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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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ENTITLED: Stereoselective Nucleophilic Addition to Chiral Alkenes

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Bachelor of Science in Chemistry

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Instructor in Charge

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HEAD OF DEPARTMENT OF Chemistry
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Introduction:

A general method for the selective formation of unnatural or unusual amino acids is an important goal in organic synthesis. Unnatural amino acids can be used as precursors to larger biologically active systems. Evans\(^1\) has suggested that the unnatural amino acid (I) can be used to build the Cyclosporine A (II) nucleus (Scheme 1). However, there is only one known synthesis of (II), which is long and inefficient.

Scheme 1

\[
\begin{align*}
&\text{Scheme 2} \\
&\text{As indicated by these few examples, there is a need for a general but stereoselective synthetic method of unnatural or unusual amino acids.}
\end{align*}
\]
We hope to develop one such method by exploring the nucleophilic additions of various organometallic reagents to chiral hydrazones, which are derived from (S)-(−)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) and selected aldehyde (scheme 3).

Currently, we are exploring techniques to obtain high diastereoselectivity in chiral hydrazines (scheme 4). The protected hydrazine will be cleaved by catalytic hydrogenation to give the protected chiral amine, and the enantiomeric excess and configuration will then be determined by comparing to a known compound.
Scheme 4

\[
\text{Reaction Scheme:}
\]

\[
\text{Product:}
\]

\[
\begin{align*}
\text{Product} & \quad \text{a CeCl}_3, \text{MeLi, THF} \\
\text{b methylchloroformate} & 
\end{align*}
\]
**Background:**

Enders has demonstrated the usefulness of chiral hydrazones derived from SAMP/RAMP in asymmetric synthesis, in which he enantioselectively creates new stereocenters α to the hydrazone carbon. The chiral hydrazine auxiliary, SAMP, can be easily generated from L-proline in four steps (scheme 5).² ³

Scheme 5

\[ \begin{align*}
\text{a LAH, THF} \\
\text{b t-Butyl nitrite} \\
\text{c NaH, methyl iodide} \\
\text{d LAH, THF}
\end{align*} \]

The SAMP/RAMP-hydrazone method has been used successfully by Enders in the enantioselective synthesis of a variety of important carbonyl compounds and amines (scheme 6).³

![Scheme 6](image-url)
Enders explains the high selectivities of these reactions via a \( \pi - 1 \)-azaallyl anion-Li cation contact species and proposes the following transition state.

The Li cation is proposed to be chelated by the azaallyl anion and the oxygen of the methyl ether. \(^4\) Recently, Collum\(^5\) has shown similar azaallyl anion-Li cation chelation in a cyclohexanone dimethylhydrazone system. Work conducted by Meyers \(^6\) using chiral oxazolines with C-4 methoxymethyl groups suggest that this substituent is important in the Li cation chelation process that leads to high stereoselectivity. He has found that the electrophiles enter from the Li chelated face. Thus, it can be deduced that in this transition state the electrophile attacks from the underside.

The high chemical yields and high stereoselectivity of this method clearly outweigh the fact that this strategy requires two additional steps to carry out the electrophilic substitution—namely the introduction of the SAMP/RAMP hydrazine and subsequent removal of the chiral auxiliary.

In our labs, Enders methodology was employed to create a new stereocenter in (III) by deprotonation \( \alpha \) to the hydrazone carbon with \( \text{LiDA} \), followed by addition of methyl iodide to give (IV) as the major product.

This reaction revealed that two products had formed. Separation by flash chromatography gave 67% of the desired UV active product. The other I\(_2\)-active product was found to have no C=N, but \(((\text{CH}_3)_3\text{C})(\text{CH}_3)_2\text{SiO}^-\) and \(\text{CH}_3\text{OCH}_2^-\) were still present. Inspection of the minor product by NMR revealed that butyl addition to the C=N of the hydrazone had occurred (Scheme 7).
Enders explains the high selectivities of these reactions via a \( \alpha \)-azaallyl anion-Li cation contact species and proposes the following transition state.

The Li cation is proposed to be chelated by the azaallyl anion and the oxygen of the methyl ether.\(^4\) Recently, Collum\(^5\) has shown similar azaallyl anion-Li cation chelation in a cyclohexanone dimethylhydrazine system. Work conducted by Meyers\(^6\) using chiral oxazolines with C-4 methoxymethyl groups suggest that this substituent is important in the Li cation chelation process that leads to high stereoselectivity. He has found that the electrophiles enter from the Li chelated face. Thus, it can be deduced that in this transition state the electrophile attacks from the underside.

The high chemical yields and high stereoselectivity of this method clearly outweigh the fact that this strategy requires two additional steps to carry out the electrophilic substitution—namely the introduction of the SAMP/RAMP hydrazine and subsequent removal of the chiral auxiliary.

In our labs, Enders methodology was employed to create a new stereocenter in (III) by deprotonation \( \alpha \) to the hydrazone carbon with LDA, followed by addition of methyl iodide to give (IV) as the major product.

This reaction revealed that two products had formed. Separation by flash chromatography gave 67% of the desired UV active product. The other I\(_2\)-active product was found to have no C-N, but ((CH\(_3\))\(_3\)C)(CH\(_3\))\(_2\)SiO- and CH\(_3\)OCH\(_2\)- were still present. Inspection of the minor product by NMR revealed that butyl addition to the C=N of the hydrazone had occurred (scheme 7).
We feel that the generation of this minor product occurred due to the inability to stoichiometrically form LDA resulting in a small quantity of free n-BuLi. The seemingly facile nucleophilic addition to the chiral hydrazone with n-BuLi was then free to occur. 

Takahashi has achieved asymmetric syntheses with chiral hydrazones formed from (−)-N-aminoephedrine (derived from L-ephedrine) or (E)-(S)-N-Benzylidene-N,3-dimethyl-2-hydrizinobutanol (derived from L-valinol), as the chiral auxiliary. He shows asymmetric nucleophilic addition with Grignard reagents or aryllithium reagents, using hydrazones derived from aromatic aldehydes, followed by hydrogenolysis on Pd-C in hydrochloric acid solution, to cleave the N-N bond (Scheme 6). 

Reactions with alkylmagnesium halides occurred with high stereoselectivity in both cases where the chiral hydrazone was derived from L-ephedrine or L-valinol.

Takahashi proposes that the high stereoselectivity arises via a magnesium chelated intermediate involving the hydroxyl group and the nitrogen atom of the hydrazone.

The L-valinol hydrazone forms a chelated six-membered intermediate, where the isopropyl group sits in the energetically favorable equatorial position, thus its bulkiness probably contributes little to stereocontrol. Therefore, Takahashi proposes

FIGURE 1
SCHEME 8

a. HCOOEt
b. LAH
c. HNO₂
d. LAH
e. ArCHO
f. RMgX
g. Hydrogen Pd/C

a. HNO₂
b. Zn / acetic acid
c. aryl aldehyde (ArCHO)
d. Grignard or lithium reagent
e. Pd-C / H₂
f. HCl
that a second Grignard reagent approaches the lone pair of electrons on the oxygen atom, and the alkyl anion consequently attacks from the re-si face of the C-N bond (Figure 1A). Takahashi has also found that in the case where aralkylmagnesium halides are used, the enantiomeric excess of the products is poor. He thus proposes that these relatively bulky reagents are hindered from approaching the lone pair of electrons of the oxygen.

When the L-ephedrine hydrazone is used, major products derived from aralkylmagnesium halides are of the opposite chirality than when alkylmagnesium halides are used. Takahashi suggests that these aralkyl reagents are hindered by the axial methyl group of the chelated intermediate (Figure 1B). 8

Takahashi has also used phenyllithium in his attempt to make N-(1,2-diphenylethylamino)ephedrine (derived from L-N-aminoephedrine), which was later cleaved to give (R)-1,2-diphenylethyl amine (ee 91%). He proposes the following transition state for this reaction.

Here, the areyllithium species is proposed to attack preferentially from the pro-S face at the 5 position of (V) as shown in the figure. 8
**Results and Discussion:**

We began our synthetic attempt at asymmetric nucleophilic addition with SAMP-phenylacetaldehyde (2a) hydrazone and methylithium. These educts were chosen because the resulting addition product could be degraded to a compound with known optical rotation, amphetamine, thus allowing easy measurement of the degree of asymmetric induction in the addition (Scheme 9).

Unfortunately, due to the strong basicity of methylithium and the relatively acidic nature of the protons adjacent to the phenyl ring enolization of the hydrazone was the major reaction pathway. The enolized product was the major reaction product, along with recovered starting material. The inertness of the enolized hydrazone is presumably due to conjugation to the phenyl nmr. (Table 1).

Noting that Takahashi had gotten exclusively addition product with phenyllithium (10eq.) and a similar system, we attempted methyl addition to the SAMP-phenylacetaldehyde hydrazone using 10eq. of MeLi. However, results similar to earlier runs were obtained (Table 1).

In an attempt to trap the anion being formed with MeLi, the reaction was repeated using 10eq. MeLi with a methyl iodide quench. To our surprise, we
discovered a trimethylated product (VI), seeming to be only one diastereomer by $^1\text{H}$ NMR.

![Chemical structure of VI](image)

(VI)

We rationalize this result by the following argument: with 10 eq. of MeLi present, a proton α to the hydrazone was removed stereoselectively by the basic MeLi. Quenching with methyl iodide gave the alkylated hydrazone product, which underwent further reaction in the form of nucleophilic attack at the C-N of the hydrazone by the excess MeLi to form the aza anion, which was subsequently quenched with methyl iodide to afford the trimethylated product (Scheme 10).

Scheme 10

![Scheme 10](image)

In an attempt to suppress the undesired deprotonation alpha to the hydrazone carbon, we employed the less basic organolithium reagents, n-BuLi and PhLi. However, the reaction gave many products by TLC and further experiments using n-BuLi and PhLi were abandoned.

Realizing the susceptibility to enolization of the SAMP-phenylacetalddehyde hydrazone system, we extended the chain by one methylene and made the SAMP-dihydrocinnamaldehyde hydrazone (2b). $^1\text{H}$ NMR spectra indicated initial experiments using 1 eq. MeLi and MeI quench showed some methylation had occurred; however, poor mass recovery and product instability caused us to seek other reaction conditions.
Lewis acid catalysis with BF$_3$·OEt$_2$ produced 19% of the desired methyl addition product, however, further optimization resulted in only a modest improvement in yield (Table 1).

Having realized that deprotonation of $\alpha$ protons may have also been a problem in the SAMP-dihydrocinnamaldehyde hydrazone system, we again tested the SAMP-phenylacetaldehyde hydrazone system now using the less basic organocerium reagent, methylcerium. Imamoto$^{11,12}$ has shown that these organolanthanides give exclusively addition products with highly enolizable ketone systems. Drawing this analogy to our system, we observed the desired methyl addition product, in 25% yield, using methylcerium reagent and SAMP-phenylacetaldehyde hydrazone. This was the only product observed along with 53% unreacted starting material by TLC.

We then attempted to use the methylcerium reagent with the SAMP-dihydrocinnamaldehyde hydrazone system. Addition of 1 eq. of methylcerium resulted in very little reaction as determined by TLC after 36 hours. However, use of 2 eq. of the methylcerium reagent at -78°C resulted in disappearance of starting material within minutes, as detected by TLC. Quenching with H$_2$O gave the hydrazine, which was unfortunately unstable at room temperature, as detected by enhanced coloration and by TLC.

In order to prevent degradation of the methylated hydrazine product, we realized that the hydrazine needed to be protected. Quenching the reaction with Di-1-Butyl dicarbonate, a reagent used in protecting amino acids$^{13,14}$, resulted in no reaction. However, use of methylchloroformate resulted in successful formation of the hydrazine protected as the carbamate in 73% yield after purification.

Diastereomeric excess was determined to be 98:2 by using isothermal capillary gas chromatography.
<table>
<thead>
<tr>
<th>Hydrazone</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Quench</th>
<th>Time</th>
<th>Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>MeLi(1eq)</td>
<td>ether</td>
<td>H₂O</td>
<td>3.5hr</td>
<td>-70-0°C</td>
<td>SM, EP</td>
</tr>
<tr>
<td>2a</td>
<td>MeLi(3eq)</td>
<td>ether</td>
<td>H₂O</td>
<td>~2 hr</td>
<td>-70-0°C</td>
<td>SM, EP</td>
</tr>
<tr>
<td>2a</td>
<td>MeLi(5eq)</td>
<td>THF</td>
<td>H₂O</td>
<td>~12hr</td>
<td>50-RT</td>
<td>SM, EP</td>
</tr>
<tr>
<td>2a</td>
<td>MeLi(1eq)</td>
<td>hexane</td>
<td>H₂O</td>
<td>5.5hr</td>
<td>-70-RT</td>
<td>SM, EP</td>
</tr>
<tr>
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<td>MeLi(10eq)</td>
<td>ether</td>
<td>H₂O</td>
<td>22hr</td>
<td>RT</td>
<td>SM, EP</td>
</tr>
<tr>
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<td>MeLi(10eq)</td>
<td>ether</td>
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<td>11hr</td>
<td>RT</td>
<td>trimethyl</td>
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<td>MeLi(10eq)</td>
<td>hexane</td>
<td>CH₃I</td>
<td>21.5hr</td>
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<td>trimethyl</td>
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<tr>
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<td>Me₂CuLi</td>
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<td>8hr</td>
<td>RT</td>
<td>N.R.</td>
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<tr>
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<td>PhLi(10eq)</td>
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<td>16hr</td>
<td>RT</td>
<td>&lt;side reactions</td>
</tr>
<tr>
<td>2b</td>
<td>MeLi(1.1eq)</td>
<td>ether</td>
<td>CH₃I</td>
<td>26hr</td>
<td>RT</td>
<td>12% product</td>
</tr>
<tr>
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<td>MeLi(1.1eq)</td>
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<td>CH₃I</td>
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<td>-78-RT</td>
<td>&lt;side reactions</td>
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<td>RT</td>
<td>19% product@</td>
</tr>
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<td>MeLi(2eq)</td>
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<td>3hr</td>
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<td>N.R.</td>
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<tr>
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<td>H₂O</td>
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<td>H₂O</td>
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<td>H₂O</td>
<td>min.</td>
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<td>30% product@</td>
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<td>Hydrazone</td>
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<td>Solvent</td>
<td>Quench</td>
<td>Time</td>
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<td>Results</td>
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<td>-----------</td>
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<td>---------</td>
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<td>------</td>
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</tr>
<tr>
<td>2b</td>
<td>&quot;MeCeCl₂&quot;</td>
<td>THF</td>
<td>H₂O</td>
<td>10hr</td>
<td>-78°C</td>
<td>&gt;reaction</td>
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<tr>
<td></td>
<td>(1.2eq)</td>
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<tr>
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<tr>
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<td>(2.2eq)</td>
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<tr>
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<td>MeCOOCl</td>
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<td>-78°C</td>
<td>73% product</td>
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<tr>
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<td>(2eq)</td>
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</table>

*attempted t-BOC anhydride quench
SM = starting material
EP = enolized product
N.R. = no reaction
@ = labile
& = protection after recovery of labile hydrazine
trimethyl= trimethylation product
Experimental Section
General Experimental Information:

$^1$H NMR spectra were recorded on a Varian XL-200 (200MHz) or General Electric QE-300 (300MHz) spectrometer in deuterochloroform with chloroform(67.26) or TMS(60.00) as an internal standard. Chemical shifts are given in ppm(8); multiplicities are designated as s(singlet); d(doublet); t(triplet); q(quartet); m(multiplet), or br(broadened). Infrared spectra were obtained on an IBM IR/32, FT-IR spectrophotometer. Peaks are reported in cm$^{-1}$ with the following relative intensities: s(strong, 67-100%), m(medium,34-66%), w(weak,0-33%). Mass spectra were taken on a Finnigan MAT-CH6 spectrometer with ionization voltages of 10 and 70eV. Data are reported in the form of m/e(intensity relative to base=100).

Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Bulb to bulb distillations were done in a Buchi GKR-50 Kugelrohr; boiling points refer to uncorrected air bath temperatures. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was done with UV light, phosphomolybdic acid, iodine, vanillin, and/or dinitrophenylhydrazine. Solvents for extraction and chromatography were technical grade and distilled from the following drying agents: hexane(CaCl$_2$); ether(CaSO$_4$/FeSO$_4$); ethyl acetate(K$_2$CO$_3$); methylene chloride(K$_2$CO$_3$). Analytical gas chromatography was done on a Varian 3700 chromatograph with flame ionization detector. H$_2$ was employed as the carrier gas for the 50m capillary OV-17 column, with a split ratio of 60:1. Retention times and integrals were obtained from a Hewlett-Packard 3390 recorder. MeLi was titrated by the diphénylacétique acid method. All reactions were done in oven or flame dried glassware in an atmosphere of dry N$_2$ or Ar.
<table>
<thead>
<tr>
<th>Reagents, Supplier, and Purification:</th>
<th>J.T. Baker</th>
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<tbody>
<tr>
<td>Ammonium Chloride</td>
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<td>Ammonium Hydroxide</td>
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<tr>
<td>Benzaldehyde</td>
<td>Aldrich (distilled)</td>
</tr>
<tr>
<td>Boron trifluoride etherate</td>
<td>Aldrich (distilled)</td>
</tr>
<tr>
<td>t-Butyl nitrite</td>
<td>Aldrich, Fluka</td>
</tr>
<tr>
<td>n-Butyllithium</td>
<td>Aldrich</td>
</tr>
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<td>Cericous Chloride (heptahydrate)</td>
<td>G. Fredrick Smith Co.</td>
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<td>J.T. Baker</td>
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<tr>
<td>Cuprous Iodide</td>
<td>Aldrich (saturated aqueous KI)</td>
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<tr>
<td>Deuteron Oxide</td>
<td>Diaprep inc.</td>
</tr>
<tr>
<td>Dihydrocinnamaldehyde</td>
<td>Eastman (distilled)</td>
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<td>Ether</td>
<td>J.T. Baker (Na/benzophenone)</td>
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<td>J.T. Baker</td>
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<tr>
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<td>Mallinckrodt</td>
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<tr>
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<td>Alfa</td>
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<td>Sodium Hydroxide</td>
<td>Mallinckrodt</td>
</tr>
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</table>
Sodium Sulfate  
Tetrahydrofuran  
Tetramethylenediamine  

Fisher Scientific  
Aldrich (K/benzophenone)  
Alfa (CaH₂)
SAMP procedure

Reduction of L-Proline with LiAlH₄

In a 2L, three-neck flask equipped with mechanical stirrer and reflux condenser with drying tube, was added 770ml dry THF and 18.8g(0.492 mol) LiAlH₄. This was neated to 65°C, then 35.4g(0.308 mol) of L-proline was added in small amounts to maintain reflux. The mixture was allowed to reflux for 4 hours. The reaction was then quenched with 35ml of 4.4M KOH and allowed to reflux for 0.25 hour in order to complete the quench. The reaction mixture was filtered, and the residue was refluxed in 400ml dry THF for 0.75 hour. The organic layers were combined and concentrated in vacuo to give a dark yellow oil, crude yield ~100%. Distillation with vigreux column gave a clear, colorless oil in 74.5% yield, b.p. 83°C/0.4 torr. NMR and IR were identical to those reported in the literature.²
**Nitrosation of L-prolinol with t-Butyl nitrite**

![Diagram](attachment:image.png)

17.95g (0.178 mol) L-prolinol was placed in a 500ml, three-neck round bottom flask equipped with a septum, 125ml addition funnel, and N₂ gas inlet, and was dissolved in 125ml of anhydrous THF. The reaction vessel was cooled to 0°C and 47.0ml (0.395 mol) t-Butyl nitrite (90% technical grade) was added dropwise. The reaction mixture was warmed to room temperature, covered with aluminum foil to exclude light and stirred. The solvent was removed in vacuo to give an orange oil. Fractional distillation gave a clear, colorless oil (L-prolinol) 22.3% yield, and a yellow oil (N-nitrosoprolinol) 69.6% yield. b.p. 123°C/0.2 torr. NMR and IR matched those reported in the literature.² The remaining starting material was resubjected to reaction conditions to obtain the desired N-nitrosoprolinol.
Methylation of N-nitroso-proline

\[
\text{N=O} \quad \overset{\text{NaH / Mel}}{\rightarrow} \quad \text{N=O}
\]

In a 500ml, three-neck round bottom flask equipped with thermometer, septum, magnetic stirrer, and N\textsubscript{2} gas inlet, was added 200 ml of dry THF and 16.5ml(0.265mol) methyl iodide. The methyl iodide solution was cooled to -44°C in an acetonitrile/CO\textsubscript{2} cold bath. In a separate flask was added excess NaH dispersion, which was washed 3x10ml hexane and the excess solvent removed in vacuo. The NaH was added to the methyl iodide solution at -44°C via gooch tube. The reaction mixture was slowly warmed to room temperature over 3 hours with the concomitant evolution of H\textsubscript{2} gas. The reaction was quenched with 10mls of H\textsubscript{2}O and then poured into 300mls of H\textsubscript{2}O. The THF/water mixture was extracted with methylene chloride (3x300ml), then the organic phase was washed with H\textsubscript{2}O(1x300ml), and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil, which upon distillation gave 77.5% of a clear yellow oil, N-nitroso-2-methoxymethyl-pyrrolidine b.p. 80°C/ 0.2torr. NMR data matched that in the literature.\textsuperscript{2}
Reduction of N-nitroso-2-methoxymethyl-pyrrolidine

\[
\begin{align*}
\text{N=O} & \quad \xrightarrow{\text{LAH}} \quad \text{NH}_2
\end{align*}
\]

17.64g (0.122mol) of N-nitroso-2-methoxymethyl-pyrrolidine was dissolved in 150ml of dry THF and added via cannula to a 250ml addition funnel. 10.0g (0.264mol) of LiAlH₄ contained in a 2L, three-neck round bottom flask equipped with an addition funnel, mechanical stirrer, and reflux condenser was suspended in 630ml dry THF. The LiAlH₄ slurry was heated to reflux and the N-nitroso-2-methoxymethyl-pyrrolidine solution was added dropwise over a 2.5 hour period. The reaction was cooled to 0°C, and quenched with 9ml 10% NaOH, followed by 13.5ml H₂O. The reaction mixture was again heated to reflux for 1 hour to complete the quench. The white aluminate salts were filtered, redissolved in 200ml dry THF, and refluxed for 1 hour. The reaction mixture was filtered off and the organic layers were combined and concentrated in vacuo. The organic phase was dissolved in 500ml methylene chloride and dried over sodium sulfate. Concentration in vacuo gave a light yellow oil, which upon distillation with vigreaux column and ice-cooled receiving flasks gave a clear, colorless oil, (S)-(−)-1-amino-2-methoxymethyl-pyrrolidine (SAMP), in 78.8% yield. b.p. 75-76°C /12 torr.

Analysis of the IR and NMR spectra revealed the product to be identical to the literature compound.³
**Hydrazone Preparation**

**General Procedure**

SAMP hydrazine (1 eq) was added to a magnetically stirred 10ml round bottom flask equipped with septa under N₂ atmosphere, and cooled to 0°C in an ice bath. The corresponding aldehyde (distilled, 1.02 eq) was added dropwise via syringe. The reaction mixture was stirred for 10 minutes at 0°C, warmed to room temperature and stirred overnight in an N₂ atmosphere. The crude mixture was poured into ~100ml methylene chloride, washed with H₂O(1x25ml), dried over sodium sulfate, filtered, and concentrated in vacuo, to give a yellow oil (95-100% crude yield). The hydrazone was purified by flash chromatography or distillation.

**TABLE 2: SAMP-hydrazone (2) prepared from aldehydes and SAMP**

<table>
<thead>
<tr>
<th>(2)</th>
<th>B</th>
<th>crude</th>
<th>pure</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅CH₂⁻</td>
<td>96%</td>
<td>70%</td>
</tr>
<tr>
<td>b</td>
<td>C₆H₅CH₂CH₂⁻</td>
<td>96%</td>
<td>70%</td>
</tr>
<tr>
<td>c</td>
<td>C₆H₅⁻</td>
<td>92%</td>
<td>62%</td>
</tr>
</tbody>
</table>
Characterization of hydrazones

(S)-(-)-N-(Benzylideneamino)-2-methoxymethyl-pyrrolidine

M.W.: 218.300

b.p.: 100°C/0.01torr (kugelrohr)

Rf 0.344 (6:1 hexane:ethyl acetate)

C_{13}H_{18}N_{2}O: calc.: C 71.53%  H 8.31%  N 12.83%
found:   C 71.26%  H 8.17%  N 12.76%

{\textit{1H} NMR: (200 MHz, TMS)}
1.96(m,4H,5-CH_{2} in pyrrolidine); 3.05(m, 1H, NCH_{2});
3.3-3.75(m, 4H, OCH\textsubscript{2}, CH, NCH\textsubscript{2}); 3.4(s, 3H, OCH\textsubscript{3});
7.25-7.58(m, 5H, aromatic H); 7.5(s, 1H, aldehyde H)

{\textit{IR:}(thin film)}
3854(w), 3671(w), 3055(m), 3024(m), 2974(s), 2878(s), 2357(w),
1734(w), 1701(w), 1684(w), 1588(s), 1558(s), 1458(m), 1447(s),
1375(m), 1340(s), 1323(m), 1306(m), 1282(m), 1242(m), 1194(s),
1151(m), 1120(s), 1070(m), 1024(m), 972(m), 914(m), 876(m).
(S)-(−)-N-(Phenylethylideneamino)-2-methoxymethyl-pyrrolidine

M.W.: 232.326

Rf 0.156 (6:1 hexane:ethyl acetate)

$^1$H NMR: (200 MHz, TMS)
1.90 (m, 4H, 8-CH$_2$ in pyrrolidine); 2.75 (m, 1H, NCH$_2$);
3.27-3.71 (m, 6H, NCH$_2$, OCH$_2$, CH); 3.39 (s, 3H, OCH$_3$);
6.68 (t, 1H, aldehyde H); 7.15 (m, 5H, aromatic H)

IR: (thin film)
1120 (s), 2880 (s), 2976 (s), 1197 (s), 2828 (s), 1454 (s), 1340 (s),
1495 (s), 1600 (m), 1635 (m), 3030 (m), 1365 (m), 974 (m), 1704 (m),
1030 (w), 904 (w), 831 (w), 1429 (w), 3065 (w), 804 (w).
(S)-(-)-N-(Benzylideneamino)-2-methoxymethyl-pyrrolidine

M.W.: 246.354

Rf: 0.133 (6:1 hexane:ethyl acetate)

$^1$H NMR: (200 MHz, TMS)
- 1.90 (m, 4H, 8-CH$_2$ in pyrrolidine); 2.55 (m, 2H, -CH$_2$-);
- 2.68 (m, 3H, NCH$_2$, CH$_2$[a to aromatic]); 3.25-3.55 (m, 4H, -OCH$_2$-CH$_2$NCH$_2$);
- 3.37 (s, 3H, OCH$_3$); 6.65 (t, 1H, aldehyde H);
- 7.25 (m, 5H, aromatic H).

IR: (thin film)
- 2924 (s), 1117 (s), 1452 (s), 1196 (s), 1495 (s), 1338 (m), 3024 (m),
- 1603 (m), 972 (m), 11302 (m), 1030 (m), 3061 (m), 904 (m), 1281 (m),
- 3085 (m), 868 (m), 1734 (w), 1653 (w), 1539 (w), 1559 (w).
Reaction of SAMP-Phenylacetaldehyde with MeLi and Mel:

To a 25ml three-neck round bottom flask equipped with septa and N₂ inlet was added 0.106g (0.4558mmol) SAMP-phenylacetaldehyde hydrazone in 920ul of dry ether. Ten equivalents (3.25ml) of 1.4M MeLi were added dropwise to the magnetically stirred hydrazone solution. The reaction was monitored by TLC and after 11 hours was subsequently quenched with 10 equivalents (0.284ml, 4.558mmol) of methyl iodide. 5ml of H₂O was added and the bilayer was extracted with ether (3x50ml). The resulting ethereal solution was washed with H₂O (1x25ml) and brine (1x25ml). The organic layer was dried over K₂CO₃, concentrated in vacuo to give a 95% yield of an orange oil. The crude material was subjected to flash chromatography on Wolem silica gel using 20:1 hexane:ethyl acetate as the solvent system to give 22% yield of an orange oil.
Analytical Data:

M.W.: 276.423

C\textsubscript{17}H\textsubscript{28}N\textsubscript{2}O: calc.: C 73.87%  H 10.21%  N 10.13%
found: C 73.71%  H 10.24%  N 9.82%

\textsuperscript{1}H NMR: (300 MHz, TMS)
0.86(d, 3H, CH\textsubscript{3}[on hydrazine C]); 1.10(d, 3H, CH\textsubscript{3}[B to aromatic]);
1.5-1.8(m, 4H, 8-CH\textsubscript{2} on pyrrolidine); 2.2(s, 3H, N-CH\textsubscript{3});
2.60-2.95(m, 4H, OCH\textsubscript{2}, NCH\textsubscript{2}, CH[\& to aromatic]); 3.05(t, 1H, NCH\textsubscript{2});
3.15(d, 1H, CH on pyrrolidine); 3.27(s, 3H, OCH\textsubscript{3});
3.40(m, 1H, CH[on hydrazine C]); 7.25(m, 5H, aromatic H).

IR(CCl\textsubscript{4})
1119(s), 1451(s), 1377(s), 1199(s), 907(s), 3027(s), 1495(s), 1024(m),
963(m), 1343(m), 1287(m), 1412(m), 3063(m), 3087(m), 1943(w),
1738(w), 1601(w), 1266(w), 876(w).

M.S. (70 eV)
277(0.8), 276(M\textsuperscript{+},4.8), 172(11.96), 171 (100.00), 114(21.43)
105(18.92), 91 (15.54), 71(14.91), 70(22.78), 58(23.58), 56(22.07),
55(10.89), 45(51.13), 43(10.3), 42(18.30), 41(113.98), 32(10.75)
Organocerium reactions

Representative Procedure

In a 15ml three-neck round bottom flask with N₂ inlet was added CeCl₃·7H₂O (2eq), which was heated to 140°C/0.5 torr with magnetic stirring for 2 hours, then cooled to room temperature. The dry CeCl₃ was treated with anhydrous THF and stirred in an N₂ atmosphere for 2 hours. The suspension was cooled to -78°C in an isopropanol/CO₂ cold bath and stirred for 2 hours, after which 2eq. MeLi was added dropwise at -78°C and stirred for one additional hour. A solution of SAMP-dihydrocinnamaldehyde hydrazone (1eq) in dry THF was added to the methylcerium reagent via syringe to give a 0.166M hydrazone solution. After 5 minutes, the reaction was quenched with excess methylchloroformate (2.2eq) and allowed to stir for 4 hours. A saturated solution of NH₄Cl was added and the reaction mixture was filtered through a pad of Celite, extracted with ethyl acetate (3x50ml), washed with brine (1x25ml), dried over K₂CO₃, and concentrated in vacuo to yield an orange oil, ~100%. The oil was purified by flash chromatography using 8:1 hexane:ethyl acetate as the solvent system to 73.6% of a yellow oil. Kugelrohr distillation (130°C/0.01 torr) gave a clear, colorless oil. Isothermal capillary gas chromatography at 200°C showed two products in a ratio of 96:4.
Analytical Data

M.W : 320.433

b.p.: 130°C/0.01 torr

Rf 0.20 (6:1 hexane:ethyl acetate)

$^1$H NMR (200 MHz, TMS)
1.20 (d, 3H, CH$_3$ [on hydrazine C]); 1.60-2.2 (m, 6H, 8-CH$_2$ on pyrrolidine, -CH$_2$-); 2.8 (m, 3H, NCH$_2$, CH$_2$ (α to aromatic));
3.0-3.4 (m, 5H, OCH$_2$, (2) CH, NCH$_2$); 3.25 (s, 3H, OCH$_3$);
3.70 (br, 3H, OCH$_3$ [acetoxy]); 7.25 (m, 5H, aromatic H).

IR (thin film)
1700 (s), 1109 (s), 2953 (s), 2874 (s), 1317 (s), 1439 (s), 1133 (m),
1190 (m), 3028 (m), 3433 (m), 3299 (m), 3082 (m), 3130 (m), 1048 (m),
1495 (m), 1553 (w), 1603 (w), 2361 (w), 1539 (w).
Summary

Stereoselective nucleophilic addition can be performed on chiral hydrazines derived from SAMP and selected aldehydes, using organocerium reagents. The route to enantiomerically pure amino acids seems to be feasible. Further work in this area will be pursued.
References

1. Evans, D.A. Presented at the fourth annual Carl Shipp Marvel Lecture Series in Organic Chemistry, University of Illinois, Urbana, IL, April, 1986.
7. Sternberg, J., personal communication.