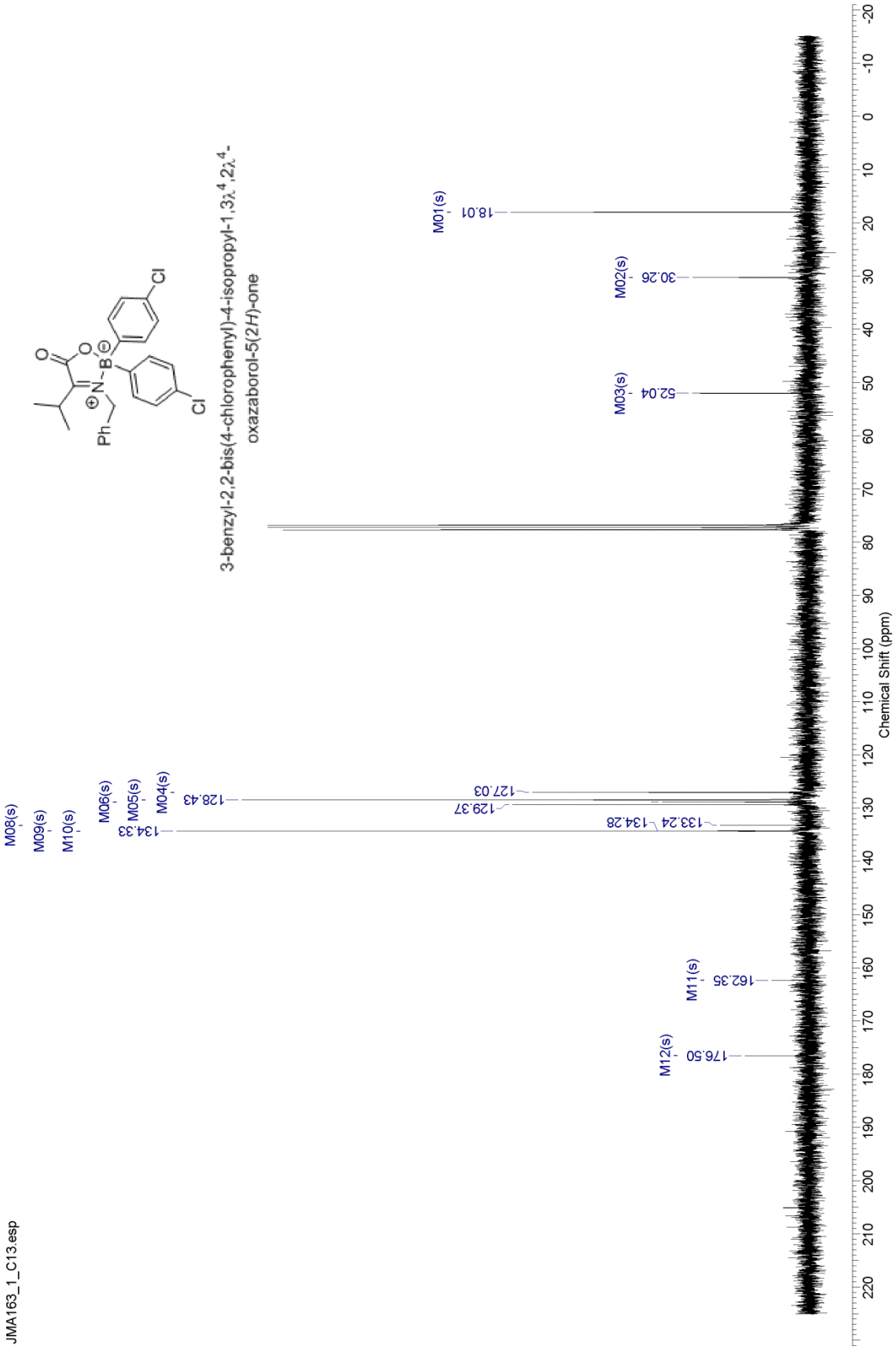
Appendix 9. ^{13}C NMR for compound 149



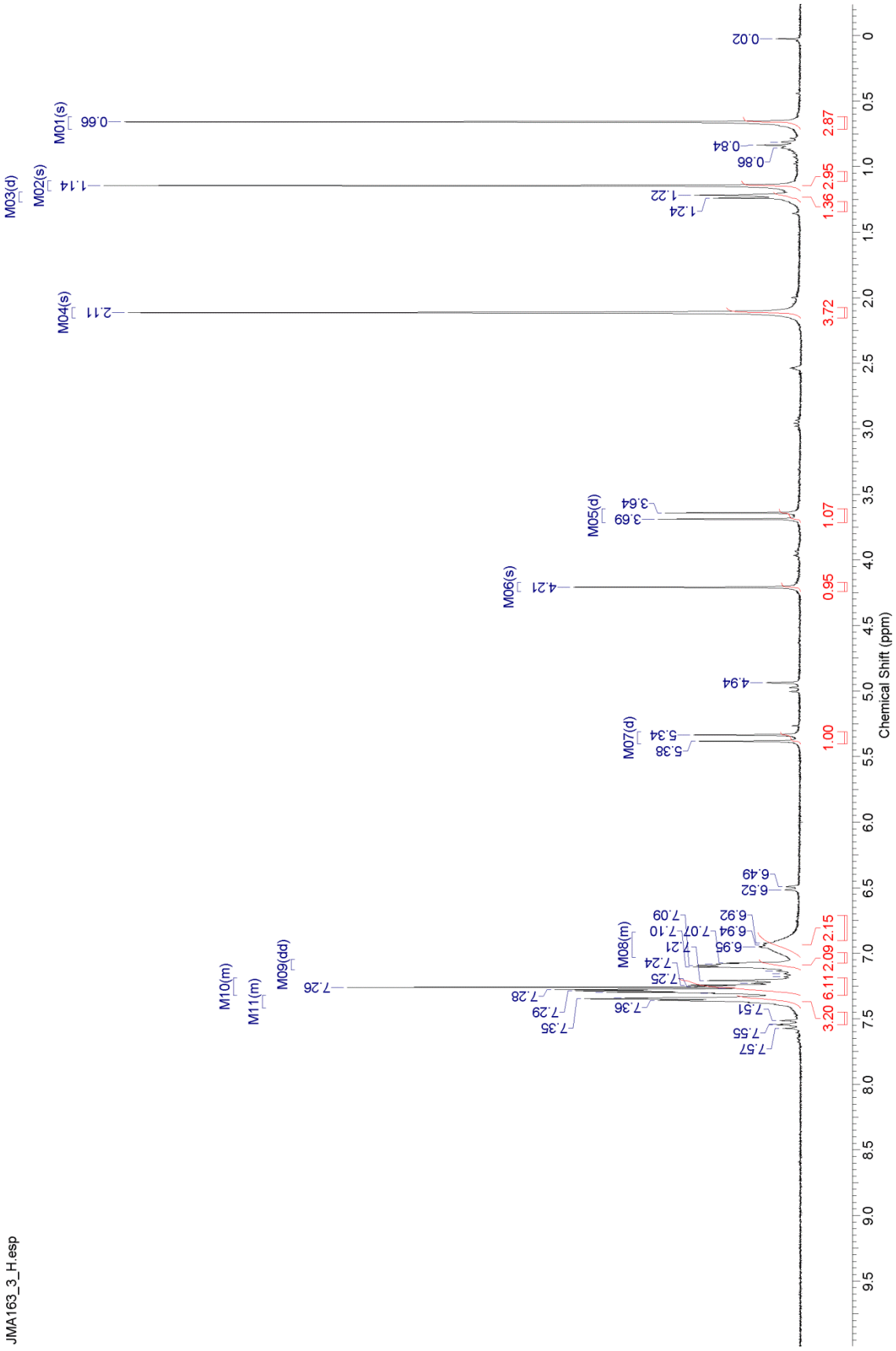
Appendix 10. ^{1}H NMR for compound 150



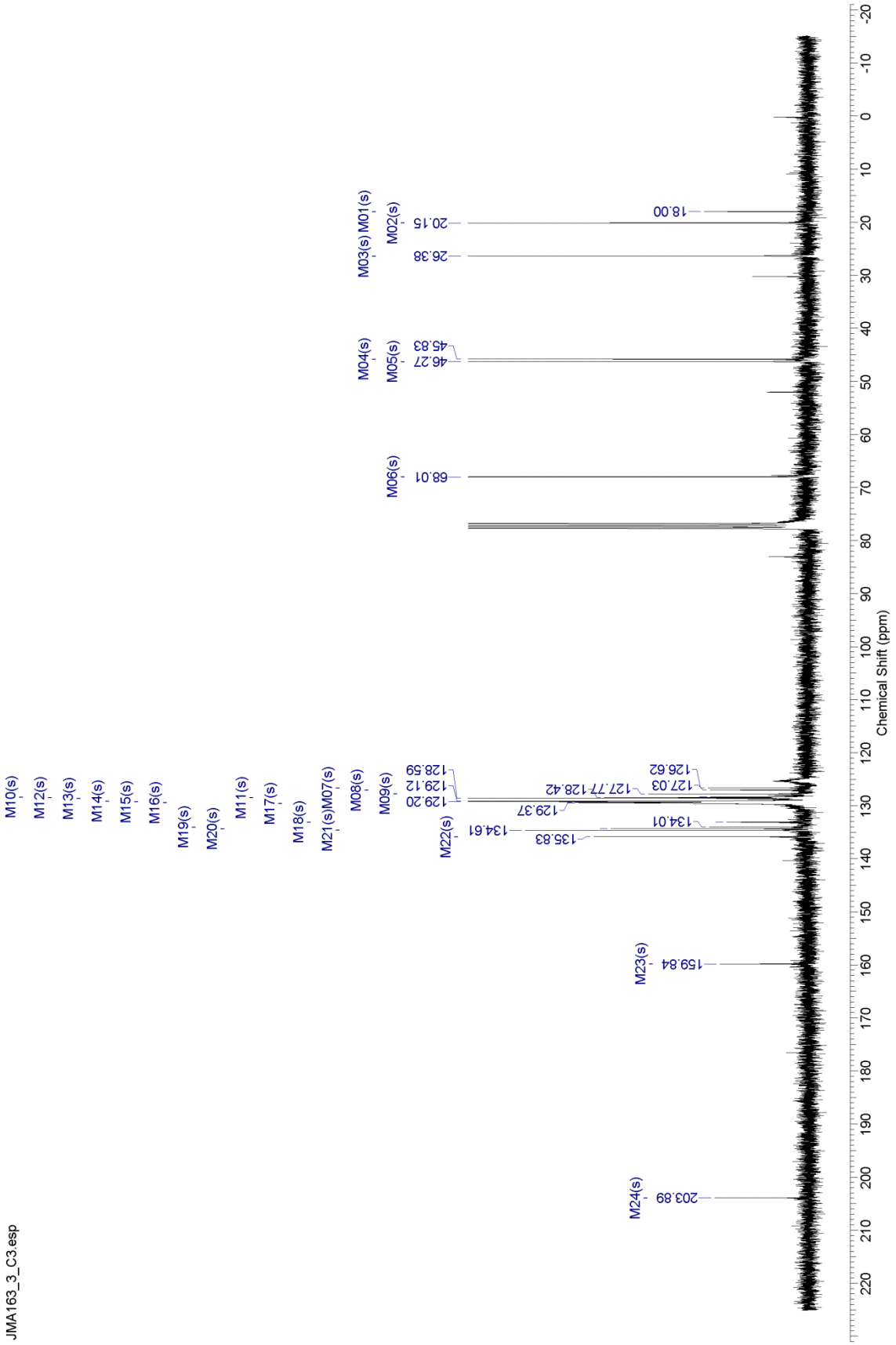
Appendix 11. ^{13}C NMR for compound 150



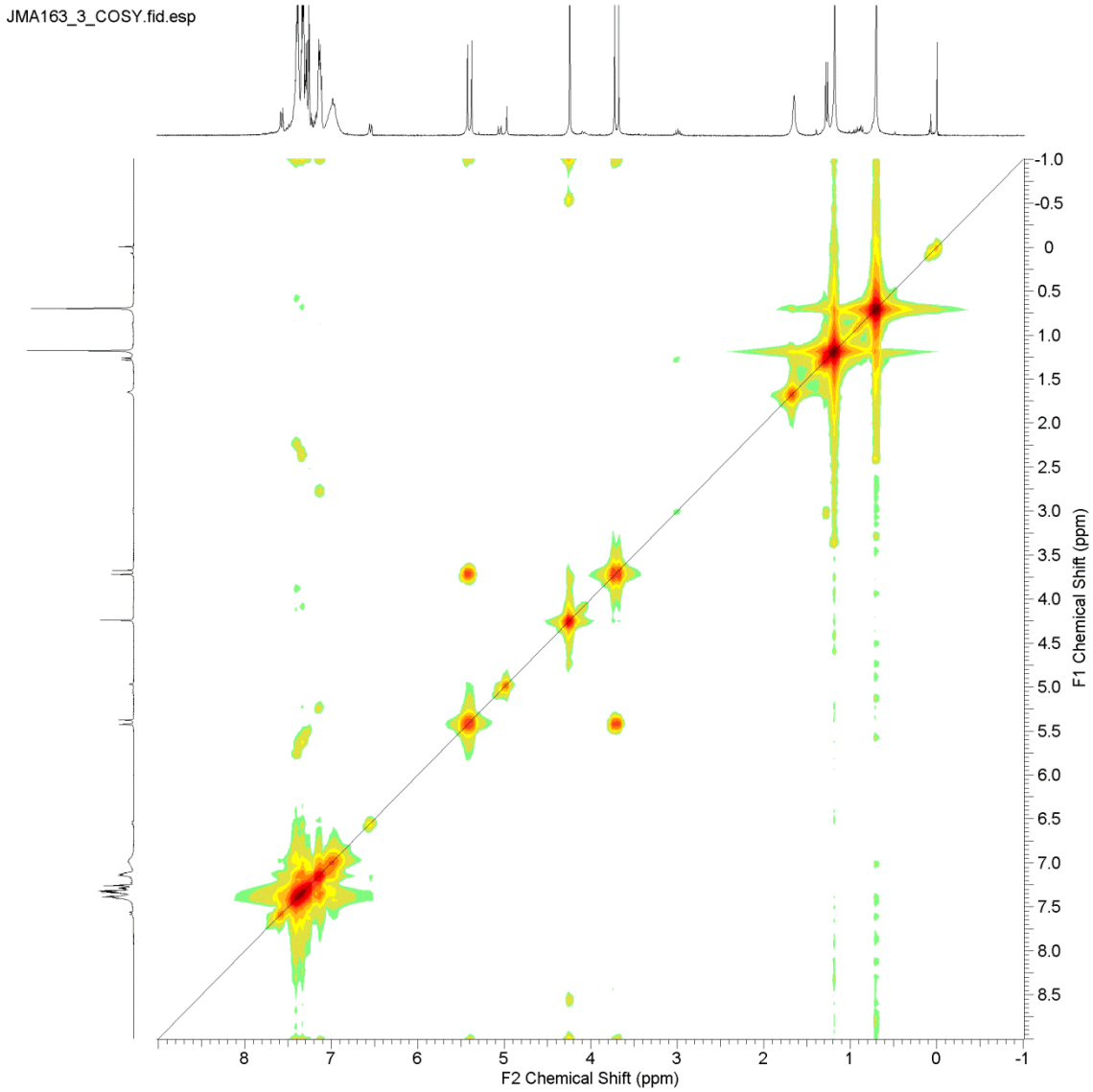
Appendix 12. ^{1}H NMR for compound 151



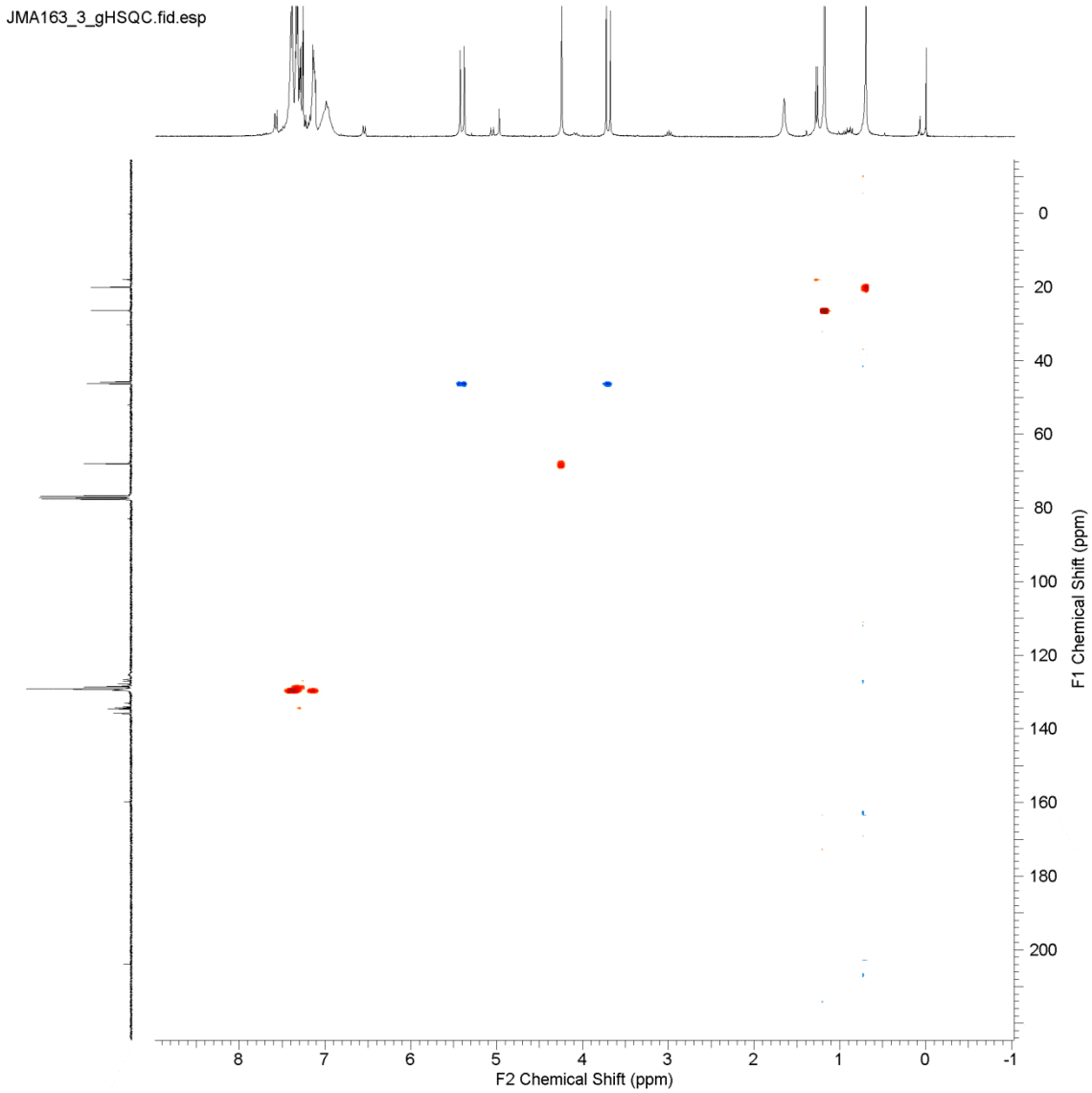
Appendix 13. ^{13}C NMR for compound 151



Appendix 14. COSY NMR for compound 151



Appendix 15. HSQC NMR for compound 151



Appendix 16. HMBC NMR for compound 151