# Studies towards the Stereoselective Electrophilic Amination of Carbanions

**by**

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**Dissertation submitted to the**
**Faculty of Chemistry, University of Bielefeld**
**for partial fulfillment of the requirements for the degree of**
***Doctor rerum naturalium*** **(Dr. rer. nat.) in Chemistry**

**Bielefeld 2002**

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**Dissertation of the Doctoral Thesis: 28th August 2002**

*To my parents*

## Acknowledgments

First of all, I would like to express my deepest gratitude to Prof. Dr. Norbert Sewald for giving me the opportunity to work in his laboratory, for his support and encouragement, for his guidance and numerous discussions we had during these years.

I would like to thank my former and present colleagues from our research group for providing a friendly and academically excellent environment. Special thanks are going to Miriam Hagenstein, Dr. Katherina Stembera, Kai Jensen and Micha Jost for their excellent help in proofreading the manuscript. Furthermore, I express my gratitude towards Miriam Hagenstein and Nadine Herrmann for their excellent research work during the practical training in our laboratory.

I would like to thank the research group of Prof. Dr. Jochen Mattay for the GC-MS analyses, Dr. Matthias Letzel and Eckhard Westermeier for the recording of the mass spectra, Gerd Lipinski and Peter Mester for the NMR measurements and Mrs. B. Michel for the elemental analyses.

Special thanks are going to Prof. Dr. Klaus Burger, to his research group and to the members of the Faculty of Chemistry for providing such a friendly and supportive environment during my stay in Leipzig.

I would like to acknowledge the Graduiertenkolleg "Mechanisms and Applications of Non-Conventional Oxidation Reactions" from the University of Leipzig for the fellowship granted during my first year as doctoral student.

Special thanks are going to Prof. Dr. Ioan Silaghi-Dumitrescu (Department of Chemistry, "Babes-Bolyai" University, Cluj-Napoca, Romania) for the computational studies presented here and for the helpful discussions about Computational Chemistry we had during last years.

Very special gratitude is expressed to Dr. Cosmina Avram, for she was a caring and supportive friend.

I would like to thank Camelia Neamtu, Gabriela Nagy, Dr. Peter Glueck, Dr. Emanoil Surducan and Ing. Vasile Surducan, my former colleagues from the National Institute for Research and Development of Isotopic and Molecular Technologies (Cluj-Napoca, Romania), for their support and friendship.

A large group of friends from Germany and especially from Romania were my home away from home and helped me tremendously through these years.

Near or far, an infinite confidence and support I found in my family.

## Abbreviations

| | | |
|---|---|---|
| δ | - | chemical shift (NMR) |
| $\tilde{\nu}$ | - | Wave number (IR) |
| Ac | - | Acetyl |
| arom. | - | aromatic |
| Bn | - | Benzyl |
| Boc | - | *tert*-Butyloxycarbonyl |
| br. | - | broad (NMR) |
| $^t$Bu | - | *tert*-Butyl |
| BuLi | - | Butyl lithium |
| CI | - | Chemical Ionisation (MS) |
| *m*-CPBA | - | *meta*-Chlorobenzoic acid |
| Cy | - | Cyclohexyl |
| d | - | Doublet (NMR) |
| d.e. | - | diastereomeric excess |
| d.r. | - | diastereomeric ratio |
| DCM | - | Dichloromethane |
| DMAP | - | 4-*N,N*-Dimethylaminopyridine |
| DMF | - | Dimethylformamide |
| DMSO | - | Dimethylsulfoxide |
| e.e. | - | enantiomeric excess |
| EI | - | Electron Impact Ionisation (MS) |
| e.r. | - | enantiomeric ratio |
| Et | - | Ethyl |
| GC | - | Gas chromatography |
| h | - | Hour(s) |
| HMPA | - | Hexamethylphosphorous triamide |
| Hz | - | Hertz (NMR) |
| IR | - | Infrared (-spectroscopy) |
| *J* | - | Coupling constant (NMR) |
| LDA | - | Lithium diisopropylamide |
| LiHMDS | - | Lithium hexamethyldisilazanide |
| KHMDS | - | Potassium hexamethyldisilazanide |
| m | - | Multiplet |

| | | |
|---|---|---|
| M | - | Metal; Molarity |
| Me | - | Methyl |
| Mes | - | Mesityl (2,4,6-trimethylphenyl) |
| MHz | - | Megahertz (NMR) |
| min | - | Minute(s) |
| Moc | - | Methyloxycarbonyl |
| MS | - | Mass Spectrometry |
| NBS | - | *N*-Bromosuccinimide |
| NMP | - | *N*-Methyl-2-pyrrolidinone |
| NMR | - | Nuclear Magnetic Resonance |
| NOE | - | Nuclear-Overhauser-Effect |
| PE | - | Petrolether |
| PG | - | Protecting group |
| Ph | - | Phenyl |
| ppm | - | parts per million (NMR) |
| $^{i}$Pr | - | *iso*-Propyl |
| q | - | Quartet (NMR) |
| $R_f$ | - | Retention factor |
| RT | - | Room temperature |
| s | - | Singlet (NMR) |
| t | - | Triplet (NMR) |
| TBAF | - | Tetrabutylammonium fluoride |
| TBDMS | - | *tert*-Butyldimethylsilyl |
| TEA | - | Triethylamine |
| TFA | - | Trifluoroacetic acid |
| THF | - | Tetrahydrofurane |
| TMEDA | - | Tetrametylethylenediamine |
| TMS | - | Tetramethylsilane |
| TMSCl | - | Trimethylsilyl chloride |
| Ref. | - | Reference |
| $t_R$ | - | Retention time |
| TLC | - | Thin Layer Chromatography |
| Ts | - | Tosyl |
| p-Tol | - | *para*-Tolyl |

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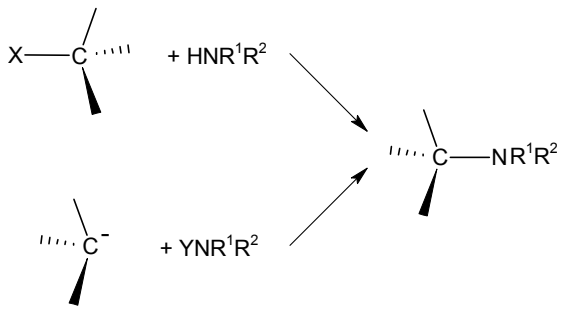
# 1. General Part

## 1.1 Introduction

The importance and practicability of amination reactions as a tool for obtaining target compounds is nowadays fully acknowledged by chemists in synthetic organic, medicinal, agricultural and natural product chemistry, as well by the pharmaceutical and agricultural industries. A rapid development of novel and more efficient amination methods has been recorded during the past decade, mostly regarding the electrophilic amination. This method provides a great improvement with respect to the classical methods such as those based on the attack of a nucleophilic nitrogen atom to an electrophilic carbon, which are hampered by the difficult access to the electrophilic precursors – particularly when multifunctional derivatives are taken into consideration – and by the frequently recurring difficult reaction conditions.[1] Among the compounds most frequently synthesized by electrophilic amination, α-amino acids, α-amino ketones and allyl amines play a prominent part. Their stereoselective synthesis has been intensively studied, and became an especially challenging testing ground for methods in asymmetric synthesis.[2]

## 1.2 Electrophilic Amination

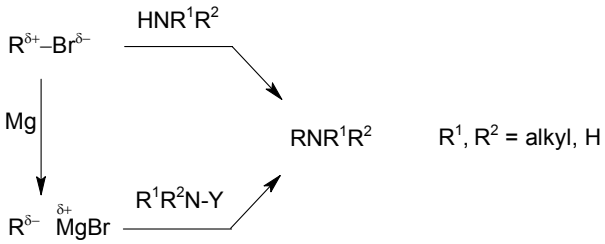
Carbon-nitrogen bonds are often formed by attack of a nucleophilic nitrogen atom to an electrophilic carbon bearing a leaving group via $S_N2$ type reaction. The reverse process, the electrophilic amination, in which a carbon nucleophile is replacing a leaving group on electrophilic nitrogen, has received increasing attention (Scheme 1).




**Scheme 1:** General methodology for the formation of carbon-nitrogen bonds.

The introduction of an amino group into organometallic compounds constitutes an example for the "umpolung" methodology for the direct formation of C-N bonds. Thus, an alternative approach to amination that involves the reaction of an electrophilic alkyl halide with ammonia or

amines is the conversion of the halide into a nucleophilic species, namely the corresponding Grignard or organolithium reagent, and its subsequent reaction with the $R^1R^2N$-Y derivative (Scheme 2).[3]




**Scheme 2:** "Umpolung" methodology for the direct formation of carbon-nitrogen bonds.

The species R-Br and R-MgBr may be considered as suppliers of [$R^{\delta+}$] and [$R^{\delta-}$], respectively, where $HNR^1R^2$ and $R^1R^2N$-Y are [$^{\delta-}NR^1R^2$] and [$^{\delta+}NR^1R^2$] synthons.

The electrophilic amination reaction enables the transfer of amino or substituted amino groups from various amination reagents into different nucleophiles. The most interesting feature of electrophilic amination reagents of the type $R^1R^2N$-Y is the attachment of a good leaving group Y to the $R^1R^2N$ group. The leaving group Y is displaced by the nucleophile during the amination process. Electrophilic reagents of the above type usually contain halogens or oxygen functions as the leaving group. *N*-Haloamines **1**, *O*-alkyl- **2**, *O*-aryl- **3**, *O*-acyl- **4**, *O*-sulfonyl- **5** and *O*-phosphinylhydroxylamines **6**, and hydroxylamine-*O*-sulfonic acid **7** are able to react directly with C nucleophiles (Figure 1). The reactions require nothing more than hydrolytic workup. Deprotonation of the amino group will occur competitively while electrophilic attack of the $H_2N^+$ group on the carbanion will be influenced by the leaving group ability of Y.

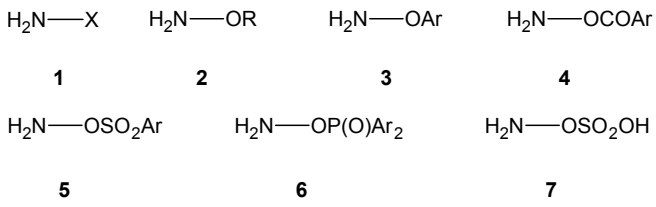



**Figure 1:** Examples of electrophilic amination reagents of the type $R^1R^2N$-Y.

Reagents **8 – 14** can also function as amino cation equivalent (Figure 2). Azides **8** react with Grignard and organolithium reagents to form triazene salts which are converted to the respective amines by either reductive or hydrolytic workup. Oximes **9** react with Grignard and organolithium reagents to produce imines which are hydrolyzed to amines. Reaction of enolates with arenediazonium salts **10** or dialkyl azodicarboxylates **11** furnishes α-hydrazono or α-hydrazido compounds, respectively, which are hydrogenated to α-amino compounds.

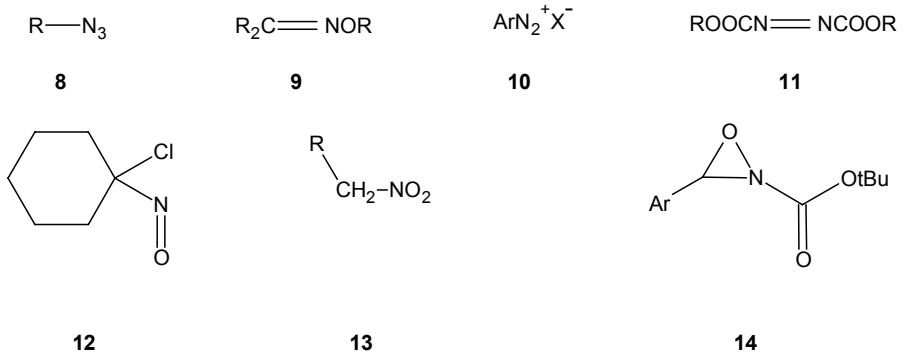



**Figure 2:** Examples of electrophilic amination reagents which function as amino cation sources.

α-Chloronitroso compound **12** and its analogues are well known dieno- and enophiles[4-7], which also form nitrone products with methyl- and phenylmagnesium halides or $Me_3Al$.[8-10] Their reactivity towards enolates has been mainly studied by Oppolzer *et al.*[11-13] Aliphatic nitro compounds **13** were also used as nitrogen sources.[14-22] *N*-Allylhydroxylamines result from 1,2-addition of allyl Grignard reagents to nitro compounds after hydrolysis of the intermediate nitrones. Finally, other electrophilic amination reagents should be mentioned such as the *N*-protected oxaziridines **14**, which transfer efficiently under mild conditions the *N*-protected fragment to *N*-nucleophiles but, however, give moderate yields with *C*-nucleophiles.[23-28]

### 1.2.1 Electrophilic Amination using Chiral Amination Reagents

Different examples of stereoselective electrophilic amination reactions, either in the presence of a chiral catalyst[29-32] or starting from substrates bearing a chiral center, have been reported in the literature.[1,33] In contrast, there are only few efficient methods for reagent-controlled stereoselective electrophilic amination.[1-3,27,33] Due to the higher availability of achiral nucleophilic substrates compared with chiral ones, the remarkable advantage offered by a stereoselective amination reagent can be easily envisioned. The following chapters present the "state of the art" in the field of electrophilic amination using chiral amination reagents.

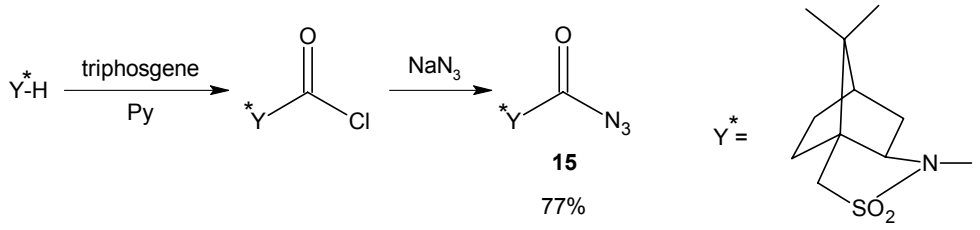
#### 1.2.1.1 Azides

Azides proved to be proficient reagents in electrophilic amination, especially when enolates were used as substrates.[33] Evans *et al.*[34] developed an optimized method starting from substrates bearing a chiral center, which allows the introduction of the [$NH_2^+$] synthon with high

stereoselectivity and high yields, and thus allows the stereoselective synthesis of a broad spectrum of amino acids. Following the optimized method developed by Evans, a range of enolates can be azidated in moderate to very good yields and diastereoselectivity: racemic α-hydroxyester enolates[34], chiral cyclic imide enolates[34], chiral lactone enolates[35] and chiral auxiliary-based enolates.[36]

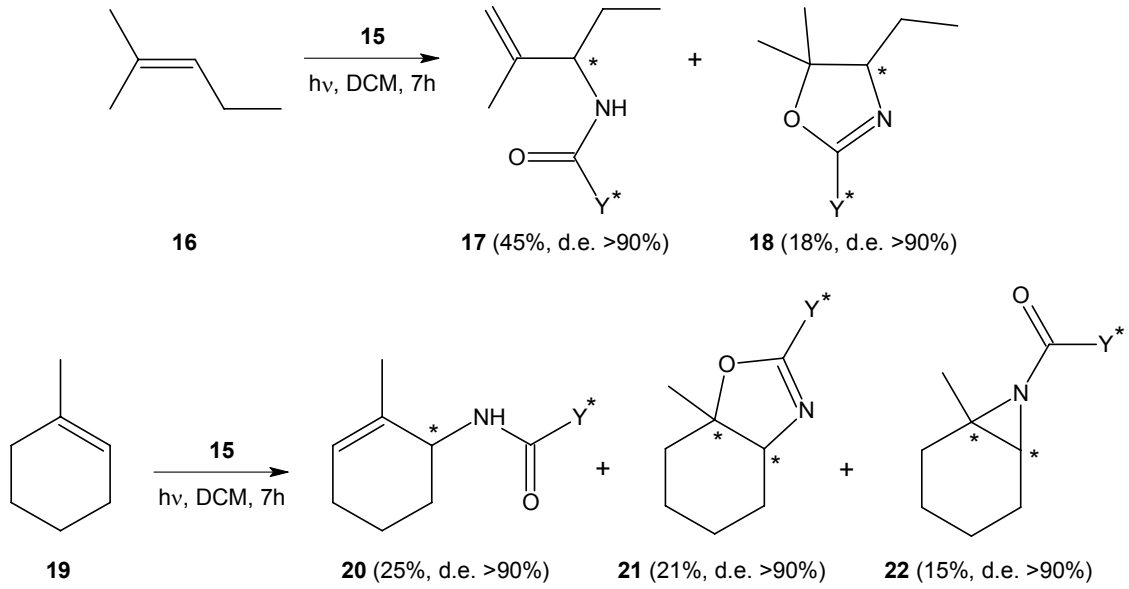
In the asymmetric azidation the chirality is mainly induced by the chiral auxiliary bound to the substrate. However, a process in which the chiral information is brought by the azidating reagent is demanding. Recently, Pellacani *et al.*[37] reported the synthesis of an optically active azidating reagent **15** and its use in electrophilic amination of alkenes and masked ketones.

The carbamoyl azide **15** is prepared in 77% overall yield from Oppolzer's sultam[38-40] via reaction with triphosgene and sodium azide (Scheme 3).



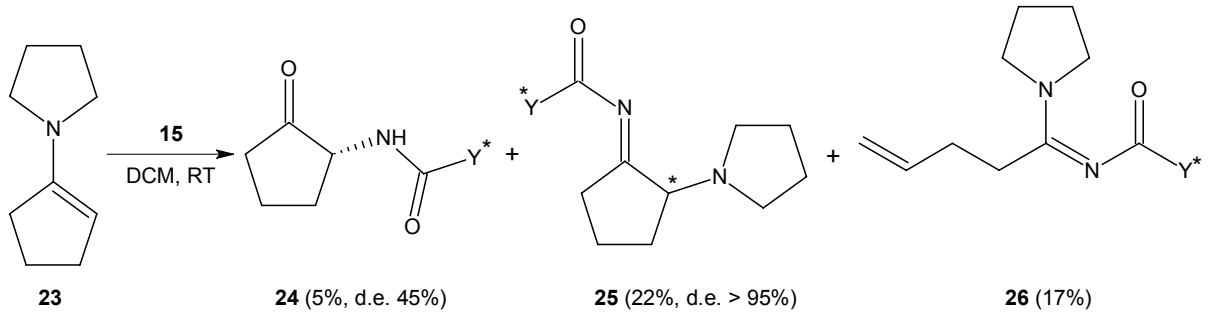

**Scheme 3:** Synthesis of the optically active azidating reagent **15**.

The authors[37] reported the thermal and photochemical behavior of **15** in the presence of simple alkenes as well as of masked ketones. Commercial prochiral alkenes **16** and **19** were tested to study the stereoselectivity of the addition of **15** (Scheme 4).



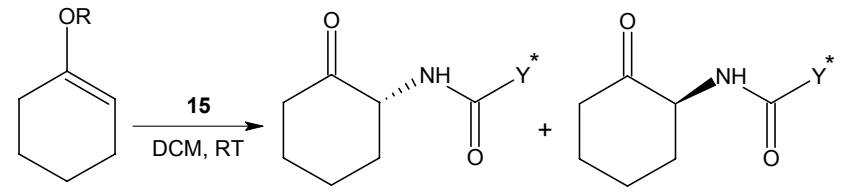

**Scheme 4:** Stereoselective electrophilic amination of some alkenes using the optically active azidating reagent **15**.

Allylic amines **17** and **20**, oxazolines **18** and **21** and the aziridine **22** may be obtained with good diastereoselectivity (d.e. >90%), as proved by $^{1}H$ and $^{13}C$ NMR spectroscopy. Starting from **19**, optically active **22** is isolated as minor product. Reaction of **15** with enamine **23** provides α-amino ketone **24** in low yield and only 45% d.e., together with substituted imine **25** and the product of ring opening **26** (Scheme 5).




**Scheme 5:** Stereoselective electrophilic amination of 1-cyclopent-1-en-1-ylpyrrolidine **23** using the optically active azidating reagent **15**.

Furthermore, the amination of enol ethers **27** and **28** has been described. After 7 h of photolysis at room temperature starting from **27** and at 0°C starting from **28**, an 80:20 mixture of diastereomers **29** and **30** is obtained in 61% and 53% yield, respectively (Scheme 6).

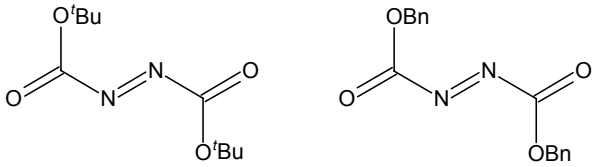



**Scheme 6:** Stereoselective electrophilic amination of enol ethers using the optically active azidating reagent **15**

### 1.2.1.2 Azodicarboxylates and Azodicarboxamides

Although the reaction of a carbon nucleophile with an azodicarboxylate to give a derivative of a hydrazine dicarboxylate was first reported in 1924,[41] this reaction was used for the first time simultaneously by several groups in stereoselective C-N bond-forming reactions only in 1986.[42-46] Azodicarboxylates are efficient sources of positive nitrogen used in the preparation of α-hydrazino and α-amino acids starting from enolates. The most frequently used strategy involves a chiral auxiliary-based enolate and di-*tert*-butyl **31** (DTBAD) or dibenzyl **32** (DBAD)

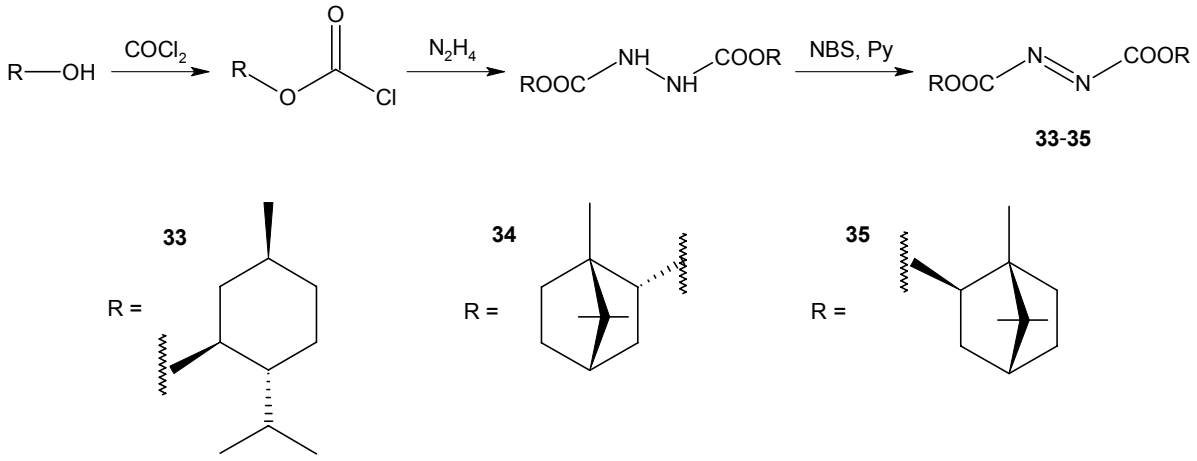
azodicarboxylates as amination reagents (Figure 3). Both compounds **31** and **32** are commercially available. Very good yields and diastereoselectivities have been reported.[1,2,33]




**31** **32**

**Figure 3:** Azodicarboxylates used as electrophilic amination reagents

The preparation of chiral dialkylazodicarboxylates and their use as electrophilic enolate amination reagents was first reported in 1995 by Vederas *et al.*[47] A series of chiral dialkyl (menthyl **33**, bornyl **34**, isobornyl **35**) azodicarboxylates was prepared by conversion of the corresponding alcohols into chloroformates, condensation with hydrazine and oxidation with *N*-bromosuccinimide and pyridine. Compounds **33**-**35** are obtained in 35-50% yield (Scheme 7).

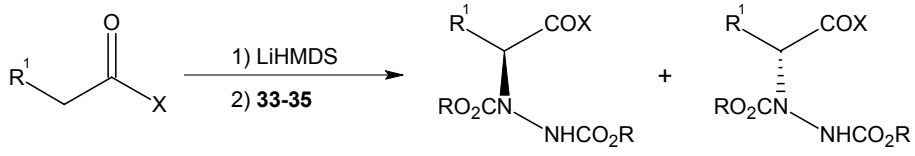



**Scheme 7:** Synthesis of chiral dialkylazodicarboxylates as reported by Vederas *et al.*[47]

Ester enolates generated by treatment of the corresponding esters with 1 equivalent of LiHMDS at

-78°C are aminated by the chiral dialkylazodicarboxylates **33-35** at -78°C (Scheme 8).

The reaction displays moderate yields (13-87%) and little (if any) stereoselectivity (d.e. 33%, **33**, $R^1$ = Ph, X = OEt). The chromatographic separation of the diastereomers generally is difficult. The menthyl and bornyl carbamate moieties in products **37** proved to be very stable and difficult to remove, even with prolonged reflux in 6M HCl or concentrated HBr, and the corresponding α-hydrazino acids could not be obtained in reasonable yield. However, the isobornyl analogues are readily hydrolyzed.




**36** (*S*)-**37** (*R*)-**37**

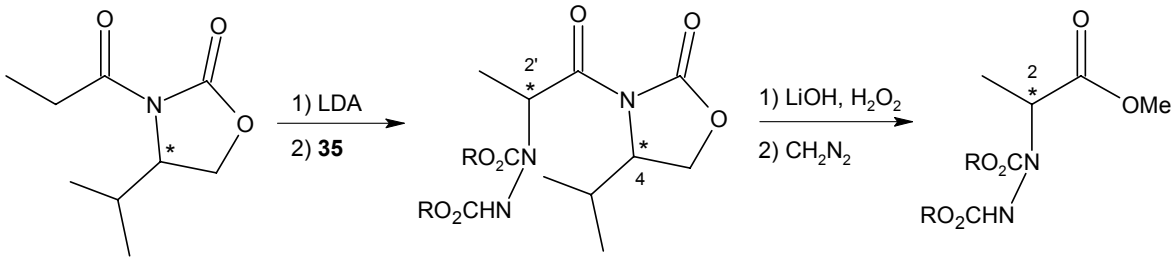
$R^1$ = Ph, $CH_2COOEt$, $CH_3$, $^tBu$

X = OEt, $NMe_2$

**Scheme 8:** Stereoselective electrophilic amination of ester enolates with the chiral diazodicarboxylates **33**-**35**.

Enolates generated from tertiary amides preferentially assume the *Z*-configuration. Reaction of *N,N*-dimethylamides with 1 equivalent LDA at -78°C followed by addition of 1.5 equivalent of di(-)-isobornyl azodicarboxylate **35** gives in each case 1:1 ratio of diastereomers (*S*)-**37** and (*R*)-**37** (Scheme 8).

Double diastereoselection was tested with chiral enolates: enantiomerically pure *N*-acyl-oxazolidinone (*S*)-**38** and its enantiomer (*R*)-**38** were aminated at -78°C with **35** (Scheme 9).



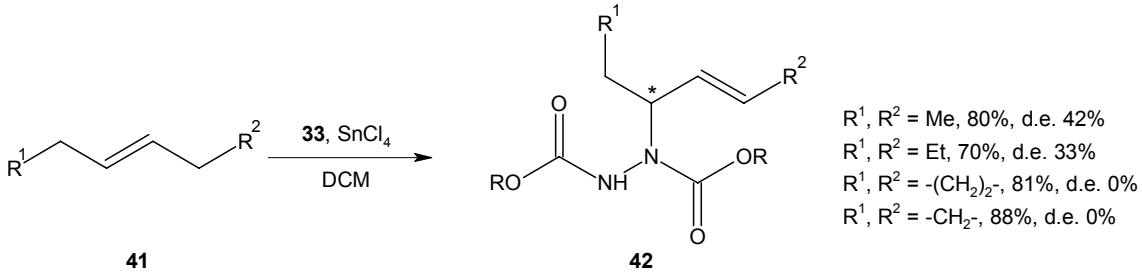

(*S*)-**38** (*S,S*)-**39** (*S*)-**40**

(*R*)-**38** (*R,R*)-**39** (*R*)-**40**

**Scheme 9:** Double diastereoselection experiment using a chiral substrate and the chiral diazodicarboxylate **35** as electrophilic amination reagent.

In both cases, only one diastereomer could be detected using $^1$H NMR spectroscopy. Removal of the oxazolidine auxiliary from compounds (*S,S*)-**39** and (*R,R*)-**39** by treatment with lithium hydroperoxide followed by acidification and treatment with diazomethane generates the corresponding methyl esters (*S*)-**40** and (*R*)-**40** which have opposite configuration at C(2). Amination of either compound (*S*)-**38** or (*R*)-**38** with dibenzylazodicarboxylate **32** gives a 9:1 ratio of diastereomers with the same relative stereochemistry. In conclusion, the geometry of the Evans enolate completely controls the diastereoselection, and the effect of the isobornyl moieties is solely to increase steric bulk and enhance the diastereomeric ratio.

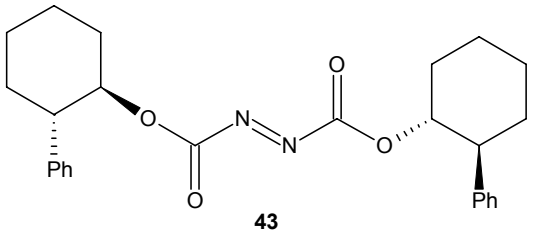
Brimble *et al.*[48] performed a diastereoselective aza-ene reaction using chiral di-(+)-menthyl azodicarboxylate **33** as the nitrogen source. Compound **33** was found to react with various alkenes in the presence of the Lewis acid catalyst $SnCl_4$, and the corresponding allylic aminated product was obtained in good yield (70-88%) and with up to 42% d.e. (Scheme 10).

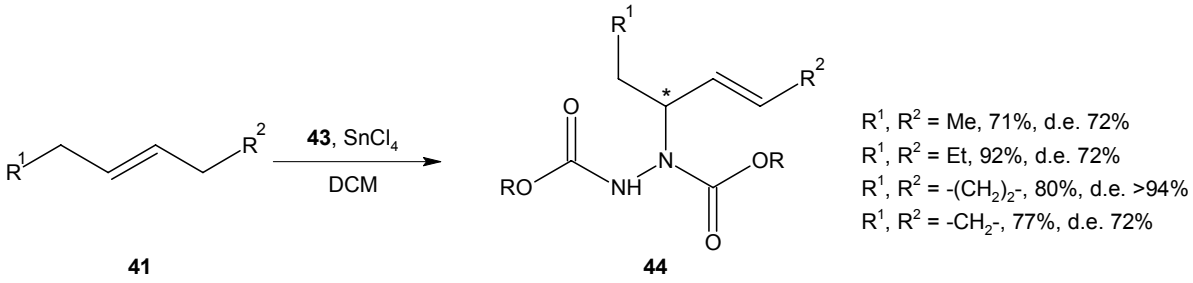



**Scheme 10:** Diastereoselective aza-ene reaction of alkenes with chiral di-(+)-menthyl azodicarboxylate **33**.

The problem with this approach was the removal of the chiral menthyl ester auxiliary, which was found to be rather difficult.

The same research group reported[49] a more successful attempt to perform stereoselective aza-ene reactions with alkenes. Chiral di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl azodicarboxylate **43** can easily be synthesized starting from (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol, and azo-ene reactions of **43** with cyclohexene, cyclopentene, *trans*-3-hexene and *trans*-4-octene in the presence of $SnCl_4$ were carried out (Scheme 11).

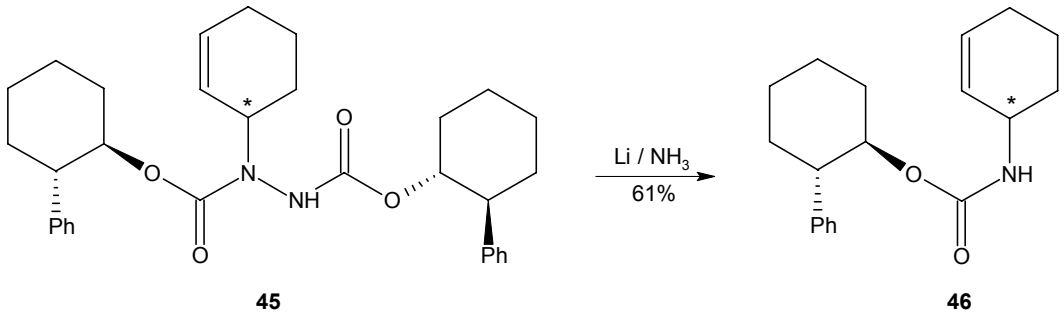



**Scheme 11:** Diastereoselective azo-ene reaction of alkenes with chiral di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate **43**.

The new amination reagent affords much higher levels of asymmetric induction in the Lewis acid mediated azo-ene reaction. Cleavage of the N-N bond of the ene adduct **45** of the cyclohexene

was effected using lithium in liquid ammonia affording the *N*-cyclohexenylcarbamate in moderate yield (Scheme 12).




**Scheme 12:** Cleavage of the hydrazine bond of the ene adduct **45**.

Brimble *et al.*[50] also investigated the potential of **35** to act as a chiral azo-enophile in asymmetric ene reactions. The azo-enophile was treated with *trans*-hex-3-ene and cyclohexene in the presence of $SnCl_4$ affording the ene adducts. However, no diastereoselectivity was observed. The authors described the synthesis of novel chiral hydrazinedicarboxylates and the unsuccessful attempts to transform them into chiral azo-enophiles bearing chiral auxiliaries like oxazolidinone, diacetone-D-glucose or pantolactone.

Macrocyclic azodicarboxylates containing a steroid skeleton were also synthesized using a similar synthetic route (Figure 4).[51]

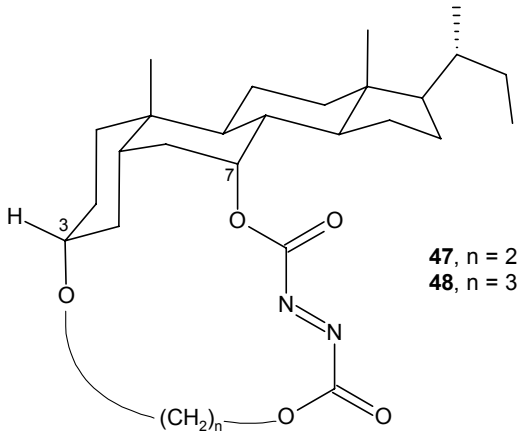
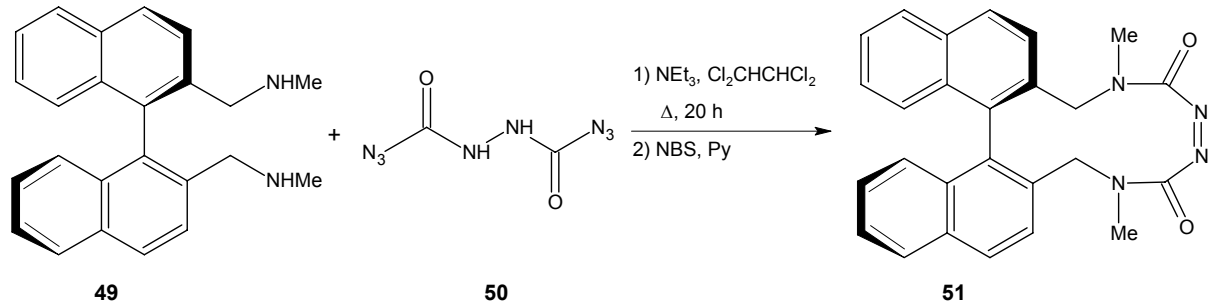



**Figure 4:** Macrocyclic azodicarboxylates containing a steroid skeleton.

Compound **47** was trapped by Diels-Alder reaction with cyclopentadiene, but no further amination studies involving **47** or **48** have been reported.

Finally, a synthesis of a chiral azodicarboxamide containing a bridging binaphtyl moiety was described by Vederas *et al.*[52], and electrophilic amination reactions of achiral ester enolates were performed. The chiral azodicarboxamide **51** is prepared by an intramolecular cyclization between the

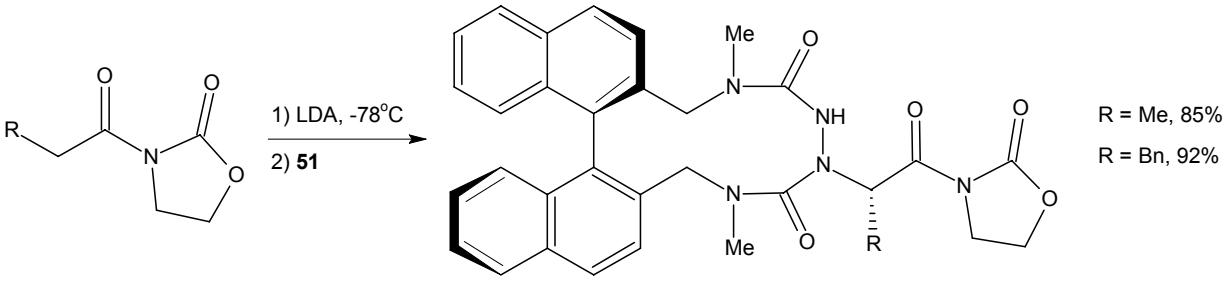
bis-(*N*-methylamine) derivative of 2,2-dimethyl-1,1'-binaphtyl **49** and *N*,*N*'-bis(azido-carbonyl)-hydrazine **50** followed by oxidation with NBS and pyridine in 15% overall yield (Scheme 13).




**49** **50** **51**

**Scheme 13:** Synthesis of the chiral azodicarboxamide **51** containing a bridging binaphtyl moiety.

Achiral oxazolidonones **52** can be aminated at -78°C using the standard procedure. Only one diastereomer can be detected for the products using $^1$H NMR spectroscopy, and X-ray crystallographic analysis of **53** (R = Me) shows that the new stereogenic center have the (*S*) absolute configuration (Scheme 14). Attempts to remove the binaphtyl moiety to produce optically pure free α-hydrazino acid remained unsuccessful.




**52** **53**

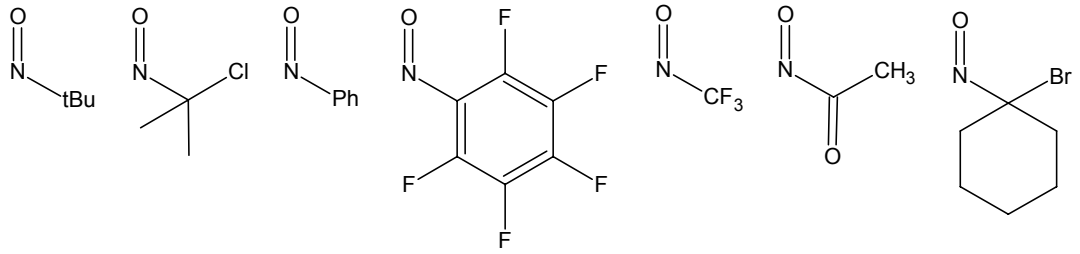
**Scheme 14:** Stereoselective electrophilic amination of achiral oxazolidonones with the chiral azodicarboxamide **51**.

### 1.2.1.3 α-Chloronitroso Compounds

Nitroso compounds are probably the most reactive electrophiles for the ene reactions, as even nonactivated aliphatic nitroso compounds have been reported to undergo the ene reaction at room temperature.[53] Some nitroso compounds which have been applied in ene reactions are depicted in

**54**-**60** (Figure 5).[6,7,54-59] The electrophile **59** is normally prepared *in situ* because of its extremely high reactivity, but the other nitroso compounds are reasonably stable.

The reaction of nitroso compounds with alkenes can give a variety of products, depending on the nature of the alkene. If the alkene is a diene, a Diels-Alder reaction between the nitroso compound and the diene is normally observed.[5,60-66] A competing reaction for nitroso compounds is the ene reaction. However, the products obtained by the two routes are very different. The Diels-Alder products are quite stable, whereas many ene products tend to undergo further *in situ* transformations.




**54** **55** **56** **57** **58** **59** **60**

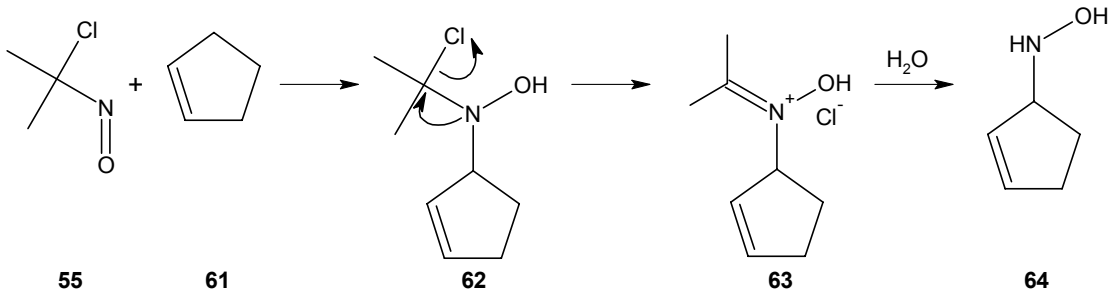
**Figure 5:** Examples of nitroso compounds which function as electrophilic nitrogen sources.

Among them are oxidation, decomposition, disproportionation, while other reactions of the intermediate hydroxylamine can give nitroxides, nitrones, azoxy compounds and amines. All types of products can be observed in a typical ene reaction with nitrosobenzene. The exact mechanism for the different transformations is unknown, but many of them involve radical reactions.[58] The various transformations that a hydroxylamine may undergo might explain some of the problems encountered in this type of chemistry. It is worth noting that the ene products derived from nitroso compounds with electron-withdrawing substituents on the α-carbon are relatively stable. The main reason for this is that they most likely are not oxidized as easily to nitroxides as the ene products from nitrosobenzene.[57-59,67]

Schenk *et al.*[6] used the α-chloronitroso compound **55** for the reaction with cyclopentene **61** in order to solve the problem of the instability of the allyl amine product formed from the reaction with nitroso compounds. The product formed (**62**) rearranges to the stable nitrone hydrochloride salt **63**, which is easily hydrolyzed to the hydroxylamine **64** (Scheme 15).

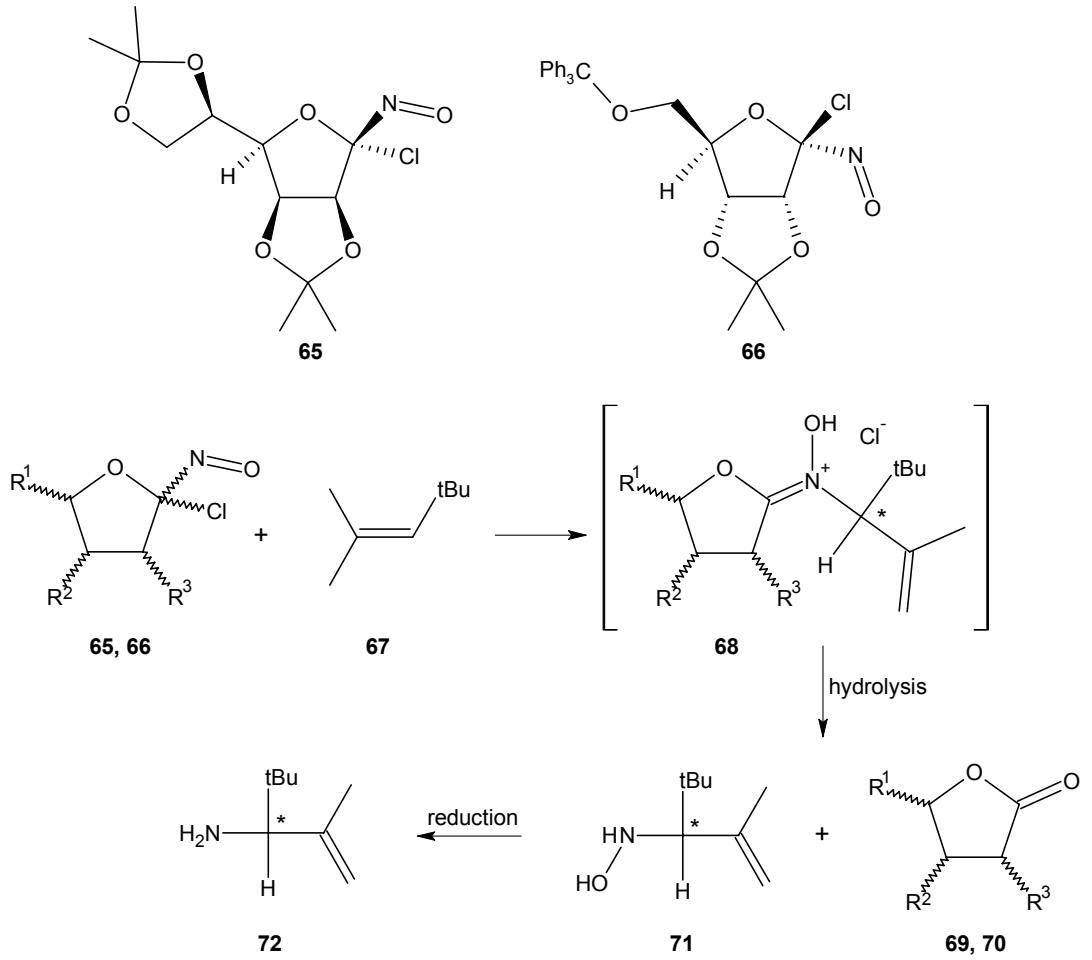
The same principle has also been used by Kresze *et al.*[7,56] for the diastereoselective ene reaction of sugar derivatives with various alkenes. The application of the two optically active nitroso sugar compounds **65** and **66** for the reaction with different alkenes gives, after removal of the sugar moiety, the optically active hydroxylamines in good yield (60-88%). *In situ* reduction may also be carried out as an alternative to the hydrolytic work-up. Stable allyl amines are isolated and

enantioselectivity (50-96% e.e.) has been determined using camphorsulfonamide or Mosher acid amide routes (Scheme 16).




**Scheme 15:** The ene reaction between cyclopentene **61** and the α-chloronitroso derivative **55**.

The major drawback is the long reaction time (days to weeks), which favors the decomposition of the α-chloronitroso reagents, but it provides a good stereoselective method for the synthesis of chiral allyl amines.




**Scheme 16:** Diastereoselective ene reaction of α-chloronitroso sugar derivatives with alkenes.

Based on preliminary studies[11,12,68-70] concerning the enantioselective amination of chiral enolates using 1-chloro-1-nitroso cyclohexane **12**, Oppolzer *et al.*[13] introduced the chiral α-chloronitroso reagents **73** and **74** and reported the enantioselective amination of prochiral ketone enolates (Figure 6).

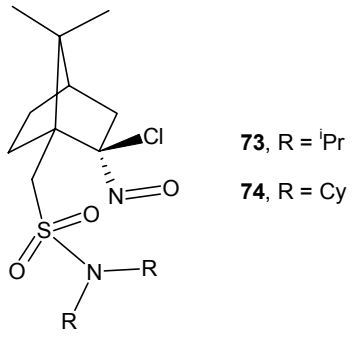
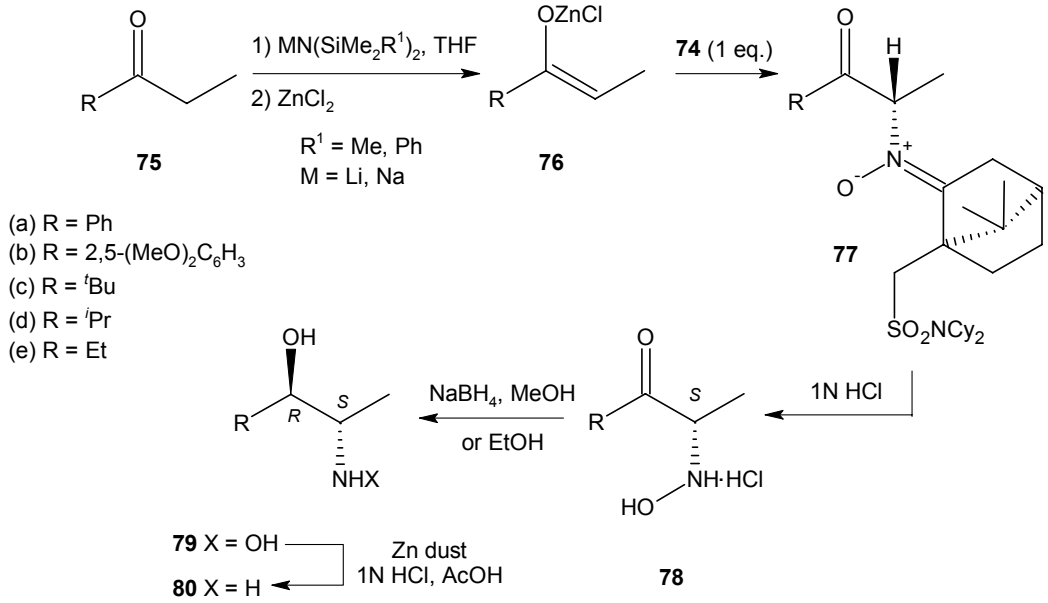



**Figure 6:** Chiral α-chloronitroso camphor sulfonamide derivatives introduced by Oppolzer.[13]

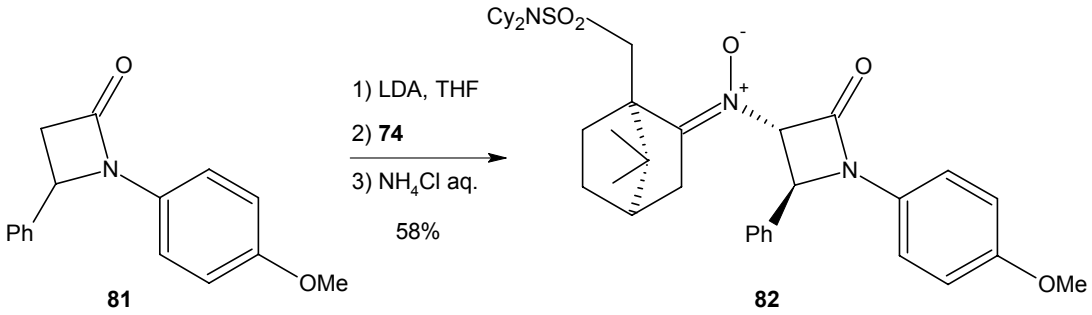
Deprotonation of propiophenone **75a** (R = Ph) with lithium hexamethyldisilazanide, transmetallation of the lithium enolate with $ZnCl_2$, and reaction of the zinc enolate **76** (R = Ph) with the nitroso reagent **74** gives exclusively the nitrone **77** (R = Ph). The configuration at α-C in **78** (R = Ph) was assigned by conversion to (-)-norephedrine **80** (R = Ph). After hydrolysis of crude **77** (R = Ph), evaporation of the aqueous phase, *erythro*-selective reduction of the α-hydroxylamino ketone hydrochloride **78** with sodium borohydride in methanol to **79**, followed by reductive cleavage of the N-O bond affords (-)-norephedrine **80** (R = Ph) in 68% overall yield (*erythro*/*threo* = 95:5, 96% e.e.).




**Scheme 17:** Stereoselective electrophilic amination of ketone enolates using the chiral α-chloronitroso reagent **74**.

In the same article, Oppolzer *et al.*[13] presented further examples for the preparation of diastereo- and enantiomerically pure β-aminols.

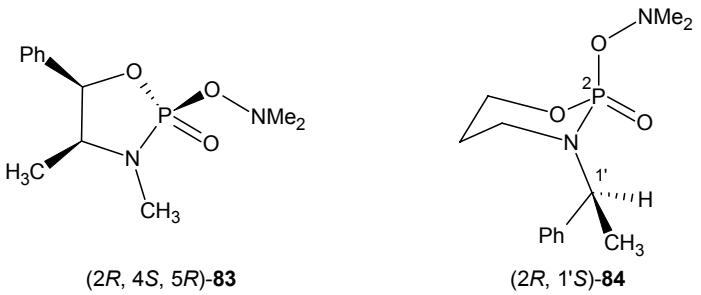
Up-to-date, there is only one more report[71] concerning the use of **74** as chiral amination reagent. The enolate derived from 1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one **81** reacts with **74** to afford nitrone **82** in a completely stereoselective fashion, but in moderate yield (Scheme 18).




**Scheme 18:** Stereoselective electrophilic amination of the lithium enolate of azetidin-2-one **81** using the chiral α-chloronitroso reagent **74**.

### 1.2.1.4 1,3,2-Oxazaphospholidine and 1,3,2-Oxazaphosphinane Derivatives

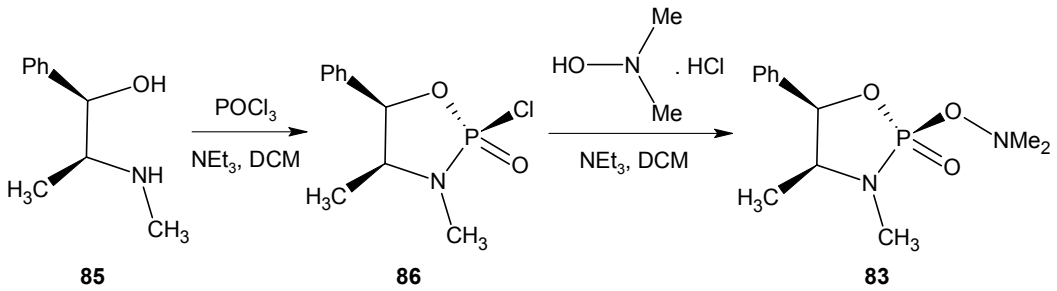
In 1982 Boche and Schrott[72] reported the first stereoselective C-N bond formation using the enantiomerically pure 1,3,2-oxazaphospholidine and 1,3,2-oxazaphosphinane derivatives **83** and **84** (Figure 7).




(2*R*, 4*S*, 5*R*)-**83** (2*R*, 1'*S*)-**84**

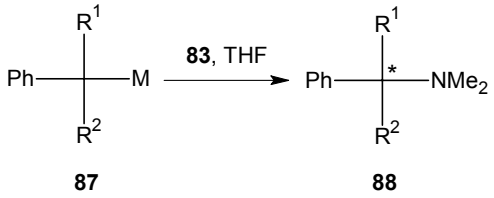
**Figure 7:** Enantiomerically pure 1,3,2-oxazaphospholidine **83** and 1,3,2-oxazaphosphinane **84** introduced by Boche and Schrott.[72]

The derivative **83** is easily accessible from (-)-ephedrine **85**, phosphorus oxychloride and *N*,*N*-dimethyl hydroxylamine (Scheme 19). A related route leads to **84**.




**Scheme 19:** Synthesis of the enantiomerically pure 1,3,2-oxazaphospholidine **83**.

The enantioselective reactions of **83** with some benzylic carbanions **87** give amines **88**. The yields of the amines are only moderate and the enantioselectivities are poor (Scheme 20).




| $R^1$ | $R^2$ | M | Amine **86** e.e.(%) | config. | yield(%) |
|---|---|---|---|---|---|
| H | Me | MgCl | 30 | S | 63 |
| H | Me | MgCl | 44 | S | 40 |
| H | $CO_2Et$ | Li | 23 | - | 50 |
| Me | $CO_2Et$ | Li | 21 | - | 56 |
| H | CN | Li | 8 | - | 62 |

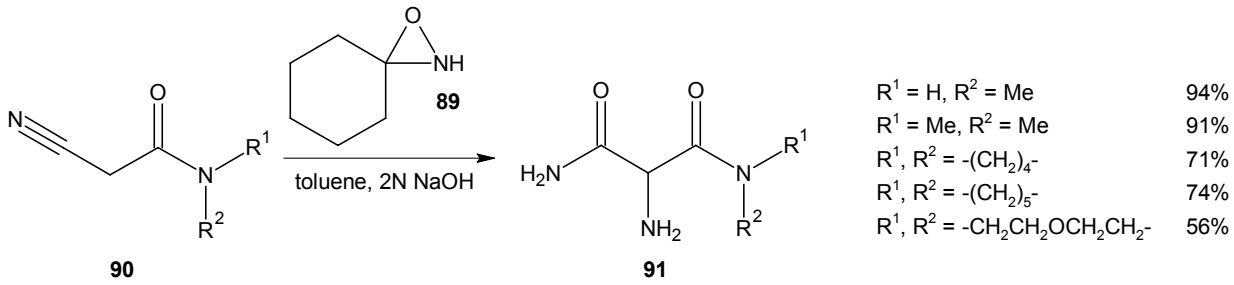
**Scheme 20:** Enantioselective reactions of 1,3,2-oxazaphospholidine **83** with some benzylic carbanions.

Similar observations have been made with **84** as the electrophilic amination reagent.[33] In both **83** and **84** the distance between the stereogenic centers and the electrophilic nitrogen atom is probably too large for an effective stereoselectivity to occur. Due to the high yields and stereoselectivities achieved in other electrophilic amination reactions, the method presented here is only of historical interest.

### 1.2.1.5 Oxaziridines

The unusual reactivity, undoubtedly related to the presence of a strained three-membered ring and a relatively weak N-O bond,[73] makes oxaziridines highly useful as amination agents. Ring opening of the strained three-membered ring is the key to their ability to react as both aminating and oxygenating reagents with nucleophiles. The site of the nucleophilic attack at the oxaziridine ring is determined by the substitution pattern at the nitrogen. Schmitz *et al.*[74] demonstrated in careful studies that N-unsubstituted oxaziridines can play an important role as electrophilic amination reagents. They are highly reactive toward N, S, O and C nucleophiles (*Nu*) and must be prepared and handled in inert solvents such as diethyl ether or toluene. The attack takes place

at the NH group of the three-membered ring with simultaneous formation of the *Nu*-N bond and rupture of the N-O bond. Hence, the synthesis of a wide range of compounds such as azines, hydrazines or diaziridines, becomes possible. The amination of C nucleophiles by spiro(cyclohexane-3'-oxaziridine) **89** has also been investigated for typical examples of C-H acidic compounds in which deprotonation is possible by treatment with aqueous alkali hydroxide. Surprisingly, the amination was accompanied by hydration of the nitrile group in all cases (Scheme 21).



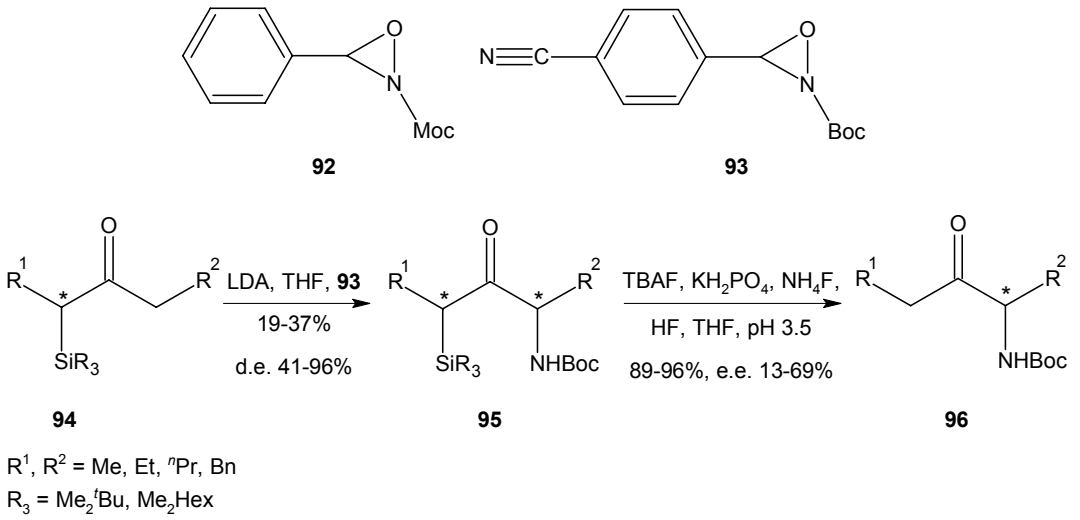

**Scheme 21:** Electrophilic amination of amide enolates **90** with oxaziridines **89**.

The attempts to synthesize oxaziridines allowing the direct transfer of a *N*-protected group to nucleophilic centers led to the synthesis of *N*-Moc and *N*-Boc oxaziridines. It has been mentioned[74] that oxaziridines act as amination reagents only when the group attached to the nitrogen is small. When this group becomes larger the site of the attack is shifted from the nitrogen to the oxygen.

In contrast to this concept, **92** and **93** are able to transfer the *N*-Moc and the *N*-Boc fragments under mild conditions to ketone, ester and amide lithium enolates.[24] *N*-Boc protected α-amino ketones of moderate enantiomeric purity can be synthesized[75] by **93**-mediated electrophilic amination of an enantiopure α-silyl ketone **94**, whereby the silyl group functions as the "traceless" directing group (Scheme 22).

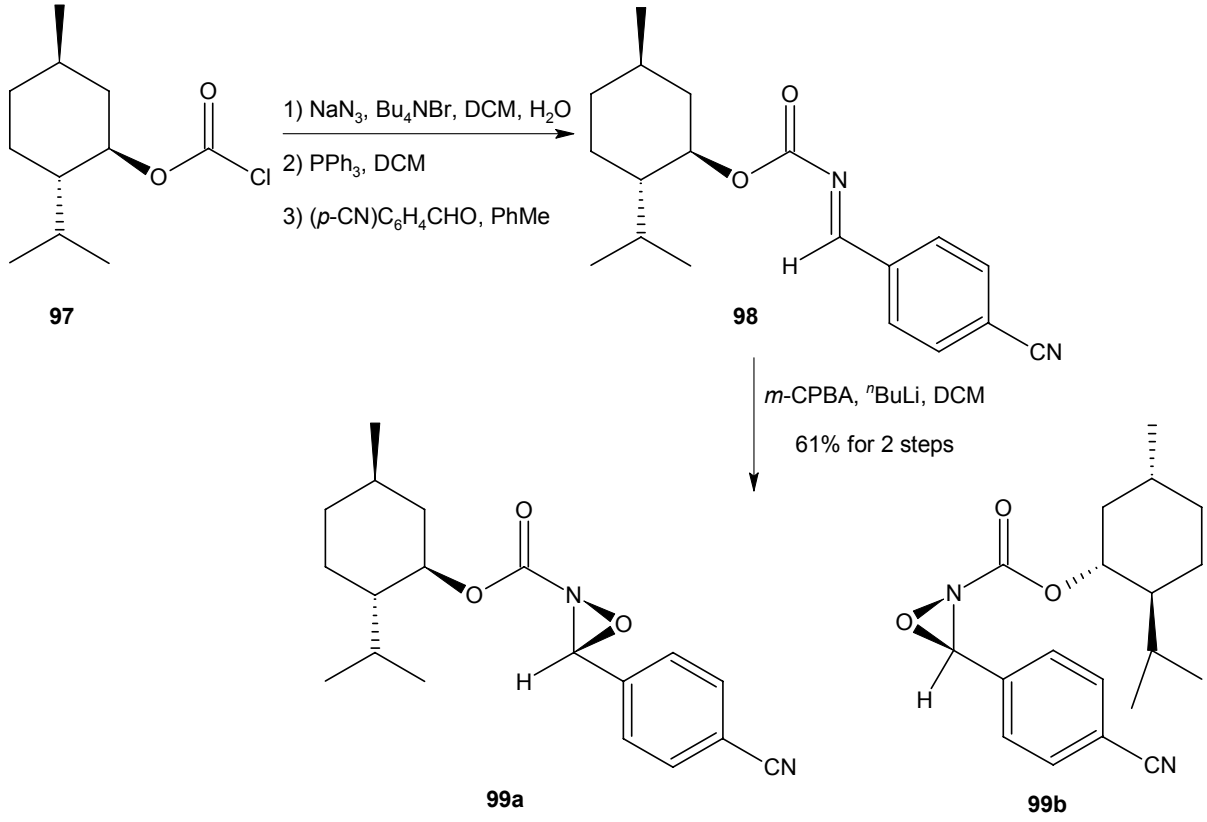
A limitation in the use of **93** in electrophilic amination stems, however, from the substantial amount of the enolate consumed by aldol condensation with 4-cyanobenzaldehyde, formed as by-product, which reduces the yields (19-37%) of the amino acids.

Recently, Armstrong *et al.*[76] reported the first example of the use of the chiral oxaziridine **99** in the electrophilic amination of enolates. They simply replaced the Boc moiety in **93** with one derived from a chiral alcohol, e.g. (-)-menthol. Oxidation of the imine **98** to **99** is performed using *m*-CPBA/$^n$BuLi and proved to be highly diastereoselective with respect to facial attack on the imine carbon. The $^1$H NMR spectrum of **99** indicated a 9:1 mixture of *trans* and *cis* isomers **99a** and **99b**, interrelated by inversion at the nitrogen atom with a barrier of ca. 16-17 kcal/mol.




**Scheme 22:** Diastereoselective electrophilic amination of chiral ketone enolates with *N*-protected oxaziridines **93**.

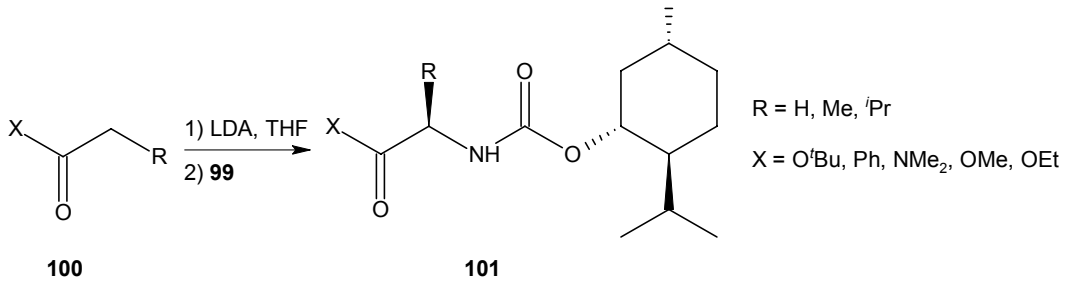
The authors reported that no other diastereomers can be detected by $^{1}H$ or $^{13}C$ NMR (Scheme 23). An X-ray crystal structure of **99a** allowed assignment of configuration.




**Scheme 23:** Synthesis of the chiral oxaziridine **99**.

Amination of ketones, esters and amides **100** with **99** affords α-amino compounds **101** in moderate yields (49-62%) and low diastereoselectivities (5-21%) (Scheme 24). The authors[76]

suggested that the low degree of stereoselectivity in the amination process could be related to low facial selectivity in the approach of the oxaziridine **99** to the enolate. Importantly, it was established that the products are not undergoing epimerization under the reaction conditions by submitting diastereomerically pure samples to the basic reaction conditions.

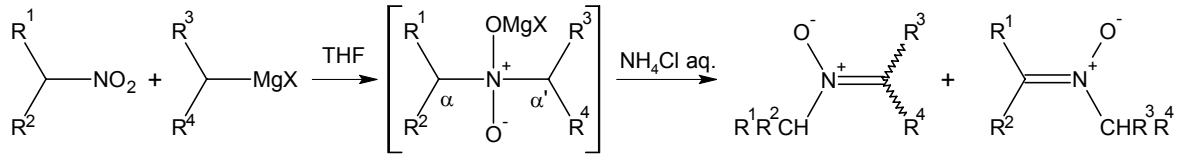



**100** **101**

**Scheme 24:** Electrophilic amination of ketones, esters and amides with the chiral oxaziridine **99**.

### 1.2.1.6 Nitro Derivatives

The use of nitro compounds as nitrogen source for the formation of a C-N bond was first reported by Bartoli *et al.*[14] The reaction between nitroalkanes, and 2-butenylmagnesium chloride provided a good approach to the synthesis of allylic nitrones. Since nitrones are highly valuable synthetic intermediates[77,78] and useful spin trapping reagents,[78-81] they enlarged the studies concerning the reaction between nitroalkanes, and organomagnesium and lithium reagents[16,18,21,22] and provided a relatively good method for the synthesis of nitrones (Scheme 25).

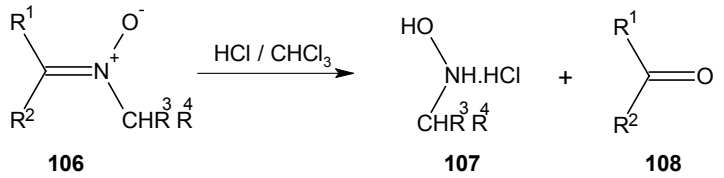



**102** **103** **104** **105** **106**

$R^1$ = H, Me, $^n$Pr, $CH_2COOMe$, 2-furyl$CH_2$, $MeCH(Cl)CH_2$, $MeCOCH_2CH_2$, $MeOOCCH_2CH_2$, $^i$Pr, Ph
$R^2$ = H, Me
$R^3$ = $CH_2$=CH, Ph
$R^4$ = Me, H

**Scheme 25:** Nitrone synthesis by the reaction between nitro derivatives and organo-magnesium reagents.

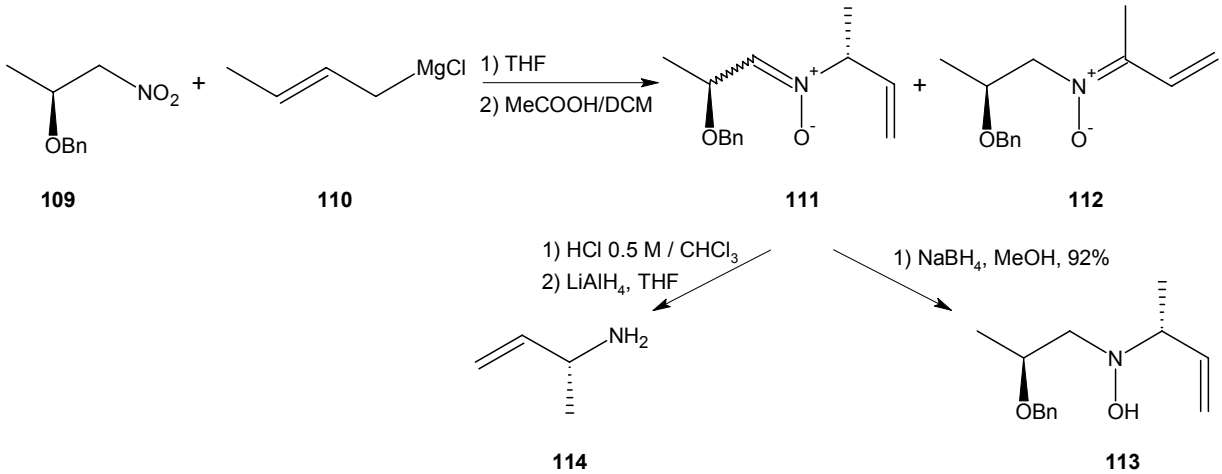
Treatment of an aliphatic nitro compound **102** with an equimolar amount of γ-methallyl or benzyl magnesium chloride **103** at low temperature (-70°C) in THF, followed by quenching with a proton source, gives conjugated and/or nonconjugated nitrones **105** and **106** in 58-81% yield.
The method could easily be extended to the synthesis of hydroxylamines by hydrolysis of intermediate nitrones (Scheme 26).




**106** **107** **108**

**Scheme 26:** Synthesis of hydroxylamines by hydrolysis of intermediate nitrones **106**

Furthermore, the same group[19] reported an enantioselective approach for the amination of allyl magnesium chlorides using the chiral nitro compound (*S*)-(2-benzyloxy)-1-nitropropane **109**. Reaction of **109** with crotyl magnesium chloride **110** in THF at -70°C gives the nitrones **111** in 86% yield as an equimolar mixture of (*E*) and (*Z*) stereoisomers, as well as the conjugated isomer **112** in 10% yield. The nitrone **111** is easily separable from **112** by column chromatography, and reduction with $NaBH_4$ in methanol affords the allyl substituted hydroxylamine **113** in 92% yield with the new chiral center of (*R*) configuration. No detectable amount of the (*S*) isomer has been found in this reaction (Scheme 27).

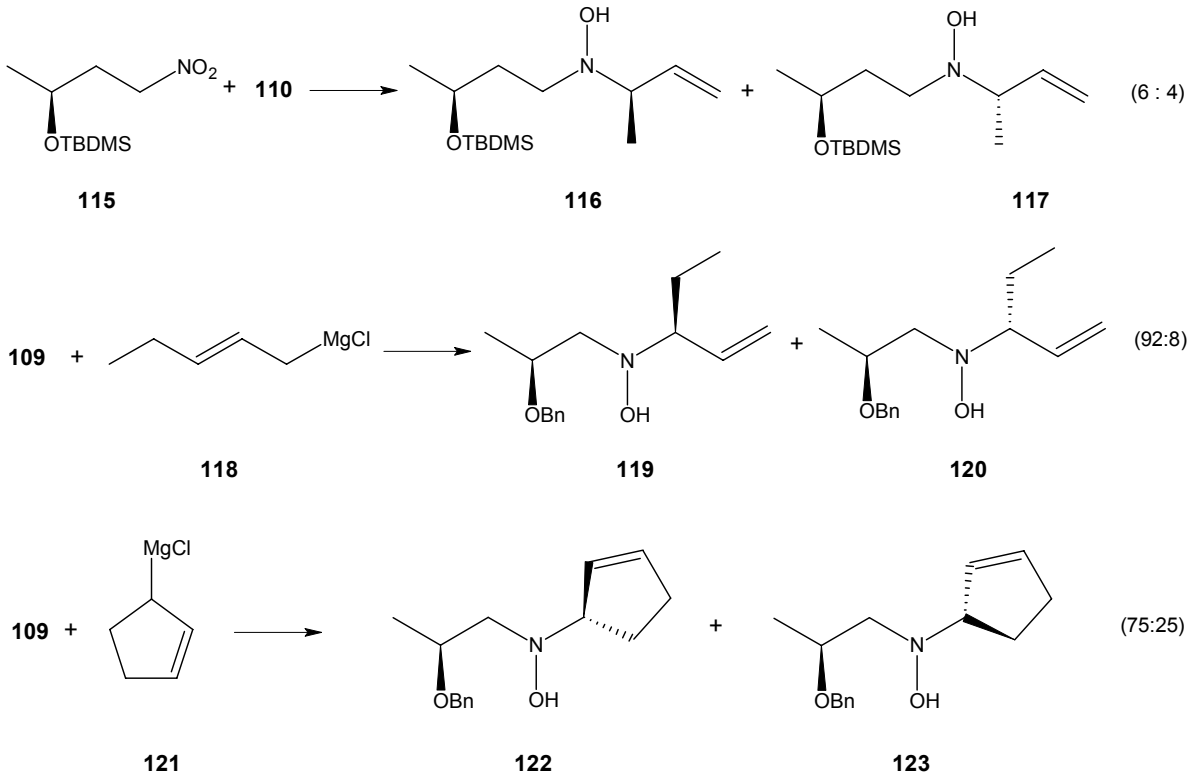



**109** **110** **111** **112** **114** **113**

**Scheme 27:** Enantioselective synthesis of allyl amines by electrophilic amination of allyl organomagnesium reagents with chiral nitroalkane derivative **109**

Chiral nitroalkane **115** gives a mixture of nitrones which after reduction produces two diastereoisomeric hydroxylamines **116** and **117** in a 6:4 ratio. Some allyl Grignard reagents other

than **110** have been used for this reaction and the relative amounts of hydroxylamines obtained after reduction of the corresponding nitrone derivatives are shown in Scheme 28.




**Scheme 28:** Diastereoselective synthesis of allyl hydroxylamines by electrophilic amination of allyl organomagnesium reagents with chiral nitroalkane reagents

More than ten years have passed since the report of Bartoli *et al.*[19] and despite of promising and good results obtained, this is the only report which presents the availability of chiral nitro alkanes derivatives to be involved in electrophilic allylic amination.

# 2. Research Objective

These are only few efficient methods for reagent-controlled stereoselective electrophilic amination compared to those based on chiral substrates or chiral catalysts. An effective stereoselective amination reagent allows greater method flexibility, due to the high availability of prochiral nucleophilic substrates. In the present work the synthesis and the reactivity of three types of enantiomerically pure electrophilic amination reagents towards carbon nucleophiles is presented, with the aim to provide a valuable method for the stereoselective synthesis of α-amino ketones and α-amino acids.

# 3. Results and Discussion

## 3.1 Synthesis of the Enantiomerically Pure Amination Reagents

An enantiomerically pure reagent used in electrophilic amination must have two characteristics. The stereocenter must be placed as closely as possible to the reaction center to ensure a good level of asymmetric induction due to a high enantiofacial differentiation. The nitrogen atom which is going to be transferred must be provided with a good leaving group. The chiral auxiliary should be easily removable and regenerable.

### 3.1.1 Synthesis of the Enantiomerically Pure *N,O*-Disubstituted Hydroxylamines Derivatives

Lithiated *N,O*-disubstituted hydroxylamine derivatives are nitrenoid species, which are susceptible to react with a C-nucleophile and to provide amines on hydrolysis.[82] Up-to-date, there are no reports concerning the synthesis of such chiral nitrenoids and their use in electrophilic amination. A special attention was given to the design of this type of reagents, which must have an easily removable protecting group connected to the nitrogen atom and should be stable in the presence of strong bases and on acidic work-up. Therefore, chiral reagents with an *N*-allyl substructure appeared to be favourable. Removal of the allyl protecting group is commonly effected by transition metal catalyzed isomerization of the allyl amine to the corresponding enamine and subsequent hydrolysis. Complexes of palladium,[83-87] rhodium[88-90] and other transition metals (Ir, Ru, Cr, Mo, Fe, Ni, Pt, Co)[89,91] have been used for such purpose.

Two types of compounds, which fulfill the mentioned conditions, were selected: (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124** and *O*-substituted *N*-[10-(1*R*,5*R*)-pin-2-enyl]hydroxylamines **125** (Figure 8).

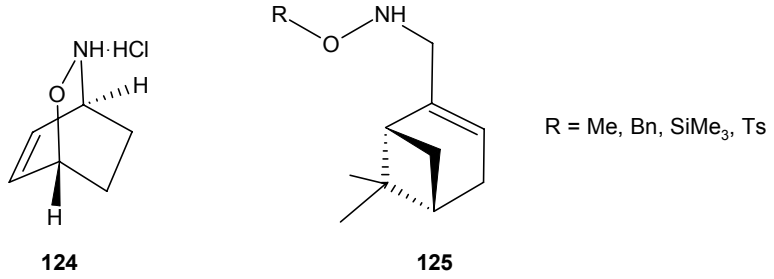
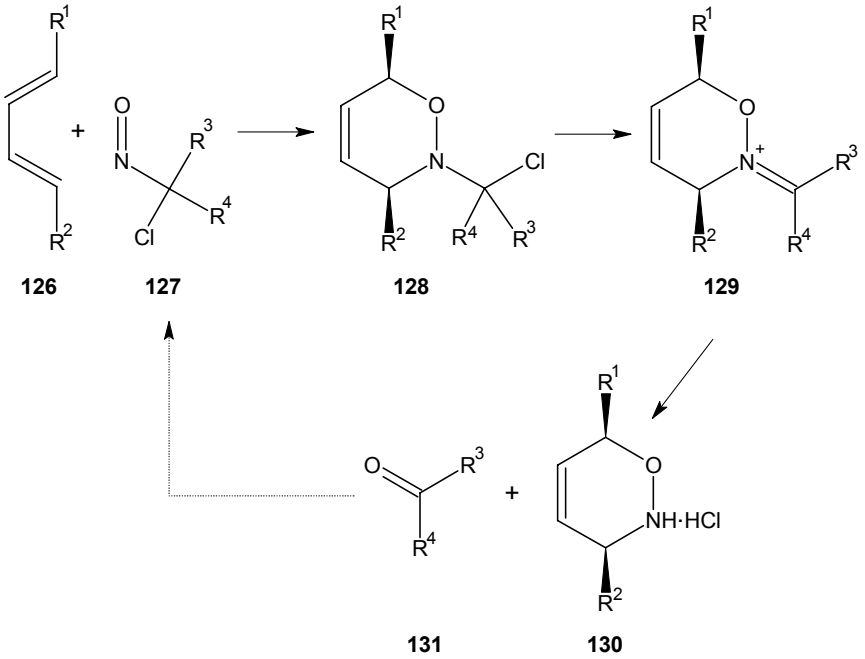



**Figure 8:** Enantiomerically pure cyclic oxazine and *N,O*-disubstituted hydroxylamine derivatives as potential sources of electrophilic nitrogen in the amination reactions of carbanions.

### 3.1.1.1 Stereoselective Synthesis of (1*R*,4*S*)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene Hydrochloride

The hetero-Diels-Alder cycloaddition[92-95] of *C*-nitroso compounds with dienes is a reliable process for the formation of 3,6-dihydro-2*H*-1,2-oxazines, which can be further manipulated to give rise to a wide range of nitrogen containing organic compounds. In recent years there has been considerable activity directed towards the development of asymmetric variants of this cycloaddition, and most work has been carried out using acyl-nitroso compounds carrying a chiral auxiliary.[96-101] However, the conditions needed for the removal of the chiral auxiliary are not always compatible with sensitive functionalities. In this context, the cycloaddition of dienes **126** with α-chloronitroso compounds **127** is attractive, since in the presence of a nucleophilic solvent the initial cycloadduct **129** can undergo solvolysis to liberate the dihydrooxazine **130** directly (Scheme 29).



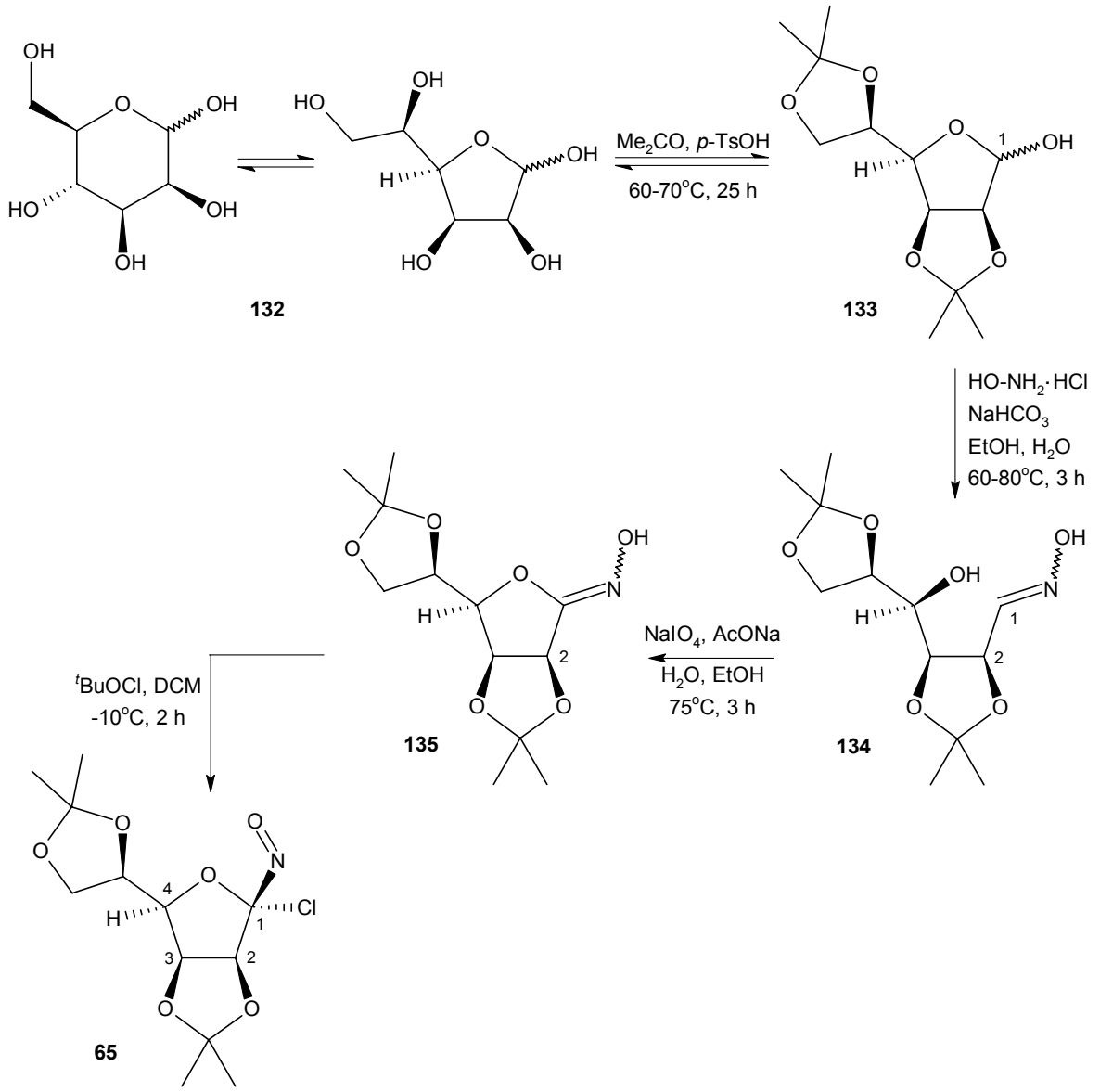

**Scheme 29:** Formation of chiral oxazines by stereoselective hetero-Diels-Alder cycloaddition.

In some cases, depending upon the structure of **127**, the carbonyl compound **131** also produced in this solvolysis can be recycled to the chloronitroso compound through chlorination of its oxime.

Carbohydrates belong to the most prominent members of the chiral pool. Their low cost, abundance and ease with which they can be obtained in a pure state are among the most important features that make carbohydrates prime chiral pool candidates from a raw materials standpoint. Therefore, it is an attractive approach to use the 2,3:5,6-di-*O*-isopropylidene-1-*C*-

nitroso-α-D-mannofuranosylchloride **65** as dienophile derived from readily available and sterically rigid carbohydrate D-(+)-mannose **132**.

The synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** can be carried out by a four-step process as shown in Scheme 30.




**Scheme 30:** Synthesis of the enantiomerically pure 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65**.

The first step[102,103] involves the protection of the starting sugar, D-(+)-mannose **132**, by condensation with water free acetone in the presence of acid catalyst (0.019 equiv. *p*-TsOH) and furnishes the 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **133** in 67% yield. The cyclic acetal formation is favoured in the furanose form of **132**, where the vicinal hydroxyl groups have a *syn* orientation. The equilibrium is shifted to the formation of **133** using excess of acetone, which actually is the solvent. The α-configuration of the anomeric carbon atom C(1) was confirmed by

comparison of the measured optical rotation $[\alpha]_D^{27}$=+25.04 (c= 1.02 in acetone) with that reported in the literature $[\alpha]_D^{20}$=+25 (c= 1.0 in acetone).[104] Subsequent conversion of the isopropylidene acetal **133** into 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134** in 92% yield is achieved by reaction with hydroxylamine in EtOH:$H_2O$ = 1:1, *via* an addition-elimination mechanism. The $^1$H NMR spectrum shows a *Z*:*E* ratio of 79:21, which is in close agreement with the literature value of *Z*:*E* = 84:16.[105] The assigment of the *Z*- isomer as the major isomer is supported by the expected deshielding of H-C(2), 5.25 ppm compared with 4.49 ppm for the (*E*) isomer (Figure 9). The *Z*-isomer is stabilized through hydrogen bonding between HO-N=C(1) and the *O*-atom on C(2) of the dioxolane ring.

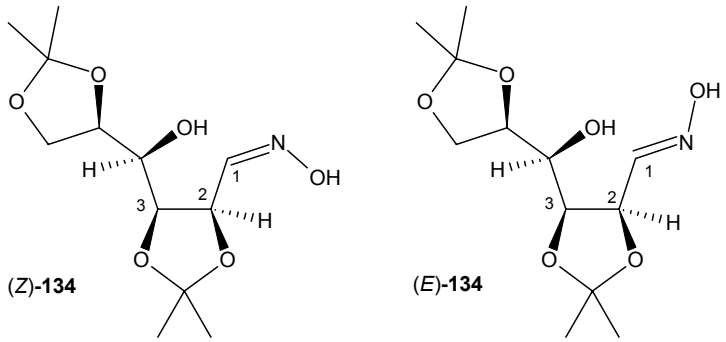
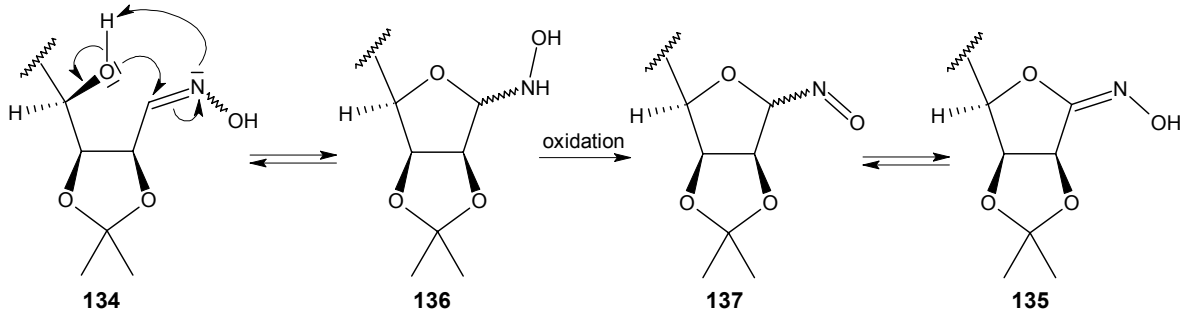



**Figure 9:** *Z* and *E*-stereoisomers of 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134**.

Oxidation of the oxime **134** with sodium metaperiodate in the presence of sodium acetate gives *N*-hydroxy-2,3:5,6-di-*O*-isopropylidene-α-D-mannoimido-1,4-lactone **135** in 74% yield.[106] The structure of imidolactone **135** is in accord with its elemental analysis and spectroscopic data. Especially diagnostic is the absence of a signal for the H-C(1) in the $^1$H NMR spectrum and the shift of C(1)=N-OH from 152.18 ppm in (*Z*)-**134** to 156.98 ppm in the $^{13}$C NMR. It is noteworthy that only one diastereomer is formed, which is in agreement with the report of Beer *et al.*[107] on the synthesis of hydroximinolactones. They synthesized imidolactone **135** starting from **134** by the oxidation with $MnO_2$, and isolated both (*Z*) and (*E*) isomers. On heating or standing in DCM solution, the lower-melting compound (*E*)-**135** isomerized to (*Z*)-**135**. In the $^1$H NMR spectrum (chloroform-*d*$^1$ as solvent), H-C(2) of **135** appeared at 5.15 ppm which is also in agreement with the value of 5.19 ppm reported by Beer *et al.*[107] for the *Z*-isomer of **135**. Concerning the reaction mechanism, it has been noted[106] that oxidation of the oxime **134** proceeds from the tautomeric, ring closed hydroxylamine form **136** to give an intermediate 1-nitroso compound **137** which tautomerises to the hydroximinolactone **135** (Scheme 31).




**Scheme 31:** Oxidation mechanism of 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134** to *N*-hydroxy-2,3:5,6-di-*O*-isopropylidene-α-D-mannoimido-1,4-lactone **135**.

Chlorination of **135** with *tert*-butyl hypochlorite in DCM at -10°C under protection from light gives enantiomerically pure 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** in quantitative yield and multigram scale.[5] The compound **65** is obtained as blue crystals. It is stable for several days at room temperature and for unlimited time at -20°C. These characteristics offer an enhanced practical utility compared to α-chloronitroso alkanes, which are also good dienophiles, but volatile, unstable and toxic blue liquids.[12] The chlorination agent, *i.e.* $^{t}$BuOCl, is prepared from *tert*-butanol and an aqueous solution of sodium hypochlorite,[108] and its concentration can easily be determined by iodometric titration. The IR spectrum of **65** shows a characteristic absorption for C-N at 1070 $cm^{-1}$ and disappearance of the C=N absorption at 1691 $cm^{-1}$. Moreover, the characteristic absorption of the nitroso group is found at 1571 $cm^{-1}$. The $^{13}$C NMR spectrum shows the signal of the C(1) atom at 125.24 ppm, a shift which is in agreement with the disappearance of the exocyclic carbon-nitrogen double bond. The structure of **65** has been established by Felber *et al.*[5] by X-ray diffraction analysis. It has been shown that the Cl substituent adopts a pseudoaxial and the nitroso group a pseudoequatorial position. The *O*-atom of the nitroso group adopts a synperiplanar orientation to the ring *O*-atom (Figure 10).

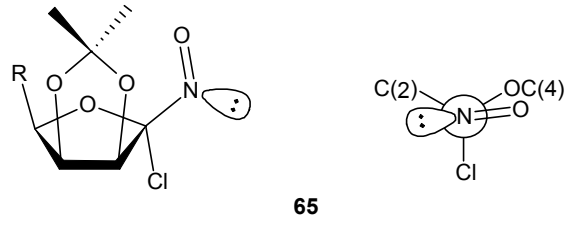
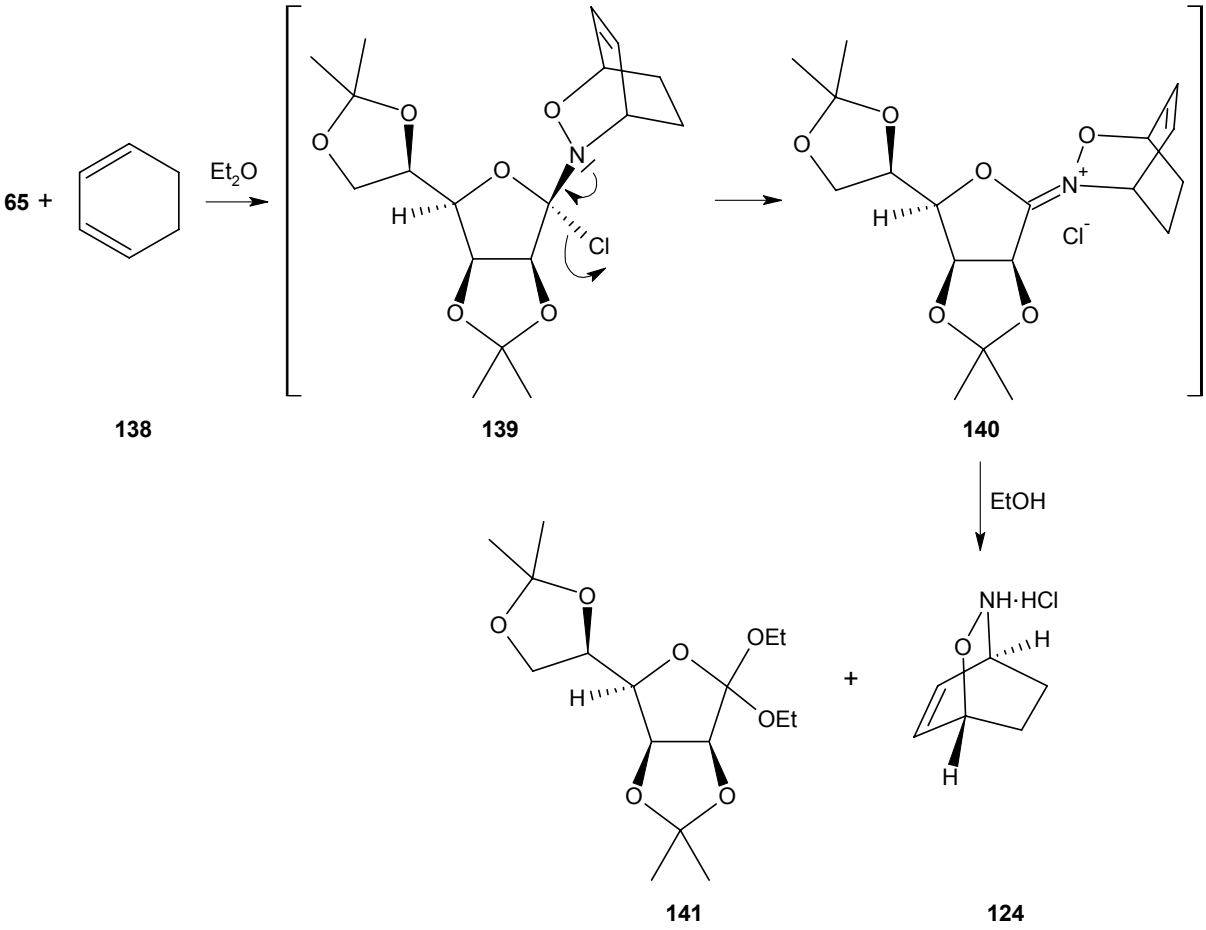



**Figure 10:** Conformation of the α-chloronitroso compound **65**.

The striking features of **65** are its high reactivity and high diastereoselectivity in the cycloaddition reactions. Compared to α-chloronitroso alkanes, *i.e.* 1-chloro-1-nitroso cyclohexane **12**, the higher

reactivity of **65** towards dienes is due to the presence of the two highly electronegative substituents at C(1), *i.e.* Cl and *O*-alkyl.

Treatment of the α-chloronitroso compound **65** with cyclohexa-1,3-diene **138** in $Et_2O$-EtOH gives the (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124**. The intermediate cycloadduct **139** collapses, due to elimination of $Cl^-$, to the iminium ion **140** which in the presence of a nucleophilic solvent (EtOH) affords the cyclic oxazine **124** as hydrochloride and 2,3:5,6-di-*O*-isopropylidene-α-D-manno-1,4-lactone diethylorthoester **141** (Scheme 32).



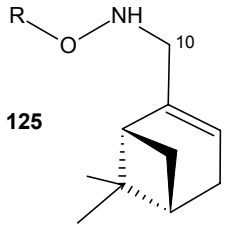

**Scheme 32:** Synthesis of (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124** by the hetero-Diels-Alder reaction between cyclohexadiene **138** and 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65**.

The initial conditions investigated for the cycloadition of cyclohexa-1,3-diene **138** with the α-chloronitroso compound **65** are similar to those described in the literature for related reactions[5,64,66,109-115] and involve $CHCl_3$-EtOH or DCM-EtOH as solvents. No reaction is observed at low temperature (-70°C).[5] Reaction at 0°C in DCM:EtOH = 3:1 affords a light blue turbid solution from which the product **124** is extracted with water and isolated by lyophilization as a light yellow solid in 68% yield. The $^1$H NMR spectra show partial decomposition of the cyclic oxazine. The procedure described by Vasella *et al.*[64] has also been followed. It consists of

repetitive extractions of the product from the organic phase with 0.05 M HCl, which substantially diminished the yield of **124** to 56%. Finally, a new procedure has been used. It simply involves the use of $Et_2O$ as solvent. Hydrochloride **124** precipitates during the reaction and can be easily isolated in 92% yield. $^1$H NMR analysis shows pure **124**. Other analytical data are also in agreement with those from literature.[5]

### 3.1.1.2 Synthesis of *O*-Substituted *N*-[10-(1*R*,5*R*)-Pin-2-enyl]hydroxylamines

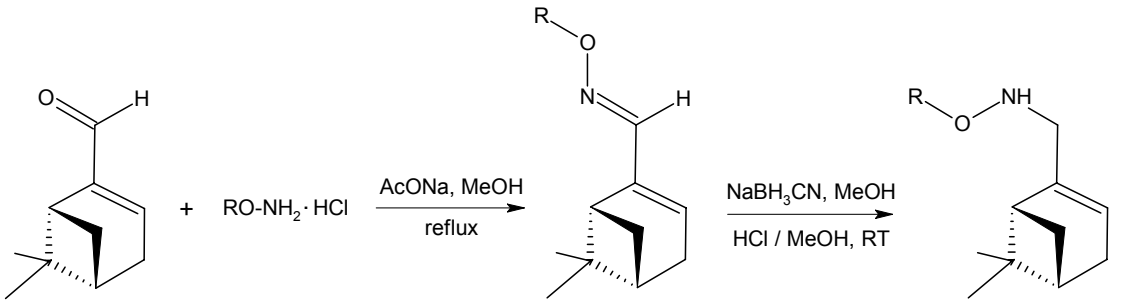
For the design of the enantiomerically pure hydroxylamines **125** a sterically rigid chiral auxiliary connected to the nitrogen atom is considered to be appropriate, *i.e.* α-pinene. Connection of the α-pinene system with the nitrogen atom at position *10* ensures the presence of an allyl type chain on the nitrogen atom. The condition of proximity of the chiral auxiliary is also fulfilled.




**125**

**Figure 11:** Target hydroxylamine derivative proposed as stereoselective amination reagent.

(1*R*,5*R*)-(-)-Myrtenal **142** has been chosen as optically active starting material for the synthesis of hydroxylamines **125**. Aldehyde **142** is commercially available in high optical purity on multigram scale. The synthesis of *O*-methyl and *O*-benzyl substituted hydroxylamines proceeds by condensation of *O*-methyl hydroxylamine **143** and *O*-benzyl hydroxylamine **144**, respectively, with the aldehyde **142**, followed by the reduction of the resulting *O*-alkyl oximes (Scheme 33).




**142** **143**, R = Me **144**, R = Bn **145**, R = Me **146**, R = Bn **147**, R = Me **148**, R = Bn

**Scheme 33:** Synthesis of the enantiomerically pure hydroxylamines **147** and **148**.

*O*-Methyl-(1*R*,5*R*)-(-)-myrtenal oxime **145** is obtained as a colorless oil, in 83% yield, after vacuum distillation. GC and $^1$H NMR analysis of the isolated **145** shows that only one stereoisomer results. The NOESY experiment does not clarify the orientation of the $OCH_3$ group.

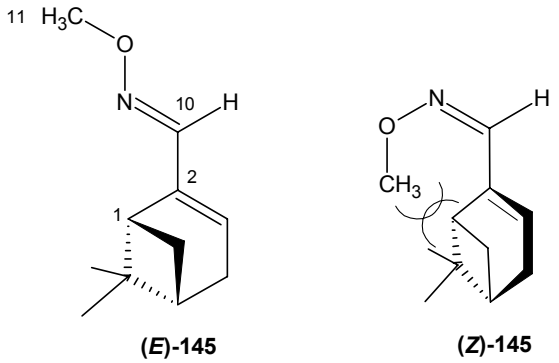



**Figure 12**: Possible stereoisomers of *O*-methyl-(1*R*,5*R*)-(-)-myrtenal oxime **145**.

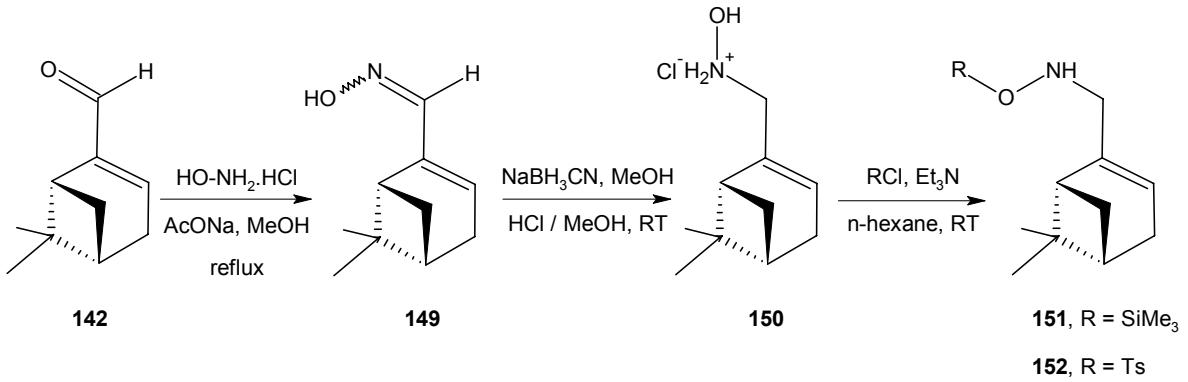
Karabatsos *et al.*[116] presented an extensive $^1$H NMR based structural study on conformations and configurations of structurally similar oxime *O*-methyl ethers. They showed that the amount of *E*-isomer increases with increasing bulkiness of the C-substituent of the C=N bond, going from a *E*:*Z* ratio of 54:46 for Et-CH=N-OMe, to 74:26 for Cy-CH=N-OMe and 100:0 for $^t$Bu-CH=N-OMe. It can be therefore concluded that the stereoisomer resulted in the synthesis of **145** has an *E* configuration. The absence of the *Z*-isomer is probably due to the repulsive interactions that occur between the *O*-methyl group and the pinene skeleton, which would force the C=C bond of the pinene system out of conjugation with the C=N bond. As expected, chiral HPLC analysis performed on a CHIRACEL OD column shows that the chirality remained unaffected. Determination of the optical activity showed (-)-**145**.

*O*-Benzyl-(1*R*,5*R*)-(-)-myrtenal oxime **146** is obtained following the same procedure, with the difference that due to a higher boiling point (125 $^o$C, 0.26 mbar) compared to **145** (53 $^o$C, 0.27 mbar), its purification proceeds by flash chromatography followed by Kugelrohr distillation. The oxime ether **146** results in 83% yield, as a colorless oil, and similarly to **145**, as *E*-isomer and single enantiomer.

Reduction of the oxime ethers **145** and **146** to the enantiomerically pure hydroxylamines **147** and **148** is performed with $NaBH_3CN$ in absolute methanol, under acidic conditions (pH 3, HCl/MeOH). The reaction proceeds smoothly at room temperature and can easily be monitored by GC. Compounds **147** and **148** are isolated as colorless oils in 70% and 85%, respectively, and have been fully characterized. The IR spectrum of **147** shows the appearance of the NH absorption at 3249 cm$^{-1}$ and disappearance of the C=N band at 1621 cm$^{-1}$. Especially diagnostic are the absence of the singlet at 7.66 ppm corresponding to H-C(10) in the $^1$H NMR spectrum,

appearance of a signal corresponding to two protons H-C(10) at 3.39 ppm, and the shift of the signal of C(10) in **145** from 150.51 ppm to 57.42 ppm in the $^{13}$C NMR spectrum. Similarly, for the hydroxylamine **148** the IR spectrum shows the characteristic NH band at 3263 cm$^{-1}$ and the shift of the signal C(10) in **146** from 150.44 ppm to 57.21 ppm in the $^{13}$C NMR spectrum.

(-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-trimethylsilyl hydroxylamine **151** and (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-tosyl hydroxylamine **152** can be synthesized starting from (1*R*,5*R*)-(-)-myrtenal **142** *via* (1*R*,5*R*)-(-)-myrtenaloxime **149** and (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-hydroxylamine hydrochloride **150** (Scheme 34).




**Scheme 34:** Synthesis of the enantiomerically pure hydroxylamines **151** and **152**.

The synthesis of (1*R*,5*R*)-(-)-myrtenaloxime **149** has been reported in the literature[117] to proceed from the aldehyde **142**, but no reaction details or yield are given. Generally, the synthesis of hydroxylamines of type **149** can be carried out in basic or acidic conditions. Following the general method described by Armesto *et al.*[118] the synthesis of oxime **149** succeeds under basic conditions, *i.e.* hydroxylamine hydrochloride in a mixture of pyridine:ethanol = 1:20, and furnishes the product in 61%. An alternative procedure involves the use of hydroxylamine hydrochloride and sodium acetate in MeOH, and affords **149** in 93% yield.

The reduction of aldoximes with $NaBH_3CN$ in absolute methanol is very pH-dependent. When the reaction is carried out at pH 4, the major product is the *N*,*N*-dialkylhydroxylamine,[119,120] while at pH 3 the monoalkylhydroxylamine is the major product. Reduction of the oxime **149** with $NaBH_3CN$ at pH 2-3, work-up at pH 9 and further extraction of product from $Et_2O$ with 1M HCl, furnishes the hydroxylamine hydrochloride **150** as single product in 93% yield. The IR spectra of **150** show the disappearance of the C=N absorption band at 1619 cm$^{-1}$ and the appearance of a broad characteristic $NH_2^+$ band at 3060 cm$^{-1}$. More relevant, analysis of $^{13}$C NMR spectrum shows the shift of the signal corresponding to C(10) from 151.39 ppm to 59.05 ppm, a value which emphasizes the reduction.

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-trimethylsilyl hydroxylamine **151** is obtained from compound **150** using trimethylsilyl chloride as silylating agent and a suitable base according to a modified literature procedure[121,122] (Table 1).

**Table 1:** Influence of base and solvent on the synthesis of hydroxylamine **151**.

| Entry | Base | Solvent | Yield (%) of 151 |
|---|---|---|---|
| 1 | Imidazole | n-Pentane | 61 |
| 2 | Py | n-Pentane | 48 |
| 3 | $Et_3N$ | n-Pentane | 67 |
| 4 | $Et_3N$ | $Et_2O$ | 68 |
| 5 | $Et_3N$ | n-Hexane | 77 |

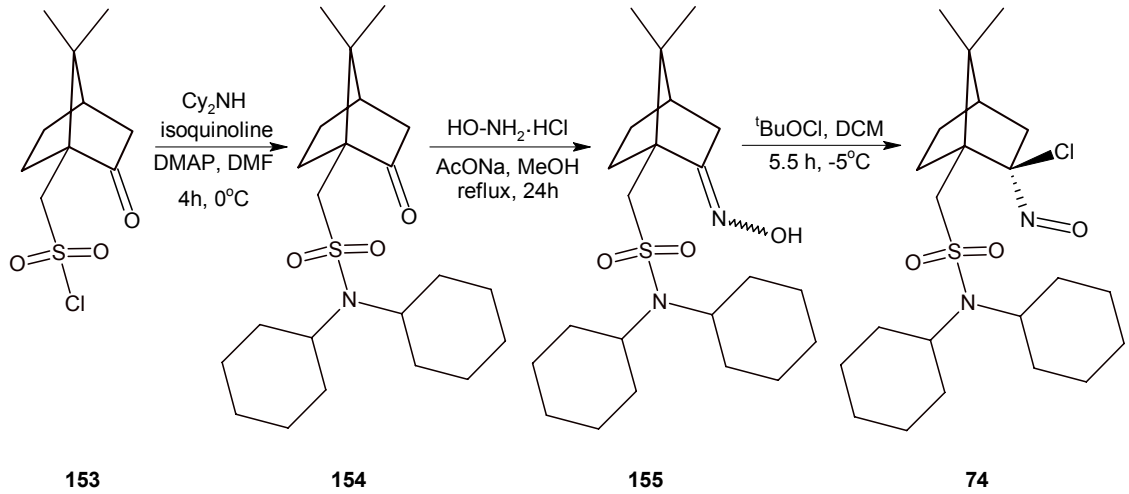
Since hydroxylamine **150** proved to be unstable as free base, neutralization and silylation have to be done in a one-pot reaction and afford **151** as colorless oil. Table 1 shows that silylation is slightly dependent upon the base strength. The strongest base from this series – triethylamine – apparently favors silylation of hydroxylamine **150** to a higher extent. The use of pyridine as solvent makes the work-up very tedious and furnished **151** in a lower yield. Variation of the solvent influences the yield of silylation, most probably by affecting the solubility of hydroxylamine **150** - as free base - in that solvent. The $^1$H NMR spectrum of **151** shows the appearance of a singlet at 0.21 ppm corresponding to the protons of the trimethylsilyl group and a signal at -0.94 ppm in the $^{13}$C NMR spectrum corresponding to the C atoms of the same functional group.

Using the same procedure, (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-tosyl hydroxylamine **152** results in 85% yield as colorless crystals, after flash chromatography and recrystallization. The IR spectrum shows the characteristic sulfonyloxy absorption band at 1164 cm$^{-1}$ and the appearance of the AA'BB' signals at 7.78 ppm (Ph-*ortho*) and 7.36 ppm (Ph-*meta*) in the $^1$H NMR spectrum confirms the tosylation of **150**.

### 3.1.2 Stereoselective Synthesis of the Enantiomerically Pure α-Chloronitroso Compounds

For the present studies concerning the stereoselective amination of ester enolates and allyl organometallic reagents, the enantiomerically pure α-chloronitroso compounds **65** and **74** have also been chosen as [$NH_2^+$] synthons. The synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** is described in Chapter 3.1.1.1. (+)-*N,N*-Dicyclohexyl-2-chloro-

2-nitrosocamphor-10-sulfonamide **74** is obtained following the procedure described by Oppolzer *et al.*[13] (Scheme 35).




**Scheme 35:** Synthesis of (+)-*N,N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**.

Starting from (+)-camphor-10-sulfonylchloride **153**, sulfonamide **154** is obtained in 82% yield. Analysis of the $^{13}C$ NMR spectrum shows the appearance of the signals corresponding to the cyclohexyl groups at 57.66 ppm (N-C) and 32.95, 32.56, 26.47 and 25.20 ppm. Moreover, the characteristic absorption of the sulfonamide group appears at 1322 $cm^{-1}$ in the IR spectrum. Reaction of **154** with hydroxylamine hydrochloride and sodium acetate in methanol affords (+)-*N,N*-dicyclohexyl-2-(hydroxyimino)-7,7-dimethyl-bicyclo[2.2.1]-heptyl-1-methanesulfonamide **155** in 96% yield. This method proved to be superior to the condensation under basic conditions ($HO\text{-}NH_2 \cdot HCl$, KOH, EtOH, 61% yield) and to that reported in the literature,[13] since it requirs no other workup than pouring the reaction mixture into ice water, filtration and washing the precipitate with distilled water. Spectroscopic data and elemental analysis confirm structure and purity of oxime **155**.

Chlorination of oximes is the most advantageous method for the synthesis of *gem*-chloronitroso compounds. It involves the treatment of the oxime with chlorine in $Et_2O$[123-125] or DCM,[126-128] NaOCl in dioxane-water[129] or with $^t$BuOCl in DCM.[5,13,60] The method involving alkylhypochlorites has distinguishing features: *gem*-chloronitroso compounds are stable under the reaction conditions, a facile workup, the yields are nearly quantitative and high-purity products are obtained. Chlorination of **155** using $^t$BuOCl ($^t$BuOH solution) in DCM affords *N,N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74** in 85% yield as blue crystals. It has been observed that the concentration of $^t$BuOCl solution plays an important role with respect to yield and product purity, most probably due to the interference of $^t$BuOH. Using a 75% $^t$BuOCl/ $^t$BuOH solution a yield of 85% is observed, while with a 19.5% $^t$BuOCl/ $^t$BuOH

solution the yield dropps to 51%. Analysis of the IR spectrum of **74** shows the characteristic N=O absorption band at 1583 $cm^{-1}$. The mass spectrum - electrospray ionization, positive ion mode - shows the peaks corresponding to the cation of **74** (Figure 13).

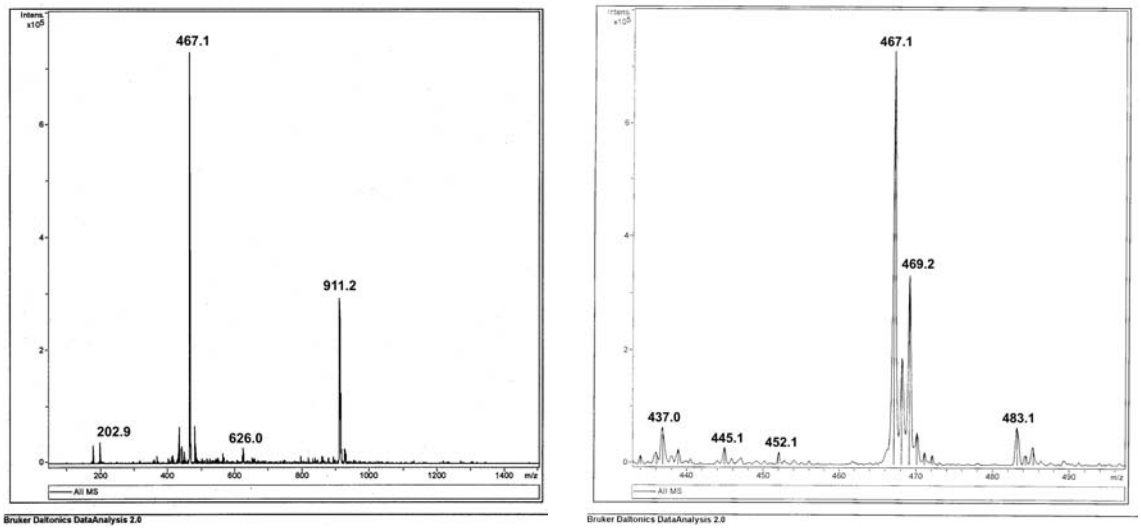
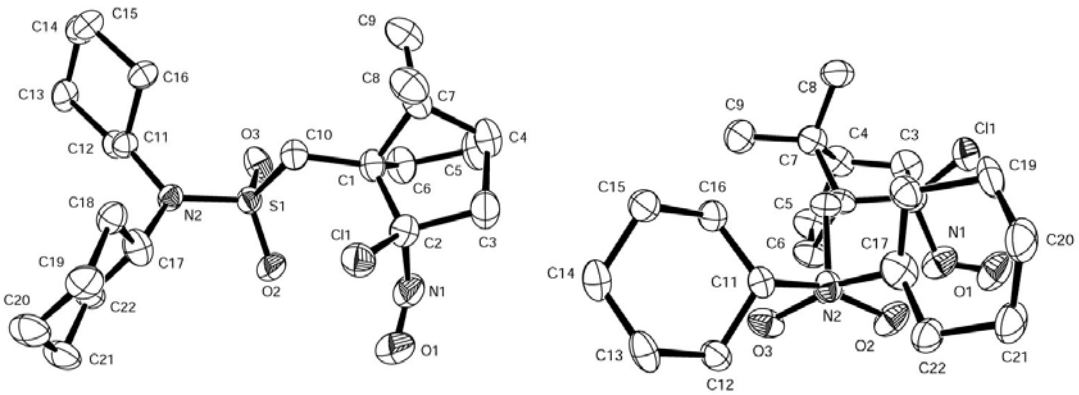



**Figure 13:** Mass spectrum (ESI, positive ion mode) of **74**

The presence of chlorine was supported by the occurrence of its isotope patterns. A base peak ion was observed at $m/z$ 467.1, assigned to $[M(C_{22}H_{37}{}^{35}ClN_2O_3S)+Na]^+$, accompanied by a peak at $m/z$ 469.2 which has been assigned to $[M(C_{22}H_{37}{}^{37}ClN_2O_3S)+Na]^+$. The ion peaks at $m/z$ 911.2 and $m/z$ 913.2 correspond to $[2M(^{35}Cl)+Na]^+$ and $[2M(^{37}Cl)+Na]^+$, respectively.

Recrystallization of **74** from AcOEt:PE affords suitable crystals for X-ray analysis. The molecular structure of the α-chloronitroso compound with the atom numbering is shown in Figure 14 and the main geometrical parameters are given in Appendix.




**a** **b**

**Figure 14:** ORTEP representation of **74** (a) and projection of the structure along S-N axis (b)

The ORTEP plot of **74** shows that the nitroso group N1=O1 is *trans* to the $CMe_2$ bridge (C8-C7-C9) and the O1 atom adopts a syn-periplanar orientation to the Cl1 atom, as shown by the torsional angle Cl1-C2-N1-O1= -12.16°. The stereochemistry at C2 atom is *R*. The bulky *N,N*-dicyclohexyl-sulfonamide group selectively shields one face of the N=O group, as can be seen from the projection of the structure along the S-N axis (Figure 14b). X-Ray diffraction analysis shows 8% co-crystallisation of (+)-*N,N*-dicyclohexyl-2-oxychloro-2-nitroso-camphor-10-sulfonamide. Its formation is most probably due to a radical process, initiated by the photodissociation of *tert*-butyl hypochlorite.[130]

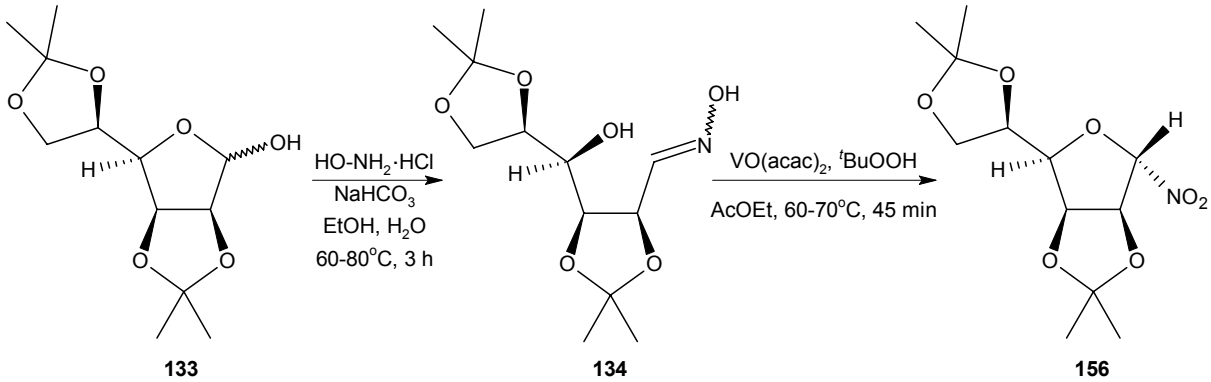
### 3.1.3 Stereoselective Synthesis of 1-Deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose

The remarkable synthetic importance of nitro compounds has ensured long-standing studies of their utilization in organic synthesis.[131] The versatility of nitro compounds in organic synthesis is largely due to their availability and easy transformation into a variety of diverse functionalities. For the present studies concerning the stereoselective electrophilic amination of allyl organometallic substrates, the enantiomerically pure 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** has been chosen as a potential [$NH_2^+$] synthon.

Conversion of the carbonyl to the nitro group (retro Nef reaction) is an important method for the preparation of nitro compounds. Such a conversion is generally effected via oximes using strong oxidants such as $CF_3COOOH$.[132,133] Anhydrous peroxytrifluoroacetic acid is not easy to handle and undoubtedly not compatible with dioxolane systems like **134**. Various convenient methods for the oxidation of sugar oximes which involve $(CF_3CO)_2O/H_2O_2/CH_3CN$[134], *m*-CPBA/$O_3$/DCM[135] or Py/$Cr_2O_7$/$H_2N$-OH/$H_2O_2$/DCM[136] have been developed.

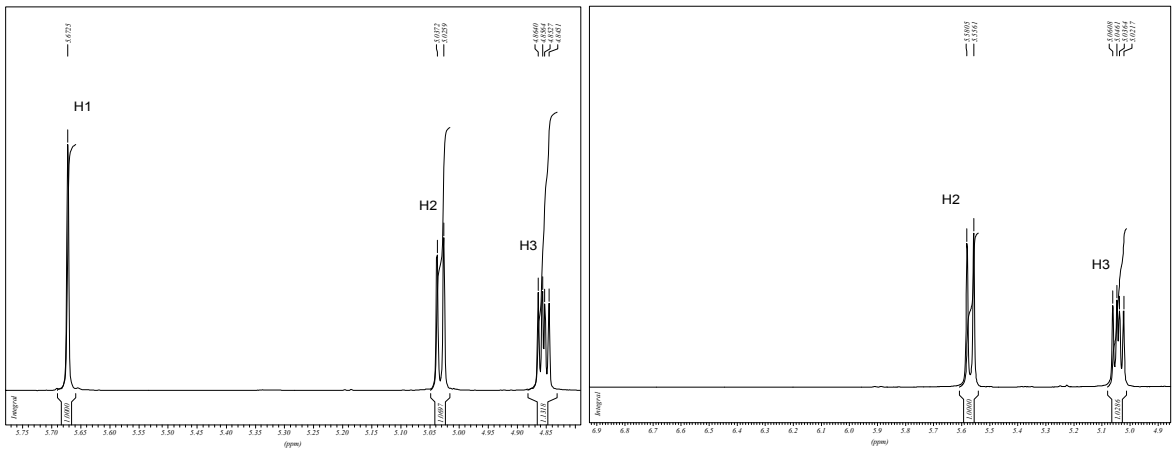
The preparation of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** succeeds according to the procedure described by Vasella *et al.*[137] (Scheme 36).

The oxidation of 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134** with *tert*-butyl hydroperoxide, catalyzed by vanadyl(IV)-acetylacetonate, furnishes 1-deoxy-1-nitrosugar **156** in 52% yield. The reaction mechanism is similar to that reported for the metal-catalyzed epoxidation of allylic alcohols.[138] The IR spectrum of **156** shows a strong absorption band at 1567 $cm^{-1}$ corresponding to the $NO_2$ functionality and the mass spectrum (electrospray ionisation, positive ion mode) shows a base peak at $m/z$ 312 which has been assigned to $[M + Na]^+$. Analysis of the $^1H$ NMR spectrum confirms the α-D-configuration at C(1). The signal of the anomeric proton appears as a singlet at 5.67 ppm, and the signal corresponding to H-C(2) appears as a doublet




**Scheme 36:** Synthesis of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156**.

($^3J_{2\text{-}3}$ = 5.6 Hz) at 5.03 ppm. The absence of a coupling between H-C(1) and H-C(2) supports the *syn* orientation of $NO_2$ towards H-C(2). The signal corresponding to H-C(1) disappears when a catalytic amount of $LiOCH_3$ is added to a solution of **156** in deuteriomethanol and H-C(2) is shifted to a higher field (5.54 ppm, doublet, $^3J_{2\text{-}3}$ = 6.2 Hz) (Figure 15).



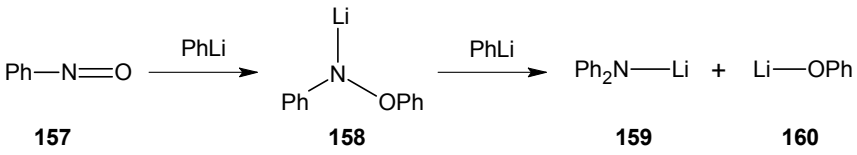

a b

**Figure 15:** $^1$H NMR spectrum of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-manno-furanose **156** (a) and of **156**+catalytic amounts of $LiOCH_3/CD_3OD$ (b).

1-Deoxy-1-nitrosugar **156** is obtained as white crystals after column chromatography and no epimerization at C(1) has been observed upon standing for several months at 0°C.

## 3.2 Studies towards the Electrophilic Amination of Carbanions using Enantiomerically Pure Nitrenoids

In 1964 Closs and Moss [139] proposed the use of the term *carbenoid* (as a noun) for the description of the "intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species". The term *nitrenoid* was coined by Koebrich in 1967 [140] when he studied the reaction of phenyllithium with nitrosobenzene **157** (Scheme 37).




**Scheme 37:** Electrophilic amination of PhLi with *in situ* generated nitrenoid **158**.[140]

On protonation, diphenylamine and phenol are formed, which are due to the lithiated precursors **159** and **160**. Most likely, **159** and **160** result from the reaction of the nucleophile phenyllithium with the electrophilic **158**, which thus should be called a *nitrenoid*.
Compounds like **161** have been defined analogously[140] and they have a long history in organic chemistry although their nitrenoid properties have been recognized only in recent years.[141]

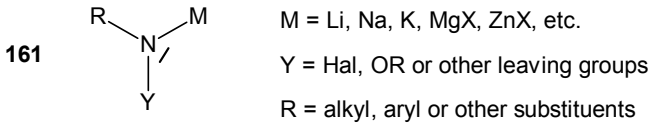
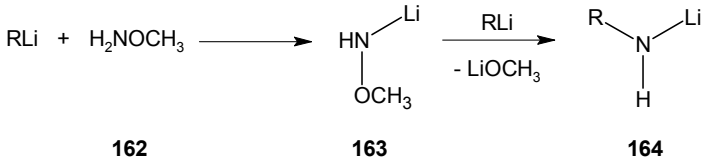



**Figure 16:** General structure of a nitrenoid as defined by Buck and Koebrich.[140]

The amination of carbanions RLi (and of others) with *O*-methylhydroxylamine **162** is known as the Schewerdina-Kotscheschkow amination reaction (Scheme 38).[142-146]

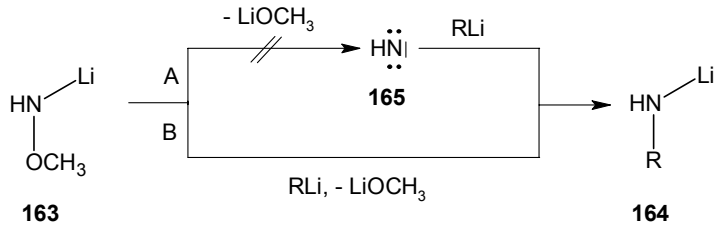



**Scheme 38:** Electrophilic amination of carbanions with lithiated *O*-methylhydroxylamine **162**.[142]

It has been suggested that deprotonation of **162** takes place first to give the nitrenoid **163**, which then reacts with a second RLi to give the *N*-lithiated amine **164**. Compound **164** is further

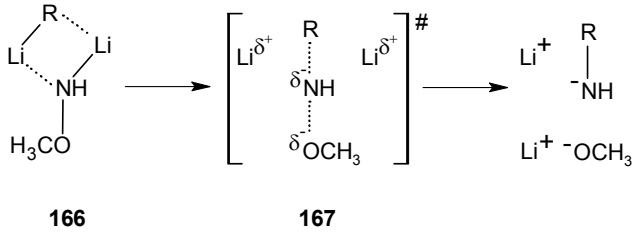
protonated to form the respective amine. To overcome the problem of using (at least) two equivalents of the organometallic reagent (*e.g.* RLi), it has been suggested to use an expendable RLi (*i.e.* MeLi) in the deprotonation step **162** → **163** and only then to employ the lithium reagent to be aminated (**163** → **164**).[147-149]

The mechanism of the electrophilic amination of carbanions with lithiated *O*-alkylhydroxylamines was studied experimentally by Beak *et al.*[82,150]. There are two possible pathways (Scheme 39). The nitrenoid **163** could undergo an α-elimination of $LiOCH_3$ to give the nitrene **165** which then adds RLi to produce **164** (pathway A in Scheme 39). In pathway B a nucleophilic substitution reaction takes place at the nitrenoid nitrogen atom of **163** to give **164** directly. The authors[82,150] demonstrated conclusively that it is pathway B which takes place. As in the case of the carbenoids in which the α-elimination to give carbenes occurs only under special conditions,[141] the formation of nitrenes from nitrenoids is also not a very favorable reaction. This is an especially unlikely pathway considering the poor leaving group $CH_3O^-$ at the nitrogen atom of **163**.




**Scheme 39:** The mechanism of the electrophilic amination of carbanions with lithiated *O*-alkyl-hydroxylamines **163** as proposed by Beak *et al.*[82,150]

Formally, the displacement process ($S_N2$-like) of pathway B involves the reaction of two anionic species, an interaction that should be repulsive. However, organolithium species are generally aggregated, and a reasonable pathway involving associated species can be envisioned. In the simplest case, a dimer **166** in which the entering carbon is disposed on the side of nitrogen and the nitrogen oxygen bond is polarized, leading to the transition state **167**, has been suggested (Scheme 40).[82]



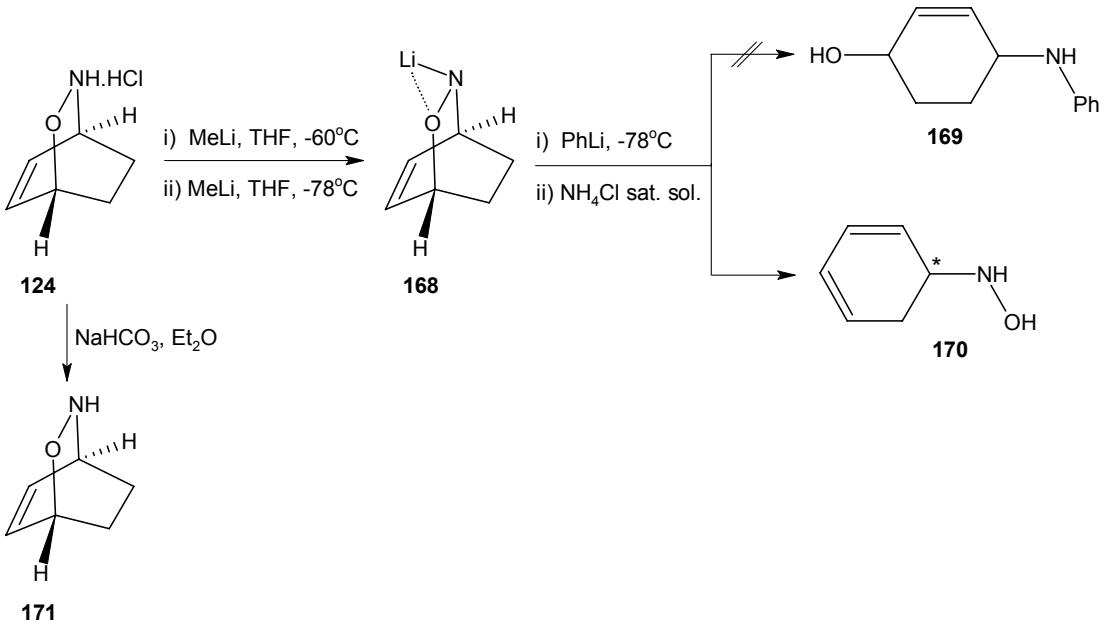

**Scheme 40:** Transition state suggested for the electrophilic amination of carbanions with lithiated *O*-alkylhydroxylamines **163**, as proposed by Beak *et al.*[82,150]

This appears to be a case in which the proximity effect operating in a lithium complex provides access to a novel reaction pathway.[151,152] In the amination method developed by Beak *et al.*[82,150], it has been suggested that the N-O bond of lithium methoxyamide **163** is bridged by the lithium atom. Boche and Wagner[153] revealed from quantum chemical calculations that the N-O bond of lithium methoxyamide **163** is longer (1.60093 Å) than the related bond in its non lithiated counterpart **162** (1.4374 Å). This would explain the relatively facile cleavage of the N-O bond in the electrophilic amination process.

In the present studies concerning the electrophilic amination of carbanions with the enantiomerically pure **168** and with the lithiated *N,O*-disubstituted hydroxylamines **147**, **148**, **151** and **152**, the amination reaction of phenyl lithium (PhLi) was used as a model procedure, in order to examine the amination potential of these reagents.

**168** is generated by the reaction of oxazine hydrochloride **124** with one equivalent of methyl lithium in THF at -60°C, followed by the addition of a second equivalent of methyl lithium at -78°C.

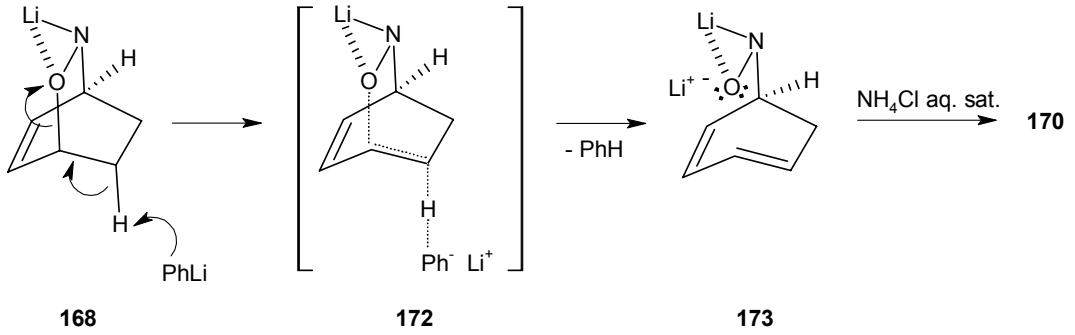
The reaction of **168** with PhLi at -78°C affords *N*-(2,4-cyclohexadien-1-yl)hydroxylamine **170** instead of expected 4-anilino-2-cyclo-hexen-1-ol **169** (Scheme 41).




**Scheme 41:** Reaction between **168** and PhLi.

*N*-(2,4-Cyclohexadien-1-yl)hydroxylamine **170** can be crystallized directly from the reaction mixture, but decomposes instantaneously when filtered off. However, the hydroxylamine **170** has been characterized by its $^{1}H$ and $^{13}C$ NMR and IR spectra and the optical activity has been determined, but no information of e.e. is available, due to the lability of the compound. No decomposition products are observed after stirring of **168** at -78°C for 1 h, quenching with $D_2O$

and $^1$H NMR analysis. The same stability of **168** is observed when *n*-hexane is used as solvent or when **168** is generated from the oxazine **171**. The reaction with PhLi in *n*-hexane also affords the hydroxylamine **170** as main product, together with unreacted oxazine **171**. Formation of the hydroxylamine **170** can be explained by the occurrence of β-elimination of the proton H-C(7) under the influence of PhLi (Scheme 42). The anti-periplanar geometry of H-C(7)-C(1)-O favours the E2 elimination pathway.

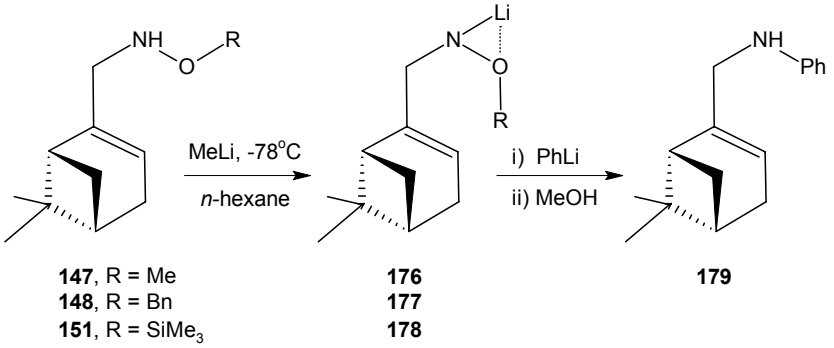



**Scheme 42:** Proposed E2 elimination mechanism for the formation of hydroxylamine **170**.

Since the formation of the required dimer of type **166** between PhLi and the amination reagent **168** showed to be unfavourable, the use of organocopper reagents, *i.e.* higher order cyanocuprates, came into attention. Higher order cyanocuprates are highly aggregated species, soft nucleophiles and have a lower basicity compared to organolithium reagents. It was assumed that using such an organocopper reagent as substrate, the amination reagent **168** will be driven into the formation of a complex which would reproduce the dimer **166**. Therefore, $Ph_2Cu(CN)Li_2$ **175** was reacted with **168** at -78°C to room temperature in THF, but only unreacted oxazine **171** was detected.

The lithium amide **168** proved to be not effective as electrophilic amination reagent of even simple carbanions. The study concerning the stereoselective amination of carbanions using chiral nitrenoids was then continued using lithiated hydroxylamines **147**, **148** and **151**.

The electrophilic amination of PhLi was carried out in a similar manner, by generating the chiral amination reagents using one equivalent of methyl lithium, in *n*-hexane at -78°C, followed by the addition of PhLi (Scheme 43). Aniline derivative **179** resulted in low to moderate yields (Table 2).




**Scheme 43:** Electrophilic amination of PhLi with nitrenoids generated from **147**, **148** and **151**.

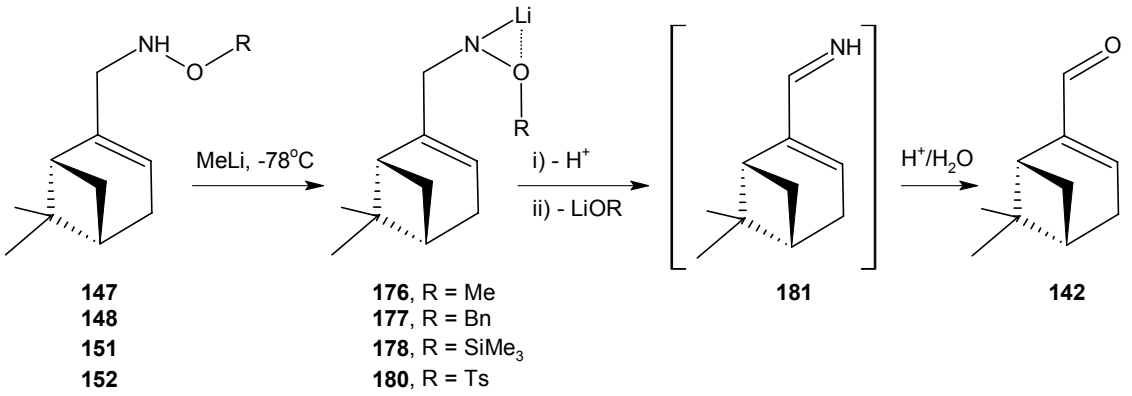
**Table 2:** Electrophilic amination of PhLi with nitrenoids generated from **147**, **148** and **151** using MeLi.

| Entry | Hydroxylamine | Reaction temperature, °C | Reaction time, h | Yield of 179, % |
|---|---|---|---|---|
| 1 | **147** | -78 | 8 | - |
| 2 | **147** | -40 | 4 | 36 |
| 3 | **148** | -40 | 5 | 27 |
| 4 | **151** | -40 | 3 | 56 |

*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-aniline **179** was fully characterized. The IR spectrum shows a medium intensity absorption band at 3421 $cm^{-1}$ corresponding to the NH functionality. In the $^{1}H$ NMR spectrum the peaks corresponding to the phenyl group appear at 7.15 ppm (2H, multiplet) and 6.58–6.67 ppm (3H, multiplet), and in the $^{13}C$ NMR spectrum the phenyl moiety can be identified by its characteristic signals at 148.47 (C-N), 129.11 (two $C_{meta}$), 117.20 (two $C_{ortho}$) and 112.91 ppm ($C_{para}$).

Myrtenal imine **181** is formed during the reaction, according to GC-MS analysis of the reaction mixture. Compound **181** has been identified by its MS (Electron Impact Ionisation method) pattern, which shows the molecular ion at $m/z$ 149 and the subsequent fragmentation peaks. Attempts to isolate the imine **181** were unsuccessful, but acidic hydrolysis furnished (1*R*)-(-)-myrtenal **142**.

The occurrence of imine **181** and the relatively low yield of **179** suggested to perform a stability study of the lithiated compounds **176**, **177**, **178** and **180**, generated prior to the amination step. Their stability is investigated by generating the chiral nitrenoid in THF or *n*-hexane, from the parent *N,O*-disubstituted hydroxylamine and methyl lithium at -78°C, followed by quenching with saturated aqueous $NH_4Cl$, hydrolysis of the mixture with 1M HCl and subsequent GC analysis. In the mentioned cases (Table 3) formation of (1*R*,5*R*)-(-)-myrtenal **142**, as product of imine **181** hydrolysis, has been observed (Scheme 44).




**147**
**148**
**151**
**152**

**176**, R = Me
**177**, R = Bn
**178**, R = $SiMe_3$
**180**, R = Ts

**181**

**142**

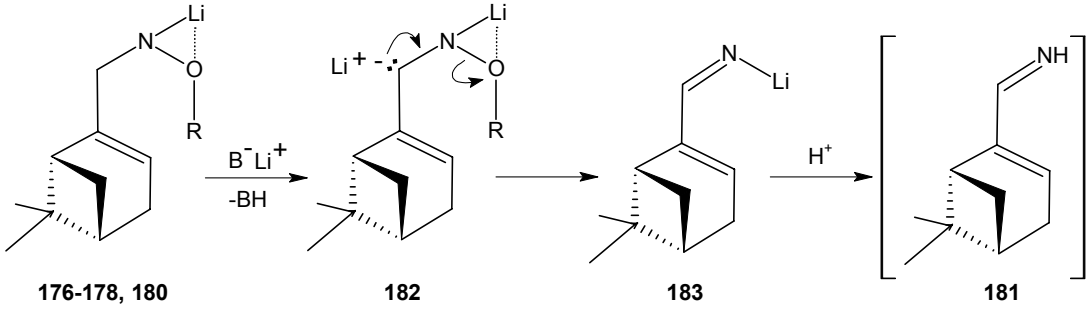
**Scheme 44:** Elimination of ROLi from lithiated *N,O*-disubstituted hydroxylamines.

**Table 3:** Stability test of the lithiated *N,O*-disubstituted hydroxylamines **176**-**178** and **180**.

| Entry | Hydroxylamine | Solvent | Reaction time, h | Ratio hydroxylamine : 142 [a] |
|---|---|---|---|---|
| 1 | **147** | THF | 1 | 100 : 0 |
| 2 | **147** | n-hexane | 1 | 71 : 29 |
| 3 | **148** | THF | 1 | 100 : 0 |
| 4 | **148** | n-hexane | 1 | 51 : 49 |
| 5 | **151** | THF | 1 | 85 : 15 |
| 6 | **151** | n-hexane | 1 | 66 : 34 |
| 7 | **152** | THF | 1 | 34 : 66 |
| 8 | **152** | n-hexane | 1 | 86 : 13 |

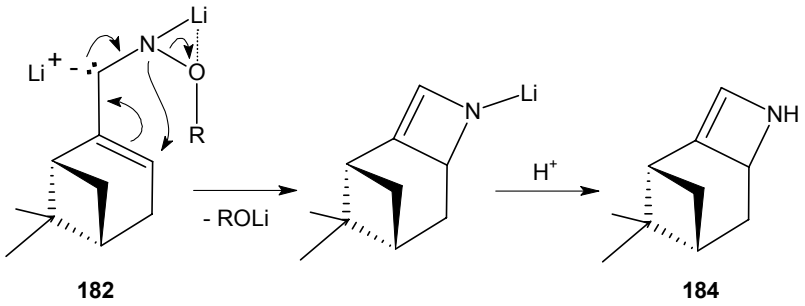
a) Determined by gas chromatography

Deprotonation in the α position to nitrogen in *N*-protected allyl amines is a known procedure for the asymmetric carbon-carbon bond formation and has been studied by Beak *et al.*[154,155] It occurs in unpolar solvents and in the presence of (-)-sparteine, and provides the allylic carbanion which reacts with carbon electrophiles either at the γ or α position. A similar behaviour can be envisioned for the lithiated *N,O*-disubstituted hydroxylamines **176**-**178** and **180**. After deprotonation with methyl lithium, the elimination of the proton in the position α to the nitrogen atom might proceed either under the influence of a local methyl lithium excess or due to an intermolecular reaction between lithiated hydroxylamines. The newly formed, relatively stable allylic carbanion **182** undergoes the elimination of ROLi, to provide the *N*-lithiated imine **183** (Scheme 45).




**Scheme 45:** Proposed mechanism for the formation of imine **181**.

It should be mentioned that formation of (1*R*,5*R*)-(-)-myrtenal **142** after hydrolysis suggests that a pathway in which **182** undergoes an intramolecular amination reaction to provide the imine **184** is less favourable (Scheme 46).




**Scheme 46:** Possible pathway for the intramolecular reaction of **173**.

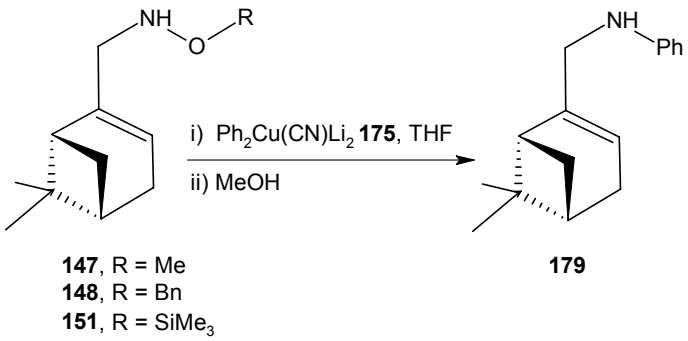
As can be seen in Table 3, the amount of imine **181**, respectively (1*R*,5*R*)-(-)-myrtenal **142**, increases when the deprotonation of hydroxylamines is performed in an unpolar non-coordinating solvent, *i.e. n*-hexane. This correlates with the decreased stability of the nitrenoids in this solvent. It is well known[156] that in such solvents organolithium compounds are associated species, whereas in a polar coordinating solvent like THF formation of a monomer-solvent complex is preferred. It can be concluded that THF has a stabilizing effect on the intermediate **182**, reducing the tendency towards elimination of ROLi by coordination to the lithium cation bonded to the nitrogen atom. Since the formation of aggregated **176**-**178** and **180** is favoured in *n*-hexane, the pathway in which α-deprotonation of lithiated *N,O*-disubstituted hydroxylamines occurs by an intermolecular reaction followed by the elimination of ROLi, may have a major contribution to the formation of **181**. These conclusions are supported by the remarks of Beak *et al.*[150], who found that reactivity of the nitrenoid **163** towards alkyl or aryllithium reagents increases when, instead of THF or $Et_2O$, *n*-hexane was used as solvent, favouring the formation of the

dimer RLi·LiNH-$OCH_3$ **166**. The results presented in Table 3 show that the proportion of imine **181** depends also on the leaving group ability of the substituent connected to the nitrogen atom.
Because of the very similar deprotonation conditions that lead to the formation of **176**-**178**, **180**, and **168**, the stability of the lithium amide **168** can be explained by its incapacity of forming geometrically favorable aggregates which would allow an intermolecular second deprotonation, most probably due to sterical hindrance.
These observations suggest that despite the relatively reduced tendency towards decomposition of *N*-lithiated hydroxylamines in THF, *n*-hexane is the proper solvent for electrophilic amination, because of the higher degree of aggregation. A procedure in which the nitrenoids are generated *in situ* using two equivalents of phenyl lithium, added at once to the hydroxylamines **147**, **148** and **151**, was carried out. The results are presented in Table 4.

**Table 4:** Electrophilic amination of PhLi with nitrenoids generated from **147**, **148** and **151** using PhLi.

| Entry | Hydroxylamine | Reaction temperature, °C | Reaction time, h | Yield of 179, % |
|---|---|---|---|---|
| 1 | **147** | -40 | 3 | 48 |
| 2 | **148** | -40 | 3.5 | 47 |
| 3 | **151** | -40 | 3 | 59 |

Very good results are obtained when phenyl lithium is transmetalated to the higher order cyanocuprate $Ph_2Cu(CN)Li_2$ **175**. Treatment of the hydroxylamines **147**, **148** and **151** with one equivalent of **175**, in THF (Scheme 47), afforded the amine **179** in good yields (Table 5).

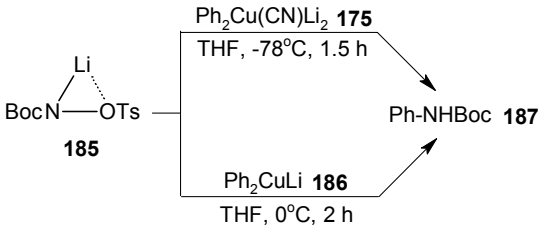



**Scheme 47:** Electrophilic amination of $Ph_2Cu(CN)Li_2$ **175** with hydroxylamines **147**, **148** and **151**.

**Table 5:** Electrophilic amination of $Ph_2Cu(CN)Li_2$ **175** with *in situ* generated nitrenoids **176**-**178** form hydroxylamines **147**, **148** and **151**.

| Entry | Hydroxylamine | Reaction temperature, °C | Reaction time, h | Yield of 179, % |
|---|---|---|---|---|
| 1 | **148** | -40 to -20 | 4 | 72 |
| 2 | **147** | -50 to RT | 5 | 70 |
| 3 | **151** | -50 to RT | 3 | 94 |

Electrophilic amination of the higher order cyanocuprate $Ph_2Cu(CN)Li_2$ **175** with lithium *tert*-butyl-*N*-tosyloxycarbamate **185** has been reported by Greck *et al.*[157] to proceed in 35% yield, whereas the Gilman cuprate $Ph_2CuLi$ **186** furnishes *N*-Boc-aniline **187** in 23% yield (Scheme 48).




**Scheme 48:** Electrophilic amination of cuprates with lithium *tert*-butyl-*N*-tosyloxycarbamate **185**.

The authors suggest an intermediate in which the nitrogen atom of the amination reagent is chelated on both Li and Cu (Figure 17) and the nucleophile R attacks on the nitrogen on the opposite site of the leaving group. This has been presumed to be a $S_N2$ process.

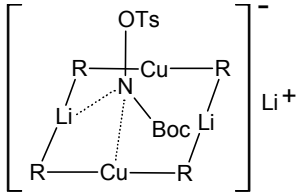



**Figure 17:** Intermediate suggested by Greck *et al.*[157] for the electrophilic amination of lower order Gilman cuprates with lithium *tert*-butyl-*N*-tosyloxycarbamate **185**.

Ricci *et al.*[121] reported a related electrophilic amination of higher order cuprates $Ar_2Cu(CN)Li_2$ with *O*-trimethylsilyl hydroxylamines R-NH-$OSiMe_3$ (R = Me, $^i$Pr, $^t$Bu) in 45-88% yield. In contrast to the report of Greck *et al.*[157], *O*-trimethylsilyl hydroxylamines have not been lithiated before addition to the cuprate.

The discovery of cyanocuprates and their application in organic synthesis resulted in a scientific controversy concerning the actual structure of these compounds.[158] Initially, two models to

describe the structure of these cyanocuprates were put forward: a bisanionic species in which two organic groups and the cyanide were bound to the same copper atom (Figure 18A) and a Gilman cyanocuprate in which only the two organic groups were bound to copper (Figure 18B). The controversy was resolved in 1999[159], in favor of proposal B.

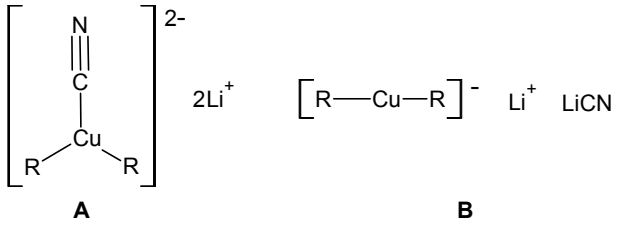
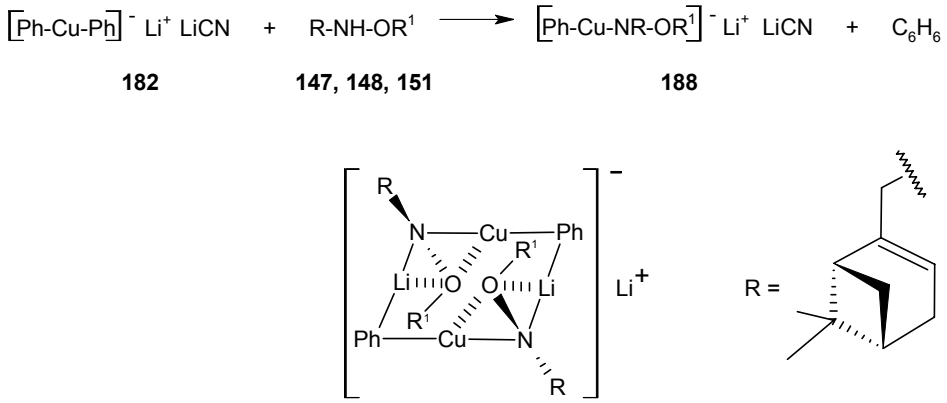



**Figure 18:** Models describing the proposed structures of cyanocuprates.[158]

The results reported by Greck *et al.*[157] and Ricci *et al.*[121], combined with those concerning the amination of $Ph_2Cu(CN)Li_2$ **175** with one equivalent of hydroxylamines **147**, **148** or **151**, and the structure of cyanocuprates suggest that after deprotonation of hydroxylamines, an intermediate in which the nitrogen anion and the oxygen atom are both coordinated by copper and lithium may be involved (Scheme 49). Further elimination of $R^1OM$ (M = Li or Cu) and recombination of Ph and NR furnished the aniline derivative **179**.

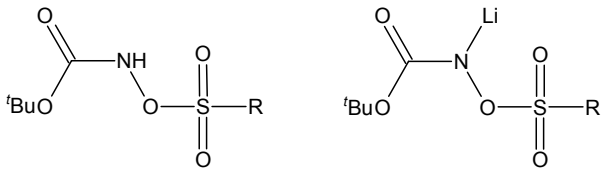
The failure of oxazine **168** to react in a similar manner is most probably due to the impossibility of adopting an intermediate similar to that shown in Scheme 49, because of greater sterical hindrance.




**Scheme 49:** Intermediate suggested for the electrophilic amination of higher order cuprates $Ph_2Cu(CN)Li_2$ **175** with hydroxylamines **147**, **148** or **151**.

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-tosyl hydroxylamine **152** gave substantially inferior results compared to **147**, **148** or **151**.

*tert*-Butyl-*N*-(tosyloxy)carbamate **189** has been used as a model for the design and application of **152**. Greck *et al.*[27,157] reported the synthesis, stability and use of **185** and of *N*-lithiated *tert*-butyl-*N*-mesityloxycarbamate **191** as electrophilic amination reagents with good results.



**189**, R = Ts
**190**, R = Mes

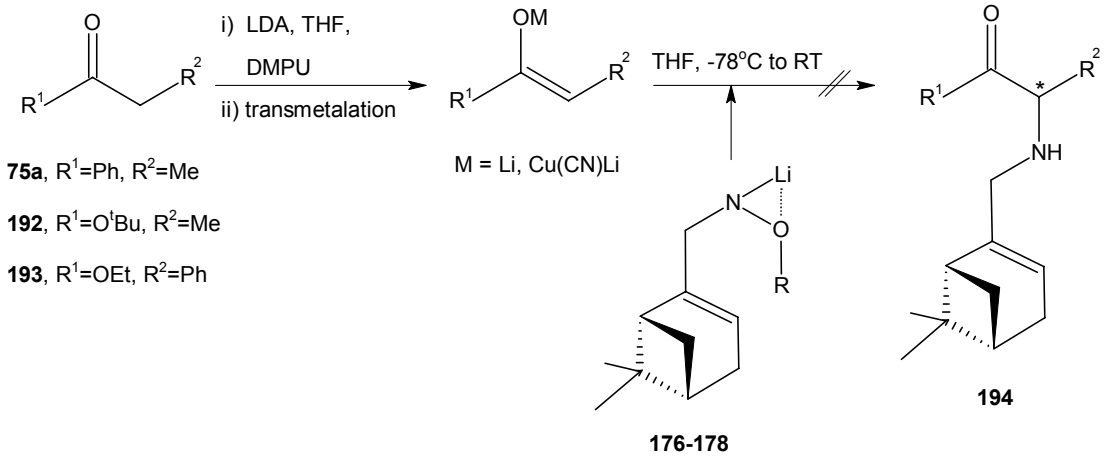
**185**, R = Ts
**191**, R = Mes

**Figure 19:** Electrophilic amination reagents introduced by Greck *et al.*[27,157]

It has been suggested that their superiority compared with other electrophilic amination reagents is due to the increased leaving group ability of the tosyl or mesityl moiety. Moreover, it has been found[160] that the presence of the *tert*-butyloxycarbonyl group on the nitrogen atom has a stabilizing effect on the nitrenoids **185** and **191**. The *N*-lithiated hydroxylamine **180** does not possess such a stabilizing group on nitrogen and under strongly basic conditions,[161] the presence of a proton in the α position to nitrogen, combined with the higher leaving group ability of the tosyl moiety, greatly favours the elimination pathway and formation of **181** (Scheme 44).

Further studies concerning the electrophilic amination of ketone and ester enolates with nitrenoids **176-178** were done in order to provide a valuable method for the stereoselective synthesis of α-amino ketones and α-amino acids.

The lithium or copper enolates derived from propiophenone **75a**, *tert*-butyl propionate **192** and ethyl phenylacetate **193** were used as substrates. *N,N'*-Dimethylpropylene urea (DMPU) was used as co-solvent. Nitrenoids **176-178** were generated before or *in situ* using methyl lithium or LDA. In all cases, with the exception of the reaction between the lithium ester enolate of **192** and nitrenoids **176** and **177**, respectively, no formation of the product **194** was observed (Scheme 50).



**75a**, $R^1$=Ph, $R^2$=Me
**192**, $R^1$=O$^t$Bu, $R^2$=Me
**193**, $R^1$=OEt, $R^2$=Ph

i) LDA, THF,
DMPU
ii) transmetalation

M = Li, Cu(CN)Li

THF, -78°C to RT

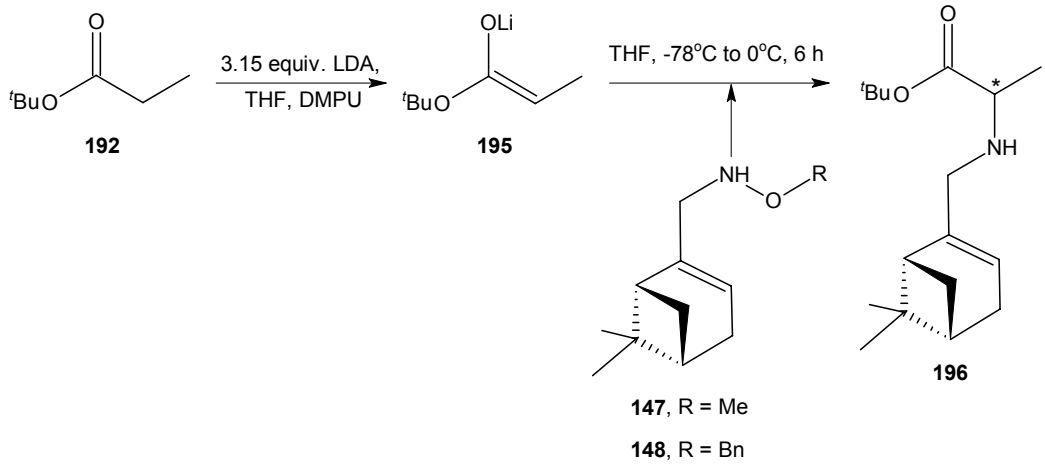
**176-178**

**194**

**Scheme 50:** Reaction strategy for the stereoselective electrophilic amination of enolates with nitrenoids **176**-**178**.

Due to its high decomposition rate, the lithiated hydroxylamine **180** was found to be inappropriate to be further involved in these electrophilic amination studies.

When the lithium enolate of the *tert*-butyl propionate **192** was generated using LDA in THF and DMPU as co-solvent, followed by the simple addition of the hydroxylamines **147** and **148**, respectively, GC-MS analysis of the reaction mixture shows traces of a product which appears as four peaks (Figures 21 and 23) with the same MS pattern (Figures 22 and 24). The electrophilic amination reagents **176** (R = Me) and **177** (R = Bn) were generated *in situ* using excess of LDA. The use of DMPU as co-solvent ensures the selective formation of the *Z*-enolate of **192** and the formation of **196** as a mixture of two diastereomers was expected (Scheme 51).




**Scheme 51:** Electrophilic amination of lithium ester enolate **195** with the *in-situ* generated nitrenoids **176** or **177**.

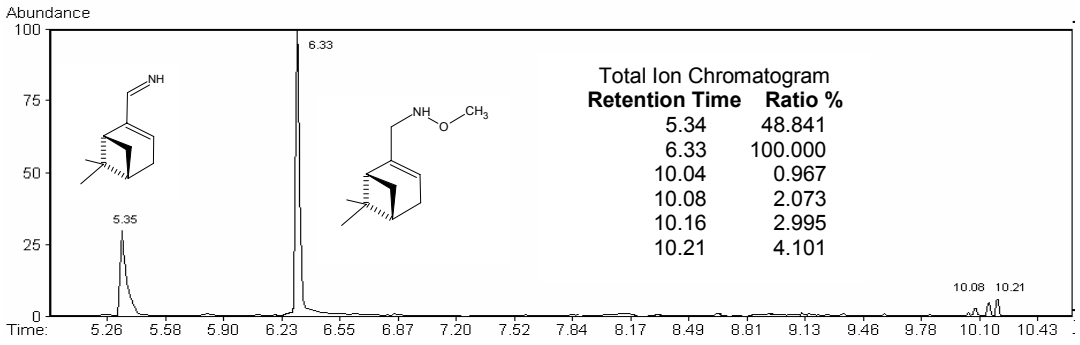



**Figure 21:** GC analysis for the electrophilic amination reaction of the lithium ester enolate **195** involving hydroxylamine **147** (GC method: *GC-MS Pr. 1*).

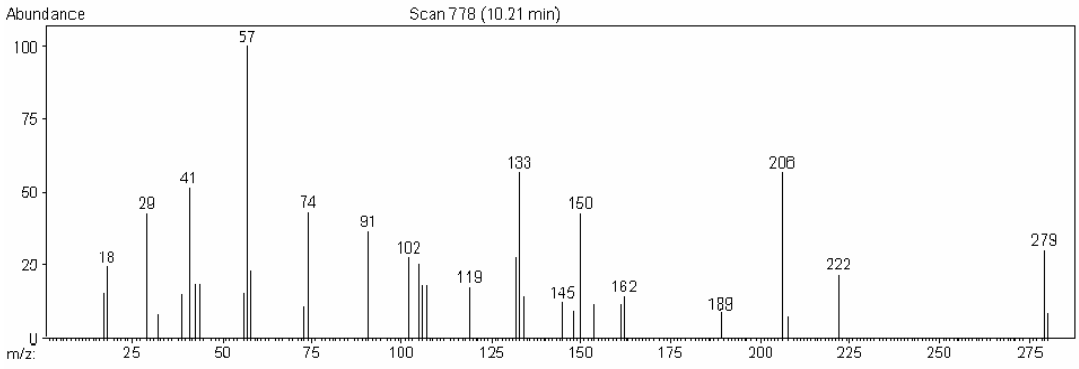



**Figure 22:** EI mass spectrum of the product resulted from the reaction between the lithium ester enolate **195** and hydroxylamine **147**

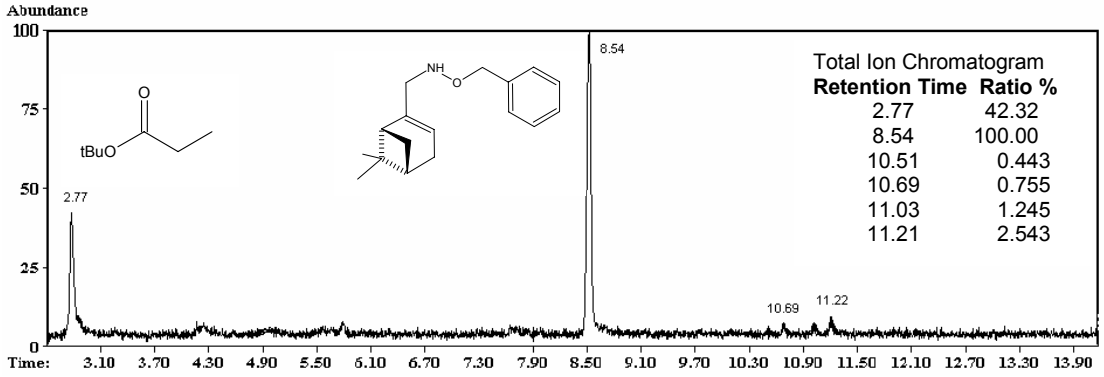



**Figure 23:** The gas chromatography analysis for the electrophilic amination reaction of the lithium ester enolate **195** involving hydroxylamine **148** (GC method: *GC-MS Pr. 2*).

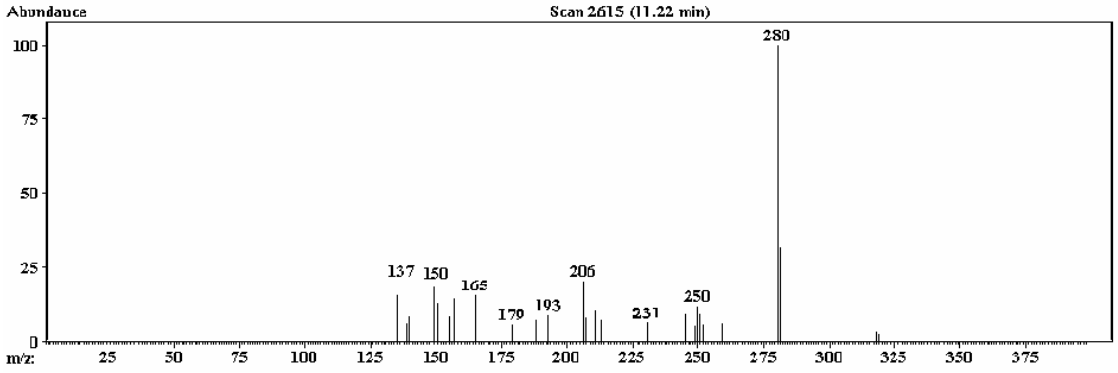
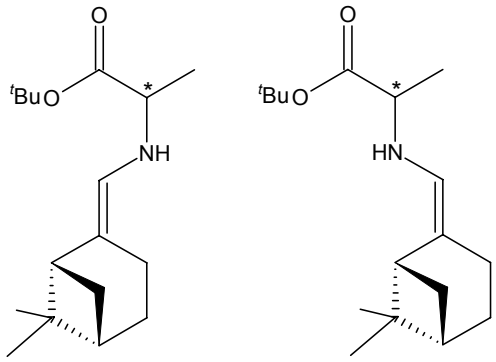



**Figure 24:** CI mass spectrum of the product resulted from the reaction between the lithium ester enolate **195** and hydroxylamine **148**

The EI mass spectrum (Figure 22) shows the molecular ion at *m*/*z* 279 and the subsequent specific fragmentation peaks at *m*/*z* 222 (22%) $[M\text{-}^{t}Bu]^{+\cdot}$, 206 (54%) $[M\text{-}BuO]^{+\cdot}$, 150 (48%)

$[M\text{-}^{t}BuOC(O)CHCH_3]^{+\cdot}$, 145 (12%) $[^{t}BuOC(O)CH(NH_2)CH_3]^{+\cdot}$ and 57 (100%) $[^{t}Bu]^{+\cdot}$. The CI mass spectrum (Figure 24) shows the base peak at *m/z* 280 $[M+H]^+$ and the subsequent fragmentation peaks at *m/z* 250 (18%) $[M+H\text{-}C_2H_6]^+$, 206 (23%) $[M+H\text{-}^{t}BuOH]^+$ and 150 (24%) $[M\text{-}^{t}BuOC(O)CHCH_3]^+$.

The observed four peaks with the same MS pattern from the chromatograms showed in Figures 21 and 23 may correspond to the four possible diastereomers of the structure **197** (Figure 25), since the rearrangement of the pinene double bond can be expected to occur under the strongly basic conditions involved. As there are only traces of four compounds with identical molecular mass present in the GC-MS spectra, no clear decision can be made which of the six possible structures (**196** and **197**) are actually formed. The formation of the imine **181** is also observed as decomposition product of the nitrenoid **176**.




**197**

**Figure 25**. Products formed in the electrophilic amination reaction of the lithium ester enolate **195** involving hydroxylamines **147** and **148**, respectively.

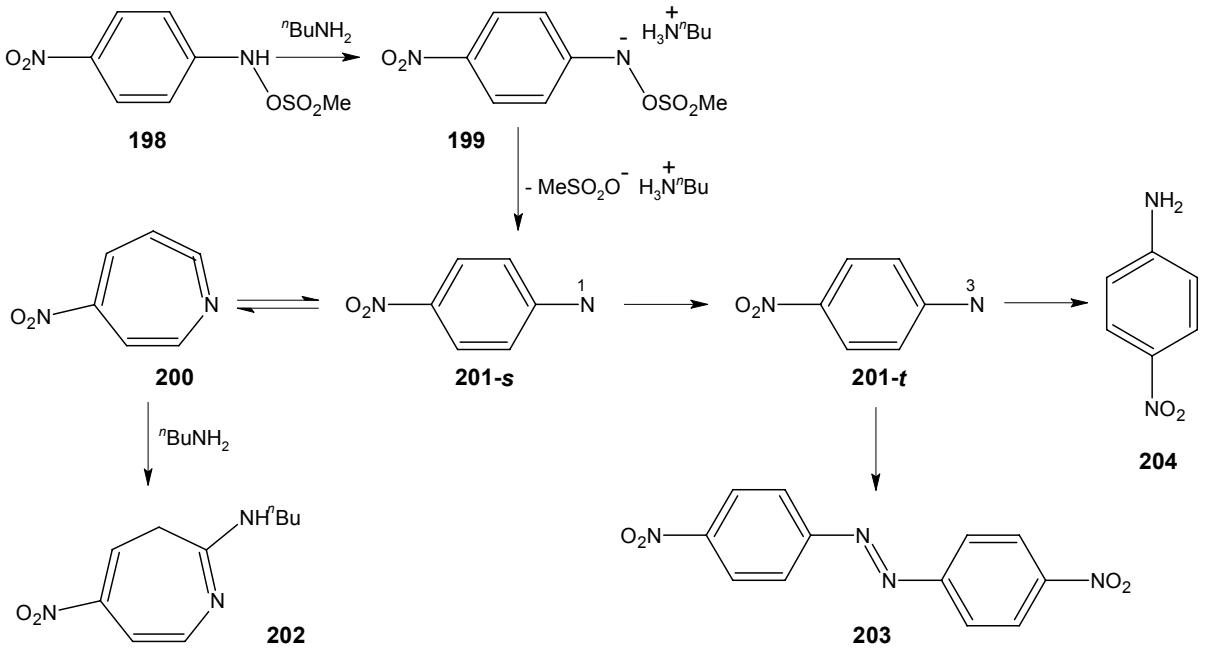
Generally enolates and especially lithium enolates are complex multimeric structures, in which the solvent and the base used for deprotonation are also involved.[162] The aggregation can dramatically affect chemical reactivity.[163,164] The maximum reactivity of an enolate-metal ion pair in solution is achieved in a medium in which the cation is strongly solvated. Polar aprotic solvents (HMPA, DMPU, NMP) are good cation solvators and are often used to minimize the degree of enolate aggregation. Concerning the present study, the use of DMPU as co-solvent slightly improves the reactivity of the lithium ester enolate **195** towards the nitrenoids **176** and **177**. Attempts to use other bases (NaHMDS), with or without co-solvent (DMPU), did not bring any enhancement of the enolate reactivity. Moreover, copper enolates were also involved in order to achieve an effective reagent-substrate complexation, but no amination has been observed.

Seebach[162] and Mohrig *et al.*[165] suggested that in the process of a lithium enolate generation using lithium amides, *i.e.* LDA, there is a proton back-transfer from the liberated base, *i.e.*

diisopropylamine, to the enolate. Consequently, deuteration of such enolates proceeds only with 30% yield. Additional employment of $^{n}$BuLi to remove the NH proton gives upon quenching with $D_2O$ the completely deuterated product. This procedure has been also applied in the present study and preliminary generated nitrenoids **176** and **177** have been involved in the amination step. Despite of these "exchangeable proton" free conditions, no amination product has been detected.

These observations lead to the following conclusions:

- Formation of the dimer **166** (Scheme 40) seems to be the key step in the electrophilic amination reactions of carbanions using nitrenoids of type **176**-**178**. Highly aggregated substrates in which the metal ion is not available for complexation with the nitrenoid show less or no reactivity. It should be mentioned that amination of chiral copper amide enolates, generated from the lithium enolate and CuCN in THF, proceeds in 51-77% yield[166] using BocNLi-OTs **185**. When lithium enolates are involved, only decomposition of the amination reagent **185** with the formation of its reduced product *tert*-butyl carbamate $BocNH_2$ in 35% yield, is observed. Boche *et al.*[161] reported that *N*-(*p*-nitrophenyl)-*O*-(methylsulfonyl)-hydroxylamine **198** generates phenylnitrene **201** under basic conditions (Scheme 52).



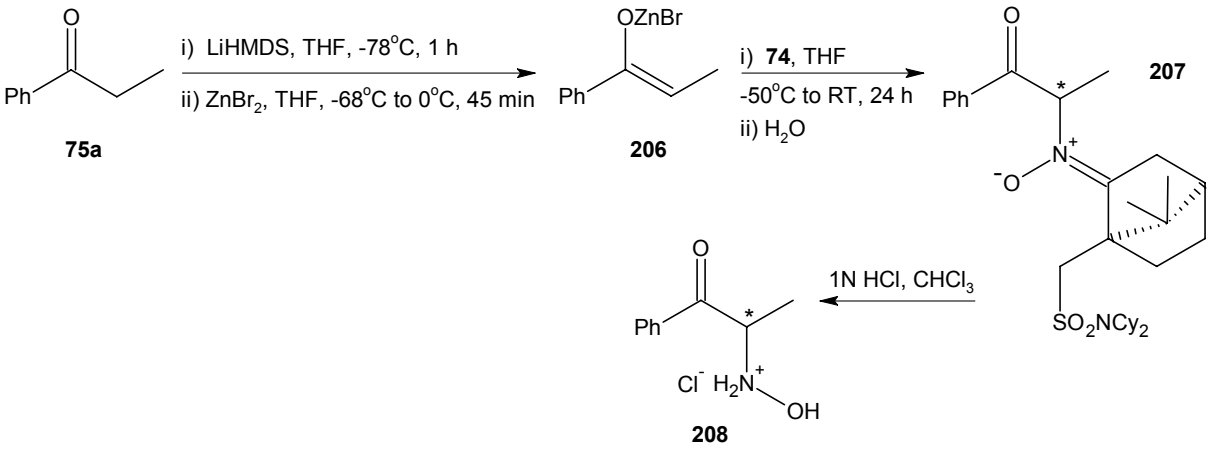

**Scheme 52:** Generation of the singlet phenylnitrene **201-*s*** by α-elimination of the good leaving group $CH_3SO_3^-$ from *N*-(*p*-nitrophenyl)-*O*-(methylsulfonyl)-hydroxylamine **197** under basic condition, as reported by Boche *et al.*[161]

The formation of *tert*-butyl carbamate $BocNH_2$ and the possibility of generating the nitrene BocN**:** from BocNLi-OTs **185**, does not exclude the pathway in which the actual amination reagent is a nitrene and not a nitrenoid. Moreover, this conclusion is also supported by the papers of Beak *et al.*[82,150] (Scheme 39), which are not excluding the occurrence of the nitrene pathway when a good leaving group is attached to nitrogen.

- Enolates are ambident nucleophiles with the negative charge more accommodated to the oxygen atom.[163,164] This study confirms that a complex of type **166** (Scheme 40) between the nitrenoids **176**-**178** and the enolate with the metal cation accommodated at the α-C, is less accessible.
- *In situ* generation of nitrenoids **176**-**178** reduces the extent of their decomposition, which is more favoured in non-polar solvents, most probably due to the lack of complexation with the solvent.

## 3.3 Studies towards the Electrophilic Amination of Enolates and Allyl Organometallic Reagents using α-Chloronitroso Reagents

As mentioned in chapter 1.2.1.3, Oppolzer *et al.*[13] were the first who reported the stereoselective electrophilic amination of ketone enolates using the enantiomerically pure α-chloronitroso reagent **74**. In the present study, the model reaction presented by Oppolzer *et al.*[13] has been followed. The generation of propiophenone lithium enolate **205** using LiHMDS and its further reaction with the α-chloronitroso compound **74**, furnishes 2-(hydroxylamino)-1-phenylpropan-1-one hydrochloride **208** in 30% yield. Transmetallation of the lithium enolate **205** with $ZnBr_2$ in THF, followed by the reaction with **74** furnishes the compound **208** in isolated 16% yield (Scheme 53). Since the α-hydroxylamino ketones are prone to rapid epimerization[13], the determination of the enantiomeric excess of **208** has not been attempted.




**Scheme 53:** Electrophilic amination of the propiophenone zinc enolate **206** with the enantiomerically pure α-chloronitroso reagent **74**, following Oppolzer's[13] procedure.

The intermediate nitrone **207** is isolated in 18% yield and can be identified by its mass spectrum (Figure 26). A base peak ion is observed at $m/z$ 565.2, assigned to $[M+Na]^+$, accompanied by the peaks with $m/z$ 543.2 $[M+H]^+$ and 581.2 $[M+K]^+$. The $^{13}C$ NMR spectrum shows the peak corresponding to the carbon atom double connected to the nitrogen ($C=N^+$) at 168.09 ppm and the peaks corresponding to C=O (193.72 ppm), phenyl (136.35, 133.57, 129.09, 128.08 ppm) and CH (70.54 ppm) of the propiophenone moiety can also be identified. The $^1H$ NMR spectrum does not provide any useful information about the structure of **207** due to its hydrolysis. 2-(Hydroxylamino)-1-phenylpropan-1-one hydrochloride **208** results after hydrolysis of the

nitrone **207** with 1M HCl/$CHCl_3$. The IR spectrum of **207** shows the characteristic C=O (1700 $cm^{-1}$) and nitrone $C=N^+$ (1598 $cm^{-1}$)[10] absorptions.

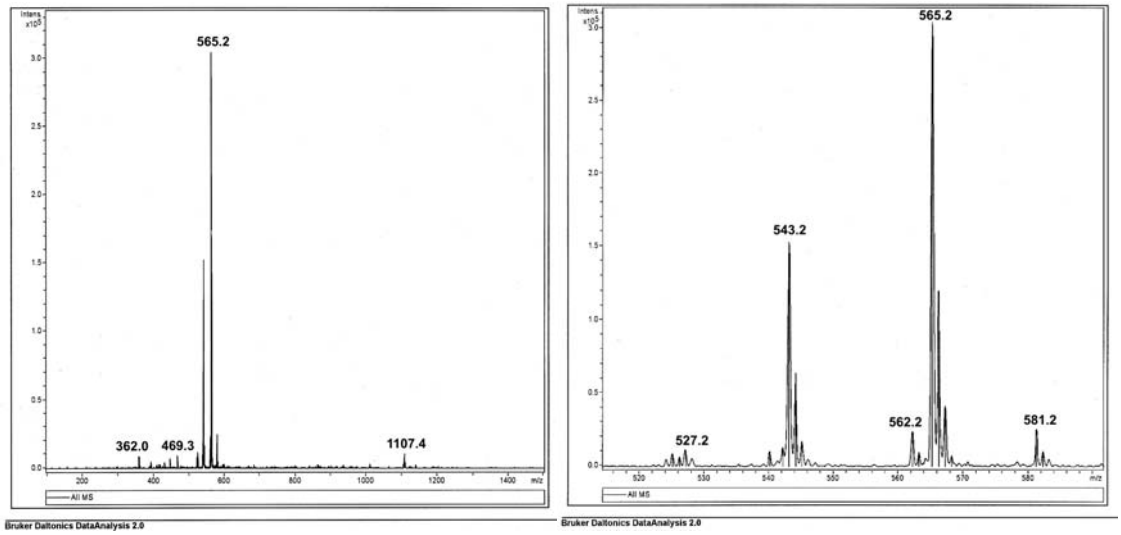
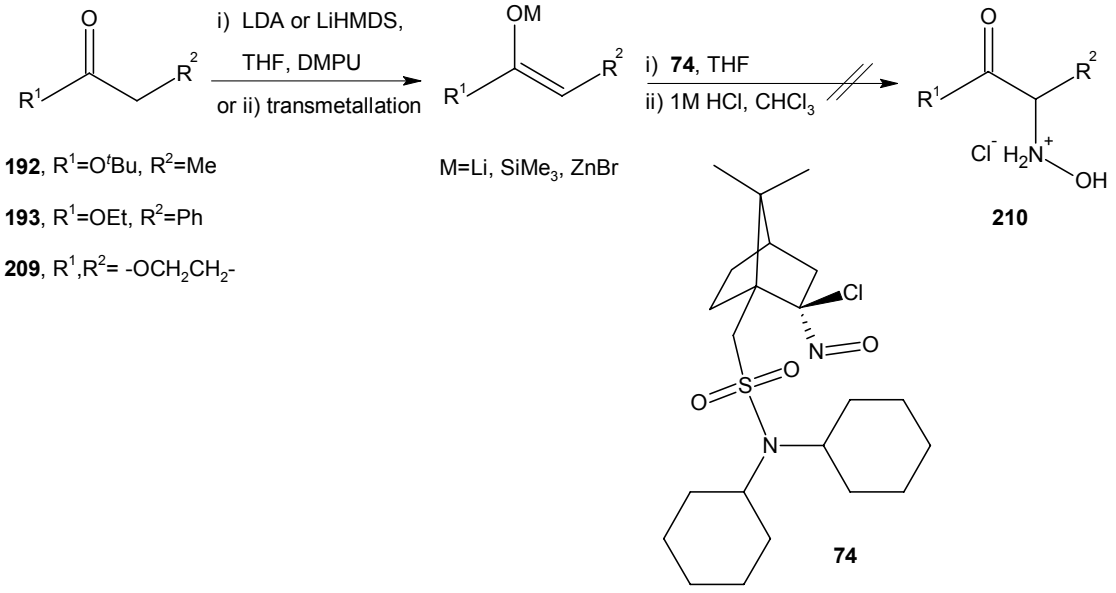



**Figure 26:** Mass spectrum (ESI, positive ion mode) of the nitrone **207**.

Furthermore, the electrophilic amination of ester enolates with the α-chloronitroso reagent **74** using the same procedure as described above was studied. Lithium ester enolates derived from γ-butyrolactone **209**[167], *tert*-butyl propionate **192** and ethyl phenylacetate **193**, as well as their silylated derivatives and the products of transmetallation with $ZnBr_2$ have been used as substrates. In all instances, only partial conversion of **74** to complex mixtures has been observed, in which no α-hydroxylamino esters **210** could be detected after hydrolysis (Scheme 54).




**Scheme 54:** Reaction strategy for the stereoselective electrophilic amination of ester enolates with (+)-*N,N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**.

Based on their results concerning the electrophilic amination of ketone enolates with **74**, Oppolzer *et al.*[13] reported that the observed C(α)-*si*-face topicity of C-N bond formation is consistent with a cyclic "chair" transition state **A**$^{\#}$ (Figure 27).

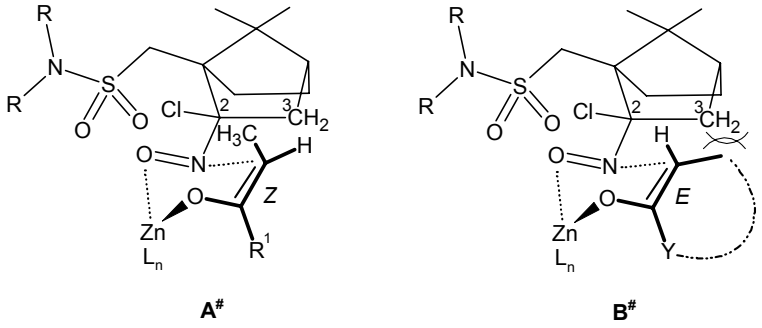
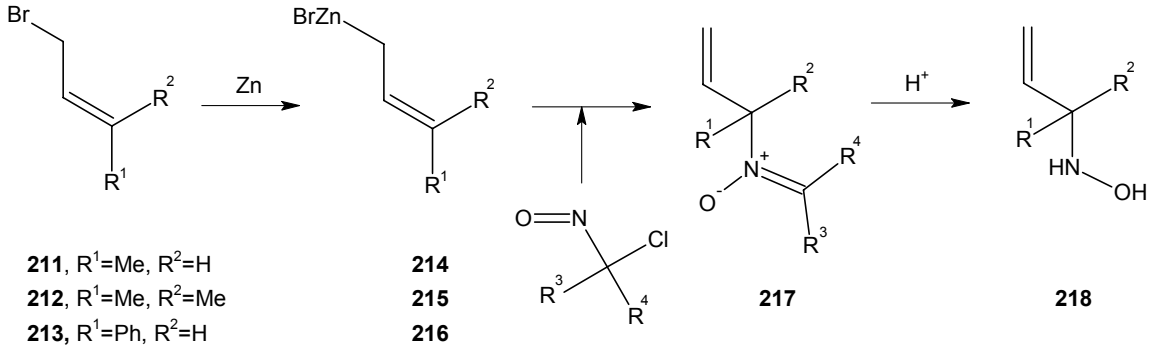



**Figure 27:** Postulated transition state of the electrophilic amination of ketone enolates with (+)-*N,N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**, as suggested by Oppolzer *et al.*[13]

Postulated transition state **A**$^{\#}$ accounts for the attack of the N=O group of **74** by the *Z*-enolate **206**, opposite to the bulky sulfonamide group and for a coordination of $Zn^{II}$ by the oxygen atom of the nitroso group *trans* to the N-C(2) bond. In the same paper, it has been reported that *E*-enolates derived from cyclic ketones such as α-tetralone, β-tetralone or cyclohexanone or from the propionate ester of 2,6-dimethylphenol reacted sluggishly with **74** and no amination products can be detected. It has been suggested that an analogous transition state **B**$^{\#}$ (Figure 27) involving the *E*-enolates suffers repulsion between the C(3) of the bornane skeleton and the enolate C(α) substituent, which is responsible for the lack of reactivity. The same occurrence of an unfavorable transition state **B**$^{\#}$ can explain the lack of reactivity of the ester enolates derived from **193** and **209**. The lithium ester enolate derived from *tert*-butyl propionate **192** has been prepared using DMPU as co-solvent to ensure the formation of the *Z*-enolate,[163] but it still displayed no reactivity, as well the corresponding zinc ester enolate. Regarding the lithium ester enolate of **192**, the lack of reactivity can be attributed to the unavailability of the lithium atom to coordinate to the oxygen atom of the N=O group as in transition state **A**$^{\#}$ (Figure 27), since it is already strongly coordinated by the co-solvent. Regarding the zinc ester enolate of **192**, a slight influence of DMPU on the coordination ability of the zinc atom to the nitroso oxygen atom cannot be excluded. This co-solvent effect combined with the slightly stronger deactivating effect of the electron-withdrawing $^{t}$BuO substituent compared to phenyl seems to have a major effect on the reactivity of the zinc ester enolate of **192**.

2,3:5,6-Di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** as an alternative nitroso compound is very unstable under the above mentioned reaction conditions and complex mixtures result when **65** is used as potential amination agent.

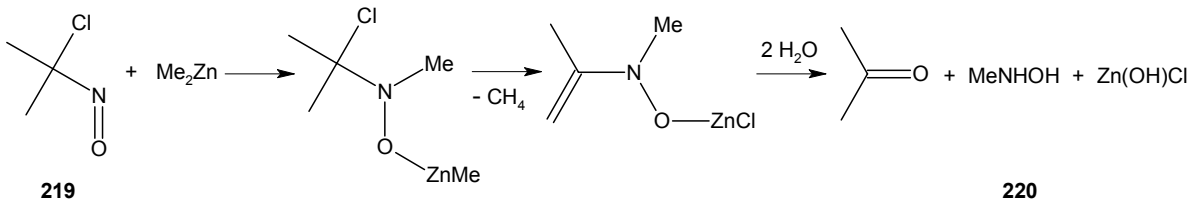
Since the procedure concerning the electrophilic amination of ketone enolates with the enantiomerically pure α-chloronitroso compound **74** proved to be inapplicable for the amination of ester enolates, the use of allylic substrates came into attention. Following mainly the same strategy as the one presented in Scheme 53, the electrophilic amination of allyl zinc bromides **214**-**216** should provide allyl hydroxylamines **218**, upon hydrolysis of the intermediate nitrones **217** (Scheme 55).




**Scheme 55:** Reaction strategy for the electrophilic amination study of allyl zinc bromides with α-chloronitroso reagents.

Allyl hydroxylamines are valuable fundamental buildings blocks in organic chemistry, but they can be easily reduced to the more important allyl amines, which can be further transformed to a range of products by functionalisation, reduction or oxidation of the double bond. Especially, the mentioned double bond oxidation could provide a variety of optically active α-amino acids when prochiral allyl halogenides are used as starting materials.

There are only few examples in the literature concerning the reaction between α-halogenonitroso compounds and organometallic reagents. It has been suggested that an 1,2-addition is the major process when 2-chloro-2-nitrosopropane **219** is treated with dimethyl zinc at 0°C, providing acetone and methylhydroxylamine **220** upon hydrolysis (Scheme 56).[168]

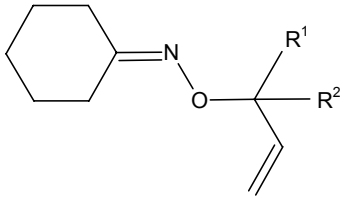



**219** **220**

**Scheme 56:** Amination of dimethyl zinc with 2-chloro-2-nitrosopropane **219**.

In the present study, 1-chloro-1-nitrosocyclohexane **12** is used as a model system, due to its inexpensive synthesis and merely the same reactivity compared to **74**.[1] 2-Butenyl **214**, 3,3-dimethylallyl **215** and 3-phenylallyl **216** zinc bromides are used as substrates that can be prepared from the corresponding bromides **211**-**213** by zinc insertion.[169-171]

The reaction of α-chloronitroso cyclohexane **12** with **214–216** proceeds very fast at -78°C in THF and instead of the expected nitrones **217**, oxime ethers **221–223** (Figure 28) are formed in almost quantitative yield (Table 6).




**221**, $R^1$=Me, $R^2$=H

**222**, $R^1$=Me, $R^2$=Me

**223**, $R^1$=Ph, $R^2$=H

**Figure 28:** Allyl oxime ethers obtained from the reaction of 1-chloro-1-nitrosocyclohexane **12** with the allyl organozinc compounds **214–216** in THF.

As can be seen from Table 6, variation of the reaction temperature had no influence on the reaction regioselectivity.

**Table 6:** Reaction conditions and yield of allyl oxime ethers **221**-**223** resulting from the reaction of 1-chloro-1-nitrosocyclohexane **12** with the allyl organozinc compounds **214–216** in THF.

| Entry | Reagent | Reaction temperature, °C | Product | Yield, % |
|---|---|---|---|---|
| 1 | **214** | -78 | **221** | 96 |
| 2 | **214** | 0 | **221** | 97 |
| 3 | **214** | 22 | **221** | 95 |
| 4 | **215** | -78 | **222** | 82 |
| 5 | **216** | -78 | **223** | 84 |

Toluene has been chosen as solvent in order to trap potential radical species. The oxime ethers **221**-**223** are formed, together with small amounts of allyl hydroxylamines **224** and **225** (Figure 29), upon quenching with methanol and acidic hydrolysis of the reaction mixture (Table 7). Unlike the observed distribution of products when **214** or **215** are reacted with **12**, only *O*-(1-phenylallyl)cyclohexanone oxime **223** is formed from **216** under the same conditions.

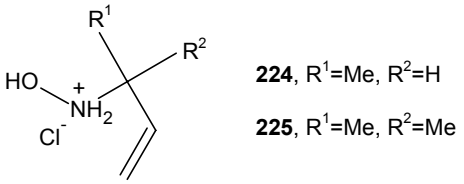



**Figure 29:** Allyl hydroxylamines resulting from the reaction of 1-chloro-1-nitroso-cyclohexane **12** with the allyl organozinc compounds **214** and **215** in toluene.

**Table 7:** Reaction conditions and yields of allyl oxime ethers **221**-**223** and allyl hydroxylamines **224** and **225** resulting from the reaction of 1-chloro-1-nitrosocyclohexane **12** with the allyl organozinc compounds **214**-**216** in toluene.

| Entry | Reagent | Reaction temperature, °C | Product | Yield, % | Product | Yield, % |
|---|---|---|---|---|---|---|
| 1 | **214** | -78 | **221** | 84 | **224** | 14 |
| 2 | **214** | 0 | **221** | 82 | **224** | 8 |
| 3 | **215** | -78 | **221** | 72 | **225** | 2 |
| 4 | **215** | 0 | **222** | 71 | **225** | 3 |
| 5 | **216** | -78 | **223** | 73 | - | - |
| 6 | **216** | 0 | **223** | 64 | - | - |

Resuming the results presented above, four types of compounds, depicted as **A**-**D**, may result in the reaction between 1-chloro-1-nitrosocyclohexane **12** and allyl organozinc compounds **214**-**216** (Figure 30). This distribution depends upon solvent and the type of regioisomer (branched or linear) of the allyl organozinc compounds involved.

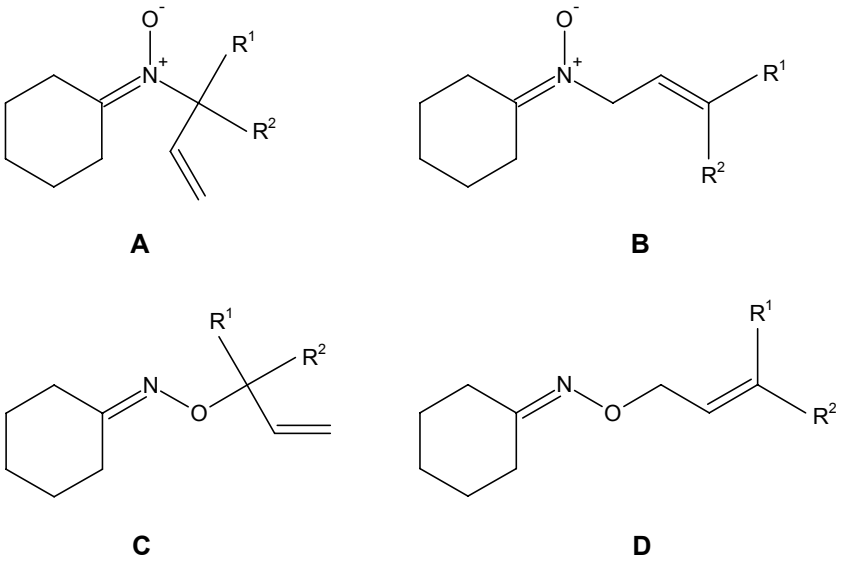



**Figure 30**. The distribution of the compounds which may result in the reaction between 1-chloro-1-nitrosocyclohexane **12** and allyl organozinc compounds **214**-**216**.

Table 8 summarises the experimental results presented above.

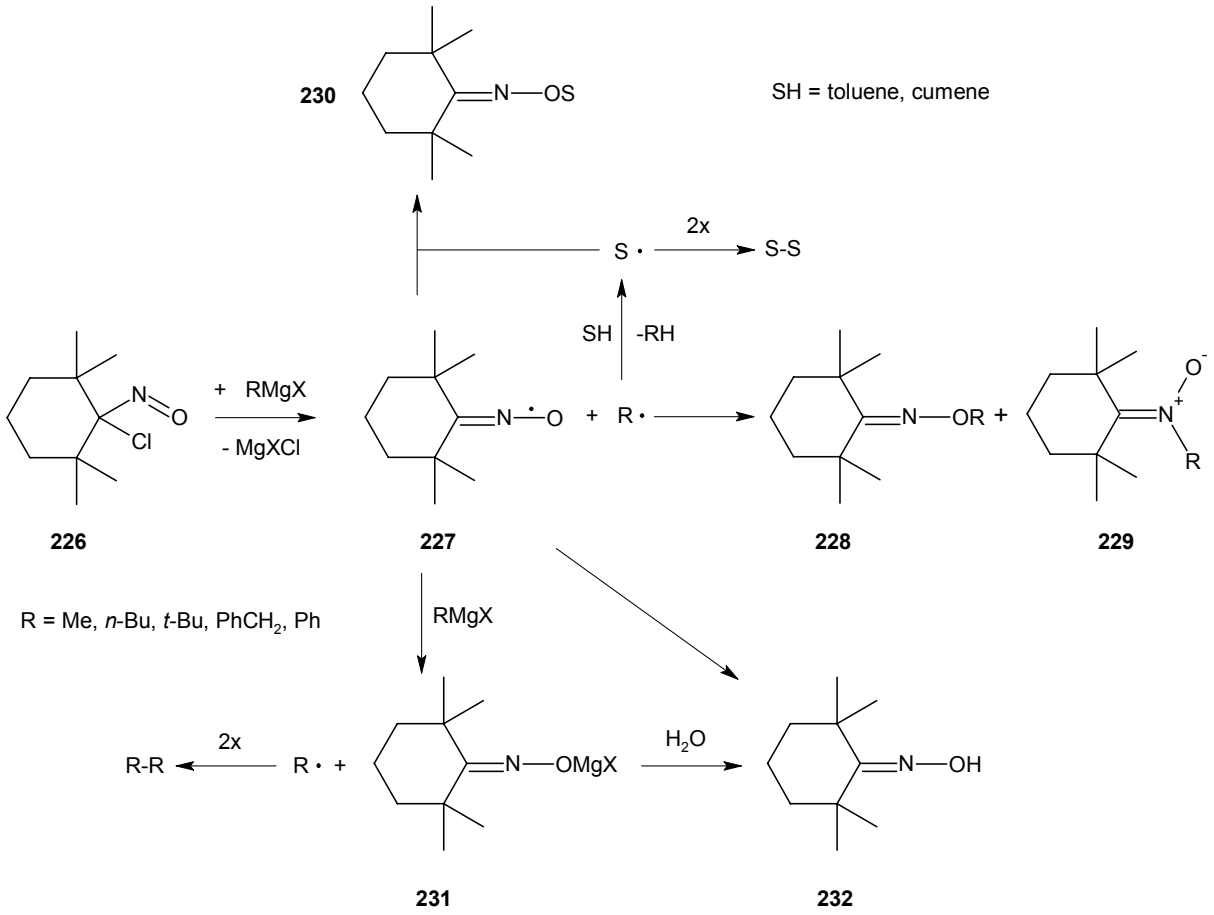
**Table 8**. The distribution of the compounds which result in the reaction between 1-chloro-1-nitrosocyclohexane **12** and allyl organozinc compounds **214**-**216**.

| Entry | Allyl organozinc compound | Solvent | Distribution of compounds | | | |
|---|---|---|---|---|---|---|
| | | | A | B | C | D |
| 1 | **214** ($R^1$=Me, $R^2$=H) | THF | - | - | **221** | - |
| 2 | **215** ($R^1$=Me, $R^2$=Me) | | - | - | **222** | - |
| 3 | **216** ($R^1$=Ph, $R^2$=H) | | - | - | **223** | - |
| 4 | **214** ($R^1$=Me, $R^2$=H) | Toluene | **224** [a)] | - | **221** | - |
| 5 | **215** ($R^1$=Me, $R^2$=Me) | | **225** [a)] | - | **222** | - |
| 6 | **216** ($R^1$=Ph, $R^2$=H) | | - | - | **223** | - |

a) The compounds **224** and **225** are the hydrolysis product of the nitrone **A**.

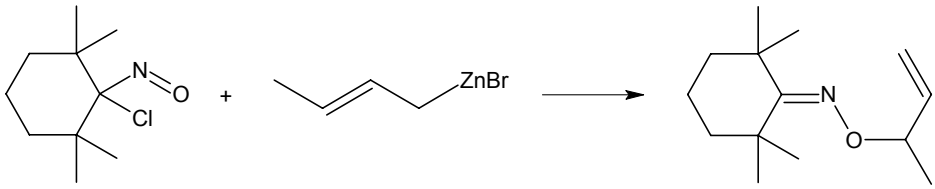
Th. J. de Boer *et al.*[8,10,172] carried out an intensive work concerning the reaction between α-chloronitroso compounds and some organometallic reagents. They showed that α-chloronitroso compounds react at 0°C with organomagnesium and organoaluminum reagents to form nitrones in low to moderate yields, via 1,2-addition, together with various other products which arise mainly through radical processes (SET), depending upon the structure of the nitroso compound and the nature of the organometallic reagent. The involvement of a SET process has

been proved using the sterically hindered 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **226** as substrate (Scheme 57). When **226** is involved, formation of nitrones **229** via 1,2-addition of the Grignard reagent to the nitroso group is completely hindered by the flanking methyl substituents. Steric requirements being less severe for an electron transfer, this becomes virtually the exclusive process with all Grignard reagents. Such an electron transfer leads to radicals $R^{\bullet}$ and relatively stable 2,2,6,6-tetramethylcyclohexanone iminoxy radical **227**. This radical pair is responsible for the formation of the final products. 2,2,6,6-Tetramethylcyclohexanone oxime **232** predominates and very low yields or traces of **228**– **230** have been observed in the reaction mixture.




**Scheme 57:** Distribution of products in the reaction of sterically hindered α-chloronitroso compound **226** with Grignard reagents, as reported by Th. J. de Boer *et al.*[8,10,172]

In the present study, 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **226** proved to be unreactive toward 2-butenyl zinc bromide **214**, in THF and temperatures below 0°C. Stirring at room temperature for 12 hours provides the oxime ether **233** in 31% yield, together with unreacted **226** (Scheme 58). No formation of a linear adduct (type D, Figure 30) is observed.

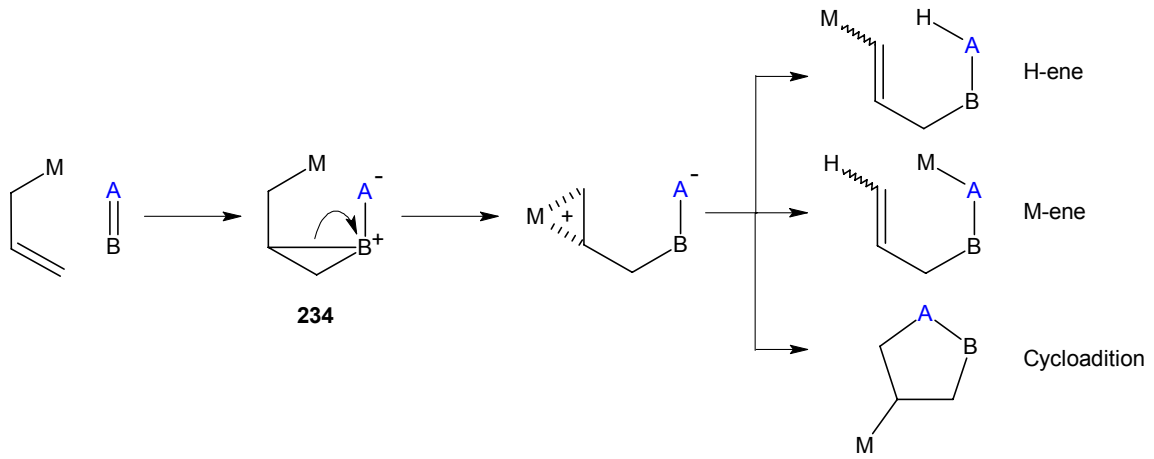



**226** **214** **233**

**Scheme 58:** Reaction of sterically hindered α-chloronitroso compound **226** with 2-butenyl zinc bromide **214** in THF.

1-Chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **226** is easily prepared in 88% yield by chlorination of 2,2,6,6-tetramethylcyclohexanone oxime **232** with $^{t}$BuOCl. For the synthesis of the oxime **232**, an improved[173] method uses 2,2,6,6-tetramethylcyclohexanone as starting material. No products supporting a radical process have been found when reactions are carried out in toluene. It can be concluded that these observations rule out the occurrence of a single electron transfer (SET) from the organozinc compound to the nitroso compound, when the reaction conditions presented in Table 5 or Table 6 are followed.

The reported mechanism[174-176] by which allylmetallic compounds react with enophiles, based on that for the non-metallic allylic compounds, shows that the principal products are those which result from the H-ene reaction, the M-ene reaction, and a [2+3] cycloaddition with shift of the metallic group. Davies *et al.*[174,177] suggested that a charge transfer complex between the ene and the enophile might be involved. It has also been mentioned that a reasonable model can involve the prior formation of a complex **234** between the ene and the enophile A=B (Scheme 59).



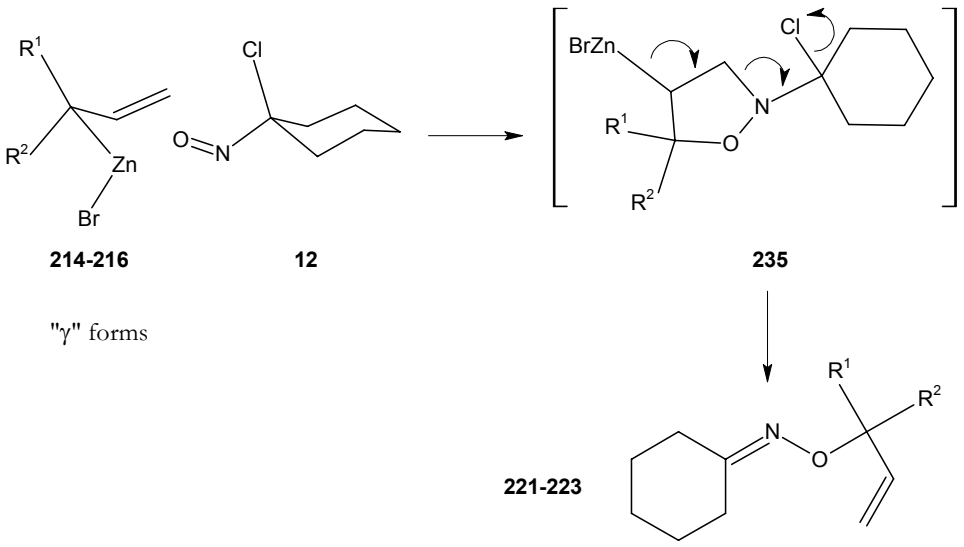

**Scheme 59:** Mechanism of the ene reaction between allylmetallic compounds and enophiles.[176]

In the present study, electrophilic trapping experiments with MeI and benzophenone, in THF at -78°C and 0°C are carried out in order to test the possible occurrence of the polar intermediate **234**. A THF solution of 1-chloro-1-nitrosocyclohexane **12** and trapping reagent is pre-cooled to

the mentioned temperature and a stoichiometric amount of organozinc reagent **214** in THF is added dropwise to the reaction mixture. TLC and GC analysis of an aliquot shows no other products except the *O*-(1-methylallyl)cyclohexanone oxime **221** and the unreacted trapping reagent. Since no products derived from charged intermediates can be detected, the formation of the complex **234** or an 1,2-addition process (Scheme 56) are unlikely. The occurrence of a charge transfer complex between the ene (donor) and the nitroso group (acceptor) appears more reasonable.

Allyl organozinc compounds of type **214–216** are σ-bond structures which can react at both α (less substituted, "linear form") or γ (most substituted, "branched form") positions of the allylic chain, when added to C=X electrophiles (aldehydes, ketones, imines).[170]

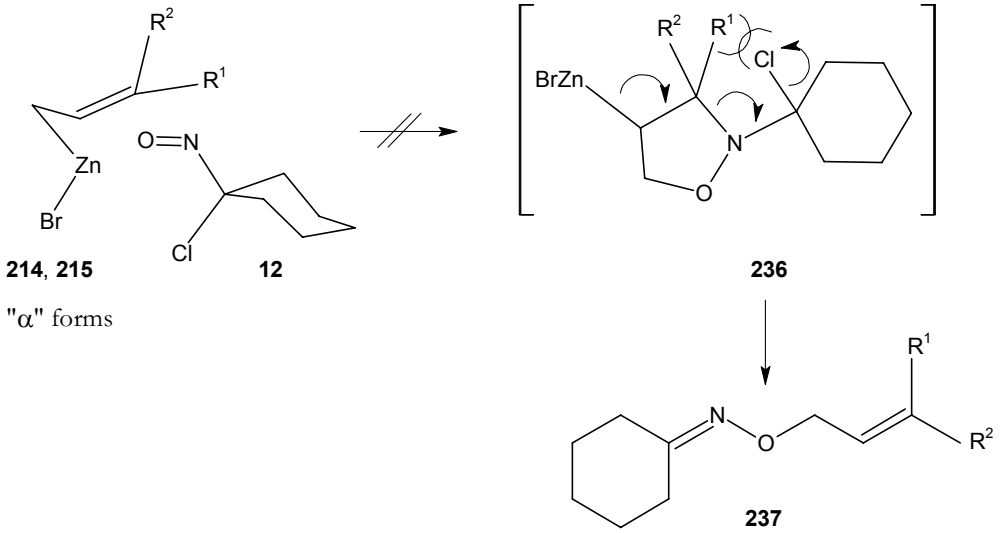
The experimental results presented above support the occurrence of a [2+3] cycloaddition, either concerted or stepwise, followed by the rapid elimination of zinc halogenide and formation of the branched oxime ethers **221**-**223** (Scheme 60).[174-176]




**Scheme 60:** The mechanism proposed for the reaction between the α-chloronitroso cyclohexane **12** and allyl organozinc compounds **214-216** in THF.

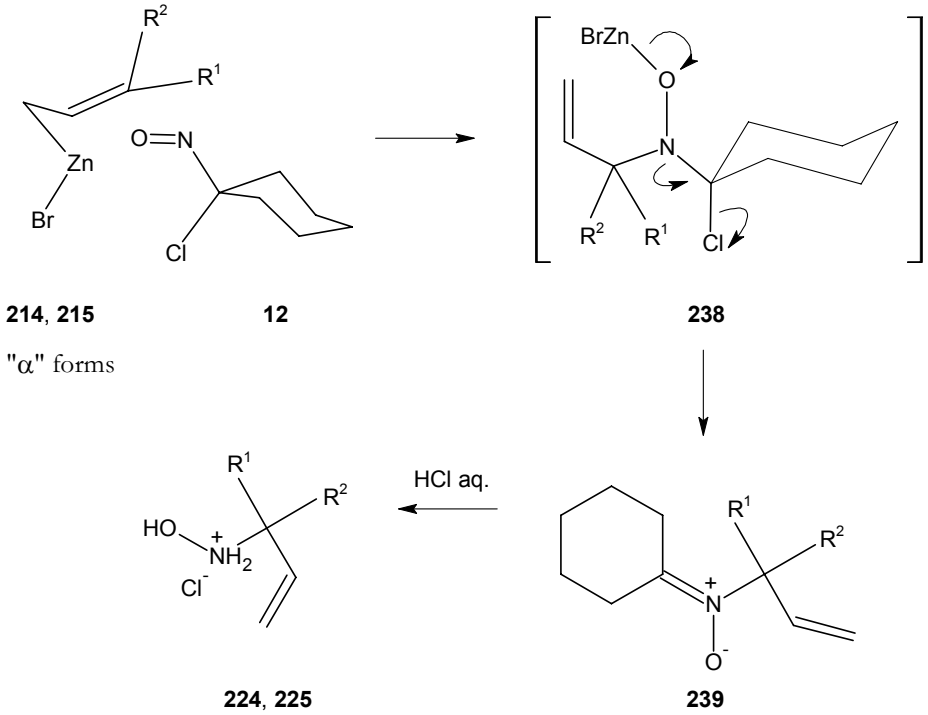
The reaction presumably initially occurs by a six-centered transition state - facilitated by both Lewis acidity of zinc and basicity of oxygen - followed by an intramolecular rearrangement to the [2+3] cycloadduct **235**.

The absence of the linear oxime ethers **237** is probably due to the sterical hindrance which could occur in the intermediate **236** (Scheme 61).




**Scheme 61:** Sterical hindrance can occur in the intermediate **236** required for the formation of the linear oxime ethers **237**.

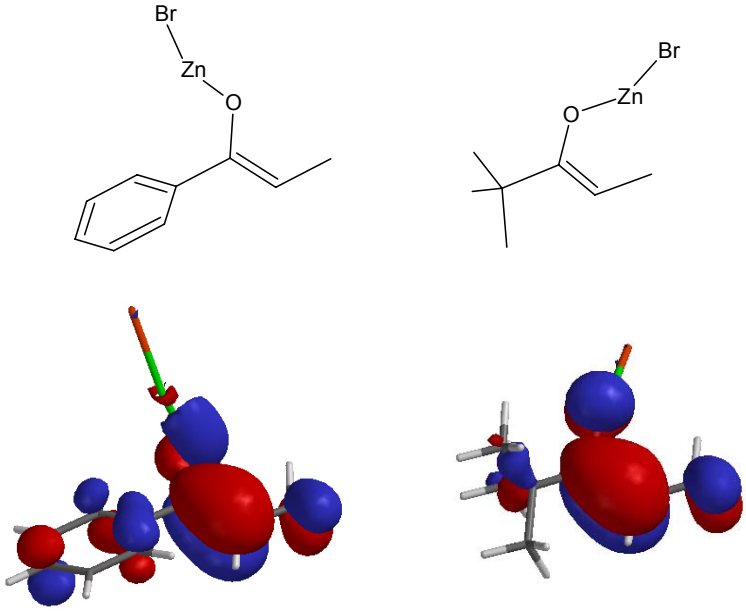
Isolation of the hydroxylamines **224** and **225** upon acidic hydrolysis of the reaction mixture, when toluene is used as solvent, sustains the formation of nitrones **239** by an accompanying M-ene process (Scheme 62).




**Scheme 62:** The mechanism proposed for the formation of allyl hydroxylamines **224** and **225** in the reaction between the α-chloronitroso cyclohexane **12** and allyl organozinc compounds **214**, **215** in toluene.

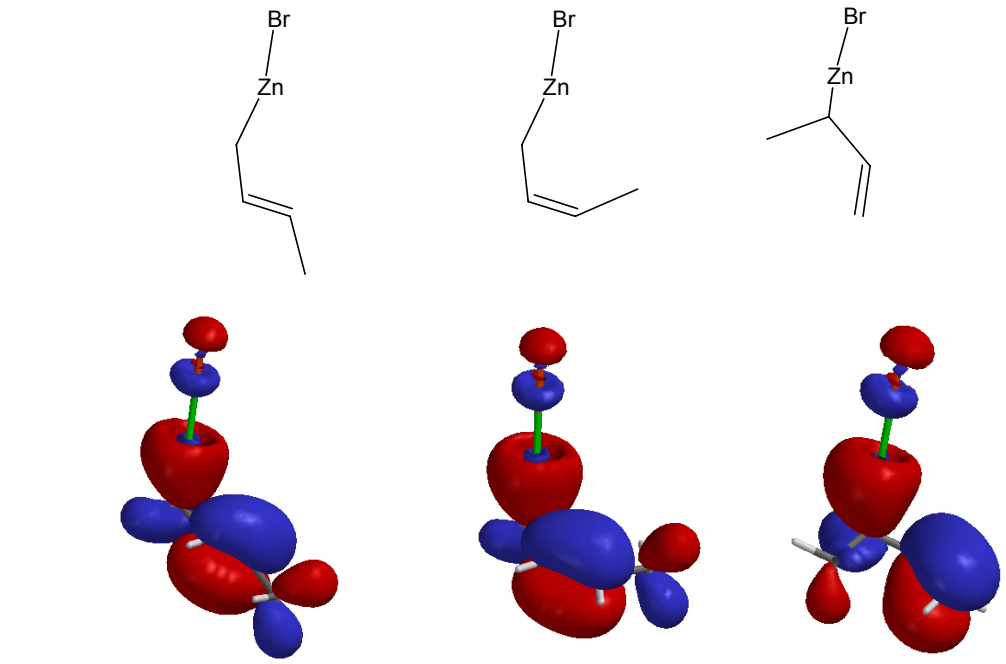
The unpolar solvent, *i.e.* toluene, partially favors a stronger Lewis acid-base interaction between zinc and oxygen, which allows the occurrence of the six-centered pericyclic transition state required for the M-ene process, instead of the [2+3] cycloaddition.

Generally, ene reactions involve an electron-rich ene and an electron-poor enophile. The process is dominated by the interaction of the HOMO of the former with the LUMO of the latter.[178] To understand why such a different pathway compared to ketone enolate **75a** occurred when the allyl organozinc compounds **214-216** reacted with the α-chloronitroso reagent **12**, computational methods have been used. Figure 31 shows the calculated HOMO (Density Functional method with the pBP/DN* basis set) of the zinc enolates of propiophenone **75a** (a) and of *tert*-butylethyl ketone **75c** (b). The calculated HOMO of 2-butenyl **214** and 3,3-dimethylallyl **215** zinc bromides are shown in Figure 32 and Figure 33, respectively.



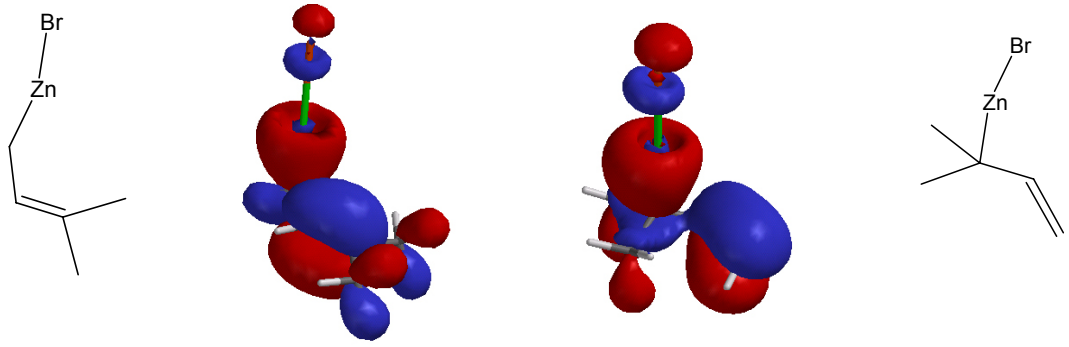

**75a** *Z*-enolate (a) **75c** *Z*-enolate (b)

**Figure 31:** The calculated HOMO (Density Functional method with the pBP/DN* basis set) of the zinc enolates of propiophenone **75a** (a) and *tert*-butylethyl ketone **75c** (b)




*E*-**214** "linear form" (a) *Z*-**214** "linear form" (b) **214** "branched form" (c)

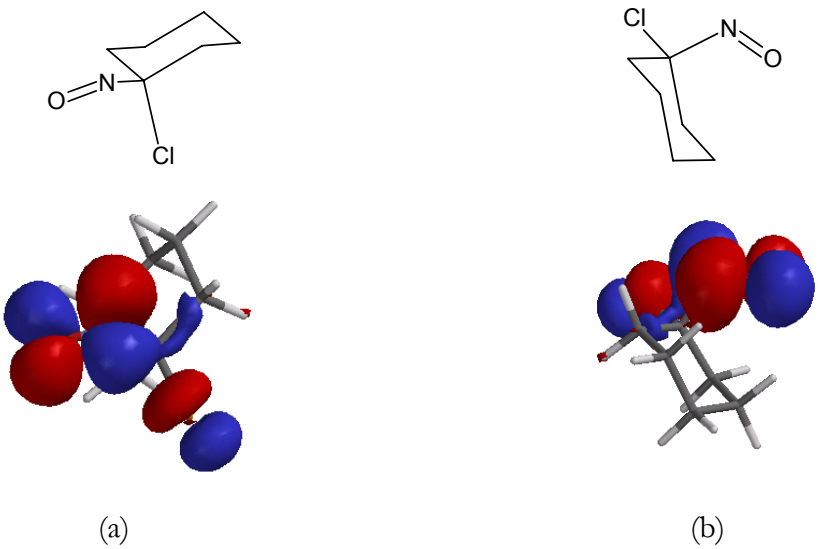
**Figure 32:** The calculated HOMO (Density Functional method with the pBP/DN* basis set) of the 2-butenylzinc bromide **214** *E-Z* isomers (a, b) and (1-methylprop-2-enyl)zinc bromide (**214** "branched form") (c)




**215** "linear form" (a) **215** "branched form" (b)

**Figure 33:** The calculated HOMO (Density Functional method with the pBP/DN* basis set) of 3,3-dimethylallyl zinc bromide **215** (a) and 1,1-dimethylallyl zinc bromide (**215** "branched form") (b)

.




(a) (b)

**Figure 34:** The calculated LUMO (Density Functional method with the pBP/DN* basis set) of 1-chloro-1-nitrosocyclohexane **12**, upper (a) and lateral (b) view.

In the case of enolates **75a** and **75c** the HOMO is delocalised over several sites, but the largest contribution to the HOMO clearly comes from the carbon which is in β-position towards oxygen.[179] Therefore, the attack of the nitrogen electrophile and bond formation should occur at this carbon (Figure 35).

In the case of allyl organozinc reagents **214** and **215**, a symmetric distribution of the HOMO at the C=C double bond is observed, together with a significant contribution from the carbon atom directly connected to the zinc. The formation of [2+3] cycloadducts **235** (Scheme 60) is favoured by such a distribution of the HOMO, as depicted in Figure 36 for the case of 2-butenyl zinc chloride **214**.

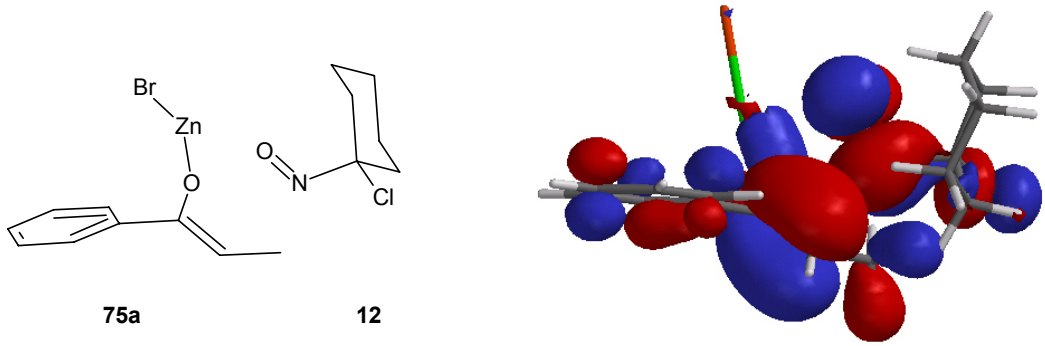
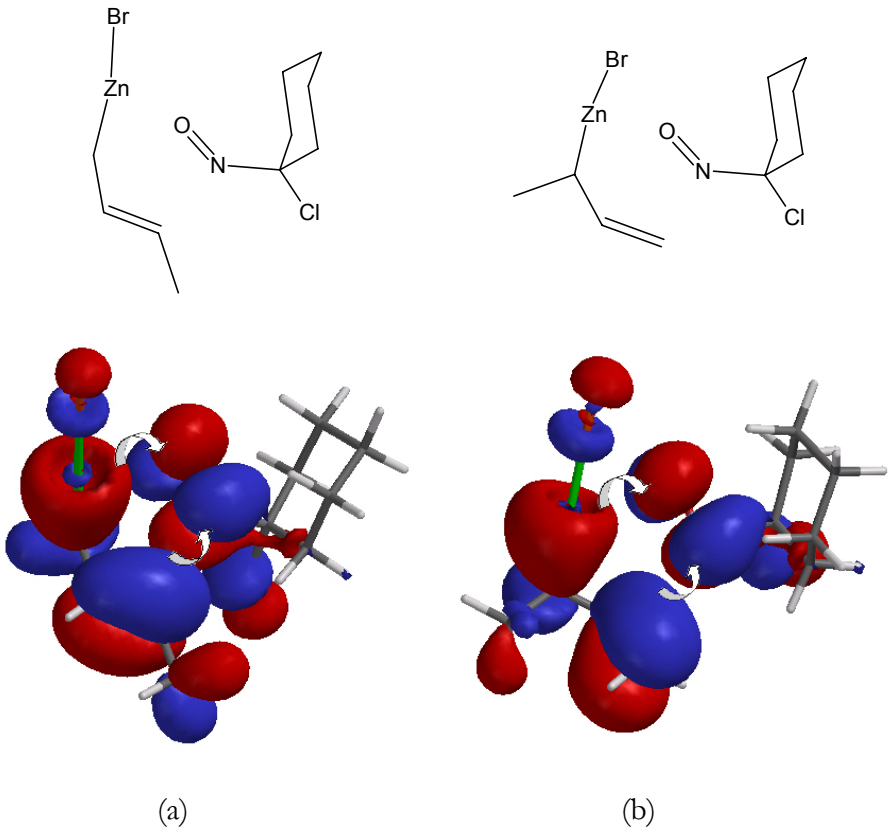


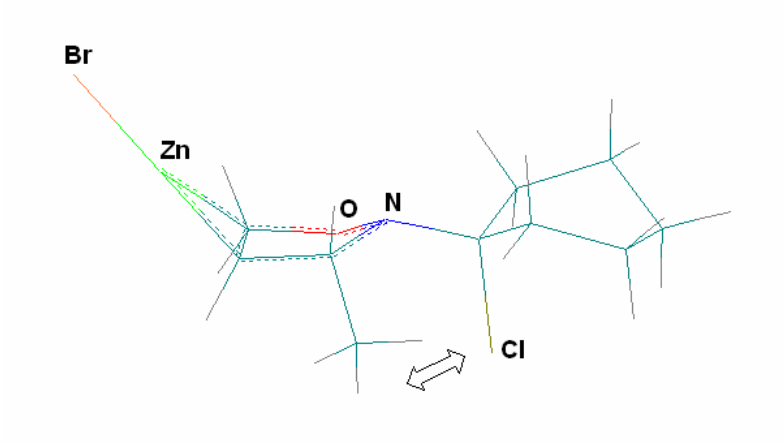

**Figure 35:** Favourable overlap of the HOMO of propiophenone zinc enolate **75a** with the LUMO of 1-chloro-1-nitrosocyclohexane **12**.



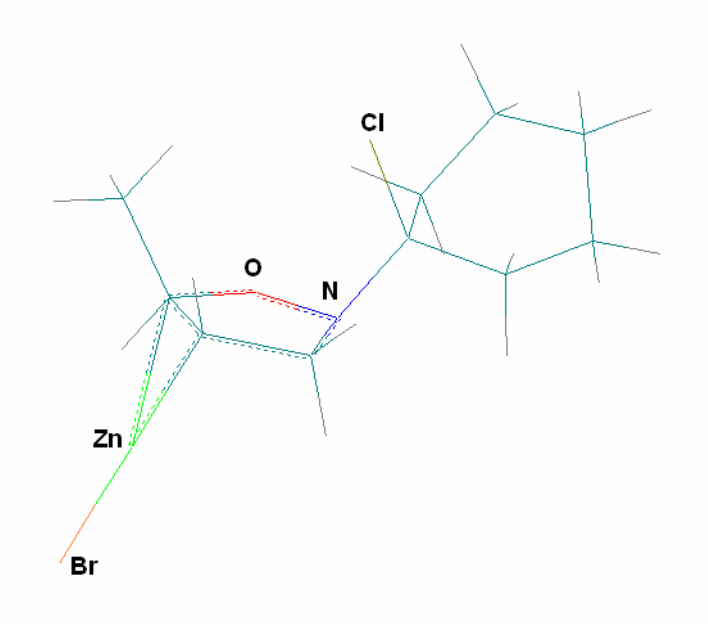

(a) (b)

**Figure 36:** Favourable overlap of the HOMO of the *E*-isomer 2-butenylzinc bromide **214** (a) and respectively (1-methylprop-2-enyl)zinc bromide (**214** "branched form") (b), with the LUMO of 1-chloro-1-nitrosocyclohexane **12**, for the formation of the [2+3] cycloadduct.

A favourable HOMO-LUMO interaction appears to be possible for both regioisomers of 2-butenyl zinc bromide (linear and branched forms). Calculation of the transition state geometry (AM1 semiempirical method) for both situations (a) and (b) from Figure 34 shows that the transition state $\mathbf{A}^{\#}$ - from which **236** ($R^1$=Me, $R^2$=H) results - is less favorable due to the sterical hindrance which occurs between the chlorine atom and the methyl group of the allylic system (Figure 37). Obviously, the sterical hindrance is even more significant when 3,3-dimethylallyl **215** and 3-phenylallyl **216** zinc bromides are involved.




**A**#




**B**#

**Figure 37:** Transition state geometries of the [2+3] cycloaddition of both 2-butenyl zinc bromide **214** regioisomers, simulated using AM1 semiempirical method.

The calculated molecular orbital (MO) coefficients for the LUMO of **12** are listed in Table 9. The close values of the contributions to LUMO from N($2p_x$) and O($2p_x$), and N($2p_y$) and O($2p_y$), respectively, means a relatively symmetric distribution of the LUMO at the nitroso group. The graphical representation of the LUMO of 1-chloro-1-nitrosocyclohexane **12** is shown in Figure 34.

This suggests that an orbital interaction may also be possible between HOMO of **214** ("linear form") and LUMO of **12** in which the nitroso group has a reverse orientation (Figure 38).

**Table 9**. MO coefficients for the LUMO of **12** obtained at the DFT (pBP/dn*) and *Ab Initio* (RHF/3-21G* and RHF/6-31G*) levels of theory

| Atomic orbital | DFT (pBP/dn*) | RHF/3-21G* | RHF/6-31G* |
|---|---|---|---|
| $N(2p_x)$ | -0.81388 | -0.24370 | -0.29475 |
| $N(2p_y)$ | -0.30839 | -0.29574 | -0.35770 |
| $N(2p_z)$ | -0.01679 | 0.01068 | 0.01292 |
| $O(2p_x)$ | 0.71288 | 0.21613 | 0.25567 |
| $O(2p_y)$ | 0.26631 | 0.26228 | 0.31028 |
| $O(2p_z)$ | -0.00377 | -0.00947 | -0.01120 |

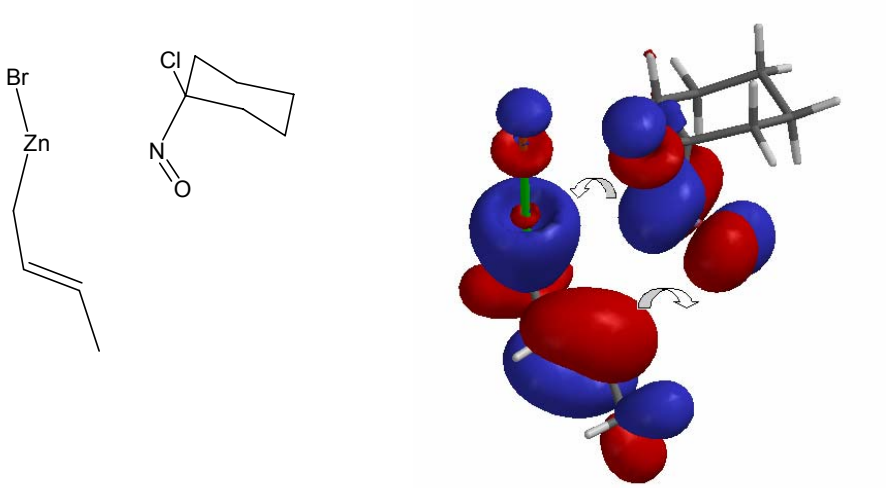
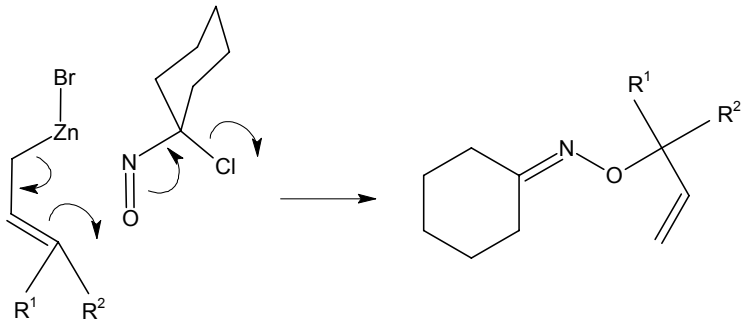



**Figure 38**. Favourable orbital interaction between HOMO of **214** ("linear form") and LUMO of **12** in which the nitroso group has a reverse orientation.

Such an orbital interaction may favor the occurrence of the M-ene process and can also explain the formation of the branched oxime ethers **221**-**223** (Scheme 63).




**214**, **215** **12** **221-223**

"linear forms"

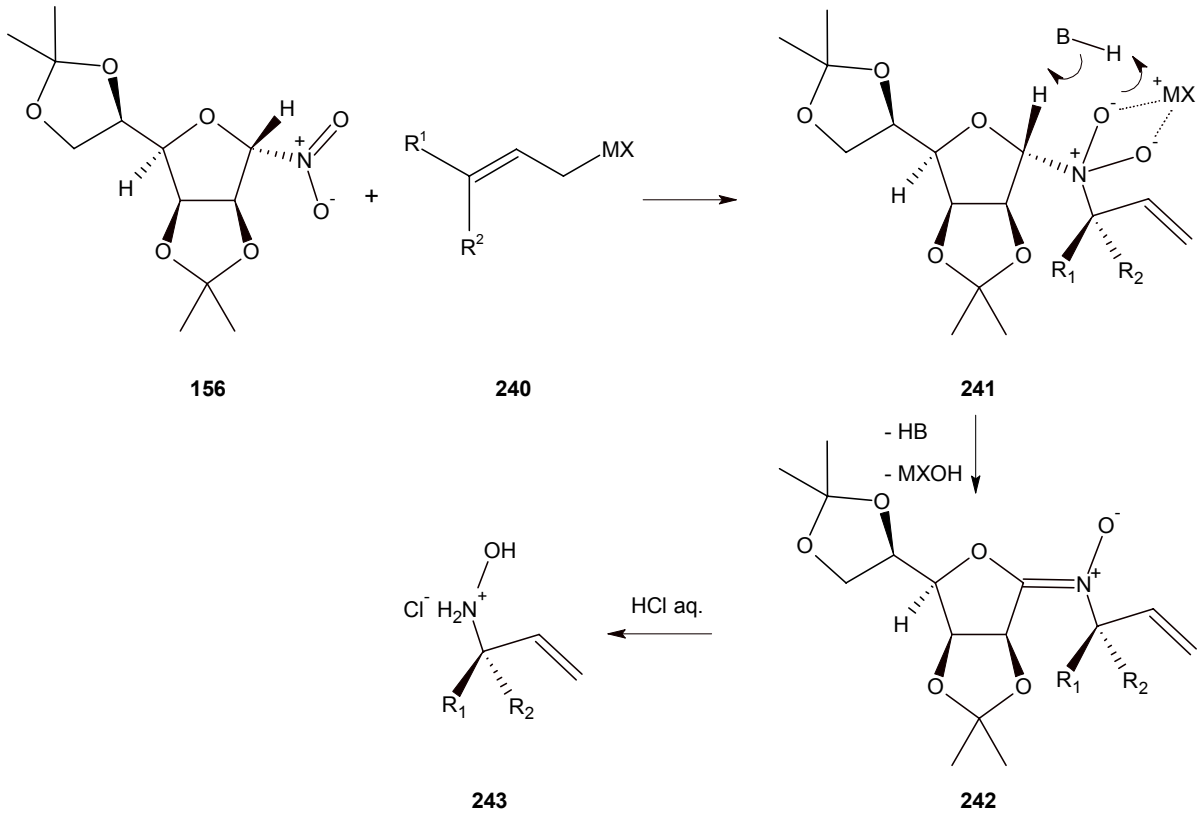
**Scheme 63**. Formation of the branched oxime ethers **221**-**223** by a M-ene process in which the nitroso group of **12** has a reverse orientation.

In conclusion, both mechanisms - the [2+3] cycloaddition and the M-ene reaction with a reverse orientation of the nitroso group - can explain the occurrence of the oxygenation reaction instead of amination. Among other aminating reagents, oxazirines (Chapter 1.2.1.5) are reported to act both as aminating and oxygenating reagents, the nucleophilic attack at the oxaziridine ring being determined by the substitution pattern at the nitrogen.

## 3.4 Studies towards the Electrophilic Amination of Allyl Organometallic Reagents using 1-Deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-manno-furanose

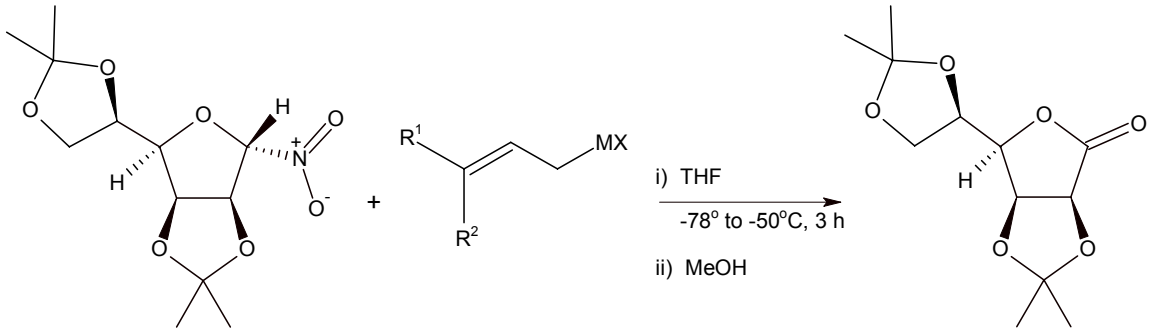
The studies towards the electrophilic amination of allyl organometallic substrates with 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** were based on the reports of Bartolli *et al.*[14,16,18,19,21] concerning the synthesis of nitrones by the allyl Grignard addition on nitroalkanes and nitroarenes (see Chapter 1.2.1.6).

The strategy followed for the electrophilic amination of allyl organometallic reagents using **156** is shown in Scheme 63. The nucleophilic attack of the allyl organometallic reagent to the nitro group would give the tetrahedral intermediate **241**, which upon quenching with a proton source and further acidic hydrolysis would furnish the hydroxylamine hydrochloride **243**.




**Scheme 63:** The strategy followed for the electrophilic amination of allyl organometallic reagents using 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156**.

The reaction of the nitrosugar **156** with 2-butenyl (**244**) or 3,3-dimethylallyl (**245**) magnesium bromides in THF at -78°C to -50°C furnished 2,3:5,6-di-*O*-isopropylidene-α-D-manno-1,4-lactone **247** as single product (Scheme 64).



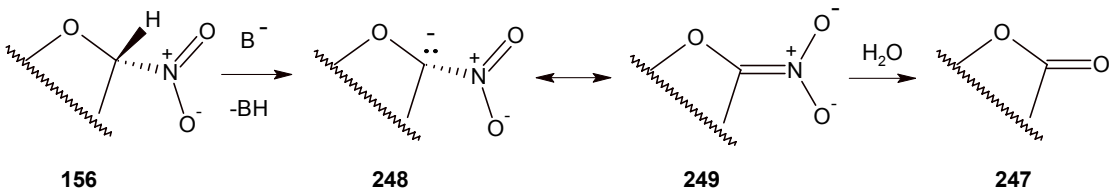

**244**, $R^1$=Me, $R^2$=H, M=Mg, X=Br

**245**, $R^1$=Me, $R^2$=Me, M=Mg, X=Br

**246**, $R^1$=Me, $R^2$=Me, M=Ti, X=$(O^iPr)_3$

**Scheme 64:** The reaction between 1-deoxy-1-nitrosugar **164** and the allyl organometallic reagents **244**-**246**.

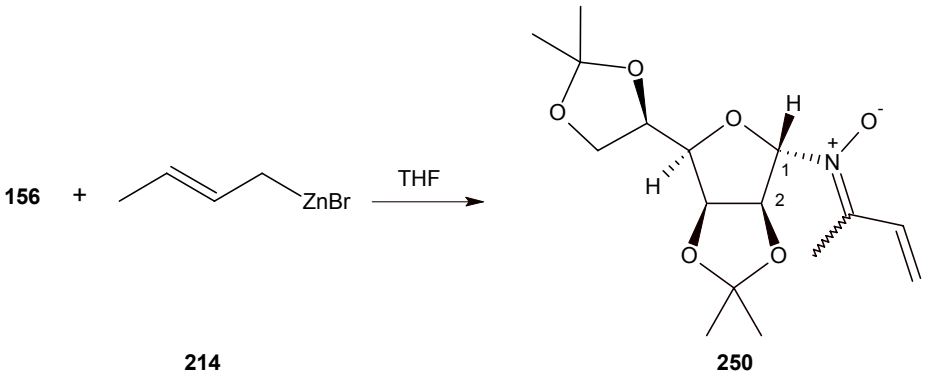
After 3 h reaction time TLC analysis confirmed the total conversion of **156** and showed the formation of **247** in 71% yield when **244** was involved, and 84% when **245** was used as substrate. The formation of the lactone **247** has been interpreted as result of the Nef reaction (Scheme 65),[180] with the metallic reagent or the conjugated base ($MeO^-$) of the quenching reagent (methanol) acting as base.




**Scheme 65:** Formation of the lactone **247** from the 1-deoxy-1-nitrosugar **156** by Nef reaction.

The base removes the relatively acidic proton in α-position to the nitro group. The anion **248** is in resonance with the *aci*-nitro form **249** which hydrolyzes to give the lactone **247** upon hydrolytic work up. Reaction of the 1-deoxy-1-nitrosugar **156** with 3,3-dimethylallyltitanium tri-isopropoxide **246** in THF gave also only lactone **247**.

In contrast, the reaction of the relatively less basic 2-butenyl zinc bromide **214** with the 1-deoxy-1-nitrosugar **156** furnishes the nitrone **250** (Scheme 66).




**Scheme 66:** Reaction of 2-butenyl zinc bromide **214** with the 1-deoxy-1-nitrosugar **156**.

No formation of the nitrone **250** is observed upon stirring at -78°C for 4 h (Table 10, Entry 1). Variation of the reaction temperature showed that up to -10°C the organozinc reagent is acting only as nucleophile, since only nitrone **250** and unreacted nitrosugar **156** are detected by TLC. When the reaction temperature is increased above -10°C the formation of the lactone **247** in a Nef reaction is observed. Reaction at 0°C affords lactone **247** as major product (68%), total conversion of the nitrosugar **156** is observed and nitrone **250** results in 7% yield. A slightly increased yield is observed upon addition of the organozinc reagent **221** to the nitrosugar **156** at -35°C, but if a longer reaction time is applied (Table 10, Entry 4) formation of the lactone **247** is

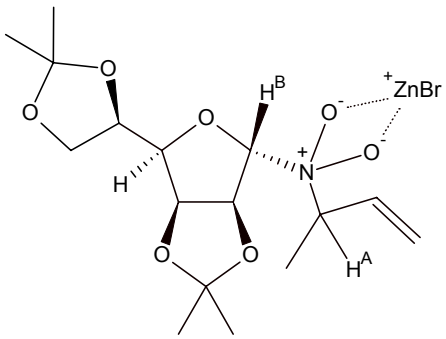
detected. The formation of the lactone **247** may occur during reaction (the organozinc reagent acts as base) or under the influence of the conjugated base ($MeO^-$) of the quenching reagent (methanol).

**Table 10:** Reaction conditions and yield of nitrone **250**.

| Entry | Reaction temperature °C | Reaction time h | Quenching agent | Yield % | Z:E [a] |
|---|---|---|---|---|---|
| 1 | -78 | 4 | MeOH | - | - |
| 2 | -78 to -10 | 6 | MeOH | 12 | 1:3 |
| 3 | 0 | 12 | MeOH | 7 | 1:3.2 |
| 4 | -35 | 14 | MeOH | 14 | 1:3.5 |
| 5 | -35 | 14 | 0.5 M TFA/DCM | - | - |
| 6 | -35 to -10 | 2.5 | 1.3 M AcOH/DCM | 17 | 1:7.5 |

[a] Determined by $^1$H NMR

Formation of the nitrone **250** is due to the stabilizing effect brought about by the conjugation of the newly formed C=N double bond with that of the allylic system. The quenching agent is first acting as proton source (Scheme 63) and then the remaining conjugated base $B^-$ may abstract $H^A$ or $H^B$ (Figure 34). Although $H^B$ is more acidic then $H^A$, the formation of a conjugated system is energetically more favorable compared to the formation of an exocyclic double bond.

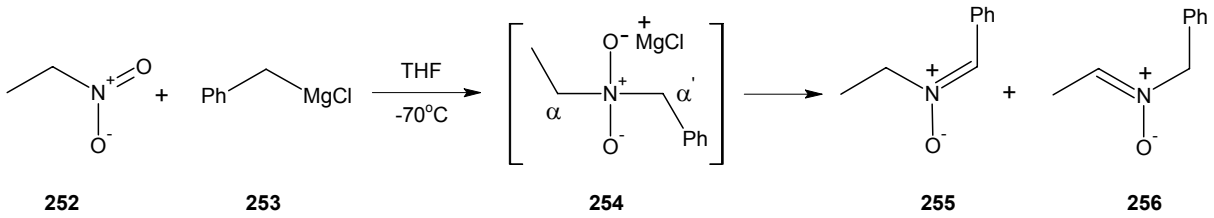



**251**

**Figure 34:** Tetrahedral intermediate formed in the reaction of 2-butenyl zinc bromide **214** with the 1-deoxy-1-nitrosugar **156**.

In order to use the relatively higher acidity of $H^B$ as a driving force for the formation of the nitrone **242** ($R^1$=Me, $R^2$=H), the strength of the conjugated base $B^-$ (Scheme 63) was reduced using stronger acids (AcOH, TFA) as quenching agents.

Bartoli *et al.*[21] used a similar strategy to obtain selectively the two nitrone regioisomers **255** and **256** resulted upon the reaction between nitroethane **252** and benzylmagnesium chloride **253** (Scheme 67).

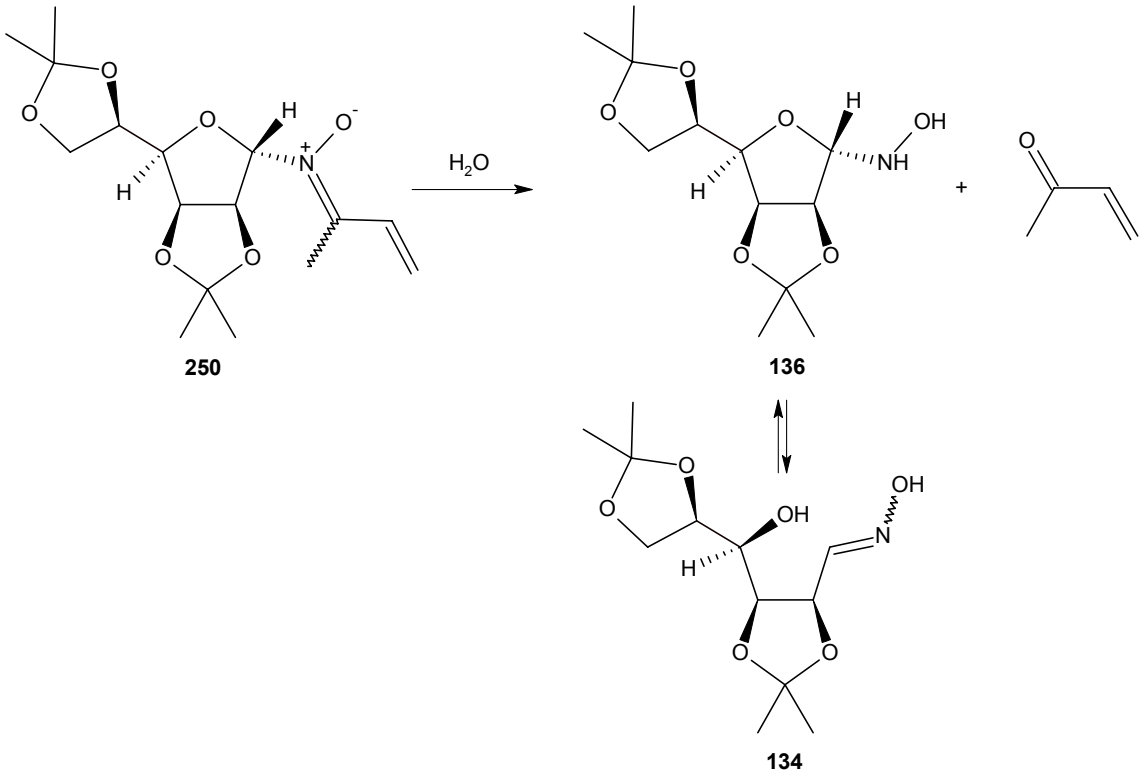



**Scheme 67**. Formation of the nitrone regioisomers **255** and **256** in the reaction of nitroethane **252** with benzylmagnesium chloride **253**.[21]

The weak conjugated base ($Cl_3CCOO^-$) resulted upon quenching with trichloroacetic acid, favours the elimination of the more acidic benzylic proton and formation of **256** only, whereas the stronger and bulky conjugated base derived from 2,6-dimethylbenzoic acid favours the formation of nitrone **255**.

In the present study, the formation of nitrone **250** only is observed upon quenching with AcOH/DCM. When TFA/DCM is involved, no nitrone **250** results, but a very complex mixture due to the deprotection of sugar moiety. Table 10 shows also that the type of quenching reagent plays a minor role on the reaction yield, which means that the significant process is the electrophilic attack of the nitrosugar on the nucleophile and not the further reaction with the conjugated base. A mixture of stereoisomers is observed (TLC, NMR) when MeOH and AcOH/DCM quenching is applied. Since the $^1$H NMR analysis shows a singlet for the C(1)-H proton (Scheme 66), it is concluded that no anomerisation occurrs at C(1) and the ratios presented in Table 10 correspond to the *Z*-*E* stereoisomers of **250**. The different *Z*:*E* ratio which results upon quenching with AcOH/DCM is most probably due to the sterical hindrance brought about by the conjugated base $AcO^-$. In the $^1$H NMR spectra the double doublet of the vinylic proton appears at 7.23 ppm, corresponding to the *Z*-isomer, and at 6.86 ppm for the *E*-isomer. The signal corresponding to the vinylic proton of the *Z*-isomer is shifted to a lower field due to its vicinity to the oxygen anion of the nitrone group.

Analysis of the mass spectrum (electrospray ionisation, positive ion mode) of **250** shows beside the expected peaks corresponding to $[M+Na]^+$ ($m/z$ 350.1), $[M+K]^+$ ($m/z$ 366.1) and $[2M+Na]^+$ ($m/z$ 677.1), a peak with $m/z$ = 625.2 which indicates the hydrolysis of the nitrone **250** to 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134** (Scheme 68).

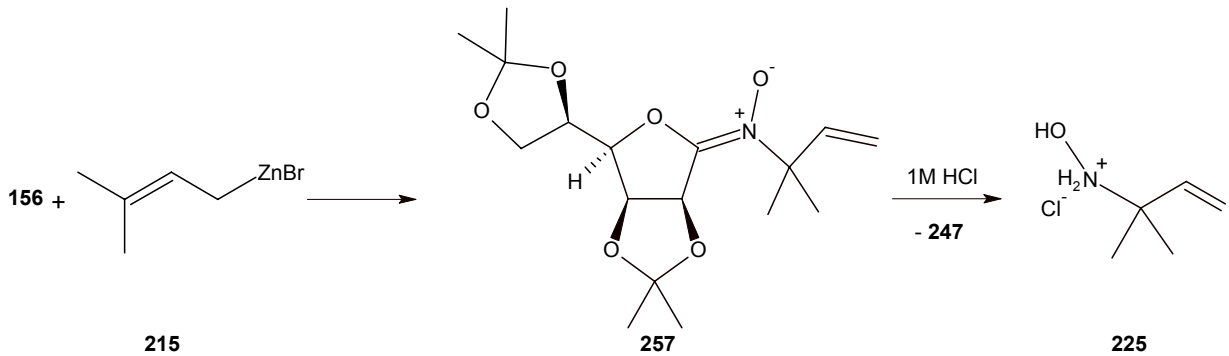



**Scheme 68:** Hydrolysis of the nitrone **250** to 2,3:5,6-di-*O*-isopropylidene-D-mannose-oxime **134**.

The peak with $m/z$ = 625.2 results due to formation of the cluster [**250**+**134**+Na]$^+$.

Hydrolysis of the nitrone **250** with 1M HCl/$CHCl_3$ followed by the TLC analysis of the organic phase confirms the formation of **134** and sustains the occurrence of such a pathway in ESI-MS.

The use of 3,3-dimethylallyl zinc bromide **215** as nucleophile - a virtual replacement of proton $H^A$ by a methyl group - affords the hydroxylamine hydrochloride **225** as the hydrolysis product of the intermediary nitrone **257** (Scheme 69). The allyl organozinc reagent **215** shows very good regioselectivity since only the formation of the branched hydroxylamine hydrochloride **225** is observed.




**Scheme 69:** Reaction of 3,3-dimethylallyl zinc bromide **215** with the 1-deoxy-1-nitrosugar **156**.

The intermediacy of **257** is proven by the appearance of the characteristic[7,56] nitrone absorptions at 1587 $cm^{-1}$ ($C=N^{+}$) and 1222 $cm^{1}$ (N-O) in the IR spectrum of the crude reaction mixture. Attempts to isolate the nitrone **257** by flash chromatography on silica gel or alumina results in the formation of mixtures of **257**, **247** and hydroxylamine **225** (as free base), as determined by NMR. When similar conditions as above are involved (Table 10, Entry 2) a significantly longer reaction time is required to obtain **225** in 27% yield, probably due to the more sterically hindered allyl organozinc reagent **215** (Table 11).

**Table 11:** Reaction conditions and yields of *N*-(1,1-dimethylallyl)hydroxylamine hydrochloride **225**.

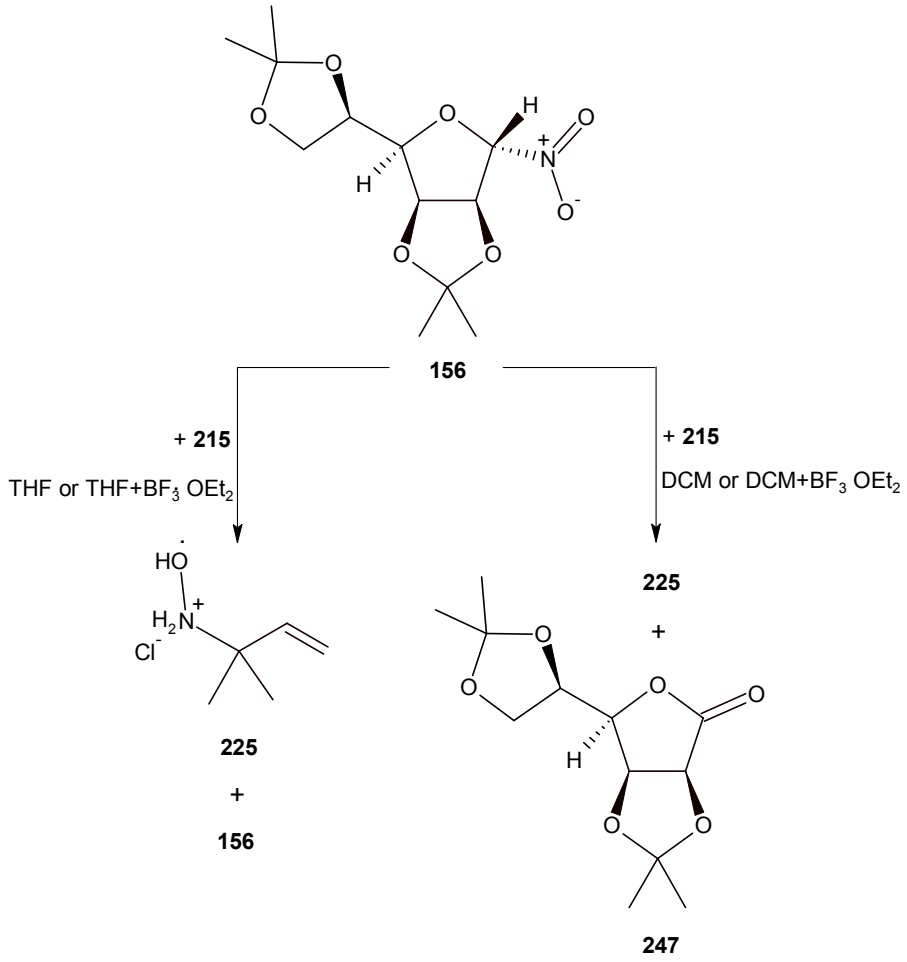
| Entry | Solvent | Temperature °C | Reaction time h | Lewis acid | Yield of 225 [a] % |
|---|---|---|---|---|---|
| 1 | THF | -35 to 0 | 23 | - | 27 |
| 2 | THF | -55 | 12 | $BF_3 \cdot OEt_2$ | - |
| 3 | THF | -30 to -20 | 5 | $BF_3 \cdot OEt_2$ | - |
| 4 | THF | -20 to 0 | 16 | $BF_3 \cdot OEt_2$ | 8 |
| 5 | DCM | -78 to -10 | 20 | - | 11 |
| 6 | DCM | -78 to -10 | 18 | $BF_3 \cdot OEt_2$ | 15 |

[a] Lactone **253** formed as by-product

The nitro group can be activated by Lewis acids ($AlCl_3$, $TiCl_4$, $BF_3 \cdot OEt_2$, $SnCl_4$).[181] Intramolecular transformations of γ-silylated nitroalkanes have been reported[181] and it has been found that the nitroalkane-Lewis acid complex is stable in the absence of an electron donating group situated in γ position towards $NO_2$. Moreover, the nitro compound can be recovered unchanged after the Lewis acid is removed.

In the present study, the stability of the **156**-$BF_3 \cdot OEt_2$ complex in THF or DCM is verified by stirring the mixture at room temperature for 48 h, under nitrogen atmosphere. TLC analysis of an aliquot showed only the presence of the nitrosugar **156**.

Upon reaction of the 1:1.1 complex **156**-$BF_3 \cdot OEt_2$ with 3,3-dimethylallyl zinc bromide **215** in THF no formation of the nitrone **257** is observed below -20°C (Table 11, Entries 2 and 3). Stirring at -20°C for 1 h and then at 0°C for 11 h, followed by the subsequent hydrolysis furnishes the hydroxylamine hydrochloride **225** in 8% yield. Only 20% of the nitrosugar **156** are converted under these conditions (Table 11, Entry 4).




**Scheme 70**: Influence of the solvent on the product distribution in the reaction between the 1-deoxy-1-nitrosugar **156** and 3,3-dimethylallyl zinc bromide **215**

A solution of 3,3-dimethylallyl zinc bromide **215** in DCM can easily be prepared by evaporating the THF *in vacuo* and addition of water free DCM at 0°C. Reaction of the nitrosugar **156** with **215** in DCM furnishes the hydroxylamine hydrochloride **225** in 11% yield (Table 11, Entry 5) and lactone **247** in 85% yield as by-product due to a Nef reaction. The yield of hydroxylamine hydrochloride **225** is not increased significantly by the addition of the Lewis acid (Table 11, Entry 6) and the lactone **247** results in 76% yield as by-product.

It can be concluded that the Lewis acid has a minor activating effect on the nitro group of **156** with respect to an increase of nitrogen electrophilicity. Decreasing the electron density on the nitro group favors mostly an increase of the α-proton acidity (Figure 35). Under these conditions, the organozinc compound **215** predominantly reacts as a base rather than as a nucleophile.

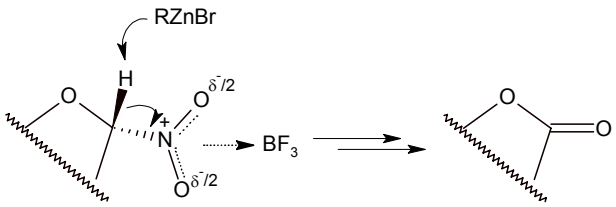
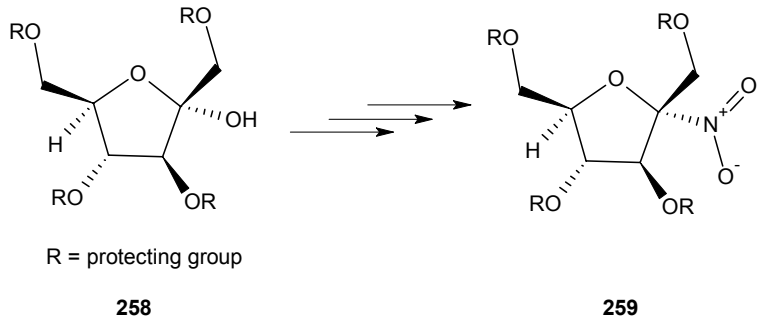



**Figure 35:** Lewis acid activation of the nitro group of **156** favors the increase of α-proton acidity.

Although the electrophilic amination of allyl organometallics with 1-deoxy-1-nitrosugar **156** has some important drawbacks (relatively high acidity of the α-hydrogen to the nitro group, poor electrophilicity of the nitrogen atom) it should be mentioned that there are still positive results concerning the synthesis of hydroxylamines, especially when a synthetically versatile allyl moiety is connected to nitrogen. Moreover, the method described here remains open for further investigations. An attractive approach is the use of *O*-protected α-D-fructofuranose **258** as optically active starting material for the synthesis of the nitrosugar **259** (Scheme 71). The absence of the acidic α-hydrogen towards the nitro group would exclude the occurrence of the Nef reaction pathway.

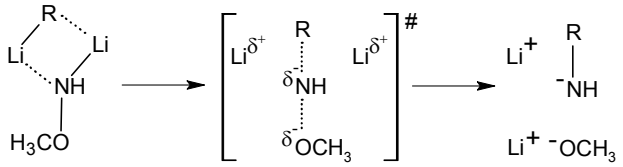



**Scheme 71**. Nitro sugar **259** proposed to be used as chiral aminating reagent of allyl organometallic compounds.

# 4. Summary

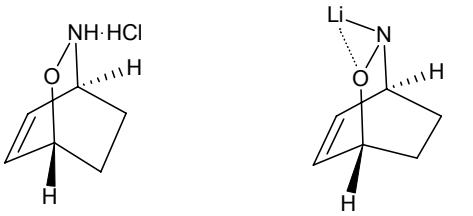
These are only few efficient methods for reagent-controlled stereoselective electrophilic amination compared to those based on chiral substrates or chiral catalysts. An effective stereoselective amination reagent allows greater method flexibility, due to the high availability of prochiral nucleophilic substrates. In the present work the reactivity of three types of enantiomerically pure electrophilic amination reagents towards carbon nucleophiles was investigated, with the aim to provide a valuable method for the stereoselective synthesis of α-amino ketones and α-amino acids.

*N*-Lithiated hydroxylamines are electrophilic species - *nitrenoids* - which react with organolithium reagents and provide amines. Although it was concluded that the electrophilic amination reaction involves a reaction of two anionic species - an interaction that should be repulsive - a $S_N2$-like transition state **167** is suggested. Organolithium species are generally aggregated. It is proposed that such a transition state is reached by a pathway involving a dimer **166**.

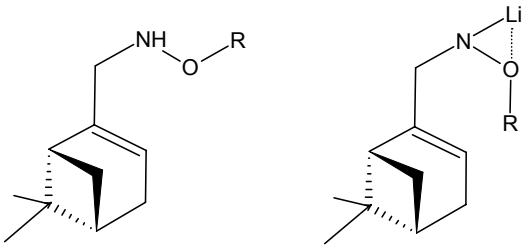



**166** **167**

Enantiomerically pure reagents on the basis of lithiated *N,O*-disubstituted hydroxylamine derivatives were prepared starting from (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124** and *O*-substituted *N*-[10-(1*R*,5*R*)-pin-2-enyl]hydroxylamines **125**.




**124** **168**

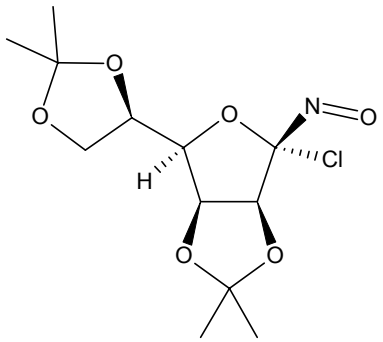



**125** **176-178, 180**

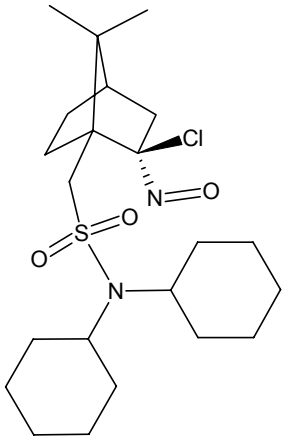
R = Me, Bn, $SiMe_3$, Ts

Their amination potential was explored using phenyl lithium as substrate. The *N*-lithium amide **168** undergoes β-elimination under the reaction conditions and proved to be improper as electrophilic amination reagent. *O*-substituted *N*-lithium-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-hydroxyl-amines **176-178** showed a good reactivity towards phenyl lithium (48-59% yield) and higher order phenyl cyanocuprate (70-94%), but were unreactive towards lithium or copper enolates. It has been suggested that formation of the associated species substrate-nitrenoid is the key step in the electrophilic amination reactions of carbanions using the nitrenoids **176**-**178**. The compound **180** (R = Ts) is unstable under the strongly basic reaction conditions. Highly aggregated substrates in which the metal ion is not available for complexation with the nitrenoid show less or any reactivity.

The second type of electrophilic amination reagents involved in this study are enantiomerically pure α-chloronitroso reagents **65** and **74**.




**65**

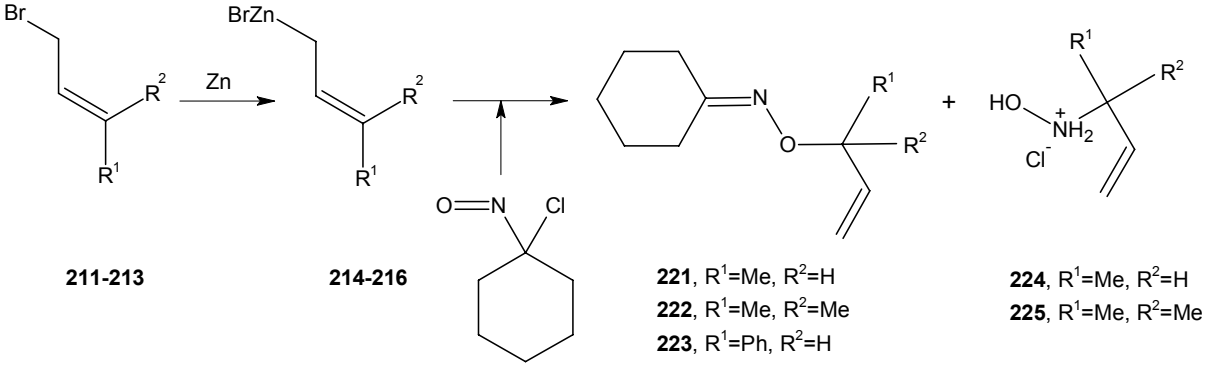



**74**

(+)-*N,N*-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74** provides the correspond-ding α-aminated ketone in moderate yields when lithium or zinc enolates derived from propiophenone are used as substrates, but was unreactive towards lithium or zinc ester enolates. 2,3:5,6-Di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** proved to be incompatible with the strongly basic conditions involved, due to its labile sugar moiety.

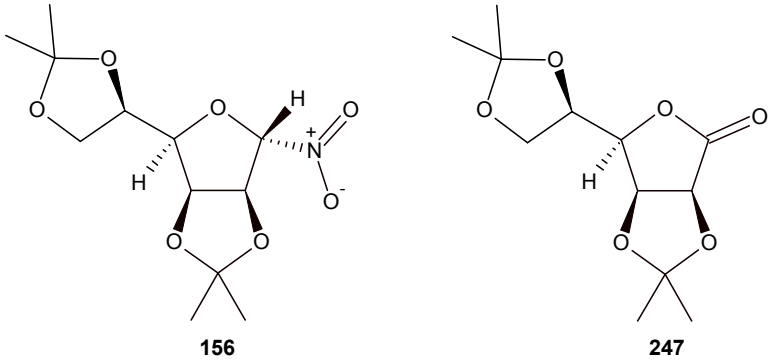
Allyl hydroxylamines could be regarded as masked synthons for the synthesis of α-amino acids. They are important buildings blocks in organic chemistry, but can be easily reduced to the more important allyl amines and further transformed to a range of products by functionalisation, reduction or oxidation of the double bond. Especially, the double bond oxidation could provide a variety of optically active α-amino acids when prochiral allyl derivatives are used as starting materials. Therefore, allyl organometallic reagents are appropriate carbanionic substrates which are prone to react with electrophilic amination reagents and to provide allyl amino compounds.

Following this strategy, a new reaction pathway - attributed to an ene reaction mechanism - occurs when allyl organozinc reagents react with α-chloronitroso cyclohexane **12**.



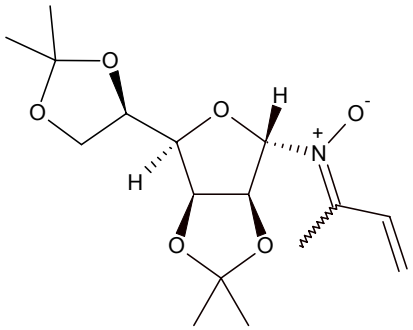

1-Chloro-1-nitrosocyclohexane **12** has been used as model system, due to its inexpensive synthesis and merely the same reactivity compared to **74**. It has been demonstrated that despite of the SET or 1,2-addition mechanisms reported to occur in the reactions between α-chloronitroso compounds and organomagnesium or organoaluminum reagents, the [2+3] cycloaddition or the M-ene reaction with a reverse orientation of the nitroso group can be responsible for the formation of the reaction products **221**-**223**. The oxime ethers **221**-**223** result exclusively in 82-97% yield if THF is used as solvent. The hydroxylamines **224** and **225** are formed in 2-14% yield, accompanied by the oxime ethers **221**-**223** (64-84%), if the reactions are performed in toluene. The procedure has not been extended to a stereoselective approach due to its low practical utility in the synthesis of allyl hydroxylamines. However, it should be mentioned that this is the first report of an ene type mechanism observed in the reaction between an allyl organometallic reagent and an α-chloronitroso compound.

The reaction between 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** and allyl organometallic (Zn, Mg, Ti) reagents was further investigated. Allyl organomagnesium and organotitanium reagents favor exclusively the occurrence of the Nef reaction pathway, with the formation of the 2,3:5,6-di-*O*-isopropylidene-α-D-manno-1,4-lactone **247**.

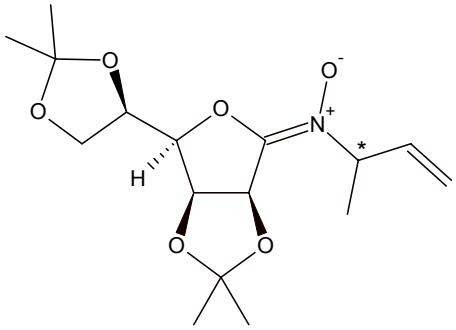



**156** **247**

Electrophilic amination of 2-butenyl zinc bromide **214** with **156** affords the conjugated sugar nitrone **250** in 7-17% yield, accompanied by the formation of lactone **247**.



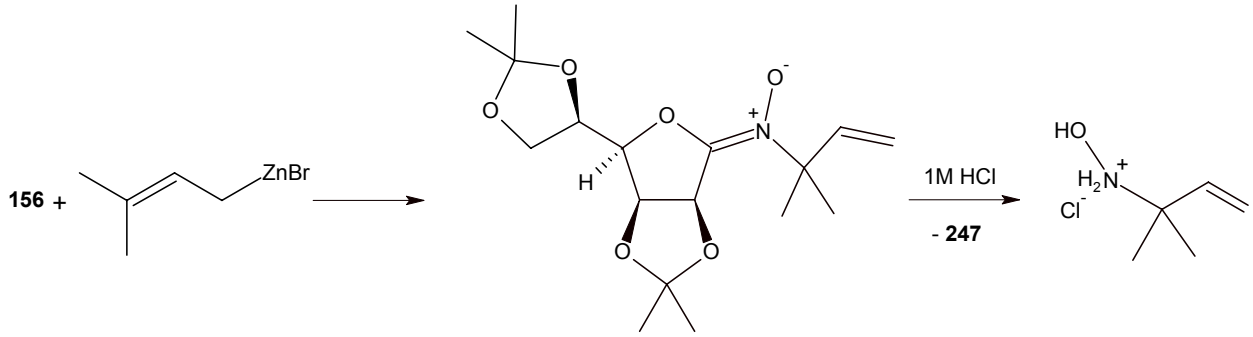
**250**



**260**

Elimination of the allylic proton is favored by the formation of a conjugated system and nitrone **250** results instead of the target compound **253**.

The use of 3,3-dimethylallyl zinc bromide **215** as substrate - a virtual replacement of the γ allylic proton by a methyl group - affords the hydroxylamine hydrochloride **225** in 8-27% yield, as the hydrolysis product of the intermediary nitrone **257**.




**215** **257** **225**

The use of a Lewis acid ($BF_3 \cdot OEt_2$) has a minor activating effect on the nitro group of **156** in concerning the increase of nitrogen electrophilicity. Decreasing of the electron density on the nitro group favors mostly the Nef reaction pathway and formation of the lactone **247**. Under these conditions, the organozinc compound is more prone to react as a base rather than as a nucleophile.

# 5. Experimental Section

## 5.1 Solvents, apparatus and methods

**Solvents:**

| | |
|---|---|
| THF, Diethylether | successively distilled over potassium hydroxide, calcium hydride and finally from sodium benzophenone ketyl, under nitrogen atmosphere |
| *n*-Hexane | distilled over sodium under nitrogen atmosphere |
| Dichloromethane | successively distilled over calcium chloride and calcium hydride |
| Toluene | successively distilled over calcium hydride and sodium |
| Petrolether | distilled fraction 35-60°C |
| Ethylacetate | distilled over calcium chloride |
| Triethylamine, Diisopropylamine | distilled over calcium hydride |

**Inert atmospheres:**

| | |
|---|---|
| Nitrogen | dried over phosphorus pentoxide |
| Argon | |

**Flash Chromatography:**

Silica gel 60, 40-63 μm (Merck)

**Thin Layer Chromatography:**

Silica gel 60 $F_{254}$ on aluminum foil (Merck)

**Melting Point Apparatus:**

Melting Point B-540 (Büchi)

Electrothermal IA 6304 (Electrothermal)

Dr. Tottoli Capillary Melting Point Apparatus (Büchi 510)

**Elemental analysis:**

CHNS-932 (Leco Corporation)

Vario EL (Heraeus)

**Gas Chromatography:**

| | |
|---|---|
| Instrument | GC-17A (Shimadzu) |
| | Autosampler AOC-20i (Shimadzu) |
| | Software CLASS VP43a |
| Column | HP-5MS capillary column (25 m, 0.25 mm ID, 0.25 μm film thickness, Hewlett Packard) |
| GC Methods | |
| *GC Pr. 1* | Injection temperature: 280°C |
| | Detector temperature: 300°C |
| | Carrier: Hydrogen |
| | Temperature program: |
| | 60°C for 2 min |
| | 60°C → 180°C at 15°C/min |
| | 180°C → 270°C at 5°C/min |
| | 270°C for 5 min |
| | Column flow: 0.4 mL $min^{-1}$ |
| | Split ratio: 49:1 |
| *GC Pr. 2* | Injection temperature: 280°C |
| | Detector temperature: 300°C |
| | Carrier: Hydrogen |
| | Temperature program: |
| | 60°C for 2 min |
| | 60°C → 270°C at 15°C/min |
| | 270°C for 10 min |
| | Column flow: 1 mL $min^{-1}$ |
| | Split ratio: 48:1 |

**GC-MS:**

| | |
|---|---|
| Instrument 1 | |
| Gas Chromatograph | Hewlett Packard HP 5890 Series II Plus |
| Mass Detector | Hewlett Packard HP 5972 A |

| | |
|---|---|
| Column | HP-5MS capillary column (30 m, 0.25 mm ID, 0.25 μm film thickness, Hewlett Packard) |
| Ionisation Energy | 70 eV |
| Carrier | Helium |
| Flow Rate | 1 mL $min^{-1}$ |
| Injector Temperature | 250°C |

Instrument 2

| | |
|---|---|
| GC-MS | Shimadzu GCMS-QP5050A |
| Column | HP-5MS capillary column (25 m, 0.25 mm ID, 0.33 μm film thickness, Hewlett Packard) |
| Ionisation Energy | 70 eV |
| Reagent Gas (Chemical Ionisation) | Isobutane |
| Carrier | Helium |
| Flow Rate | 0.7 mL $min^{-1}$ |
| Injector Temperature | 250°C |
| Split Ratio | 25:1 |

GC-MS Methods:

| | |
|---|---|
| *GC-MS Pr. 1* | Instrument 1<br>Temperature program:<br>70°C for 2 min<br>70°C → 270°C at 25°C/min<br>270°C for 3 min |
| *GC-MS Pr. 2* | Instrument 2<br>Temperature program:<br>75°C for 5 min<br>75°C → 270°C at 15°C/min<br>270°C for 5 min |
| *GC-MS Pr. 3* | Instrument 2<br>Temperature program:<br>60°C for 2 min<br>60°C → 180°C at 15°C/min |

| | |
|---|---|
| | 180°C → 270°C at 5°C/min |
| | 270°C for 5 min |

**Analytical HPLC:**

| | |
|---|---|
| Instruments: | Pump: LDC Gradient Master 1601 |
| | Detector: Spectra System UV 100 (Thermo Separation Products) |
| | Integrator: CI-10B (LDC/Milton Roy) |
| Column | CHIRACEL OD (Daicel Chemical Industries Ltd.) |

Solvents: *n*-Hexane:$^{i}$PrOH = 1000:40

**IR Spectroscopy**

FT-IR Spectrometer Genesis (Mattson Instruments); WinFIRST software package

FT-IR Spectrometer FT/IR-410 (Jasco); Jasco Canvas software package

**Polarimetry**

Digital Polarimeter DIP-360 (Jasco)

**Mass Spectrometry:**

Esquire 3000–Ion Trap Mass Spectrometer (Bruker Daltonik GmbH); Electrospray Ionisation (ESI) Method

VG Autospec X (Micromass Co. UK Ltd.); Ionisation Energy 70 eV

**$^{1}$H-NMR Spectroscopy:**

Varian GEMINI 200 (199.975 MHz)

Varian GEMINI 2000 (200.041 MHz)

Varian UNITY 400 (399.952 MHz)

Bruker AC-250-P (250.133 MHz)

Bruker DRX 500 (500.130 MHz)

**$^{13}$C-NMR Spectroscopy:**

Varian GEMINI 200 (50.289 MHz)

Varian GEMINI 2000 (50.305 MHz)

Bruker AC-250-P (62.896 MHz)

Bruker DRX 500 (125.758 MHz)

**X-ray measurements:**

Nonius KappaCCD X-ray diffractometer

**Kugelrohr Distillation**

Büchi Glass Oven B-580

**Cryostat**

Lauda RLS 6

**Molecular Modeling Calculations**

Software: Spartan 5.1, Wavefunction, Inc, 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612 U.S.A

Methods: The following steps were followed for determination of the HOMO and LUMO energies and electronic distributions:

i) conformer analysis using MMFF force field;

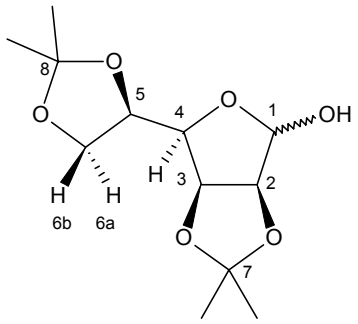
ii) geometry optimisation and determination of the HOMO and LUMO energies, respectively electronic distributions using Density Functional Theory (pBP/dn* basis set) and *Ab Initio* calculations at the RHF/3-21G* and RHF/6-31G* levels.

## 5.2 Synthesis of the Enantiomerically Pure Amination Reagents

### 5.2.1 Synthesis of 2,3:5,6-Di-O-isopropylidene-1-C-nitroso-α-D-mannofuranosyl-chloride

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose **133**

399 mg *p*-Toluenesulfonic acid monohydrate (2.10 mmol, 1.9 mol %) were added in one portion to a suspension of 20 g D-(+)-mannose **132** (111 mmol) in 640 mL dry acetone. The suspension was refluxed at 60-70°C for 25 hours. The solution was then stirred with 7 g $K_2CO_3$ at room temperature until pH 8. The mixture was filtered through Celite 500 and evaporation of the solvent *in vacuo* from the filtrate gave a light yellow solid. The solid was dissolved in dichloromethane and was filtered through a bed of silica gel topped with Celite 500. After evaporation of the solvent *in vacuo,* the light yellow solid was suspended in 150 mL diethyl ether and was stirred at room temperature for 30 min. Filtration, washing with diethyl ether and drying *in vacuo* afforded 8.54 g of a white solid. *n*-Hexane was successively added to mother liquor and crystallization at 4°C gave a second crop (10.76 g) of colorless crystals.




| | | |
|---|---|---|
| **Molecular formula:** | $C_{12}H_{20}O_6$ [260.28] | |
| **Yield:** | 67% (19.3 g, colorless crystals) | [lit.[102] 85%] |
| **TLC:** | $R_f$ = 0.21 [$Et_2O$:PE = 3:2] | |
| **Melting point**: | 121-122°C | [lit.[102] 119-121°C] |
| **Optical rotation:** | $[\alpha]_D^{26}$ = +9.8 (c = 1.3 in $CHCl_3$) | |
| | [lit.[102] $[\alpha]_D^{24}$ = +11.8 (c = 1.3 in $CHCl_3$)] | |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3436 (O-H), 2989 (C-H), 2948 ($CH_3$), 2900 ($CH_2$), 1459 ($CH_2$), 1375 ($CH_3$), 1253, 1226, 1203 (C-O-C), 1166, 1087, 1070 (C-O-C), 1035, 975, 856, 838, 514.

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 5.38 (1 H, br s, $\mathbf{H_1}$), 4.82 (1 H, dd, $^3J_{3\text{-}4}$= 3.7 Hz, $^3J_{3\text{-}2}$= 5.9 Hz, $\mathbf{H_3}$), 4.62 (1 H, d, $^3J_{2\text{-}3}$= 5.9 Hz, $\mathbf{H_2}$), 4.37-4.45 (1H, m, $\mathbf{H_5}$), 4.19 (1 H, dd, $^3J_{4\text{-}3}$= 3.7 Hz, $^3J_{4\text{-}5}$= 7.2 Hz, $\mathbf{H_4}$), 4.10 (1 H, dd, $^3J_{6a\text{-}5}$= 6.0, $^2J_{6a\text{-}6b}$= 8.6 Hz, $\mathbf{H_{6a}}$), 4.05 (1 H, dd,

$^{3}J_{6b\text{-}5}$= 5.1 Hz, $^{2}J_{6a\text{-}6b}$= 8.6 Hz, **$H_{6b}$**), 3.00 (1 H, br, O**H**), 1.46 (6 H, s, 2x $CH_3$), 1.38 (3 H, s, $CH_3$), 1.33 (3H, s, $CH_3$).

**$^{13}$C-NMR** ($CDCl_3$, 62 MHz) δ [ppm]: 112.6 (**$C_7$**), 109.1 (**$C_8$**), 101.2 (**$C_1$**), 85.5 (**$C_2$**), 80.1 (**$C_3$**), 79.6 (**$C_4$**), 73.3 (**$C_5$**), 66.5 (**$C_6$**), 26.8 ($CH_3$), 25.8 ($CH_3$), 25.1 ($CH_3$), 24.4 ($CH_3$).

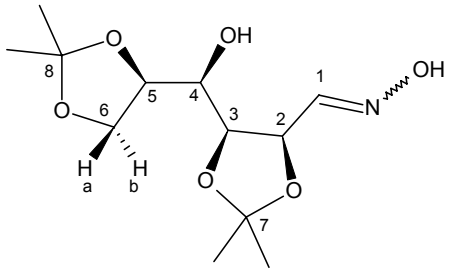
**MS (ESI)** *m/z*: 283.0 $[M+Na]^+$, 229.0 $[M+K]^+$, 543.0 $[2M+Na]^+$.

**Elemental analysis (%):** Calcd: C 55.37 H 7.74

Found: C 55.62 H 7.81

2,3:5,6-Di-*O*-isopropylidene-D-mannose oxime **134**

A solution of 44.8 g hydroxylamine hydrochloride (645 mmol, 4.5 eq.) and 44.9 g $NaHCO_3$ (534 mmol, 3.7 eq.) in 220 mL water was stirred at room temperature until $CO_2$ evolution stopped. Ethanol (220 mL) and 37.8 g 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **133** (143 mmol, 1 eq.) were added, and the reaction mixture was stirred at 60-80 °C for 3 hours. Extraction with ethyl acetate (300 mL), drying ($Na_2SO_4$), evaporation of the solvent *in vacuo* and recrystallization from ethyl acetate/*n*-hexane (1:1) gave 36.2 g (131.2 mmol, 92%) colorless crystals.




**Molecular formula:** $C_{12}H_{21}NO_6$ [275.98]

**Yield:** 92% (36.2 g, colorless crystals) [lit.[105] 92%]

**TLC:** $R_f$ = 0.34 [AcOEt:PE = 3:2]

**Melting point**: 137.5 -140°C [lit.[105] 139 -141°C]

**Optical rotation:** $[\alpha]_D^{27}$ = -115.9 (c = 1.0 in $CH_2Cl_2$)

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3534 (OH), 3378 (OH), 3293 (OH), 2992 (CH), 2939 ($CH_3$), 2917 ($CH_2$), 2894 (CH), 1654 (C=N), 1560, 1459 ($CH_3$), 1430 ($CH_2$), 1382 ($CH_3$), 1259, 1213 (C-O-C), 1160, 1145, 1076 (C-O-C), 1062, 944, 910, 896, 858, 678, 570, 514.

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]:

(*Z*)-Isomer: 9.86 (1H, s, N-O**H**), 7.12 (1H, d, $^{3}J_{1\text{-}2}$= 3.4 Hz, **$H_1$**), 5.25 (1H, dd, $^{3}J$= 7.6 Hz, $^{3}J_{1\text{-}2}$= 3.4 Hz, **$H_2$**), 4.64-4.52 (2H, m, **$H_3$** and C-O**H**), 4.25-3.95 (3H, m, **$H_{6a,b}$** and **$H_5$**), 3.70 (1H, dd, $^{3}J$= 6.7 Hz, $^{3}J$= 2.5 Hz, **$H_4$**), 1.52 (3H, s, $CH_3$), 1.43 (3H, s, $CH_3$), 1.41 (3H, s, $CH_3$), 1.35 (3H, s, $CH_3$).

(*E*)-Isomer (characteristic signals): 8.33 (1H, s, N-O**H**), 7.61 (1H, d, $^3J_{1\text{-}2}$= 7.6 Hz, $\mathbf{H_1}$), 4.79 (1H, m, $\mathbf{H_3}$), 4.49 (1H, dd, $^3J$= 1.5 Hz, $^3J_{1\text{-}2}$= 7.3 Hz, $\mathbf{H_2}$), 2.51 (1H, d, $^3J$= 6.9 Hz, $\mathbf{H_4}$).

(*Z*):(*E*) = 79:21

**$^{13}$C-NMR (**$CDCl_3$, 62 MHz) δ [ppm]:

(*Z*)-Isomer: 152.1 ($\mathbf{C_1}$), 109.7 ($\mathbf{C_7}$), 108.3 ($\mathbf{C_8}$), 78.4 ($\mathbf{C_2}$), 77.8 ($\mathbf{C_3}$), 72.9 ($\mathbf{C_4}$), 67.6 ($\mathbf{C_5}$), 65.1 ($\mathbf{C_6}$), 26.1 ($CH_3$), 25.9 (2 x $CH_3$), 24.7 ($CH_3$).

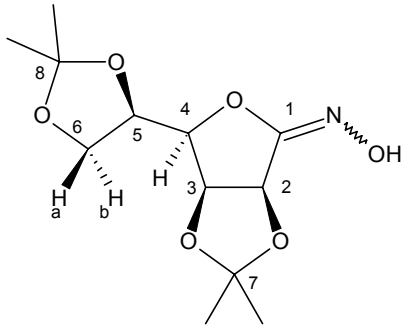
(*E*)-Isomer: 149.7 ($\mathbf{C_1}$), 109.7 ($\mathbf{C_7}$), 109.5 ($\mathbf{C_8}$), 76.7 ($\mathbf{C_2}$), 76.2 ($\mathbf{C_3}$), 75.0 ($\mathbf{C_4}$), 69.7 ($\mathbf{C_5}$), 66.9 ($\mathbf{C_6}$), 26.7 ($CH_3$), 26.7 ($CH_3$), 25.3 ($CH_3$), 24.5 ($CH_3$).

**MS (ESI)** *m/z* (%): 298.03 $[M+Na]^+$, 314.0 $[M+K]^+$, 573.05 $[2M+Na]^+$.

| **Elemental analysis (%):** | Calcd: C 52.35 | H 7.69 | N 5.09 |
|---|---|---|---|
| | Found: C 52.48 | H 7.70 | N 5.01 |

*N*-Hydroxy-2,3:5,6-di-*O*-isopropylidene-α-D-mannoimido-1,4-lactone **135**

A solution of 28 g sodium metaperiodate (131 mmol, 1.2 eq.) in 300 mL water was added via syringe pump, during 1 h, to a solution of 30 g 2,3:5,6-di-*O*-isopropyliden-D-mannose oxime **134** (109 mmol, 1 eq.) and 8.94 g sodium acetate (109 mmol, 1 eq.) in 700 mL ethanol at a bath temperature of 75°C. The mixture was stirred at that temperature until the starting oxime had disappeared, as indicated by TLC [AcOEt:PE = 3:2] (ca. 2 h). The mixture was filtered and the residue was washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was extracted with ethyl acetate. The extract was washed successively with a 10% aqueous sodium sulphite solution and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. Crystallization from dichloromethane/*n*-hexane (2:1) afforded 22 g (80.5 mmol, 74%) of hydroximolactone **135**, as colorless crystals.




| **Molecular formula:** | $C_{12}H_{19}NO_6$ [273.28] | |
|---|---|---|
| **Yield:** | 74% (22.0 g, colorless crystals) | [lit.[106] 93%] |
| **TLC:** | $R_f$ = 0.34 [AcOEt:PE = 3:2] | |
| **Melting point**: | 175.5-176.5°C | [lit.[106] 174-174.5°C] |
| **Optical rotation:** | $[\alpha]_D^{27}$ = +99.5 (c = 1.1 in $CHCl_3$) | |

[lit.[106] $[\alpha]_D^{26}$ = +98.6 (c = 1.1 in $CHCl_3$)]

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3411 (OH), 3315(OH), 2985 (C-H), 2958 ($CH_3$), 2939 ($CH_3$), 2892 (CH), 1691 (C=N), 1459 ($CH_2$), 1376 ($CH_3$), 1265, 1228 (C-O-C), 1159, 1116, 1087, 1068 (C-O-C), 973, 937, 858, 792, 686, 663, 511.

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 7.61 (1H, br., N-O**H**), 5.15 (1H, d, $^3J_{2\text{-}3}$ = 5.5 Hz, $\mathbf{H_2}$), 4.87 (1H, dd, $^3J_{2\text{-}3}$ = 5.5 Hz, $^3J_{3\text{-}4}$ = 3.7 Hz, $\mathbf{H_3}$), 4.50 (1H, ddd, $^3J_{5\text{-}4}$ = 8.4 Hz, $^3J_{5\text{-}6a}$ = 5.5 Hz, $^3J_{5\text{-}6b}$ = 4.4 Hz, $\mathbf{H_5}$), 4.30 (1H, dd, $^3J_{5\text{-}4}$ = 8.5 Hz, $^3J_{3\text{-}4}$ = 3.7 Hz, $\mathbf{H_4}$), 4.19 (2H, m, $\mathbf{H_6}$), 1.49 (3H, s, $CH_3$), 1.47 (3H, s, $CH_3$), 1.41 (3H, s, $CH_3$), 1.40 (3H, s, $CH_3$).

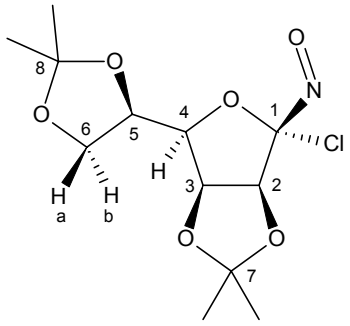
**$^{13}$C-NMR** ($CDCl_3$, 62 MHz) δ [ppm]: 156.9 ($\mathbf{C_1}$), 114.3 ($\mathbf{C_7}$), 109.8 ($\mathbf{C_8}$), 82.6 ($\mathbf{C_2}$), 77.5 ($\mathbf{C_3}$, $\mathbf{C_4}$), 72.7 ($\mathbf{C_5}$), 66.7 ($\mathbf{C_6}$), 27.2 ($CH_3$), 26.9 ($CH_3$), 25.9 ($CH_3$), 25.1 ($CH_3$).

**MS (ESI)** *m/z:* 295.98 $[M+Na]^+$, 569.03 $[2M+Na]^+$.

| **Elemental analysis (%):** | Calcd: C 52.74 | H 7.01 | N 5.13 |
|---|---|---|---|
| | Found: C 52.71 | H 6.94 | N 5.01 |

2,3:5,6-Di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65**

A solution of 9.63 g $^t$BuOCl (75% w/w in $^t$BuOH) (66 mmol, 1 eq.) in 85 mL water free dichloromethane was added dropwise during 1 h under nitrogen and protection against light, to a pre-cooled (-10°C) solution of 18.0 g *N*-hydroxy-2,3:5,6-di-*O*-isopropyliden-α-D-mannoimido-1,4-lactone **135** (66 mmol, 1 eq.) in 175 mL water free dichloromethane. After stirring for 15 min. at -10°C, the reaction mixture was warmed-up to room temperature and the solvent was carefully evaporated *in vacuo*. The blue residue was dissolved in *n*-hexane and filtered. Crystallisation from *n*-hexane afforded 20.1 g (65.34 mmol, 99%) **65** as blue needles.




| **Molecular formula:** | $C_{12}H_{18}ClNO_6$ [307.72] | |
|---|---|---|
| **Yield:** | 99 % (20.1 g, blue needles) | [lit.[106] 89%] |
| **TLC:** | $R_f$ = 0.57 [AcOEt:PE = 3:2] | |
| **Melting point:** | 78-81°C | [lit.[106] 80°C] |
| **Optical rotation:** | $[\alpha]_D^{27}$ = -1668 (c = 1.0 in $CH_2Cl_2$) | |

[lit.[106] $[\alpha]_D^{25}$ = -1400 (c = 5.0 in $CHCl_3$)]

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2989 (C-H), 2960 ($CH_3$), 2937 (CH), 2894 (CH), 1571 (N=O), 1457 ($CH_2$), 1382 ($CH_3$), 1259, 1214 (C-O-C), 1186, 1155, 1114, 1070 (C-N), 1002, 973, 892, 846 (C-Cl), 819, 755, 511.

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 5.54 (1H, d, $^3J_{2\text{-}3}$= 5.5 Hz, **$H_2$**), 5.00 (1H, dd, $^3J_{3\text{-}2}$= 5.6 Hz, $^3J_{3\text{-}4}$= 3.5 Hz, **$H_3$**), 4.54 (1H, ddd, $^3J_{4\text{-}5}$= 8.1 Hz, $^3J_{5\text{-}6a}$= 6.0 Hz, $^3J_{5\text{-}6b}$= 4.1 Hz, **$H_5$**), 4.24 (1H, dd, $^3J_{4\text{-}5}$= 8.2 Hz, $^3J_{4\text{-}3}$= 3.6 Hz, **$H_4$**), 4.17 (1H, dd, $^2J_{6a\text{-}6b}$= 9.0 Hz, $^3J_{6a\text{-}5}$= 6.0 Hz, **$H_{6a}$**), 4.07 (1H, dd, $^2J_{6a\text{-}6b}$= 9.1 Hz, $^3J_{6b\text{-}5}$= 4.0 Hz, **$H_{6b}$**), 1.49 (3H, s, $CH_3$), 1.40 (3H, s, $CH_3$), 1.29 (6H, s, 2 x $CH_3$).

**$^{13}$C-NMR** ($CDCl_3$, 62 MHz) δ [ppm]: 125.2 (**$C_1$**), 115.0 (**$C_7$**), 109.8 (**$C_8$**), 88.7 (**$C_2$**), 82.3 (**$C_3$**), 79.5 (**$C_4$**), 72.1 (**$C_5$**), 66.7 (**$C_6$**), 26.8 ($CH_3$), 25.3 ($CH_3$), 25.1 ($CH_3$), 24.6 ($CH_3$).

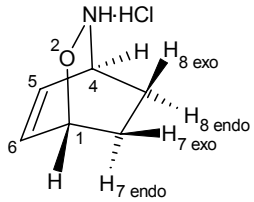
**MS (ESI)** *m/z*: 207.8 $[M+H\text{-}C_5H_9O_2]^+$, 330.0 $[M(C_{12}H_{18}{}^{35}ClNO_6)+Na]^+$, 332.0 $[M(C_{12}H_{18}{}^{37}ClNO_6)+Na]^+$.

| **Elemental analysis (%):** | Calcd: C 46.84 | H 5.90 | Cl 11.52 | N 4.55 |
|---|---|---|---|---|
| | Found: C 46.90 | H 5.88 | Cl 11.49 | N 4.51 |

### 5.2.2 Synthesis of (1*R*,4*S*)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride

(1*R*,4*S*)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124**

A solution of 7.80 g 2,3:5,6-di-*O*-isopropylidene-1-*C*-nitroso-α-D-mannofuranosylchloride **65** (25.33 mmol, 1 eq.) in 100 mL water free diethyl ether was pre-cooled to -10°C and protected against light. Cyclohexa-1,3-diene **138** (6.09 g, 75.99 mmol, 3 eq.) was added dropwise, followed by 30 mL absolute ethanol. The stirring was continued for 2 h at -10°C and 3 h at room temperature, the white precipitate was filtered off, washed with water free diethyl ether and dried *in vacuo* to afford 3.44 g (23.30 mmol, 92 %) **124** as white powder.




| **Molecular formula:** | $C_6H_{10}ClNO$ [147.6] | |
|---|---|---|
| **Yield:** | 92% (3.44 g, white powder) | [lit.[5] 70%] |
| **Melting point**: | 132-134°C | [lit.[5] 135°C] |
| **Optical rotation:** | $[\alpha]_D^{27}$ = +23.9 (c = 5.0 in $CHCl_3$) | |

[lit.[5] $[\alpha]_D^{25}$ = +24.4 (c = 5.0 in $CHCl_3$)]

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3600-3300 ($NH_2^+$), 3054-2450 (CH), 1542 (NH), 1454 ($CH_2$), 1419 (CH), 1384 (=CH), 1282 (C-O), 1220 (N-O), 1176, 1122, 1087, 1062, 1027, 991, 944, 923, 860, 815, 802, 779, 715.

**$^1$H-NMR** ($D_2O$, 250 MHz) δ [ppm]: 6.88 (1H, ddd, $^3J_{6\text{-}5}$= 8.5 Hz, $^3J_{6\text{-}1}$= 5.8 Hz, $^4J_{6\text{-}4}$= 1.6 Hz, **$H_6$**), 6.63 (1H, ddd, $^3J_{5\text{-}6}$= 8.3 Hz, $^3J_{5\text{-}4}$= 6.4 Hz, $^3J_{5\text{-}1}$= 1.6 Hz, **$H_5$**), 4.98 (1H, dddd, $^3J_{1\text{-}6}$ = 5.8 Hz, $^3J_{1\text{-}5}$= 1.6 Hz, $^3J_{1\text{-}7endo}$= 1.5 Hz, $^3J_{1\text{-}7exo}$= 1.5 Hz, **$H_1$**), 4.52 (1H, m, **$H_4$**), 2.24 (1H, dddd, $^2J_{7endo\text{-}7exo}$= 18.0 Hz, $^3J_{7endo\text{-}8endo}$= 9.4 Hz, $^3J_{7endo\text{-}8exo}$= 3.8 Hz, $^3J_{7endo\text{-}1}$= 1.5 Hz, **$H_{7endo}$**), 2.13 (1H, dddd, $^2J_{7exo\text{-}7endo}$= 17.9 Hz, $^3J_{7exo\text{-}8exo}$= 10.4 Hz, $^3J_{7exo\text{-}8endo}$= 3.2 Hz, $^3J_{7exo\text{-}1}$= 1.5 Hz, **$H_{7exo}$**), 1.62 (1H, dddd, $^2J_{8endo\text{-}8exo}$= 17.4 Hz, $^3J_{8endo\text{-}7endo}$= 9.6 Hz, $^3J_{8endo\text{-}7exo}$= 3.0 Hz, $^3J_{8endo\text{-}4}$= 1.5 Hz, **$H_{8endo}$**), 1.57 (1H, dddd, $^2J_{8exo\text{-}8endo}$= 17.6 Hz, $^3J_{8exo\text{-}7exo}$= 10.6 Hz, $^3J_{8exo\text{-}7endo}$= 3.6 Hz, $^3J_{8exo\text{-}4}$= 1.4 Hz, **$H_{8exo}$**).

**$^{13}$C-NMR** ($D_2O$, 62 MHz) δ [ppm]: 138.4 (**$C_6$**), 131.5 (**$C_5$**), 73.9 (**$C_1$**), 51.8 (**$C_4$**), 24.4 (**$C_7$**), 19.8 (**$C_8$**).

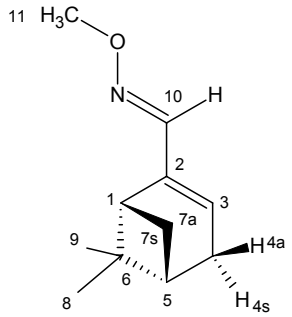
**MS (ESI)** *m/z*: 111.9 $[M\text{-}Cl]^+$, 133.8 $[M\text{-}HCl+Na]^+$.

| **Elemental analysis (%):** | Calcd: C 48.82 | H 6.83 | Cl 24.02 | N 9.49 |
|---|---|---|---|---|
| | Found: C 49.00 | H 6.79 | Cl 23.68 | N 9.18 |

### 5.2.3 Synthesis of the Enantiomerically Pure *N,O*-Disubstituted Hydroxylamines

*O*-Methyl-(1*R*,5*R*)-(-)-myrtenal oxime **145**

A solution of 4.54 g *O*-methylhydroxylamine hydrochloride **143** (54.3 mmol, 1.5 eq.) and 5.34 g sodium acetate (65.2 mmol, 1.8 eq.) in 60 mL methanol was stirred for 10 min at room temperature. (1*R*,5*R*)-(-)-Myrtenal **142** (5.44 g, 36.2 mmol, 1 eq.) was added and the mixture was refluxed for 4 h. After completion, the solvent was evaporated *in vacuo*, 100 mL water were added to the residue, extracted with 100 mL diethyl ether and dried over $MgSO_4$. Evaporation of diethyl ether *in vacuo* gave a yellow oil which was vacuum distilled (53°C, 0.27 mbar) and furnished 5.38 g (30.05 mmol, 83%) **145** as colorless oil.




**Molecular formula:** $C_{11}H_{17}NO$ [179.26]

**Yield:** 83% (5.38 g, colorless oil)

**TLC:** $R_f$ = 0.73 [AcOEt:PE = 1:12]

**Boiling point**: 53°C (0.27 mbar)

**Optical rotation:** $[\alpha]_D^{25}$ = -17.7 (c = 1.3 in $CHCl_3$)

**GC** (*GC Pr. 2*): $t_R$= 10.47 min

**HPLC** (CHIRACEL OD) $t_R$= 8.53 min (*n*-hexane:$^i$PrOH = 1000:40)

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 2972 ($CH_2$), 2937 ($CH_3$), 2872 ($OCH_3$), 1621 (C=N), 1465 ($CH_2$), 1427 ($CH_3$), 1382 (C-$Me_2$), 1367 (C-$Me_2$), 1265, 1205, 1180, 1083, 1041 (C-O), 896 (C=C-H), 792, 653.

**$^1$H-NMR** ($CDCl_3$, 200 MHz) δ [ppm]: 7.66 (1H, s, $\mathbf{H_{10}}$), 5.83 (1H, m, $\mathbf{H_3}$), 3.85 (3H, s, $\mathbf{H_{11}}$), 2.83 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$= 1.9 Hz, $\mathbf{H_1}$), 2.47 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J_{7s\text{-}1}$= 5.6 Hz, $^3J$= 5.6 Hz, $\mathbf{H_{7s}}$), 2.45 (1H, m, $\mathbf{H_{4s}}$), 2.38 (1H, ddd, $^2J_{4a\text{-}4s}$= 19.6 Hz, $^3J$= 3.1 Hz, $^3J$= 3.1 Hz, $\mathbf{H_{4a}}$), 2.13 (1H, m, $\mathbf{H_5}$), 1.33 (3H, s, $\mathbf{H_8}$), 1.15 (1H, d, $^2J_{7a\text{-}7s}$= 8.8 Hz, $\mathbf{H_{7a}}$), 0.81 (3H, s, $\mathbf{H_9}$).

**$^{13}$C-NMR (**$CDCl_3$, 50 MHz) δ [ppm]: 150.5 ($\mathbf{C_{10}}$), 143.3 ($\mathbf{C_2}$), 131.4 ($\mathbf{C_3}$), 62.0 ($\mathbf{C_{11}}$), 41.2 ($\mathbf{C_5}$), 40.8 ($\mathbf{C_1}$), 38.1 ($\mathbf{C_6}$), 32.8 ($\mathbf{C_4}$), 31.6 ($\mathbf{C_7}$), 26.4 ($\mathbf{C_8}$), 21.3 ($\mathbf{C_9}$).

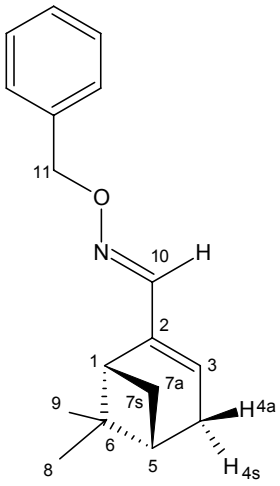
**MS (EI)** *m*/*z* (%): 179 $[M]^{+\cdot}$ (42), 164 $[M–CH_3]^+$ (25), 148 $[M–OCH_3]^+$ (70), 136 $[C_{10}H_{14}]^+$ (80), 132 (45), 118 (25), 106 $[C_7H_7NH]^{+\cdot}$ (50), 105 $[C_7H_7N]^+$ (65), 104 (62), 93 (30), 91 $[C_7H_7]^+$ (79), 79 (60), 77 $[C_6H_5]^+$ (98), 65 (32), 53 (44), 51 (41), 43 (33), 41 $[C_3H_7]^+$ (100), 39 (97), 29 (68), 27 (70), 15 (34).

| **Elemental analysis (%):** | Calcd: C 73.70 | H 9.56 | N 7.81 |
|---|---|---|---|
| | Found: C 73.36 | H 9.39 | N 7.75 |

<u>*O*-Benzyl-(1*R*,5*R*)-(-)-myrtenal oxime **146**</u>

A solution of 3.18 g *O*-benzylhydroxylamine hydrochloride **144** (19.97 mmol, 1.5 eq.) and 1.97 g sodium acetate (23.94 mmol, 1.8 eq.) in 50 mL methanol was stirred for 10 min at room temperature. (1*R*,5*R*)-(-)-Myrtenal **142** (2 g, 13.30 mmol, 1 eq.) was added and the mixture was refluxed for 3 h. After completion of the reaction, filtration of the reaction mixture over Celite

500 and evaporation of the solvent *in vacuo* afforded a light-yellow oil which was purified by flash chromatography on silica gel (AcOEt:PE = 1:12) and Kugelrohr distillation. 2.82 g (11.04 mmol, 83 %) of analytically pure **146** resulted as colorless oil.




| | |
|---|---|
| **Molecular formula:** | $C_{17}H_{21}NO$ [255.37] |
| **Yield:** | 83% (2.82 g, colorless oil) |
| **TLC:** | $R_f$ = 0.61 [AcOEt:PE = 1:12] |
| **Boiling point:** | 125°C (0.26 mbar) |
| **Optical rotation:** | $[\alpha]_D^{24}$ = -7.2 (c = 1.1 in $CHCl_3$) |

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3064 (ar. C-H), 3029 (=C-H), 2971 (CH), 2917 (CH), 2882 (O-$CH_2$), 1621 (C=N), 1496 (C=C arom.), 1467 ($CH_2$), 1454 ($CH_2$), 1426 ($CH_3$), 1365 ($CH_3$), 1330, 1205, 1051, 1025 (ar. CH), 945 (ar. CH), 927 (ar. CH), 696.

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 7.74 (1H, s, $\mathbf{H_{10}}$), 7.28-7.74 (5H, m, Ph), 5.82 (1H, m, $\mathbf{H_3}$), 5.08 (2H, s, $\mathbf{H_{11}}$), 2.85 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$= 1.9 Hz, $\mathbf{H_1}$), 2.47 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J_{7s\text{-}1}$= 5.6 Hz, $^3J$= 5.6 Hz, $\mathbf{H_{7s}}$), 2.45 (1H, m, $\mathbf{H_{4s}}$), 2.36 (1H, ddd, $^2J_{4a\text{-}4s}$= 19.6 Hz, $^3J$= 3.1 Hz, $^3J$= 3.1 Hz, $\mathbf{H_{4a}}$), 2.13 (1H, m, $\mathbf{H_5}$), 1.33 (3H, s, $\mathbf{H_8}$), 1.15 (1H, d, $^2J_{7a\text{-}7s}$= 8.8 Hz, $\mathbf{H_{7a}}$), 0.81 (3H, s, $\mathbf{H_9}$).

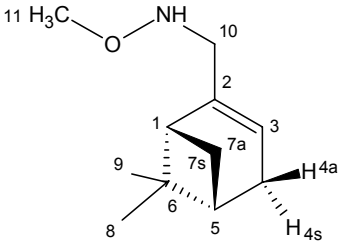
**$^{13}$C-NMR (**$CDCl_3$, 62 MHz) δ [ppm]: 150.4 ($\mathbf{C_{10}}$), 143.0 ($\mathbf{C_2}$), 137.5 (**C,** *Ph*), 131.0 ($\mathbf{C_3}$), 128.3 (4 x **C**H, *Ph*), 127.8 (**C**H, *Ph*), 76.0 ($\mathbf{C_{11}}$), 40.7 ($\mathbf{C_1}$), 40.4 ($\mathbf{C_5}$), 37.6 ($\mathbf{C_6}$), 32.3 ($\mathbf{C_7}$), 31.1 ($\mathbf{C_4}$), 26.0 ($\mathbf{C_8}$), 20.8 ($\mathbf{C_9}$).

**GC-MS**: $t_R$ (*GC-MS Pr. 2)* = 17.17 min; **(CI)** *m/z* (%): 256 $[M+H]^+$ (62), 240 $[M–CH_3]^{+\cdot}$ (8), 148 $[M–OCH_2Ph]^{+\cdot}$ (55), 107 $[OCH_2Ph]^+$ (30); **(EI)** *m/z* (%) : 255 $[M]^{+\cdot}$, 164 $[M–CH_2Ph]^+$ (40), 91 $[C_7H_7]^+$ (100), 77 $[C_6H_5]^+$ (12), 65 (14), 51 (10), 41 (12), 39 (10), 27 (8).

| | | | |
|---|---|---|---|
| **Elemental analysis (%):** | Calcd: C 79.96 | H 8.29 | N 5.49 |
| | Found: C 79.88 | H 8.39 | N 5.47 |

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-methyl hydroxylamine **147**

50 mL of a solution of HCl in absolute methanol (~5 M) were added dropwise, under stirring at room temperature, to a solution of 5 g *O*-methyl-(1*R*,5*R*)-(-)-myrtenal oxime **145** (27.93 mmol, 1 eq.) in 100 mL absolute methanol. Stirring was continued for 5 min and then 5.26 g (83.79 mmol, 3 eq.) $NaBH_3CN$ were added in 5 portions during 2 h. After stirring overnight at room temperature, a solution of 6M KOH was added until pH 9 was reached and the methanol was evaporated *in vacuo*. The reaction mixture was diluted with 50 mL water and extracted with diethyl ether (4 x 75 mL). The organic phases were combined, washed with 100 mL brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The resulting light-yellow oil was purified by flash chromatography on neutral alumina (AcOEt:PE = 1:40) and Kugelrohr distillation (65-70°C, 0.4-0.8 Torr), to afford 3.53 g (19.47 mmol, 70%) **147** as colorless oil.




| | |
|---|---|
| **Molecular formula:** | $C_{11}H_{19}NO$ [181.27] |
| **Yield:** | 70% (3.53 g, colorless oil) |
| **TLC:** | $R_f$ = 0.65 [neutral alumina, AcOEt:PE = 1:40] |
| **Boiling point:** | 65-70°C (0.4–0.8 Torr) |
| **Optical rotation:** | $[\alpha]_D^{23}$ = -19.2 (c = 1.0 in $CHCl_3$) |

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3249 (NH), 3032 (=C-H), 2989 (CH), 2930 (CH), 2829 ($CH_2$), 1655 (C=C), 1467 ($CH_2$), 1364 ($CH_3$), 1131, 1020, 908, 877, 842.

**$^1$H-NMR** ($CDCl_3$, 200 MHz) δ [ppm]: 5.43 (1H, m, $\mathbf{H_3}$), 5.27 (1H, br., N**H**), 3.45 (1H, ddd, $^2J_{10b\text{-}10a}$= 13.2 Hz, *J*= 3.1 Hz, *J*= 3.1 Hz, $\mathbf{H_{10a}}$), 3.34 (1H, ddd, $^2J_{10b\text{-}10a}$= 13.2 Hz, *J*= 3.1 Hz, *J*= 3.1 Hz, $\mathbf{H_{10b}}$), 2.38 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.4 Hz, $^3J$= 5.65 Hz, $^3J$= 5.65 Hz, $\mathbf{H_{7s}}$), 2.05-2.28 (4H, m, $\mathbf{H_4}$, $\mathbf{H_1}$, $\mathbf{H_5}$), 1.27 (3H, s, $\mathbf{H_8}$), 1.16 (1H, d, $^2J_{7s\text{-}7a}$= 8.4 Hz, $\mathbf{H_{7a}}$), 0.82 (3H, s, $\mathbf{H_9}$).

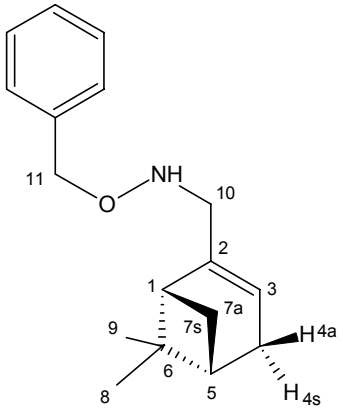
**$^{13}$C-NMR** ($CDCl_3$, 50 MHz) δ [ppm]: 144.7 ($\mathbf{C_2}$), 120.7 ($\mathbf{C_3}$), 61.9 ($\mathbf{C_{11}}$), 57.4 ($\mathbf{C_{10}}$), 44.8 ($\mathbf{C_5}$), 41.1 ($\mathbf{C_1}$), 38.4 ($\mathbf{C_6}$), 32.0 ($\mathbf{C_4}$), 31.7 ($\mathbf{C_7}$), 26.6 ($\mathbf{C_8}$), 21.4 ($\mathbf{C_9}$).

**GC-MS**: $t_R$ (*GC-MS Pr. 1*) = 6.33 min; **(EI)** *m*/*z* (%): 181 $[M]^{+\cdot}$ (5), 166 $[M–CH_3]^+$ (5), 150 $[M–OCH_3]^+$ (7), 134 $[C_{10}H_{14}]^+$ (20), 119 $[C_9H_{11}]^+$ (43), 106 $[C_8H_{10}]^+$ (56), 93 (41), 91 $[C_7H_7]^+$ (100), 79 (62), 77 $[C_6H_5]^+$ (42), 60 $[CH_3ON(H)=CH_2]^+$ (65), 53 (24), 41 (51), 39 (38), 28 (30).

| | | | |
|---|---|---|---|
| **Elemental analysis (%):** | Calcd: C 72.88 | H 10.56 | N 7.73 |
| | Found: C 72.68 | H 10.51 | N 7.69 |

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-benzyl hydroxylamine **148**

50 mL of a solution of HCl in absolute methanol (~5 M) was added dropwise, under stirring at room temperature, to a solution of 5.07 g *O*-benzyl-(1*R*,5*R*)-(-)-myrtenal oxime **146** (19.89 mmol, 1 eq.) in 150 mL absolute methanol. The stirring was continued for 5 min. and then 3.75 g (59.67 mmol, 3 eq.) $NaBH_3CN$ were added in 5 portions during 3 h. After stirring overnight at room temperature, a solution of 6M KOH was added until pH 9 was reached and methanol was evaporated *in vacuo*. The reaction mixture was diluted with 50 mL water and extracted diethyl ether (5 x 25 mL). The organic phases were combined, washed with 150 mL brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The resulting light–yellow oil was purified by vacuum distillation (104°C, 0.017 mbar), to afford 4.35 g (16.90 mmol, 85 %) **148** as colorless oil.




| | |
|---|---|
| **Molecular formula:** | $C_{17}H_{23}NO$ [257.37] |
| **Yield:** | 85% (4.35 g, colorless oil) |
| **TLC:** | $R_f$ = 0.13 [AcOEt:PE = 1:12] |
| **Boiling point:** | 104°C (0.017 mbar) |
| **Optical rotation:** | $[\alpha]_D^{23}$ = -27.0 (c = 0.6 in $CHCl_3$) |

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3263 (NH), 3029 (=C-H), 2985 (CH), 2913 (CH), 1654 (C=C), 1496 (C=C aromatic), 1454 ($CH_2$), 1365 ($CH_3$), 1205, 1081, 1051, 1002, 794, 744, 698.

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 7.27-7.37 (5H, m, Ph), 5.46 (1H, m, $\mathbf{H_3}$), 4.71 (2H, s, $\mathbf{H_{11}}$), 3.49 (1H, dd, $^2J_{10b\text{-}10a}$= 13.2 Hz, *J*= 1.3 Hz, $\mathbf{H_{10a}}$), 3.47 (1H, ddd, $^2J_{10a\text{-}10b}$= 13.2 Hz, *J*= 3.1 Hz, *J*= 1.3 Hz, $\mathbf{H_{10b}}$), 2.40 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J$= 5.6 Hz, $^3J$= 5.6 Hz, $\mathbf{H_{7s}}$), 2.30 (1H, br. d, $^2J_{4a\text{-}4s}$= 17.6 Hz, $\mathbf{H_{4s}}$), 2.21 (1H, br. d, $^2J_{4a\text{-}4s}$= 17.6 Hz, $\mathbf{H_{4a}}$), 2.18 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$= 1.3 Hz, $\mathbf{H_1}$), 2.09 (1H, m, $\mathbf{H_5}$), 1.28 (3H, s, $\mathbf{H_8}$), 1.18 (1H, d, $^2J_{7s\text{-}7a}$ = 8.8 Hz, $\mathbf{H_{7a}}$), 0.83 (3H, s, $\mathbf{H_9}$).

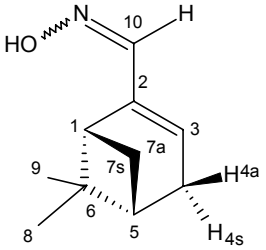
**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 144.1 (**C,** *Ph*), 137.8 ($\mathbf{C_2}$), 128.4 (2 x **CH**, *Ph*), 128.3 (2 x **CH**, *Ph*), 127.7 (**CH**, *Ph*), 120.4 ($\mathbf{C_3}$), 75.9 ($\mathbf{C_{11}}$), 57.2 ($\mathbf{C_{10}}$), 44.3 ($\mathbf{C_1}$), 40.7 ($\mathbf{C_5}$), 38.0 ($\mathbf{C_6}$), 31.6 ($\mathbf{C_4}$), 31.3 ($\mathbf{C_7}$), 26.2 ($\mathbf{C_8}$), 21.1 ($\mathbf{C_9}$).

**GC-MS**: $t_R$ (*GC-MS Pr. 3*) = 20.41 min; **(CI)** *m/z* (%): 258 $[M+H]^+$ (63), 150 $[M–OCH_2Ph]^{+\cdot}$ (98), 135 $[M\text{-}HNOCH_2Ph]^{+\cdot}$ (20), 123 $[PhCH_2ONH_2]^{+\cdot}$ (5), 107 $[PhCH_2O]^{+\cdot}$ (100); **(EI)** *m/z* (%): 257 $[M]^{+\cdot}$ (2), 149 $[M–HOCH_2Ph]^{+\cdot}$ (10), 134 $[C_{10}H_{14}]^+$ (22), 106 $[PhCH=O]^+$ (80), 91 $[C_7H_7]^+$ (100), 79 $[C_6H_7]^+$ (78), 77 $[C_6H_5]^+$ (82), 67 $[C_5H_7]^+$ (18), 51 (30), 41 (19), 39 (18), 30 (28), 27 (11).

| **Elemental analysis (%):** | Calcd: C 79.33 | H 9.01 | N 5.44 |
|---|---|---|---|
| | Found: C 79.38 | H 9.34 | N 5.42 |

(1*R*,5*R*)-(-)-Myrtenaloxime **149**

A solution of 4.52 g hydroxylamine hydrochloride (65.40 mmol, 1.2 eq.) and 6.23 g sodium acetate (75.90 mmol, 1.4 eq.) in 250 mL methanol was stirred for 10 min at room temperature. (1*R*,5*R*)-(-)-Myrtenal **142** (8.14 g, 54.20 mmol, 1 eq.) was added and the mixture was refluxed for 4 h. After completion (TLC on silica gel, AcOEt:PE = 1:4), the reaction mixture was poured into 200 mL of ice water, the white precipitate was filtered off, washed with cold water and dried *in vacuo*. 8.3 g (50.2 mmol, 93 %) analytically pure (GC) **149** resulted as white powder.




| | |
|---|---|
| **Molecular formula:** | $C_{10}H_{15}NO$ [165.23] |
| **Yield:** | 93% (8.3 g, white powder) |
| **TLC:** | $R_f$ = 0.41 [AcOEt:PE = 2:8] |
| **Melting point**: | 64-66 °C |
| **Optical rotation:** | $[\alpha]_D^{23}$ = -24.7 (c = 1.0 in MeOH) |
| **GC** (*GC Pr. 2*): | $t_R$ = 11.19 min |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3253 (OH), 3052 (=C-H), 2981 ($CH_3$), 2919 ($CH_3$), 2879 ($CH_2$), 2825 (CH), 1619 (conj. C=N), 1463 ($CH_2$), 1425 (CH), 1365 ($CMe_2$), 1315 (OH), 1290 (N-O), 989 (C=C), 956, 889, 802, 717, 653.

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 8.08 (1H, O**H**, br), 7.73 (1H, s, $\mathbf{H_{10}}$), 5.92 (1H, m, $\mathbf{H_3}$), 2.73 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$= 1.3 Hz, $\mathbf{H_1}$), 2.45 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J_{7s\text{-}1}$= 5.6 Hz, $^3J$= 5.6 Hz, $\mathbf{H_{7s}}$), 2.42 (1H, m, $\mathbf{H_{4s}}$), 2.38 (1H, ddd, $^2J_{4a\text{-}4s}$= 19.5 Hz, $^3J$= 3.1 Hz, $^3J$= 3.1 Hz, $\mathbf{H_{4a}}$), 2.15 (1H, m, $\mathbf{H_5}$), 1.32 (3H, s, $\mathbf{H_8}$), 1.16 (1H, d, $^2J_{7a\text{-}7s}$= 8.8 Hz, $\mathbf{H_{7a}}$), 0.81 (3H, s, $\mathbf{H_9}$).

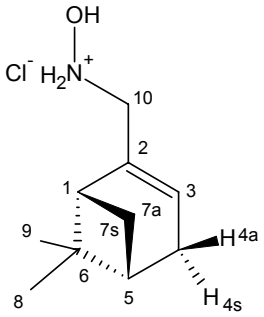
**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 151.3 ($\mathbf{C_{10}}$), 142.5 ($\mathbf{C_2}$), 132.1 ($\mathbf{C_3}$), 40.5 ($\mathbf{C_1}$), 40.5 ($\mathbf{C_5}$), 37.7 ($\mathbf{C_6}$), 32.3 ($\mathbf{C_7}$), 31.1 ($\mathbf{C_4}$), 25.9 ($\mathbf{C_8}$), 20.8 ($\mathbf{C_9}$).

**MS (EI)** *m/z* (%): 165 $[M]^{+\cdot}$ (38), 150 $[M–CH_3]^+$ (20), 148 $[M–OH]^{+\cdot}$ (62), 146 $[C_{10}H_{12}N]^{+\cdot}$, 133 $[C_9H_{11}N]^{+\cdot}$ (25), 132 $[C_9H_{10}N]^{+\cdot}$ (30), 131 $[C_9H_9N]^{+\cdot}$ (12), 122 $[C_9H_{14}]^{+\cdot}$ (100), 121 $[C_9H_{13}]^+$ (37), 106 [m/z *132* – C≡N]$^{+\cdot}$ (36), 105 $[C_8H_9]^+$ (39), 104 $[C_8H_8]^{+\cdot}$ (32), 91 $[C_7H_7]^+$ (43), 77 $[C_6H_5]^+$ (66), 67 (20), 65 (22), 55 (19), 53 (26), 51 (24), 43 $[C_3H_7]^+$ (26), 41 $[C_3H_5]^+$ (55), 39 (52).

| **Elemental analysis (%):** | Calcd: C 72.69 | H 9.15 | N 8.48 |
|---|---|---|---|
| | Found: C 72.37 | H 9.26 | N 8.40 |

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-hydroxylamine hydrochloride **150**

A solution of HCl in absolute methanol (~5M) was added dropwise to maintain a pH of 2-3 to a solution of 1.7 g (1*R*,5*R*)-(-)-myrtenaloxime **149** (10.3 mmol, 1 eq.) and 1.94 g $NaBH_3CN$ (30.9 mmol, 3 eq.) in 50 mL absolute methanol. After stirring at room temperature for 4 h, a solution of KOH 6 M was added until pH 9 was reached and methanol was evaporated *in vacuo*. The reaction mixture was diluted with 50 mL water and extracted five times with 25 mL diethyl ether. The combined organic phases were extracted with a solution of 1M HCl, the volume of the aqueous phase was reduced *in vacuo* and lyophilized to afford 1.95 g (9.6 mmol, 93 %) **150** as white crystals.




| **Molecular formula:** | $C_{10}H_{18}ClNO$ [203.71] |
|---|---|
| **Yield:** | 93% (1.95 g, white crystals) |
| **Melting point**: | 98-100°C |
| **Optical rotation:** | $[\alpha]_D^{24}$ = -28.45 (c = 1.0 in $H_2O$) |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3442 (OH br), 3060 (NH valence br), 2915 (CH), 2829 (CH), 2713 (CH), 1652 (C=C), 1573 (NH deformation), 1446 ($CH_2$), 1429 (N-O), 1224 (C-N), 1016 (C-C stretching), 971, 802, 794, 671.

**$^1$H-NMR** (DMSO-$D_6$, 250 MHz) δ [ppm]: 11.49 (2H, br., $NH_2^+$), 6.11 (1H, m, $\mathbf{H_3}$), 3.63 (2H, s, $\mathbf{H_{10}}$), 2.51 (1H, m, $\mathbf{H_1}$), 2.13-2.44 (3H, m, $\mathbf{H_{7s}}$, $\mathbf{H_4}$), 2.05 (1H, $\mathbf{H_5}$), 1.26 (3H, s, $\mathbf{H_8}$), 1.12 (1H, d, $^2J_{7s\text{-}7a}$ = - 8.54 Hz, $\mathbf{H_{7a}}$), 0.81 (3H, s, $\mathbf{H_9}$).

**$^{13}$C-NMR** (DMSO-$D_6$, 62 MHz) δ [ppm]: 137.4 ($\mathbf{C_2}$), 126.2 ($\mathbf{C_3}$), 54.7 ($\mathbf{C_{10}}$), 43.7 ($\mathbf{C_5}$), 39.5 ($\mathbf{C_1}$), 37.5 ($\mathbf{C_6}$, $\mathbf{C_4}$), 31.0 ($\mathbf{C_7}$), 25.7 ($\mathbf{C_8}$), 20.7 ($\mathbf{C_9}$).

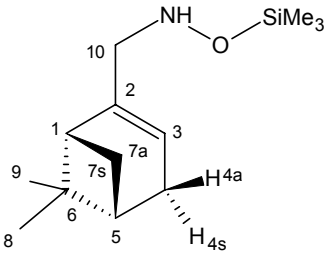
**$^{13}$C-NMR** ($D_2O$, 62 MHz) δ [ppm]: 139.3 (**$C_2$**), 132.1 (**$C_3$**), 59.0 (**$C_{10}$**), 47.3 (**$C_5$**), 42.9 (**$C_1$**), 40.5 (**$C_6$**), 34.3 (**$C_4$**), 34.2 (**$C_7$**), 28.4 (**$C_8$**), 23.5 (**$C_9$**).

**MS (ESI)** *m/z* (%): 190 $[M\text{-}HCl+Na]^+$, 168 $[M\text{-}Cl]^+$, 135 $[C_{10}H_{15}(10\text{-pinenyl})]^+$.

| **Elemental analysis (%):** | Calcd: C 58.96 | H 8.91 | N 6.88 |
|---|---|---|---|
| | Found: C 58.74 | H 8.86 | N 6.73 |

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-trimethylsilyl hydroxylamine **151**

A slurry of 1 g (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-hydroxylamine hydrochloride **150** (4.91 mmol, 1 eq.) and 1.49 g $Et_3N$ (14.73 mmol, 3 eq.) in 20 mL *n*-hexane (distilled over Na) was stirred at room temperature for 3 h, under $N_2$. Trimethylsilyl chloride (0.54 g, 4.91 mmol, 1 eq.) (distilled over $CaH_2$) was added via syringe and the stirring was continued overnight. Conversion of the hydroxylamine hydrochloride **150** was monitored by TLC (silica gel, AcOEt:PE = 2:1), with the free base of **150** as reference. Filtration and evaporation of solvent *in vacuo* afforded a light yellow oil which was distilled *in vacuo* (75°C, 0.038 mbar) to give 0.91 g (3.78 mmol, 77%) **151** as colorless oil.




| | |
|---|---|
| **Molecular formula:** | $C_{13}H_{25}NOSi$ [239.43] |
| **Yield:** | 77% (0.91 g, colorless oil) |
| **TLC:** | $R_f$ = 0.32 [AcOEt:PE = 2:1] |
| **Boiling point:** | 75°C (0.038 mbar) |
| **Optical rotation:** | $[\alpha]_D^{22}$ = -31.8 (c = 1.1 in $CH_2Cl_2$) |

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3259 (NH), 3027 (=C-H), 2987 (CH), 2915 (CH), 2832 ($CH_2$), 1654 (C=C), 1465 ($CH_2$), 1365 ($CH_3$), 1248 (Si-$CH_3$), 908, 877, 842

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 5.43 (1H, m, **$H_3$**), 5.15 (1H, br, N**H**), 3.38 (2H, br. s, **$H_{10}$**), 2.37 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J_{7s\text{-}1}$= 5.6 Hz, $^3J$= 5.6 Hz, **$H_{7s}$**), 2.28 (1H, br. d, $^2J_{4a\text{-}4s}$= 17.6 Hz, **$H_{4s}$**), 2.19 (1H, br. d, $^2J_{4a\text{-}4s}$= 17.6 Hz, **$H_{4a}$**), 2.14 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$=1.9 Hz, **$H_1$**), 2.08 (1H, m, **$H_5$**), 1.28 (3H, s, **$H_8$**), 1.16 (1H, d, $^2J_{7s\text{-}7a}$ = 8.8 Hz, **$H_{7a}$**), 0.81 (3H, s, **$H_9$**), 0.13 (9H, s, Si(C**H**$_3$)$_3$)

**$^1$H-NMR** ($C_6D_6$, 500 MHz) δ [ppm]: 5.27 (1H, m, **$H_3$**), 4.78 (1H, t, $^3J_{NH\text{-}10}$= 8 Hz, N**H**), 3.42 (1H, br. s, **$H_{10}$**), 2.29 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J$= 5.6 Hz, $^3J$= 5.6 Hz, **$H_{7s}$**), 2.15 (1H, br. d, $^2J_{4a\text{-}4s}$= 17.6

Hz, $\mathbf{H_{4s}}$), 2.03-2.10 (2H, m, $\mathbf{H_1}$, $\mathbf{H_{4a}}$), 1.95 (1H, m, $\mathbf{H_5}$), 1.20 (3H, s, $\mathbf{H_8}$), 1.18 (1H, d, $^2J_{7s\text{-}7a}$= 8.8 Hz, $\mathbf{H_{7a}}$), 0.82 (3H, s, $\mathbf{H_9}$), 0.21 (9H, s, Si(C$\mathbf{H}_3$)$_3$)

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 143.8 ($\mathbf{C_2}$), 120.7 ($\mathbf{C_3}$), 59.8 ($\mathbf{C_{10}}$), 44.9 ($\mathbf{C_5}$), 40.6 ($\mathbf{C_1}$), 38.0 ($\mathbf{C_6}$), 31.6 ($\mathbf{C_4}$), 31.3 ($\mathbf{C_7}$), 26.2 ($\mathbf{C_8}$), 21.1 ($\mathbf{C_9}$), - 0.9 [Si($\mathbf{C}$H$_3$)$_3$].

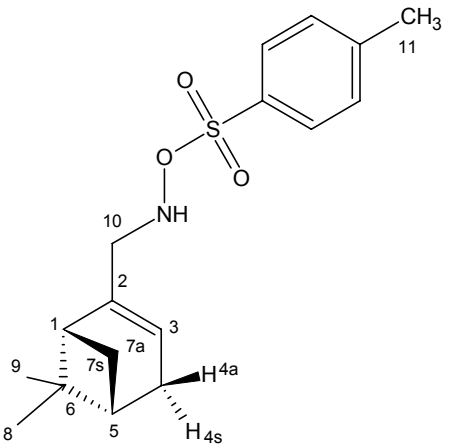
**$^{13}$C-NMR** ($C_6D_6$, 125 MHz) δ [ppm]: 144.5 ($\mathbf{C_2}$), 120.6 ($\mathbf{C_3}$), 60.1 ($\mathbf{C_{10}}$), 45.1 ($\mathbf{C_5}$), 41.0 ($\mathbf{C_1}$), 38.1 ($\mathbf{C_6}$), 32.0 ($\mathbf{C_4}$), 31.6 ($\mathbf{C_7}$), 26.3 ($\mathbf{C_8}$), 21.2 ($\mathbf{C_9}$), - 0.7 [Si($\mathbf{C}$H$_3$)$_3$].

**GC-MS**: $t_R$ (*GC-MS Pr. 3*) = 11.68 min; **(EI)** *m/z* (%): 240 $[M+H]^+$ (28), 239 $[M]^{+\cdot}$ (32), 224 $[M–CH_3]^+$ (12), 168 $[M+H–SiMe_3]^{+\cdot}$ (18), 150 $[M–OSiMe_3]^+$ (25), 134 $[C_{10}H_{14}]^+$ (98), 118 $[CH_2NHOSiMe_3]^{+\cdot}$ (100), 107 $[C_6H_5NH_2]^{+\cdot}$ (40), 105 $[Me_3SiONH_2]^{+\cdot}$ (95), 104 $[Me_3SiONH]^+$ (38), 101 (80), 91 $[C_7H_7]^+$ (20), 90 $[Me_3SiOH]^{+\cdot}$ (80), 79 $[C_6H_7]^+$ (20), 74 $[Me_3SiH]^{+\cdot}$ (82), 72 $[C_3H_8Si]^{+\cdot}$ (63), 69 (12), 64 (12), 59 (16), 53 (20), 45 (20), 43 (25), 41 (42), 39 (10), 30 (10); **(CI)** *m/z* (%): 240 $[M+H]^+$, 150 $[M–OSiMe_3]^{+\cdot}$ (100).

| **Elemental analysis (%):** | Calcd: C 65.21 | H 10.52 | N 5.85 |
|---|---|---|---|
| | Found: C 65.32 | H 10.41 | N 6.10 |

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-*O*-tosyl hydroxylamine **152**

A slurry of 0.5 g (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-hydroxylamine hydrochloride **150** (2.45 mmol, 1 eq.) and 0.74 g $Et_3N$ (7.35 mmol, 3 eq.) in 20 mL *n*-hexane (distilled over Na) was stirred at room temperature for 1 h under $N_2$. Tosyl chloride (0.47 g, 2.45 mmol, 1 eq.) (recrystallized from PE) was added in portions and stirring was continued overnight. Conversion of the hydroxylamine hydrochloride **150** was monitored by TLC (silica gel, AcOEt:PE = 2:1), with the free base of **150** as reference. Filtration and evaporation of the solvent *in vacuo* afforded a light yellow oil which was dissolved in diethyl ether and washed sequentially with 45 mL 0.1 M HCl, 15 mL satd. $NaHCO_3$ sol. and 30 mL brine. Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded a light yellow solid. Flash chromatography (silica gel, $^t$BuOMe:MeOH = 10:1) and crystallization from $Et_2O$/*n*-hexane (1:1) afforded 0.68 g (2.1 mmol, 85 %) **152** as colorless crystals.




**Molecular formula:** $C_{17}H_{23}NO_3S$ [321.435]

**Yield:** 85% (0.68 g, colorless crystals)

**TLC:** $R_f$ = 0.66 [$^t$BuOMe:MeOH = 10:1]

**Melting point:** 131-133°C

**Optical rotation:** $[\alpha]_D^{23}$ = -22.1 (c = 1.1 in $CHCl_3$)

**GC** (*GC Pr. 2*): $t_R$ = 15.41 min

**IR (KBr)**, $\tilde{\nu}$ [$cm^{-1}$]: 3394 (NH), 2913 (CH), 1658 (C=C), 1598 (Ph), 1334 ($SO_2O$), 1164 ($SO_2O$), 1093, 811, 748, 661.

**$^1$H-NMR** ($CDCl_3$, 500 MHz) **δ [ppm]:** 7.78 (2H, d, $^3J_{ortho}$= 6.3 Hz, $^3J_{meta}$= 1.8 Hz, Ph-*ortho*), 7.36 (2H, d, $^3J_{ortho}$= 6.3 Hz, $^3J_{meta}$= 2.5 Hz Ph-*meta*), 6.29 (1H, br, N**H**), 5.41 (1H, m, **H$_3$**), 3.41 (2H, br. s, **H$_{10}$**), 2.46 (3H, s, Ph-C**H$_3$**), 2.40 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.8 Hz, $^3J_{7s\text{-}1}$= 5.6 Hz, $^3J$= 5.6 Hz, **H$_{7s}$**), 2.33 (1H, ddd, $^3J_{1\text{-}7s}$= 5.6 Hz, $^4J$= 5.6 Hz, $^4J$= 1.9 Hz, **H$_1$**), 2.26 (1H, br. d, $^2J_{4a\text{-}4s}$= 19.5 Hz, **H$_{4s}$**), 2.18 (1H, br. d, $^2J_{4a\text{-}4s}$= 19.5 Hz, **H$_{4a}$**), 2.08 (1H, m, **H$_5$**), 1.29 (3H, s, **H$_8$**), 1.14 (1H, d, $^2J_{7s\text{-}7a}$= 8.8 Hz, **H$_{7a}$**), 0.82 (3H, s, **H$_9$**).

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 144.8 (**C$_{para}$**), 141.6 (**C$_2$**), 129.8 (**C**-S), 129.6 (2 x **C$_{ortho}$**), 129.5 (2 x **C$_{meta}$**), 122.9 (**C$_3$**), 57.9 (**C$_{10}$**), 43.8 (**C$_5$**), 40.7 (**C$_1$**), 38.0 (**C$_6$**), 31.6 (**C$_4$**), 31.4 (**C$_7$**), 26.1 (**C$_8$**), 21.6 (**C**-Ph), 21.1 (**C$_9$**).

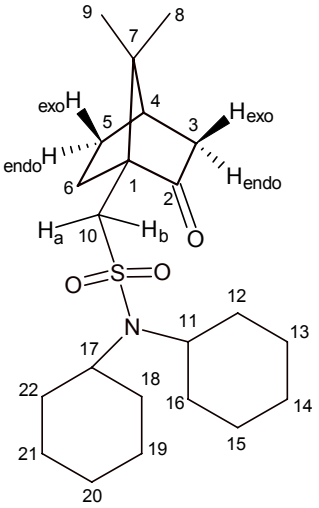
**MS (ESI)** *m/z:* 344.0 $[M + Na]^+$, 664.7 $[2M + Na]^+$.

| **Elemental analysis (%):** | Calcd: C 63.52 | H 7.21 | N 4.36 |
|---|---|---|---|
| | Found: C 63.50 | H 7.04 | N 4.23 |

### 5.2.4 Synthesis of (+)-*N,N*-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide

(+)-*N,N*-Dicyclohexyl-camphor-10-sulfonamide **154**

A solution of 10.26 g isoquinoline (81.35 mmol, 2.04 eq.), 14.46 g dicyclohexylamine (79.76 mmol, 2 eq.) and 0.98 g DMAP (7.98 mmol, 0.2 eq.) in 50 mL DMF was cooled to 0°C and 10 g (+)-camphor-10-sulfonylchloride **153** (39.88 mmol, 1 eq.) in 50 mL DMF was added dropwise during 2 h. Stirring was continued for 2 h at 0°C and after completion of the reaction, 150 mL dichloromethane were added and the reaction mixture was washed four times with 100 mL 10% citric acid. Evaporation of solvent *in vacuo* and two consecutive crystallizations from EtOH/$H_2O$ (2:1) afforded 12.93 g (32.70 mmol, 82%) **154** as white solid.




| | | |
|---|---|---|
| **Molecular formula:** | $C_{22}H_{37}NO_3S$ [395.60] | |
| **Yield:** | 82% (12.93 g, white solid) | [lit.[182] 60%] |
| **TLC:** | $R_f$ = 0.45 [AcOEt:PE = 4:10] | |
| **Melting point**: | 134-135 °C | [lit.[182] 134-135°C] |
| **Optical rotation:** | $[\alpha]_D^{26}$ = +26 (c = 1.1 in $CHCl_3$) | |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2935 (CH), 2852 (CH), 1747 (C=O), 1322 ($SO_2N$), 1225 (C-N), 1164 ($SO_2N$), 1145, 1110, 1049, 979.

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 3.32 (1H, d, $^2J_{10a\text{-}10b}$= 14.4 Hz, $\mathbf{H_{10a}}$), 3.31 (2H, m, $\mathbf{H_{11}}$, $\mathbf{H_{17}}$), 2.79 (1H, d, $^2J_{10a\text{-}10b}$= 14.4 Hz, $\mathbf{H_{10b}}$), 2.60 (1H, ddd, $^2J_{5exo\text{-}5endo}$= 11.9 Hz, $^3J_{5exo\text{-}6}$= 8.8 Hz, $^3J_{5exo\text{-}4}$= 4.4 Hz, $\mathbf{H_{5exo}}$), 2.37 (1H, dd, $^2J_{3exo\text{-}3endo}$= 18.2 Hz, $^3J_{3exo\text{-}4}$= 4.4 Hz, $\mathbf{H_{3exo}}$), 2.07 (1H, dd, $^3J_{4\text{-}5exo}$= 4.4 Hz, $^3J_{4\text{-}3exo}$= 4.4 Hz, $\mathbf{H_4}$), 2.02 (1H, dd, $^2J_{5endo\text{-}5exo}$= 11.9 Hz, $^3J_{5endo\text{-}6}$= 8.8 Hz, $\mathbf{H_{5endo}}$), 1.92 (1H, d, $^2J_{3endo\text{-}3exo}$= 18.2 Hz, $\mathbf{H_{3endo}}$), 1.74-1.81 (12H, m, $\mathbf{H_{Cy}}$), 1.58-1.64 (3H, m, $\mathbf{H_{Cy}}$, $\mathbf{H_6}$),

1.39 (1H, m, $\mathbf{H_6}$), 1.26-1.34 (4H, m, $\mathbf{H_{Cy}}$), 1.19 (3H, s, $\mathbf{H_9}$), 1.10-1.14 (2H, m, $\mathbf{H_{Cy}}$), 0.89 (3H, s, $\mathbf{H_8}$).

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 215.8 ($\mathbf{C_2}$), 59.0 ($\mathbf{C_1}$), 57.6 ($\mathbf{C_{11}}$, $\mathbf{C_{17}}$), 52.2 ($\mathbf{C_{10}}$), 47.5 ($\mathbf{C_7}$), 43.0 ($\mathbf{C_4}$), 42.6 ($\mathbf{C_3}$), 32.9 ($\mathbf{C_{Cy}}$), 32.5 ($\mathbf{C_{Cy}}$), 26.8 ($\mathbf{C_5}$), 26.4 ($\mathbf{C_{Cy}}$), 25.3 ($\mathbf{C_6}$), 25.2 ($\mathbf{C_{Cy}}$), 20.3 ($\mathbf{C_9}$), 19.9 ($\mathbf{C_8}$).

**MS (ESI)** *m/z:* 418.2 $[M + Na]^+$, 434.1 $[M + K]^+$.

| **Elemental analysis (%):** | Calcd: C 66.79 | H 9.43 | N 3.54 |
|---|---|---|---|
| | Found: C 66.81 | H 9.45 | N 3.50 |

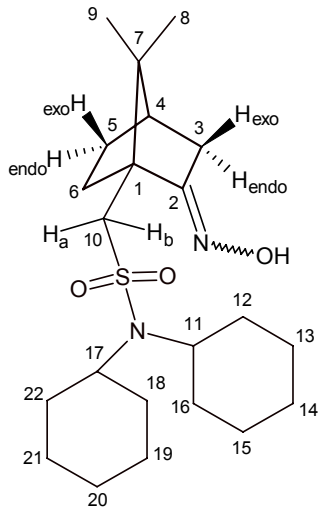
(+)-*N,N*-Dicyclohexyl-camphor-10-sulfonamide oxime **155**

**Method A**

A solution of 4.5 g KOH (80.20 mmol, 6.35 eq.) in 40 mL ethanol was added to a suspension of 2.63 g hydroxylamine hydrochloride (37.89 mmol, 3 eq.) and 5.0 g (+)-*N,N*-dicyclohexyl-(camphor-10-sulfonamide) **154** (12.63 mmol, 1 eq.) in 60 mL ethanol. The reaction mixture was refluxed for 6 h, neutralised with 1M HCl and 200 mL water were added. The white precipitate was filtered off and washed with water. Recrystallization from *n*-heptane/toluene (5:2) afforded 3.22 g (7.8 mmol, 61%) oxime **155** as white crystals.

**Method B**

A solution of 2.36 g hydroxylamine hydrochloride (34.01 mmol, 3 eq.) and 2.98 g sodium acetate (36.27 mmol, 3.2 eq.) in 120 mL methanol was stirred for 10 min at room temperature. (+)-*N,N*-Dicyclohexyl-(camphor-10-sulfonamide) **154** (4.49 g, 11.34 mmol, 1 eq.) was added and the mixture was refluxed for 24 h. After completion (TLC on silica gel, AcOEt:PE = 4:10), the reaction mixture was poured into 200 mL of ice water, the white precipitate was filtered off, washed with cold water and dried *in vacuo* to afford 4.46 g (10.86 mmol, 96%) **155** as white powder.




**Molecular formula:** $C_{22}H_{38}N_2O_3S$ [410.61]

**Yield:** 96% (4.46 g, white crystals) [lit.[13] 96%]

**TLC:** $R_f$ = 0.66 [$^t$BuOMe:MeOH = 10:1]

**Melting point:** 169-170 °C

**Optical rotation:** $[\alpha]_D^{24}$ = +0.8 (c = 1.5 in $CHCl_3$)

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3367 (OH), 2937 (CH), 2856 (CH), 1687 (C=N), 1454 ($CH_2$), 1396 ($CMe_2$), 1324 ($SO_2N$), 1164, 1145, 1108, 1049, 981.

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 3.35 (1H, d, $^2J_{10a\text{-}10b}$= 14.4 Hz, $\mathbf{H_{10a}}$), 3.33 (2H, m, $\mathbf{H_{11}}$, $\mathbf{H_{17}}$), 2.89 (1H, d, $^2J_{10a\text{-}10b}$= 14.4 Hz, $\mathbf{H_{10b}}$), 2.62 (1H, dd, $^2J_{3exo\text{-}3endo}$= 18.2 Hz, $^3J_{3exo\text{-}4}$= 4.1 Hz, $\mathbf{H_{3exo}}$), 2.56 (1H, m, $\mathbf{H_{5exo}}$), 2.13 (1H, d, $^2J_{3endo\text{-}3exo}$= 18.2 Hz, $\mathbf{H_{3endo}}$), 1.93 (1H, m, $\mathbf{H_4}$), 1.72-1.85 (13H, m, $\mathbf{H_{Cy}}$, $\mathbf{H_{5endo}}$), 1.58-1.65 (2H, m, $\mathbf{H_{Cy}}$), 1.28-1.35 (6H, m, $\mathbf{H_{Cy}}$, $\mathbf{H_6}$), 1.10-1.17 (2H, m, $\mathbf{H_{Cy}}$), 1.09 (3H, s, $\mathbf{H_9}$), 0.86 (3H, s, $\mathbf{H_8}$).

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 169.4 ($\mathbf{C_2}$), 57.5 ($\mathbf{C_{11}}$, $\mathbf{C_{17}}$), 53.9 ($\mathbf{C_{10}}$), 53.1 ($\mathbf{C_1}$), 49.9 ($\mathbf{C_7}$), 43.4 ($\mathbf{C_4}$), 33.3 ($\mathbf{C_3}$), 33.1 ($\mathbf{C_{Cy}}$), 32.3 ($\mathbf{C_{Cy}}$), 28.2 ($\mathbf{C_5}$), 27.0 ($\mathbf{C_6}$), 26.4 ($\mathbf{C_{Cy}}$), 25.1 ($\mathbf{C_{Cy}}$), 19.4 ($\mathbf{C_9}$), 19.3 ($\mathbf{C_8}$).

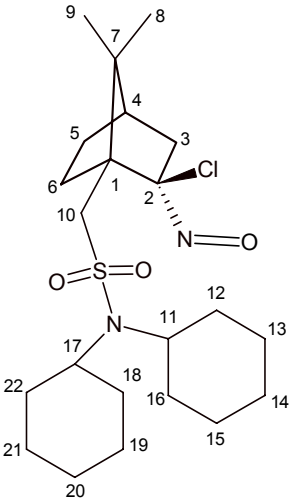
**MS (ESI)** *m/z*: 411.1 $[M + H]^+$, 433.2 $[M + Na]^+$.

| **Elemental analysis (%):** | | | |
|---|---|---|---|
| Calcd: | C 64.35 | H 9.33 | N 6.82 |
| Found: | C 64.37 | H 9.06 | N 6.61 |

(+)-*N,N*-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**

A solution of 3 g (+)-*N,N*-dicyclohexyl-camphor-10-sulfonamide oxime **155** (7.31 mmol, 1 eq.) in 60 mL water free dichloromethane was cooled to -10°C, under $N_2$ atmosphere and protection against light. A solution of 1.48 g $^t$BuOCl (10.23 mmol, 1.4 eq., 75% w/w in $^t$BuOH) in 30 mL

water free dichloromethane was added dropwise during 2 h and the resulting blue solution was stirred for 2.5 h at -5°C. Evaporation of solvent *in vacuo* and recrystallization from AcOEt/PE (1:5) furnished 2.76 g (6.21 mmol, 85%) **74** as blue crystals.




| | | |
|---|---|---|
| **Molecular formula:** | $C_{22}H_{37}ClN_2O_3S$ [445.06] | |
| **Yield:** | 85% (2.76 g, blue crystals) | [lit.[13] 81%] |
| **TLC:** | $R_f$ = 0.38 [AcOEt:PE = 1:5] | |
| **Melting point**: | 159-160°C (decomp.) | |
| **Optical rotation:** | $[\alpha]_D^{26}$ = -90.2 (c = 0.5 in $CHCl_3$) | |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2933 ($CH_3$), 2854 ($CH_2$), 1583 (N=O), 1450 (CH), 1324 ($SO_2N$), 1166 ($SO_2N$), 1143 (C-Cl), 1108, 1051, 981, 894, 854, 775 (C-Cl).

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 3.39 (1H, d, $^2J_{10a\text{-}10b}$= 14.4 Hz, $\mathbf{H_{10a}}$), 3.27 (1H, ddd, $^2J_{5exo\text{-}5endo}$= 14.1 Hz, $^3J_{5exo\text{-}6}$= 9.1 Hz, $^3J_{5exo\text{-}4}$= 3.1 Hz, $\mathbf{H_{5exo}}$), 3.12-3.17 (2H, m, $\mathbf{H_{11}}$, $\mathbf{H_{17}}$), 2.78 (1H, d, $^2J_{10b\text{-}10a}$= 14.4 Hz, $\mathbf{H_{10b}}$), 2.52 (1H, dd, $^2J_{3exo\text{-}3endo}$= 14.1 Hz, $^3J_{3exo\text{-}4}$= 5.5 Hz, $\mathbf{H_{3exo}}$), 2.22 (1H, m, $\mathbf{H_{5endo}}$), 2.14-2.19 (2H, m, $\mathbf{H_4}$, $\mathbf{H_{6a}}$), 1.92 (1H, d, $^2J_{3endo\text{-}3exo}$= 14.4 Hz, $\mathbf{H_{3endo}}$), 1.89 (1H, m, $\mathbf{H_{6b}}$), 1.75-1.80 (6H, m, $\mathbf{H_{Cy}}$), 1.65-1.71 (8H, m, $\mathbf{H_{Cy}}$), 1.56-1.62 (2H, m, $\mathbf{H_{Cy}}$), 1.24-1.31 (4H, m, $\mathbf{H_{Cy}}$), 1.23 (1H, s, $\mathbf{H_9}$), 1.16 (3H, s, $\mathbf{H_8}$).

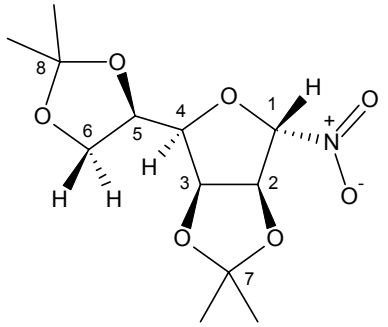
**$^{13}$C-NMR** ($CDCl_3$, 62 MHz) δ [ppm]: 123.7 ($\mathbf{C_2}$), 58.3 ($\mathbf{C_1}$), 57.4 ($\mathbf{C_{11}}$, $\mathbf{C_{17}}$), 54.3 ($\mathbf{C_7}$), 53.7 ($\mathbf{C_{10}}$), 45.9 ($\mathbf{C_4}$), 43.7 ($\mathbf{C_3}$), 33.1 ($\mathbf{C_{Cy}}$), 32.3 ($\mathbf{C_{Cy}}$), 28.4 ($\mathbf{C_5}$), 27.4 ($\mathbf{C_6}$), 26.4 ($\mathbf{C_{Cy}}$), 26.4 ($\mathbf{C_{Cy}}$), 25.2 ($\mathbf{C_{Cy}}$), 20.3 ($\mathbf{C_9}$), 20.8 ($\mathbf{C_8}$).

**MS (ESI)** *m/z*: 467.1 [M($C_{22}H_{37}{}^{35}ClN_2O_3S$) + Na]$^+$, 469.2 [M($C_{22}H_{37}{}^{37}ClN_2O_3S$) + Na]$^+$, 911.2 [2M($C_{22}H_{37}{}^{35}ClN_2O_3S$) + Na]$^+$, 913.2 [2M($C_{22}H_{37}{}^{37}ClN_2O_3S$) + Na]$^+$.

| | | | |
|---|---|---|---|
| **Elemental analysis (%):** | Calcd: C 59.37 | H 8.38 | N 6.29 |
| | Found: C 59.25 | H 8.41 | N 6.20 |

### 5.2.5 Synthesis of 1-Deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-*D*-manno-furanose

53 mg $VO(acac)_2$ (0.2 mmol, 0.04 eq.) were added to a solution of 1.38 g 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime **134** (5 mmol, 1 eq.) in 30 mL ethyl acetate. The green solution was warmed up to 60°C and 1.37 mL $^t$BuOOH (11 mmol, 2.2 eq., 80% solution in $^t$BuOO$^t$Bu) were added carefully, under nitrogen atmosphere. The resulting red-brownish solution was heated to 60°C for 45 min, 50 mL $H_2O$ were added, the organic phase was separated, washed with 20 mL brine and dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded a dark-red sirup which was purified by flash chromatography on silica gel (AcOEt:PE = 1:4), to afford 0.75 g (2.6 mmol, 52%) **156** as colorless crystals.




| | |
|---|---|
| **Molecular formula:** | $C_{12}H_{19}NO_7$ [289.28] |
| **Yield:** | 52% (0.75 g, colorless crystals) [lit.[137] 54%] |
| **Melting point**: | 111-112°C [lit.[137] 111-112°C] |
| **TLC:** | $R_f$ = 0.26 [AcOEt:PE = 1:4] |
| **Optical rotation:** | $[\alpha]_D^{26}$ = +17.9 (c = 0.9 in $CHCl_3$) |
| | [lit.[137] $[\alpha]_D$ = +18.3 (c = 0.9 in $CHCl_3$)] |
| **GC** (*GC Pr. 2*): | $t_R$ = 14.34 min |

**IR** (KBr), $\tilde{\nu}$ [cm$^{-1}$]: 3001 (C-H), 2942 ($CH_3$), 2908 ($CH_2$), 1567 ($NO_2$ asymm.), 1485 ($CH_2$), 1374 ($NO_2$ sym.), 1266, 1214 (C-O-C), 1166, 1142, 1085 (C-O-C), 994, 971, 945, 847, 811.

**$^1$H-NMR** ($CD_2Cl_2$, 500 MHz) δ [ppm]: 5.65 (1H, s, $\mathbf{H_1}$), 5.06 (1H, d, $^3J_{2\text{-}3}$= 5.6 Hz, $\mathbf{H_2}$), 4.85 (1H, dd, $^3J_{2\text{-}3}$= 5.6 Hz, $^3J_{3\text{-}4}$= 3.7 Hz, $\mathbf{H_3}$), 4.46 (1H, dd, $^3J_{3\text{-}4}$= 3.7 Hz, $^3J_{4\text{-}5}$= 7.2 Hz $\mathbf{H_4}$), 4.40 (1H, ddd, $^3J_{4\text{-}5}$= 7.2 Hz, $^3J_{5\text{-}6a}$= 6.2 Hz, $^3J_{5\text{-}6b}$= 5.0 Hz, $\mathbf{H_5}$), 4.12 (1H, dd, $^2J_{6a\text{-}6b}$= 8.8 Hz, $^3J_{5\text{-}6a}$= 6.2 Hz, $\mathbf{H_{6a}}$), 4.07 (1H, dd, $^2J_{6a\text{-}6b}$= 8.8 Hz, $^3J_{5\text{-}6b}$= 5.0 Hz, $\mathbf{H_{6b}}$), 1.49 (3H, s, C$\mathbf{H}_3$), 1.42 (3H, s, C$\mathbf{H}_3$), 1.35 (6H, s, 2 x C$\mathbf{H}_3$).

**$^{13}$C-NMR** ($CD_2Cl_2$, 125 MHz) δ [ppm]: 114.7 ($\mathbf{C_7}$), 111.3 ($\mathbf{C_1}$), 109.7 ($\mathbf{C_8}$), 86.7 ($\mathbf{C_2}$), 85.7 ($\mathbf{C_3}$), 79.8 ($\mathbf{C_4}$), 72.9 ($\mathbf{C_5}$), 66.9 ($\mathbf{C_6}$), 26.9 (**C**$H_3$), 26.1 (**C**$H_3$), 25.2 (**C**$H_3$), 24.8 (**C**$H_3$).

**MS (ESI)** *m/z* (%): 312.0 $[M+Na]^+$, 500.5 $[2M+Na–C_5H_9O_2]^+$, 601.4 $[2M+Na]^+$.

| **Elemental analysis (%):** | Calcd: C 49.82 | H 6.62 | N 4.84 |
|---|---|---|---|
| | Found: C 49.73 | H 6.36 | N 4.73 |

## 5.3 Electrophilic Amination of Carbanions using Enantiomerically Pure Nitrenoids

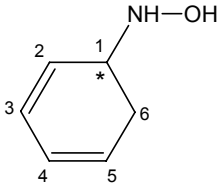
Experimental procedure for the reaction between PhLi and the lithium amide **168** in THF

A suspension of 0.8 g (5.42 mmol, 1 eq.) (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124** in 20 mL water free THF was cooled to -60°C and 1 eq. MeLi (3.3 mL, 1.6 M in $Et_2O$) was added via syringe. The mixture was allowed to reach room temperature, while a clear, colorless solution resulted, and then cooled to -78°C. The free base was lithiated by the addition of 1 eq. MeLi (3.3 mL, 1.6 M in $Et_2O$). The light yellow solution was stirred for 15 min at -78°C and 1.05 eq. PhLi (5.69 mmol, 3.2 mL, 1.8 M in cyclohexane:$Et_2O$ = 70:30) were added. The light brownish solution was allowed to reach room temperature during 4 h, under TLC monitoring. The mixture was quenched with 10 mL satd. $NH_4Cl$ sol., the organic phase was separated, washed with 20 mL brine and dried over $Na_2SO_4$. *N*-(2,4-Cyclohexadienyl)-hydroxylamine **170** was crystallized by slowly adding PE to the THF solution and cooling to -20°C. The white precipitate formed, decomposed during filtration. For the characterization of **170**, small samples were taken and washed in PE before analysis.

Experimental procedure for the reaction between PhLi and the lithium amide **168** in *n*-hexane

A suspension of 0.5 g (3.38 mmol, 1 eq.) (1*R*,4*S*)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride **124** in 25 mL *n*-hexane was cooled to -60°C and 1 eq. MeLi (2.2 mL, 1.6 M in $Et_2O$) was added via syringe. The mixture was allowed to reach room temperature, while a clear, colorless solution resulted, and then cooled to -78°C. The free base was lithiated by adding 1 eq. MeLi (2.2 mL, 1.6 M in $Et_2O$). The light yellow solution was stirred for 15 min at -78°C and 1.05 eq. PhLi (3.55 mmol, 2 mL, 1.8 M in cyclohexane:$Et_2O$ = 70:30) was added. The light brownish solution was allowed to reach room temperature during 3 h, under TLC monitoring. The mixture was quenched with 2 mL absolute methanol and the volume of the organic phase was reduced *in vacuo*. The white slurry was dissolved in 3 mL THF and *N*-(2,4-cyclohexadienyl)-hydroxylamine **170** was crystallized by slowly adding PE to the THF solution and cooling to -20°C.

*N*-(2,4-Cyclohexadienyl)-hydroxylamine **170**




**Molecular formula:** $C_6H_9NO$ [111.14]

**TLC:** $R_f$ = 0.27 [DCM:MeOH = 20:1]

**Optical rotation:** $[\alpha]_D^{27}$ = -179.7 (c = 0.7 in THF)

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3239 (NH), 3143 (OH), 3120 (=CH), 3037 (=CH), 2867 ($CH_2$), 2821 (CH), 1637 (C=C), 1521 (NH), 1456 ($CH_2$), 1405 ($CH_2$), 1369 (OH), 1317, 1270, 1222, 1166, 1076 (C-N), 1058 (C-N), 991, 970, 946, 898, 836, 779, 673 (=CH), 660 (=CH), 568, 503.

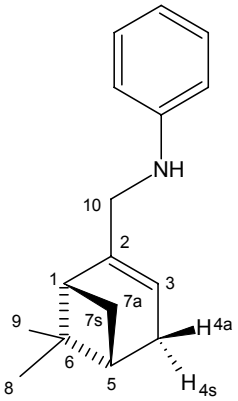
**$^1$H-NMR** ($C_6D_6$, 250 MHz) δ [ppm]: 5.82 (1H, dddd, $^3J_{2\text{-}3}$= 9.5 Hz, $^3J_{2\text{-}1}$= 5.0 Hz, $^4J_{2\text{-}4}$= 1.2 Hz, $^5J_{2\text{-}5}$= 1.2 Hz, **$H_2$**), 5.73 (1H, dddd, $^3J_{3\text{-}2}$= 9.5 Hz, $^3J_{3\text{-}4}$= 4.1 Hz, $^4J_{3\text{-}5}$= 1.2 Hz, $^4J_{3\text{-}1}$= 1.2, **$H_3$**), 5.66 (1H, dddt, $^3J_{4\text{-}5}$= 9.5 Hz, $^3J_{4\text{-}3}$= 4.1 Hz, $^4J_{4\text{-}2}$= 1.2 Hz, $^4J_{4\text{-}6}$= 1.2 Hz, **$H_4$**), 5.57 (1H, ddddd, $^3J_{5\text{-}4}$= 9.5 Hz, $^3J_{5\text{-}6a}$= 4.0 Hz, $^3J_{5\text{-}6b}$= 4.6 Hz, $^4J_{5\text{-}3}$= 1.2 Hz, $^5J_{5\text{-}2}$= 1.2 Hz, **$H_5$**), 3.57 (1H, dddd, $^3J_{1\text{-}6b}$= 8.3 Hz, $^3J_{1\text{-}6a}$= 7.3 Hz, $^3J_{1\text{-}2}$= 5.0 Hz, $^4J_{1\text{-}3}$=1.2 Hz, **$H_1$**), 2.51 (1H, dddd, $^2J_{6a\text{-}6b}$= 18.2 Hz, $^3J_{6a\text{-}1}$= 7.3 Hz, $^3J_{6a\text{-}5}$= 4.0 Hz, $^4J_{6a\text{-}4}$= 1.2 Hz, **$H_{6a}$**), 2.11 (1H, dddd, $^2J_{6b\text{-}6a}$= 18.1 Hz, $^3J_{6b\text{-}1}$= 8.2 Hz, $^3J_{6b\text{-}5}$= 4.6 Hz, $^4J_{6b\text{-}4}$= 1.2 Hz, **$H_{6b}$**).

**$^{13}$C-NMR** ($C_6D_6$, 62 MHz) δ [ppm]: 126.7 (**$C_2$**), 125.6 (**$C_3$**), 124.9 (**$C_4$**), 123.7 (**$C_5$**), 55.2 (**$C_1$**), 26.4 (**$C_6$**).

Electrophilic amination of PhLi with nitrenoids **176**-**178** generated from parent hydroxylamines **147**, **148** and **151**, using MeLi (detailed working procedure given for nitrenoid **176**)

A solution of 1.0 g (5.51 mmol, 1 eq.) (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-methyl hydroxylamine **147** in 10 mL *n*-hexane was cooled to -78°C, under $N_2$ atmosphere, and 3.45 mL MeLi (5.51 mmol, 1 eq., 1.6 M in $Et_2O$) was added dropwise via syringe. The resulting colorless solution was stirred at -78°C for 1 h, warmed-up to -40°C and one equivalent of PhLi (5.51 mmol, 3.45 mL, 1.6 M in cyclohexane:$Et_2O$ = 70:30) was added. The color turned to orange, but after stirring for 3 h at -40°C no **147** was detected (GC). After quenching with 1 mL absolute methanol, 10 mL *tert*-butylmethyl ether were added and the yellow mixture was washed successively with 15 mL satd. $NH_4Cl$ sol., 15 mL satd. $NaHCO_3$ sol. and 30 mL brine. Drying over $MgSO_4$ and evaporation of solvent *in vacuo* furnished a light-yellow oil which was purified by flash chromatography (silica gel, $Et_2O$:PE = 1:10, 1% vol. $Et_3N$) to afford 0.45 g (1.98 mmol, 36%) **179** as colorless oil.

(-)-*N*-[10-(1*R*,5*R*)-Pin-2-enyl]-aniline **179**




**Molecular formula:** $C_{16}H_{21}N$ [227.35]

**TLC:** $R_f$ = 0.39 [$Et_2O$:PE = 1:10, 1% $NEt_3$]

**Optical rotation:** $[\alpha]_D^{23}$ = -20.3 (c = 0.5 in $CHCl_3$)

**GC** (*GC Pr. 2)*: $t_R$= 15.83 min

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3421 (NH), 3050 (CH arom.), 3020 (CH arom.), 2985 (=C-H), 2913 ($CH_3$), 2831 ($CH_2$), 1602 (C=C), 1506 (C=C arom.), 1467 (CH), 1429, 1315, 1263, 1178, 1093, 748 (C-H arom.), 690 (C-H arom.).

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 7.12-7.18 (2H, m, Ph), 6.58-6.67 (3H, m, Ph), 5.44 (1H, m, $\mathbf{H_3}$), 4.14 (1H, br., N**H**), 3.61 (2H, br. s, $\mathbf{H_{10}}$), 2.39 (1H, ddd, $^2J_{7s\text{-}7a}$= 8.5 Hz, $^3J$= 5.6 Hz, $^3J$= 5.6 Hz, $\mathbf{H_{7s}}$), 2.14-2.31 (2H, m, $\mathbf{H_4}$), 2.05-2.12 (2H, m, $\mathbf{H_1}$, $\mathbf{H_5}$), 1.28 (3H, s, $\mathbf{H_8}$), 1.17 (1H, d, $^2J_{7s\text{-}7a}$= 8.5 Hz, $\mathbf{H_{7a}}$), 0.85 (3H, s, $\mathbf{H_9}$).

**$^{13}$C-NMR** ($CDCl_3$, 62 MHz) δ [ppm]: 148.4 (**C** *arom.*), 145.4 ($\mathbf{C_2}$), 129.1 (2 x **C**H *arom.*), 117.9 ($\mathbf{C_3}$), 117.2 (2 x **C**H *arom.*), 112.9 (**C**H *arom.*), 49.0 ($\mathbf{C_{10}}$), 44.2 ($\mathbf{C_5}$), 41.0 ($\mathbf{C_1}$), 38.1 ($\mathbf{C_6}$), 31.6 ($\mathbf{C_4}$), 31.1 ($\mathbf{C_7}$), 26.2 ($\mathbf{C_8}$), 21.1 ($\mathbf{C_9}$).

**MS (EI)** *m/z* (%): 228 $[M+H]^+$ (8), 227 $[M]^{+\cdot}$ (68), 226 $[M-H]^+$ (9), 212 $[M-CH_3]^+$ (3), 211 $[M-H-CH_3]^{+\cdot}$ (5), 134 $[Ph\text{-}NH_2\text{-}CH_2\text{-}CH{=}CH_2]^+$ (40), 119 $[Ph\text{-}NH\text{-}CH{=}CH_2]^{+\cdot}$ (50), 106 $[Ph\text{-}NH\text{-}CH_2]^+$ (100), 93 $[Ph\text{-}NH_2]^{+\cdot}$ (63), 91 $[C_7H_7]^+$ (75), 77 $[C_6H_5]^+$ (68), 73 (10), 65 (9), 55 (7), 43 (17), 41 (20), 29 (6), 27 (6).

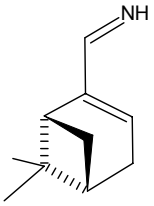
| **Elemental analysis (%):** | | | |
|---|---|---|---|
| Calcd: | C 84.53 | H 9.31 | N 6.16 |
| Found: | C 84.29 | H 9.25 | N 5.81 |

General procedure followed to determine the stability of lithiated hydroxylamines **147, 148, 151,** and **152** in THF, respectively *n*-hexane

A solution of 0.3 mmol hydroxylamines **147**, **148**, **151** or **152** in 2 mL THF, respectively *n*-hexane, was cooled to -78°C and 0.3 mmol MeLi (0.19 mL, 1.6 M in $Et_2O$) was added slowly via syringe.

After 1 h, an aliquot was quenched with saturated aqueous $NH_4Cl$, the organic phase was separated, 2 mL 1M HCl were added and the mixture was stirred for 15 min at room temperature. The organic phase was dried over $Na_2SO_4$ and the mixture was analysed by GC.

1-[(5*R*,7*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)]methanimine **181**




**Molecular formula:** $C_{10}H_{15}N$ [149.23]

**GC-MS**: $t_R$(*GC-MS Pr. 1*) = 5.35 min; **(EI)** *m*/*z* (%): 149 $[M]^{+\cdot}$ (29), 148 $[M-H]^+$ (38), 134 $[M-CH_3]^+$ (100), 121 $[M-HN{=}CH_2]^{+\cdot}$ (4), 106 $[C_7H_8N]^{+\cdot}$ (96), 93 $[C_7H_9]^+$ (25), 79 $[C_6H_7]^+$ (45), 77 $[C_6H_5]^+$ (42), 67 $[C_5H_7]^+$ (78), 27 $[HCN]^+$ (22).

Electrophilic amination of PhLi with nitrenoids **176**-**178** generated *in situ* from parent hydroxylamines **147, 148** and **151**, using PhLi (detailed working procedure given for nitrenoid **177**)

A solution of 0.70 g (2.72 mmol, 1 eq.) (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-benzyl hydroxylamine **148** in 5 mL *n*-hexane was cooled to -78°C, under $N_2$ atmosphere, and 1.7 mL PhLi (2.72 mmol, 1 eq., 1.6 M in cyclohexane:$Et_2O$ = 70:30) was added dropwise via syringe. The resulting light-yellow solution was stirred at –78°C for 15 min, warmed-up to -40°C and another mol-equivalent of PhLi was added. The colour turned to orange and after stirring for 3 h at -40°C no **148** was detected (GC). After quenching with 1 mL absolute methanol, 10 mL *tert*-butylmethyl ether were added and the yellow mixture was washed successively with 15 mL satd. $NH_4Cl$ sol., 15 mL satd. $NaHCO_3$ sol. and 20 mL brine. Drying over $Na_2SO_4$ and evaporation of the solvent *in vacuo* furnished a light-yellow oil which was purified by flash chromatography (silica gel, $Et_2O$:PE = 1:10, 1% vol. $Et_3N$) to afford 0.29 g (1.28 mmol, 47%) **179** as colorless oil.

.

Electrophilic amination of $Ph_2Cu(CN)Li_2$ **182** with hydroxylamines **147, 148** and **151** (detailed working procedure given for hydroxylamine **151**)

Phenyl lithium (2.65 mL, 4.24 mmol, 2 eq., 1.6M solution in cyclohexane : $Et_2O$ = 7 : 3) was added to 10 mL water free THF and transferred *via canula* to 0.19 g CuCN (2.18 mmol, 1 eq.) pre-dried *in vacuo* and pre-cooled to -40°C. After stirring for 20 min at that temperature, all CuCN

dissolved and a red-brownish solution resulted. The reaction mixture was cooled to –50°C and a solution of 0.51 g (-)-*N*-[10-(1*R*,5*R*)-pin-2-enyl]-*O*-trimethylsilyl hydroxylamine **151** (2.18 mmol, 1 eq.) in 10 mL water free THF was added dropwise, during 15 min. The mixture was allowed to reach -20°C during 1 h, warmed up to room temperature and the stirring continued for 2 h. The resulting light-brownish solution was quenched with 5 mL satd. $NH_4Cl$ sol., 5 mL diethyl ether were added, the organic phase was separated, washed with 10 mL brine and filtrated through a Celite 500 pad. Evaporation of solvent *in vacuo* afforded a light yellow oil which was purified by flash chromatography on silica gel ($Et_2O$:PE = 1:10, 1% vol. $Et_3N$) to furnish 0.47 g (2.05 mmol, 94%) **179** as colorless oil.

General experimental procedure for the reaction between the lithium enolates of propiophenone **75a**, *tert*-butyl propionate **192** and ethyl phenylacetate **193** with the nitrenoids **176-178** (DMPU as co-solvent)

A solution of 15 mL water free THF, 5 mL DMPU and 0.63 g diisopropylamine (6.22 mmol, 3.2 eq.) was cooled to -50°C, under nitrogen atmosphere, and 3.8 mL *n*BuLi (6.12 mmol, 3.15 eq., 1.6M in hexane) were added dropwise. The light yellow solution was stirred at -50°C for 15 min, cooled to -78°C and 1.95 mmol (1eq.) of the corresponding carbonyl compound were added dropwise. Stirring was continued at -78°C for 1 h, 3.89 mmol (2 eq.) of compounds **147**-**149**, respectively, in 2 mL THF were added, the solution was warmed up to 0°C during 3 h, under TLC and GC-MS monitoring, and then stirred at room temperature for 6 h. Formation of the *N*-substituted α-amino ester **196** could only be detected by GC-MS when *tert*-butyl propionate **192** was used as substrate and nitrenoids **176** or **177** as amination reagents. The lithium enolates of propiophenone **75a** and ethyl phenylacetate **193** displayed no reactivity towards nitrenoids **176-178**.

## 5.4 Electrophilic Amination of Enolates and Allyl Organometallic Reagents using α-Chloronitroso Reagents

Electrophilic amination of propiophenone zinc enolate **206** with (+)-*N*,*N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**

A stirred solution of LiHMDS (1.9 mL, 1.88 mmol, 1.05 eq., 1 M solution in THF) in 5 mL water free THF was cooled to -78°C under nitrogen atmosphere and 0.24 g propiophenone **75a** (1.78 mmol, 1 eq.) were added. Stirring was continued at -78°C for 1 h. Propiophenone **75a**

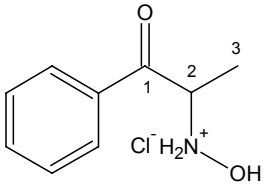
conversion was monitored by quenching an aliquot with TMSCl in *n*-hexane and GC analysis. A solution of 0.81 g $ZnBr_2$ (3.59 mmol, 2 eq., dried at 130°C *in vacuo*) in 5 mL water free THF was added at -68°C to the lithium enolate *via canula*. The light yellow solution was left to reach 0°C during 40 min and then cooled to -50°C. A solution of 0.8 g **74** (1.79 mmol, 1 eq.) in 3 mL water free THF was added to the enolate via syringe and the mixture was left to reach the room temperature during 5 h, under TLC monitoring, and then stirred at room temperature for 24 h. The light blue solution was quenched with 1 mL $H_2O$, 10 mL ethyl acetate were added, the organic phase was washed with 10 mL satd. $NH_4Cl$ sol. and dried over $MgSO_4$. Evaporation of solvent *in vacuo* afforded a white foam which was purified by gradient flash chromatography on silica gel (AcOEt:PE = 2:2 to 3:2) to afford 0.18 g nitrone **207** (0.33 mmol, 19%), as a white foam.

Hydrolysis of the nitrone **207** with 1M HCl/$CHCl_3$ afforded 0.06 g 2-(hydroxylamino)-1-phenylpropan-1-one hydrochloride **208** (0.3 mmol, 16%) as a white crystalline solid.

Electrophilic amination of propiophenone lithium enolate **206** with (+)-*N,N*-dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide **74**

A stirred solution of LiHMDS (1.9 mL, 1.88 mmol, 1.05 eq., 1 M solution in THF) in 5 mL water free THF, was cooled to -78°C under nitrogen atmosphere and 0.24 g propiophenone **75a** (1.78 mmol, 1 eq.) were added. Stirring was continued at -78°C for 1 h. Propiophenone **75a** conversion was monitored by quenching an aliquot with TMSCl in *n*-hexane and GC analysis. The light yellow solution was left to reach 0°C during 40 min. A solution of 0.8 g **74** (1.79 mmol, 1 eq.) in 5 mL THF was added to the enolate via syringe and the mixture was stirred for 3 h, under TLC monitoring. The light blue solution was quenched with 3 mL $H_2O$, the organic phase was separated and hydrolyzed with 20 mL 1M HCl. Lyophilization of the aqueous phase afforded 0.10 g 2-(hydroxylamino)-1-phenylpropan-1-one hydrochloride **208** (0.53 mmol, 30%) as a white crystalline solid.

2-(Hydroxylamino)-1-phenylpropan-1-one hydrochloride **208**




**Molecular formula:** $C_9H_{12}ClNO_2$ [201.65]

**Appearance:** white crystalline solid

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3425 (OH br), 2796 (CH), 1687 (C=O), 1637 (NH), 1448 (CH), 1403

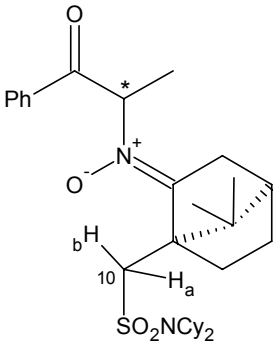
(N-O), 1232, 1145, 1001, 975.

**$^{1}$H-NMR** (DMSO-$D_6$, 500 MHz) δ [ppm]: 8.02 (2H, d, $^{3}J$= 7.5 Hz, $\mathbf{H}_{ortho}$), 7.72 (1H, dd, $^{3}J$=7.5 Hz, $^{3}J$=7.5 Hz, $\mathbf{H}_{para}$), 7.56 (2H, dd, $^{3}J$=7.5 Hz, $^{3}J$=7.5 Hz, $\mathbf{H}_{meta}$), 5.29 (1H, q, $^{3}J_{2\text{-}3}$=6.9 Hz, C**H**), 1.43 (3H, d, $^{3}J_{3\text{-}2}$= 6.9 Hz, C$\mathbf{H}_3$).

**$^{13}$C-NMR** (DMSO-$D_6$, 125 MHz) δ [ppm]: 195.2 (C=O), 134.9 ($C_{arom}$), 133.2 ($CH_{arom}$), 129.1 ($CH_{arom}$), 128.8 ($CH_{arom}$), 60.4 (CH), 13.9 ($CH_3$).

**MS (ESI)** m/z : 166.2 $[M\text{-}Cl]^+$, 188.2 $[M\text{-}HCl+Na]^+$.

2-[7,7-dimethyl-1-[*N*-(1-oxo-1-phenylprop-2-yl)(oxido)imino]bicyclo[2.2.1]hept-2-yl] methane-sulfonamide **207**




**Molecular formula:** $C_{31}H_{46}N_2O_4S$ [542.77]

**Yield:** 19% (0.18 g, white foam)

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2931 (CH), 2854 (CH), 1700 (C=O), 1598 ($C=N^+$), 1450 (CH), 1322 ($SO_2$), 1164 ($SO_2N$), 1143, 1110, 1049, 1027, 981.

**MS (ESI)** m/z: 543.2 $[M+H]^+$, 565.2 $[M+Na]^+$, 581.2 $[M+K]^+$.

General procedure for the preparation of 2-butenyl **214**, 3,3-dimethylallyl **215** and 3-phenylallyl **216** zinc bromides

To a slurry of 1.94 g zinc powder (29.6 mmol, 2 eq., granulation <63 μm, Fluka) in 20 mL water free THF, 0.13 mL 1,2-dibromoethane (1.48 mmol, 0.05 eq.) were added and the mixture was refluxed for 5 min and further cooled to room temperature. This procedure was repeated three times. Trimethylsilyl chloride (0.04 mL, 0.29 mmol, 0.01 eq.) was added, the mixture was stirred at room temperature for 30 min. A solution of 12.88 mmol (1 eq.) of allyl bromide **214**, **215**, **216**, respectively, in 20 mL THF containing 0.15 mL dodecane (0.65 mmol, 0.05 eq.) as internal standard was added at 0°C to the zinc slurry via syringe pump. The concentration of the organozinc solutions were determined by gas chromatography using the iodine method.[171]

The toluene solutions of **214**-**216** were prepared by evaporation of the THF *in vacuo*, followed by addition of water free toluene under nitrogen atmosphere.

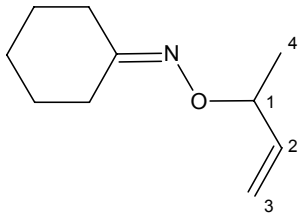
General procedure for reaction of organozinc reagents **214**-**216** with 1-chloro-1-nitroso-cyclohexane **12** in THF

A solution of 1 g 1-chloro-1-nitrosocyclohexane **12** (6.77 mmol, 1 eq.) in 5 mL of water free THF was cooled to -78°C and 6.77 mmol (1 eq.) organozinc reagent **214**-**216** in THF were added dropwise via syringe under stirring, until the blue colour had disappeared. The resulting light-yellow solution was quenched immediately with 1 mL of absolute methanol and left to reach room temperature. TLC analysis showed formation of a single product and total conversion of **12**. *tert*-Butylmethyl ether (10 mL) was added and after washing with 20 mL of a satd. $NH_4Cl$ sol., the organic phase was dried over $Na_2SO_4$ and the solvents evaporated *in vacuo*. The products **221**-**223** were obtained analytically pure (GC analysis) after flash chromatography on silica gel.

General procedure for reaction of organozinc reagents **214–216** with 1-chloro-1-nitroso-cyclohexane **12** in toluene

A solution of 0.5 g 1-chloro-1-nitrosocyclohexane **12** (3.39 mmol, 1 eq.) in 5 mL of water free toluene was cooled to –78°C and 3.39 mmol (1 eq.) organozinc reagent **214–216** in toluene were added dropwise, via syringe, under stirring, until the blue colour had disappeared. The resulting light-yellow solution was quenched immediately with 1 mL of absolute methanol and left to reach room temperature. After evaporation of solvents *in vacuo,* the residue was dissolved in 20 mL chloroform and extracted five times with 10 mL 1M HCl. Gas chromatography analysis of the organic phase showed the formation of cyclohexanone as the hydrolysis product of intermediary nitrones. Flash chromatography on silica gel of the organic phase afforded analytically pure oxime ethers **221**-**223**. The collected aqueous phases were neutralised with $KHCO_3$, extracted with ether and dried over $Na_2SO_4$. Hydroxylamine hydrochlorides **224** and **225** were isolated by precipitation from ether solution using gaseous hydrochloric acid.

*O*-(1-methylallyl)cyclohexanone oxime **221**




**Molecular formula:** $C_{10}H_{17}NO$ [167.25]

**Appearance:** colorless oil

**Yield:** see Table 6 and 7

**TLC:** $R_f$= 0.57 [AcOEt:PE = 4:10]

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3081 (=$CH_2$), 2981 (CH), 2932 ($CH_2$), 2859 ($CH_3$), 1642 (C=N), 1448 ($CH_2$), 1371 ($CH_3$), 1239 (N-O), 1134 (C-O), 945 (C=CH).

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 5.91 (1H, ddd, $^3J_{2\text{-}3}$= 17.3 Hz (trans), $^3J_{2\text{-}3}$= 10.6 Hz (cis), $^3J_{2\text{-}1}$= 5.8 Hz, **$H_2$**), 5.19 (1H, ddd, $^3J_{3\text{-}2}$= 17.3 Hz, $^4J_{3\text{-}1}$= 1.5 Hz, $^2J_{3cis\text{-}3trans}$= 1.4 Hz, **$H_3$** *trans*), 5.10 (1H, ddd, $^3J_{3\text{-}2}$= 10.6 Hz, $^4J_{3\text{-}1}$= 1.5 Hz, $^2J_{3cis\text{-}3trans}$= 1.4 Hz, **$H_3$** *cis*), 4.59 (1H, dtq, $^3J_{1\text{-}2}$= 5.8 Hz, $^4J_{1\text{-}3}$= 1.5 Hz, $^3J_{1\text{-}4}$= 6.4 Hz, **$H_1$**), 2.45-2.50 (2H, m, C**$H_2$**), 2.17-2.22 (2H, m, C**$H_2$**), 1.56-1.68 (6H, m, C**$H_2$**), 1.29 (3H, d, $^3J_{4\text{-}1}$= 6.4 Hz, **$H_4$**).

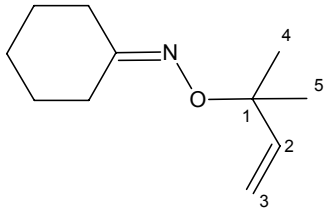
**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 160.0 (**C**=N), 140.2 (**$C_2$**), 114.7 (**$C_3$**), 78.5 (**$C_1$**), 32.3 ($CH_2$), 27.2 ($CH_2$), 25.9 ($CH_2$), 25.8 ($CH_2$), 25.4 ($CH_2$), 19.8 (**$C_4$**).

**GC-MS**: $t_R$ (*GC-MS Pr. 2*) = 9.59 min; **(EI)** *m/z* (%): 167 $[M]^{+\cdot}$ (14), 152 $[M\text{-}CH_3]^+$ (10), 113 $[C_6H_{10}NO]^+$ (14), 96 $[C_6H_{10}N]^+$ (17), 85 $[C_4H_7NO]^+$ (19), 55 $[C_4H_7]^+$ (100); **(CI)** *m/z*: 168 $[M+H]^+$.

**Elemental analysis (%):** Calcd: C 71.81 H 10.25 N 8.37

Found: C 71.97 H 10.16 N 8.12

*O*-(1,1-dimethylallyl)cyclohexanone oxime **222**




**Molecular formula:** $C_{11}H_{19}NO$ [181.27]

**Appearance:** colorless oil

**Yield:** see Table 6 and 7

**TLC:** $R_f$= 0.52 [$^t$BuOMe:PE = 1:10]

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3084 (=$CH_2$), 2987 (CH), 2932 ($CH_2$), 2859 ($CH_3$), 1642 (C=N), 1449 ($CH_2$), 1373 ($CH_3$), 1253 (N-O), 1153 (C-O), 945 (C=CH).

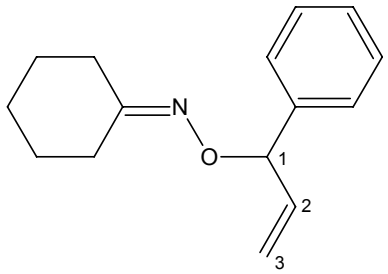
**$^1$H-NMR** ($CD_2Cl_2$, 500 MHz) δ [ppm]: 6.01 (1H, dd, $^3J_{2\text{-}3}$= 17.5 Hz (trans), $^3J_{2\text{-}3}$= 10.6 Hz (cis), **$H_2$**), 5.09 (1H, dd, $^3J_{3\text{-}2}$= 17.5 Hz, $^2J_{3cis\text{-}3trans}$= 1.5 Hz, **$H_3$** *trans*), 5.00 (1H, dd, $^3J_{3\text{-}2}$= 10.9 Hz, $^2J_{3cis\text{-}3trans}$= 1.5 Hz, **$H_3$** *cis*), 2.42-2.45 (2H, m, C**$H_2$**), 2.13-2.16 (2H, m, C**$H_2$**), 1.55-1.63 (6H, m, C**$H_2$**), 1.31 (6H, s, **$H_4$**, **$H_5$**).

**$^{13}$C-NMR** ($CD_2Cl_2$, 125 MHz) δ [ppm]: 159.2 (C=N), 145.4 (**$C_2$**), 112.2 (**$C_3$**), 79.0 (**$C_1$**), 32.7 ($CH_2$), 27.6 ($CH_2$), 26.3 ($CH_2$), 26.2 ($CH_2$), 25.9 (**$C_4$**, **$C_5$**), 25.5 ($CH_2$).

**GC-MS**: $t_R$ (*GC-MS Pr. 2*) = 9.96 min; **(EI)** *m/z* (%): 181 $[M]^{+\cdot}$ (5), 166 $[M\text{-}CH_3]^+$ (2), 151 $[M\text{-}C_2H_6]^{+\cdot}$ (3), 114 $[C_6H_{12}NO]^+$ (7), 69 $[C_5H_9]^+$ (100), 55 $[C_4H_7]^+$ (5); 41 $[C_3H_5]^+$ (55); **(CI)** *m/z*: 182 $[M+H]^+$, 114 $[C_6H_{12}NO]^+$.

| **Elemental analysis (%):** | Calcd: C 72.88 | H 10.56 | N 7.73 |
|---|---|---|---|
| | Found: C 72.55 | H 10.63 | N 7.45 |

<u>*O*-(1-phenylylallyl)cyclohexanone oxime **223**</u>




| **Molecular formula:** | $C_{15}H_{19}NO$ [229.32] |
|---|---|
| **Appearance:** | light yellow oil |
| **Yield:** | see Table 6 and 7 |
| **TLC:** | $R_f$= 0.43 [$^t$BuOMe:PE = 1:5] |

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3084 (=$CH_2$), 3062 (=CH), 3029 (=CH), 2982 (CH), 2932 ($CH_2$), 2858 ($CH_3$), 1641 (C=N), 1449 ($CH_2$), 1346 ($CH_3$), 1254 (N-O), 1026 (C-O), 990 (CH), 931 (CH), 918 (CH), 888 (CH), 700 (CH).

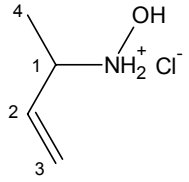
**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ [ppm]: 7.22-7.33 (5H, *arom*), 6.06 (1H, ddd, $^3J_{2\text{-}3}$= 17.2 Hz (trans), $^3J_{2\text{-}3}$= 10.6 Hz (cis), $^3J_{2\text{-}1}$= 6.2 Hz, **$H_2$**), 5.54 (1H, dt, $^3J_{1\text{-}2}$= 6.2 Hz, $^3J_{1\text{-}3}$= 1.2 Hz, **$H_1$**), 5.24 (1H, dd, $^3J_{3\text{-}2}$= 17.2 Hz, $^2J_{3cis\text{-}3trans}$= 1.2 Hz, **$H_3$** *trans*), 5.20 (1H, dd, $^3J_{3\text{-}2}$= 10.6 Hz, $^2J_{3cis\text{-}3trans}$= 1.2 Hz, **$H_3$** *cis*), 2.52-2.57 (2H, m, C**$H_2$**), 2.15-2.19 (2H, m, C**$H_2$**), 1.51-1.70 (6H, m, C**$H_2$**).

**$^{13}$C-NMR** ($CDCl_3$, 63 MHz) δ [ppm]: 161.0 (C=N), 140.8 (Ph), 138.4 (**$C_2$**), 128.2 (Ph), 127.4 (Ph), 127.0 (Ph), 116.2 (**$C_3$**), 84.8 (**$C_1$**), 32.1 ($CH_2$), 27.0 ($CH_2$), 25.8 ($CH_2$), 25.7 ($CH_2$), 25.6 ($CH_2$).

**GC-MS**: $t_R$ (*GC-MS Pr. 2*) = 14.72 min; **(EI)** *m/z* (%): 230 $[M+H]^+$ (2), 117 $[C_9H_9]^+$ (100), 115 $[C_9H_7]^+$ (20), 105 $[C_8H_9]^+$ (5), 91 $[C_7H_7]^+$ (10), 77 $[C_6H_5]^+$ (5); **(CI)** m/z: 230 $[M+H]^+$, 117 $[C_9H_9]^+$.

| **Elemental analysis (%):** | Calcd: C 78.56 | H 8.35 | N 6.11 |
|---|---|---|---|
| | Found: C 78.40 | H 8.33 | N 6.12 |

*N*-(1-methylallyl)hydroxylamine hydrochloride **224**




**Molecular formula:** $C_4H_{10}ClNO$ [123.58]

**Appearance:** white solid

**Yield:** see Table 7

**Melting point:** 58-61°C

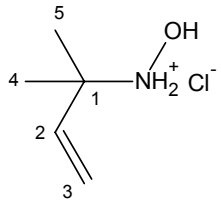
**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3465 (OH br), 3040 (NH valence, br), 2507 (CH), 1633 (NH deformation), 1450 ($CH_2$), 1426 (N-O), 1381 (CH), 1003 (C-N), 947 (C=CH).

**$^1$H-NMR** ($D_2O$, 500 MHz) δ [ppm]: 5.62 (1H, dddq, $^3J_{2\text{-}3}$= 17.3 Hz (trans), $^3J_{2\text{-}3}$= 10.2 Hz (cis), $^3J_{2\text{-}1}$= 7.4 Hz, $^4J_{2\text{-}4}$= 1.45 Hz, **$H_2$**), 5.23 (1H, ddd, $^3J_{3\text{-}2}$= 17.3 Hz, $^4J_{3\text{-}1}$= 2.5 Hz, $^2J_{3cis\text{-}3trans}$= 1.2 Hz, **$H_3$** *trans*), 5.19 (1H, ddd, $^3J_{3\text{-}2}$= 10.2 Hz, $^4J_{3\text{-}1}$= 2.2 Hz, $^2J_{3cis\text{-}3trans}$= 1.0 Hz, **$H_3$** *cis*), 3.71 (1H, dtq, $^3J_{1\text{-}2}$= 7.4 Hz, $^4J_{1\text{-}3}$= 1.5 Hz, $^3J_{1\text{-}4}$= 6.6 Hz, **$H_1$**), 1.10 (3H, dd, $^3J_{4\text{-}1}$= 6.6 Hz, $^4J_{4\text{-}2}$= 1.2 Hz, **$H_4$**).

**$^{13}$C-NMR** ($D_2O$, 125 MHz) δ [ppm]: 135.9 (**$C_2$**), 122.4 (**$C_3$**), 59.7 (**$C_1$**), 13.9 (**$C_4$**).

**MS (EI)** *m/z* (%): 87 $[M\text{-}HCl]^{+\cdot}$ (7), 72 $[C_3H_6NO]^+$ (35), 55 $[C_4H_7]^+$ (60), 41 $[C_3H_5]^+$ (100), 40 $[C_3H_4]^+$ (69), 39 $[C_3H_3]^+$ (42).

*N*-(1,1-dimethylallyl)hydroxylamine hydrochloride **225**




**Molecular formula:** $C_5H_{12}ClNO$ [137.61]

**Appearance:** white solid

**Yield:** see Table 7

**Melting point:** 60-63°C

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3467 (OH br), 3037 (NH valence, br), 2509 (CH), 1635 (NH deformation), 1448 ($CH_2$), 1426 (N-O), 1382 (CH), 1010 (C-N), 948 (C=CH).

**$^1$H-NMR** (DMSO-$D_6$, 500 MHz) δ [ppm]: 10.41 (b, N**$H_2^+$**), 6.03 (1H, dd, $^3J_{2\text{-}3}$= 17.5 Hz (trans), $^3J_{2\text{-}3}$= 10.6 Hz (cis), **$H_2$**), 5.35 (1H, d, $^3J_{3\text{-}2}$= 17.5 Hz, **$H_3$** *trans*), 5.31 (1H, d, $^3J_{3\text{-}2}$= 10.6 Hz, **$H_3$** *cis*), 1.36 (6H, s, **$H_4$**, **$H_5$**).

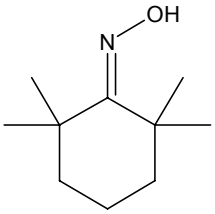
**$^{13}$C-NMR** (DMSO-$D_6$, 125 MHz) δ [ppm]: 137.2 (**$C_2$**), 117.5 (**$C_3$**), 61.6 (**$C_1$**), 21.08 (**$C_4$**, **$C_5$**).

**MS (EI)** *m/z* (%): 101 $[M\text{-}HCl]^{+\cdot}$ (6), 86 $[C_4H_8NO]^+$ (11), 84 $[C_5H_{10}N]^+$ (5), 74 $[C_3H_8NO]^+$ (8), 69 $[C_5H_9]^+$ (53), 46 $[C_2H_8N]^+$ (15), 41 $[C_3H_5]^+$ (100), 40 $[C_3H_4]^+$ (30), 39 $[C_3H_3]^+$ (25).

Synthesis of 1-chloro-2,2,6,6-tetramethyl-1-nitrosocyclohexane **226**

A solution of 6.77 g hydroxylamine hydrochloride (97.4 mmol, 3 eq.) and 8.52 g sodium acetate (103.87 mmol, 3.2 eq.) in 120 mL methanol was stirred for 30 min at room temperature. 2,2,6,6-Tetramethylcyclohexanone (5 g, 32.46 mmol, 1 eq.) was added and the mixture was refluxed for 3 days. After completion, the reaction mixture was poured into ice water, the white precipitate was filtered off and washed with cold water. Recrystallisation from methanol afforded 4 g (73%) analytically pure 2,2,6,6-tetramethylcyclohexanone oxime **232** as white crystals.

2,2,6,6-tetramethylcyclohexanone oxime **232**




**Molecular formula:** $C_{10}H_{19}NO$ [169.26]

**Yield:** 73% (4 g, white crystals) [lit.[173] 57%]

**TLC:** $R_f$= 0.36 [AcOEt:PE = 1:10]

**Melting point:** 154-155°C [lit.[173] 148.5°C]

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3304 (OH), 2930 ($CH_3$), 2866 ($CH_2$), 1646 (C=N), 1561 (N-O), 1459 ($CH_3$), 1381 ($CH_2$), 1360 ($CH_3$), 1220 (N-O), 935 (N-O).

**$^1$H-NMR** ($CDCl_3$, 500 MHz) δ [ppm]: 8.74 (1H, br, OH), 1.60-1.65 (2H, m, C**H**$_2$), 1.51-1.56 (4H, m, 2xC**H**$_2$), 1.36 (6H, s, 2xC**H**$_3$), 1.21 (6H, s, 2xC**H**$_3$).

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ [ppm]: 168.6 (C=N), 40.5 ($CH_2$), 37.9 (C), 37.6 ($CH_2$), 37.0 (C), 30.5 (2x$CH_3$), 26.7 (2x$CH_3$), 17.4 ($CH_2$).

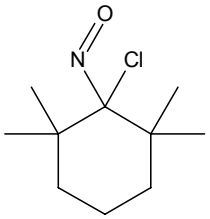
**MS (EI)** *m/z* (%): 169 $[M]^{+\cdot}$ (10), 154 $[M\text{-}CH_3]^+$ (12), 152 $[M\text{-}OH]^+$ (32), 141 $[C_8H_{15}NO]^+$ (7), 137 $[C_{10}H_{17}]^+$ (10), 126 $[C_8H_{14}N]^+$ (8), 100 $[C_5H_{10}NO]^+$ (35), 87 $[C_5H_9NO]^+$ (19), 69 $[C_5H_9]^+$ (100), 55 $[C_4H_7]^+$ (60), 41 $[C_3H_5]^+$ (63), 27 $[HCN]^+$ (20).

| **Elemental analysis** (%): | Calcd: C 70.96 | H 11.31 | N 8.28 |
|---|---|---|---|
| | Found: C 70.93 | H 11.12 | N 8.21 |

A solution of 3.1 g $^t$BuOCl (20 mmol, 1.1 eq., 70% w/w in $^t$BuOH) in 30 mL water free dichloromethane was added dropwise during 30 min. under nitrogen and protection against light,

to a pre-cooled (0°C) solution of 3.05 g 2,2,6,6-tetramethylcyclohexanone oxime **232** (18 mmol, 1 eq.) in 50 mL water free dichloromethane. After stirring for 1.5 h at 0°C, the reaction mixture was warmed-up to room temperature and the solvent was evaporated *in vacuo*. The blue residue was recrystallised from methanol affording 3.23 g (88%) of **226** as blue crystals.

1-chloro-2,2,6,6-tetramethyl-1-nitrosocyclohexane **226**



**Molecular formula:** $C_{12}H_{18}ClNO$ [203.71]

**Yield:** 88% (3.23 g, blue crystals)

**TLC:** $R_f$= 0.64 [AcOEt:PE = 1:10]

**Melting point:** 115-117°C

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2977 ($CH_3$), 2939 ($CH_3$), 2872 ($CH_2$), 1578 (N=O), 1471 ($CH_3$), 1386 ($CH_3$), 1370 ($CH_3$), 1202 ($CH_3$), 627 (C-Cl).

**$^1$H-NMR** ($CD_2Cl_2$, 500 MHz) δ [ppm]: 2.71 (2H, m, C**H**$_2$), 2.38 (1H, m, *4*-C**H**$_2$), 2.11 (1H, m, *4*-C**H**$_2$), 1.94 (2H, m, C**H**$_2$), 1.34 (6H, s, C**H**$_3$), 0.21 (6H, s, C**H**$_3$).

**$^{13}$C-NMR** ($CD_2Cl_2$, 125 MHz) δ [ppm]: 136.3 (C), 42.1 (2xC), 40.2 (2x$CH_2$), 27.5 ($CH_3$), 25.7 ($CH_3$), 19.9 ($CH_2$).

**MS (EI)** *m/z* (%): 168 $[M\text{-}Cl]^{+\cdot}$ (6), 160 $[C_9H_{15}{}^{37}Cl]^{+\cdot}$ (4), 158 $[C_9H_{15}{}^{35}Cl]^{+\cdot}$ (13), 145 $[C_8H_{12}{}^{37}Cl]^+$ (14), 143 $[C_8H_{12}{}^{35}Cl]^+$ (43), 137 $[C_{10}H_{17}]^+$ (53), 133 $[C_7H_{12}{}^{37}Cl]^+$ (4), 131 $[C_7H_{12}{}^{35}Cl]^+$ (13), 123 $[C_9H_{15}]^+$ (25), 107 $[C_8H_{11}]^+$ (18), 105 $[C_8H_9]^+$ (19), 103 $[C_8H_7]^+$ (53), 97 $[C_7H_{13}]^+$ (15), 95 $[C_7H_{11}]^+$ (37), 91 $[C_7H_7]^+$ (15), 83 $[C_6H_{11}]^+$ (24), 81 $[C_6H_9]^+$ (38), 79 $[C_6H_7]^+$ (18), 77 $[C_6H_5]^+$ (25), 69 $[C_5H_9]^+$ (100), 67 $[C_5H_7]^+$ (37), 57 $[C_4H_9]^+$ (35), 55 $[C_4H_7]^+$ (45), 43 $[C_3H_7]^+$ (25), 41 $[C_3H_5]^+$ (72).

| **Elemental analysis (%):** | | | | |
|---|---|---|---|---|
| | Calcd: | C 58.96 | H 8.91 | N 6.88 |
| | Found: | C 58.94 | H 8.66 | N 6.81 |

Reaction of organozinc reagent **214** with 1-chloro-2,2,6,6-tetramethyl 1-nitrosocyclohexane **226** in THF

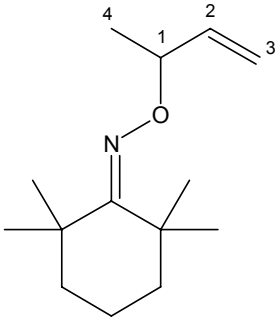
A solution of 0.35 g 1-chloro-2,2,6,6-tetramethyl 1-nitrosocyclohexane **226** (1.71 mmol, 1 eq.) 10 mL of water free THF was cooled to –78°C and 1.71 mmol (1 eq.) organozinc reagent **214** dissolved in THF were added dropwise via syringe. The mixture was stirred at -78°C for 1 h, allowed to reach 4°C during 2.5 h under TLC and GC monitoring, and then stirred at room

temperature for 12 h. The slightly blue solution was quenched with 5 mL satd. $NaHCO_3$ sol. and the white precipitate formed was dissolved by adding 10 mL satd. $NH_4Cl$ sol. Separation of the organic phase, drying over $Na_2SO_4$ and evaporation of solvent *in vacuo* afforded 0.12 g *O*-(1-methylallyl)-2,2,6,6-tetra-methylcyclohexanone oxime **233** (0.53 mmol, 31%). To monitor the possible photochemical decomposition a sample of **226** in THF was run in parallel.

Reaction of organozinc reagent **214** with 1-chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane **226** in toluene

A similar procedure as above was followed, with the exception that a toluene solution of the organozinc reagent has been used. *O*-(1-Methylallyl)-2,2,6,6-tetramethylcyclohexanone oxime **233** resulted in 28% yield.

*O*-(1-methylallyl)-2,2,6,6-tetramethylcyclohexanone oxime **233**




**Molecular formula:** $C_{14}H_{25}NO$ [223.35]

**Appearance:** colorless oil

**TLC:** $R_f$= 0.62 [PE]

**GC** (*GC Pr. 2)*: $t_R$ = 10.6 min

**IR** (neat), $\tilde{\nu}$ [$cm^{-1}$]: 3082 (=$CH_2$), 2959 (CH), 2930 ($CH_2$), 2867 ($CH_3$), 1645 (C=N), 1464 ($CH_2$), 1382 ($CH_3$), 1362 ($CH_3$), 1232 (N-O), 1160 (C-O), 946 (C=CH).

**$^1$H-NMR** ($CD_2Cl_2$, 500 MHz) δ [ppm]: 5.92 (1H, ddd, $^3J_{2\text{-}3}$= 17.3 Hz (trans), $^3J_{2\text{-}3}$= 10.6 Hz (cis), $^3J_{2\text{-}1}$= 5.7 Hz, **$H_2$**), 5.18 (1H, ddd, $^3J_{3\text{-}2}$= 17.3 Hz, $^4J_{3\text{-}1}$= 1.5 Hz, $^2J_{3cis\text{-}3trans}$= 1.4 Hz, **$H_3$** *trans*), 5.07 (1H, ddd, $^3J_{3\text{-}2}$= 10.6 Hz, $^4J_{3\text{-}1}$= 1.5 Hz, $^2J_{3cis\text{-}3trans}$ = 1.4 Hz, **$H_3$** *cis*), 4.51 (1H, dtq, $^3J_{1\text{-}2}$= 5.7 Hz, $^4J_{1\text{-}3}$= 1.4 Hz, $^3J_{1\text{-}4}$= 6.7 Hz, **$H_1$**), 1.56-1.6 (2H, m, C**$H_2$**), 1.47-1.50 (4H, m, C**$H_2$**), 1.28 (3H, s, C**$H_3$**), 1.27 (3H, d, $^3J_{4\text{-}1}$= 6.7 Hz, **$H_4$**), 1.26 (3H, s, C**$H_3$**), 1.16 (3H, s, C**$H_3$**), 1.14 (3H, s, C**$H_3$**).

**$^{13}$C-NMR** ($CD_2Cl_2$, 125 MHz) δ [ppm]: 167.1 (C=N), 140.7 (**$C_2$**), 114.4 (**$C_3$**), 79.5 (**$C_1$**), 41.4 ($CH_2$), 38.5 ($CH_2$), 38.3 (C), 37.1 (C), 31.1 ($CH_3$), 31.1 ($CH_3$), 27.5 ($CH_3$), 27.5 ($CH_3$), 19.9 (**$C_4$**), 18.0 ($CH_2$).

**MS (EI)** *m*/*z* (%): 223 $[M]^{+\cdot}$ (5), 208 $[M\text{-}CH_3]^+$ (4), 169 $[M\text{-}C_4H_6]^{+\cdot}$ (18), 152 $[C_{10}H_{18}N]^+$ (25), 100 $[C_5H_{10}NO]^+$ (18), 87 $[C_5H_9NO]^+$ (8), 69 $[C_5H_9]^+$ (75), 55 $[C_4H_7]^+$ (100), 41 $[C_3H_5]^+$ (30), 29 $[C_2H_5]^+$ (12), 27 $[HCN]^+$ (20).

**Elemental analysis (%):** Calcd: C 75.28 H 11.28 N 6.27
Found: C 75.22 H 11.14 N 6.20

## 5.5 Electrophilic Amination of Allyl Organometallic Reagents using 1-Deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose

General procedure for the preparation of allyl organomagnesium reagents **244**, **245**

1.41 g magnesium turnings (58.22 mmol, 3 eq.) were added into a 100 mL two-necked flask. The flask was evacuated, filled with nitrogen and 20 mL water free THF were added. The suspension was cooled to 0°C, 1.16 mmol 1,2-dibromoethane (0.04 eq., 0.22 g, 0.2 mL) were added dropwise and the mixture was stirred for 30 min. The temperature was maintained at 0°C and 19.41 mmol allyl bromide **211**, respectively **212**, (1 eq.) in 10 mL water free THF were added dropwise via syringe pump during 5 h. The stirring was continued overnight at 0°C. The dark-brown Grignard solution was titrated using *N*-phenyl-1-naphtylamine as indicator.[183] This procedure afforded a 0.1 M solution of **244**, respectively 0.3 M solution of **245** in THF.

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with allyl magnesium reagents

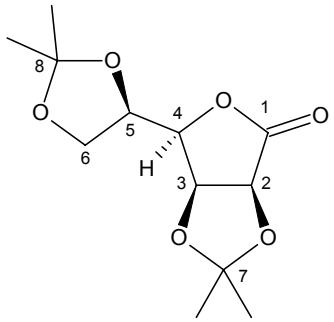
A solution of 0.5 g 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-*D*-mannofuranose **156** (1.72 mmol, 1 eq.) in 5 mL water free THF was cooled to -78°C, under nitrogen atmosphere and 2.07 mmol (1.2 eq.) Grignard reagent were added dropwise via syringe. The mixture was left to warm up, while the reaction was monitored by TLC. Total conversion of **156** was observed after 3 h reaction time. The mixture was quenched at -50°C with 2 mL absolute methanol, 10 mL *tert*-butylmethyl ether were added and the solution was washed with 10 mL satd. $NH_4Cl$ sol. and 20 mL brine. Drying over $Na_2SO_4$, evaporation of the solvent *in vacuo* and gradient flash chromatography on silica gel (AcOEt:PE = 1:2 and 1:1) of the resulting light-yellow solid afforded 2,3:5,6-di-*O*-isopropylidene-α-D-manno-1,4-lactone **247** as single product.

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 3,3-dimethylallyltitanium triisopropoxide **246**

The solution of 3,3-dimethylallyltitanium triisopropoxide **246** in THF was prepared immediately before the reaction with **156**, from 1 eq. 3,3-dimethylallylzinc bromide **215** and 1.01 eq. commercially available $ClTi(O^iPr)_3$.

3,3-Dimethylallylzinc bromide **215** (2.07 mmol, 0.37 M in THF, 1.2 eq) was cooled to -78°C and 0.55 g (2.1 mmol, 1.21 eq.) $ClTi(O^iPr)_3$ were added via syringe. The dark-red solution was stirred at -78°C for 30 min and then added *via canula* to a solution of 0.5 g **156** (1.72 mmol, 1 eq) in 10 mL water free THF. The mixture was left to warm up, while the reaction was monitored by TLC. Total conversion of **156** was observed after 4 h reaction time. The mixture was quenched at -42°C with 2 mL absolute methanol, 10 mL *tert*-butylmethyl ether were added and the solution was washed with 10 mL satd. $NH_4Cl$ sol. and 20 mL brine. Drying over $Na_2SO_4$, evaporation of the solvent *in vacuo* and gradient flash chromatography on silica gel (AcOEt:PE = 1:2 and 1:1) of the resulting light-yellow solid afforded 0.32 g (1.25 mmol, 73%) 2,3:5,6-di-*O*-isopropylidene-α-D-manno-1,4-lactone **247** as single product.

2,3:5,6-Di-*O*-isopropylidene-α-D-manno-1,4-lactone **247**




| | |
|---|---|
| **Molecular formula:** | $C_{12}H_{18}O_6$ [258.26] |
| **Appearance:** | white solid |
| **Melting point:** | 122-124°C [lit.[184]121-122°C] |
| **TLC:** | $R_f$= 0.44 [AcOEt:PE = 3:2] |
| **Optical rotation:** | $[\alpha]_D^{25}$ =+43 (c = 1.0 in $CHCl_3$) |
| | [lit.[184] $[\alpha]_D^{20}$ =+49 (c=1.2 in $CHCl_3$)] |

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 3054 (C-H), 2989 ($CH_3$), 1793 (C=O), 1421 ($CH_2$), 1376, 1265, 1218 (C-O-C), 1186, 1151, 1118, 1070 (C-O-C), 997, 975, 944, 896, 842.

**$^1$H-NMR** ($CD_2Cl_2$, 250 MHz) δ [ppm]: 4.79-4.86 (2H, m, $\mathbf{H_2}$, $\mathbf{H_3}$), 4.37-4.40 (2H, m, $\mathbf{H_5}$, $\mathbf{H_4}$), 4.05 (2H, m, $\mathbf{H_6}$), 1.44 (3H, s, C$\mathbf{H_3}$), 1.43 (3H, s, C$\mathbf{H_3}$), 1.40 (3H, s, C$\mathbf{H_3}$), 1.35 (3H, s, C$\mathbf{H_3}$).

**$^{13}$C-NMR** ($CD_2Cl_2$, 62.89 MHz) δ [ppm]: 173.7 ($\mathbf{C_1}$), 114.6 ($\mathbf{C_7}$), 110.0 ($\mathbf{C_8}$), 78.7 ($\mathbf{C_2}$), 76.5 ($\mathbf{C_3}$),

76.3 (**C**$_4$), 73.1 (**C**$_5$), 66.7 (**C**$_6$), 27.0 ($CH_3$), 26.9 ($CH_3$), 25.9 ($CH_3$), 25.2 ($CH_3$).

**MS (ESI)** *m/z:* 281.1 $[M+Na]^+$, 538.7 $[2M-H+Na]^+$.

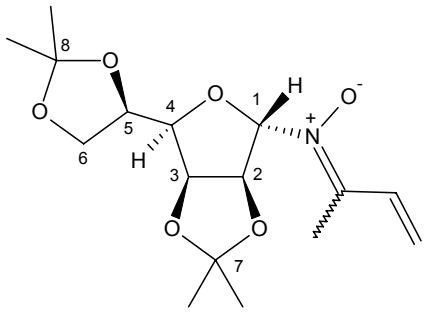
**Elemental analysis (%):** Calcd: C 55.81 H 7.02

Found: C 55.78 H 7.10

General procedure for the reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 2-butenyl zinc bromide **214**

A solution of 0.5 g **156** (1.72 mmol, 1 eq.) in 5 mL water free THF was cooled to the mentioned temperature (Chapter 3.4, Table 10) and 1.89 mmol (1.1 eq.) 2-butenyl zinc bromide **214** (THF solution) were added via syringe. The reaction mixture was stirred at that temperature (Chapter 3.4, Table 10, Entries 1, 3-5) or left to warm up (Chapter 3.4, Table 10, Entries 4, 6), while monitored by TLC. For the entries 2 and 4 the quenching with 2 mL absolute methanol was applied as soon as the formation of lactone **247** was detected by TLC, while for entries 1 and 3 absolute methanol (2 mL) was added after 4, respectively 12 hours. For the entries 5 and 6 (Chapter 3.4, Table 10) 5.2 mL solution 0.5 M TFA/DCM (1.5 eq) and respectively, 2.16 mL solution 1.3 M AcOH/DCM was used, and the quenching was done as soon as formation of lactone **247** has been observed. Further, 10 mL *tert*-butylmethyl ether was added and the mixture was washed with 10 mL satd. $NH_4Cl$ sol. and dried over $Na_2SO_4$. The purification was done by gradient flash chromatography on silica gel (AcOEt:PE = 1:1, AcOEt:PE:EtOH = 20:2:1). Nitrone **250** resulted as light yellow oil which solidified upon standing at 0°C.

*N*-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-1-methyl-2-propenylidene nitrone **250**




**Molecular formula:** $C_{16}H_{25}NO_6$ [327.37]

**Appearance:** colorless vitreous solid

**Optical rotation:** $[\alpha]_D^{25}$ =+23 (c = 1.0 in $CHCl_3$)

**TLC:** $R_f$= 0.27 [AcOEt:PE:EtOH = 20:2:1]

**IR** (KBr), $\tilde{\nu}$ [$cm^{-1}$]: 2987 (CH), 2938 (CH), 1521 (C=N$^+$), 1456 (CH), 1373, 1261, 1209, 1161, 1114, 1066, 847, 755.

**$^{1}$H-NMR** ($CD_2Cl_2$, 500 MHz) δ [ppm]:

*(Z)*–Isomer: 6.86 (1H, dd, $^{3}J_{trans}$ = 16.9 Hz, $^{3}J_{cis}$ = 11.3 Hz, C**H**=$CH_2$), 6.05 (1H, s, C**H**-N), 5.60 (1H, d, $^{3}J_{trans}$= 16.9 Hz, CH=C**H**$_2$-*trans*), 5.47 (1H, d, $^{3}J_{cis}$= 11.3 Hz, CH=C**H**$_2$-*cis*), 5.29 (1H, d, $^{3}J_{2\text{-}3}$= 6.2 Hz, **H$_2$**), 5.05 (1H, dd, $^{3}J_{2\text{-}3}$= 6 Hz, $^{3}J_{3\text{-}4}$= 4.1 Hz, **H$_3$**), 4.62 (1H, dd, $^{3}J_{3\text{-}4}$= 4.3 Hz, $^{3}J_{4\text{-}5}$= 7.5 Hz, **H$_4$**), 4.01-4.09 (3H, m, **H$_5$**, **H$_6$**), 2.14 (3H, s, N=C-C**H**$_3$), 1.47 (3H, s, $CH_3$), 1.38 (3H, s, $CH_3$), 1.33 (3H, s, $CH_3$), 1.32 (3H, s, $CH_3$).

*(E)*–Isomer: 7.23 (1H, dd, $^{3}J_{trans}$= 17.7 Hz, $^{3}J_{cis}$= 11.5 Hz, C**H**=$CH_2$), 5.88 (1H, s, C**H**-N), 5.81 (1H, d, $^{3}J_{trans}$= 18.2 Hz, CH=C**H**$_2$-*trans*), 5.70 (1H, d, $^{3}J_{cis}$= 11.9 Hz, CH=C**H**$_2$-*cis*), 5.33 (1H, d, $^{3}J_{2\text{-}3}$= 5.9 Hz, **H$_2$**), 5.11 (1H, dd, $^{3}J_{2\text{-}3}$= 5.9 Hz, $^{3}J_{3\text{-}4}$= 3.5 Hz, **H$_3$**), 4.66 (1H, dd, $^{3}J_{3\text{-}4}$= 4 Hz, $^{3}J_{4\text{-}5}$= 7.8 Hz, **H$_4$**), 4.31-4.39 (3H, m, **H$_5$**, **H$_6$**), 2.20 (3H, s, N=C-C**H**$_3$), 1.48 (3H, s, $CH_3$), 1.39 (3H, s, $CH_3$), 1.34 (3H, s, $CH_3$), 1.32 (3H, s, $CH_3$).

**$^{13}$C-NMR** ($CD_2Cl_2$, 125 MHz) δ [ppm]:

*(Z)*–Isomer: 147.3 (**C**=N), 127.1 (=**C**$H_2$), 120.6 (**C**H=), 112.7 (**C$_7$**), 109.3 (**C$_8$**), 95.6 (**C$_1$**), 85.7 (**C$_2$**), 84.0 (**C$_3$**), 80.8 (**C$_4$**), 73.2 (**C$_5$**), 66.6 (**C$_6$**), 26.7 ($CH_3$), 25.8 ($CH_3$), 25.2 ($CH_3$), 24.1 ($CH_3$), 12.9 (=C-**C**$H_3$).

*(E)*–Isomer: 146.8 (**C**=N), 128.6 (=**C**$H_2$), 123.8 (**C**H=), 112.1 (**C$_7$**), 109.1 (**C$_8$**), 96.9 (**C$_1$**), 85.5 (**C$_2$**), 84.1 (**C$_3$**), 80.5 (**C$_4$**), 73.6 (**C$_5$**), 66.7 (**C$_6$**), 26.8 ($CH_3$), 26.0 ($CH_3$), 25.2 ($CH_3$), 24.4 ($CH_3$), 13.4 (=C-**C**$H_3$).

**MS (ESI)** *m/z:* 350.11 $[M+Na]^+$, 366.11 $[M+K]^+$, 625.22, 677.17 $[2M+Na]^+$.

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 3,3-dimethylallyl zinc bromide **215** in THF

A solution of 0.5 g **156** (1.72 mmol, 1 eq.) in 10 mL water free THF was cooled to -35°C and 2.59 mmol **215** (0.37 M in THF, 1.5 eq.) were added dropwise, via syringe. The mixture was left to warm up to 0°C during 3 h, while monitored by TLC, then stirred at 0°C for 20 h and quenched with 5 mL methanol. The solvent was evaporated *in vacuo* and the resulting light yellow foam was dissolved in chloroform and hydrolysed with 20 mL 1M HCl. From the organic phase 0.24 g **156** (48%) was recovered by flash chromatograpy on silica gel (AcOEt:PE = 1:2 and 3:2). 65 mg hydroxylamine hydrochloride **225** (0.47 mmol, 27%) resulted after lyophilization of the aqueous phase.

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 3,3-dimethylallyl zinc bromide **215** in THF and in the presence of $BF_3 \cdot OEt_2$

A solution of 0.51 g **156** (1.76 mmol, 1 eq.) in 10 mL water free THF was cooled to -55°C and a solution of $BF_3 \cdot OEt_2$ (0.25 mL, 1.94 mmol, 1.1 eq.) was added dropwise via syringe followed by the addition of 3.52 mmol **215** (0.49 M in THF, 2 eq.). The light yellow solution was stirred for 12 h at -55°C, then 5 h from -30 to -20°C. TLC monitoring showed only unreacted **156**. Stirring was continued at -20°C for 1 h and then the mixture was warmed up to 0°C and stirred for 16 h, while monitored by TLC. The mixture was quenched with 1 mL absolute methanol, washed with 10 mL satd. $NH_4Cl$ sol. and worked up as above. 0.41 g **156** (80%) was recovered and 21 mg hydroxylamine hydrochloride **225** (0.15 mmol, 8%) resulted as white powder.

Preparation of 3,3-dimethylallyl zinc bromide **215** solution in dichloromethane

The solution of 3,3-dimethylallyl zinc bromide **215** in dichloromethane was prepared from its THF solution by evaporation of THF *in vacuo* at 0°C, followed by the addition of water free dichloromethane under nitrogen atmosphere. After stirring the dichloromethane solution of **215** at 0°C for 12 h, GC analysis of an aliquot using iodine method[171] showed a practically negligible decrease of concentration (less then 5%).

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 3,3-dimethylallyl zinc bromide **215** in dichloromethane

A solution of 0.5 g **156** (1.72 mmol, 1 eq.) in 5 mL water free dichloromethane was cooled to -78°C and 2.07 mmol **215** (0.35 M in dichloromethane, 1.2 eq.) was added dropwise via syringe. The light yellow solution was left to reach -10°C during 20 h, while monitored by TLC. The mixture was quenched with 1 mL absolute methanol and worked up as above. Hydroxylamine hydrochloride **225** (26 mg, 0.19 mmol, 11%) resulted as white powder. From the organic phase 0.43 g lactone **247** were isolated by evaporation of the solvent.

Reaction of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose **156** with 3,3-dimethylallyl zinc bromide **215** in dichloromethane and in the presence of $BF_3 \cdot OEt_2$

A solution of 0.5 g **156** (1.72 mmol, 1 eq.) in 5 mL water free dichloromethane was cooled to -78°C and a solution of $BF_3 \cdot OEt_2$ (0.24 mL, 1.94 mmol, 1.1 eq.) was added dropwise, via syringe.

The colorless solution was stirred at -78°C for 10 min and 2.07 mmol **215** (0.35 M in dichloromethane, 1.2 eq.) was added dropwise via syringe. The light yellow solution was stirred for 4 h at -70°C, while monitored by TLC, and then left to reach -10°C during 14 h. The mixture was quenched at -10°C with methanol, warmed up to room temperature and washed with 10 mL $NH_4Cl$ satd. sol. The solvent was evaporated *in vacuo* and the resulted light yellow foam was dissolved in chloroform and hydrolyzed with 20 mL 1M HCl. Hydroxylamine hydrochloride **225** (35 mg, 0.26 mmol, 15%) resulting after lyophilization of the aqueous phase. Evaporation of the organic phase furnished 0.41 g lactone **247**.

# 6. Appendix

## X-Ray Diffraction Analysis of (+)-*N,N*-Dicyclohexyl-(2-chloro-2-nitrosocamphor-10-sulfonamide) 74

**Table 12.** Crystal data and structure refinement.

| | |
|---|---|
| Measurement device | Nonius KappaCCD |
| Empirical formula | C22 H37 Cl N2 O3 S 92% |
| | C22 H37 Cl N2 O4 S 8% impurity |
| Formula weight | 446.37 |
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system, space group | Orthorhombic, P 21 21 21 |
| Unit cell dimensions | a = 8.9650(4) Å alpha = 90.000(4) deg. |
| | b = 15.8530(7) Å beta = 90.000(4) deg. |
| | c = 16.2330(8) Å gamma = 90.000(4) deg. |
| Volume | 2307.07(18) $Å^3$ |
| Z, Calculated density | 4, 1.285 $Mg/m^3$ |
| Absorption coefficient | 0.282 $mm^{-1}$ |
| F(000) | 963 |
| Crystal size, colour and habit | 0.30 x 0.29 x 0.28 $mm^3$, blue cuboid |
| Theta range for data collection | 3.39 to 30.00 deg. |
| Index ranges | -12<=h<=12, -22<=k<=22, -22<=l<=22 |
| Reflections collected / unique | 6710 / 6710 [R(int) = 0.0000] |
| Completeness to theta = 30.00 | 99.6% |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.9253 and 0.9202 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 6710 / 2 / 321 |
| Goodness-of-fit on $F^2$ | 1.023 |
| Final R indices [I>2sigma(I)] | R1 = 0.0459, wR2 = 0.1182 [5855] |
| R indices (all data) | R1 = 0.0556, wR2 = 0.1259 |
| Absolute structure parameter | -0.04(6) |
| Largest diff. peak and hole | 0.505 and -0.260 $eÅ^{-3}$ |

Remarks Disorder: C(1)-C(6):C(1A)-C(6A) 83:17%
C(7)-C(12):C(7A)-C(12A) 84:16%
Cl(1):Cl(1A),O(4) 92:8%

**Table 13.** Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$). U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | 1004(1) | 4760(1) | 8700(1) | 29(1) |
| Cl(1) | -1315(1) | 2648(1) | 9438(1) | 40(1) |
| Cl(1A) | -227(12) | 2110(6) | 9600(6) | 62(3) |
| O(4) | -1680(3) | 2370(7) | 9020(5) | 310(6) |
| N(1) | 1672(2) | 5185(1) | 9524(1) | 29(1) |
| N(2) | -2232(2) | 3429(1) | 8052(2) | 49(1) |
| O(1) | 1843(2) | 5089(1) | 8015(1) | 41(1) |
| O(2) | -571(2) | 4850(1) | 8699(1) | 45(1) |
| O(3) | -3250(2) | 3557(1) | 8515(1) | 62(1) |
| C(1) | 3213(3) | 5488(2) | 9639(2) | 28(1) |
| C(2) | 3581(3) | 6282(2) | 9148(2) | 32(1) |
| C(3) | 5166(7) | 6610(4) | 9379(4) | 39(1) |
| C(4) | 6319(3) | 5921(2) | 9275(2) | 40(1) |
| C(5) | 5940(3) | 5127(2) | 9763(2) | 35(1) |
| C(6) | 4389(3) | 4808(2) | 9512(3) | 33(1) |
| C(1A) | 3314(17) | 5412(9) | 9354(10) | 28(4) |
| C(2A) | 3443(15) | 6362(8) | 9529(11) | 33(3) |
| C(3A) | 4890(3) | 6600(2) | 9330(2) | 35(6) |
| C(4A) | 6251(17) | 6141(9) | 9733(10) | 44(4) |
| C(5A) | 6005(19) | 5294(10) | 9522(11) | 34(4) |
| C(6A) | 4480(2) | 4890(12) | 9763(11) | 33(5) |
| C(7) | 810(8) | 5149(4) | 10313(3) | 45(2) |
| C(8) | 1417(3) | 4569(2) | 10952(2) | 34(1) |
| C(9) | 305(6) | 4495(4) | 11683(3) | 41(1) |
| C(10) | -121(4) | 5349(2) | 12015(2) | 50(1) |
| C(11) | -742(6) | 5929(3) | 11348(3) | 47(1) |
| C(12) | 316(5) | 5996(3) | 10614(2) | 36(1) |

| | | | | |
|---|---|---|---|---|
| C(7A) | 658(19) | 5077(11) | 10223(12) | 4(2) |
| C(8A) | 712(16) | 4353(8) | 10732(7) | 27(3) |
| C(9A) | 490(3) | 4486(16) | 11552(15) | 29(5) |
| C(10A) | -885(19) | 5161(9) | 11731(9) | 39(3) |
| C(11A) | -330(3) | 5987(18) | 11324(19) | 44(6) |
| C(12A) | 50(2) | 5860(13) | 10474(13) | 29(5) |
| C(13) | 1394(2) | 3652(1) | 8750(1) | 31(1) |
| C(14) | 551(2) | 3108(1) | 8132(1) | 31(1) |
| C(15) | 458(3) | 3476(2) | 7240(1) | 42(1) |
| C(16) | 125(4) | 2695(2) | 6700(1) | 50(1) |
| C(17) | 129(3) | 1970(1) | 7320(1) | 41(1) |
| C(18) | -1280(3) | 2015(2) | 7832(2) | 46(1) |
| C(19) | -1043(3) | 2827(1) | 8365(1) | 37(1) |
| C(20) | 1 349(3) | 2237(1) | 7941(1) | 38(1) |
| C(21) | 1507(3) | 1626(2) | 8671(1) | 44(1) |
| C(22) | 2899(3) | 2330(2) | 7563(2) | 50(1) |

**Table 14**. Bond lengths [Å] and angles [deg].

| | |
|---|---|
| S(1)-O(2) | 1.4191(16) |
| S(1)-O(1) | 1.4400(16) |
| S(1)-N(1) | 1.6134(16) |
| S(1)-C(13) | 1.7922(19) |
| Cl(1)-C(19) | 1.781(2) |
| Cl(1A)-O(4) | 1.66(2) |
| O(4)-C(19) | 1.41(2) |
| N(1)-C(7A) | 1.463(18) |
| N(1)-C(1) | 1.474(3) |
| N(1)-C(7) | 1.497(6) |
| N(1)-C(1A) | 1.541(15) |
| N(2)-O(3) | 1.200(3) |
| N(2)-C(19) | 1.519(3) |
| C(1)-C(6) | 1.522(4) |
| C(1)-C(2) | 1.527(4) |
| C(2)-C(3) | 1.559(7) |
| C(3)-C(4) | 1.513(8) |

| | |
|---|---|
| C(4)-C(5) | 1.525(5) |
| C(5)-C(6) | 1.534(4) |
| C(1A)-C(6A) | 1.49(2) |
| C(1A)-C(2A) | 1.54(2) |
| C(2A)-C(3A) | 1.40(3) |
| C(3A)-C(4A) | 1.57(4) |
| C(4A)-C(5A) | 1.40(2) |
| C(5A)-C(6A) | 1.56(3) |
| C(7)-C(8) | 1.488(7) |
| C(7)-C(12) | 1.496(7) |
| C(8)-C(9) | 1.555(5) |
| C(9)-C(10) | 1.506(7) |
| C(10)-C(11) | 1.526(6) |
| C(11)-C(12) | 1.526(5) |
| C(7A)-C(8A) | 1.42(2) |
| C(7A)-C(12A) | 1.42(3) |
| C(8A)-C(9A) | 1.36(3) |
| C(9A)-C(10A) | 1.66(3) |
| C(10A)-C(11A) | 1.55(3) |
| C(11A)-C(12A) | 1.43(4) |
| C(13)-C(14) | 1.523(3) |
| C(14)-C(19) | 1.544(3) |
| C(14)-C(15) | 1.563(3) |
| C(14)-C(20) | 1.586(3) |
| C(15)-C(16) | 1.546(3) |
| C(16)-C(17) | 1.527(3) |
| C(17)-C(18) | 1.514(4) |
| C(17)-C(20) | 1.546(3) |
| C(18)-C(19) | 1.566(3) |
| C(20)-C(22) | 1.526(3) |
| C(20)-C(21) | 1.537(3) |
| O(2)-S(1)-O(1) | 118.81(11) |
| O(2)-S(1)-N(1) | 109.13(10) |
| O(1)-S(1)-N(1) | 107.16(9) |
| O(2)-S(1)-C(13) | 107.01(10) |
| O(1)-S(1)-C(13) | 106.76(10) |

| | |
|---|---|
| N(1)-S(1)-C(13) | 107.47(9) |
| C(19)-O(4)-Cl(1A) | 103.5(15) |
| C(7A)-N(1)-C(1) | 121.5(8) |
| C(7A)-N(1)-C(7) | 8.8(9) |
| C(1)-N(1)-C(7) | 112.8(3) |
| C(7A)-N(1)-C(1A) | 139.5(10) |
| C(1)-N(1)-C(1A) | 18.4(5) |
| C(7)-N(1)-C(1A) | 131.0(7) |
| C(7A)-N(1)-S(1) | 111.3(8) |
| C(1)-N(1)-S(1) | 126.06(19) |
| C(7)-N(1)-S(1) | 120.1(3) |
| C(1A)-N(1)-S(1) | 107.7(6) |
| O(3)-N(2)-C(19) | 115.5(2) |
| N(1)-C(1)-C(6) | 113.7(2) |
| N(1)-C(1)-C(2) | 113.8(2) |
| C(6)-C(1)-C(2) | 111.3(3) |
| C(1)-C(2)-C(3) | 110.2(3) |
| C(4)-C(3)-C(2) | 110.8(4) |
| C(3)-C(4)-C(5) | 112.7(3) |
| C(4)-C(5)-C(6) | 109.6(3) |
| C(1)-C(6)-C(5) | 111.0(3) |
| C(6A)-C(1A)-C(2A) | 114.1(14) |
| C(6A)-C(1A)-N(1) | 117.6(12) |
| C(2A)-C(1A)-N(1) | 105.5(11) |
| C(3A)-C(2A)-C(1A) | 107.2(19) |
| C(2A)-C(3A)-C(4A) | 120(2) |
| C(5A)-C(4A)-C(3A) | 103.0(18) |
| C(4A)-C(5A)-C(6A) | 118.1(15) |
| C(1A)-C(6A)-C(5A) | 106.0(15) |
| C(8)-C(7)-C(12) | 115.8(4) |
| C(8)-C(7)-N(1) | 115.5(4) |
| C(12)-C(7)-N(1) | 113.5(4) |
| C(7)-C(8)-C(9) | 110.1(4) |
| C(10)-C(9)-C(8) | 111.6(3) |
| C(9)-C(10)-C(11) | 112.4(3) |
| C(10)-C(11)-C(12) | 111.7(3) |

| | |
|---|---|
| C(7)-C(12)-C(11) | 112.1(4) |
| C(8A)-C(7A)-C(12A) | 123.7(16) |
| C(8A)-C(7A)-N(1) | 121.8(13) |
| C(12A)-C(7A)-N(1) | 111.2(15) |
| C(9A)-C(8A)-C(7A) | 116.2(16) |
| C(8A)-C(9A)-C(10A) | 112.2(18) |
| C(11A)-C(10A)-C(9A) | 103.2(17) |
| C(12A)-C(11A)-C(10A) | 112(2) |
| C(7A)-C(12A)-C(11A) | 119(2) |
| C(14)-C(13)-S(1) | 115.34(13) |
| C(13)-C(14)-C(19) | 117.47(17) |
| C(13)-C(14)-C(15) | 115.21(17) |
| C(19)-C(14)-C(15) | 106.55(17) |
| C(13)-C(14)-C(20) | 113.47(17) |
| C(19)-C(14)-C(20) | 102.32(16) |
| C(15)-C(14)-C(20) | 99.62(16) |
| C(16)-C(15)-C(14) | 103.70(17) |
| C(17)-C(16)-C(15) | 103.25(17) |
| C(18)-C(17)-C(16) | 108.9(2) |
| C(18)-C(17)-C(20) | 102.70(17) |
| C(16)-C(17)-C(20) | 102.98(19) |
| C(17)-C(18)-C(19) | 103.20(19) |
| O(4)-C(19)-N(2) | 107(3) |
| O(4)-C(19)-C(14) | 135.3(10) |
| N(2)-C(19)-C(14) | 112.71(18) |
| O(4)-C(19)-C(18) | 86(5) |
| N(2)-C(19)-C(18) | 103.67(18) |
| C(14)-C(19)-C(18) | 103.20(18) |
| O(4)-C(19)-Cl(1) | 29(5) |
| N(2)-C(19)-Cl(1) | 109.31(16) |
| C(14)-C(19)-Cl(1) | 114.36(14) |
| C(18)-C(19)-Cl(1) | 113.02(16) |
| C(22)-C(20)-C(21) | 106.7(2) |
| C(22)-C(20)-C(17) | 114.12(19) |
| C(21)-C(20)-C(17) | 113.26(19) |
| C(22)-C(20)-C(14) | 113.92(18) |

| | |
|---|---|
| C(21)-C(20)-C(14) | 116.04(17) |
| C(17)-C(20)-C(14) | 92.72(17) |

Symmetry transformations used to generate equivalent atoms:

**Table 15.** Anisotropic displacement parameters ($Å^2x10^3$).

The anisotropic displacement factor exponent takes the form:

$-2\pi^2[ h^2a^{*2}U11 + ... + 2hka^*b^*U12]$

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| S(1) | 31(1) | 28(1) | 28(1) | -1(1) | -5(1) | 3(1) |
| Cl(1) | 40(1) | 44(1) | 34(1) | -2(1) | 7(1) | -4(1) |
| N(1) | 26(1) | 33(1) | 27(1) | 0(1) | 0(1) | -5(1) |
| N(2) | 38(1) | 50(1) | 60(1) | -9(1) | -16(1) | 3(1) |
| O(1) | 63(1) | 34(1) | 27(1) | 1(1) | 3(1) | 2(1) |
| O(2) | 30(1) | 46(1) | 60(1) | -13(1) | -13(1) | 6(1) |
| O(3) | 36(1) | 67(1) | 83(1) | -12(1) | -6(1) | 6(1) |
| C(1) | 26(1) | 30(1) | 28(1) | 0(1) | 2(1) | -5(1) |
| C(2) | 36(1) | 27(1) | 34(2) | 1(1) | 4(1) | -4(1) |
| C(3) | 37(3) | 37(2) | 4 3(2) | -5(1) | 6(2) | -20(2) |
| C(4) | 31(1) | 45(2) | 44(2) | -3(1) | 6(1) | -11(1) |
| C(5) | 29(1) | 38(2) | 38(2) | 6(1) | -5(1) | -3(1) |
| C(6) | 27(1) | 34(1) | 37(2) | 4(1) | -1(1) | -3(1) |
| C(7) | 57(3) | 47(2) | 31(2) | -5(2) | 3(2) | -2(2) |
| C(8) | 34(1) | 37(1) | 32(1) | 3(1) | -2(1) | -5(1) |
| C(9) | 34(2) | 58(2) | 32(2) | 9(2) | 10(1) | -9(1) |
| C(10) | 44(2) | 72(2) | 33(1) | 6(1) | 13(1) | 9(2) |
| C(11) | 44(2) | 62(2) | 34(2) | -1(1) | 12(2) | 14(2) |
| C(12) | 35(2) | 40(2) | 33(2) | -1(1) | 3(1) | 5(1) |
| C(13) | 36(1) | 27(1) | 29(1) | 2(1) | -5(1) | 2(1) |
| C(14) | 39(1) | 29(1) | 24(1) | 1(1) | -4(1) | -2(1) |
| C(15) | 59(2) | 40(1) | 26(1) | 4(1) | -6(1) | 0(1) |
| C(16) | 71(2) | 48(1) | 32(1) | -2(1) | -9(1) | -4(1) |
| C(17) | 57(1) | 37(1) | 31(1) | -8(1) | 1(1) | -6(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(18) | 51(1) | 43(1) | 43(1) | -10(1) | -3(1) | -9(1) |
| C(19) | 37(1) | 40(1) | 35(1) | -2(1) | -4(1) | -1(1) |
| C(20) | 45(1) | 35(1) | 33(1) | -5(1) | 3(1) | 2(1) |
| C(21) | 55(1) | 37(1) | 40(1) | 4(1) | 3(1) | 10(1) |
| C(22) | 54(2) | 47(1) | 50(1) | -5(1) | 14(1) | 8(1) |

**Table 16**. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 3288 | 5654 | 10232 | 34 |
| H(2A) | 2831 | 6725 | 9267 | 39 |
| H(2B) | 3542 | 6155 | 8551 | 39 |
| H(3A) | 5427 | 7095 | 9023 | 47 |
| H(3B) | 5165 | 6806 | 9958 | 47 |
| H(4A) | 7302 | 6136 | 9457 | 48 |
| H(4B) | 6398 | 5775 | 8684 | 48 |
| H(5A) | 5953 | 5254 | 10360 | 42 |
| H(5B) | 6695 | 4686 | 9653 | 42 |
| H(6A) | 4405 | 4638 | 8925 | 39 |
| H(6B) | 4131 | 4305 | 9844 | 39 |
| H(1B) | 3466 | 5342 | 8748 | 34 |
| H(2C) | 2714 | 6680 | 9192 | 39 |
| H(2D) | 3241 | 6478 | 10118 | 39 |
| H(3A1) | 4991 | 7212 | 9458 | 42 |
| H(3A2) | 5002 | 6548 | 8723 | 42 |
| H(4C) | 7208 | 6347 | 9505 | 53 |
| H(4D) | 6254 | 6218 | 10338 | 53 |
| H(5A1) | 6806 | 4954 | 9778 | 40 |
| H(5A2) | 6121 | 5242 | 8918 | 40 |
| H(6C) | 4434 | 4299 | 9568 | 40 |
| H(6D) | 4351 | 4896 | 10368 | 40 |
| H(7A) | -146 | 4872 | 10147 | 54 |
| H(8A) | 2385 | 4787 | 11154 | 41 |
| H(8B) | 1588 | 4005 | 10708 | 41 |
| H(9A) | -604 | 4196 | 11496 | 49 |

| | | | | |
|---|---|---|---|---|
| H(9B) | 766 | 4157 | 12128 | 49 |
| H(10A) | 767 | 5616 | 12266 | 60 |
| H(10B) | -880 | 5277 | 12452 | 60 |
| H(11A) | -908 | 6497 | 11583 | 56 |
| H(11B) | -1717 | 5709 | 11158 | 56 |
| H(12A) | -192 | 6299 | 10161 | 43 |
| H(12B) | 1202 | 6330 | 10776 | 43 |
| H(7B) | -223 | 4893 | 9890 | 4 |
| H(8C) | -54 | 3950 | 10537 | 33 |
| H(8D) | 1697 | 4081 | 10658 | 33 |
| H(9C) | 1425 | 4708 | 11798 | 34 |
| H(9D) | 263 | 3942 | 11822 | 34 |
| H(10C) | -1827 | 4967 | 11476 | 47 |
| H(10D) | -1045 | 5239 | 12330 | 47 |
| H(11C) | -1110 | 6424 | 11366 | 53 |
| H(11D) | 566 | 6193 | 11623 | 53 |
| H(12C) | -871 | 5955 | 10148 | 34 |
| H(12D) | 764 | 6307 | 10316 | 34 |
| H(13A) | 2477 | 3568 | 8663 | 37 |
| H(13B) | 1155 | 3450 | 9312 | 37 |
| H(15A) | -352 | 3898 | 7196 | 50 |
| H(15B) | 1412 | 3743 | 7078 | 50 |
| H(16A) | -857 | 2747 | 6426 | 60 |
| H(16B) | 906 | 2615 | 6276 | 60 |
| H(17A) | 307 | 1405 | 7065 | 50 |
| H(18A) | -1388 | 1508 | 8184 | 55 |
| H(18B) | -2174 | 2069 | 7477 | 55 |
| H(21A) | 2011 | 1111 | 8487 | 66 |
| H(21B) | 515 | 1484 | 8883 | 66 |
| H(21C) | 2094 | 1894 | 9107 | 66 |
| H(22A) | 3324 | 1770 | 7463 | 75 |
| H(22B) | 3544 | 2642 | 7943 | 75 |
| H(22C) | 2825 | 2637 | 7041 | 75 |

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