Studies towards the Stereoselective Electrophilic Amination of Carbanions

by

Sorin V. Filip, M. Sc.

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
Chairman of the Examination Committee: Prof. Dr. L. Weber

1st Examiner: Prof. Dr. N. Sewald

2nd Examiner: Prof. Dr. J. Mattay

Secretary: Dr. A. Brockhincke

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 Stemmer, 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>chemical shift (NMR)</td>
</tr>
<tr>
<td>ν~</td>
<td>Wave number (IR)</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>arom.</td>
<td>aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>br.</td>
<td>broad (NMR)</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>Butyl lithium</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionisation (MS)</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chlorobenzoic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (NMR)</td>
</tr>
<tr>
<td>d.e.</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact Ionisation (MS)</td>
</tr>
<tr>
<td>e.r.</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphorous triamide</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (NMR)</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared (-spectroscopy)</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (NMR)</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyldisilazanide</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazanide</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
</tbody>
</table>
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)
'iPr  - iso-Propyl
q  - Quartet (NMR)
Rf  - 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  - Tetramethyl ethylenediamine
TMS  - Tetramethylsilane
TMSCl  - Trimethylsilyl chloride
Ref.  - Reference
tR  - Retention time
TLC  - Thin Layer Chromatography
Ts  - Tosyl
p-Tol  - para-Tolyl
# Table of contents

1. **GENERAL PART** .................................................................................................................. 1
   1.1 INTRODUCTION ................................................................................................................. 1
   1.2 ELECTROPHILIC AMINATION ........................................................................................ 1
      1.2.1 Electrophilic Amination using Chiral Amination Reagents ........................................ 3
         1.2.1.1 Azides ................................................................................................................ 3
         1.2.1.2 Azodicarboxylates and Azodicarboxamides ...................................................... 5
         1.2.1.3 α-Chloronitroso Compounds ........................................................................... 10
         1.2.1.4 1,3,2-Oxazaphospholidine and 1,3,2-Oxazaphosphinane Derivatives .............. 14
         1.2.1.5 Oxaziridines ....................................................................................................... 15
         1.2.1.6 Nitro Derivatives ................................................................................................. 18
   2. **RESEARCH OBJECTIVE** ................................................................................................. 21
   3. **RESULTS AND DISCUSSION** ...................................................................................... 22
      3.1 SYNTHESIS OF THE ENANTIOMERICALLY PURE AMINATION REAGENTS .............. 22
         3.1.1 Synthesis of the Enantiomerically Pure N,O-Disubstituted Hydroxylamines Derivatives .......................................................................................................................... 22
            3.1.1.1 Stereoselective Synthesis of (1R,4S)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene Hydrochloride ............................................................................................................. 23
            3.1.1.2 Synthesis of O-Substituted N-[10-(1R,5R)-Pin-2-enyl]hydroxylamines ............ 28
         3.1.2 Stereoselective Synthesis of the Enantiomerically Pure α-Chloronitroso Compounds .............................................................................................................................. 31
         3.1.3 Stereoselective Synthesis of 1-Deoxy-2,3:5,6-di-O-isopropylidene-1-nitro-α-D- mannofuranose ................................................................................................................. 34
      3.2 STUDIES TOWARDS THE ELECTROPHILIC AMINATION OF CARBANIONS USING ENANTIOMERICALLY PURE NITRENIOIDS ............................................................................ 36
      3.3 STUDIES TOWARDS THE ELECTROPHILIC AMINATION OF ENOLATES AND ALLEY ORGANOMETALLIC REAGENTS USING α-CHLORONITROSO REAGENTS .................. 52
      3.4 STUDIES TOWARDS THE ELECTROPHILIC AMINATION OF ALLEY ORGANOMETALLIC REAGENTS USING 1-DEOXY-2,3:5,6-DI-O-ISOPROPYLIDENE-1-NITRO-α-D-MANNO- FURANOSE ................................................................................................................................. 69
   4. **SUMMARY** ..................................................................................................................... 78
   5. **EXPERIMENTAL SECTION** .......................................................................................... 82
      5.1 SOLVENTS, APPARATUS AND METHODS .................................................................... 82
5.2 SYNTHESIS OF THE ENANTIOMERICALLY PURE AMINATION REAGENTS .......................87

5.2.1 Synthesis of 2,3,5,6-Di-O-isopropylidene-1-C-nitroso-\(\alpha\)-D-mannofuranosyl-
chloride ................................................................................................................................87

5.2.2 Synthesis of \((1R,4S)-3\)-Aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride ...............91

5.2.3 Synthesis of the Enantiomerically Pure \(N,O\)-Disubstituted Hydroxylamines ..........92

5.2.4 Synthesis of \((+)-N,N\)-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide.102

5.2.5 Synthesis of 1-Deoxy-2,3:5,6-di-O-isopropylidene-1-nitro-\(\alpha\)-D-mannofuranose...106

5.3 ELECTROPHILIC AMINATION OF CARBANIONS USING ENANTIOMERICALLY PURE

NITRENIOIDS ...........................................................................................................................107

5.4 ELECTROPHILIC AMINATION OF ENOLATES AND ALLYL ORGANOMETALLIC

REAGENTS USING \(\alpha\)-CHLORONITROSO REAGENTS ...........................................................111

5.5 ELECTROPHILIC AMINATION OF ALLYL ORGANOMETALLIC REAGENTS USING

1-Deoxy-2,3:5,6-di-O-isopropylidene-1-nitro-\(\alpha\)-D-mannofuranose......................121

6. APPENDIX ...................................................................................................... 127
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, \(\alpha\)-amino acids, \(\alpha\)-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).

\[ X-\overset{\ddots}{C}- \overset{\ddots}{C} + HNR'R'' \rightarrow \overset{\ddots}{C}-NR'R'' \]
\[ \vdots + YNR'R'' \]  

**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'R₂N-Y derivative (Scheme 2).[^3]

![Scheme 2: “Umpolung” methodology for the direct formation of carbon-nitrogen bonds.](image)

The species R-Br and R-MgBr may be considered as suppliers of \( [R^{\delta+}] \) and \( [R^{\delta-}] \), respectively, where HNR'R₂ and R'R₂N-Y are \( [^{\delta-}NR'R_2] \) and \( [^{\delta+}NR'R_2] \) synths.

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'R₂N-Y is the attachment of a good leaving group Y to the R'R₂N 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 H₃N⁺ 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'R₂N-Y.](image)

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 \( \alpha \)-hydrazono or \( \alpha \)-hydrazido compounds, respectively, which are hydrogenated to \( \alpha \)-amino compounds.
3. Electrophilic Amination using Chiral Amination Reagents

Different examples of stereoselective electrophilic amination reactions, either in the presence of a chiral catalyst or starting from substrates bearing a chiral center, have been reported in the literature. In contrast, there are only few efficient methods for reagent-controlled stereoselective electrophilic amination. 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. Evans et al. developed an optimized method starting from substrates bearing a chiral center, which allows the introduction of the \([\text{NH}_2^+\)] 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, chiral cyclic imide enolates, chiral lactone enolates and chiral auxiliary-based enolates.

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. 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 via reaction with triphosgene and sodium azide (Scheme 3).

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

The authors 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 1H and 13C 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.\(^{1,2,33}\)

\[ \begin{align*}
\text{31} & \quad \text{O}^\text{Bu} \quad N \quad N \quad \text{O}^\text{Bu} \\
\text{32} & \quad \text{O}^\text{Bn} \quad N \quad N \quad \text{O}^\text{Bn}
\end{align*} \]

**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 \textit{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).

\[ \begin{align*}
\text{RO H} & \xrightarrow{\text{COCl}_2} \text{RO Cl} \\
\text{N}_2\text{H}_4 & \xrightarrow{\text{NBS, Py}} \text{ROOC} \quad \text{NH} \quad \text{COOR}
\end{align*} \]

**Scheme 7:** Synthesis of chiral dialkylazodicarboxylates as reported by Vederas \textit{et al.}\(^{47}\)

Ester enolates generated by treatment of the corresponding esters with 1 equivalent of LiHMDS at \(-78^\circ\text{C}\) are aminated by the chiral dialkylazodicarboxylates 33-35 at \(-78^\circ\text{C}\) (Scheme 8).

The reaction displays moderate yields (13-87%) and little (if any) stereoselectivity (d.e. 33%, 33, \(R^1 = \text{Ph}, X = \text{OEt}\)). 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 \(\alpha\)-hydrazino acids could not be obtained in reasonable yield. However, the isobornyl analogues are readily hydrolyzed.

\[ \begin{align*}
33 & \quad R = \text{menthyl} \\
34 & \quad R = \text{bornyl} \\
35 & \quad R = \text{isobornyl}
\end{align*} \]
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).

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 ¹H 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. 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 \(\text{SnCl}_4\), and the corresponding allylic aminated product was obtained in good yield (70-88\%) and with up to 42\% d.e. (Scheme 10).

![Diagram of Scheme 10](image)

**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 a more successful attempt to perform stereoselective aza-ene reactions with alkenes. Chiral di-(\(-)-(1R,2S)\)-2-phenyl-1-cyclohexyl azodicarboxylate \(43\) can easily be synthesized starting from \((-)-(1R,2S)\)-2-phenyl-1-cyclohexanol, and aza-ene reactions of \(43\) with cyclohexene, cyclopentene, \(\text{trans}-3\)-hexene and \(\text{trans}-4\)-octene in the presence of \(\text{SnCl}_4\) were carried out (Scheme 11).

![Diagram of Scheme 11](image)

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

The new amination reagent affords much higher levels of asymmetric induction in the Lewis acid mediated aza-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. 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 SnCl₄ 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).  

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., 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).

![Scheme 13: Synthesis of the chiral azodicarboxamide 51 containing a bridging binaphtyl moiety.](image)

Achiral oxazolidonones 52 can be aminated at -78°C using the standard procedure. Only one diastereomer can be detected for the products using ¹H 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.

![Scheme 14: Stereoselective electrophilic amination of achiral oxazolidonones with the chiral azodicarboxamide 51.](image)

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. Some nitroso compounds which have been applied in ene reactions are depicted in
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. 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.

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, azaoxy 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. 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.

Schenk et al. 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. 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\textsuperscript{11,12,68-70} concerning the enantioselective amination of chiral enolates using 1-chloro-1-nitroso cyclohexane \textsuperscript{12}, Oppolzer \textit{et al.}\textsuperscript{13} introduced the chiral \(\alpha\)-chloronitroso reagents \textsuperscript{73} and \textsuperscript{74} and reported the enantioselective amination of prochiral ketone enolates (Figure 6).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure6.png}
\caption{Chiral \(\alpha\)-chloronitroso camphor sulfonamide derivatives introduced by Oppolzer.\textsuperscript{13}}
\end{figure}

Deprotonation of propiophenone \textsuperscript{75}a (R = Ph) with lithium hexamethyldisilazanide, transmetallation of the lithium enolate with \(\text{ZnCl}_2\), and reaction of the zinc enolate \textsuperscript{76} (R = Ph) with the nitroso reagent \textsuperscript{74} gives exclusively the nitrone \textsuperscript{77} (R = Ph). The configuration at \(\alpha\)-C in \textsuperscript{78} (R = Ph) was assigned by conversion to (-)-norephedrine \textsuperscript{80} (R = Ph). After hydrolysis of crude \textsuperscript{77} (R = Ph), evaporation of the aqueous phase, \textit{erythro}-selective reduction of the \(\alpha\)-hydroxylamino ketone hydrochloride \textsuperscript{78} with sodium borohydride in methanol to \textsuperscript{79}, followed by reductive cleavage of the N-O bond affords (-)-norephedrine \textsuperscript{80} (R = Ph) in 68\% overall yield (\textit{erythro}/\textit{threo} = 95:5, 96\% e.e.).

\begin{scheme}
\centering
\includegraphics[width=0.8\textwidth]{scheme17.png}
\caption{Stereoselective electrophilic amination of ketone enolates using the chiral \(\alpha\)-chloronitroso reagent \textsuperscript{74}.}
\end{scheme}
In the same article, Oppolzer et al.\textsuperscript{13} presented further examples for the preparation of diastereoisomERIC AND enantiomerically pure β-aminols.

Up-to-date, there is only one more report\textsuperscript{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).

\begin{center}
\textbf{Scheme 18:} Stereoselective electrophilic amination of the lithium enolate of azetidin-2-one 81 using the chiral α-chloronitroso reagent 74.
\end{center}

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

In 1982 Boche and Schrott\textsuperscript{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).

\begin{center}
\textbf{Figure 7:} Enantiomerically pure 1,3,2-oxazaphospholidine 83 and 1,3,2-oxazaphosphinane 84 introduced by Boche and Schrott.\textsuperscript{72}
\end{center}

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).

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. 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, 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. 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 \( \textit{N} to \textit{N} \) 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.](image)

The attempts to synthesize oxaziridines allowing the direct transfer of a \( \textit{N} \)-protected group to nucleophilic centers led to the synthesis of \( \textit{N} \)-Moc and \( \textit{N} \)-Boc oxaziridines. It has been mentioned\(^7^4\) 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 \( \textit{N} \)-Moc and the \( \textit{N} \)-Boc fragments under mild conditions to ketone, ester and amide lithium enolates.\(^2^4\) \( \textit{N} \)-Boc protected \( \alpha \)-amino ketones of moderate enantiomeric purity can be synthesized\(^7^5\) by 93-mediated electrophilic amination of an enantiopure \( \alpha \)-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 \textit{et al.}\(^7^6\) 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 \( \mu \text{-CPBA/} \text{BuLi} \) and proved to be highly diastereoselective with respect to facial attack on the imine carbon. The \( ^1 \text{H NMR} \) spectrum of 99 indicated a 9:1 mixture of \textit{trans} and \textit{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 \( \alpha \)-amino compounds 101 in moderate yields (49-62%) and low diastereoselectivities (5-21%) (Scheme 24). The authors...
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.

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.\textsuperscript{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\textsuperscript{77,78} and useful spin trapping reagents,\textsuperscript{78-81} they enlarged the studies concerning the reaction between nitroalkanes, and organomagnesium and lithium reagents\textsuperscript{16,18,21,22} and provided a relatively good method for the synthesis of nitrones (Scheme 25).

Scheme 25: Nitrone synthesis by the reaction between nitro derivatives and organomagnesium 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).

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

Furthermore, the same group\textsuperscript{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).

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.\textsuperscript{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. 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, rhodium and other transition metals (Ir, Ru, Cr, Mo, Fe, Ni, Pt, Co) have been used for such purpose.

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

![Figure 8](image-url) 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 (1R,4S)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene Hydrochloride

The hetero-Diels-Alder cycloaddition of C-nitroso compounds with dienes is a reliable process for the formation of 3,6-dihydro-2H-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. 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 with α-chloronitroso compounds is attractive, since in the presence of a nucleophilic solvent the initial cycloadduct can undergo solvolysis to liberate the dihydrooxazine 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 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-
Results and Discussion

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 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
Results and Discussion

Comparison of the measured optical rotation $[\alpha]_D^{25}=+25.04$ (c = 1.02 in acetone) with that reported in the literature $[\alpha]_D^{20}=+25$ (c = 1.0 in acetone). 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$_2$O = 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. The assignment 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.

\[ \text{Figure 9: } \text{Z and E-stereoisomers of 2,3:5,6-di-O-isopropylidene-D-mannose-oxime 134.} \]

Oxidation of the oxime 134 with sodium metaperiodate in the presence of sodium acetate gives N-hydroxy-2,3:5,6-di-O-isopropylidene-$\alpha$-D-mannoimido-1,4-lactone 135 in 74% yield. 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. 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-$d_6$ 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. for the Z-isomer of 135. Concerning the reaction mechanism, it has been noted 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).
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. 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. The chlorination agent, i.e. BuOCl, is prepared from tert-butanol and an aqueous solution of sodium hypochlorite, 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. 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).

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 Et₂O-EtOH gives the (1R,4S)-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 (1R,4S)-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 reactions⁵,⁶,⁴,⁶⁴,⁶⁶,¹⁰⁹-¹¹⁵ and involve CHCl₃-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 ¹H 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 Et₂O 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-(1R,5R)-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.

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

(1R,5R)-(−)-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).

Scheme 33: Synthesis of the enantiomerically pure hydroxylamines 147 and 148.
O-Methyl-(1R,5R)-(-)-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-(1R,5R)-(-)-myrtenal oxime 145.](image)

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 an \(E:Z\) ratio of 54:46 for Et-CH=N-OMe, to 74:26 for Cy-CH=N-OMe and 100:0 for tBu-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 (\(\cdot\)).\(145\).

O-Benzyl-(1R,5R)-(-)-myrtenal oxime \(146\) is obtained following the same procedure, with the difference that due to a higher boiling point (125 °C, 0.26 mbar) compared to \(145\) (53 °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\(_3\)CN 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-((1R,5R)-pin-2-enyl]-O-trimethylsilyl hydroxylamine 151 and (-)-N-[10-((1R,5R)-pin-2-enyl]-O-tosyl hydroxylamine 152 can be synthesized starting from (1R,5R)-(−)-myrtenal 142 via (1R,5R)-(−)-myrtenoxime 149 and (-)-N-[10-((1R,5R)-pin-2-enyl]-hydroxylamine hydrochloride 150 (Scheme 34).

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

The synthesis of (1R,5R)-(−)-myrtenoxime 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$_3$CN 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$_3$CN at pH 2-3, work-up at pH 9 and further extraction of product from Et$_2$O 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.
Results and Discussion

(-)-N-[10-(1R,5R)-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\textsuperscript{121,122} (Table 1).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%) of 151</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imidazole</td>
<td>n-Pentane</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Py</td>
<td>n-Pentane</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Et\textsubscript{3}N</td>
<td>n-Pentane</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{3}N</td>
<td>Et\textsubscript{2}O</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>Et\textsubscript{3}N</td>
<td>n-Hexane</td>
<td>77</td>
</tr>
</tbody>
</table>

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 \textsuperscript{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 \textsuperscript{13}C NMR spectrum corresponding to the C atoms of the same functional group.

Using the same procedure, (-)-N-[10-(1R,5R)-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 sulfonyleoxy absorption band at 1164 cm\textsuperscript{-1} and the appearance of the AA'BB' signals at 7.78 ppm (Ph-\textit{ortho}) and 7.36 ppm (Ph-\textit{meta}) in the \textsuperscript{1}H NMR spectrum confirms the tosylation of 150.

3.1.2 Stereoselective Synthesis of the Enantiomerically Pure \(\alpha\)-Chloronitroso Compounds

For the present studies concerning the stereoselective amination of ester enolates and allyl organometallic reagents, the enantiomerically pure \(\alpha\)-chloronitroso compounds 65 and 74 have also been chosen as [NH\textsubscript{2}\textsuperscript{+}] synthons. The synthesis of 2,3:5,6-di-O-isopropylidene-1-C-nitroso-\(\alpha\)-D-mannofuranosylechloride 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).

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-NH$_2$·HCl, KOH, EtOH, 61% yield) and to that reported in the literature,13 since it requires 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$_2$O$^{123-125}$ or DCM,$^{126-128}$ NaOCl in dioxane-water$^{129}$ or with 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 BuOCl (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 BuOCl solution plays an important role with respect to yield and product purity, most probably due to the interference of BuOH. Using a 75% BuOCl/ BuOH solution a yield of 85% is observed, while with a 19.5% BuOCl/ BuOH
solution the yield drops 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).

![Mass spectrum (ESI, positive ion mode) of 74](image)

**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(C₂₂H₃₇ClN₂O₃S)+Na]⁺, accompanied by a peak at m/z 469.2 which has been assigned to [M(C₂₂H₃₇ClN₂O₃S)+Na]⁺. The ion peaks at m/z 911.2 and m/z 913.2 correspond to [2M(Cl)+Na]⁺ and [2M(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.

![ORTEP representation of 74](image)

**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 CMe2 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 [NH2]+ 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 CF3COOOH.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 (CF3CO)2O/H2O2/CH3CN134, m-CPBA/O3/DCM135 or Py/Cr2O7/H2N-OH/H2O2/DCM136 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 NO2 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 \(^1\)H 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.

\(^{3}J_{2,3} = 5.6\) 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, \(^{3}J_{2,3} = 6.2\) Hz) (Figure 15).

Figure 15: \(^{1}\)H NMR spectrum of 1-deoxy-2,3:5,6-di-O-isopropylidene-1-nitro-α-D-mannofuranose 156 (a) and of 156+catalytic amounts of LiOCH\(_3\)/CD\(_3\)OD (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 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 when he studied the reaction of phenyllithium with nitrosobenzene (Scheme 37).

\[
\begin{align*}
\text{Ph} - \text{N} = \text{O} & \quad \text{PhLi} \\
\text{Ph} & \quad \text{Li} & \quad \text{Ph} & \quad \text{N} & \quad \text{OPh} \\
157 & & 158 & & 159 & & 160
\end{align*}
\]

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

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 and they have a long history in organic chemistry although their nitrenoid properties have been recognized only in recent years.

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{M} \\
\text{M} = \text{Li, Na, K, MgX, ZnX, etc.} \\
\text{Y} = \text{Hal, OR or other leaving groups} \\
\text{R} = \text{alkyl, aryl or other substituents}
\end{align*}
\]

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

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

\[
\begin{align*}
\text{RLi} + \text{H}_2\text{NOCH}_3 & \rightarrow \text{HN} & \quad \text{RLi} \\
\text{HN} & \quad \text{Li} & \quad \text{ROCH}_3 & \rightarrow \text{R} & \quad \text{N} & \quad \text{Li} \\
162 & & 163 & & 164
\end{align*}
\]

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

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 \( \text{162} \rightarrow \text{163} \) and only then to employ the lithium reagent to be aminated \( \text{163} \rightarrow \text{164} \).\(^{147-149}\)

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 \( \text{163} \) could undergo an \( \alpha \)-elimination of LiOCH\(_3\) to give the nitrene \( \text{165} \) which then adds RLi to produce \( \text{164} \) (pathway A in Scheme 39). In pathway B a nucleophilic substitution reaction takes place at the nitrenoid nitrogen atom of \( \text{163} \) to give \( \text{164} \) 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 \( \alpha \)-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\(_3\)O at the nitrogen atom of \( \text{163} \).

![Scheme 39](image)

**Scheme 39:** The mechanism of the electrophilic amination of carbanions with lithiated O-alkyl-hydroxylamines \( \text{163} \) 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 \( \text{166} \) in which the entering carbon is disposed on the side of nitrogen and the nitrogen oxygen bond is polarized, leading to the transition state \( \text{167} \), has been suggested (Scheme 40).\(^{82}\)

![Scheme 40](image)

**Scheme 40:** Transition state suggested for the electrophilic amination of carbanions with lithiated O-alkylhydroxylamines \( \text{163} \), 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.\textsuperscript{151,152} In the amination method developed by Beak \textit{et al.}\textsuperscript{82,150}, it has been suggested that the N-O bond of lithium methoxyamide 163 is bridged by the lithium atom. Boche and Wagner\textsuperscript{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-cyclohexen-1-ol 169 (Scheme 41).

\begin{center}
\begin{tikzpicture}

\node (A) at (0,0) {124};
\node (B) at (1,1) {\text{NH.HCl}};
\node (C) at (1.5,0) {\text{Li}};
\node (D) at (2,1) {168};
\node (E) at (3,0) {\text{PhLi}, -78°C};
\node (F) at (3,1) {\text{NH}_4\text{Cl sat. sol.}};

\draw[->, thick] (A) -- (B) node[midway, above] {i) MeLi, THF, -60°C} node[midway, below] {NaHCO$_3$, Et$_2$O};
\draw[->, thick] (B) -- (C) node[midway, above] {\text{MeLi}, THF, -78°C};
\draw[->, thick] (C) -- (D) node[midway, above] {\text{MeLi}, THF, -78°C};
\draw[->, thick] (D) -- (E) node[midway, above] {ii) \text{MeLi}, THF, -78°C};
\draw[->, thick] (E) -- (F) node[midway, above] {i)};

\node (G) at (6,0) {169};
\node (H) at (6,1) {\text{NH}};
\node (I) at (6.5,0) {\text{OH}};
\node (J) at (7,1) {\text{Ph}};

\node (K) at (9,0) {170};
\node (L) at (9,1) {\text{NH}};
\node (M) at (9.5,0) {\text{OH}};
\node (N) at (10,1) {\text{H}};

\end{tikzpicture}
\end{center}

\textbf{Scheme 41:} Reaction between 168 and PhLi.

\(\text{N-(2,4-Cyclohexadien-1-yl)hydroxylamine 170}\) 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$_2$O.
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 $\beta$-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.

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$_2$Cu(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).
Results and Discussion

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylamine</th>
<th>Reaction temperature, °C</th>
<th>Reaction time, h</th>
<th>Yield of 179, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>147</td>
<td>-78</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>147</td>
<td>-40</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>148</td>
<td>-40</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>151</td>
<td>-40</td>
<td>3</td>
<td>56</td>
</tr>
</tbody>
</table>

N-[10-(1R,5R)-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\(_{\text{meta}}\)), 117.20 (two C\(_{\text{ortho}}\)) and 112.91 ppm (C\(_{\text{para}}\)).

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 (1R)-(−)-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\(_4\)Cl, hydrolysis of the mixture with 1M HCl and subsequent GC analysis. In the mentioned cases (Table 3) formation of (1R,5R)-(−)-myrtenal 142, as product of imine 181 hydrolysis, has been observed (Scheme 44).
Results and Discussion

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylamine</th>
<th>Solvent</th>
<th>Reaction time, h</th>
<th>Ratio hydroxylamine : 142 a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>147</td>
<td>THF</td>
<td>1</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>147</td>
<td>n-hexane</td>
<td>1</td>
<td>71 : 29</td>
</tr>
<tr>
<td>3</td>
<td>148</td>
<td>THF</td>
<td>1</td>
<td>100 : 0</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>n-hexane</td>
<td>1</td>
<td>51 : 49</td>
</tr>
<tr>
<td>5</td>
<td>151</td>
<td>THF</td>
<td>1</td>
<td>85 : 15</td>
</tr>
<tr>
<td>6</td>
<td>151</td>
<td>n-hexane</td>
<td>1</td>
<td>66 : 34</td>
</tr>
<tr>
<td>7</td>
<td>152</td>
<td>THF</td>
<td>1</td>
<td>34 : 66</td>
</tr>
<tr>
<td>8</td>
<td>152</td>
<td>n-hexane</td>
<td>1</td>
<td>86 : 13</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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).
Results and Discussion

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

It should be mentioned that formation of (1R,5R)-(−)-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 (1R,5R)-(−)-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 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., who found that reactivity of the nitrenoid 163 towards alkyl or aryllithium reagents increases when, instead of THF or Et₂O, n-hexane was used as solvent, favouring the formation of the
results and discussion. The results presented in Table 3 show that the proportion of imine 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>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylamine</th>
<th>Reaction temperature, °C</th>
<th>Reaction time, h</th>
<th>Yield of 179, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>147</td>
<td>-40</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>148</td>
<td>-40</td>
<td>3.5</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>-40</td>
<td>3</td>
<td>59</td>
</tr>
</tbody>
</table>

Very good results are obtained when phenyl lithium is transmetalated to the higher order cyanocuprate Ph₂Cu(CN)Li₂, 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 Ph₂Cu(CN)Li₂ 175 with hydroxylamines 147, 148 and 151.
Table 5: Electrophilic amination of \( \text{Ph}_2\text{Cu(CN)Li}_2 \) 175 with \textit{in situ} generated nitrenoids 176-178 form hydroxylamines 147, 148 and 151.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylamine</th>
<th>Reaction temperature, °C</th>
<th>Reaction time, h</th>
<th>Yield of 179, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td>-40 to -20</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>147</td>
<td>-50 to RT</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>-50 to RT</td>
<td>3</td>
<td>94</td>
</tr>
</tbody>
</table>

Electrophilic amination of the higher order cyanocuprate \( \text{Ph}_2\text{Cu(CN)Li}_2 \) 175 with lithium \textit{tert}-butyl-N-tosyloxycarbamate 185 has been reported by Greck \textit{et al}.157 to proceed in 35% yield, whereas the Gilman cuprate \( \text{Ph}_2\text{CuLi} \) 186 furnishes \( \text{N-Boc-aniline} \) 187 in 23% yield (Scheme 48).

Scheme 48: Electrophilic amination of cuprates with lithium \textit{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 \textit{et al}.157 for the electrophilic amination of lower order Gilman cuprates with lithium \textit{tert}-butyl-N-tosyloxycarbamate 185.

Ricci \textit{et al}.121 reported a related electrophilic amination of higher order cuprates \( \text{Ar}_2\text{Cu(CN)Li}_2 \) with \( \text{O-trimethylsilyl hydroxylamines} \) \( \text{R-NH-OSiMe}_3 \) (R = Me, Pr, Bu) in 45-88% yield. In contrast to the report of Greck \textit{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\(^\text{159}\), in favor of proposal B.

\[
\begin{align*}
\text{A} & \quad : \quad \text{N} \quad \text{Cu} \quad \text{R} \quad \text{R} \\
\text{B} & \quad : \quad 2\text{Li}^+ \quad [\text{R} \quad \text{Cu} \quad \text{R}]^- \quad \text{Li}^+ \quad \text{LiCN}
\end{align*}
\]

**Figure 18:** Models describing the proposed structures of cyanocuprates.\(^\text{158}\)

The results reported by Greck \textit{et al.}\(^\text{157}\) and Ricci \textit{et al.}\(^\text{121}\), combined with those concerning the amination of Ph\(_2\)Cu(CN)Li\(_2\) \(^\text{175}\) with one equivalent of hydroxylamines \(^\text{147, 148 or 151}\), 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\(^1\)OM (M = Li or Cu) and recombination of Ph and NR furnished the aniline derivative \(^\text{179}\).

The failure of oxazine \(^\text{168}\) 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.

\[
\begin{align*}
\text{Ph-Cu-Ph}^- \quad \text{Li}^+ \quad \text{LiCN} & \quad + \quad \text{R-NH-OR}^1 \\
& \quad \rightarrow \quad \text{Ph-Cu-NR-OR}^1^- \quad \text{Li}^+ \quad \text{LiCN} \quad + \quad \text{C}_6\text{H}_6
\end{align*}
\]

**Scheme 49:** Intermediate suggested for the electrophilic amination of higher order cuprates Ph\(_2\)Cu(CN)Li\(_2\) \(^\text{175}\) with hydroxylamines \(^\text{147, 148 or 151}\).

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

\textit{tert}-Butyl-N-(tosyloxy)carbamate \(^\text{189}\) has been used as a model for the design and application of \(^\text{152}.\) Greck \textit{et al.}\(^\text{27,157}\) reported the synthesis, stability and use of \(^\text{185}\) and of \(N\)-lithiated \textit{tert}-butyl-\(N\)-mesityloxy carbamate \(^\text{191}\) as electrophilic amination reagents with good results.
Figure 19: Electrophilic amination reagents introduced by Greck et al.\textsuperscript{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\textsuperscript{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,\textsuperscript{161} the presence of a proton in the $\alpha$ 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 $\alpha$-amino ketones and $\alpha$-amino acids.

The lithium or copper enolates derived from propiophenone 75a, tert-butylopropionate 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 \textit{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).

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.](image)

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

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

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\%) \([\text{M-}t\text{Bu}]^+\), 206 (54\%) \([\text{M-BuO}]^+\), 150 (48\%)

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\%) \([\text{M-}t\text{Bu}]^+\), 206 (54\%) \([\text{M-BuO}]^+\), 150 (48\%)

[M'-BuOC(O)CHCH₃]⁺, 145 (12%) [BuOC(O)CH(NH₂)CH₃]⁺ and 57 (100%) [Bu⁺]. 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-C₂H₆]⁺, 206 (23%) [M+H-BuOH]⁺ and 150 (24%) [M'-BuOC(O)CHCH₃]⁺.

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.

![Figure 25](image)

**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. The aggregation can dramatically affect chemical reactivity. 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 and Mohrig et al. 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 nBuLi to remove the NH proton gives upon quenching with D₂O 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 carbani ons 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 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 BocNH₂ 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](image)

**Scheme 52:** Generation of the singlet phenylnitrene 201-s by α-elimination of the good leaving group CH₃SO₃⁻ from N-(p-nitrophenyl)-O-(methylsulfonyl)-hydroxylamine 197 under basic condition, as reported by Boche et al.¹⁶¹
The formation of tert-butyl carbamate BocNH₂ 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 nitr enoid. 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.\textsuperscript{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.\textsuperscript{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\textsubscript{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\textsuperscript{13}, the determination of the enantiomeric excess of 208 has not been attempted.

\begin{equation}
\begin{align*}
\text{Ph} & \quad \text{OZnBr} \\
\text{O} & \quad \text{Ph} \\
\text{75a} & \quad \text{i) LiHMDS, THF, -78°C, 1 h} \\
& \quad \text{ii) ZnBr\textsubscript{2}, THF, -68°C to 0°C, 45 min} \\
\text{Ph} & \quad \text{O} \\
\text{206} & \quad \text{i) 74, THF} \\
& \quad \text{-50°C to RT, 24 h} \\
& \quad \text{ii) H\textsubscript{2}O} \\
\text{Ph} & \quad \text{N} \\
\text{207} & \quad \text{-} \\
\text{O} & \quad \text{Ph} \\
\text{Cl} & \quad \text{H} \\
\text{208} & \quad \text{1N HCl, CHCl\textsubscript{3}} \\
\text{SO\textsubscript{2}NCy\textsubscript{2}}
\end{align*}
\end{equation}

Scheme 53: Electrophilic amination of the propiophenone zinc enolate 206 with the enantiomerically pure α-chloronitroso reagent 74, following Oppolzer’s\textsuperscript{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 \(m/\text{z} \approx 565.2\), assigned to \([M+Na]^+\), accompanied by the peaks with \(m/\text{z} \approx 543.2\ [M+H]^+\) and 581.2 \([M+K]^+\). The \(^{13}\text{C}\) NMR spectrum shows the peak corresponding to the carbon atom double connected to the nitrogen (C=N\textsuperscript{+}) 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 \(^{1}\text{H}\) 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/CHCl₃. The IR spectrum of 207 shows the characteristic C=O (1700 cm⁻¹) and nitrone C=N⁺ (1598 cm⁻¹) 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, tert-butyl propionate 192 and ethyl phenylacetate 193, as well as their silylated derivatives and the products of transmetallation with ZnBr₂ 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(\(\alpha\))-si-face topiety of C-N bond formation is consistent with a cyclic “chair” transition state \(A^\#\) (Figure 27).

\[
\begin{align*}
&\text{CH}_2\text{Cl} \\
&\text{NO} \\
&\text{SN} \\
&\text{O} \quad \text{O} \\
&\text{R} \\
&\text{Zn} \\
&\text{O} \\
&\text{CH}_3 \quad \text{H} \\
&\text{R} \\
&\text{Z} \\
&\text{1} \\
&\text{Ln} \\
&\text{A}^\# \\
&\text{CH}_2\text{Cl} \\
&\text{NO} \\
&\text{SN} \\
&\text{O} \quad \text{O} \\
&\text{R} \\
&\text{Zn} \\
&\text{O} \\
&\text{H} \\
&\text{Y} \\
&\text{E} \\
&\text{Ln} \\
&\text{B}^\# \\
&\text{2} \quad \text{3} \quad \text{2} \quad \text{3}
\end{align*}
\]

**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 \(\alpha\)-tetralone, \(\beta\)-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(\(\alpha\)) 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 '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).
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).

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction temperature, °C</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214</td>
<td>-78</td>
<td>221</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>214</td>
<td>0</td>
<td>221</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>214</td>
<td>22</td>
<td>221</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>215</td>
<td>-78</td>
<td>222</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>216</td>
<td>-78</td>
<td>223</td>
<td>84</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction temperature, °C</th>
<th>Product</th>
<th>Yield, %</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214</td>
<td>-78</td>
<td>221</td>
<td>84</td>
<td>224</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>214</td>
<td>0</td>
<td>221</td>
<td>82</td>
<td>224</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
<td>-78</td>
<td>221</td>
<td>72</td>
<td>225</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>215</td>
<td>0</td>
<td>222</td>
<td>71</td>
<td>225</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>216</td>
<td>-78</td>
<td>223</td>
<td>73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>216</td>
<td>0</td>
<td>223</td>
<td>64</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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 organozine compounds 214-216 (Figure 30). This distribution depends upon solvent and the type of regioisomer (branched or linear) of the allyl organozine 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>
<thead>
<tr>
<th>Entry</th>
<th>Allyl organozinc compound</th>
<th>Solvent</th>
<th>Distribution of compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>214 (R1=Me, R2=H)</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>215 (R1=Me, R2=Me)</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>216 (R1=Ph, R2=H)</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>214 (R1=Me, R2=H)</td>
<td>Toluene</td>
<td>224 a)</td>
</tr>
<tr>
<td>5</td>
<td>215 (R1=Me, R2=Me)</td>
<td>Toluene</td>
<td>225 a)</td>
</tr>
<tr>
<td>6</td>
<td>216 (R1=Ph, R2=H)</td>
<td>Toluene</td>
<td>-</td>
</tr>
</tbody>
</table>

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

Th. J. de Boer et al.\textsuperscript{8,10,172} carried out an intensive work concerning the reaction between \(\alpha\)-chloronitroso compounds and some organometallic reagents. They showed that \(\alpha\)-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 $R^*$ 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.

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{O} \\
\text{+} & \quad \text{RMgX} & \quad \text{- MgXCl} \\
\text{N} & \quad \text{O} & \quad \text{+} & \quad \text{R} \\
\text{SH} & \quad \text{toluene, cumene} & \quad \text{S} & \quad \text{2x} & \quad \text{S-S} \\
\text{SH} & \quad \text{-RH} & \quad \text{R} & \quad \text{Me, n-Bu, t-Bu, PhCH}_2, \text{Ph} \\
\text{R-R} & \quad \text{2x} & \quad \text{R} & \quad \text{RMgX} & \quad \text{H}_2\text{O} & \quad \text{N-OH} \\
\text{230} & \quad \text{227} & \quad \text{228} & \quad \text{229} & \quad \text{231} & \quad \text{232}
\end{align*}
\]

**Scheme 57:** Distribution of products in the reaction of sterically hindered $\alpha$-chloronitroso compound 226 with Grignard reagents, as reported by Th. J. de Boer et al.\textsuperscript{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.
1-Chloro-1-nitroso-2,2,6,6-tetramethylcyclohexane \( \text{226} \) is easily prepared in 88% yield by chlorination of 2,2,6,6-tetramethylcyclohexanone oxime \( \text{232} \) with \('\text{BuOCl}\). For the synthesis of the oxime \( \text{232} \), 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 \textit{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 \( \text{234} \) between the ene and the enophile A=B (Scheme 59).

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 \( \text{234} \). A THF solution of 1-chloro-1-nitrosocyclohexane \( \text{12} \) 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 \(O-(1\text{-methylallyl})\text{cyclohexanone oxime} 221 \) 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 \(\sigma\)-bond structures which can react at both \(\alpha\) (less substituted, “linear form”) or \(\gamma\) (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 \(\alpha\)-chloronitroso cyclohexane 12 and allyl organozinc compounds 214-216 in THF.](image)

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, \textit{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.\textsuperscript{178} To understand why such a different pathway compared to ketone enolate 75a occurred when the allyl organozinc compounds 214-216 reacted with the $\alpha$-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 \textit{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.

![Figure 31: The calculated HOMO (Density Functional method with the pBP/DN$^*$ basis set) of the zinc enolates of propiophenone 75a (a) and \textit{tert}-butylethyl ketone 75c (b)]
Results and Discussion

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)

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)
Results and Discussion

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. 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.
Results and Discussion

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 $A^#$ - 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.
**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 \textit{Ab Initio} (RHF/3-21G* and RHF/6-31G*) levels of theory

<table>
<thead>
<tr>
<th>Atomic orbital</th>
<th>DFT (pBP/dn*)</th>
<th>RHF/3-21G*</th>
<th>RHF/6-31G*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2px)</td>
<td>-0.81388</td>
<td>-0.24370</td>
<td>-0.29475</td>
</tr>
<tr>
<td>N(2py)</td>
<td>-0.30839</td>
<td>-0.29574</td>
<td>-0.35770</td>
</tr>
<tr>
<td>N(2pz)</td>
<td>-0.01679</td>
<td>0.01068</td>
<td>0.01292</td>
</tr>
<tr>
<td>O(2px)</td>
<td>0.71288</td>
<td>0.21613</td>
<td>0.25567</td>
</tr>
<tr>
<td>O(2py)</td>
<td>0.26631</td>
<td>0.26228</td>
<td>0.31028</td>
</tr>
<tr>
<td>O(2pz)</td>
<td>-0.00377</td>
<td>-0.00947</td>
<td>-0.01120</td>
</tr>
</tbody>
</table>

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).
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-mannofuranose

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.\textsuperscript{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).

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.

The base removes the relatively acidic proton in α-position to the nitro group. The anion 248 is in resonance with the αi-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 triisopropoxide 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).

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction temperature °C</th>
<th>Reaction time h</th>
<th>Quenching agent</th>
<th>Yield %</th>
<th>Z:E (^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>4</td>
<td>MeOH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-78 to -10</td>
<td>6</td>
<td>MeOH</td>
<td>12</td>
<td>1:3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>12</td>
<td>MeOH</td>
<td>7</td>
<td>1:3.2</td>
</tr>
<tr>
<td>4</td>
<td>-35</td>
<td>14</td>
<td>MeOH</td>
<td>14</td>
<td>1:3.5</td>
</tr>
<tr>
<td>5</td>
<td>-35</td>
<td>14</td>
<td>0.5 M TFA/DCM</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-35 to -10</td>
<td>2.5</td>
<td>1.3 M AcOH/DCM</td>
<td>17</td>
<td>1:7.5</td>
</tr>
</tbody>
</table>

\(^{a}\) 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 than \(H^{A}\), the formation of a conjugated system is energetically more favorable compared to the formation of an exocyclic double bond.

![Figure 34](image)

*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 (\(R^{1} = \text{Me}, R^{2} = \text{H}\)), 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.  

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 1H NMR analysis shows a singlet for the C(1)-H proton (Scheme 66), it is concluded that no anomerisation occurs 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 1H 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/CHCl₃ 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 H¹ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>Reaction time h</th>
<th>Lewis acid</th>
<th>Yield of 225 (^{a}) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>-35 to 0</td>
<td>23</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>-55</td>
<td>12</td>
<td>BF(_3)·OEt(_2)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>-30 to -20</td>
<td>5</td>
<td>BF(_3)·OEt(_2)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>-20 to 0</td>
<td>16</td>
<td>BF(_3)·OEt(_2)</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>-78 to -10</td>
<td>20</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>-78 to -10</td>
<td>18</td>
<td>BF(_3)·OEt(_2)</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^{a}\) Lactone 253 formed as by-product

The nitro group can be activated by Lewis acids (AlCl\(_3\), TiCl\(_4\), BF\(_3\)·OEt\(_2\), SnCl\(_4\))\(^{181}\) Intramolecular transformations of \(\gamma\)-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 \(\gamma\) 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\(_3\)·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\(_3\)·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 $\alpha$-proton acidity.

Although the electrophilic amination of allyl organometallics with 1-deoxy-1-nitrosugar 156 has some important drawbacks (relatively high acidity of the $\alpha$-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 $\alpha$-D-fructofuranose 258 as optically active starting material for the synthesis of the nitrosugar 259 (Scheme 71). The absence of the acidic $\alpha$-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.

\[
\begin{align*}
\text{Li}^+\text{NH} & \quad \text{Li}^+\text{OCH}_3 \\
\text{H}_3\text{CO} & \\
166 & \quad 167
\end{align*}
\]

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

\[
\begin{align*}
\text{NH} & \quad \text{H} \\
\text{H} & \\
124 & \quad 168 \\
\text{NH} & \quad \text{O} \\
\text{R} & \\
125 & \quad 176-178, 180
\end{align*}
\]

R = Me, Bn, SiMe₃, Ts
Their amination potential was explored using phenyl lithium as substrate. The N-lithium amide undergoes β-elimination under the reaction conditions and proved to be improper as electrophilic amination reagent. O-substituted N-lithium-N-[10-(1R,5R)-pin-2-enyl]-hydroxylamines 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. The compound (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 and .

(+)-N,N-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide provides the corresponding 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 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 building 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.
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.
Electrophilic amination of 2-butenyl zinc bromide 214 with 156 affords the conjugated sugar nitronate 250 in 7-17% yield, accompanied by the formation of lactone 247.

Elimination of the allylic proton is favored by the formation of a conjugated system and nitronate 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 nitronate 257.

The use of a Lewis acid (BF₃·OEt₂) 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

Petroleumether 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

Temperature program:

- 70°C for 2 min
- 70°C → 270°C at 25°C/min
- 270°C for 3 min

**GC-MS Pr. 2**

Instrument 2

Temperature program:

- 75°C for 5 min
- 75°C → 270°C at 15°C/min
- 270°C for 5 min

**GC-MS Pr. 3**

Instrument 2

Temperature program:

- 60°C for 2 min
- 60°C → 180°C at 15°C/min
Experimental Section

180°C $\rightarrow$ 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: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)
Experimental Section

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 K₂CO₃ 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: C₁₂H₂₀O₆ [260.28]
Yield: 67% (19.3 g, colorless crystals) [lit.¹⁰² 85%]
TLC: Rᵣ = 0.21 [Et₂O:PE = 3:2]
Melting point: 121-122°C [lit.¹⁰² 119-121°C]
Optical rotation: [α]D²₆ = +9.8 (c = 1.3 in CHCl₃)
[α]D²₄ = +11.8 (c = 1.3 in CHCl₃)

IR (KBr), ν [cm⁻¹]: 3436 (O-H), 2989 (C-H), 2948 (CH₃), 2900 (CH₂), 1459 (CH₂), 1375 (CH₃), 1253, 1226, 1203 (C-O-C), 1166, 1087, 1070 (C-O-C), 1035, 975, 856, 838, 514.

¹H-NMR (CDCl₃, 250 MHz) δ [ppm]: 5.38 (1 H, br s, H₁), 4.82 (1 H, dd, J₁₂₅ = 3.7 Hz, J₁₂₃ = 5.9 Hz, H₅), 4.62 (1 H, d, J₁₂₃ = 5.9 Hz, H₂), 4.37-4.45 (1H, m, H₅), 4.19 (1 H, dd, J₁₂₅ = 3.7, J₆₅ = 7.2 Hz, H₆a), 4.10 (1 H, dd, J₆₅ = 6.0, J₆₅ = 8.6 Hz, H₆b), 4.05 (1 H, dd,
Experimental Section

\[ J_{6b-5} = 5.1 \text{ Hz}, J_{6a-6b} = 8.6 \text{ Hz}, H_{6b}, \] 3.00 (1 H, br, OH), 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) \( \delta \) [ppm]: 112.6 (C\(_7\)), 109.1 (C\(_8\)), 101.2 (C\(_9\)), 85.5 (C\(_2\)), 80.1 (C\(_3\)), 79.6 (C\(_4\)), 73.3 (C\(_6\)), 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-\( \alpha \)-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\(_2\)SO\(_4\)), evaporation of the solvent \textit{in vacuo} and recrystallization from ethyl acetate/n-hexane (1:1) gave 36.2 g (131.2 mmol, 92%) colorless crystals.

\[
\begin{align*}
\text{Molecular formula:} & \quad \text{C}_{12}\text{H}_{21}\text{NO}_6 [275.98] \\
\text{Yield:} & \quad 92\% (36.2 \text{ g, colorless crystals}) \quad \text{[lit.}\text{\textsuperscript{105} 92\%]} \\
\text{TLC:} & \quad R_f = 0.34 \quad [\text{AcOEt:PE = 3:2}] \\
\text{Melting point:} & \quad 137.5 -140°C \quad \text{[lit.}\text{\textsuperscript{105} 139 -141°C]} \\
\text{Optical rotation:} & \quad \left[\alpha\right]^{27}_{D} = -115.9 \quad (c = 1.0 \text{ in CH}_2\text{Cl}_2) \\
\end{align*}
\]

IR (KBr), \( \tilde{\nu} \) [cm\(^{-1}\)]: 3534 (OH), 3378 (OH), 3293 (OH), 2992 (CH), 2939 (CH\(_3\)), 2917 (CH\(_3\)), 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) \( \delta \) [ppm]:

(Z)-Isomer: 9.86 (1H, s, N-OH), 7.12 (1H, d, \( J_{1,2} = 3.4 \text{ Hz} \), H\(_2\)), 5.25 (1H, dd, \( J = 7.6 \text{ Hz} \), \( J_{1,2} = 3.4 \text{ Hz} \), H\(_1\)), 4.64-4.52 (2H, m, H\(_3\) and C-OH), 4.25-3.95 (3H, m, H\(_{6a,b}\) and H\(_5\)), 3.70 (1H, dd, \( J = 6.7 \text{ Hz} \), \( J = 2.5 \text{ Hz} \), 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\(_3\)).

88
(E)-Isomer (characteristic signals): 8.33 (1H, s, N-OH), 7.61 (1H, d, \(^3J_{1-2}=7.6\) Hz, H\(_2\)), 4.79 (1H, m, H\(_3\)), 4.49 (1H, dd, \(^3J=1.5\) Hz, \(^3J_{1-2}=7.3\) Hz, H\(_1\)), 2.51 (1H, d, \(^3J=6.9\) Hz, H\(_4\)).

(Z): (E) = 79:21

\(^{13}\)C-NMR (CDCl\(_3\), 62 MHz) \(\delta\) [ppm]:

(Z)-Isomer: 152.1 (C\(_1\)), 109.7 (C\(_7\)), 108.3 (C\(_8\)), 78.4 (C\(_2\)), 77.8 (C\(_3\)), 72.9 (C\(_4\)), 67.6 (C\(_5\)), 65.1 (C\(_6\)), 26.1 (CH\(_3\)), 25.9 (2 x CH\(_3\)), 24.7 (CH\(_3\)).

(E)-Isomer: 149.7 (C\(_1\)), 109.7 (C\(_7\)), 109.5 (C\(_8\)), 76.7 (C\(_2\)), 76.2 (C\(_3\)), 75.0 (C\(_4\)), 69.7 (C\(_5\)), 66.9 (C\(_6\)), 26.7 (CH\(_3\)), 26.7 (CH\(_3\)), 25.3 (CH\(_3\)), 24.5 (CH\(_3\)).

MS (ESI) \(m/\xi\) (%): 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

\(\text{N-Hydroxy-2,3:5,6-di-O-isopropylidene-}\)\(\alpha\)-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\(_2\)SO\(_4\)), and concentrated \textit{in vacuo}. Crystallization from dichloromethane/\(\mu\)-hexane (2:1) afforded 22 g (80.5 mmol, 74%) of hydroximolactone 135, as colorless crystals.

\[\text{Molecular formula:} \quad \text{C}_{12}\text{H}_{19}\text{NO}_6 [273.28] \]

\[\text{Yield:} \quad 74\% (22.0 \text{ g, colorless crystals}) \quad \text{[lit.] 93\%} \]

\[\text{TLC:} \quad R_f = 0.34 \quad \text{[AcOEt:PE = 3:2]} \]

\[\text{Melting point:} \quad 175.5-176.5^\circ\text{C} \quad \text{[lit. 174-174.5^\circ\text{C}]} \]

\[\text{Optical rotation:} \quad [\alpha]_{D}^{27} = +99.5 \ (c = 1.1 \text{ in CHCl}_3) \]
Experimental Section

[\text{lit.}^{106} \ [\alpha]_{D}^{26} = +98.6 \ (c = 1.1 \ \text{in CHCl}_3)]

\textbf{IR (KBr, } \tilde{\nu} \ [\text{cm}^{-1}]: 3411 \ (\text{OH}), 3315 \ (\text{OH}), 2985 \ (\text{C-H}), 2958 \ (\text{CH}_3), 2939 \ (\text{CH}_3), 2892 \ (\text{CH}), 1691 \ (\text{C}=\text{N}), 1459 \ (\text{CH}_2), 1376 \ (\text{CH}_2), 1265, 1228 \ (\text{C-O-C}), 1159, 1116, 1087, 1068 \ (\text{C-O-C}), 973, 937, 858, 792, 686, 663, 511.

\textbf{\textsuperscript{1}H-NMR (CDCl}_3, 250 MHz) \ \delta \ [\text{ppm}]: 7.61 \ (1\text{H, br., N-OH}), 5.15 \ (1\text{H, d, } \beta_{2,3} = 5.5 \ \text{Hz, H}_2), 4.87 \ (1\text{H, dd, } \beta_{2,3} = 5.5 \ \text{Hz, H}_3), 4.50 \ (1\text{H, ddd, } \beta_{5,6a} = 8.4 \ \text{Hz, H}_4), 4.30 \ (1\text{H, dd, } \beta_{5,6b} = 4.4 \ \text{Hz, H}_5), 4.19 \ (2\text{H, m, H}_6), 1.49 \ (3\text{H, s, CH}_3), 1.47 \ (3\text{H, s, CH}_3), 1.41 \ (3\text{H, s, CH}_3).

\textbf{\textsuperscript{13}C-NMR (CDCl}_3, 62 MHz) \ \delta \ [\text{ppm}]: 156.9 \ (C_1), 114.3 \ (C_7), 109.8 \ (C_8), 82.6 \ (C_2), 77.5 \ (C_3, C_4), 72.7 \ (C_5), 66.7 \ (C_6), 27.2 \ (CH_3), 26.9 \ (CH_3), 25.9 \ (CH_3), 25.1 \ (CH_3).

\textbf{MS (ESI) } m/z: 295.98 \ [\text{M+Na}^+]$, 569.03 \ [2\text{M+Na}^+]$.

\textbf{Elemental analysis (\%)}:

\begin{tabular}{ccc}
Calcd: & C 52.74 & H 7.01 & N 5.13 \\
Found: & C 52.71 & H 6.94 & N 5.01 \\
\end{tabular}

2,3:5,6-Di-O-isopropylidene-1-C-nitroso-\(\alpha\)-D-mannofuranosylchloride 65

A solution of 9.63 g \(t\text{BuOCl} \ (75\% \ \text{w/w in } t\text{BuOH}) \ (66 \ \text{mmol, 1 eq.}) \) 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-\(\alpha\)-D-mannookynimo-1,4-lactone 135 \ (66 \ \text{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 \textit{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.

\begin{itemize}
\item \textbf{Molecular formula:} \ C_{12}H_{18}ClNO_{6} \ [307.72]
\item \textbf{Yield:} \ 99 \% \ (20.1 \ g, \ blue \ needles) \ [\text{lit.}^{106} \ 89\%]
\item \textbf{TLC:} \ \text{R}_f = 0.57 \ [\text{AcOEt:PE = 3:2}]
\item \textbf{Melting point:} \ 78-81°C \ [\text{lit.}^{106} \ 80°C]
\item \textbf{Optical rotation:} \ [\alpha]_{D}^{27} = -1668 \ (c = 1.0 \ \text{in CH}_2\text{Cl}_2)
\end{itemize}
Experimental Section

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) $\delta$ [ppm]: 5.54 (1H, d, $\gamma$J$_{2,3}$ = 5.5 Hz, H$_2$), 5.00 (1H, dd, $\gamma$J$_{3,2}$ = 5.6 Hz, $\gamma$J$_{3,4}$ = 3.5 Hz, H$_3$), 4.54 (1H, ddd, $\gamma$J$_{3,4}$ = 8.1 Hz, $\gamma$J$_{5,6a}$ = 6.0 Hz, $\gamma$J$_{5,6b}$ = 4.1 Hz, H$_5$), 4.24 (1H, dd, $\gamma$J$_{5,6a}$ = 8.2 Hz, $\gamma$J$_{4,5}$ = 3.6 Hz, H$_4$), 4.17 (1H, dd, $\gamma$J$_{6a,6b}$ = 9.0 Hz, $\gamma$J$_{6a,5}$ = 6.0 Hz, H$_{6a}$), 4.07 (1H, dd, $\gamma$J$_{6a,6b}$ = 9.1 Hz, $\gamma$J$_{6b,5}$ = 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) $\delta$ [ppm]: 125.2 (C$_1$), 115.0 (C$_7$), 109.8 (C$_8$), 88.7 (C$_3$), 82.3 (C$_4$), 79.5 (C$_5$), 72.1 (C$_6$), 66.7 (C$_7$), 26.8 (CH$_3$), 25.3 (CH$_3$), 25.1 (CH$_3$), 24.6 (CH$_3$).

MS (ESI) $m$/z: 207.8 [M+H-C$_6$H$_5$O]$,^+$, 330.0 [M(C$_{12}$H$_{18}$ClNO)$_6$]+Na$,^+$, 332.0 [M(C$_{12}$H$_{18}$ConClNO)$_6$]+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 (1R,4S)-3-Aza-2-oxabicyclo[2.2.2]oct-5-ene hydrochloride (1R,4S)-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-$\alpha$-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$_6$H$_{10}$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$_3$)
Table of Contents

Experimental Section
5.2.3 Synthesis of the Enantiomerically Pure N,O-Disubstituted Hydroxylamines

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

O-Methyl-(1R,5R)-(-)-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. (1R,5R)-(-)-Myrtenal 142 (54.4 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 MgSO4. 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.
Experimental Section

Molecular formula: \( \text{C}_{11}\text{H}_{17}\text{NO} \) [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: \( [\alpha]_D^21 = -17.7 \) (c = 1.3 in CHCl₃)

GC (GC Pr. 2): \( t_R = 10.47 \text{ min} \)

HPLC (CHIRACEL OD) \( t_R = 8.53 \text{ min} \) (n-hexane:iPrOH = 1000:40)

IR (neat), \( \tilde{\nu} \) [cm⁻¹]: 2972 (CH₂), 2937 (CH₃), 2872 (OCH₃), 1621 (C=N), 1465 (CH₂), 1427 (CH₂), 1382 (C-Me₂), 1367 (C-Me₂), 1265, 1205, 1180, 1083, 1041 (C-O), 896 (C=C-H), 792, 653.

\(^1\)H-NMR (CDCl₃, 200 MHz) \( \delta \) [ppm]: 7.66 (1H, s, H₁₀), 5.83 (1H, m, H₃), 3.85 (3H, s, H₁₁), 2.83 (1H, ddd, \( J_{1,7s} = 5.6 \text{ Hz}, J_{2,7s} = 5.6 \text{ Hz}, J_{3,7s} = 1.9 \text{ Hz} \), H₄), 2.47 (1H, ddd, \( J_{7s,7a} = 8.8 \text{ Hz}, J_{8,7s} = 5.6 \text{ Hz}, J_{7a,7s} = 5.6 \text{ Hz}, J_{8,7a} = 5.6 \text{ Hz} \), H₇s), 2.38 (1H, m, H₄a), 2.13 (1H, m, H₅), 1.33 (3H, s, H₈), 1.15 (1H, d, \( J_{7a,7s} = 8.8 \text{ Hz}, J_{7s,7a} = 8.8 \text{ Hz} \), H₇a), 0.81 (3H, s, H₉).

\(^{13}\)C-NMR (CDCl₃, 50 MHz) \( \delta \) [ppm]: 150.5 (C₁₀), 143.3 (C₂), 131.4 (C₃), 62.0 (C₁₁), 41.2 (C₆), 40.8 (C₁), 38.1 (C₄), 32.8 (C₇), 31.6 (C₈), 26.4 (C₉), 21.3 (C₉).

MS (EI) \( m/z \) (%): 179 [M⁺] (42), 164 [M–CH₃]⁺ (25), 148 [M–OCH₃]⁺ (70), 136 [C₆H₄]⁺ (80), 132 (45), 118 (25), 106 [C₆H₄NH]⁺ (50), 105 [C₆H₅N]⁺ (65), 104 (62), 93 (30), 91 [C₆H₄]⁺ (79), 79 (60), 77 [C₆H₅]⁺ (98), 65 (32), 53 (44), 51 (41), 43 (33), 41 [C₆H₄]⁺ (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

O-Benzyl-(1R,5R)-(−)-myrtenal oxime 146

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. (1R,5R)-(−)-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.

![Chemical structure](image)

**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$_2$), 2872 (ar. CH), 1621 (C=N), 1496 (C=C arom.), 1467 (CH$_3$), 1454 (CH$_3$), 1426 (CH$_3$), 1365 (ar. CH), 1330, 1205, 1051, 1025 (ar. CH), 945 (ar. CH), 927 (ar. CH), 696.

**$^1$H-NMR** (CDCl$_3$, 250 MHz) $\delta$ [ppm]: 7.74 (1H, s, H$_{10}$), 7.28-7.74 (5H, m, Ph), 5.82 (1H, m, H$_3$), 5.08 (2H, s, H$_{11}$), 2.85 (1H, ddd, $^3J_{7s-7a} = 5.6$ Hz, $^4J = 5.6$ Hz, $^4J = 1.9$ Hz, H$_1$), 2.47 (1H, ddd, $^3J_{7a-7s} = 8.3$ Hz, $^3J_{7s-1} = 6.7$ Hz, $^3J = 6.7$ Hz, H$_7s$), 2.45 (1H, m, H$_{4a}$), 2.36 (1H, ddd, $^3J_{4a-4s} = 19.6$ Hz, $^3J = 3.1$ Hz, $^3J = 3.1$ Hz, H$_{4s}$), 2.13 (1H, m, H$_8$), 1.33 (3H, s, H$_8$), 1.15 (1H, d, $^3J_{7a-7s} = 8.8$ Hz, H$_{7a}$), 0.81 (3H, s, H$_9$).

**$^{13}$C-NMR** (CDCl$_3$, 62 MHz) $\delta$ [ppm]: 150.4 (C$_{10}$), 143.0 (C$_{2}$), 137.5 (C$_{9}$, Ph), 131.0 (C$_{3}$), 128.3 (4 x CH, Ph), 127.8 (CH, Ph), 76.0 (C$_{11}$), 40.7 (C$_{5}$), 40.4 (C$_{3}$), 37.6 (C$_{6}$), 32.3 (C$_{4}$), 31.1 (C$_{4}$), 26.0 (C$_{8}$), 20.8 (C$_{9}$).

**GC-MS:** $t_R$ (GC-MS Pr. 2) = 17.17 min; (CI) $m/z$ (%): 256 [M+H]$^+$ (62), 240 [M–CH$_{2}$Ph]$^+$ (8), 148 [M–OCH$_3$Ph]$^+$ (55), 107 [OCH$_3$Ph]$^+$ (30); (EI) $m/z$ (%): 255 [M]$^+$, 164 [M–CH$_2$Ph]$^+$ (40), 91 [C$_6$H$_4$]$^+$ (100), 77 [C$_5$H$_4$]$^+$ (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-(1R,5R)-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-(1R,5R)-(−)-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.) NaBH₃CN 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 × 75 mL). The organic phases were combined, washed with 100 mL brine, dried over MgSO₄ 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: C₁₁H₁₉NO [181.27]
Yield: 70% (3.53 g, colorless oil)
TLC: Rf = 0.65 [neutral alumina, AcOEt:PE = 1:40]
Boiling point: 65–70°C (0.4–0.8 Torr)
Optical rotation: [α]D²³ = −19.2 (c = 1.0 in CHCl₃)

IR (neat), ν [cm⁻¹]: 3249 (NH), 3032 (=C-H), 2989 (CH), 2930 (CH), 2829 (CH₂), 1655 (C=C), 1467 (CH₂), 1364 (CH₃), 1131, 1020, 908, 877, 842.

¹H-NMR (CDCl₃, 200 MHz) δ [ppm]: 5.43 (1H, m, H₃), 5.27 (1H, br., NH), 3.45 (1H, ddd, J₁₀b-₁₀a = 13.2 Hz, J = 3.1 Hz, J₁₀a = 13.2 Hz, J₁₀H₁₀a), 3.34 (1H, ddd, J₁₀b-₁₀a = 13.2 Hz, J = 3.1 Hz, J₁₀H₁₀a), 2.38 (1H, ddd, J₇s-₇a = 8.4 Hz, J₇a = 5.65 Hz, J₇H₇a), 2.05-2.28 (4H, m, H₄, H₁, H₅), 1.27 (3H, s, H₈), 1.16 (1H, d, J₇s-₇a = 8.4 Hz, H₇a), 0.82 (3H, s, H₉).

¹³C-NMR (CDCl₃, 50 MHz) δ [ppm]: 144.7 (C₂), 120.7 (C₃), 61.9 (C₁₀), 57.4 (C₉), 44.8 (C₄), 41.1 (C₅), 38.4 (C₆), 32.0 (C₇), 31.7 (C₈), 26.6 (C₉), 21.4 (C₁₀).

GC-MS: tᵣ (GC-MS Pr. f) = 6.33 min; (EI) m/z (%): 181 [M⁺]⁺ (5), 166 [M–CH₃]⁺ (5), 150 [M–OCH₃]⁺ (7), 134 [C₁₄H₁₄]⁺ (20), 119 [C₉H₁₄]⁺ (43), 106 [C₈H₁₀]⁺ (56), 93 (41), 91 [C₇H₇]⁺ (100), 79 (62), 77 [C₆H₅]⁺ (42), 60 [CH₃ON(H)=CH₂]⁺ (65), 53 (24), 53 (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-(1R,5R)-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-(1R,5R)(-)-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.) NaBH₄CN 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 MgSO₄ 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: C₁₇H₂₃NO [257.37]
Yield: 85% (4.35 g, colorless oil)
TLC: Rᵣ = 0.13 [AcOEt:PE = 1:12]
Boiling point: 104°C (0.017 mbar)
Optical rotation: [α]D² = -27.0 (c = 0.6 in CHCl₃)

IR (neat), ν [cm⁻¹]: 3263 (NH), 3029 (=C-H), 2985 (CH), 2913 (CH), 1654 (C=C), 1496 (C=C aromatic), 1454 (CH₂), 1365 (CH₃), 1205, 1081, 1051, 1002, 794, 744, 698.

¹H-NMR (CDCl₃, 500 MHz) δ [ppm]: 7.27-7.37 (5H, m, Ph), 5.46 (1H, m, H₉), 4.71 (2H, s, H₁₁), 3.49 (1H, dd, 2J₁₀a-₁₀b = 13.2 Hz, J = 1.3 Hz, H₁₀a), 3.47 (1H, ddd, 2J₁₀a-₁₀b = 13.2 Hz, J = 3.1 Hz, J = 1.3 Hz, H₁₀b), 2.40 (1H, ddd, 2J₇s-₇a = 8.8 Hz, ³J = 5.6 Hz, ²J = 5.6 Hz, H₇s), 2.30 (1H, br. d, ²J₄a-₄s = 17.6 Hz, H₄a), 2.21 (1H, br. d, ²J₄a-₄s = 17.6 Hz, H₄a), 2.18 (1H, ddd, ³J₁-₇s = 5.6 Hz, ³J = 5.6 Hz, ³J = 1.3 Hz, H₁), 2.09 (1H, m, H₉), 1.28 (3H, s, H₈), 1.18 (1H, d, ²J₇s-₇a = 8.8 Hz, H₇a), 0.83 (3H, s, H₉).

¹³C-NMR (CDCl₃, 125 MHz) δ [ppm]: 144.1 (C₇, Ph), 137.8 (C₂), 128.4 (2 x CH, Ph), 128.3 (2 x CH, Ph), 127.7 (CH, Ph), 120.4 (C₈), 75.9 (C₁₀), 57.2 (C₉), 44.3 (C₁₁), 40.7 (C₅), 38.0 (C₆), 31.6 (C₄), 31.3 (C₇), 26.2 (C₈), 21.1 (C₉).
Experimental Section

**GC-MS:** $t_R$ (GC-MS Pr. 3) = 20.41 min; (Cl) $m/\zeta$ (%): 258 [M+H]$^+$ (63), 150 [M–OCH$_2$Ph]$^+$ (98), 135 [M–HOCH$_2$Ph]$^+$ (20), 123 [PhCH$_2$ONH$_2$]$^+$ (5), 107 [PhCH$_2$O]$^+$ (100); (EI) $m/\zeta$ (%): 257 [M]$^+$ (2), 149 [M–HOCH$_2$Ph]$^+$ (10), 134 [C$_{10}$H$_{14}$]$^+$ (22), 106 [PhCH=O]$^+$ (80), 91 [C$_5$H$_7$]$^+$ (100), 79 [C$_7$H$_7$]$^+$ (78), 77 [C$_8$H$_7$]$^+$ (82), 67 [C$_9$H$_7$]$^+$ (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

(1R,5R)-(−)-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. (1R,5R)-(−)-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) $\delta$ [ppm]:** 8.08 (1H, OH, br), 7.73 (1H, s, H$_{10}$), 5.92 (1H, m, H$_{3}$), 2.73 (1H, ddd, $^3J_{1,7a} = 5.6$ Hz, $^4J = 5.6$ Hz, $^5J = 1.3$ Hz, H$_{1}$), 2.45 (1H, ddd, $^2J_{5,7a} = 8.8$ Hz, $^3J_{5,3} = 5.6$ Hz, $^4J = 5.6$ Hz, H$_3$), 2.42 (1H, m, H$_{4a}$), 2.38 (1H, ddd, $^2J_{4a,4s} = 19.5$ Hz, $^3J = 3.1$ Hz, $^4J = 3.1$ Hz, H$_4$), 2.15 (1H, m, H$_{9}$), 1.32 (3H, s, H$_{8}$), 1.16 (1H, d, $^2J_{7a,7s} = 8.8$ Hz, H$_{7a}$), 0.81 (3H, s, H$_9$).

**$^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$ [ppm]:** 151.3 (C$_{10}$), 142.5 (C$_2$), 132.1 (C$_3$), 40.5 (C$_v$), 40.5 (C$_8$), 37.7 (C$_9$), 32.3 (C$_{7a}$), 31.1 (C$_{4a}$), 25.9 (C$_8$), 20.8 (C$_9$).
MS (EI) $m/z$ (%): 165 [M]$^+$ (38), 150 [M–CH$_3$]$^+$ (20), 148 [M–OH]$^+$ (62), 146 [C$_{10}$H$_{12}$N]$^+$, 133 [C$_9$H$_{11}$N]$^+$ (25), 132 [C$_9$H$_{10}$N]$^+$ (30), 131 [C$_9$H$_9$N]$^+$ (12), 122 [C$_8$H$_{14}$]$^+$ (100), 121 [C$_9$H$_{13}$]$^+$ (37), 106 [m/z $132 - \text{C}≡\text{N}$]$^+$ (36), 105 [C$_8$H$_7$]$^+$ (39), 104 [C$_8$H$_6$]$^+$ (32), 91 [C$_7$H$_5$]$^+$ (43), 77 [C$_6$H$_5$]$^+$ (66), 67 (20), 65 (22), 55 (19), 53 (26), 51 (24), 43 [C$_7$H$_5$]$^+$ (26), 41 [C$_9$H$_3$]$^+$ (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-(1R,5R)-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 (1R,5R)-(−)-myrtenaloxime 149 (10.3 mmol, 1 eq.) and 1.94 g NaBH$_3$CN (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:** $[\alpha]_D^{14}$ = -28.45 (c = 1.0 in H$_2$O)

**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) $\delta$ [ppm]: 11.49 (2H, br., NH$_2^+$), 6.11 (1H, m, H$_4$), 3.63 (2H, s, H$_{10}$), 2.51 (1H, m, H$_3$), 2.13-2.44 (3H, m, H$_{7a}$, H$_4$), 2.05 (1H, H$_5$), 1.26 (3H, s, H$_8$), 1.12 (1H, d, $J_{7a-7a}$ = - 8.54 Hz, H$_{7a}$), 0.81 (3H, s, H$_9$).

**$^{13}$C-NMR** (DMSO-D$_6$, 62 MHz) $\delta$ [ppm]: 137.4 (C$_2$), 126.2 (C$_3$), 54.7 (C$_{10}$), 43.7 (C$_9$), 39.5 (C$_1$), 37.5 (C$_6$, C$_4$), 31.0 (C$_7$), 25.7 (C$_8$), 20.7 (C$_9$).
13C-NMR (D2O, 62 MHz) δ [ppm]: 139.3 (C2), 132.1 (C3), 59.0 (C10), 47.3 (C5), 42.9 (C1), 40.5 (C6), 34.3 (C4), 34.2 (C7), 28.4 (C8), 23.5 (C9).

**MS (ESI) m/z (%):** 190 [M-HCl+Na]+, 168 [M-Cl-]+, 135 [C10H15(10-pininenyl)]+.

**Elemental analysis (%):**

Calcd: C 58.96  H 8.91  N 6.88

Found: C 58.74  H 8.86  N 6.73

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

A slurry of 1 g (-)-N-[10-(1R,5R)-pin-2-enyl]-hydroxylamine hydrochloride 150 (4.91 mmol, 1 eq.) and 1.49 g Et3N (14.73 mmol, 3 eq.) in 20 mL n-hexane (distilled over Na) was stirred at room temperature for 3 h, under N2. Trimethylsilyl chloride (0.54 g, 4.91 mmol, 1 eq.) (distilled over CaH2) 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:** C13H25NOSi [239.43]

**Yield:** 77% (0.91 g, colorless oil)

**TLC:** Rf = 0.32 [AcOEt:PE = 2:1]

**Boiling point:** 75°C (0.038 mbar)

**Optical rotation:** [a]D20 = -31.8 (c = 1.1 in CH2Cl2)

**IR (neat), ν [cm−1]:** 3259 (NH), 3027 (=C-H), 2987 (CH), 2915 (CH), 2832 (CH2), 1654 (C=C), 1465 (CH2), 1365 (CH3), 1248 (Si-CH3), 908, 877, 842

1H-NMR (CDCl3, 500 MHz) δ [ppm]: 5.43 (1H, m, H1), 5.15 (1H, br, NH), 3.38 (2H, br. s, H10), 2.37 (1H, ddd, J7s-7a= 8.8 Hz, J7s-1= 5.6 Hz, J7a-1= 5.6 Hz, H7s), 2.28 (1H, br. d, J4a-4s= 17.6 Hz, H4s), 2.19 (1H, br. d, J4a-4s= 17.6 Hz, H4a), 2.15 (1H, ddd, J1-7s= 5.6 Hz, J7s-7a = 8.8 Hz, 3H, H7a), 1.28 (3H, s, H8), 1.16 (1H, d, J7s-7a = 8.8 Hz, H7a), 0.81 (3H, s, H9), 0.13 (9H, s, Si(CH3)3)

1H-NMR (CD2D2O, 500 MHz) δ [ppm]: 5.27 (1H, m, H1), 4.78 (1H, t, J3H1=8 Hz, NH), 3.42 (1H, br. s, H10), 2.29 (1H, ddd, J7s-7a = 8.8 Hz, J3= 5.6 Hz, J7s-7a = 5.6 Hz, H7a), 2.15 (1H, br. d, J4a-4s= 17.6 Hz, J7s-7a = 8.8 Hz, J3= 5.6 Hz, J7a-1= 5.6 Hz, H7a).
Hz, H₄a), 2.03-2.10 (2H, m, H₄a), 1.95 (1H, m, H₃c), 1.20 (3H, s, H₈), 1.18 (1H, d, J₇c-₇a = 8.8 Hz, H₇a), 0.82 (3H, s, H₉), 0.21 (9H, s, Si(CH₃)₃).

1³C-NMR (CDCl₃, 125 MHz) δ [ppm]: 143.8 (C₂), 120.7 (C₃), 59.8 (C₁₀), 44.9 (C₅), 40.6 (C₁), 38.0 (C₇), 31.6 (C₄), 31.3 (C₇), 26.2 (C₉), 21.1 (C₈), -0.9 [Si(CH₃)₃].

1³C-NMR (C₆D₆, 125 MHz) δ [ppm]: 144.5 (C₂), 120.6 (C₃), 60.1 (C₁₀), 45.1 (C₅), 41.0 (C₁), 38.1 (C₇), 32.0 (C₄), 31.6 (C₇), 26.3 (C₉), 21.2 (C₈), -0.7 [Si(CH₃)₃].

GC-MS: tR (GC-MS Pr. 3) = 11.68 min; (EI) m/z (%): 240 [M+H]⁺ (28), 239 [M]⁺ (32), 224 [M–CH₃]⁺ (12), 168 [M+H–SiMe₃]⁺ (18), 150 [M–SiMe₃]⁺ (25), 134 [C₆H₅]⁺ (98), 118 [CH₃NHOSiMe₃]⁺ (100), 107 [C₆H₅NH₂]⁺ (40), 105 [Me₂SiONH₂]⁺ (95), 104 [Me₂SiONH]⁺ (38), 101 (80), 91 [C₆H₅]⁺ (20), 90 [Me₂SiOH]⁺ (80), 79 [C₆H₅]⁺ (20), 74 [Me₂SiH]⁺ (82), 72 [C₆H₅Si]⁺ (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–SiMe₃]⁺ (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-(1R,5R)-Pin-2-enyl]-O-tosyl hydroxylamine 152

A slurry of 0.5 g (-)-N-[10-(1R,5R)-pin-2-enyl]-hydroxylamine hydrochloride 150 (2.45 mmol, 1 eq.) and 0.74 g Et₃N (7.35 mmol, 3 eq.) in 20 mL n-hexane (distilled over Na) was stirred at room temperature for 1 h under N₂. 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. NaHCO₃ sol. and 30 mL brine. Drying over MgSO₄ and evaporation of the solvent in vacuo yielded a light yellow solid. Flash chromatography (silica gel, ʰBuOMe:MeOH = 10:1) and crystallization from Et₂O/n-hexane (1:1) afforded 0.68 g (2.1 mmol, 85 %) 152 as colorless crystals.
Molecular formula: $\text{C}_{17}\text{H}_{23}\text{NO}_3\text{S} \ [321.435]$  

Yield: 85% (0.68 g, colorless crystals)  

TLC: $R_f = 0.66 \ [\text{tBuOMe:MeOH} = 10:1]$  

Melting point: $131-133^\circ\text{C}$  

Optical rotation: $\left[\alpha\right]_D^\text{23} = -22.1 \ (c = 1.1 \text{ in CHCl}_3)$  

GC (GC Pr. 2): $t_R = 15.41 \text{ min}$  

IR (KBr), $\tilde{\nu} \ [\text{cm}^{-1}]$: 3394 (NH), 2913 (CH), 1658 (C=C), 1598 (Ph), 1334 (SO$_2$O), 1164 (SO$_2$O), 1093, 811, 748, 661.  

$^1\text{H-NMR} \ (\text{CDCl}_3, \ 500 \text{ MHz} \ \delta \ [\text{ppm}]): 7.78 \ (2\text{H}, \text{ d}, \ ^3J_{\text{ortho}} = 6.3 \text{ Hz}, \ ^3J_{\text{meta}} = 1.8 \text{ Hz}, \text{ Ph-ortho}), 7.36 \ (2\text{H}, \text{ d}, \ ^3J_{\text{ortho}} = 6.3 \text{ Hz}, \ ^3J_{\text{meta}} = 2.5 \text{ Hz Ph-meta}), 6.29 \ (1\text{H}, \text{ br}, \text{ NH}), 5.41 \ (1\text{H}, \text{ m}, \text{ H}_3), 3.41 \ (2\text{H}, \text{ br., s, H}_{10}), 2.46 \ (3\text{H}, \text{ s, Ph-CH}_3), 2.40 \ (1\text{H}, \text{ ddd}, \ ^2J_{\text{1-7s}} = 8.8 \text{ Hz}, \ ^2J_{\text{1-7a}} = 5.6 \text{ Hz, H}_7), 2.33 \ (1\text{H}, \text{ ddd}, \ ^2J_{\text{1-7s}} = 5.6 \text{ Hz, H}_7), 2.26 \ (1\text{H}, \text{ br. d, } \ ^2J_{\text{4a-4s}} = 19.5 \text{ Hz, H}_4)$, 2.18 \ (1H, br. d, $\ ^2J_{\text{4a-4s}} = 19.5 \text{ Hz, H}_4)$, 2.08 \ (1H, m, H$_6$), 1.29 \ (3H, s, H$_8$), 1.14 \ (1H, d, $\ ^3J_{\text{1-7a}} = 8.8 \text{ Hz, H}_7$), 0.82 \ (3H, s, H$_9$).  

$^{13}\text{C-NMR} \ (\text{CDCl}_3, \ 125 \text{ MHz} \ \delta \ [\text{ppm}]): 144.8 \ (\text{C}_{\text{meta}}), 141.6 \ (\text{C}_2), 129.8 \ (\text{C}-\text{S}), 129.6 \ (2 \times \text{C}_{\text{ortho}}), 129.5 \ (2 \times \text{C}_{\text{meta}}), 122.9 \ (\text{C}_3), 57.9 \ (\text{C}_6), 43.8 \ (\text{C}_4), 40.7 \ (\text{C}_7), 38.0 \ (\text{C}_8), 31.6 \ (\text{C}_4), 31.4 \ (\text{C}_3), 26.1 \ (\text{C}_8), 21.6 \ (\text{C}-\text{Ph}), 21.1 \ (\text{C}_9)$.  

MS (ESI) $m/\text{z} \ 344.0 \ [\text{M + Na}]^+\text{, } 664.7 \ [2\text{M + Na}]^+$.  

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/H₂O (2:1) afforded 12.93 g (32.70 mmol, 82%) 154 as white solid.

Molecular formula: C₂₂H₃₇NO₃S [395.60]
Yield: 82% (12.93 g, white solid) [lit. 182 60%]
TLC: Rᵣ = 0.45 [AcOEt:PE = 4:10]
Melting point: 134-135°C [lit. 182 134-135°C]
Optical rotation: [α]_D^26 = +26 (c = 1.1 in CHCl₃)

IR (KBr), ν [cm⁻¹]: 2935 (CH), 2852 (CH), 1747 (C=O), 1322 (SO₂N), 1225 (C-N), 1164, 1145, 1110, 1049, 979.

¹H-NMR (CDCl₃, 500 MHz) δ [ppm]: 3.32 (1H, d, J₁₀a-₁₀b = 14.4 Hz, H₁₀a), 3.31 (2H, m, H₁₁, H₁₇), 2.79 (1H, d, J₁₀a-₁₀b = 14.4 Hz, H₁₁₀), 2.60 (1H, ddd, J₅exo-₅endo = 11.9 Hz, J₅exo-₆ = 8.8 Hz, J₅exo-₄ = 4.4 Hz, H₅exo), 2.37 (1H, dd, J₅exo-₅endo = 18.2 Hz, J₅exo-₆ = 4.4 Hz, H₅exo), 2.07 (1H, dd, J₅endo-₅exo = 11.9 Hz, J₅endo-₆ = 8.8 Hz, H₅endo), 1.92 (1H, d, J₃endo-₃exo = 18.2 Hz, H₃sendo), 1.74-1.81 (12H, m, H₂₅₇₉), 1.58-1.64 (3H, m, H₂₈, H₂₉, H₃₀),
1.39 (1H, m, H₆), 1.26-1.34 (4H, m, H₇H₁₀), 1.19 (3H, s, H₉), 1.10-1.14 (2H, m, H₈H₉), 0.89 (3H, s, H₈).

¹³C-NMR (CDCl₃, 125 MHz) δ [ppm]: 215.8 (C₂), 59.0 (C₁), 57.6 (C₄C₇), 52.2 (C₉), 47.5 (C₇), 43.0 (C₄), 42.6 (C₃), 32.9 (C₁₁C₁₇), 32.5 (C₃C₄), 26.8 (C₉), 26.4 (C₇C₈), 25.3 (C₈), 25.2 (C₉C₁₀), 20.3 (C₆), 19.9 (C₅).


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.
Experimental Section

Molecular formula: \( C_{22}H_{38}N_{2}O_{3}S \) [410.61]

Yield: 96% (4.46 g, white crystals) [lit.\(^{13}\) 96%]

TLC: \( R_f = 0.66 \) [tBuOMe:MeOH = 10:1]

Melting point: 169-170 °C

Optical rotation: \([\alpha]_D^{24} = +0.8 \) (c = 1.5 in CHCl\(_3\))

IR (KBr), \( \bar{\nu} [\text{cm}^{-1}]\): 3367 (OH), 2937 (CH), 2856 (CH), 1687 (C=N), 1454 (CH\(_2\)), 1396 (CMe\(_2\)), 1324 (SO\(_2\)N), 1164, 1145, 1108, 1049, 981.

\(^1\)H-NMR (CDCl\(_3\), 500 MHz) \( \delta \) [ppm]: 3.35 (1H, d, \( 2J_{10a-10b} = 14.4 \) Hz, \( H_{10a} \)), 3.33 (2H, m, \( H_{11} \)), 2.89 (1H, d, \( 2J_{10a-10b} = 14.4 \) Hz, \( H_{11b} \)), 2.62 (1H, dd, \( 2J_{3\text{exo}-3\text{endo}} = 18.2 \) Hz, \( 3J_{3\text{exo}-4} = 4.1 \) Hz, \( H_{3\text{exo}} \)), 2.56 (1H, m, \( H_{3\text{endo}} \)), 2.13 (1H, d, \( 2J_{3\text{endo}-3\text{exo}} = 18.2 \) Hz, \( H_{3\text{endo}} \)), 1.93 (1H, m, \( H_{4} \)), 1.72-1.85 (13H, m, \( H_{\text{Cy}} \), \( H_{3\text{endo}} \)), 1.58-1.65 (2H, m, \( H_{6} \)), 1.28-1.35 (6H, m, \( H_{\text{Cy}} \), \( H_{7} \)), 1.10-1.17 (2H, m, \( H_{\text{Cy}} \)), 1.09 (3H, s, \( H_{9} \)), 0.86 (3H, s, \( H_{8} \)).

\(^{13}\)C-NMR (CDCl\(_3\), 125 MHz) \( \delta \) [ppm]: 169.4 (\( C_{2} \)), 57.5 (\( C_{11} \), \( C_{17} \)), 53.9 (\( C_{10} \)), 53.1 (\( C_{1} \)), 49.9 (\( C_{7} \)), 43.4 (\( C_{4} \)), 33.3 (\( C_{3} \)), 33.1 (\( C_{5} \)), 32.3 (\( C_{6} \)), 28.2 (\( C_{9} \)), 27.0 (\( C_{8} \)), 26.4 (\( C_{12} \)), 25.1 (\( C_{13} \)), 19.4 (\( C_{8} \)), 19.3 (\( C_{9} \)).

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\(_2\)N-Dicyclohexyl-2-chloro-2-nitrosocamphor-10-sulfonamide 74

A solution of 3 g (+)-N\(_2\)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.\textsuperscript{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\(_2\)N), 1166 (SO\(_2\)N), 1143 (C-Cl), 1108, 1051, 981, 894, 854, 775 (C-Cl).

\(^1\)H-NMR (CDCl\(_3\), 250 MHz) \(\delta\) [ppm]: 3.39 (1H, d, \(J_{10a-10b} = 14.4\) Hz, \(H_{10a}\)), 3.27 (1H, ddd, \(J_{5exo-5endo} = 9.1\) Hz, \(J_{5exo-4} = 3.1\) Hz, \(H_{5exo}\)), 3.12-3.17 (2H, m, \(H_{11}, H_{17}\)), 2.78 (1H, d, \(J_{10b-10a} = 14.4\) Hz, \(H_{10b}\)), 2.52 (1H, dd, \(J_{3exo-3endo} = 14.1\) Hz, \(J_{3exo-4} = 5.5\) Hz, \(H_{3exo}\)), 2.22 (1H, m, \(H_{5endo}\)), 2.14-2.19 (2H, m, \(H_{4}, H_{6a}\)), 1.92 (1H, d, \(J_{endo-exo} = 14.4\) Hz, \(H_{endo}\)), 1.89 (1H, m, \(H_{6b}\)), 1.75-1.80 (6H, m, \(H_{C6}\)), 1.65-1.71 (8H, m, \(H_{C6}\)), 1.56-1.62 (2H, m, \(H_{C6}\)), 1.24-1.31 (4H, m, \(H_{C6}\)), 1.23 (1H, s, \(H_{9}\)), 1.16 (3H, s, \(H_{8}\)).

\(^{13}\)C-NMR (CDCl\(_3\), 62 MHz) \(\delta\) [ppm]: 123.7 (C\(_2\)), 58.3 (C\(_1\)), 57.4 (C\(_{11}, C_{17}\)), 54.3 (C\(_7\)), 53.7 (C\(_{10}\)), 45.9 (C\(_4\)), 43.7 (C\(_3\)), 33.1 (C\(_{C6}\)), 32.3 (C\(_{C5}\)), 28.4 (C\(_8\)), 27.4 (C\(_6\)), 26.4 (C\(_{C3}\)), 26.4 (C\(_{C4}\)), 25.2 (C\(_{C7}\)), 20.3 (C\(_9\)), 20.8 (C\(_8\)).

MS (ESI) \(m/z\): 467.1 [M(C\(_{22}H_{37}ClN_2O_3S\) + Na\(^+\)], 469.2 [M(C\(_{22}H_{37}ClN_2O_3S\) + Na\(^+\)], 911.2 [2M(C\(_{22}H_{37}ClN_2O_3S\) + Na\(^+\)], 913.2 [2M(C\(_{22}H_{37}ClN_2O_3S\) + 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-mannofuranose

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 tBuOOH (11 mmol, 2.2 eq., 80% solution in tBuOO'Bu) were added carefully, under nitrogen atmosphere. The resulting red-brownish solution was heated to 60°C for 45 min, 50 mL H₂O were added, the organic phase was separated, washed with 20 mL brine and dried over Na₂SO₄. 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:** C₁₂H₁₉NO₇ [289.28]

**Yield:** 52% (0.75 g, colorless crystals) [lit.¹³⁷ 54%]

**Melting point:** 111-112°C [lit.¹³⁷ 111-112°C]

**TLC:**

Rₚ = 0.26 [AcOEt:PE = 1:4]

**Optical rotation:**

[α]₀D²⁶ = +17.9 (c = 0.9 in CHCl₃) [lit.¹³⁷ [α]₀D = +18.3 (c = 0.9 in CHCl₃)]

**GC (GC Pr. 2):**

tᵣ = 14.34 min

**IR (KBr), ν [cm⁻¹]:** 3001 (C-H), 2942 (CH₃), 2908 (CH₂), 1567 (NO₂ asymm.), 1485 (CH₂), 1374 (NO₂ sym.), 1266, 1214 (C-O-C), 1166, 1142, 1085 (C-O-C), 994, 971, 945, 847, 811.

**¹H-NMR (CD₂Cl₂, 500 MHz) δ [ppm]:** 5.65 (1H, s, H₁), 5.06 (1H, d, J₂,₃ = 5.6 Hz, H₂), 4.85 (1H, dd, J₃,₄ = 5.6 Hz, J₄,₅ = 3.7 Hz, H₃), 4.46 (1H, dd, J₅,₆α = 3.7 Hz, J₅,₆β = 7.2 Hz H₅), 4.40 (1H, ddd, J₄,₅ = 7.2 Hz, J₅,₆α = 6.2 Hz, J₅,₆β = 5.0 Hz, H₆a), 4.12 (1H, dd, J₆a,₆b = 8.8 Hz, J₆b,₆a = 6.2 Hz, H₆b), 4.07 (1H, dd, J₆a,₆b = 8.8 Hz, J₆b,₆a = 5.0 Hz, H₆ab), 1.49 (3H, s, CH₃), 1.42 (3H, s, CH₃), 1.35 (6H, s, 2 x CH₃).

**¹³C-NMR (CD₂Cl₂, 125 MHz) δ [ppm]:** 114.7 (C₄), 111.3 (C₅), 109.7 (C₆), 86.7 (C₇), 85.7 (C₈), 79.8 (C₉), 72.9 (C₁₀), 66.9 (C₁₁), 26.9 (CH₃), 26.1 (CH₃), 25.2 (CH₃), 24.8 (CH₃).

**MS (ESI) m/z (%):** 312.0 [M+Na]⁺, 500.5 [2M+Na–C₅H₉O₂]⁺, 601.4 [2M+Na]⁺.
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.) (1R,4S)-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 Et₂O) 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 Et₂O). 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:Et₂O = 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. NH₄Cl sol., the organic phase was separated, washed with 20 mL brine and dried over Na₂SO₄. 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.) (1R,4S)-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 Et₂O) 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 Et₂O). 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:Et₂O = 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: \( \text{C}_6\text{H}_9\text{NO} \) [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.

¹H-NMR (C\(_6\)D\(_6\), 250 MHz) \( \delta \) [ppm]: 5.82 (1H, dddd, 3\( \stackrel{2}{J} \)= 9.5 Hz, 3\( \stackrel{1}{J} \)= 5.0 Hz, 4\( \stackrel{2}{J} \)= 1.2 Hz, 5\( \stackrel{1}{J} \)= 1.2 Hz, \( H_2 \)), 5.73 (1H, dddd, 3\( \stackrel{2}{J} \)= 9.5 Hz, 3\( \stackrel{1}{J} \)= 4.1 Hz, 4\( \stackrel{2}{J} \)= 1.2 Hz, 5\( \stackrel{1}{J} \)= 1.2 Hz, \( H_3 \)), 5.66 (1H, dddt, 3\( \stackrel{4}{J} \)= 9.5 Hz, 3\( \stackrel{3}{J} \)= 4.1 Hz, 4\( \stackrel{4}{J} \)= 1.2 Hz, 5\( \stackrel{3}{J} \)= 1.2 Hz, \( H_4 \)), 5.57 (1H, ddddd, 3\( \stackrel{5}{J} \)= 9.5 Hz, 3\( \stackrel{4}{J} \)= 4.0 Hz, 4\( \stackrel{5}{J} \)= 4.6 Hz, 5\( \stackrel{4}{J} \)= 1.2 Hz, \( H_5 \)), 3.57 (1H, dddd, 3\( \stackrel{1}{J} \)= 8.3 Hz, 3\( \stackrel{0}{J} \)= 7.3 Hz, 4\( \stackrel{1}{J} \)= 1.2 Hz, \( H_1 \)), 2.51 (1H, dddd, 3\( \stackrel{6}{J} \)= 18.2 Hz, 4\( \stackrel{6}{J} \)= 7.3 Hz, 5\( \stackrel{5}{J} \)= 4.0 Hz, 6\( \stackrel{6}{J} \)= 1.2 Hz, \( H_6 \)).

¹³C-NMR (C\(_6\)D\(_6\), 62 MHz) \( \delta \) [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-(1R,5R)-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\(_2\)O) 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\(_2\)O = 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\(_4\)Cl sol., 15 mL satd. NaHCO\(_3\) sol. and 30 mL brine. Drying over MgSO\(_4\) and evaporation of solvent \textit{in vacuo} furnished a light-yellow oil which was purified by flash chromatography (silica gel, Et\(_2\)O:PE = 1:10, 1% vol. Et\(_3\)N) to afford 0.45 g (1.98 mmol, 36%) 179 as colorless oil.

---

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

Molecular formula: \( \text{C}_{16} \text{H}_{21} \text{N} \) \([227.35]\)

TLC: \( R_f = 0.39 \) \([\text{Et}_2\text{O}:\text{PE} = 1:10, 1\% \text{NEt}_3]\)

Optical rotation: \( [\alpha]_{D}^{23} = -20.3 \) (c = 0.5 in CHCl\(_3\))

GC (GC Pr. 2): \( t_R = 15.83 \text{ min} \)

IR (neat), ~\( \nu \) [cm\(^{-1}\)]: 3421 (NH), 3050 (CH arom.), 3020 (CH arom.), 2985 (\(=\text{C}-\text{H}\)), 2913 (CH\(_3\)), 2831 (CH\(_2\)), 1602 (C=C), 1467 (CH), 1429, 1315, 1263, 1178, 1093, 748 (C-H arom.), 690 (C-H arom.).

\(^1\)H-NMR (CDCl\(_3\), 250 MHz) \( \delta \) [ppm]: 7.12-7.18 (2H, m, Ph), 6.58-6.67 (3H, m, Ph), 5.44 (1H, m, H\(_3\)), 4.14 (1H, br., NH), 3.61 (2H, br. s, H\(_{10}\)), 2.39 (1H, ddd, \( J_{7\alpha,7\gamma} = 8.5 \) Hz, \( J_7 = 5.6 \) Hz, \( J_8 = 5.6 \) Hz, H\(_{7\alpha}\)), 2.14-2.31 (2H, m, H\(_4\)), 2.05-2.12 (2H, m, H\(_5\), H\(_6\)), 1.28 (3H, s, H\(_8\)), 1.17 (1H, d, \( J_{7\alpha,7\gamma} = 8.5 \) Hz, H\(_{7\alpha}\)), 0.85 (3H, s, H\(_9\)).

\(^{13}\)C-NMR (CDCl\(_3\), 62 MHz) \( \delta \) [ppm]: 148.4 (C arom.), 145.4 (C\(_3\)), 129.1 (2 x CH arom.), 117.9 (C\(_3\)), 117.2 (2 x CH arom.), 112.9 (CH arom.), 49.0 (C\(_{10}\)), 44.2 (C\(_1\)), 41.0 (C\(_8\)), 38.1 (C\(_2\)), 31.6 (C\(_4\)), 31.1 (C\(_7\)), 26.2 (C\(_9\)), 21.1 (C\(_6\)).

MS (EI) \( m/z \) (%): 228 [M+H]\(^+\) (8), 227 [M]\(^+\) (68), 226 [M–H]\(^+\) (9), 212 [M–CH\(_3\)]\(^+\) (3), 211 [M–H–CH\(_3\)]\(^+\) (5), 134 [Ph-NH\(_2\)-CH\(_2\)-CH=CH\(_2\)]\(^+\) (40), 119 [Ph-NH-CH=CH\(_2\)]\(^+\) (50), 106 [Ph-NH-CH\(_3\)]\(^+\) (100), 93 [Ph-NH\(_2\)]\(^+\) (63), 91 [C\(_7\)H\(_5\)]\(^+\) (75), 77 [C\(_6\)H\(_5\)]\(^+\) (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

A solution of 0.3 mmol hydroxylamines 147, 148, 151, and 152 in THF, respectively, was cooled to -78°C and 0.3 mmol MeLi (0.19 mL, 1.6 M in Et\(_2\)O) was added slowly via syringe.
After 1 h, an aliquot was quenched with saturated aqueous NH₄Cl, 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 Na₂SO₄ and the mixture was analysed by GC.

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

\[
\text{Molecular formula: } C_{10}H_{15}N [149.23]
\]

GC-MS: \( t_{R}(GC-MS \Pr.) = 5.35 \text{ min} \); (EI) \( m/z \) (%): 149 [M]⁺ (29), 148 [M-H]⁺ (38), 134 [M-CH₃]⁺ (100), 121 [M-HN=CH₂]⁺ (4), 106 [C₇H₆N]⁺ (96), 93 [C₇H₄]⁺ (25), 79 [C₆H₅]⁺ (45), 77 [C₆H₅]⁺ (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-(1R,5R)-pin-2-enyl]-O-benzyl hydroxylamine 148 in 5 mL \(n\)-hexane was cooled to -78°C, under N₂ atmosphere, and 1.7 mL PhLi (2.72 mmol, 1 eq., 1.6 M in cyclohexane:Et₂O = 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. NH₄Cl sol., 15 mL satd. NaHCO₃ sol. and 20 mL brine. Drying over Na₂SO₄ and evaporation of the solvent in vacuo furnished a light-yellow oil which was purified by flash chromatography (silica gel, Et₂O:PE = 1:10, 1% vol. Et₃N) to afford 0.29 g (1.28 mmol, 47%) 179 as colorless oil.

Electrophilic amination of Ph₂Cu(CN)Li 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 : Et₂O = 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-(1R,5R)-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. NH₄Cl 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 (Et₂O:PE = 1:10, 1% vol. Et₃N) 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-butyI 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 nBuLi (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 (1 eq.) 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-butyI 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 ZnBr₂ (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 H₂O, 10 mL ethyl acetate were added, the
organic phase was washed with 10 mL satd. NH₄Cl sol. and dried over MgSO₄. 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/CHCl₃ 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 H₂O, 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

\[
\begin{align*}
\text{Molecular formula:} & \quad \text{C}_{9}\text{H}_{12}\text{ClNO}_{2} [201.65] \\
\text{Appearance:} & \quad \text{white crystalline solid} \\
\text{IR (KBr), } \tilde{\nu} \ [\text{cm}^{-1}] & \quad 3425 (\text{OH br}), 2796 (\text{CH}), 1687 (\text{C}=\text{O}), 1637 (\text{NH}), 1448 (\text{CH}), 1403
\end{align*}
\]
(N-O), 1232, 1145, 1001, 975.

$^1$H-NMR (DMSO-D$_6$, 500 MHz) $\delta$ [ppm]: 8.02 (2H, d, $^3J$= 7.5 Hz, H$_{ortho}$), 7.72 (1H, dd, $^3J$=7.5 Hz, $^3J$=7.5 Hz, H$_{para}$), 7.56 (2H, dd, $^3J$=7.5 Hz, $^3J$=7.5 Hz, H$_{meta}$), 5.29 (1H, q, $^3J_{2,3}$=6.9 Hz, CH), 1.43 (3H, d, $^3J_{3,2}$= 6.9 Hz, CH$_3$).

$^{13}$C-NMR (DMSO-D$_6$, 125 MHz) $\delta$ [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-Cl]+, 188.2 [M-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$_2$O$_4$S [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$_2$N), 1143, 1110, 1049, 1027, 981.


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-nitrosocyclohexane 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. NH₄Cl sol., the organic phase was dried over Na₂SO₄ 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-nitrosocyclohexane 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 KHCO₃, extracted with ether and dried over Na₂SO₄. Hydroxylamine hydrochlorides 224 and 225 were isolated by precipitation from ether solution using gaseous hydrochloric acid.

O-(1-methylallyl)cyclohexanone oxime 221

![Structure of O-(1-methylallyl)cyclohexanone oxime 221](image)

**Molecular formula:** C₁₀H₁₇NO [167.25]

**Appearance:** colorless oil

**Yield:** see Table 6 and 7
**Experimental Section**

**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) \( \delta \) [ppm]: 5.91 (1H, ddd, \( ^3J_{2,3} = 17.3 \) Hz (trans), \( ^1J_{2,3} = 10.6 \) Hz (cis), \( ^3J_{2,1} = 5.8 \) Hz, H\(_2\)), 5.19 (1H, ddd, \( ^3J_{3,2} = 17.3 \) Hz, \( ^4J_{3,1} = 1.5 \) Hz, \( ^2J_{3\text{cis},3\text{trans}} = 1.4 \) Hz, H\(_3\) trans), 5.10 (1H, ddd, \( ^3J_{3,2} = 10.6 \) Hz, \( ^1J_{3,1} = 1.5 \) Hz, \( ^2J_{3\text{cis},3\text{trans}} = 1.4 \) Hz, H\(_3\) cis), 5.10 (1H, ddd, \( ^3J_{3,2} = 10.6 \) Hz, \( ^1J_{3,1} = 1.5 \) Hz, \( ^2J_{3\text{cis},3\text{trans}} = 1.4 \) Hz, H\(_3\) cis), 4.59 (1H, dtq, \( ^3J_{1,2} = 5.8 \) Hz, \( ^4J_{1,3} = 1.5 \) Hz, \( ^2J_{1\text{cis},1\text{trans}} = 1.4 \) Hz, H\(_4\) cis), 2.45-2.50 (2H, m, C\(_2\)H\(_2\)), 2.17-2.22 (2H, m, CH\(_2\)), 1.56-1.68 (6H, m, CH\(_2\)), 1.29 (3H, d, \( ^3J_{4,1} = 6.4 \) Hz, H\(_4\)).

**\(^13\)C-NMR** (CDCl\(_3\), 125 MHz) \( \delta \) [ppm]: 160.0 (C=N), 140.2 (C\(_2\)), 114.7 (C\(_3\)), 78.5 (C\(_1\)), 32.3 (CH\(_2\)), 25.9 (CH\(_2\)), 25.4 (CH\(_2\)), 25.8 (CH\(_2\)), 19.8 (C\(_4\)).

**GC-MS:** \( t_r \) (GC-MS Pr. 2) = 9.59 min; (EI) \( m/\varepsilon \) (%): 167 [M]+ (14), 152 [M-CH\(_3\)]+ (10), 113 [C\(_9\)H\(_{10}\)NO]+ (14), 96 [C\(_8\)H\(_{10}\)NO]+ (17), 85 [C\(_6\)H\(_{10}\)NO]+ (19), 55 [C\(_4\)H\(_7\)NO]+ (100); (CI) \( m/\varepsilon \): 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](image)

**Molecular formula:** C\(_{11}\)H\(_{19}\)NO [181.27]

**Appearance:** colorless oil

**Yield:** see Table 6 and 7

**TLC:** \( R_f = 0.52 \) [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\(_2\)Cl\(_2\), 500 MHz) \( \delta \) [ppm]: 6.01 (1H, dd, \( ^3J_{2,3} = 17.5 \) Hz (trans), \( ^1J_{2,3} = 10.6 \) Hz (cis), H\(_2\)), 5.09 (1H, dd, \( ^3J_{3,2} = 17.5 \) Hz, \( ^2J_{3\text{cis},3\text{trans}} = 1.5 \) Hz, H\(_3\) trans), 5.00 (1H, dd, \( ^3J_{3,2} = 10.9 \) Hz, \( ^2J_{3\text{cis},3\text{trans}} = 1.5 \) Hz, H\(_3\) cis), 2.42-2.45 (2H, m, CH\(_2\)), 1.55-1.63 (6H, m, CH\(_2\)), 1.31 (6H, s, H\(_4\), H\(_5\)).

**\(^13\)C-NMR** (CD\(_2\)Cl\(_2\), 125 MHz) \( \delta \) [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]+ (5), 166 [M-CH3]+ (2), 151 [M-C2H3]+ (3), 114 [C6H12NO]+ (7), 69 [C5H3]+ (100), 55 [C4H3]+ (5); (CI) \( m/z \) 182 [M+H]+, 114 [C6H12NO]+.

Elemental analysis (%):

Calcd: C 72.88  H 10.56  N 7.73  O

Found: C 72.55  H 10.63  N 7.45

O-(1-phenylylally)cyclohexanone oxime

\[
\begin{align*}
\text{Molecular formula:} & \quad C_{15}H_{19}NO \ [229.32] \\
\text{Appearance:} & \quad \text{light yellow oil} \\
\text{Yield:} & \quad \text{see Table 6 and 7} \\
\text{TLC:} & \quad R_f = 0.43 \ [\text{BuOMe:PE} = 1:5] \\
\text{IR \ (neat),} & \quad \tilde{\nu} \ [\text{cm}^{-1}]: \ 3084 \ (=\text{CH}_2), \ 3062 \ (=\text{CH}), \ 3029 \ (=\text{CH}), \ 2982 \ (\text{CH}), \ 2932 \ (\text{CH}_2), \ 2858 \ (\text{CH}_3), \ 1641 \ (\text{C=N}), \ 1449 \ (\text{CH}_2), \ 1346 \ (\text{CH}_3), \ 1254 \ (\text{N-O}), \ 1026 \ (\text{C-O}), \ 990 \ (\text{CH}), \ 931 \ (\text{CH}), \ 918 \ (\text{CH}), \ 888 \ (\text{CH}), \ 700 \ (\text{CH}). \\
\text{\( ^1\text{H-NMR} \) (CDCl3, 250 MHz) \( \delta \) [ppm]: \ 7.22-7.33 \ (5H, \text{arom}), \ 6.06 \ (1H, \text{dd}, \ 3J_2,3 = 10.6 \ Hz \ (\text{trans}), \ 3J_2,1 = 6.2 \ Hz \ (\text{cis}), \ 3J_1,2 = 6.2 \ Hz \ (\text{H}_2), \ 5.54 \ (1H, \text{dt}, \ 3J_1,2 = 6.2 \ Hz, \ 3J_1,3 = 1.2 \ Hz, \ \text{H}_3), \ 5.24 \ (1H, \text{dd}, \ 3J_3,2 = 17.2 \ Hz, \ 3J_3,\text{cis-trans} = 1.2 \ Hz, \ \text{H}_3 \ (\text{trans}), \ 5.20 \ (1H, \text{dd}, \ 3J_3,2 = 10.6 \ Hz, \ 3J_3,\text{cis-trans} = 1.2 \ Hz, \ \text{H}_3 \ (\text{cis}), \ 2.52-2.57 \ (2\text{H}, \text{m, CH}_2), \ 2.15-2.19 \ (2\text{H}, \text{m, CH}_2), \ 1.51-1.70 \ (6\text{H}, \text{m, CH}_2). \\
\text{\( ^{13}\text{C-NMR} \) (CDCl3, 63 MHz) \( \delta \) [ppm]: \ 161.0 \ (\text{C=N}), \ 140.8 \ (\text{Ph}), \ 138.4 \ (\text{C}_2), \ 128.2 \ (\text{Ph}), \ 127.4 \ (\text{Ph}), \ 127.0 \ (\text{Ph}), \ 116.2 \ (\text{C}_3), \ 84.8 \ (\text{C}_4), \ 32.1 \ (\text{CH}_2), \ 27.0 \ (\text{CH}_2), \ 25.8 \ (\text{CH}_2), \ 25.7 \ (\text{CH}_2), \ 25.6 \ (\text{CH}_3). \\
\text{GC-MS:} \ t_R \ (GC-MS Pr. 2) = 14.72 \ min; \ (EI) \ m/z \ (\%) : \ 230 \ [M+H]^+ \ (2), \ 117 \ [C_6H_3]^+ \ (100), \ 115 \ [C_5H_3]^+ \ (20), \ 105 \ [C_4H_3]^+ \ (5), \ 91 \ [C_3H_3]^+ \ (10), \ 77 \ [C_2H_3]^+ \ (5); \ (CI) \ m/z : \ 230 \ [M+H]^+, \ 117 \ [C_6H_3]^+. \\
\text{Elemental analysis (%):} \quad \text{Calcd: C 78.56 H 8.35 N 6.11} \\
\text{Found: C 78.40 H 8.33 N 6.12}
Experimental Section

N-(1-methylallyl)hydroxylamine hydrochloride 224

\[
\begin{align*}
\text{Molecular formula:} & \quad C_4H_{10}ClNO \ [123.58] \\
\text{Appearance:} & \quad \text{white solid} \\
\text{Yield:} & \quad \text{see Table 7} \\
\text{Melting point:} & \quad 58-61 \degree C
\end{align*}
\]

IR (KBr), \( \tilde{\nu} \ [\text{cm}^{-1}] \): 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).

\(^1H\)-NMR (D\(_2\)O, 500 MHz) \( \delta \ [\text{ppm}] \): 5.62 (1H, dddq, \( ^3J_{2,3} = 17.3 \text{ Hz} \) (trans), \( ^4J_{2,3} = 10.2 \text{ Hz} \) (cis), \( ^3J_{2,1} = 7.4 \text{ Hz}, ^4J_{2,1} = 1.45 \text{ Hz}, H_2 \)), 5.23 (1H, ddd, \( ^3J_{3,2} = 17.3 \text{ Hz}, ^4J_{3,2} = 2.5 \text{ Hz}, ^2J_{\text{cis,trans}} = 1.2 \text{ Hz}, H_3 \) (trans)), 5.19 (1H, ddd, \( ^3J_{3,2} = 10.2 \text{ Hz}, ^4J_{3,2} = 2.2 \text{ Hz}, ^2J_{\text{cis,trans}} = 1.0 \text{ Hz}, H_3 \) (cis)), 3.71 (1H, dtq, \( ^3J_{1,2} = 7.4 \text{ Hz}, ^4J_{1,2} = 1.5 \text{ Hz}, ^3J_{1,4} = 6.6 \text{ Hz}, H_1 \)), 1.10 (3H, dd, \( ^3J_{4,1} = 6.6 \text{ Hz}, ^4J_{4,1} = 1.2 \text{ Hz}, H_4 \)).

\(^{13}C\)-NMR (D\(_2\)O, 125 MHz) \( \delta \ [\text{ppm}] \): 135.9 (C\(_2\)), 122.4 (C\(_3\)), 59.7 (C\(_4\)), 13.9 (C\(_5\)).

MS (EI) \( m/z \ [%] \): 87 [M-HCl]+ (7), 72 [C\(_3\)H\(_6\)NO]+ (35), 55 [C\(_3\)H\(_4\)]+ (60), 41 [C\(_3\)H\(_3\)]+ (100), 40 [C\(_3\)H\(_4\)]+ (69), 39 [C\(_3\)H\(_3\)]+ (42).

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

\[
\begin{align*}
\text{Molecular formula:} & \quad C_5H_{12}ClNO \ [137.61] \\
\text{Appearance:} & \quad \text{white solid} \\
\text{Yield:} & \quad \text{see Table 7} \\
\text{Melting point:} & \quad 60-63 \degree C
\end{align*}
\]

IR (KBr), \( \tilde{\nu} \ [\text{cm}^{-1}] \): 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).

\(^1H\)-NMR (DMSO-D\(_6\), 500 MHz) \( \delta \ [\text{ppm}] \): 10.41 (b, NH\(_2\)\(^+\)), 6.03 (1H, dd, \( ^3J_{2,3} = 17.5 \text{ Hz} \) (trans), \( ^3J_{2,3} = 10.6 \text{ Hz} \) (cis), \( ^4J_{2,3} = 1.5 \text{ Hz}, H_3 \)), 5.35 (1H, d, \( ^3J_{3,2} = 17.5 \text{ Hz}, H_4 \) (trans)), 5.31 (1H, d, \( ^3J_{3,2} = 10.6 \text{ Hz}, H_4 \) (cis)), 1.36 (6H, s, H\(_4\), H\(_5\)).

\(^{13}C\)-NMR (DMSO-D\(_6\), 125 MHz) \( \delta \ [\text{ppm}] \): 137.2 (C\(_2\)), 117.5 (C\(_3\)), 61.6 (C\(_4\)), 21.08 (C\(_5\), C\(_6\)).
Experimental Section

**MS** (EI) \( m/z \) (%): 101 [M-HCl\(^+\)]\(^+\) (6), 86 [C\(_5\)H\(_6\)NO\(^+\)]\(^+\) (11), 84 [C\(_5\)H\(_{10}\)N\(^+\)]\(^+\) (5), 74 [C\(_3\)H\(_4\)NO\(^+\)]\(^+\) (8), 69 [C\(_5\)H\(_4\)]\(^+\) (53), 46 [C\(_2\)H\(_8\)N\(^+\)]\(^+\) (15), 41 [C\(_3\)H\(_4\)]\(^+\) (100), 40 [C\(_3\)H\(_4\)]\(^+\) (30), 39 [C\(_3\)H\(_3\)]\(^+\) (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**

![Image of 2,2,6,6-tetramethylcyclohexanone oxime]

- **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), \( \bar{\nu} \) [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) \( \delta \) [ppm]: 8.74 (1H, br, OH), 1.60-1.65 (2H, m, CH\(_2\)), 1.51-1.56 (4H, m, 2xCH\(_2\)), 1.36 (6H, s, 2xCH\(_3\)), 1.21 (6H, s, 2xCH\(_3\)).
- **\(^13\)C-NMR** (CDCl\(_3\), 125 MHz) \( \delta \) [ppm]: 168.6 (C=N), 40.5 (CH\(_2\)), 37.9 (C), 37.6 (CH\(_2\)), 37.0 (C), 30.5 (2xCH\(_3\)), 26.7 (2xCH\(_3\)), 17.4 (CH\(_3\)).
- **MS** (EI) \( m/z \) (%): 169 [M\(^+\)]\(^+\) (10), 154 [M-CH\(_3\)]\(^+\) (12), 152 [M-OH\(^+\)]\(^+\) (32), 141 [C\(_9\)H\(_{15}\)NO\(^+\)]\(^+\) (7), 137 [C\(_9\)H\(_{13}\)]\(^+\) (10), 126 [C\(_8\)H\(_{14}\)N\(^+\)]\(^+\) (8), 100 [C\(_8\)H\(_{15}\)NO\(^+\)]\(^+\) (35), 87 [C\(_8\)H\(_{16}\)NO\(^+\)]\(^+\) (19), 69 [C\(_8\)H\(_4\)]\(^+\) (100), 55 [C\(_4\)H\(_4\)]\(^+\) (60), 41 [C\(_3\)H\(_3\)]\(^+\) (63), 27 [HCN\(^+\)]\(^+\) (20).
- **Elemental analysis** (%): Caled: 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 BuOCl (20 mmol, 1.1 eq., 70% w/w in 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

![Structure](image)

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), ν [cm⁻¹]: 2977 (CH₃), 2939 (CH₃), 2872 (CH₂), 1578 (N=O), 1471 (CH₃), 1386 (CH₃), 1370 (CH₃), 1202 (CH₄), 627 (C-Cl).

¹H-NMR (CD₂Cl₂, 500 MHz) δ [ppm]: 2.71 (2H, m, C₅H₂), 2.38 (1H, m, 4-C₅H₂), 2.11 (1H, m, 4-C₅H₂), 1.94 (2H, m, CH₂), 1.34 (6H, s, C₆H₃), 0.21 (6H, s, C₆H₃).

¹³C-NMR (CD₂Cl₂, 125 MHz) δ [ppm]: 136.3 (C), 42.1 (2xCH), 40.2 (2xCH₂), 27.5 (CH₂), 25.7 (CH₃), 19.9 (CH₂).

MS (EI) m/z (%): 168 [M-Cl]+ (6), 160 [C₅H₃¹⁵Cl]+ (4), 158 [C₅H₅³⁵Cl]+ (13), 145 [C₆H₁₁³⁵Cl]+ (14), 143 [C₆H₁₂³⁵Cl]+ (43), 137 [C₆H₁₁]⁺ (53), 133 [C₆H₁₂³⁷Cl]+ (4), 131 [C₆H₁₂³⁷Cl]+ (13), 123 [C₆H₁₃]+ (25), 107 [C₅H₁]⁺ (18), 105 [C₆H₁]⁺ (19), 103 [C₆H₁]⁺ (53), 97 [C₆H₁]⁺ (15), 95 [C₆H₁]⁺ (37), 91 [C₆H₁]⁺ (15), 83 [C₆H₁]⁺ (24), 81 [C₆H₁]⁺ (38), 79 [C₆H₁]⁺ (18), 77 [C₆H₁]⁺ (29), 69 [C₆H₁]⁺ (100), 67 [C₆H₁]⁺ (37), 57 [C₆H₁]⁺ (35), 55 [C₆H₁]⁺ (45), 43 [C₆H₁]⁺ (25), 41 [C₆H₁]⁺ (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.
temperature for 12 h. The slightly blue solution was quenched with 5 mL satd. NaHCO₃ sol. and the white precipitate formed was dissolved by adding 10 mL satd. NH₄Cl sol. Separation of the organic phase, drying over Na₂SO₄ and evaporation of solvent *in vacuo* afforded 0.12 g *O*-(1-methylallyl)-2,2,6,6-tetramethylcyclohexanone 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

![Structure of O-(1-methylallyl)-2,2,6,6-tetramethylcyclohexanone oxime 233](image_url)

**Molecular formula:** C₁₄H₂₅NO [223.35]

**Appearance:** colorless oil

**TLC:** Rf = 0.62 [PE]

**GC (GC Pr. 2):** tᵣ = 10.6 min

**IR (neat), ν [cm⁻¹]:** 3082 (=CH₂), 2959 (CH), 2867 (CH₃), 1645 (C=N), 1464 (CH₂), 1382 (CH₃), 1362 (CH₃), 1362 (CH₃), 1382 (CH₃), 1232 (N-O), 946 (C=CH).

**¹H-NMR (CD₂Cl₂, 500 MHz) δ [ppm]:** 5.92 (1H, ddd, 3 J₂,₃ = 17.3 Hz (trans), 3 J₂,₃ = 10.6 Hz (cis), 3 J₂,₁ = 5.7 Hz, H₂), 5.18 (1H, ddd, 3 J₁,₂ = 17.3 Hz, 4 J₁,₃ = 1.5 Hz, 3 J₁,₃ = 1.4 Hz, H₁, trans), 5.07 (1H, ddd, 3 J₁,₂ = 10.6 Hz, 4 J₁,₁ = 1.5 Hz, 3 J₁,₃ = 1.4 Hz, H₁, trans), 4.51 (1H, dtq, 3 J₁,₁ = 5.7 Hz, 3 J₁,₃ = 1.4 Hz, 3 J₃,₃ = 6.7 Hz, H₃), 1.56-1.6 (2H, m, CH₂), 1.47-1.50 (4H, m, CH₂), 1.18 (2H, s, CH₃), 1.27 (3H, d, 3 J₃,₃ = 6.7 Hz, H₄), 1.26 (3H, s, CH₃), 1.16 (3H, s, CH₃), 1.14 (3H, s, CH₃).

**¹³C-NMR (CD₂Cl₂, 125 MHz) δ [ppm]:** 167.1 (C=N), 140.7 (C₂), 114.4 (C₁), 79.5 (C₂), 41.4 (CH₂), 38.5 (CH₂), 38.5 (C), 37.1 (C), 31.1 (CH₂), 31.1 (CH₂), 27.5 (CH₂), 27.5 (CH₂), 19.9 (C₂), 18.0 (CH₂).
**MS (EI) m/z (%)**: 223 [M]+ (5), 208 [M-CH₃]+ (4), 169 [M-C₄H₆]+ (18), 152 [C₁₀H₁₈N]+ (25), 100 [C₅H₁₀NO]+ (18), 87 [C₅H₉NO]+ (8), 69 [C₄H₆]+ (75), 55 [C₄H₇]+ (100), 41 [C₃H₅]+ (30), 29 [C₂H₅]+ (12), 27 [HCN]+ (20).

**Elemental analysis (%):**

<table>
<thead>
<tr>
<th></th>
<th>Calcd:</th>
<th>Found:</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>75.28</td>
<td>75.22</td>
</tr>
<tr>
<td>H</td>
<td>11.28</td>
<td>11.14</td>
</tr>
<tr>
<td>N</td>
<td>6.27</td>
<td>6.20</td>
</tr>
</tbody>
</table>

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. NH₄Cl sol. and 20 mL brine. Drying over Na₂SO₄, 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(OiPr)_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(OiPr)_3 were added via syringe. The dark-red solution was stirred at -78°C for 30 min and then added via cannula 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.\textsuperscript{184}121-122°C]
TLC: R_f = 0.44 [AcOEt:PE = 3:2]
Optical rotation:
\[ [\alpha]_D^{25} = +43 \text{ (c = 1.0 in CHCl}_3) \]
\[ [\alpha]_D^{20} = +49 \text{ (c=1.2 in CHCl}_3]\]

IR (KBr), ν [cm\textsuperscript{-1}]: 3054 (C-H), 2989 (CH\textsubscript{3}), 1793 (C=O), 1421 (CH\textsubscript{2}), 1376, 1265, 1218 (C-O-C), 1186, 1151, 1118, 1070 (C-O-C), 997, 975, 944, 896, 842.

\textsuperscript{1}H-NMR (CD\textsubscript{2}Cl\textsubscript{2}, 250 MHz) δ [ppm]: 4.79-4.86 (2H, m, H\textsubscript{2}, H\textsubscript{3}), 4.37-4.40 (2H, m, H\textsubscript{5}, H\textsubscript{4}), 4.05 (2H, m, H\textsubscript{6}), 1.44 (3H, s, CH\textsubscript{3}), 1.43 (3H, s, CH\textsubscript{3}), 1.40 (3H, s, CH\textsubscript{3}), 1.35 (3H, s, CH\textsubscript{3}).

\textsuperscript{13}C-NMR (CD\textsubscript{2}Cl\textsubscript{2}, 62.89 MHz) δ [ppm]: 173.7 (C\textsubscript{1}), 114.6 (C\textsubscript{2}), 110.0 (C\textsubscript{6}), 78.7 (C\textsubscript{4}), 76.5 (C\textsubscript{3}), 67.7 (C\textsubscript{5}), 67.4 (C\textsubscript{3}), 57.0 (C\textsubscript{3}), 51.1 (C\textsubscript{3}), 46.4 (C\textsubscript{3}), 45.5 (C\textsubscript{3}), 42.8 (C\textsubscript{3}), 40.7 (C\textsubscript{3}), 37.9 (C\textsubscript{3}), 36.1 (C\textsubscript{3}), 31.4 (C\textsubscript{3}), 29.4 (C\textsubscript{3}), 28.2 (C\textsubscript{3}), 24.7 (C\textsubscript{3}), 21.4 (C\textsubscript{3}), 20.7 (C\textsubscript{3}), 19.6 (C\textsubscript{3}), 18.9 (C\textsubscript{3}), 18.5 (C\textsubscript{3}), 18.0 (C\textsubscript{3}), 17.4 (C\textsubscript{3}), 17.0 (C\textsubscript{3}), 16.6 (C\textsubscript{3}), 16.2 (C\textsubscript{3}), 15.9 (C\textsubscript{3}), 15.6 (C\textsubscript{3}), 15.3 (C\textsubscript{3}), 14.9 (C\textsubscript{3}), 14.5 (C\textsubscript{3}), 14.2 (C\textsubscript{3}), 13.9 (C\textsubscript{3}), 13.6 (C\textsubscript{3}), 13.4 (C\textsubscript{3}), 13.1 (C\textsubscript{3}), 12.8 (C\textsubscript{3}), 12.6 (C\textsubscript{3}), 12.3 (C\textsubscript{3}), 12.1 (C\textsubscript{3}), 11.9 (C\textsubscript{3}), 11.7 (C\textsubscript{3}), 11.5 (C\textsubscript{3}), 11.3 (C\textsubscript{3}), 11.1 (C\textsubscript{3}), 10.9 (C\textsubscript{3}), 10.7 (C\textsubscript{3}), 10.5 (C\textsubscript{3}), 10.3 (C\textsubscript{3}), 10.1 (C\textsubscript{3}), 9.9 (C\textsubscript{3}), 9.7 (C\textsubscript{3}), 9.5 (C\textsubscript{3}), 9.3 (C\textsubscript{3}), 9.1 (C\textsubscript{3}), 8.9 (C\textsubscript{3}), 8.7 (C\textsubscript{3}), 8.5 (C\textsubscript{3}), 8.3 (C\textsubscript{3}), 8.1 (C\textsubscript{3}), 7.9 (C\textsubscript{3}), 7.7 (C\textsubscript{3}), 7.5 (C\textsubscript{3}), 7.3 (C\textsubscript{3}), 7.1 (C\textsubscript{3}), 6.9 (C\textsubscript{3}), 6.7 (C\textsubscript{3}), 6.5 (C\textsubscript{3}), 6.3 (C\textsubscript{3}), 6.1 (C\textsubscript{3}), 5.9 (C\textsubscript{3}), 5.7 (C\textsubscript{3}), 5.5 (C\textsubscript{3}), 5.3 (C\textsubscript{3}), 5.1 (C\textsubscript{3}), 4.9 (C\textsubscript{3}), 4.7 (C\textsubscript{3}), 4.5 (C\textsubscript{3}), 4.3 (C\textsubscript{3}), 4.1 (C\textsubscript{3}), 3.9 (C\textsubscript{3}), 3.7 (C\textsubscript{3}), 3.5 (C\textsubscript{3}), 3.3 (C\textsubscript{3}), 3.1 (C\textsubscript{3}), 2.9 (C\textsubscript{3}), 2.7 (C\textsubscript{3}), 2.5 (C\textsubscript{3}), 2.3 (C\textsubscript{3}), 2.1 (C\textsubscript{3}), 1.9 (C\textsubscript{3}), 1.7 (C\textsubscript{3}), 1.5 (C\textsubscript{3}), 1.3 (C\textsubscript{3}), 1.1 (C\textsubscript{3}), 0.9 (C\textsubscript{3}), 0.7 (C\textsubscript{3}), 0.5 (C\textsubscript{3}), 0.3 (C\textsubscript{3}), 0.1 (C\textsubscript{3}).
Experimental Section

76.3 (C₄H₄), 73.1 (C₅H₅), 66.7 (C₆H₆), 27.0 (CH₃), 26.9 (CH₃), 25.9 (CH₃), 25.2 (CH₃).

**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-\( \alpha \)-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. NH₄Cl sol. and dried over Na₂SO₄. 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-\( \alpha \)-D-mannofuranosyl)-1-methyl-2-propenylidene nitrone 250**

\[
\text{C}_{16}H_{25}NO_{6} [327.37] \\
\text{colorless vitreous solid} \\
\left[a\right]_{D}^{25} = +23 (c = 1.0 \text{ in CHCl}_3) \\
R_\text{TLC} = 0.27 [\text{AcOEt:PE:EtOH} = 20:2:1] \\
\text{IR (KBr), } \tilde{\nu} [\text{cm}^{-1}]: 2987 (\text{CH}), 2938 (\text{CH}), 1521 (\text{C=\( N^+ \))}, 1456 (\text{CH}), 1373, 1261, 1209, 1161, 1114, 1066, 847, 755.
\textbf{1H-NMR} (CD₂Cl₂, 500 MHz) \(\delta\) [ppm]:

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

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

\textbf{13C-NMR} (CD₂Cl₂, 125 MHz) \(\delta\) [ppm]:

(Z)-Isomer: 147.3 (\(\text{C} = \text{N}\)), 127.1 (\(-\text{CH}_2\)), 120.6 (\(\text{CH}=-\)), 112.7 (\(\text{C}_7\)), 109.3 (\(\text{C}_4\)), 95.6 (\(\text{C}_3\)), 85.7 (\(\text{C}_2\)), 84.0 (\(\text{C}_5\)), 80.8 (\(\text{C}_6\)), 73.2 (\(\text{C}_5\)), 66.6 (\(\text{C}_6\)), 26.7 (\(\text{CH}_3\)), 25.8 (\(\text{CH}_3\)), 25.2 (\(\text{CH}_3\)), 24.1 (\(\text{CH}_3\)), 12.9 (\(-\text{C-CH}_3\)).

(E)-Isomer: 146.8 (\(\text{C} = \text{N}\)), 128.6 (\(-\text{CH}_2\)), 123.8 (\(\text{CH}=-\)), 112.1 (\(\text{C}_7\)), 109.1 (\(\text{C}_6\)), 96.9 (\(\text{C}_4\)), 85.5 (\(\text{C}_2\)), 84.1 (\(\text{C}_5\)), 80.5 (\(\text{C}_6\)), 73.6 (\(\text{C}_5\)), 66.7 (\(\text{C}_6\)), 26.8 (\(\text{CH}_3\)), 26.0 (\(\text{CH}_3\)), 25.2 (\(\text{CH}_3\)), 24.4 (\(\text{CH}_3\)), 13.4 (\(-\text{C-CH}_3\)).


**Reaction of 1-deoxy-2,3:5,6-di-O-isopropylidene-1-nitro-\(\alpha\)-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 \textit{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 chromatography 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 BF₃·OEt₂

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 BF₃·OEt₂ (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. NH₄Cl 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 showed a practically negligible decrease of concentration (less than 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 BF₃·OEt₂

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 BF₃·OEt₂ (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 NH₄Cl 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.

<table>
<thead>
<tr>
<th>Measurement device</th>
<th>Nonius KappaCCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C22 H37 Cl N2 O3 S 92%</td>
</tr>
<tr>
<td></td>
<td>C22 H37 Cl N2 O4 S 8% impurity</td>
</tr>
<tr>
<td>Formula weight</td>
<td>446.37</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, P 21 21 21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.9650(4) Å alpha = 90.000(4) deg.</td>
</tr>
<tr>
<td></td>
<td>b = 15.8530(7) Å beta = 90.000(4) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 16.2330(8) Å gamma = 90.000(4) deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>2307.07(18) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.285 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.282 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>963</td>
</tr>
<tr>
<td>Crystal size, colour and habit</td>
<td>0.30 x 0.29 x 0.28 mm³, blue cuboid</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.39 to 30.00 deg.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-12&lt;=h&lt;=12, -22&lt;=k&lt;=22, -22&lt;=l&lt;=22</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>6710 / 6710 [R(int) = 0.0000]</td>
</tr>
<tr>
<td>Completeness to theta = 30.00</td>
<td>99.6%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9253 and 0.9202</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>6710 / 2 / 321</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.023</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0459, wR2 = 0.1182 [5855]</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0556, wR2 = 0.1259</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.04(6)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.505 and -0.260 eÅ⁻³</td>
</tr>
</tbody>
</table>
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 (Å²x10^3). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>1004(1)</td>
<td>4760(1)</td>
<td>8700(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>Cl(1)</td>
<td>-1315(1)</td>
<td>2648(1)</td>
<td>9438(1)</td>
<td>40(1)</td>
</tr>
<tr>
<td>Cl(1A)</td>
<td>-227(12)</td>
<td>2110(6)</td>
<td>9600(6)</td>
<td>62(3)</td>
</tr>
<tr>
<td>O(4)</td>
<td>-1680(3)</td>
<td>2370(7)</td>
<td>9020(5)</td>
<td>310(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>1672(2)</td>
<td>5185(1)</td>
<td>9524(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>-2232(2)</td>
<td>3429(1)</td>
<td>8052(2)</td>
<td>49(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>1843(2)</td>
<td>5089(1)</td>
<td>8015(1)</td>
<td>41(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>-571(2)</td>
<td>4850(1)</td>
<td>8699(1)</td>
<td>45(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>-3250(2)</td>
<td>3557(1)</td>
<td>8515(1)</td>
<td>62(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>3213(3)</td>
<td>5488(2)</td>
<td>9639(2)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3581(3)</td>
<td>6282(2)</td>
<td>9148(2)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>5166(7)</td>
<td>6610(4)</td>
<td>9379(4)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>6319(3)</td>
<td>5921(2)</td>
<td>9275(2)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>5940(3)</td>
<td>5127(2)</td>
<td>9763(2)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>4389(3)</td>
<td>4808(2)</td>
<td>9512(3)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(1A)</td>
<td>3314(17)</td>
<td>5412(9)</td>
<td>9354(10)</td>
<td>28(4)</td>
</tr>
<tr>
<td>C(2A)</td>
<td>3443(15)</td>
<td>6362(8)</td>
<td>9529(11)</td>
<td>33(3)</td>
</tr>
<tr>
<td>C(3A)</td>
<td>4890(3)</td>
<td>6600(2)</td>
<td>9330(2)</td>
<td>35(6)</td>
</tr>
<tr>
<td>C(4A)</td>
<td>6251(17)</td>
<td>6141(9)</td>
<td>9733(10)</td>
<td>44(4)</td>
</tr>
<tr>
<td>C(5A)</td>
<td>6005(19)</td>
<td>5294(10)</td>
<td>9522(11)</td>
<td>34(4)</td>
</tr>
<tr>
<td>C(6A)</td>
<td>4480(2)</td>
<td>4890(12)</td>
<td>9763(11)</td>
<td>33(5)</td>
</tr>
<tr>
<td>C(7)</td>
<td>810(8)</td>
<td>5149(4)</td>
<td>10313(3)</td>
<td>45(2)</td>
</tr>
<tr>
<td>C(8)</td>
<td>1417(3)</td>
<td>4569(2)</td>
<td>10952(2)</td>
<td>34(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>305(6)</td>
<td>4495(4)</td>
<td>11683(3)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>-121(4)</td>
<td>5349(2)</td>
<td>12015(2)</td>
<td>50(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>-742(6)</td>
<td>5929(3)</td>
<td>11348(3)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>316(5)</td>
<td>5996(3)</td>
<td>10614(2)</td>
<td>36(1)</td>
</tr>
</tbody>
</table>
Table 14. Bond lengths [Å] and angles [deg].

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)-O(2)</td>
<td>1.4191(16)</td>
</tr>
<tr>
<td>S(1)-O(1)</td>
<td>1.4400(16)</td>
</tr>
<tr>
<td>S(1)-N(1)</td>
<td>1.6134(16)</td>
</tr>
<tr>
<td>S(1)-C(13)</td>
<td>1.7922(19)</td>
</tr>
<tr>
<td>Cl(1)-C(19)</td>
<td>1.781(2)</td>
</tr>
<tr>
<td>Cl(1A)-O(4)</td>
<td>1.66(2)</td>
</tr>
<tr>
<td>O(4)-C(19)</td>
<td>1.41(2)</td>
</tr>
<tr>
<td>N(1)-C(7A)</td>
<td>1.463(18)</td>
</tr>
<tr>
<td>N(1)-C(1)</td>
<td>1.474(3)</td>
</tr>
<tr>
<td>N(1)-C(7)</td>
<td>1.497(6)</td>
</tr>
<tr>
<td>N(1)-C(1A)</td>
<td>1.541(15)</td>
</tr>
<tr>
<td>N(2)-O(3)</td>
<td>1.200(3)</td>
</tr>
<tr>
<td>N(2)-C(19)</td>
<td>1.519(3)</td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.522(4)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.527(4)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.559(7)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.513(8)</td>
</tr>
<tr>
<td>Bond</td>
<td>Distance (Å)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.525(5)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.534(4)</td>
</tr>
<tr>
<td>C(1A)-C(6A)</td>
<td>1.49(2)</td>
</tr>
<tr>
<td>C(1A)-C(2A)</td>
<td>1.54(2)</td>
</tr>
<tr>
<td>C(2A)-C(3A)</td>
<td>1.40(3)</td>
</tr>
<tr>
<td>C(3A)-C(4A)</td>
<td>1.57(4)</td>
</tr>
<tr>
<td>C(4A)-C(5A)</td>
<td>1.40(2)</td>
</tr>
<tr>
<td>C(5A)-C(6A)</td>
<td>1.56(3)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.488(7)</td>
</tr>
<tr>
<td>C(7)-C(12)</td>
<td>1.496(7)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.555(5)</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.506(7)</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.526(6)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.526(5)</td>
</tr>
<tr>
<td>C(7A)-C(8A)</td>
<td>1.42(2)</td>
</tr>
<tr>
<td>C(7A)-C(12A)</td>
<td>1.42(3)</td>
</tr>
<tr>
<td>C(8A)-C(9A)</td>
<td>1.36(3)</td>
</tr>
<tr>
<td>C(9A)-C(10A)</td>
<td>1.66(3)</td>
</tr>
<tr>
<td>C(10A)-C(11A)</td>
<td>1.55(3)</td>
</tr>
<tr>
<td>C(11A)-C(12A)</td>
<td>1.43(4)</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.523(3)</td>
</tr>
<tr>
<td>C(14)-C(19)</td>
<td>1.544(3)</td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.563(3)</td>
</tr>
<tr>
<td>C(14)-C(20)</td>
<td>1.586(3)</td>
</tr>
<tr>
<td>C(15)-C(16)</td>
<td>1.546(3)</td>
</tr>
<tr>
<td>C(16)-C(17)</td>
<td>1.527(3)</td>
</tr>
<tr>
<td>C(17)-C(18)</td>
<td>1.514(4)</td>
</tr>
<tr>
<td>C(17)-C(20)</td>
<td>1.546(3)</td>
</tr>
<tr>
<td>C(18)-C(19)</td>
<td>1.566(3)</td>
</tr>
<tr>
<td>C(20)-C(22)</td>
<td>1.526(3)</td>
</tr>
<tr>
<td>C(20)-C(21)</td>
<td>1.537(3)</td>
</tr>
<tr>
<td>O(2)-S(1)-O(1)</td>
<td>118.81(11)</td>
</tr>
<tr>
<td>O(2)-S(1)-N(1)</td>
<td>109.13(10)</td>
</tr>
<tr>
<td>O(1)-S(1)-N(1)</td>
<td>107.16(9)</td>
</tr>
<tr>
<td>O(2)-S(1)-C(13)</td>
<td>107.01(10)</td>
</tr>
<tr>
<td>O(1)-S(1)-C(13)</td>
<td>106.76(10)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (°)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>N(1)-S(1)-C(13)</td>
<td>107.47(9)</td>
</tr>
<tr>
<td>C(19)-O(4)-Cl(1A)</td>
<td>103.5(15)</td>
</tr>
<tr>
<td>C(7A)-N(1)-C(1)</td>
<td>121.5(8)</td>
</tr>
<tr>
<td>C(7A)-N(1)-C(7)</td>
<td>8.8(9)</td>
</tr>
<tr>
<td>C(1)-N(1)-C(7)</td>
<td>112.8(3)</td>
</tr>
<tr>
<td>C(7A)-N(1)-C(1A)</td>
<td>139.5(10)</td>
</tr>
<tr>
<td>C(1)-N(1)-C(1A)</td>
<td>18.4(5)</td>
</tr>
<tr>
<td>C(7)-N(1)-C(1A)</td>
<td>131.0(7)</td>
</tr>
<tr>
<td>C(7A)-N(1)-S(1)</td>
<td>111.3(8)</td>
</tr>
<tr>
<td>C(1)-N(1)-S(1)</td>
<td>126.06(19)</td>
</tr>
<tr>
<td>C(7)-N(1)-S(1)</td>
<td>120.1(3)</td>
</tr>
<tr>
<td>C(1A)-N(1)-S(1)</td>
<td>107.7(6)</td>
</tr>
<tr>
<td>O(3)-N(2)-C(19)</td>
<td>115.5(2)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(6)</td>
<td>113.7(2)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(2)</td>
<td>113.8(2)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(2)</td>
<td>111.3(3)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>110.2(3)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>110.8(4)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)</td>
<td>112.7(3)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)</td>
<td>109.6(3)</td>
</tr>
<tr>
<td>C(1)-C(6)-C(5)</td>
<td>111.0(3)</td>
</tr>
<tr>
<td>C(6A)-C(1A)-C(2A)</td>
<td>114.1(14)</td>
</tr>
<tr>
<td>C(6A)-C(1A)-N(1)</td>
<td>117.6(12)</td>
</tr>
<tr>
<td>C(2A)-C(1A)-N(1)</td>
<td>105.5(11)</td>
</tr>
<tr>
<td>C(3A)-C(2A)-C(1A)</td>
<td>107.2(19)</td>
</tr>
<tr>
<td>C(2A)-C(3A)-C(4A)</td>
<td>120.2(2)</td>
</tr>
<tr>
<td>C(5A)-C(4A)-C(3A)</td>
<td>103.0(18)</td>
</tr>
<tr>
<td>C(4A)-C(5A)-C(6A)</td>
<td>118.1(15)</td>
</tr>
<tr>
<td>C(1A)-C(6A)-C(5A)</td>
<td>106.0(15)</td>
</tr>
<tr>
<td>C(8)-C(7)-C(12)</td>
<td>115.8(4)</td>
</tr>
<tr>
<td>C(8)-C(7)-N(1)</td>
<td>115.5(4)</td>
</tr>
<tr>
<td>C(12)-C(7)-N(1)</td>
<td>113.5(4)</td>
</tr>
<tr>
<td>C(7)-C(8)-C(9)</td>
<td>110.1(4)</td>
</tr>
<tr>
<td>C(10)-C(9)-C(8)</td>
<td>111.6(3)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)</td>
<td>112.4(3)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)</td>
<td>111.7(3)</td>
</tr>
<tr>
<td>Bond Description</td>
<td>Angle (°)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>C(7)-C(12)-C(11)</td>
<td>112.1(4)</td>
</tr>
<tr>
<td>C(8A)-C(7A)-C(12A)</td>
<td>123.7(16)</td>
</tr>
<tr>
<td>C(8A)-C(7A)-N(1)</td>
<td>121.8(13)</td>
</tr>
<tr>
<td>C(12A)-C(7A)-N(1)</td>
<td>111.2(15)</td>
</tr>
<tr>
<td>C(9A)-C(8A)-C(7A)</td>
<td>116.2(16)</td>
</tr>
<tr>
<td>C(8A)-C(9A)-C(10A)</td>
<td>112.2(18)</td>
</tr>
<tr>
<td>C(11A)-C(10A)-C(9A)</td>
<td>103.2(17)</td>
</tr>
<tr>
<td>C(12A)-C(11A)-C(10A)</td>
<td>112(2)</td>
</tr>
<tr>
<td>C(7A)-C(12A)-C(11A)</td>
<td>119(2)</td>
</tr>
<tr>
<td>C(14)-C(13)-S(1)</td>
<td>115.34(13)</td>
</tr>
<tr>
<td>C(13)-C(14)-C(19)</td>
<td>117.47(17)</td>
</tr>
<tr>
<td>C(13)-C(14)-C(15)</td>
<td>115.21(17)</td>
</tr>
<tr>
<td>C(19)-C(14)-C(15)</td>
<td>106.55(17)</td>
</tr>
<tr>
<td>C(13)-C(14)-C(20)</td>
<td>113.47(17)</td>
</tr>
<tr>
<td>C(19)-C(14)-C(20)</td>
<td>102.32(16)</td>
</tr>
<tr>
<td>C(15)-C(14)-C(20)</td>
<td>99.62(16)</td>
</tr>
<tr>
<td>C(16)-C(15)-C(14)</td>
<td>103.70(17)</td>
</tr>
<tr>
<td>C(17)-C(16)-C(15)</td>
<td>103.25(17)</td>
</tr>
<tr>
<td>C(18)-C(17)-C(16)</td>
<td>108.9(2)</td>
</tr>
<tr>
<td>C(18)-C(17)-C(20)</td>
<td>103.70(17)</td>
</tr>
<tr>
<td>C(16)-C(17)-C(20)</td>
<td>102.98(19)</td>
</tr>
<tr>
<td>C(17)-C(18)-C(19)</td>
<td>103.20(19)</td>
</tr>
<tr>
<td>O(4)-C(19)-N(2)</td>
<td>107(3)</td>
</tr>
<tr>
<td>O(4)-C(19)-C(14)</td>
<td>135.3(10)</td>
</tr>
<tr>
<td>N(2)-C(19)-C(14)</td>
<td>112.71(18)</td>
</tr>
<tr>
<td>O(4)-C(19)-C(18)</td>
<td>86(5)</td>
</tr>
<tr>
<td>N(2)-C(19)-C(18)</td>
<td>103.67(18)</td>
</tr>
<tr>
<td>C(14)-C(19)-C(18)</td>
<td>103.20(18)</td>
</tr>
<tr>
<td>O(4)-C(19)-Cl(1)</td>
<td>29(5)</td>
</tr>
<tr>
<td>N(2)-C(19)-Cl(1)</td>
<td>109.31(16)</td>
</tr>
<tr>
<td>C(14)-C(19)-Cl(1)</td>
<td>114.36(14)</td>
</tr>
<tr>
<td>C(18)-C(19)-Cl(1)</td>
<td>113.02(16)</td>
</tr>
<tr>
<td>C(22)-C(20)-C(21)</td>
<td>106.7(2)</td>
</tr>
<tr>
<td>C(22)-C(20)-C(17)</td>
<td>114.12(19)</td>
</tr>
<tr>
<td>C(21)-C(20)-C(17)</td>
<td>113.26(19)</td>
</tr>
<tr>
<td>C(22)-C(20)-C(14)</td>
<td>113.92(18)</td>
</tr>
</tbody>
</table>
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 (Å²x10³).

The anisotropic displacement factor exponent takes the form:

\[-2\pi^2 [ h^2a^{*2}U_{11} + ... + 2hka^{*}b^{*}U_{12}] \]

<table>
<thead>
<tr>
<th></th>
<th>U11</th>
<th>U22</th>
<th>U33</th>
<th>U23</th>
<th>U13</th>
<th>U12</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>31(1)</td>
<td>28(1)</td>
<td>28(1)</td>
<td>-1(1)</td>
<td>-5(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>Cl(1)</td>
<td>40(1)</td>
<td>44(1)</td>
<td>34(1)</td>
<td>-2(1)</td>
<td>7(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>26(1)</td>
<td>33(1)</td>
<td>27(1)</td>
<td>0(1)</td>
<td>0(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>38(1)</td>
<td>50(1)</td>
<td>60(1)</td>
<td>-9(1)</td>
<td>-16(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>63(1)</td>
<td>34(1)</td>
<td>27(1)</td>
<td>1(1)</td>
<td>3(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>30(1)</td>
<td>46(1)</td>
<td>60(1)</td>
<td>-13(1)</td>
<td>-13(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>36(1)</td>
<td>67(1)</td>
<td>83(1)</td>
<td>-12(1)</td>
<td>-6(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>26(1)</td>
<td>30(1)</td>
<td>28(1)</td>
<td>0(1)</td>
<td>2(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>36(1)</td>
<td>27(1)</td>
<td>34(2)</td>
<td>1(1)</td>
<td>4(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>37(3)</td>
<td>37(2)</td>
<td>4 3(2)</td>
<td>-5(1)</td>
<td>6(2)</td>
<td>-20(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>31(1)</td>
<td>45(2)</td>
<td>44(2)</td>
<td>-3(1)</td>
<td>6(1)</td>
<td>-11(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>29(1)</td>
<td>38(2)</td>
<td>38(2)</td>
<td>6(1)</td>
<td>-5(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>27(1)</td>
<td>34(1)</td>
<td>37(2)</td>
<td>4(1)</td>
<td>-1(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>57(3)</td>
<td>47(2)</td>
<td>31(2)</td>
<td>-5(2)</td>
<td>3(2)</td>
<td>-2(2)</td>
</tr>
<tr>
<td>C(8)</td>
<td>34(1)</td>
<td>37(1)</td>
<td>32(1)</td>
<td>3(1)</td>
<td>-2(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>34(2)</td>
<td>58(2)</td>
<td>32(2)</td>
<td>9(2)</td>
<td>10(1)</td>
<td>-9(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>44(2)</td>
<td>72(2)</td>
<td>33(1)</td>
<td>6(1)</td>
<td>13(1)</td>
<td>9(2)</td>
</tr>
<tr>
<td>C(11)</td>
<td>44(2)</td>
<td>62(2)</td>
<td>34(2)</td>
<td>-1(1)</td>
<td>12(2)</td>
<td>14(2)</td>
</tr>
<tr>
<td>C(12)</td>
<td>35(2)</td>
<td>40(2)</td>
<td>33(2)</td>
<td>-1(1)</td>
<td>3(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>36(1)</td>
<td>27(1)</td>
<td>29(1)</td>
<td>2(1)</td>
<td>-5(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>39(1)</td>
<td>29(1)</td>
<td>24(1)</td>
<td>1(1)</td>
<td>-4(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>59(2)</td>
<td>40(1)</td>
<td>26(1)</td>
<td>4(1)</td>
<td>-6(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(16)</td>
<td>71(2)</td>
<td>48(1)</td>
<td>32(1)</td>
<td>-2(1)</td>
<td>-9(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(17)</td>
<td>57(1)</td>
<td>37(1)</td>
<td>31(1)</td>
<td>-8(1)</td>
<td>1(1)</td>
<td>-6(1)</td>
</tr>
</tbody>
</table>
Table 16. Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å²x10^3).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1A)</td>
<td>3288</td>
<td>5654</td>
<td>10232</td>
<td>34</td>
</tr>
<tr>
<td>H(2A)</td>
<td>2831</td>
<td>6725</td>
<td>9267</td>
<td>39</td>
</tr>
<tr>
<td>H(2B)</td>
<td>3542</td>
<td>6155</td>
<td>8551</td>
<td>39</td>
</tr>
<tr>
<td>H(3A)</td>
<td>5427</td>
<td>7095</td>
<td>9023</td>
<td>47</td>
</tr>
<tr>
<td>H(3B)</td>
<td>5165</td>
<td>6806</td>
<td>9958</td>
<td>47</td>
</tr>
<tr>
<td>H(4A)</td>
<td>7302</td>
<td>6136</td>
<td>9457</td>
<td>48</td>
</tr>
<tr>
<td>H(4B)</td>
<td>6398</td>
<td>5775</td>
<td>8684</td>
<td>48</td>
</tr>
<tr>
<td>H(5A)</td>
<td>5953</td>
<td>5254</td>
<td>10360</td>
<td>42</td>
</tr>
<tr>
<td>H(5B)</td>
<td>6695</td>
<td>4686</td>
<td>9653</td>
<td>42</td>
</tr>
<tr>
<td>H(6A)</td>
<td>4405</td>
<td>4638</td>
<td>8925</td>
<td>39</td>
</tr>
<tr>
<td>H(6B)</td>
<td>4131</td>
<td>4305</td>
<td>9844</td>
<td>39</td>
</tr>
<tr>
<td>H(1B)</td>
<td>3466</td>
<td>5342</td>
<td>8748</td>
<td>34</td>
</tr>
<tr>
<td>H(2C)</td>
<td>2714</td>
<td>6680</td>
<td>9192</td>
<td>39</td>
</tr>
<tr>
<td>H(2D)</td>
<td>3241</td>
<td>6478</td>
<td>10118</td>
<td>39</td>
</tr>
<tr>
<td>H(3A1)</td>
<td>4991</td>
<td>7212</td>
<td>9458</td>
<td>42</td>
</tr>
<tr>
<td>H(3A2)</td>
<td>5002</td>
<td>6548</td>
<td>8723</td>
<td>42</td>
</tr>
<tr>
<td>H(4C)</td>
<td>7208</td>
<td>6347</td>
<td>9505</td>
<td>53</td>
</tr>
<tr>
<td>H(4D)</td>
<td>6254</td>
<td>6218</td>
<td>10338</td>
<td>53</td>
</tr>
<tr>
<td>H(5A1)</td>
<td>6806</td>
<td>4954</td>
<td>9778</td>
<td>40</td>
</tr>
<tr>
<td>H(5A2)</td>
<td>6121</td>
<td>5242</td>
<td>8918</td>
<td>40</td>
</tr>
<tr>
<td>H(6C)</td>
<td>4434</td>
<td>4299</td>
<td>9568</td>
<td>40</td>
</tr>
<tr>
<td>H(6D)</td>
<td>4351</td>
<td>4896</td>
<td>10368</td>
<td>40</td>
</tr>
<tr>
<td>H(7A)</td>
<td>-146</td>
<td>4872</td>
<td>10147</td>
<td>54</td>
</tr>
<tr>
<td>H(8A)</td>
<td>2385</td>
<td>4787</td>
<td>11154</td>
<td>41</td>
</tr>
<tr>
<td>H(8B)</td>
<td>1588</td>
<td>4005</td>
<td>10708</td>
<td>41</td>
</tr>
<tr>
<td>H(9A)</td>
<td>-604</td>
<td>4196</td>
<td>11496</td>
<td>49</td>
</tr>
<tr>
<td>H</td>
<td>766</td>
<td>4157</td>
<td>12128</td>
<td>49</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>----</td>
</tr>
<tr>
<td>H(9B)</td>
<td>767</td>
<td>5616</td>
<td>12266</td>
<td>60</td>
</tr>
<tr>
<td>H(10A)</td>
<td>-880</td>
<td>5277</td>
<td>12452</td>
<td>60</td>
</tr>
<tr>
<td>H(10B)</td>
<td>-908</td>
<td>6497</td>
<td>11583</td>
<td>56</td>
</tr>
<tr>
<td>H(11A)</td>
<td>-1717</td>
<td>5709</td>
<td>11158</td>
<td>56</td>
</tr>
<tr>
<td>H(11B)</td>
<td>-192</td>
<td>6299</td>
<td>10161</td>
<td>43</td>
</tr>
<tr>
<td>H(12A)</td>
<td>-223</td>
<td>4893</td>
<td>9890</td>
<td>4</td>
</tr>
<tr>
<td>H(7B)</td>
<td>-54</td>
<td>3950</td>
<td>10537</td>
<td>33</td>
</tr>
<tr>
<td>H(8C)</td>
<td>1697</td>
<td>4081</td>
<td>10658</td>
<td>33</td>
</tr>
<tr>
<td>H(8D)</td>
<td>1425</td>
<td>4708</td>
<td>11798</td>
<td>34</td>
</tr>
<tr>
<td>H(9C)</td>
<td>263</td>
<td>3942</td>
<td>11822</td>
<td>34</td>
</tr>
<tr>
<td>H(9D)</td>
<td>-1827</td>
<td>4967</td>
<td>11476</td>
<td>47</td>
</tr>
<tr>
<td>H(10C)</td>
<td>-1045</td>
<td>5239</td>
<td>12330</td>
<td>47</td>
</tr>
<tr>
<td>H(11C)</td>
<td>-1110</td>
<td>6424</td>
<td>11366</td>
<td>53</td>
</tr>
<tr>
<td>H(11D)</td>
<td>566</td>
<td>6193</td>
<td>11623</td>
<td>53</td>
</tr>
<tr>
<td>H(12C)</td>
<td>-871</td>
<td>5955</td>
<td>10148</td>
<td>34</td>
</tr>
<tr>
<td>H(12D)</td>
<td>764</td>
<td>6307</td>
<td>10316</td>
<td>34</td>
</tr>
<tr>
<td>H(13A)</td>
<td>2477</td>
<td>3568</td>
<td>8663</td>
<td>37</td>
</tr>
<tr>
<td>H(13B)</td>
<td>1155</td>
<td>3450</td>
<td>9312</td>
<td>37</td>
</tr>
<tr>
<td>H(15A)</td>
<td>-352</td>
<td>3898</td>
<td>7196</td>
<td>50</td>
</tr>
<tr>
<td>H(15B)</td>
<td>1412</td>
<td>3743</td>
<td>7078</td>
<td>50</td>
</tr>
<tr>
<td>H(16A)</td>
<td>-857</td>
<td>2747</td>
<td>6426</td>
<td>60</td>
</tr>
<tr>
<td>H(16B)</td>
<td>906</td>
<td>2615</td>
<td>6276</td>
<td>60</td>
</tr>
<tr>
<td>H(17A)</td>
<td>307</td>
<td>1405</td>
<td>7065</td>
<td>50</td>
</tr>
<tr>
<td>H(18A)</td>
<td>-1388</td>
<td>1508</td>
<td>8184</td>
<td>55</td>
</tr>
<tr>
<td>H(18B)</td>
<td>-2174</td>
<td>2069</td>
<td>7477</td>
<td>55</td>
</tr>
<tr>
<td>H(21A)</td>
<td>2011</td>
<td>1111</td>
<td>8487</td>
<td>66</td>
</tr>
<tr>
<td>H(21B)</td>
<td>515</td>
<td>1484</td>
<td>8883</td>
<td>66</td>
</tr>
<tr>
<td>H(21C)</td>
<td>2094</td>
<td>1894</td>
<td>9107</td>
<td>66</td>
</tr>
<tr>
<td>H(22A)</td>
<td>3324</td>
<td>1770</td>
<td>7463</td>
<td>75</td>
</tr>
<tr>
<td>H(22B)</td>
<td>3544</td>
<td>2642</td>
<td>7943</td>
<td>75</td>
</tr>
<tr>
<td>H(22C)</td>
<td>2825</td>
<td>2637</td>
<td>7041</td>
<td>75</td>
</tr>
</tbody>
</table>
REFERENCES:

References


