APPLICATION OF \(\alpha\)-AMINOORGANOSTANNANES TO THE PREPARATION OF \(\beta\)-AMINOALCOHOLS

by

Adela Ncube

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in fulfilment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Chemistry

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Abstract

Preparation of non-conjugated dipole-stabilized $\alpha$-aminoorganolithiums by tin-lithium exchange is explored. The configurational stability of enantiomerically enriched $\alpha$-aminoorganolithiums is also investigated. These organolithiums can react with aldehydes to provide both racemic and chiral non-racemic $\beta$-aminoalcohols.

$N$-(1-tributylstannyl)alkyl-$N,N,N'$-trimethylureas are prepared from stannyl phthalimides which, in turn are prepared from hydroxystannanes generated from aldehydes and tributyltinlithium. The trimethylurea organostannanes transmetalate completely with $n$-BuLi at $-78$ °C. The resulting organolithiums do not trap with electrophiles; instead, the amide group migrates from the nitrogen to the carbanion (1,2 migration) to give the more stable lithium amides.

$N$-alkyl 2-(trimethylsilyl)ethoxycarbonyl (Teoc) protected $\alpha$-aminoorganostannanes are also prepared from stannyl phthalimides. These $\alpha$-aminoorganostannanes undergo complete tin-lithium exchange with $n$-BuLi at $-78$ °C. Reaction of the resulting organolithiums with either CO$_2$ or benzaldehyde give low yield of isolated product, presumably due to decomposition of the organolithiums. The Teoc group seems to be a poor protecting group for stabilizing $\alpha$-aminoorganolithiums.

$N$-t-Butylthiomethyl $t$-Boc protected $\alpha$-aminoorganostannanes transmetalate with $n$-BuLi at $-78$ °C to give $\alpha$-aminoorganolithiums which can react with different aldehydes to give $\beta$-aminoalcohols in good yields. Aromatic aldehydes give approximately a 2:1 ratio of the anti:syn diastereomers, whereas aliphatic aldehydes give almost a 1:1 mixture of the two diastereomers. The enantiomerically enriched N-t-butylthiomethyl $t$-Boc protected $\alpha$-aminoorganolithiums racemize very slowly at $-95$ °C (2-3%) and they react with aldehydes with complete retention of stereochemistry to give $\beta$-aminoalcohols in high enantiomeric excess (91-94%). The protected $\beta$-aminoalcohols may be converted to oxazolidinones which are then hydrolyzed to primary $\beta$-aminoalcohols. Oxazolidinones with straight chains alpha to the nitrogen ($R = n$-$C_3$H$_7$, $n$-$C_4$H$_9$ and $n$-$C_5$H$_{11}$) give low yields of the primary $\beta$-aminoalcohols. The $\beta$-aminoalcohols with these groups may be deprotected via aminoacetal intermediates, which can undergo
transacetalization with 1,3-propanedithiol to the primary β-aminoalcohols. Hydrolysis of enantiomerically enriched oxazolidinones give primary β-aminoalcohols with high enantiomeric excess. *Anti* β-aminoalcohols can cyclize with inversion under Mitsunobu conditions, to *trans* oxazolidinones which can then hydrolyze to give *syn* primary β-aminoalcohols.

Finally, stannylimines are prepared from the acylstannanes and (R)-α-methylbenzylamine and α-naphthylethylamine as chiral auxiliaries. The stannylimines undergo diastereoselective reduction with DIBAL-H at −78 °C to give stannylamines with moderate diastereomeric excess (56-62%). Removal of the chiral auxiliaries when tin is still present in the molecule is difficult. When t-Boc protected stannylamines (with the chiral auxiliary still in place) are treated with *n*-BuLi or *t*-BuLi, the *t*-Boc group is attacked instead of transmetalation.
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To
my parents
for being my first teachers
and
Ron
for loving me
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABq</td>
<td>AB quartet</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAL-H</td>
<td>binaphthol-modified lithium aluminum hydride</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
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<td>t-Bu</td>
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</tr>
<tr>
<td>Boc, t-Boc</td>
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<tr>
<td>d</td>
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<tr>
<td>DBU</td>
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<td>DCC</td>
<td>dicyclohexyl carbodiimide</td>
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<td>DEAD</td>
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<tr>
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<td>dihydroquinine</td>
</tr>
<tr>
<td>DHQD</td>
<td>dihydroquinidine</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-((N,N-dimethyamino)pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>E, E⁺</td>
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</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>EI</td>
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<td>equivalents</td>
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<td>ES</td>
<td>electrospray</td>
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</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>FABHRMS</td>
<td>fast atom bombardment high resolution mass spectrometry</td>
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GC  gas chromatography
GC-MS gas chromatography-mass spectrometry
h hour(s)
HMPA hexamethylphosphoric triamide
HOBT l-hydroxybenzotriazole
HPLC high performance liquid chromatography
i-Pr isopropyl
IR infrared
LDA lithium diisopropylamide
L-Selectride® lithium tri-sec-butylborohydride
m multiplet
Me methyl
min minutes
MNDO modified neglect of diatomic differential overlap
mp melting point
Ms mesyl, methanesulfonyl
MS mass spectrometry
MTPA \( \alpha \)-methoxy-\( \alpha \)-(trifluoromethyl)phenylacetyl
m/z mass/charge
NMR nuclear magnetic resonance
PCC pyridinium chlorochromate
Ph phenyl
PPTS pyridinium p-toluenesulfonate
PHAL 1,3-phthalazinediyl
PNB p-nitrobenzoic acid
q quartet
Rf retention factor
rt room temperature
s singlet
SET single electron transfer
S\( _{N2} \) substitution nucleophilic bimolecular
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra-\textit{n}-butylammonium iodide</td>
</tr>
<tr>
<td>TBDMS, TBS</td>
<td>\textit{tert}-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>\textit{N},\textit{N},\textit{N},\textit{N}^-tetramethylethylenediamine</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
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<td>volume/volume</td>
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<td>weight/weight</td>
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Chapter 1

Introduction

1.0 General: β-Aminoalcohols

The synthesis of β-aminoalcohols has drawn the attention of organic chemists over the years. This is mainly because β-aminoalcohols are building blocks of many very important biologically active synthetic and natural compounds. For example, the diterpenoid paclitaxel (Figure 1) has an anti β-aminoalcohol side chain with (2R, 3S) absolute stereochemistry. Paclitaxel has been isolated from the tree Taxus brevifolia.\(^1\) It has been approved by the Food and Drug Administration for the treatment of metastatic ovarian and breast cancer.\(^2\)

Some Human Immunodeficiency Virus I (HIV-I) protease inhibitors are also significant β-aminoalcohols. The inhibitor shown below was found to block the spread of HIV-1 in T-lymphoid cells but suffered from aqueous insolubility. Studies are still underway to try and synthesize the inhibitor that would give the best results by changing the R group.\(^3\)

Amicoumacin B is a natural product isolated from the culture broth of \textit{Bacillus pumilus}. It exhibits potent antiulcerogenicity against stress ulcers whilst being non-central suppressive, non-anticholinergic and non-antihistaminergic.\(^4\)
Figure 1: Biologically active \(\beta\)-aminoalcohols

Besides being found in biologically active molecules, \(\beta\)-aminoalcohols are also used as chiral ligands and auxiliaries for asymmetric synthesis. For example, \((1S,2R)-(-)-2-(N,N\text{-dibutylamino})-1\text{-phenylpropan-1-ol} \ 1\) (Scheme 1), catalyses the enantioselective addition of dialkylzinc reagents to aliphatic and aromatic aldehydes to give alcohols in high enantiomeric excess.\(^5\)

Scheme 1
The synthesis of these β-aminoalcohols in high enantiomeric and diastereomeric excess is very important. Chiral α-aminoorganolithiums 2 (Scheme 2) can act as precursors to these very important molecules. The organolithiums can be generated by the transmetalation of the α-aminoorganostannanes 3. For this method to be feasible, the chosen α-aminoorganostannane 3 should undergo complete transmetalation to give 2. This transmetalation should proceed without any racemization and the resulting organolithium 2 should be configurationally stable under the conditions used. Also, 2 should be able to react with electrophiles (in this case aldehydes) with complete retention of stereochemistry. Finally, the two protecting groups, R¹ and R² should be easily removed to give either primary or secondary β-aminoalcohols.

Scheme 2

Over the past few years it has been the challenge of organic chemists to find a system that would fulfill all these requirements.
1.1 Generation of α-Aminoorganolithiums

1.1.1 Deprotonation of α-protons

α-Aminocarbanions have become very useful synthetic equivalents for making new carbon-carbon bonds. Their preparation has involved the addition of an activating group, Z, to the amine and deprotonation of the α-hydrogen to give the α-aminocarbanion 4 (Scheme 3). The activating group Z can provide stabilization in the transition state leading to 4 by complexation with the metal M, by dipole stabilization and/or by resonance delocalization. After trapping with the appropriate electrophile, the activating group is removed to generate the desired amine.6

Scheme 3

A number of activating groups have been developed; however, some had drawbacks. For example, nitrosoamines first reported by Keefer and Fodor7 and later extensively studied by Seebach8 are limited by the hazards in using these substances because they are potential carcinogens. Amides have also been used as precursors to dipole-stabilized α-aminoorganolithiums. However, the disadvantage is that the amides are difficult to remove. In addition, some steric bulkiness had to be created around the amide in order to hinder approach of the butyllithium base to the carbonyl carbon which
would lead to addition instead of the desired deprotonation of the \( \alpha \)-hydrogen. Initially triisopropylbenzamides 5 (Scheme 4) were used; unfortunately, they could not be cleaved under a variety of acidic and basic conditions. 2,2-Diethylbutamides 6 were then employed and these could be cleaved, but only under very harsh conditions.\(^9\)

**Scheme 4**

\[
\begin{align*}
\text{Ar} & \text{N} \xrightarrow{1. \text{s-BuLi} \text{, Et}_2\text{O}, -78 \degree \text{C}} \text{Ar} \text{N} \xrightarrow{2. \text{MeOD}} \text{HN} \\
\text{Et}_3\text{C} & \text{N} \xrightarrow{1. \text{s-BuLi} \text{, Et}_2\text{O}, -78 \degree \text{C}} \text{Et}_3\text{C} \text{N} \xrightarrow{2. \text{Me(C}_2\text{H}_5)_I} \xrightarrow{\text{HCl, H}_2\text{O, reflux}} \text{HN}
\end{align*}
\]

5 \( \text{Ar} = 2,4,6-i-\text{Pr}_3\text{C}_6\text{H}_2 \)

A much better activating group, the formamidine, was introduced by Meyers in 1980 (Scheme 5).\(^10\) The decreased reactivity of the imine carbon relative to the carbonyl carbon towards nucleophilic attack eliminated the need for a bulky group to shield the imine carbon.

**Scheme 5**

\[
\begin{align*}
\text{NMe}_2 & \xrightarrow{s-\text{BuLi}} \text{N} \xrightarrow{1. \text{E}^+ \text{, 2. KOH}} \text{E}
\end{align*}
\]

The acidity of the \( \alpha \)-protons is considerably enhanced when they are allylic or benzylic, and their chemistry is also somewhat different. The most important difference is
the occurrence of a single electron transfer (SET) process in the reaction of the lithiated formamidines of 5, 6 and 7-membered ring saturated heterocycles. For example, reaction of benzophenone with the lithiated piperidine 7 (Scheme 6) affords only benzophenone ketyl, indicating oxidation of the lithioformamidines rather than addition.11

Reaction of 7 with alkyl halides results in low yield of alkylation product 8, with oxidation product 9 also being produced. Conformationally locked systems such as 7 (R1 = Bu') seem less likely to oxidize. It was suggested that the conformationally mobile systems might undergo ring inversion, thus placing the C-Li bond in an electronically unfavorable axial orientation, thereby encouraging SET.11

One way that has been found to minimize the SET process is addition of hexamethylphosphoric triamide (HMPA) to the lithiated formamidines prior to addition of the alkyl halides. The mechanism by which HMPA hinders SET is not well understood. The second method is the transmetalation of the organolithium to a cuprate. This was surprising because cuprates are known to undergo SET reactions.12 The authors did not discuss how cuprates avoid SET in these alkylation reactions. With electrophiles other than alkyl halides (e.g. carbonyls), which are not prone to electron transfer, no HMPA is required.11
The formamidines were widely applied by Meyers et al. for synthesis of natural products. Unfortunately, they do not work well for acyclic systems because the α-protons are not as acidic and give incomplete deprotonation with alkyllithiums.

Beak later showed that the t-butoxycarbonyl group (t-Boc) can also act as a dipole-stabilizing group, which directs α-lithiation.13

1.1.2 Transmetalation of α-aminoorganostannanes

The organolithiums described above were made by direct deprotonation. However, not all systems have protons which are acidic enough to be removed by bases. The transmetalation of α-aminoorganostannanes with organolithiums has been found to be a convenient route to organolithiums that are difficult to prepare by other means.

Seyferth discovered the first transmetalation reaction in the late 1950's.14 The transmetalation reaction is an equilibrium in which the driving force is the relative difference in base strength of the organolithium species RLi and R²Li (Scheme 7).15 As a result, alkyl-substituted anionic species would be more difficult to obtain than unsubstituted ones. However, correct choice of solvents and substituents can allow a nearly quantitative shift towards R²Li. This was shown to be true when R¹ and R are alkyl or aryl groups, and R² was allyl, benzyl, vinyl or even cyclopropyl.16, 17, 18
What later became even more useful was the report by Peterson in 1971 that transmetalations were also possible with systems where $R^2$ was an $\alpha$-heterosubstituted alkyl. These first transmetalations involved use of $N,N$-dialkylaminomethylstannanes (Scheme 8) which have no destabilizing alkyl substitution at the anionic center.

McGarvey later did a study on the relative stability of $\alpha$-alkoxyorganolithiums and alkylolithiums. As shown in Figure 2, the stability of the $\alpha$-alkoxyorganolithiums decreases with substitution at the carbanionic center. The $\alpha$-aminoorganolithiums are believed to follow the same trend.
Figure 2: Relative stabilities of α-alkoxyorganolithiums and alkyllithiums.

The mechanism of the transmetalation reaction is not well understood. It has been assumed to proceed through a four-centered transition state 11 (Figure 3). Reich and Philips have reported that they observed an intermediate “ate” complex 12 by low temperature $^1$H, $^{13}$C and $^{119}$Sn nuclear magnetic resonance (NMR) studies of tetraalkylstannanes and alkyllithiums (mostly tetramethylstannane and methyllithium) in a solvent system made up of tetrahydrofuran (THF) and HMPA. However, McGarvey and coworkers did not observe any of these stannylate complexes in similar NMR experiments with α-alkoxyorganostannanes. They used slightly different conditions than Reich and Philips: THF, Et$_2$O or 1,2-dimethoxyethane (DME) as solvents and tributyltin compounds. Reich and Philips suggested that these conditions were unfavorable for the formation of “ate” complexes in NMR-detectable amounts. Perhaps the HMPA plays a role in the stability of these complexes, or the stannylate complexes might not be involved at all in the transmetalation of α-alkoxyorganostannanes.
Figure 3: Proposed complexes for the transmetalation of organostannanes.

\[ \text{R}^3\text{Sn} \quad \text{Li}^+ \quad \text{R}^4\text{Sn} \]

Transmetalation has proven to be superior to the more conventional methods, (i.e. reaction of lithium metal with organic halides and halogen metal exchange between organolithium reagents and organic halides).\(^{15}\) It avoids contamination of the newly synthesized organolithium reagent by lithium halides. The presence of tetraalkylstannanes in the solution is not a limitation, since these hydrocarbon-like species are almost unreactive and in most cases are easily separated at the end of the reaction.

1.2 Preparation of \(\alpha\)-Aminoorganostannanes

The standard procedure for preparation of cyclic aminoorganostannanes involves deprotonation of the active pyrrolidine or proline and reaction of the organolithium with trialkylstannyl chloride (Scheme 9).\(^{25}\)
For acyclic systems which can not rely on deprotonation, Pearson and Lindbeck reported a method that involves N-alkylation of carbanates with $\alpha$-iodoalkylstannanes (Scheme 10).\textsuperscript{26} The limitation to this procedure is that $\alpha$-iodoalkylstannanes other than (iodomethyl)trialkylstannane ($R^1 = H$) or (iodoethyl)trialkylstannane ($R^1 = Me$) are not readily available. Elimination of the iodide also occurs instead of alkylation, leading to low yields. In addition, optically active $\alpha$-iodoalkylstannanes are not available.

Pearson \textit{et al.} later introduced a method that can allow the introduction of other side chains $R^1$ (Scheme 11). Initially they showed that condensation of either chiral oxazolidinones 13 ($X = O$) or imidazolidinones 13 ($X = NMe$) with aldehydes in the presence of $p$-toluenesulfonylic acid gave crystalline sulfones 14 as single diastereomers. Displacement of these sulfones with $Bu_3SnLi$ proceeded with complete retention of configuration to give the chiral stannanes 15.\textsuperscript{27}
This method only gives chiral \(\alpha\)-aminoorganostannanes when one has a chiral oxazolidinone or chiral imidazolidinone. Simple acyclic protecting groups like \(r\)-Boc give racemic \(\alpha\)-aminoorganostannanes.\(^{28}\)

The other method that gave enantiomerically enriched acyclic \(\alpha\)-aminoorganostannanes was reported by Chong and Park (Scheme 12).\(^{29}\) The key step is the enantioselective reduction of acylstannanes 16 with binaphthol modified LiAlH\(_4\) (BINAL-H\(_4\)). The resulting \(\alpha\)-hydroxystannanes 17 (96% ee) underwent the subsequent steps shown in Scheme 12 and gave \(\alpha\)-aminoorganostannanes 18 (94% ee, 42% yield from acylstannanes). The reduction step is the one that contributes most to the poor overall yield.
Two groups concurrently reported another method to α-aminooorganostannanes.\textsuperscript{11,12} It involves the condensation of benzotriazole, an aldehyde and either an amine or an aldehyde to give the N-[1-benzotriazole-1-yl]alkyl]amides and -amines (Scheme 13). These compounds were then treated with tributyltinlithium to give the α-aminooorganostannanes. This method is very short and give the products in very high yields. However, it has only been used to make racemic aminooorganostannanes.
1.3 Configurational Stability of Organolithiums

Organolithium species in which the carbanionic center is sp\(^3\) hybridized are isoelectronic with amines and might also undergo pyramidal inversion like the amines. Lestinger and Traynhan prepared the first optically active organolithium, (R)-2-octyllithium, from (R)-2-octyl iodide and n-BuLi at -78 °C.\(^{32}\) The reaction of the octyllithium with CO\(_2\) gave product that had undergone 80% racemization. This indicated that simple alkyllithiums were not configurationally stable even at low temperatures. The first configurationally stable organolithium, cyclopropyllithium 19 (X = Me) in which ring strain presents a substantial energy barrier to inversion was reported in 1964.\(^{33}\) Further work involving related organolithiums in which X was an electron withdrawing substituent (OR, Cl, F), indicated that these substituents increase the barrier to inversion.\(^{34}\)
One of the most important contributions in this field was made by Still and Sreekumar in 1980. They showed that α-alkoxyorganolithiums 20 were configurationally stable up to -30 °C. These organolithiums were trapped with different electrophiles without any racemization. The configurational stability of these organolithiums is believed to depend on the chelation between oxygen and the Li ion as shown in Figure 4.

Organolithiums 21 with other heteroatoms (X = SePh, SPh, Br), have been reported to be configurationally stable at very low temperatures (-78 to -125 °C).

The α-aminoorganolithium 22 was also found to be configurationally stable at -78 °C. The equatorial α-aminoorganolithium can also be formed but it is less stable, therefore it quickly isomerizes to the axial isomer. The authors suggested the stability of the axial isomer was due to the ability of the carbanion lone pair to interact with Y-C orbitals. In the equatorial isomer, the same interaction is not possible due to steric interactions.

**Figure 4:** Chiral organolithiums

![Diagram of chiral organolithiums](image-url)
### 1.3.1 Configurational stability of α-Aminoorganolithiums

Early studies on configurational stability of aminoorganolithiums were reported by Meyers and coworkers. They obtained the organolithiums 24 (Scheme 14) by deprotonation of the chiral formamidines 23. These organolithiums are pyramidal and therefore can undergo inversion. The configurational stability of these organolithiums depends on chelation of the Li ion to the nitrogen and oxygen as shown. It was shown that selectivity decreases in formamidines lacking an oxygen atom. Alkylation occurs with a net inversion of configuration.

**Scheme 14**

The deprotonation step of the formamidines was believed to be the stereoselective step. It was shown that only the α-proton is removed when n-butyllithium is added to the chiral formamidines. This was shown when DMSO-d$_6$ was introduced into the lithiated formamidine and gave the α-D product, which was identical to an authentic sample. However, when MeI (or any other alkyl halide) was added, the alkyl group entered from the β-face to afford the S-enantiomer.
The authors also showed that deprotonation occurred with no primary kinetic isotope effect. Therefore, the rate determining step was not deprotonation but possibly the formation of the complex 25 (Scheme 15) prior to deprotonation.

**Scheme 15**

Experiments were also done to investigate the alkylation of 3° carbanions. With all these experiments the authors suggested that the overall mechanism summarized in Scheme 15 occurred. The authors showed that all deprotonations take place from the α-
face. alkylation on 2° carbanion occurs from the β-face with very high selectivity and net inversion. Alkylation on the 3° carbanion occurs from the α-face with net retention. Experimental data and molecular mechanics computational data indicated that the organolithiums can exist in two conformations: Cα and Cβ, where the chelate is on the α-face or the β-face respectively. The Cα conformation is the one shown in Scheme 14. For the first alkylation (R = H), molecular mechanics calculations indicated that the Cα is more stable than Cβ by 2.3 kcal/mol due to repulsive interaction between the vinyl hydrogen and the methyl-H of the t-butyl group in Cβ. Therefore, when R = H, the organolithium exist as the Cα. Since the α-face is blocked by the chelate, Meyers suggested this to be the reason why first alkylation occurs from the β-face.\(^{42}\) When R = Me, it was shown that both Cα and Cβ have approximately the same energy because Cα is also destabilized due to the interaction between the methyl group and the methyl of the t-butyl group. Therefore, it is not clear why the second alkylation occur from the α-face.

Studies indicated that these organolithiums were not configurationally stable even at very low temperatures (-80 °C to -100 °C).\(^{42}\) Therefore, it is believed that these alkylations are conformationally controlled and the organolithiums are capable of inverting to the more stable diastereomer.

Gawley investigated the alkylation of chiral oxazolines 26 (Scheme 16).\(^{43}\) The diastereomeric ratio was not affected by either the structure of the base or the deprotonation temperature, but it was affected by the temperature of the alkyl halide quench. As a result, stereoselective deprotonation as the source of asymmetric induction was ruled out initially.
Experimental evidence later suggested that the $\beta$-proton is removed stereoselectively, but the resulting anion equilibrates to a thermodynamic mixture of diastereomeric lithiated species and that this latter process accounts for the stereoselectivity observed in the overall process. Hence, the oxazolines behaved in the same manner as the formamidines. What was required for good asymmetric induction was a nonrotating bond between the ligating nitrogen and the stereocenter of the chiral auxiliary. For the oxazolines, this was provided by the ring, and for the formamidines, the bidentate chelation served this purpose.

Gawley also studied the non-benzylic piperidinooxazolines (Scheme 17). Alkylation of these systems was found to be 100% stereoselective.\textsuperscript{44} Unlike the tetrahydroisoquinolyloxazolines which afford benzylic organolithiums, it was assumed, on both experimental and theoretical grounds, that the organolithium species of these piperidine systems do not undergo pyramidal inversion. Therefore, deprotonation is 100% stereoselective, and the organolithium 27 is a single epimer. Dipole stabilization requires that the lithium be equatorial, so it is impossible for the alkylation to occur with inversion of configuration.\textsuperscript{44}
Scheme 17

The selectivity was rationalized by assuming prior coordination of the alkyl lithium to the oxazoline nitrogen, and orientation of the alkyl group to be \textit{anti} to the isopropyl group as shown in Figure 5. In 28a, this would place the butyl group on the convex face of the molecule, while in 28b, the butyl group would be on the concave face, severely crowded by the axial hydrogens of the piperidine. Thus, it was concluded that steric effects must be responsible for the observed selectivity.$^{44}$

\textbf{Figure 5}: Coordination complexes for the deprotonation of piperidino-\textit{oxazolines}.

A similar coordination complex was also postulated to account for the stereoselective deprotonation of tetrahydroisoquinolyloxazolines 25.$^{44}$ However, because the resulting organolithiums are benzylic, they can undergo pyramidal inversion to give the more stable diastereomer. As a result, they give lower diastereoselectivity than the
piperidino-oxazolines. Although the piperidino-oxazolines are configurationally stable, their alkylation gives very low yields due to SET discussed in section 1.1.1.

Beak and Kerrick later reported the preparation of the organolithium 29 (Scheme 18) by deprotonation of \( t \)-Boc pyrrolidine in the presence of sparteine.\(^{45} \) This organolithium reacted with electrophiles to give enantiomerically enriched products. The enantioselectivity observed is believed to be the result of an asymmetric deprotonation. In order to determine the configurational stability of 29, chiral aminostannane 30 was transmetalated in the absence of sparteine and the organolithium was trapped with trimethylsilyl chloride (TMSCl). The product was obtained in very low yield and very low enantiomeric excess. Hence, the organolithium 29 is not chemically and configurationally stable in the absence of sparteine.

**Scheme 18**

The first report on configurational stability of nonconjugated, acyclic dipole stabilized \( \alpha \)-aminoorganostannanes came from Pearson and Lindbeck (Scheme 19).\(^{46} \)
They showed that transmetalation of stannane 31a (X = NMe) and quenching the resulting organolithium 32a with an electrophile gave only 33a as the product. This indicated that the organolithium 32a was configurationally stable at -78 °C and reacted with the electrophiles without any racemization. However, when the other diastereomer 31b (X = NMe) was subjected to the same conditions, it gave a mixture of 33b and 33a.

Scheme 19

When the oxazolidinones 31 (X = O) were transmetalated, 33a was the only product isolated even when the starting material was 31b. Although transmetalation of the two diastereomeric stannanes 31a and 31b initially give 32a and 32b, respectively, 32b was found to equilibrate within 40 min at -78 °C to the more stable diastereomer 32a. The steric hindrance between the syn R' and the Me groups in 32b makes it unstable compared to 32a where these two groups are trans. For the case where X = O, 32b
completely epimerizes to 32a. This difference in configurational stability was attributed by Pearson to the weaker chelation between the lithium atom and the carbonyl oxygen. This chelation is believed to be responsible for configurational stability. Pearson suggested that the carbamate carbonyl oxygen does not chelate to the Li atom as strongly as the urea carbonyl oxygen, making 32b (X = O) less configurationally stable than 32b (X = NMe).

The configurational stability of these systems depends on the relative stability of the two diastereomers. Therefore, only the more stable diastereomer is accessible in pure form by this method.

Chong and Park later reported the first enantiomerically enriched acyclic dipole stabilized α-aminoorganolithiums without any diastereomeric bias. They showed that the α-aminoorganostannanes 34 (Scheme 20) can undergo tin-lithium exchange without any racemization to give α-aminoorganolithiums 35 that are configurationally stable at −95 °C for 10 min. These organolithiums react with carbon dioxide with retention of configuration.

Scheme 20

\[
\text{MeN} \quad \text{Or-Bu} \quad n-\text{BuLi, THF} \quad -95 \, ^{\circ}\text{C} \quad \text{MeN} \quad \text{Or-Bu} \quad \text{CO}_2, H^+ \quad 75-97\% \quad \text{MeN} \quad \text{Or-Bu} \quad \text{CO}_2\text{H}
\]

\[
34a \quad R = \text{Et, } 94\% \text{ ee}
\]

\[
34b \quad R = \text{i-Pr, } 92\% \text{ ee}
\]
However, racemization was observed at higher temperatures. For example, at -78 °C, slight racemization occurred which increased with time. Racemization was even faster at -55 °C. The racemization of these α-aminoorganolithiums was also accelerated by more coordinating solvents such as DME and HMPA, with HMPA giving completely racemic products. These coordinating solvents disrupt the chelation between the lithium atom and the carbonyl oxygen shown in 35 which is believed to be vital for configurational stability.

The first enantiomerically enriched acyclic α-aminoorganolithium 36 (Scheme 21) that is stabilized only by chelation was also reported by Chong. This system is less configurationally stable than the dipole-stabilized organolithium 35; however, it is stable at -95 °C. Like the dipole stabilized systems, this organolithium racemizes faster in the presence of DME and at higher temperatures.

Scheme 21

Gawley and Zhang later prepared the cyclic counterparts, 37 (Scheme 22). These organolithiums were found to be more stable than the acyclic organolithium 36. They were found to be configurationally stable at -78 °C for up to 75 min in THF (with or without N,N,N',N'-tetramethylethylenediamine (TMEDA) or DME. However, their chemical stability decreases in the presence of TMEDA. They are also configurationally
stable at \(-60 \, ^\circ\text{C}\) only in a THF/TMEDA solvent system. In the absence of TMEDA, racemization is faster, especially in DME.

**Scheme 22**

Yamamoto\(^4^9\) and Chong\(^4^7\) were not successful in their attempt to obtain unchelated acyclic \(2^o\) \(\alpha\)-aminoorganolithiums by transmetalation. Surprisingly, Gawley and Zhang were able to prepare \(N\)-methyl \(2\)-li thiopyridinrs and piperidines (39 and 38 respectively) which were configurationally stable at temperatures as high as \(-40 \, ^\circ\text{C}\) in THF in the presence of TMEDA (Scheme 23).\(^4^8\) The TMEDA was more necessary for chemical stability than configurational stability, i.e. the organolithiums underwent decomposition faster than racemization. These unchelated organolithiums are the only ones stable at such a high temperature making them the most configurationally stable \(\alpha\)-aminoorganolithiums reported to date.
Scheme 23

Gawley and Zhang explained this unusual configurational stability using the crystal structures of \([\alpha\text{-}(\text{dimethylamino})\text{benzyl} \text{ lithium. diethyl ether}]_2\) 40 and S-\(\alpha\text{-}\) (methylpivaloylamino)benzyl lithium. sparteine 41 reported by Boche.\(^{50}\) For 40 the heterochiral dimer is favored over the homochiral one due to the indicated steric hindrance. Like the organolithiums described above, these carbanions are also pyramidal, but they differ in that the lithium of 40 is bridged by the nitrogen, while the lithium of 41 is not. The carbonyl oxygen of 41 is also chelated to the lithium, consistent with structural theories regarding other dipole-stabilized organolithiums discussed above.
Figure 6: Structures of α-aminoorganolithiums

Gawley and Zhang assumed that there is also bridging in the organolithiums 38, 39 and 37 (Scheme 24), similar to the Boche crystal of 40. Since these organolithiums are enantiomerically enriched, they predicted the formation of a homochiral dimer. This bridging was then used to explain the unusual stability of 38 and 39, since both the carbanionic carbon and nitrogen are stereogenic in the bridged species 42. They rationalized that 42 can not undergo inversion unless both the C-Li and the N-Li bonds are broken simultaneously.

They also postulated that the chelated lithiopyrrolidine 37 may be in equilibrium with a bridged species such as 43, but inversion of 37 may occur with the lithium still held in place by the methoxy group. In addition to racemization by the same route as 37, the authors suggested that 36 might also racemize by the inversion of its bridged species 44. This pathway is not possible in 43 where the carbanion is in a ring. Thus, Gawley and Zhang concluded that the presence of the chelating methoxy accounts for the decreased
configurational stability of 37 relative to 38 and 39, while the presence of the ring is responsible for the increased stability of 37 over 36. Though chelation had proven to increase configurational stability in the past, according to Gawley and Zhang's discoveries, it can also decrease configurational stability.

Scheme 24

Both N-methyl-2-lithiopiperidine and pyrrolidine (38 and 39) were found to react with different electrophiles giving 2-substituted heterocycles in very good yields. In the piperidine system, the reaction with carbonyl electrophiles occurred with nearly 100% retention of stereochemistry and alkyl halides reacted with inversion. In the pyrrolidine
series, reaction with carbonyls also occurred with 100% retention, but racemization occurred with alkyl halides.

Around the same time that Gawley and Zhang made this report, Meyers and Elworthy also reported their investigations on the effect of Li-O vs. Li-N complexation on configurational stability of aminoorganolithiums. They compared the transmetalation of the lithioformamidines 46a and Beak's t-Boc system 46b (Scheme 25). The organolithium 47a was found to be configurationally stable between -78 °C and -55 °C in THF and also trapped with Me$_2$SO$_4$ without any racemization. However, N-t-Boc lithiopyrrolidine 47b showed complete loss of optical activity after 30 min at -78 °C.

Scheme 25

![Scheme 25](image)

These results suggested that configurational stability relies on the ligands present to associate with the lithium atom. The authors now believe that the harder oxygen atom in 47b, (which is generally believed to bind strongly to the lithium ion) may actually loosen the lithium-carbon attraction and allow carbanion inversion to occur more readily. They based this on earlier suggestions that this was also responsible for the increase in basicity of organolithium reagents in an aggregate.
Having a nitrogen-protecting group that can chelate with the lithium atom seemed to have been the requirement for configurational stability. However, as shown by some of the examples above, this is no longer the general rule of thumb, especially in cyclic aminoorganolithiums. To highlight Gawley and Zhang's conclusions, Figure 7 makes a direct comparison of lithiopyrrolidine 29, 37 and 39. Lithiopyrrolidine 29, which has the lithium chelated to the more coordinating carbonyl oxygen, is actually less stable than 37 which is chelated to an ether group. Finally, 39, which is not chelated at all, is the most stable, indicating that chelation actually decreases configurational stability in these cases.

Figure 7: Configurational stability of lithiopyrrolidines

![Chemical structures of 29, 37, and 39]

29 Not Stable  37 Stable up to -60 °C  39 Stable up to -40 °C

Generally, cyclic α-aminoorganolithiums are more configurationally stable than their acyclic counterparts. This is due to an energy barrier to inversion presented by ring strain. For example, 37 (Scheme 22) is more stable than 36 (Scheme 21). However, there is one case where this rule is broken. N-\textit{t}-Boc lithiopyrrolidine 29 (Figure 8), racemizes completely at -78 °C\textsuperscript{44} whereas its acyclic cousin 35 underwent only 12% racemization at -78 °C after 3 h.\textsuperscript{29}
From what is known so far, the addition of coordinating solvents to acyclic α-aminoorganolithiums facilitates racemization. On the other hand, coordinating solvents seem to enhance configurational stability in cyclic organolithiums. This opposite behavior might suggest that the mechanism of inversion is also different. However, in order to get a good insight into this subject, the mechanism of these pyramidal inversions still need to be closely investigated. In addition, a much more configurationally stable system is still required especially for the acyclic systems.

1.4 Synthesis of β-Aminoalcohols

There are a lot of methods that have been developed for the synthesis of β-aminoalcohols; however, they often have their own limitations. One of the widely used methods involves the use of chiral aminoaldehydes. Aminoaldehydes are synthesised primarily by the reduction of α-aminoacids. Diisobutylaluminum hydride (DIBAL) reduction of methyl or ethyl esters is often accompanied by overreduction to the corresponding alcohol; the same applies to the LiAlH₄ reduction of imidazolides. The resulting aminoalcohols can then be oxidized back to the aminoaldehydes making the
An efficient method that does not involve racemization or overrreduction was reported by Fehrentz and Castro (Scheme 26). The reduction of N-methoxy-N-methyl carboxamides 48 with LiAlH₄ proceeds through a stable lithium chelated intermediate 49. Further reduction of the lithium salt is precluded by intramolecular complexation and the aldehyde is obtained upon hydrolysis.

Aminoaldehydes are then converted to the aminoalcohols by addition of organometallics, and Grignard reagents are commonly used. Simple addition of Grignards at -78 °C in THF affords the β-aminoalcohols, but with low diastereoselectivity. The diastereoselectivity was improved by carrying out the reaction at 25 °C, which favored the chelation controlled Cram product 50a (Scheme 27). At higher temperatures a greater proportion of NH protons should be removed to give the transition state 51 prior to addition to the carbonyl group, resulting in preferential formation of syn alcohol. Unfortunately, aminoaldehydes are not very stable at high temperatures, therefore, low yields were reported.
It was shown that choosing a metal other than magnesium and changing the ligand can improve the diastereoselectivity. Doubly protected substrates, in particular the N,N-dibenzylamino aldehydes, were found to be configurationally stable at room temperature. These aldehydes react with Grignard and organolithium reagents to give the anti diastereomer in >90% de.\textsuperscript{56}

β-Aminoalcohols can also be obtained by the diastereoselective reduction of aminoketones. For example, Chung and Kang reported the reduction of α-amino enones \textsuperscript{52} (Scheme 28) derived from α-amino acids. Reduction of the amino enones with lithium tri-sec-butylborohydride (L-Selectride\textsuperscript{9}) gave the syn β-aminoalcohol in very high diastereoselectivity, via a non-chelation control. The β-aminoalcohols were obtained in >98% de after a single recrystallization.\textsuperscript{57}
The major disadvantage of both aminoa1dehydes and aminoketones is that they are chemically and configurationally unstable. As a result, they have to be used immediately after preparation. Also, since the chiral sources are amino acids, the type of β-aminoalcohols that can be synthesised is restricted (i.e. R depends on available α-amino acids).

β-Aminoalcohols have also been synthesised from chiral cyanohydrins. These are prepared by the enantioselective addition of HCN to aldehydes and ketones catalyzed by the enzymes (R) and (S)-oxynitrilase to give (R)- and (S)-cyanohydrins, respectively (Scheme 29). These cyanohydrins are first protected by the tert-butylidimethylsilyl (TBDMS) group and then addition of Grignard reagents gives an imine which then undergoes diastereoselective reduction with NaBH₄. The β-aminoalcohols were obtained in 93-99% ee and 80-98% de with the anti being the major diastereomer due to chelation control.
The syn \( \beta \)-aminoalcohols are obtained when DIBAL is added to the O-protected cyanohydrin before the organolithium reagent is added. This procedure, however, gives lower diastereoselectivity.\(^60\)

Despite the high enantiomeric purity of the cyanohydrins obtained by HCN addition to aldehydes, HCN is very toxic, making the method less favorable. Attempts have been made to find other sources of CN e.g. KCN; unfortunately this gave cyanohydrins in very low enantiomeric excess.\(^61\)

Regioselective ring opening of chiral epoxides is another method that has been developed for synthesis of \( \beta \)-aminoalcohols. The epoxides are obtained by Sharpless asymmetric epoxidation of allylic alcohols.\(^62\) Initially the epoxides were opened with titanium diazidodiisopropoxide with complete regioselectivity and gave 53 (Scheme 30) in very high yield. The hydrogenolysis of 53 gave the required \( \beta \)-aminoalcohol.\(^63\) Riera and coworkers later reported the use of benzhydrylamine in order to avoid the use of
potentially risky azides. The regioselectivity was lower for this method ($C_3/C_2 = 88/12$) which also led to lower yields of 54. However, because of the toxicity of azides, Riera suggested that use of benzhydrylamine might be preferred at larger scale.

Scheme 30

![Chemical Reaction Scheme]

What might be a more direct route to β-aminoalcohols to date, is the asymmetric aminohydroxylation (AA) recently reported by Sharpless. This reaction, like the Sharpless asymmetric dihydroxylation (AD), is also catalyzed by osmium tetroxide with the alkaloid chiral ligands (DHQ)$_2$-PHAL (a phthalazine core attached to two hydroquinine units) and (DHQD)$_2$-PHAL (a phthalazine core attached to two hydroquinidine units). Initially Chloramine-T (TsNCINa) was used as the source of nitrogen and $H_2O$ as the source of the hydroxyl group. The optical yields obtained under these conditions were not very good (33 to 81%). To improve the stereoselectivity, Sharpless started investigating other sources of nitrogen, and the best results were
obtained with N-chloro-N-sodio-2-trimethylsilyl ethyl carbamate (TeocNCINa) (Scheme 31).\(^{66}\)

**Scheme 31**

![Scheme 31 Diagram]

The examples that the authors reported involve only \(E\) alkenes 55 with aromatic \(R\) groups and \(R'\) being an ester in most cases. No comment was made regarding the use of aliphatic alkenes and \(Z\) alkenes with this new nitrogen source. It is not clear whether this method can also give \(anti\) \(\beta\)-aminoalcohols.

The only example that involves the use of acyclic \(\alpha\)-aminoorganolithiums was reported by Pearson and Lindbeck.\(^{26}\) This was achieved by transmetalation of \(\alpha\)-aminoorganostannanes 56 (Scheme 32) and trapping the resulting organolithiums with different aldehydes to give the \(\beta\)-aminoalcohols 57. Deprotection by transfer hydrogenolysis gave the primary \(\beta\)-aminoalcohols in very high yields. Unfortunately, this only worked for small \(R\) groups (Me and H); when \(R\) is an ethyl group, deprotonation of the benzyl carbamate was found to compete with Sn-Li exchange leading to very low yields.\(^{29}\) Also, this method only gave racemic \(\beta\)-aminoalcohols.
There is still a need for making enantiomerically enriched α-aminoorganostannanes which can be used to make β-aminoalcohols in high enantiomeric excess. These organostannanes should be able to have different R groups and the resulting organolithiums should also react with different aldehydes in order to have a general route to primary β-aminoalcohols.
1.5 References


Preparation and Transmetalation of Trimethylurea

Organostannanes

2.1 Introduction

As discussed in Chapter 1, most of the organolithiums that have been studied have carbamates (or oxazolidinones for cyclic systems), alkoxy or simple alkyl protecting groups. Pearson and Lindbeck reported the only example that has a urea (imidazolidinone) protecting group. They discovered that the imidazolidinone organolithiums 59a (Scheme 33), were more configurationally stable than the oxazolidinone organolithium 59b. Pearson and Lindbeck presumed that the imidazolidinone carbonyl oxygen must chelate to the Li ion much more than the oxazolidinone carbonyl oxygen.

Scheme 33

We decided to investigate the transmetalation of acyclic trimethylurea organostannanes 60 (Scheme 34). We wanted to see if the resulting organolithiums 61
would be more chemically and configurationally stable than carbamate protected \( \alpha \)-aminoorganolithiums.

**Scheme 34**

2.2 Results and Discussion

2.2.1 Preparation of aminoorganostannanes

Preparation of trimethylurea organostannanes 60 had not been reported prior to this work. We decided to apply methods that had been developed for the synthesis of carbamates. The most direct way was the N-alkylation of carbamates with \( \alpha \)-iodoalkylstannanes, first reported by Pearson and Lindbeck.\(^2\) The \( \alpha \)-iodostannane 62 was prepared according to the method of Chong and Park.\(^3\) However, reaction of 62 with trimethylurea in the presence of NaH did not give the desired \( \alpha \)-aminoorganostannane 63b. Instead, elimination occurred to give the alkene 64 as mixture of stereoisomers. This was not too surprising because Chong and Park had had the same problem.\(^3\) The only case where this kind of reaction worked was when Pearson and Lindbeck made the
carbamate 66 from iodostannane 65, albeit, in very low yield. Perhaps the iodostannane 62 is too sterically hindered to react with the trimethylurea anion.

Scheme 35

Note: All the compounds with different R groups will be numbered alphabetically as follows:

<table>
<thead>
<tr>
<th>no.</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Me</td>
<td>Et</td>
<td>n-C₃H₇</td>
<td>n-C₄H₉</td>
<td>n-C₅H₁₁</td>
<td>i-Pr</td>
<td>c-C₃H₁₁</td>
</tr>
</tbody>
</table>

The most successful method for making tributylstannyl carbamates was reported by Chong and Park. The main precursors are the phthalimides 67 prepared from α-hydroxystannanes which, in turn are prepared from aldehydes and tributyltinlithium (Scheme 36). We applied this method to the preparation of the α-aminoorganostannanes 63. Cleavage of the phthalimide with hydrazine gave primary α-aminostannanes.
Protection of the aminostannanes with dimethylcarbamoyl chloride gave the dimethylurea 68. Treatment of 68 with NaH and MeI gave the required α-aminoorganostannanes 63 in good yields.

Scheme 36

2.2.2 Transmetalation of α-aminoorganostannanes

Transmetalation of 63b with n-Buli at −78 °C led to >95% transmetalation (based on isolated n-Bu₃Sn) in 5 min (Scheme 37). However, attempted trapping of the resulting organolithium with CO₂ gave no product and no identifiable byproducts. If the acid was being formed at all, it might have been too polar due to the presence of many heteroatoms and was lost during aqueous workup. Attempts to trap the organolithium with PhCHO also gave no isolable product.
Assuming that we were facing a polarity problem, we tried to circumvent this by using a bigger R group: cyclohexyl. We were hoping that it would give a less polar product that would be easier to isolate. Unfortunately, transmetalation of 63g and attempted trapping of the organolithium with either CO₂ or PhCHO also gave no product.

Scheme 37

![Scheme 37](image)

Since we did not isolate any product resulting from protonation of the organolithium, this indicated that the organolithiums were not stable and decomposed before reacting with the electrophiles. Lowering the reaction temperature to -95 °C did not give any isolable product as well. If decomposition was indeed occurring, one possible pathway was via α-elimination, i.e. breaking of the nitrogen-carbon bond to give the lithiated species 69 and the carbene 70 (Scheme 38). In order to investigate this possibility, we introduced the alkene 71 in the reaction mixture before transmetalation to trap the putative carbene. Unfortunately, no cyclopropane 72 was observed, and no trimethylurea was isolated. Since carbenes are known to add to alkenes very readily, this suggested that no carbene was being formed." Hence, we could not obtain any experimental evidence for the proposed decomposition pathway.
Attempts were also made to detect the decomposition products by low temperature $^1$H NMR spectroscopy. $n$-BuLi was added to a solution of $\alpha$-aminoorganostannane 63b in THF-d$_8$ at $-78 \, ^{\circ}C$ and a $^1$H NMR experiment was performed immediately. To our disappointment, no useful information was obtained from the spectrum.

We decided to prepare an aldehyde that had a long chain and was also UV active. The intent here was to make an $\alpha$-aminoorganostannane which would give a hydrophobic product which might be easier to detect and isolate. Aldehyde 76 was prepared as outlined in Scheme 39. Coupling of the bromide 73$^b$ and benzylmagnesium chloride in the presence of dilithium tetrachlorocuprate (Li$_2$CuCl$_4$) gave the tetrahydropyranyl (THP) ether 74 in quantitative yield. The THP group was easily removed by pyridinium $p$-toluenesulfonate (PPTS) and gave the alcohol 75. However, oxidation of the alcohol using pyridinium chlorochromate (PCC) gave a very low yield of 76 (44%). Most of the product may have been trapped in the chromium salts during workup. A much better yield of the aldehyde (78%) was achieved using the Swern oxidation.
Scheme 39

The aminoorganostannane 63h was then prepared from the aldehyde 76 in 50% overall yield, using our established protocol (Scheme 40).

Scheme 40

As was the case before, transmetalation of 63h and subsequent treatment of the reaction mixture with benzaldehyde did not give the aminoalcohol 78 (Scheme 41). Thin layer chromatography (TLC) indicated the presence of UV active material that was very polar. Analysis of this crude mixture by GC-MS showed the presence of many products, with 79 and 80 being the major components. These two products were so polar that MeOH had to be used to elute product 79 from the column. If the same type of
byproducts were also produced in the transmetalations of 63b and 63g (Scheme 37), this polarity explains why we could not isolate any of these byproducts. Since they had small R groups (R = Et. c-C₆H₁₁), the byproducts would be even more polar and would also be hard to detect because they are not ultraviolet (UV) active.

The minor product 80 was due to protonation of the organolithium and the major product 79 was due to 1,2 migration of the amide group (Scheme 42). This was very disappointing, since Pearson and Lindbeck had successfully transmetalated the imidazolidinones 58a (Scheme 33) and trapped the resulting organolithiums with different electrophiles. Perhaps the organolithiums are only stable when the urea group is in a ring since it can not undergo the 1,2 migration.

The lithium amide 81 is expected to be more stable than the carbanion 77 (Scheme 42). This is based on the pKₐ of their conjugate acids. Generally, the pKₐ of an
amine (N-H) is around 35. The pKₐ of an alkane (C-H) is between 47-50. However, the congener acid of the carbanion 77 would be more acidic than this because the carbamate will enhance its acidity. Nevertheless, it is still less than that of the amine, and that difference must be enough to make the lithium amide 81 much more stable than the carbanion 77. Based on this argument, the migration that we encountered is justified by formation of the more stable lithium amide 81.

Scheme 42

The only anionic 1,2 migrations that have been reported involve migration of the carbonyl from oxygen to carbon (O-C migrations). For example, when Gawley and Zhang lithiated the benzylic carbamate 82 (Scheme 43), the amide group migrated to the benzylic position giving the alkoxide 84 which gave the alcohol 85 in high yield. They also observed the same migration when they transmetalated the alkoxyorganostannane 86. The resulting organolithium underwent migration to give the alkoxide 88, which gave the hydroxyamide 89 on workup. This migration seems to be sterically controlled because organolithiums from the transmetalation of N,N-diisopropyl stannyl carbamates do not undergo migration. Formation of alkoxides is not surprising at all because of the big difference in pKₐ of alcohols (pKₐ =16) and pKₐ ~41 and <48 for the conjugate acids of the carbanions for 83 and 87 respectively.
There have been no reports on 1,2 migrations where the carbonyl migrates from nitrogen to carbon (N-C migrations), as we observed with trimethylurea organolithiums. A number of transmetalations have been done with acyclic carbamates and no such migration had been observed. For example, organolithiums 90 are chemically stable at -78 °C and can be trapped with different electrophiles (Scheme 44)\(^5\). One would expect a carbamate carbonyl to be more electrophilic than a urea carbonyl, and therefore more prone to migration. As a result, it was not obvious why the trimethylurea organolithiums engaged in 1,2 migrations when their carbamate counterparts are reasonably stable.
To try and explain why this migration was being observed in ureas and not in carbamates, we did semi-empirical molecular orbital calculations (MOPAC) using the MNDO Hamiltonian. It was shown that both carbamates and ureas can exist in two conformations (Scheme 45). In each case the conformation where the lithium atom is chelated to the carbonyl oxygen is the most stable, as indicated by low heat of formation ($\Delta H_f$). This was expected because the carbonyl oxygen chelates to the lithium atom much more strongly than either nitrogen or ether-type oxygen.

The difference in $\Delta H_f$ between 91a and 91b ($\Delta \Delta H_f = 9.1$ kcal/mol) is higher than that between 92a and 92b ($\Delta \Delta H_f = 6.4$ kcal/mol). Due to this big difference in energy between 91a and 91b, the carbanion must exist mainly as 91a. The minor conformations 91b and 92b might be the ones that favor migration. However, we do not have any experimental evidence to support this idea. Since $\Delta \Delta H_f$ is smaller for the ureas, 92b is more readily accessible compared to 91b, and this might be why migration can occur in ureas and not in carbamates.
2.2.3 Summary

Trimethylurea organostannanes 63 were successfully prepared from phthalimides. They transmetalated completely with n-BuLi at -78 °C. Unfortunately, attempts to trap the resulting organolithiums with electrophiles were not successful. The α-aminoorganolithium 77 underwent 1,2 migration to give the more stable lithium amide 81. MNDO calculations are consistent with the rationalization that the minor conformation 92b might be responsible for the 1,2 migration. Therefore, acyclic urea α-aminoorganolithiums proved to be chemically unstable. As a result, their configurational stability could not be studied.
2.3 Experimental

2.3.1 General.

All reactions were carried out with dry glassware under an atmosphere of argon unless otherwise noted. Low temperature baths were prepared as follows: 0 °C (ice-water); -20 °C (ice-NaCl); -40 °C (dry ice-ethylene glycol/water 30:70 v/v); -78 °C (dry ice-acetone); -95 °C (N₂-MeOH). Diethyl ether, tetrahydrofuran and hexane were distilled from sodium/benzophenone ketyl: CH₂Cl₂ and CH₃CN were distilled over CaH₂. Anhydrous ethanol was distilled from magnesium ethoxide and stored over 3Å molecular sieves. Diisopropylamine and triethylamine were distilled from CaH₂ and stored over 3Å molecular sieves. N,N-Dimethylformamide (DMF) was distilled from CaH₂ under reduced pressure and stored over 3Å molecular sieves.

Trimethylurea was prepared according to the method of Snyder and Stock.¹⁵ Tributyltin hydride was prepared according to Szammer and Otvos and was freshly distilled before use.¹⁶ Phthalimides were prepared according to Chong and Park.⁵ Br(CH₂)₈OTHP was previously prepared in our lab from 1.8-octanediol.⁶ Other reagents were purchased (Aldrich): Aldehydes were chromatographed or distilled before use.

Thin layer chromatography was carried out on 0.25 mm silica gel 60 F₂₅₄ aluminum sheets (Merck 5554). Developed plates were visualized under UV light and stained with a 5% solution of phosphomolybdic acid in EtOH. Flash chromatography was performed using Merck 9385 silica gel 60 (230-400 mesh). Melting points were taken on a MEL-TEMP apparatus. Infrared spectra were recorded as neat liquids between NaCl plates or as KBr pellets on an MB-100 Fourier transform infrared spectrophotometer.¹ H
and $^{13}$C NMR spectra were recorded using Bruker AC-200 and AM-250 spectrometers using CDCl$_3$ as solvent unless otherwise noted. Tetramethylsilane ($^1$H, $\delta$ 0.0) and CDCl$_3$ ($^{13}$C, $\delta$ 77.0) were used as internal references. $^1$H NMR data are presented as follows: chemical shift (multiplicity, integration, J in Hz, assignment). For AB quartets, $\Delta \delta$ (in ppm) represents the difference between the chemical shift of signal A and that of signal B ($\delta_A - \delta_B$). For $^{13}$C NMR signals, coupling constants for satellites due to $^{117/119}$Sn (where discernible) are reported in parentheses in Hz; an asterisk (*) indicates signals that could be unequivocally attributed to the major diastereomer or rotamer. For $^{13}$C JMOD acquisitions, the negative signals are shown in brackets. Mass spectra were recorded on VG 7070E (fast atom bombardment), VG Quatro II (electrospray) and HP G1800A (electron ionization) spectrometers. For compounds containing tin, the masses indicated are those of $^{120}$Sn and the intensities are relative to the base peak. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

2.3.2 General procedure for the Preparation of N-tributylstannyldimethylureas 68

Reaction 1:

To a 0.1 M solution of the corresponding phthalimide in EtOH was added hydrazine hydrate (50 equiv) and H$_2$O (a few drops). The mixture was stirred at reflux for the specified time and the solvent was removed in vacuo. The residue was dissolved in Et$_2$O and washed with water. The organic solution was dried (MgSO$_4$), filtered through Celite and concentrated in vacuo to give colorless oils which were used without further purification.
Reaction 2:

To a cooled (0 °C) 0.2 M solution of the crude amine in CH₂Cl₂ was added Et₃N (1.3 equiv) and dimethylcarbamoyl chloride (1.2 equiv). The solution was warmed to room temperature (rt) and stirred for the specified time. The mixture was washed with water, dried (MgSO₄), filtered through Celite and concentrated in vacuo. The resulting oils were purified by flash chromatography (35 g of silica/g of substrate: 2:1 hexane/Et₂O).

2.3.3 *N*-(1-Tributylstannylpropyl)-*N*,*N*'-dimethylurea 68b

![Structural formula]

This dimethylurea was prepared from 67b according to the general procedure described in section 2.3.2 with a reaction time of 4 h for reaction 1, and 2 h for reaction 2. The product was obtained as a colorless oil in 75% yield: IR (neat) 3337, 2954, 2921, 1624, 1528, 1455, 1033 cm⁻¹; ¹H NMR (200 MHz) δ 4.66 (d, 1 H, J = 6.6, NH), 3.20 (q, 1 H, J = 7.1, CHN), 2.91 (s, 6 H, N(CH₃)₂), 1.81-1.60 (m, 2 H, CH₃CH₂CHN), 1.54-1.01 (m, 12 H, SnCH₂(CH₂)₂CH₃), 0.97-0.75 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂CHN);

¹³C NMR (50 MHz) δ 158.7, 43.4, 36.3, 29.3 (²J = 20), 28.1, 27.6 (²J = 55), 13.7, 12.7, 10.1 (¹J = 317, 304); MS, FAB m/z (relative intensity) 363 (M⁺ - C₄H₉, 100), 289 (8), 249 (15), 207 (25), 129 (40). Anal. Calcd for C₁₈H₄₀N₂O₇Sn: C, 51.57; H, 9.62; N, 6.68. Found: C, 51.74; H, 9.59; N, 6.69.
2.3.4  \textit{N}-(1-Cyclohexyl-1-tributylstannylmethyl)-\textit{N},\textit{N}-dimethylurea 68g

\begin{center}
\includegraphics[width=0.2\textwidth]{68g}
\end{center}

This dimethylurea was prepared from 67g according to the general procedure described in section 2.3.2 with a reaction time of 24 h for reaction 1, and 5 h for reaction 2. The product was obtained as a white solid in 65\% yield: mp 75-79 °C; IR (KBr) 3304, 2901, 1617, 1535, 1452, 1360, 1230, 1069 cm\(^{-1}\); \textit{\textit{1}}H NMR (250 MHz) \(\delta\) 4.70 (d, 1 H, \(J = 7.2 \text{ Hz, NH}\)), 3.10 (t, 1 H, \(J = 7.6 \text{ Hz, CHN}\)), 2.87 (s, 6 H, N(CH\(_3\))\(_2\)), 1.67-1.16 (m, 21 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and c-CH\((\text{CH}_2)\_2\text{CH}_2(\text{CH}_2)\_2\)\)), 0.91-0.71 (m, 17 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and c-CH\((\text{CH}_2)\_2\text{CH}_2(\text{CH}_2)\_2\)\)): \textit{\textit{13}}C NMR (63 MHz) \(\delta\) 158.7, 48.8, 42.1, 36.3, 32.5, 31.8, 29.4 (\(^2J = 19\)), 27.7 (\(^2J = 56\)), 26.7, 26.5, 26.3, 13.8, 10.3 (\(^1J = 315, 308\)); MS, FAB \(m/\text{z}\) (relative intensity) 417 (M\(^+\) - C\(_4\)H\(_9\), 28), 377 (10), 305 (12), 235 (26), 185 (100), 119 (30). Anal. Calcd for C\(_{22}\)H\(_{46}\)N\(_2\)OSn: C, 55.83; H, 9.80; N, 5.92. Found: C, 56.02; H, 9.64; N, 5.79.

2.3.5  \textit{General procedure for the preparation of} \textit{N}-tributylstannyl trimethylureas 63

NaH (2 equiv) was washed with hexanes several times. A 0.5 M solution of the appropriate dimethylurea in DMF was added to the NaH. The reaction mixture was stirred for 10 min, cooled to 0 °C and MeI (2 equiv) was slowly added. The reaction was stirred at 0 °C for 5 min, warmed to \(\text{rt}\) and stirred for the specified time. The mixture was quenched carefully with saturated NH\(_4\)Cl, diluted with Et\(_2\)O, washed with H\(_2\)O followed
by saturated NaCl. The organic solution was dried (MgSO₄). filtered through Celite and concentrated in vacuo. The crude products were purified by flash chromatography (40 g silica/g of substrate; 2:1 hexane/Et₂O) to give the stannanes as colorless oils.

2.3.6 \( N-(1\text{-Tributylstannylpropyl})-N.N.N\text{-trimethylurea 63b} \)

![Chemical structure of 63b](image)

This trimethylurea was prepared from 68b according to the general procedure described in section 2.3.5 with a reaction time of 48 h in 70% yield: IR (neat) 2904, 1631, 1497, 1459, 1368, 1120, 1067 cm⁻¹; \(^{1}H\) NMR (200 MHz) \( \delta \) 3.00 (t, 1 H, J = 8.1, CHN), 2.84 (s, 3 H, CH₃N), 2.74 (s, 6 H, N(CH₃)₂), 1.88-1.59 (m, 2 H, CH₃CH₂CHN), 1.55-1.21 (m, 12 H, SnCH₂(CH₂)₂CH₃), 0.99-0.69 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂CHN); \(^{13}C\) NMR (50 MHz) \( \delta \) 165.2, 54.1, 38.9, 38.3, 29.2 (\(^{3}J = 29\)), 27.6 (\(^{3}J = 55\)), 25.3, 13.6, 12.8, 10.1 (\(^{3}J = 309, 297\)); MS, FAB \( m/z \) (relative intensity) 377 (M⁺-C₄H₉, 85), 291 (10), 221 (18), 177 (25), 143 (100). Anal. Calcd for C₁₉H₂₅N₂Sn: C, 52.67; H, 9.77; N, 6.46. Found: C, 52.46; H, 9.69; N, 6.22.
2.3.7 N-(1-Cyclohexyl-1-tributylstannymethyl)-N,N,N-trimethylurea 63g

![Urea Structure]

This trimethylurea was prepared from 68g according to the general procedure described in section 2.3.5 with a reaction time of 72 h in 73% yield: IR (neat) 2908, 1629, 1420, 1367, 1233, 1036 cm⁻¹; ¹H NMR (200 MHz) δ 2.83 (s, 3 H, CH₃N), 2.73 (6 H, N(CH₃)₂), 2.73-2.68 (m, 1 H, CHN), 1.88-1.15 (m, 21 H, c-CH(CH₃)₂CH₂(CH₃)₂ and SnCH₂(CH₃)₂CH₃), 0.92-0.68 (m, 17 H, c-CH(CH₂)₂CH₂(CH₃)₂ and SnCH₂(CH₂)₂CH₃); ¹³C NMR (63 MHz) δ 164.8, 60.1, 39.8, 39.3, 38.8, 32.8, 32.1, 29.3 (³J = 18), 27.6 (³J = 56), 27.0, 26.8, 26.4, 25.9, 13.7, 10.8 (¹J = 308, 294); MS. FAB m/z (relative intensity) 431 (M⁺-C₄H₉, 80), 337 (12), 315 (10), 219 (16), 197 (100), 119 (16). Anal Calcd for C₂₃H₄₈N₂O₆Sn: C, 56.68; H, 9.93; N, 5.75. Found: C, 56.69; H, 9.79; N, 5.71.

2.3.8 (9-Phenyl)nonyl tetrahydropyranyl ether 74

![Ether Structure]

Benzyl magnesium chloride (7.9 mL, 15.9 mmol, 1.2 M in THF) was slowly added to a cooled (-40 °C) solution of Br(CH₂)₈OTHP (3.1 g, 10.6 mmol) and Li₂CuCl₄ (1.1 mL, 0.11 mmol, 0.1 M in THF) in THF (70 mL). The solution was stirred at -40 °C
for 30 min, slowly warmed to rt and stirred overnight. The reaction mixture was quenched with saturated NH₄Cl (100 mL) and extracted with Et₂O (2 x 100 mL). The combined organic solution was washed with 1 N HCl (2 x 80 mL), dried (MgSO₄), filtered through Celite and concentrated in vacuo. The resulting crude oil was purified by flash chromatography (200g silica; 10:1 hexane/Et₂O) to give the product as a colorless oil (3.2 g) in 100% yield: IR (neat) 3025, 2928, 2854, 1602, 1495, 1454, 1353, 1128, 1074, 1031 cm⁻¹;¹H NMR (250 MHz) δ 7.25 (m, 5 H, ArH), 4.57 (dd, 1 H, J = 2.8, 4.0, c-OCH(CH₂)O), 3.91-3.88 (m, 1 H, c-OCH(CH₂)₃CH₂O), 3.78-3.68 (m, 1 H, Ph(CH₂)₈CH₂O), 3.53-3.45 (m, 1 H, c-OCH(CH₂)₃CH₂O), 3.42-3.33 (m, 1 H, Ph(CH₂)₈CH₂O), 2.59 (t, 2 H, J = 7.7, PhCH(CH₂)₈), 1.84-1.47 (m, 10 H, PhCH₂CH₃(CH₂)₅CH₂CH₂O and c-OCH(CH₂)₃CH₂O), 1.40-1.15 (m, 10 H, Ph(CH₂)₂(CH₂)₅(CH₂)₂O),¹³C NMR (63 MHz) δ 142.8, 128.3, 128.1, 125.5, 98.8, 67.6, 62.2, 35.9, 31.4, 30.8, 29.7, 29.4, 29.3, 29.2, 26.2, 25.5, 19.6; MS, EI m/z (relative intensity) 304 (M⁺, 2), 104 (30), 91(79), 85(100). Anal. Calcd for C₃₀H₆₂O₂: C, 78.90; H, 10.59. Found: C, 78.69; H, 10.39.

2.3.9 9-Phenylnonan-1-ol 75

This alcohol was prepared from 74 according to the method of Miyashita et al.⁸ as a yellowish oil in 89% yield: IR (neat) 3334, 2926, 2854, 1602, 1495, 1047 cm⁻¹;¹H NMR (250 MHz) δ 7.24 (m, 5 H, ArH), 3.59 (t, 2 H, J = 6.6, CH₂OH), 2.59 (t, 2 H, J =
7.7, PhCH₂), 1.96 (s, 1 H, OH), 1.63–1.50 (m, 4 H, PhCH₂CH₂(CH₂)₅CH₃), 1.29 (m, 10 H, Ph(CH₂)₂(CH₂)₅); ¹³C NMR (63) δ 142.8, 128.3, 128.1, 125.5, 62.8, 35.9, 32.7, 31.4, 29.4, 29.3, 29.2, 25.7; MS, Ei m/z (relative intensity) 220 (M⁺, 13), 202 (M⁺-H₂O, 5), 104 (94), 91 (100). Anal. Calcd for C₁₅H₂₃O: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.78.

2.3.10 9-Phenylnonanal 76

This aldehyde was prepared by the Swern oxidation¹⁰ of 75 as a white solid in 78% yield: mp 31–35 °C; IR (KBr) 3058, 3026, 2927, 2855, 1720, 1602, 1495, 1044 cm⁻¹; ¹H NMR (250 MHz) δ 9.71 (t, 1 H, J = 1.8, CHO), 7.25 (m, 5 H, ArH), 2.59 (t, 2 H, J = 7.7, PhCH₂), 2.38 (dt, 2 H, J = 7.3, 1.8, CH₂CHO), 1.62–1.56 (m, 4 H, PhCH₂CH₂(CH₂)₄CH₃), 1.30 (m, 8 H, Ph(CH₂)₂(CH₂)₄); ¹³C NMR (63 MHz) δ 202.7, 142.7, 128.3, 128.1, 125.5, 43.7, 35.8, 31.3, 29.2, 29.1, 29.0, 28.9, 21.9; MS, Ei m/z (relative intensity) 218 (M⁺, 5), 104 (55), 91 (100). Anal. Calcd for C₁₅H₂₂O: C, 86.47; H, 10.16. Found: C, 86.62; H, 10.03.

2.3.11 N-[1-Tributylstannyl-(9-phenyl)nonyl]phthalimide 67h
This phthalimide was prepared from 76 according to the method of Chong and Park as a yellow oil in 69% yield: IR (neat) 2906, 1770, 1705, 1379, 1065 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 7.81 (m, 2 H, ArH), 7.76 (m, 2 H, ArH), 7.27 (m, 5 H, PhCH\(_2\)), 3.95 (dd, 1 H, J = 6.7, 9.3, CHN), 2.56 (t, 2 H, J = 7.7, PhCH\(_2\)), 1.93-1.87 (m, 1 H, Ph(CH\(_2\))\(_7\))CH\(_2\)), 1.79-1.60 (m, 1 H, Ph(CH\(_2\))\(_5\))CH\(_2\)), 1.58-1.40 (m, 20 H, PhCH\(_2\)(CH\(_2\))\(_4\)) and SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 1.00-0.54 (m, 19 H, PhCH\(_2\)CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\) and SnCH\(_2\)C(CH\(_2\))\(_2\)CH\(_3\)); \(^{13}\)C NMR (63 MHz) \(\delta\) 160.9, 142.8, 133.6, 132.1, 128.3, 128.1, 125.5, 122.7, 37.5, 35.9, 32.9, 31.4, 29.3, 29.2, 29.1, 28.9, 28.1, 27.3 (\(^2\)J = 57), 13.6, 10.3 (\(^1\)J = 326, 310); MS, FAB m/z (relative intensity) 582 (M\(^+\) - C\(_4\)H\(_9\), 92), 266 (49), 177 (100). Anal. Calcd for C\(_{35}\)H\(_{53}\)NO\(_2\)Sn: C, 65.84; H, 8.37; N, 2.19. Found: C, 66.09; H, 8.22; N, 2.10.

2.3.12 \(N\{1\text{-}\text{Tributylstanny1-(9-phenyl)nonyl}\}-\text{N',N'-dimethylenea 63h}\)

This dimethylurea was prepared from 67h according to the general procedure described in section 2.3.2 with a reaction time of 10 h for reaction 1, and 2 h for reaction 2. The product was obtained as colorless oil in 81% yield: IR (neat) 3335, 2903, 1630, 1526, 1458, 1363, 1220, 1065 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 7.25 (m, 5 H, ArH), 4.63 (d, 1 H, J = 6.5, NH), 3.20 (q, 1 H, J = 7.0, CHN), 2.85 (s, 6 H, N(CH\(_3\))\(_2\)), 2.59 (t, 2 H, J = 7.7, PhCH\(_2\)). 1.68-1.23 (m, 22 H, PhCH\(_2\)(CH\(_2\))\(_2\)(CH\(_2\))\(_2\)(CH\(_2\))\(_3\))CHN and
Sn(CH$_2$)$_2$CH$_3$), 0.97-0.72 (m, 19 H, Ph(CH$_2$)$_3$(CH$_2$)$_2$(CH$_2$)$_3$CHN and SnCH$_2$(CH$_2$)$_2$CH$_3$); $^{13}$C NMR (63 MHz) δ 158.5, 142.6, 128.3, 128.0, 125.3, 41.5, 36.0, 35.8, 35.0, 31.3, 29.1, 29.0, 28.2, 28.0, 27.4 ($^1$J = 55), 13.5, 10.0 ($^1$J = 316, 303); MS, FAB m/z (relative intensity) 523 (M$^+$ - C$_4$H$_9$, 100), 177 (50), 164 (25). Anal. Calcd for C$_{30}$H$_{36}$N$_2$OSn: C, 62.18; H, 9.74; N, 4.83. Found: C, 63.35; H, 9.67; N, 4.82.

2.3.13 N-[1-Tributylstanny]-[9-phenyl]nonyl]-N,N,N'-trimethylurea 63h

This trimethylurea was prepared from 63h according to the general procedure described in section 2.3.5 with a reaction time of 15 h in 91% yield: IR (neat) 2901, 1630, 1495, 1367, 1122, 1055 cm$^{-1}$; $^1$H NMR (250 MHz) δ 7.25 (m, 5 H, ArH), 3.04 (t, 1 H, J = 8.0, CHN), 2.82 (s, 3 H, CH$_3$N), 2.72 (s, 6 H, (CH$_3$)$_2$N), 2.59 (t, 2 H, J = 7.7, PhCH$_2$), 1.63-1.23 (m, 24 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and PhCH$_2$(CH$_2$)$_3$(CH$_2$)$_3$CHN), 0.95-0.78 (m, 17 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and Ph(CH$_2$)$_4$CH$_2$(CH$_2$)$_3$CHN); $^{13}$C NMR (63 MHz) δ *165.9, 164.9, 142.6, 128.2, 127.9, 125.3, 52.1 ($^1$J = 366), 38.7, 38.5, 38.4, *38.3, 35.8, 32.2, 31.3, 29.4, 29.2, 29.1, 28.9, 27.4 ($^1$J = 60), 13.5, 10.1 ($^1$J = 308, 296); MS, FAB m/z (relative intensity) 537 (M$^+$ - C$_4$H$_9$, 100), 303 (80), 179 (96), 164 (49). Anal. Calcd for C$_{31}$H$_{38}$N$_2$OSn: C, 62.74; H, 9.85; N, 4.72. Found: C, 63.00; H, 9.57; N, 4.71.
2.3.14 Attempted preparation of carboxylic acids

To a cooled (-78 °C) 0.15 M solution of the stannane 63 in THF was added n-BuLi (1.5 equiv, 1.6 M in hexanes). The reaction was shown to be complete after 15 min by TLC; no starting material present, only one spot with high retention factor (Rf) due to Bu₄Sn. A stream of CO₂ was bubbled through the reaction flask for 2 min. The reaction mixture was warmed to rt, diluted with Et₂O and extracted with 2 N NH₄OH (several times). The combined base washes were acidified (2 N HCl) and extracted with Et₂O (several times). The combined organic solution was dried (MgSO₄), filtered through Celite and concentrated in vacuo. No acid was isolated for any of the reactions.

2.3.15 Attempted preparation of aminoalcohols

Transmetalation was performed as described in section 2.3.14. Benzaldehyde (1.3 equiv) was added to the resulting solution and the reaction was stirred at -78 °C for another 15 min. The reaction was quenched with saturated NH₄Cl and warmed to rt. The reaction mixture was diluted with Et₂O, washed with water, dried (MgSO₄), filtered through Celite and concentrated in vacuo. No product was isolated from reactions of stannanes 63b and 63g. The crude product from reaction of stannane 63h was purified by flash chromatography (100 g silica/g of substrate; 5:1 hexane/Et₂O up to 100% MeOH) to give Bu₄Sn (95%), and products 79 (45%) and 80 (15%).
2.3.16 *N,N-Dimethyl (2-methylamino)-10-phenyldecanamide* 79

\[
\text{HNMe} \quad \begin{array}{c}
\text{Ph(} \text{CH}_n \text{)}
\end{array} \quad \text{NMe}_2
\]

IR (neat) 3317, 2926, 2853, 1645, 1456, 1259, 1136, 1047 cm\(^{-1}\); \(^1H\) NMR (250 MHz) \(\delta\)
7.26 (m, 5H, ArH), 4.3 (s, 1H, CH\(_3\)NH), 3.59 (t, 1H, \(J = 6.3\), CHN), 3.05 (s, 3H, CONCH\(_3\)(CH\(_3\))), 2.99 (s, 3H, CONCH\(_3\)(CH\(_3\))), 2.58 (t, 2H, \(J = 7.6\), PhCH\(_3\)), 2.39 (s, 3H, CH\(_3\)NH), 1.60 (m, 4H, PhCH\(_2\)CH\(_2\)(CH\(_2\))\(_3\)CH\(_2\)), 1.30 (m, 10H, Ph(CH\(_2\))\(_2\)(CH\(_2\))\(_3\)CH\(_2\)); \(^{13}C\)
NMR (JMOD, 63 MHz) \(\delta\) 173.4, 142.7, (128.2), (128.0), (125.4), (59.3), (36.8), 35.8, (35.6), 32.6, 31.3, 29.5, 29.2, 29.1, 25.5; MS. ES \(m/z\) (relative intensity) 306 (M\(^+\) + 2, 22), 305 (M\(^+\) + 1, 100). Anal. Calcd for C\(_{10}\)H\(_{12}\)N\(_2\)O: C. 74.95; H. 10.59; N. 9.20. Found: C. 74.72; H. 10.32; N. 9.12.

2.3.17 *N-(9-phenylnonanyl)-N,N',N'-trimethylurea* 80

\[
\text{MeN} \quad \begin{array}{c}
\text{Ph(} \text{CH}_n \text{)}
\end{array} \quad \text{NMe}_2
\]

IR (neat) 2925, 2853, 1645, 1494, 1380, 1141, 1045 cm\(^{-1}\); \(^1H\) NMR (250 MHz) \(\delta\)
7.26 (m, 5H, ArH), 3.12 (t, 2H, \(J = 7.5\), CH\(_2\)N), 2.78 (s, 9H, CH\(_3\)NCON(CH\(_3\))\(_2\)), 2.59 (t, 2H, \(J = 7.6\), PhCH\(_2\)), 1.63-1.52 (m, 4H, PhCH\(_2\)CH\(_2\)(CH\(_2\))\(_3\)CH\(_2\)CH\(_2\)), 1.28-1.20 (m, 10H, Ph(CH\(_2\))\(_2\)(CH\(_2\))\(_3\)(CH\(_2\))\(_2\)N); \(^{13}C\) NMR (63 MHz) \(\delta\) 165.6, 142.9, 128.2, 125.5, 50.4, 38.7,
36.4, 35.9, 31.5, 29.5, 29.4, 29.3, 27.5, 26.8; MS, ES m/z (relative intensity) 306 (M^+ + 2, 25), 305 (M^+ + 1, 100).
2.4 References

14. MNDO calculations were performed by Dr. Dmitrienko, University of Waterloo.
Chapter 3

Preparation and Transmetalation of Teoc Protected α-
Aminoorganostannanes

3.1 Introduction

Chong and Park’s t-Boc α-aminoorganostannanes 93 (Scheme 46, R' = Me) transmetalate completely and trapping of the resulting organolithiums with CO₂ give aminoacids in very high yields.¹ The α-aminoorganolithiums 94 are configurationally stable at −95 °C. The major drawback with this system is that the N-methyl group can not be removed; therefore these organolithiums can not be used for the preparation of primary amines. Attempts to use removable N-protecting groups (R' = Bn and allyl) led to incomplete transmetalation for organolithiums with big R groups (R = i-Pr, c-C₆H₁₁).² This was mainly due to steric hindrance imposed by these bigger groups.

Scheme 46

We thought it would be useful to replace the t-Boc group with a smaller group that could allow introduction of any R and R' groups without adversely affecting the yield

69
of the final product. In addition, the resulting organolithiums should be chemically and configurationally stable at temperatures higher than -95 °C. Based on this, we decided to use a smaller carbamate, 2-(trimethylsilyl)ethoxycarbonyl (Teoc). Since Teoc is smaller than the t-Boc group, we expected it to give α-aminoorganostannanes which can transmetalate completely regardless of the size of the second protecting group R' and the substituents R (Scheme 47).

**Scheme 47**

```
\[ \text{R}^1 \text{N} - \text{SnBu}_3 - \text{TMS} \rightarrow \text{R}^1 \text{N} - \text{E} \text{SnBu}_3 \]
```

The effect of Teoc on configurational stability of organolithiums compared to the t-Boc group is not very clear. This is mainly due to the lack of understanding regarding the mechanism of racemization of these organolithiums as discussed in Chapter 1. However, if the chelation shown in Figure 9 plays a major role in configurational stability, there would be a slight difference in the effect of Teoc compared to t-Boc group. The t-butyl group is inductively electron donating, making the carbonyl oxygen more basic, and it can chelate to the Li atom more strongly. The 2-(trimethylsilyl)ethyl group on Teoc is also electron donating by hyperconjugation (stabilization of cations β to silicon by the silicon).³ It has been shown that this group increases the basicity of ethers compared to normal alkyl groups (Scheme 48).⁴
Scheme 48

\[
\text{Me}_3\text{Si} - \text{CH}_2 - \text{CH}_2 - \text{OCH}_3 \xrightarrow{\text{Me}_3\text{Si}^+} \text{CH}_2 = \text{CH}_2 \text{OCH}_3
\]

However, this hyperconjugation has been shown to be less effective than the electron donation by inductive effect given by the \textit{t}-butyl group in other reactions.\textsuperscript{5} Assuming this to be the same in this case, the trimethylsilyl ethyl group would be less electron donating than the \textit{t}-butyl group. Based on this argument, chelation shown in 96 (Figure 9) is expected to be weaker than that shown in 95. In acyclic \(\alpha\)-aminoorganolithiums, strong chelation between the Li atom and the carbonyl is believed to enhance configurational stability. If that is always the case, then 96 would be less configurationally stable than 95.

**Figure 9:** Teoc and \textit{t}-Boc protected \(\alpha\)-aminoorganolithiums

Another advantage of the Teoc group is that it is easily removed using acid or fluoride ion. The byproducts are gases, making the deprotection a very clean reaction.
3.2 Results and Discussion

3.2.1 Protection of amines with the Teoc Group

The Teoc group has not been widely used for the protection of amines. Carpino and Tsao first reported the use of this group in 1978. Earlier reports involving its use in peptide and amino acid chemistry suggested that introduction of this group could be troublesome. Meyers used this group in the total synthesis of maytansinoids. The amine was first converted to the phenyl carbamate 97 (Scheme 49), which was then reacted with trimethylsilylethanol to give the Teoc-protected amine 98. This method was not very attractive to us because it involves two steps.

Scheme 49

The most direct way to introduce the Teoc group involves the use of 2-trimethylsilylethyl derivatives 99, where X is a good leaving group. Carpino and Tsao used an azidoformate (X = N₃). However, this is limited by the toxic nature of azides. Rich and Shute used 2-trimethylsilylethyl chloroformate (X = Cl) which works very well because chloride is a good leaving group. Unfortunately, the use of this reagent is limited by the fact that phosgene, which is very toxic, is required for its preparation.
Rowosky and Wright successfully protected amino acids using 2-trimethylsilylethyl 4-nitrophenyl carbonate which is commercially available, but expensive.\(^7\) We decided to use 2-trimethylsilylethyl phenyl carbonate \(100\) (Table 1) in order to avoid using expensive 4-nitrophenyl chloroformate required to make Rowosky's reagent. The carbonate \(100\) was made from phenyl chloroformate and trimethylsilylethanol in 90% yield.\(^7\)

Since this compound had not been used for putting on the Teoc group, we had to find the best conditions. We decided to protect \(\alpha\)-methylbenzylamine because it is sterically similar to our secondary \(\alpha\)-aminoorganostannanes. Initially we used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a strong nonnucleophilic base.\(^{10}\) unfortunately, very low yields were obtained (Table 1, entry 1). We then decided to use catalytic amounts of \(4-(N,N\text{-dimethylamino})\)pyridine (DMAP) since it is a good acylation catalyst.\(^{11}\) The yield increased and the best results were obtained with \(\text{CH}_2\text{Cl}_2\) as solvent (entry 4). We also tried to use other bases but they did not give us better yields (entries 5 and 6).
Table 1: Protection of α-methylbenzylamine with the Teoc group

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent/Condition</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>THF, reflux (o/n)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>2</td>
<td>DBU/DMAP</td>
<td>THF, rt (o/n)-reflux (4 hrs)</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>DBU/DMAP</td>
<td>CH₂Cl₂, reflux (o/n)</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>DBU/DMAP</td>
<td>CH₂Cl₂, rt (o/n)</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N/DMAP</td>
<td>CH₂Cl₂, reflux (48 hrs)</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr₂NEt/DMAP</td>
<td>CH₂Cl₂, reflux (o/n)</td>
<td>71</td>
</tr>
</tbody>
</table>

As in Chapter 2, we applied Chong and Park's method for preparing the α-aminoorganostannanes.¹ The phthalimides 67 were cleaved with hydrazine to give the primary amines (Scheme 50). Attempts to protect these primary aminoorganostannanes with Teoc using the same conditions used in entry 4 (Table 1) were not successful, only very low yield of the product being isolated. Cleavage of the phthalimide to the amine was shown to be complete by TLC; hence, the protection was the problem. Despite being sterically similar to α-methylbenzylamine, the aminoorganostannanes were proving to be less nucleophilic. Perhaps they were not stable under these conditions and decomposed before they could react with the carbonate. In order to overcome this problem, we
decided to use 2-(trimethylsilylethyl) \( p \)-nitrophenyl carbonate, which has a better leaving group. The carbonate was successfully made from \( p \)-nitrophenyl chloroformate and 2-trimethylsilylethanol.\(^7\) Even with this more reactive carbonate, the product was still obtained in low yields with DBU and catalytic amounts of DMAP in CH\(_2\)Cl\(_2\). We then tried to use the method that was used by Rowosky and Wright.\(^7\) Using 2 M aqueous Na\(_2\)CO\(_3\) as the base in EtOH, stirring the reaction at reflux for a few hours gave the carbamates in good yields (Scheme 50). The carbamates were then protected with either the benzyl or the methyl group, and gave the \( \alpha \)-aminoorganostannanes \( 103 \) and \( 104 \), respectively, in very high yields. The benzyl group was chosen because it is easily removed either by hydrogenolysis or under dissolving metal conditions.

Scheme 50

\[
\begin{align*}
\text{Scheme 50} \\
67 & \quad R = \text{Me, Et, i-Pr} \\
102 & \quad R = \text{SnBu\(_3\)} \\
103 & \quad R' = \text{Bn, } X = \text{Br} \\
104 & \quad R' = \text{Me, } X = \text{I}
\end{align*}
\]
Transmetalation of Teoc protected α-aminoorganostannanes

Transmetalation of the α-aminoorganostannanes with n-BuLi at −78 °C gave >90% transmetalation based on the amount of tetrabutyltin isolated (Table 2). Unfortunately, trapping of the organolithiums with benzaldehyde (entries 1 and 2) gave lower yield of products than expected. Since transmetalation was almost complete and no protonated organolithium was isolated, we speculated that perhaps the organolithiums were not very stable at −78 °C and decomposed before they could be trapped. Lowering the temperature to −95 °C did increase the yield (entry 2). However, as mentioned in section 3.1, we wanted to find a system that would allow us to do these reactions at temperatures higher than −78 °C. This was the highest temperature at which these types of organolithiums were generated at that time.

Perhaps the reaction of benzaldehyde with the organolithiums was too slow to the extent that the organolithiums decomposed before they could react. To overcome this, we decided to use a more reactive electrophile, CO2. Unfortunately, trapping the organolithiums with CO2 increased the yield only for one case (entries 3), and when R = Et, the yield actually dropped (entry 4). Therefore, we could not draw any conclusions regarding the effect of the electrophile. These results were also not systematic with the size of the R group. Organostannanes with small groups (R = Me and Et), are expected to give much better yields than those with bigger groups (R = i-Pr).

To make a direct comparison with the N-methyl t-Boc systems reported by Chong and Park,1 we decided to transmetalate N-methyl Teoc organostannane 104 (R = Me,
entry 6). Trapping the resulting organolithium with CO$_2$ gave 70% yield of the acid, which was much lower than 99% yield they reported.

**Table 2:** Transmetalation of the Teoc protected α-aminoorganostannanes

![Chemical structure image]

<table>
<thead>
<tr>
<th><strong>Entry</strong></th>
<th><strong>R</strong></th>
<th><strong>R$^1$</strong></th>
<th><strong>E$^+$</strong></th>
<th><strong>Product</strong></th>
<th><strong>Yield(%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Bn</td>
<td>PhCHO</td>
<td>105a</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>&quot;</td>
<td>&quot;</td>
<td>105b</td>
<td>69, 81$^a$</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>&quot;</td>
<td>CO$_2$</td>
<td>106a</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>&quot;</td>
<td>&quot;</td>
<td>106b</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>&quot;</td>
<td>&quot;</td>
<td>106f</td>
<td>56, 63$^a$</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>Me</td>
<td>&quot;</td>
<td>107b</td>
<td>70</td>
</tr>
</tbody>
</table>

$^a$ Reaction done at $-95^\circ$C

From a synthetic point of view, these yields are not drastically low. It is just that much better yields had been obtained with t-Boc aminoorganostannanes. These results were suggesting that the Teoc α-aminoorganolithiums might be chemically less stable.
than the t-Boc α-aminoorganolithiums. Since our main goal was to find a system that would give better results than the t-Boc system, we decided not to proceed and investigate their configurational stability.

Generally dipole stabilization is believed to play an important role in the formation of α-heteroatom carbanions.\(^\text{12}\) In order for the organolithiums 108 to be dipole stabilized, the Teoc group should be able to induce a formal positive charge on nitrogen (Figure 10a). However, because of hyperconjugation, the resonance shown in Figure 10b might contribute as well, destabilizing the organolithium. This might be why the Teoc protected α-aminoorganolithiums were found to be chemically less stable compared to their t-Boc counterparts.

**Figure 10:** Resonance structures for Teoc protected α-aminoorganolithiums

\[
\text{R'NO}_2\text{CO}_2\text{TMS} \quad \text{RNO}_2\text{CO}_2\text{TMS}
\]

(a)

\[
\text{RNO}_2\text{CO}_2\text{TMS} \quad \text{RNO}_2\text{CO}_2\text{TMS}
\]

(b)

The 1,2 migration that we encountered with trimethylurea organostannanes in Chapter 2 could be another pathway by which these organolithiums decompose. As discussed in Chapter 2, the conformation 109 (Scheme 51) is believed to be the one
 responsible for migration. For the Teoc organolithiums, this conformation might be possible, but for the t-Boc organolithiums, this conformation would be less likely to form due to steric hindrance. However, we have no experimental evidence for 1,2 migration because we did not isolate any products to verify this. Nevertheless, this does not imply that they were not formed since we did not put extra effort to isolate them as we did with trimethylurea systems.

Scheme 51

3.2.3 Summary

Teoc protected \( \alpha \)-aminoorganostannanes were prepared using 2-(trimethylsilyl) ethyl \( p \)-nitrophenyl carbonate as the protecting reagent. These organostannanes underwent almost complete transmetalation with \( n \)-BuLi at \(-78^\circ\) C. Unfortunately, trapping with either benzaldehyde or CO\(_2\) gave low yield of products. Thus, Teoc protected \( \alpha \)-aminoorganolithiums were found to be chemically less stable than the t-Boc \( \alpha \)-aminoorganolithiums. As a result, studies on their configurational stability were not pursued.
3.3 Experimental

3.3.1 General

All the procedures outlined in section 2.3.1 also apply here with the following addition: 2-trimethylsilylethyl 4-nitrophenyl carbonate and 2-trimethylsilylethyl phenyl carbonate were prepared according to the method of Rowosky and Wright.\(^7\)

3.3.2 2-(Trimethylsilyl)ethyl N-(1-phenylethyl)carbamate 101

![Chemical Structure](attachment:structure.png)

To a solution of \(\alpha\)-methylbenzylamine (213 \(\mu\)L, 1.6 mmol) in \(\text{CH}_2\text{Cl}_2\) (6 mL) was added DBU (321 \(\mu\)L, 1.3 mmol) and DMAP (18.5 mg, 0.16 mmol). 2-(Trimethylsilyl)ethyl phenyl carbonate (473 mg, 2.0 mmol) was added slowly and the reaction was stirred at rt for 15 h. The reaction mixture was diluted with \(\text{Et}_2\text{O}\) (30 mL), washed with \(\text{H}_2\text{O}\) and 1 N HCl (20 mL). The organic solution was dried (MgSO\(_4\)), filtered through Celite and concentrated \(\text{in vacuo}\). The crude product was purified by flash chromatography (20 g silica; 10 : 1 hexane/\(\text{Et}_2\text{O}\)) and gave the product as a colorless oil (354 mg) in 81% yield: IR(neat) 3234, 3031, 2946, 1701, 1518, 1242, 1055 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 7.33-7.21 (m, 5 H, ArH), 5.09 (broad, 1 H, NH), 4.82 (m, 1 H, \(\text{CH}_3\text{CHN}\)), 4.11 (m, 2 H, O\(\text{CH}_2\text{CH}_2\text{TMS}\)), 1.43 (d, 3 H, \(J = 6.9, \text{CH}_3\text{CHN}\)), 0.93 (m, 2 H, O\(\text{CH}_2\text{CH}_2\text{TMS}\)), 0.0 (s, 9 H, Si(CH\(_3\))\(_3\)); \(^13\)C NMR (63 MHz) \(\delta\) 155.9, 143.7, 128.3, 127.0, 125.8, 62.7, 50.3, 22.3, 17.6, -1.7 (\(J_{\text{Si-C}} = 51 \text{ Hz}\)); MS, EI \(m/z\) (relative intensity) 250 (M\(^+\))
- Me, 1), 222 (17), 192 (4), 178 (16), 118 (29), 105 (41), 73 (100). Anal. Calcd for 
C_{14}H_{23}NO_{2}Si: C, 63.35; H, 8.73; N, 5.27. Found: C, 63.16; H, 8.54; N, 5.27.

3.3.3 General procedure for the preparation of 2-(trimethylsilyl)ethyl N-
(tributylstanny1) carbamates

Reaction 1

The primary aminostannanes were prepared from the appropriate phthalimide 67
as described in section 2.3.2.

Reaction 2:

To a solution of the crude stannylamine (1 equiv) in 2 M Na_{2}CO_{3} (10 equiv) at 55
°C was added a 1 M solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (2 equiv)
in warm EtOH. The temperature was raised to 75 °C and more ethanol was added (to
make a 0.1 M solution of stanny1amine in EtOH) over a period of 15 min. The mixture
was stirred at reflux for the specified time. EtOH was removed in vacuo and the residue
was diluted with Et_{2}O. The ethereal layer was washed with water until all the yellow
color due to 4-nitrophenol had been removed. The organic solution was dried (MgSO_{4}),
filtered through Celite and concentrated in vacuo. The crude oil was purified by flash
chromatography (30 g of silica/g of substrate; 8 : 1 Hexane/Et_{2}O) to give the carbamates
as colorless oils.
3.3.4 2-(Trimethylsilyl)ethyl N-(1-tributylstannylethyl)carbamate 102a

![Chemical structure]

This carbamate was prepared from 67a according to the general procedure described in section 3.3.3 with a reaction time of 3.5 h for reaction 1 and 5 h for reaction 2, in 84% yield: IR (neat) 3329, 2954, 2922, 1697, 1511, 1249, 1045 cm⁻¹; ¹H NMR (250 MHz) δ 4.72 (d, 1 H, J = 7.3, NH), 4.12 (t, 2 H, J = 8.5, OCH₂CH₂TMS), 3.25 (m, 1 H, CHN), 1.55-1.25 (m, 15 H, SnCH₂(CH₃)₂CH₃ and CH₃CHN), 0.97-0.84 (m, 17 H, OCH₂CH₂TMS and SnCH₂(CH₂)₂CH₃), 0.12 (s, 9 H, Si(CH₃)₃); ¹³C NMR (63 MHz) δ 158.3, 64.2, 36.8, 30.6 (²J = 19), 29.0 (³J = 55), 22.2, 19.3, 15.2, 10.9, 0.0; MS, FAB m/z (relative intensity) 421 (M⁺ - C₄H₉, 52), 394 (100), 322 (25), 176 (54). Anal. Calcd for C₂₀H₄₈NO₂SiSn: C, 50.22; H, 9.48; N, 2.93. Found: C, 49.94; H, 9.33; N, 2.94.

3.3.5 2-(Trimethylsilyl)ethyl N-(1-tributylstannylpropyl)carbamate 102b

![Chemical structure]

This carbamate was prepared from 67b according to the general procedure described in section 3.3.3, with a reaction time of 5.5 h for reaction 1 and 5 h for reaction 2,
2, in 75% yield: IR (neat) 3331, 2955, 2924, 1700, 1506, 1462, 1249, 1036 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 4.75 (d, 1 H, \(J = 7.2\), HN), 4.09 (t, 2 H, \(J = 8.4\), O\(\text{CH}_2\)\(\text{CH}_2\)TMS), 3.13 (q, 1 H, \(J = 7.5\), CHN). 1.72-1.51 (m, 2 H, \(\text{CH}_3\)\(\text{CH}_2\)CHN), 1.49-1.20 (m, 12 H, Sn\(\text{CH}_2(\text{CH}_2)_2\)\(\text{CH}_3\)), 0.97-0.78 (m, 20 H, Sn\(\text{CH}_2(\text{CH}_2)_2\)\(\text{CH}_3\)), O\(\text{CH}_2\)\(\text{CH}_2\)TMS and CH\(_3\)\(\text{CH}_2\)CHN), 0.0 (s, 9 H, Si(\(\text{CH}_3\)_3)); \(^{13}\)C NMR (63 MHz) \(\delta\) 159.6, 62.9, 43.0, 29.2 (\(^3\)J = 19), 27.8, 27.5 (\(^3\)J = 52), 17.7, 13.6, 12.6, 9.7 (\(^1\)J = 311 Hz), -1.5; MS, FAB m/z (relative intensity) 435 (M\(^+\) - C\(_4\)H\(_9\), 62), 408 (100), 336 (30), 176 (41). Anal. Calcd for C\(_{21}\)H\(_{47}\)NO\(_2\)SiSn: C, 51.22; H, 9.62; N, 3.84. Found: C, 51.42; H, 9.59; N, 2.78.

3.3.6 2-(Trimethylsilyl)ethyl N-(2-methyl-1-tributylstannylpropyl)carbamate 102f

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{i-Pr} & \quad \text{SnBu}_3 \quad \text{SiMe}_3 \\
\end{align*}
\]

This carbamate was prepared from 67f according to the general procedure described in section 3.3.3, with a reaction time of 24 h for reaction 1 and 7 h for reaction 2, in 65% yield: IR (neat) 3335, 2955, 2926, 2100, 1506, 1462, 1249, 1036 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 4.76 (d, 1 H, \(J = 8.3\), HN), 4.09 (t, 2 H, \(J = 8.4\), O\(\text{CH}_2\)\(\text{CH}_2\)TMS), 3.08 (dd, 1 H, \(J = 7.3\), 8.3, CHN), 1.95 (m, 1 H, (\(\text{CH}_3\)_2\(\text{CH}\)), 1.52-1.20 (m, 12 H, Sn\(\text{CH}_2(\text{CH}_2)_2\)\(\text{CH}_3\)), 0.89-0.74 (m, 23 H, Sn\(\text{CH}_2(\text{CH}_2)_2\)\(\text{CH}_3\), (\(\text{CH}_3\)_2\(\text{CH}\) and O\(\text{CH}_2\)\(\text{CH}_2\)TMS), -0.03 (s, 9 H, Si(\(\text{CH}_3\)_3)); \(^{13}\)C NMR (63 MHz) \(\delta\) 158.5, 64.2, 50.9, 34.1, 30.7 (\(^3\)J = 19), 29.0 (\(^3\)J = 57), 23.1, 22.7, 19.3, 15.1, 11.8 (\(^1\)J = 315, 302), 0.0; MS, FAB
$m/z$ (relative intensity) 449 ($M^+ - C_4H_9$, 51), 422 (100), 350 (33), 177 (74). Anal. Calcd for $C_{22}H_{49}NO_2SiSn$: 52.18; H, 9.75; N, 2.76. Found: C, 51.92; H, 9.50; N, 2.92.

3.3.7 2-(Trimethylsilyl)ethyl N-benzyl-N-(1-tributylstannylethyl)carbamate 103a

![Diagram of the compound](image)

This compound was prepared according to the general procedure described in section 2.3.5 from 102a and BnBr with a reaction time of 7 h in 85% yield: IR (neat) 3029, 2954, 2921, 1681, 1462, 1316, 1249 cm$^{-1}$; $^1$H NMR (200 MHz, $C_6D_6$) $\delta$ 7.78 (m, 5 H, ArH), 4.81 (d, 1 H, $J = 15.3$, PhCH$_2$), 4.34-4.20 (m, 2 H, OCH$_2$CH$_2$TMS), 4.17 (d, 1 H, $J = 15.3$, PhCH$_2$), 2.85 (q, 1 H, $J = 7.3$, CHN), 1.78-1.43 (m, 15 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and CH$_3$CHN), 1.19-0.92 (m, 17 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and OCH$_2$CH$_2$TMS), -0.07 (s, 9 H, Si(CH$_3$)$_3$); $^{13}$C NMR (50 MHz, $C_6D_6$) $\delta$ 157.0, 138.9, 128.7, 128.5, *128.3, 127.6, 63.8, 51.6, 43.5, 29.7 ($^2$J = 19), 28.1 ($^3$J = 57), 18.2, 17.7, 14.0, 11.2 ($^1$J = 314), -1.6; MS, FAB $m/z$ (relative intensity) 511 ($M^+ - C_4H_9$, 30), 487 (100), 417 (32), 206 (78). Anal. Calcd for $C_{27}H_{51}NO_2SiSn$: C, 57.04; H, 9.04; N, 2.46. Found: C, 56.89; H, 8.96; N, 2.28.
3.3.8 2-(Trimethylsilyl)ethyl N-benzyl-N-(1-tributylstannylpropyl)carbamate 103b

This compound was prepared according to the general procedure described in section 2.3.5 from 102b and BnBr with a reaction time of 3.5 h in 80% yield: IR (neat) 2955, 2922, 1681, 1429, 1240 cm⁻¹; ¹H NMR (200 MHz, C₆D₆) δ 7.33-7.13 (m, 5 H, ArH), 4.89 (d, 1 H, J = 15.1, PhCH₂), 4.34-4.23 (m, 2 H, OCH₂CH₂TMS), 4.10 (d, 1 H, J = 15.1, PhCH₃), 2.78 (t, 1 H, J = 7.6, CHN), 2.02-1.95 (m, 2 H, CH₃CH₂CHN), 1.69-1.41 (m, 12 H, SnCH₂(CH₂)₂CH₃), 1.06-0.91 (m, 20 H, SnCH₂(CH₂)₂CH₃, OCH₂CH₂TMS and CH₃CH₂CHN), -0.05 (s, 9 H, Si(CH₃)₃); ¹³C NMR (50 MHz, C₆D₆) δ 156.5, 138.4, 128.0, 127.8, *127.7, 127.2, 63.3, 52.5, 51.1, 29.2 (²J = 18), 27.6 (³J = 58), 25.2, 17.7, 13.5, 12.6 (²J = 20), 11.0 (¹J = 325, 311), -1.5: MS, FAB m/z (relative intensity) 525 (M⁺ - C₄H₈, 30), 502 (100), 427 (34), 220 (42). Anal. Calcd for C₂₉H₅₃NO₂SiSn: C, 57.73; H, 10.03; N, 2.40. Found: C, 58.00; H, 9.85; N, 2.52.

3.3.9 2-(Trimethylsilyl)ethyl N-benzyl-N-(2-methyl-1-tributylstannylpropyl)carbamate 103f
This compound was prepared according to the general procedure described in section 2.3.5 from 102f and BnBr with a reaction time of 15 h in 81% yield: IR (neat) 3029, 2919, 1681, 1461, 1284, 1099 cm⁻¹; ¹H NMR (200 MHz, C₆D₆) δ 7.50-7.14 (m, 5 H, ArH), 5.10 (d, 1 H, J = 14.7, PhCH₂), 4.33 (m, 2 H, OCH₂CH₂TMS), 4.02 (d, 1 H, J = 14.7, PhCH₂), 2.65 (d, 1 H, J = 3.1, CHN), 1.80-1.34 (m, 13 H, (CH₃)₂CH and SnCH₂(CH₂)₂CH₃), 1.19-0.92 (m, 23 H, (CH₃)₂CH, SnCH₂(CH₂)₂CH₃, and OCH₂CH₂TMS), 0.0 (s, 9 H, Si(CH₃)₃); ¹³C NMR (50 MHz, C₆D₆) δ 157.1, *139.0, 138.7, *130.0, 129.3, 128.9, 128.0, 63.9, 58.0, *57.2, *55.9, 54.6, 31.5, 29.9 (¹J = 18), 28.3 (¹J = 60), 22.1, 22.0, 18.5, 14.2, 12.1 (¹J = 322, 308), 10.9, -1.9; MS, FAB m/z (relative intensity) 539 (M⁺ - C₄H₃, 54), 512 (100), 437 (38), 234 (52), 177(35). Anal. Calcd for C₉H₈NO₂SiSn: C, 58.49; H, 9.14; N, 2.35. Found: C, 58.30; H, 9.34; N, 2.40.

3.3.10 2-(Trimethylsilyl)ethyl N-methyl-N-(1-tributylstannylpropyl)carbamate 104b

This compound was prepared from 102b according to the general procedure described in section 2.3.5 with a reaction time of 3 h in 90% yield: IR (neat) 2924, 1685, 1461, 1185, 1054 cm⁻¹; ¹H NMR (200 MHz, C₆D₆) δ 4.34-4.24 (m, 2 H, OCH₂CH₂TMS), 2.98-2.83 (m, 4 H, CH₃N and CHN), 2.00-1.42 (m, 14 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂), 1.20-0.95 (m, 20 H, SnCH₂(CH₂)₂CH₃, CH₃CH₂ and OCH₂CH₂TMS), 0.0 (s, 9
H. Si(CH$_3$)$_3$); $^{13}$C NMR (50 MHz, C$_6$D$_6$) δ 157.1, 63.4, 54.3, 36.4, 29.8 ($^2$J = 18), 28.1 ($^3$J = 56), *27.9, 25.7, 14.0, 13.0, 11.3 ($^1$J = 321, 307), 10.0, -1.5; MS, FAB m/z (relative intensity) 449 (M$^+$ - C$_4$H$_9$, 100), 350 (48), 188 (84). Anal. Calcd for C$_{22}$H$_{49}$NO$_2$SiSn: C, 52.18; H, 9.75; N, 2.76. Found: C, 52.40; H, 9.54; N, 2.88.

3.3.11 General procedure for the preparation of N-benzyl Teoc protected amino alcohols

The β-aminoalcohols were prepared as described in section 2.3.15. The crude alcohols were purified by flash chromatography (30 g of silica/g of substrate; 10:1 hexane/Et$_2$O).

3.3.12 N-Benzyl-N-[2-(trimethylsilyl)ethoxycarbonyl]-2-amino-1-phenyl-1-propanol

105a

This aminoalcohol was prepared from 103a according to the general procedure described in section 3.3.11, as a mixture of diastereomers in 66% yield: mp 60-64 °C; IR (KBr) 3463, 2947, 1666, 1431, 1250, 1088 cm$^{-1}$; $^1$H NMR (250 MHz), δ 7.35-7.12 (m, 10H, ArH), 4.93 (m, 1H, CH(OH)Ph), 4.60 (d, 1 H, J = 16.1, PhCH$_2$), 4.29-4.18 (m, 3 H, PhCH$_2$ and OCH$_2$CH$_2$TMS), 3.48 (m, 1 H, CHN), 1.16 (d, 3 H, J = 7.0, CH$_3$CHN), 1.06 (m, 2 H, OCH$_2$CH$_2$TMS), 0.05 (s, 9 H, Si(CH$_3$)$_3$); $^{13}$C NMR (50 MHz, C$_6$D$_6$) δ 157.8, 144.0, 139.0, 129.0, 128.9, 128.7, 128.5, 127.5, *127.1, 126.7, 77.1, 64.2, 62.8, 52.3,
18.2, 11.0, -1.38 (J_{Si-C} = 51 Hz); MS, ES m/z (relative intensity) 387 (M⁺ + 2, 29), 386 (M⁺ + 1, 100). Anal. Calcd for C_{22}H_{31}NO_{3}Si: C, 68.53; H, 8.10; N, 3.63. Found: C, 68.68; H, 8.02; N, 3.56.

3.3.13 *N*-Benzyl-*N*-[2-(trimethylsilyl)ethoxycarbonyl]-2-amino-1-phenyl-1-butanol 105b

![Chemical Structure](image)

This aminoalcohol was prepared from 103b according to the general procedure described in section 3.3.11 at -95 °C, as a mixture of diastereomers in 81% yield: IR (neat) 3398, 2952, 1680, 1446, 1248 cm⁻¹: ¹H NMR (250 MHz), δ 7.38-7.09 (m, 10 H, ArH), 5.40 (m, 0.3 H, CH(OH)Ph), 5.22 (m, 0.7 H, CH(OH)Ph), 4.83 (d, 1 H, J = 15.3, PhCH₂), 4.34 (m, 2 H, OCH₂CH₂TMS), 4.03 (d, 1 H, J = 15.3, PhCH₂), 3.45-3.40 (m, 1 H, CHN), 2.47-2.45 (m, 1 H, CH₃CH₂), 1.79-1.70 (m, 1 H, CH₃CH₂), 1.02 (m, 2 H, OCH₂CH₂TMS), 0.74 (t, 3 H, J = 7.5, CH₃CH₂), 0.0 (s, 9 H, Si(CH₃)₃); ¹³C NMR (50 MHz, C₆D₆) δ 158.0, 143.9, 138.4, 128.9, 128.6, 128.3, 127.8, 127.4, *127.2, 126.2, 77.3, *74.4, 69.6, 64.2, 54.0, 23.0, *18.0, 17.8, 11.5, *-1.5, -1.6; MS, ES m/z (relative intensity) 401 (M⁺ + 2, 20), 400 (M⁺ + 1, 100). Anal. Calcd for C_{33}H_{33}NO_{3}Si: C, 69.13; H, 8.32; N, 3.50. Found: C, 68.96; H, 8.37; N, 3.66.
3.3.14 General procedure for the Preparation of N-alkyl Teoc protected amino acids

The amino acids were prepared as described in section 2.3.14. The products were obtained as colorless thick oils. Samples for analysis were purified by pipette column (1:1 hexane/Et₂O and 1% AcOH).

3.3.15 N-Benzyl-N-[2-(trimethylsilyl)ethoxycarbonyl]-2-aminopropanoic acid 106a

This compound was prepared from 103a according to the general procedure described in section 3.3.14 in 86% yield: IR (neat) 3023, 2950, 2896, 1701, 1442, 1245, 1012 cm⁻¹; ¹H NMR (250 MHz) δ 10.61 (broad singlet, 1 H, CO₂H), 7.32-7.27 (m, 5 H, ArH), 4.64 (d, 1 H, J = 16.3, PhCH₃), 4.40-4.36 (m, 2 H, PhCH₂ and CHN), 4.20 (t, 2 H, J = 8.7, OCH₂CH₂TMS). 1.32 (d, 3 H, J = 7.1, CH₃CHN), 1.00 (m, 2 H, OCH₂CH₂TMS), -0.01 (s, 9 H, Si(CH₃)₃); ¹³C NMR (63 MHz) δ 177.0, 156.7, 138.0, 128.3, *127.9, 127.5, 127.0, 64.3, 54.8, *50.4, 49.8, 17.5, *15.6, 15.0, -1.7 (J_Si-C = 52 Hz); MS, ES m/z (relative intensity) 325 (M⁺ + 2, 28), 324 (M⁺ + 1, 100). Anal. Calcd for C₁₆H₂₅NO₄Si: C, 59.41; H, 7.79; N, 4.33. Found: C, 59.20; H, 7.64; N, 4.28.
3.3.16 *N*-Benzy1-*N*-[2-(trimethylsilyl)ethoxycarbonyl]-2-aminobutanoic acid 106b

This compound was prepared from 103b according to the general procedure described in section 3.3.14 at -95 °C in 62% yield: IR(neat) 3069, 2956, 1700, 1441, 1252, 1054 cm⁻¹; ¹H NMR (250 MHz) δ 9.70 (broad singlet, 1 H, CO₂H), 7.28-7.24 (m, 5 H, ArH), 4.61 (m, 1 H, CH₃), 4.31 (ABq, 2 H, <δ = 0.23, J = 15.8, PhCH₂), 4.23 (m, 2 H, OCH₂CH₂TMS), 2.02-1.91 (m, 1 H, CH₂CH₂CH₂CH₃), 1.79-1.76 (m, 1 H, CH₂CH₂CH₃), 1.00 (m, 2 H, OCH₂CH₂TMS), 0.78 (distorted triplet, 3 H, J = 6.3, CH₃CH₃), 0.02 (s, 9 H, Si(CH₃)₃); ¹³C NMR (63 MHz) δ *177.2, 176.6, 157.3, 137.7, 128.3, *128.0, 127.7, 127.3, 64.5, 50.8, *23.3, 22.6, 17.7, 11.1, -1.6 (Jₛ,ₗ = 51 Hz); MS, ES m/z (relative intensity) 339 (M⁺ + 2, 22), 338 (M⁺ + 1, 100), 310 (M⁺ - 28, 44). Anal. Calcd for C₁₇H₂₇NO₄Si: C, 60.50; H, 8.06; N, 4.15. Found: C, 60.39; H, 7.87; N, 4.02.

3.3.17 *N*-Benzy1-*N*-[2-(trimethylsilyl)ethoxycarbonyl]-2-amino-3-methylbutanoic acid 106f
This compound was prepared from 103f according to the general procedure described in section 3.3.14 at \(-95^\circ\text{C}\) in 63% yield: IR (neat) 3047, 2961, 1697, 1444, 1258 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 10.35 (broad singlet, CO\(_2\)H), 7.23 (m, 5 H, ArH), 4.51 (m, 2 H, PhCH\(_2\) and CHN), 4.22 (m, 2 H, OCH\(_2\)CH\(_2\)TMS), 4.01 (d, 1 H, \(J = 10.2\), PhCH\(_2\)), 2.34 (m, 1 H, (CH\(_3\))\(_2\)CH), 1.19-1.16 (m, 2 H, OCH\(_2\)CH\(_2\)TMS), 0.95 (d, 3 H, \(J = 6.0\), (CH\(_3\))\(_2\)CH), 0.76 (d, 3 H, \(J = 6.0\), (CH\(_3\))\(_2\)CH), 0.01 (s, 9 H, Si(CH\(_3\))\(_3\)); \(^{13}\)C NMR (63 MHz) \(\delta\) 157.5, 137.4, 128.1, 127.6, 127.1, 66.1, 64.6, 50.5, 27.6, 20.0, 19.0, 17.9, 17.6, -1.7 (J\(_{\text{Si,C}} = 49\) Hz); MS, ES \(m/z\) (relative intensity) 353 (M\(^+\) + 2, 15), 338 (M\(^+\) + 1, 100), 324 (M\(^+\) - 28, 53). Anal. Calcd for C\(_{18}\)H\(_{36}\)NO\(_4\)Si: C, 61.50; H, 8.35; N, 3.98. Found: C, 61.65; H, 8.19; N, 3.91.

3.3.18 N-Methyl-N-[2-(trimethylsilyl)ethoxycarbonyl]-2-aminopropanoic acid 107b

![Chemical Structure](image)

This compound was prepared from 104b according to the general procedure described in section 3.3.14 in 70% yield: IR (neat) 3033, 2960, 1696, 1402, 1250, 1164, 1053 cm\(^{-1}\); \(^1\)H NMR (250 MHz), \(\delta\) 10.72 (broad singlet, CO\(_2\)H), 4.73 (dd, 0.6 H, \(J = 4.8, 10.6, \text{CHN}\)), 4.55(dd, 0.4 H, \(J = 4.8, 10.6, \text{CHN}\)), 4.22 (t, 2 H, \(J = 8.3, \text{OCH}_2\text{CH}_2\text{TMS}\)), 2.87 (s, 1 H, CH\(_3\)N), 2.85 (s, 2H, CH\(_3\)N), 2.10-1.99 (m, 1 H, CH\(_3\)CH\(_2\)CHN), 1.80-1.67 (m, 1 H, CH\(_3\)CH\(_2\)CHN), 1.07-0.92 (m, 5 H, CH\(_3\)CH\(_2\)CHN and OCH\(_2\)CH\(_2\)TMS), 0.05 (s, 9
H, Si(CH₃)₃; ¹³C NMR (63 MHz) δ 176.7, 157.7, 64.2, 59.7, 30.1, *22.2, 21.7, 17.6, 10.7, -1.6; MS, ES m/z (relative intensity) 263 (M⁺ + 2, 15), 262 (M⁺ + 1, 100), 233 (M⁺ - 28, 45). Anal. Calcd for C₁₁H₂₃NO₃Si: C, 50.54; H, 8.87; N, 5.36. Found: C, 50.36; H, 8.64; N, 5.19.
3.4 References


Chapter 4

Preparation and Transmetalation of $N$-t-Butylthiomethyl Boc Protected
$\alpha$-Aminoorganostannanes

4.1 Introduction

In an attempt to find N-protecting groups that could be easily removed and also be able to stabilize the resulting organolithiums, Park prepared the methoxymethyl (MOM) Boc protected $\alpha$-aminoorganostannane 111. Theoretically, the two protecting groups should be easily removed by acid. Transmetalation of 111 with $n$-BuLi and trapping of the resulting organolithium with benzaldehyde gave the $\beta$-aminoalcohol 112 in 95% yield as a 1:1 mixture of diastereomers. However, the two diastereomers had 83% ee, indicating that transmetalation and trapping had occurred with loss of optical purity.

Scheme 52

Generally it is believed that carbarnate protected $\alpha$-aminoorganolithiums are stabilized by chelation between the carbonyl oxygen and the Li atom (Scheme 53). Since
racemization was not observed at \(-95\, ^\circ\text{C}\) with $N$-Methyl Boc protected $\alpha$-aminoorganolithiums. The MOM group must have been causing this racemization. Park suggested that the methoxy group might have been competing with the Boc carbonyl for chelation to the Li atom. The resulting chelation complex \textbf{114} is expected to be weaker than \textbf{113}, so the Li is not held as tightly and pyramidal inversion can take place.

\textbf{Scheme 53}

Park also speculated that racemization might be occurring by an inverse $S_N2$-type process. While the Li ion is chelated to the carbonyl oxygen, a second Li atom can also chelate to the methoxy oxygen. This Li atom would then attack the original Li-C bond from the backside causing inversion as shown in Scheme 54.

\textbf{Scheme 54}
In an attempt to develop systems which would not racemize as quickly, we decided to replace the N-methoxymethyl group with N-\(t\)-butylthiomethyl group i.e. replacing oxygen with sulfur (Scheme 55). We made this choice based on the hard-soft-acid-base (HSAB) concept.\(^2\) A hard/hard or soft/soft donor/acceptor pair makes a much stronger coordination complex than a hard/soft or soft/hard pair. Lithium and oxygen are both hard atoms and that is why they chelate strongly. Sulfur, being a soft atom, is not expected to make a strong complex with Li like oxygen. Therefore, it is not as likely to compete with the carbonyl oxygen and this would eliminate the racemization that Park encountered with the MOM protecting group. The \(N-\textit{t}\)-butylthiomiethyl group is also expected to be easily removed under acidic conditions.

![Scheme 55](image)

### 4.2 Results and Discussion

#### 4.2.1 Preparation of \(\alpha\)-aminoorganostannanes

Park reported that iminodicarbonates 115 can be prepared by the Mitsunobu reaction of methyl \(\textit{t}\)-butyl iminodicarbonate and hydroxystannanes (Scheme 56).\(^1\)
Unfortunately, when we attempted this reaction it gave very low yields especially for branched R groups (R = i-Pr and c-C₆H₁₁), presumably due to steric hindrance.

Scheme 56

![Scheme 56 diagram]

We then decided to go back to the old route using phthalimides. We had to introduce the two groups, t-butoxycarbonyl and methoxycarbonyl separately to make the iminodicarbonate 115. Normally diacylation of amino groups is difficult to accomplish. Ragnarsson and Grehn had reported that they were able to introduce a second Boc group to Boc-Gly-OBn using Boc₂O/DMAP in acetonitrile and obtained the N,N-diacyl compound in very high yields (Scheme 57).

Scheme 57

![Scheme 57 diagram]

The carbamates 116 were prepared by cleavage of the phthalimides 67 and protection of the resulting primary amines with methyl chloroformate (Scheme 58). Treatment of the carbamates with Boc₂O and catalytic amounts of DMAP gave the
iminodicarbonates 115. Although this method is longer than the previous one, the iminodicarbonates were obtained in good overall yields even with branched R groups (Table 3). For small R groups, both methods give almost the same results.

Reduction of the iminodicarbonates with LiAlH₄ gave aminoalcohols 117. Elimination of the methoxycarbonyl group also occurred but it was not significant, as can be seen by the good yields. By analogy of the protocol developed by Park for the preparation of MOM protected stannanes, treatment of the alcohol with mesyl chloride followed by 1-BuSH gave the α-aminoorganostannanes 118. These were obtained in 29-40% overall yield from the aldehydes.

**Scheme 58**
Table 3: Overall yield of the iminodicarbonates 115 from aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield of 115a</th>
<th>Yield of 115b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>n-C5H11</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>c-C6H11</td>
<td>21</td>
<td>-</td>
</tr>
</tbody>
</table>

a Iminodicarbonate prepared by the method in Scheme 55
b Iminodicarbonate Prepared by the method in Scheme 57

4.2.2 Transmetalation of α-aminoorganostannanes

Treatment of organostannanes 118 with n-BuLi at -78 °C led to >90% transmetalation (based on isolated Bu₄Sn), for organostannanes where R is a straight chain (Table 4, entries 1-3). Trapping of the resulting organolithiums with benzaldehyde gave β-aminoalcohols 119 and 120. However, the yields were very low (35-55%), and the yields for branched chains were even lower due to incomplete transmetalation caused by steric hindrance (Table 4, entries 4-5). TLC analysis of the products showed only one
spot, which might suggest the presence of only one diastereomer. However, this is not very reliable because the two diastereomers might have close $R_f$ values. Analysis of the $\beta$-aminoalcohols by $^1$H NMR spectroscopy was difficult because of the presence of rotamers caused by hindered rotation around the C-N bond.

We observed later on that treatment of the $\beta$-aminoalcohols with NaH or KH gave the oxazolidinones 122 and 123 which were easy to analyze by $^1$H NMR spectroscopy. As analysis by TLC had suggested, only one diastereomer was present. The coupling constant $J_{ab}$ for the oxazolidinones was around 8 Hz. Futagawa and coworkers had made oxazolidinones where $R$ was CO$_2$H with different $R'$ groups. They found that all the cis oxazolidinones had $J_{ab}$ around 9 Hz and $J_{ab}$ for the trans oxazolidinones was around 5 Hz. Based on this data, we concluded that our oxazolidinones had cis geometry. The cis oxazolidinones 122 must arise from cyclization of the anti $\beta$-aminoalcohols 119 (Table 4). This indicated that transmetalation of the racemic $\alpha$-aminoorganostannanes 118 and trapping of the resulting $\alpha$-aminoorganolithiums with benzaldehyde gave only the anti diastereomer 119.
Table 4: Transmetalation of α-aminoorganostannanes and trapping with aldehydes.

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Product</th>
<th>Yield (%)</th>
<th>de (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>119a</td>
<td>55</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td></td>
<td>119b</td>
<td>54</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>n-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td></td>
<td>119e</td>
<td>55</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td></td>
<td>119f</td>
<td>35</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>c-C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td></td>
<td>119g</td>
<td>40</td>
<td>&gt;98</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;OC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>119h</td>
<td>50</td>
<td>&gt;98</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>c-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>119i, 120i</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>i-Pr</td>
<td>119j, 120j</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined from <sup>1</sup>H NMR spectra of oxazolidinones
The *syn* β-aminoalcohol 120 was not being formed at all as was indicated by the absence of the *trans* oxazolidinone 123. Trapping of the organolithium with another aromatic aldehyde, *p*-anisaldehyde, also gave only the *anti* diastereomer (entry 6). These results were surprising since the *N*-methoxymethyl Boc protected α-aminoorganostannane gave a 1:1 mixture of diastereomers. The only byproduct that we isolated was the alcohol 121 which was a result of the reaction between excess *n*-BuLi and the aldehydes. We did not isolate any other byproducts to account for half of the starting material. Trapping with aliphatic aldehydes gave a slight increase in the yield and an approximately 1:1 mixture of diastereomers (entries 7 and 8). Therefore, the diastereoselectivity was only observed after trapping with aromatic aldehydes.

In their studies on trapping of α-alkoxyorganolithiums with benzaldehyde, McGarvey and Kimura observed this kind of diastereoselectivity (Scheme 59). However, in their case, they obtained the opposite diastereomer, *syn*. and the diols were isolated in very high yield (65-96%). They attributed their diastereoselectivity to the formation of diastereomeric transition states 124a and 124b. The minor transition state 124b is not favored due to an eclipsing R/Ph interaction which is absent in 124a. Diastereoselectivity was high with branched R groups (*t*-Bu and *i*-Pr) and when M was MgBr.
Therefore, our results were giving opposite diastereoselectivity to what was expected mechanistically. We were not experiencing a facial discrimination like that observed by McGarvey and Kimura. These results raised the idea that, in the case of aromatic aldehydes, the rate of formation of the syn diastereomer might be slower than that of the anti diastereomer so the organolithium decomposes before trapping. The rate of formation of the byproduct 121 might also be faster than that of the syn diastereomer since it was always observed. On this note, we decided to trap the organolithiums with excess aldehyde (2 equiv instead of 1.3 equiv). We wanted to make sure that there was enough aldehyde in solution even after some had reacted with excess n-BuLi. TLC
analysis of the crude product after trapping with 2 equiv of aldehyde, indicated the presence of two spots. Upon cyclization of the crude mixture to the oxazolidinones, we did isolate both the cis and trans oxazolidinones.

Table 5: Trapping α-aminoorganolithiums with excess aldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Product</th>
<th>Yield (%)</th>
<th>cis : trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>122a, 123a</td>
<td>90</td>
<td>2.5 : 1.0</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td></td>
<td>122b, 123b</td>
<td>77</td>
<td>1.9 : 1.0</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>CH₃OC₆H₄</td>
<td>122h, 123h</td>
<td>80</td>
<td>2.5 : 1.0</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>Ph</td>
<td>122g, 123g</td>
<td>68bic</td>
<td>2.8 : 1.0</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>c-C₈H₁₁</td>
<td>122i, 123i</td>
<td>70</td>
<td>1.0 : 1.3</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>i-Pr</td>
<td>122j, 123j</td>
<td>69</td>
<td>1.0 : 1.3</td>
</tr>
</tbody>
</table>

a Overall yield from 118.

b used 5 equiv n-Buli and 5 equiv PhCHO.

The yields shown in Table 5 are the overall yields of the oxazolidinones from the aminooorganostannanes 118. There was a significant increase in yield of the trapped product. Even with the isopropyl group, which gave only 35% yield with 1.3 equiv of
aldehyde, the yield almost doubled with excess aromatic aldehyde (entry 4). Although both diastereomers were isolated, the anti diastereomer still dominated (approximately 2:1 ratio). Nevertheless, trapping of the organolithiums with excess aliphatic aldehydes did not increase the yield significantly and the two diastereomers were still isolated in about 1:1 ratio.

The β-aminoalcohols were converted to the oxazolidinones for two other reasons: the syn and anti diastereomers and the byproduct 121 had very close Rf values which made separation very difficult. To our great benefit, the cis and trans oxazolidinones had very different Rf values which were also different from that of the byproduct, making their separation easier. The other reason, which is more important, is that the oxazolidinones later became useful for deprotection to primary β-aminoalcohols as will be shown in subsequent sections.

4.2.3 Preparation of enantiomerically enriched α-aminoorganostannanes

Having successfully transmetalated racemic N-t-butylthiomethyl Boc α-aminoorganostannanes and trapped the resulting organolithiums, the next step was to study the configurational stability of the enantiomerically enriched α-aminoorganolithiums and also to synthesize enantiomerically enriched β-aminoalcohols. As discussed in Chapter 1, only two methods have been reported for the asymmetric synthesis of α-aminoorganostannanes and they both have some limitations. Our attempts to develop a new route to enantiomerically enriched α-aminoorganostannanes are discussed in Chapter 5. At the time we initiated these studies, we found the resolution of
stannylamines to be a convenient method. Thus, cleavage of the phthalimides 67 and reaction of the resulting primary amine with (S)-O-methylmandelic acid gave the two diastereomers 125 and 126 as a 1:1 mixture (Scheme 60). The two diastereomers were easily separated by column chromatography. We will explain later in this section how we arrived at the absolute configuration of the two diastereomers.

**Scheme 60**

![Scheme 60](image)

Attempts to remove the chiral auxiliary from the less polar diastereomer 125 using MeLi were not successful. Only starting material was recovered even after using 6 equiv of MeLi. We then tried to use triethyl oxonium fluoroborate (Et$_3$OBF$_4$), a mild agent for hydrolysis of amide bonds. This reagent was supposed to react with the amide to give the salt 127 (Scheme 61). The reaction was shown to be complete by TLC, and a yellow oil was isolated. However, it was unclear by $^1$H NMR spectroscopic analysis whether it was actually the salt 127. Hydrolysis of this material with aqueous NaHCO$_3$ did not give the expected primary amine but unidentifiable byproducts.
Since the Boc protected stannylamines are very stable and the unprotected amines are known to be unstable, we decided to introduce the Boc group before removal of the auxiliary (Scheme 62). Thus, treatment of 125 with Boc₂O and DMAP gave 128. Cleavage of the chiral auxiliary with MeLi gave the carbamate 129. Unfortunately, in low yield (53%). Since hydrazine had given us great success with cleavage of phthalimides, we decided to use it to cleave the chiral auxiliary. We were pleased to find that treatment of 128 with hydrazine gave the carbamate 129 in quantitative yield.

Introduction of the methoxycarbonyl group to give 130 was initially attempted by treating 129 with methyl chloroformate in the presence of Et₃N but no reaction occurred. We decided to deprotonate the carbamate 129 with NaH in the presence of the methyl chloroformate. No reaction occurred after stirring at rt for 24 h. When we used LDA as the base, the reaction was very messy with no product being formed. Perhaps the anion was not stable, and it decomposed before reacting with methyl chloroformate. We decided to use methyl cyanoformate, which is known to be a good acylating agent for lithium enolates. Thus, methyl cyanoformate was reacted with the lithium anion of 129 at −78 °C to give the product 130 in very good yield. The iminodicarbonates 130 were carried through subsequent steps already discussed to give the required enantiomerically enriched α-aminoorganostannanes 132.
The carbamate 129 was treated with TFA to remove the Boc group. The resulting primary amine was converted to a Mosher amide. Unfortunately, the $^{19}$F NMR spectra of the Mosher amides did not give baseline separation for the two signals (Figure 11). Nevertheless, we were able to make use of the $^{13}$C satellites of the major diastereomer. Comparison of these $^{13}$C satellites (each being 0.55% intensity) and the minor diastereomer indicated that the Mosher amide B was 96% de. Thus, the carbamate 129 was also assumed to be 96% ee. Since the conversion of carbamate 129 to the organostannanes 132 does not involve the stereogenic centre, it is therefore reasonable to infer that organostannanes 132 were also 96% ee. Comparison of the optical rotation of carbamate 129 with that reported in the literature suggested that it had R configuration. Thus for the mandelamides 125 and 126, the less polar diastereomer must have had (1R, 2S) configuration while the more polar diastereomer had (1S, 2S) configuration.

Scheme 62
Figure 11: Partial $^{19}$F NMR spectra of Mosher amides A and B
4.2.4 Configurational stability of α-Aminoorganolithiums

Transmetalation of 132 and trapping the resulting organolithium 133 with benzaldehyde gave β-aminoalcohol 134 (Table 6). The enantiomeric excess of 134 was determined by high performance liquid chromatography (HPLC) and it was presumed to equate with the enantiomeric purity of the intermediate organolithium 133 (Figure 12). Transmetalation of 132b at -78 °C and trapping of 133 after 30 min led to 12% racemization (entry 1). Lowering the temperature to -95 °C decreased the rate of racemization to 2%, indicating that configurational stability was temperature dependent (entry 2). As discussed in preceding sections, intramolecular coordination of the Li atom and carbonyl oxygen is believed to be responsible for configurational stability. THF is a coordinating solvent, and as a result, it might interfere with the intramolecular coordination and promote racemization. We decided to use a less coordinating solvent, Et$_2$O; however, it gave only about 5% transmetalation after 15 min. Use of a 1:1 mixture of THF:Et$_2$O gave almost the same result as using only THF (entry 3).
**Table 6**: Configurational stability of α-aminoorganolithiums

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Temp(°C)</th>
<th>Time(min)</th>
<th>Yield(%)</th>
<th>ee(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anti</td>
</tr>
<tr>
<td>1</td>
<td>Et</td>
<td>-78</td>
<td>30</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-95</td>
<td>15</td>
<td>79</td>
<td>94</td>
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<td>3</td>
<td>&quot;</td>
<td>-78&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
<td>63</td>
<td>82</td>
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<tr>
<td>4</td>
<td>&quot;</td>
<td>-78&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>-78</td>
<td>30</td>
<td>68</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>-95</td>
<td>15</td>
<td>60</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by HPLC analysis (Chiracel OD)

<sup>b</sup> Et<sub>2</sub>O-THF mixture used as solvent

<sup>c</sup> LiBr was added to the stannane solution before transmetalation

nd means the enantiomeric excess was not recorded.
Figure 12: HPLC analysis of ε-aminoalcohols 119b and 134b.  

Eluted with hexane/i-PrOH 99.5:0.5 (v/v) and a flow rate of 0.25 mL/min.

*a*
When transmetalation was carried out in the presence of LiBr, there was a dramatic increase in the rate of racemization (entry 4). This verified the significance of intramolecular coordination between the Li atom and the carbonyl oxygen, shown in the proposed structure of the intermediate organolithium 133, for its configurational stability. In the presence of LiBr, there is competition between intramolecular and intermolecular coordination (Scheme 63). Formation of complex 133b will allow the organolithium to undergo rapid inversion. The extra Li ion from LiBr could also increase rate of inversion by doing an S_N2 attack on the original C-Li bond. The yield of the product also dropped in the presence of LiBr and no other byproducts were isolated. Therefore, the organolithiums might have decomposed before reacting with benzaldehyde, indicating that intramolecular chelation is also required for chemical stability.

Another interesting observation was the difference in enantiomeric excess between the two diastereomers. The anti diastereomer always had a higher ee than the syn diastereomer (entries 1, 2 and 4). This confirmed the conclusion we had made earlier concerning the difference in the rate of formation of the two diastereomers. The rate of formation of the syn diastereomer must be slower than that of the anti diastereomer, therefore the organolithium stays in solution longer before trapping and thus undergoes
more racemization. Unfortunately, we were unable to rationalize this difference in the rate of reaction.

To study the configurational stability of an organolithium with a different R group, \textbf{132e} (R = C_5H_{11}) was also transmetalated (entries 5 and 6). This gave similar results to what was observed with organolithiums derived from \textbf{132b} (R = Et).

Although these \textit{N}-t-butylthiomethyl Boc protected \(\alpha\)-aminoorganolithiums racemize at -78 °C, they can be trapped at -95 °C to give \(\beta\)-aminoalcohols in high enantiomeric purity. This verified Park's proposal that the methoxy oxygen in \textbf{113} (Figure 13) was competing with the carbonyl oxygen for chelation to the Li atom leading to racemization. The 2% racemization in \textbf{133} might be due to a slight coordination of the sulfur to the Li atom. As we had predicted, these results suggest that there is a big difference between oxygen and sulfur in their affinity for coordinating to the Li atom. Therefore, \textit{N}-t-butylthiomethyl Boc \(\alpha\)-aminoorganolithiums \textbf{133} fall in-between the \textit{N}-methyl (\textbf{94}) and the \textit{N}-methoxymethyl (\textbf{113}) Boc \(\alpha\)-aminoorganolithiums (Figure 11), in terms of configurational stability.

\textbf{Figure 13: }\(\alpha\)-Aminoorganolithiums in decreasing configurational stability

\[\text{MeN} \quad \text{Or-Bu} \quad \text{O} \quad \text{MeN} \quad \text{Or-Bu} \quad \text{O} \quad \text{MeN} \quad \text{Or-Bu} \quad \text{O} \]

\[\text{R} \quad \text{Li} \quad \text{R} \quad \text{Li} \quad \text{R} \quad \text{Li} \]
4.2.5 Deprotection to primary β-aminoalcohols

One of our major goals for this project was to be able to use this methodology for the synthesis of primary β-aminoalcohols. We chose the Boc and t-butylthiomethyl protecting groups because they are both acid labile. Therefore, we tried to deprotect the anti β-aminoalcohol 119b by treating it with 2 N HCl. To our disappointment, no primary β-aminoalcohol 136 was isolated (Scheme 64). Instead the aminoacetal 137 was obtained in 95% yield. We proposed the mechanism shown in Scheme 63 to explain the formation of the aminoacetal. When the aminoalcohol reacts with the acid, it can form the intermediate 135a or 135b. Since the Boc group is very labile under acidic conditions, 135a is the one that is more likely formed. This intermediate can then take two routes: route A involves the attack of the imine carbon by water and this would give formaldehyde and the required primary β-aminoalcohol 136. Route B involves an intramolecular attack on the imine carbon by the OH to give the aminoacetal 137. Therefore, route B predominated; however, this was surprising because the cyclization of 135 is a 5-endo-trig ring closure which is unfavorable by Baldwin’s rules.11
It was clear from these results that deprotection was not possible in the presence of the OH. To get around this problem, one had to protect the alcohol first so that it does not interfere. Since the deprotection was being done with acid, the alcohol protecting group had to be stable under acidic conditions. The benzyl group seemed to be suitable for this function. Using the standard procedure for putting on a benzyl group, treatment of the β-aminoalcohol 119b with NaH in the presence of BnBr, did not give the benzyl ether 138b; instead the oxazolidinone 122b was formed in 70% yield (Table 7, entry 1). This was due to the alkoxide intramolecularly attacking the carbonyl group instead of reacting with BnBr. Normally the protection of secondary alcohols is difficult; as a result, the intramolecular reaction was preferred in this case.

Studies had shown that Williamson ether synthesis can be improved by using phase transfer catalysis. Thus, using aqueous NaOH as the base, TBAI as the phase
transfer catalyst and THF as the organic solvent, the required product 138 was formed. However, 122 was still observed as well, but as the minor product (entries 2 and 3). In entry 3 the yields were lower due to incomplete reaction. TBAI also acted as a source of iodide ion to make the more reactive BnI.

**Table 7: Protection of alcohol 119 with BnBr**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>138</td>
</tr>
<tr>
<td>1</td>
<td>Et</td>
<td>NaH</td>
<td>0</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Et</td>
<td>NaOH</td>
<td>67</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>c-C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>&quot;</td>
<td>53</td>
</tr>
</tbody>
</table>

<sup>a</sup> reaction done using phase transfer catalysis

The product from entry 2, 138<sub>b</sub>, was treated with 2 N HCl and gave the deprotected aminoalcohol 139 in excellent yield (Scheme 65). Selective removal of the primary benzyl group proved to be a challenge. We first attempted this by hydrogenolysis, i.e. using H<sub>2</sub> in the presence of Pd/C catalyst.<sup>13</sup> Starting material was
consumed, but no product was isolated, only unidentifiable byproducts. We then used milder conditions, transfer hydrogenolysis with either cyclohexadiene\textsuperscript{14} or ammonium formate\textsuperscript{15} as the hydrogen source, but in both cases no reaction occurred. Bronislaw and Bartsch reported that having an amine in the structure or adding an amine to the solution prohibited O-debenzylation in some cases.\textsuperscript{16} Perhaps that is why we were not being successful with our debenzylation. We then tried dissolving metal reduction,\textsuperscript{17} which we had avoided initially because selectivity was not expected and we risked the removal of both the primary and secondary benzyl groups. Furthermore, this method has not been commonly used in the literature for O-debenzylation. Surprisingly, only the required primary benzyl group was removed and gave the product 136b in good yield.

Although we were able to make the primary β-arinoalcohols, this method was not satisfactory. Protection of the alcohol occurred in low yields making the overall process unsuitable. Since the β-aminoalcohols were easily cyclized to oxazolidinones, we decided to hydrolyze the oxazolidinones to primary β-aminoalcohols. Wee and McLeod
had used aqueous KOH to hydrolyze an oxazolidinone which was a precursor to microgin. Treatment of the oxazolidinones 122 with 2 M KOH gave the primary β-aminoalcohols; unfortunately, the aminoacetals 137 that we had experienced before were also isolated (Table 8, entries 1-2). As discussed before, this was due to competition between intramolecular and intermolecular reaction of the intermediate 140. The only difference in this case is that the nucleophile for the intermolecular reaction, OH, is more powerful, thus, favoring route A. In order to eliminate intramolecular reaction, we decided to use a base with a smaller counterion, LiOH instead of KOH. LiOH had also been successfully used for hydrolysis of oxazolidinones. We expected the Li ion to coordinate to the oxygen in 140 more strongly than the K ion, thereby making the oxygen less nucleophilic. This did increase the ratio of 136 to 137, and in some cases route B was totally eliminated (entry 3).

When hydrolysis was performed on the oxazolidinone 122e (R = n-C5H11, entry 7), the results were totally opposite to that of the other oxazolidinones. The aminoacetal 137e was the only product isolated with no traces of the β-aminoalcohol. This was very surprising because normally compounds with the R group varying only in chain length behave in almost the same manner. To investigate whether our reactions were general, we used three different kinds of groups: R = Et and Me representing small chains; R= n-C5H11 representing long chains and the branched chains represented by R= i-Pr and c-C6H11. The difference we were observing between R = Et and n-C5H11 was suggesting that the straight chains were behaving differently. We were not sure whether the behavior of the oxazolidinones had altered between C2 and C5 since we had no data for C3 and C4, so
we prepared the oxazolidinones for C3 and C4. Hydrolysis of these oxazolidinones gave a 1:1 mixture of aminoacetal and aminoalcohol (entries 5 and 6).

**Table 8: Hydrolysis of oxazolidinones to primary β-aminoalcohols**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>M</th>
<th>136 : 137</th>
<th>Yield of 141</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Ph</td>
<td>K</td>
<td>1.5 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>CH3OC6H4-</td>
<td>K</td>
<td>2 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>Li</td>
<td>100 : 0</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&gt;90 : &lt;10</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>n-C3H7</td>
<td>&quot;</td>
<td>&quot;</td>
<td>1 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>n-C4H9</td>
<td>&quot;</td>
<td>&quot;</td>
<td>1 : 1</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>n-C5H11</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0 : 100</td>
<td>84 (137e)</td>
</tr>
<tr>
<td>8</td>
<td>i-Pr</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&gt;90 : &lt;10</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>CH3OC6H4-</td>
<td>&quot;</td>
<td>&gt;90 : &lt;10</td>
<td>66</td>
</tr>
</tbody>
</table>

* Ratio determined by 1H NMR spectroscopy

* Overall yield from 122
Consequently, straight chain alkyl groups (C₃ or larger) gave unacceptable yields of primary β-aminoalcohols with this methods. Hydrolysis of an oxazolidinone with a branched chain (entry 8) gave the β-aminoalcohol as the major product. Finally, since primary β-aminoalcohols are known to decompose, we converted them to the stable HCl salts 141.

The formation of aminoacetals by the hydrolysis of oxazolidinones with straight chains (R = n-C₄H₇, n-C₅H₁₀, n-C₅H₁₁), might be due to a hydrophobic effect. This is when nonpolar compounds are suspended in a polar solvent, mostly water, and their relative insolubility causes them to associate, diminishing the water hydrocarbon interface area. This association brings reactive partners into close proximity, increasing the rate of reaction. In the Diels-Alder reaction of cyclopentadiene and butenone, for example, use of water as solvent increases the reaction rate by 730-fold compared to use of isooctane. In our case when the R group became longer, maybe the oxazolidinone became more hydrophobic. The intermediate 140 will decrease its interface with the aqueous solution making its attack by –OH very slow. As a result, the intramolecular reaction, i.e. formation of aminoacetals, would be favored.

Attempts to hydrolyze the trans oxazolidinones under the same conditions gave very low yields due to their higher stability compared to the cis analogues. This was achieved when we used a slightly higher boiling solvent, n-propanol (Scheme 66).
The oxazolidinones where R' is an aliphatic group (122i and 122j) were also resistant to hydrolysis even with high boiling solvents.

The oxazolidinone hydrolysis did not give access to all the primary β-aminoalcohols we were interested in. Since the aminoacetals were always the major byproduct in these deprotections, we decided to convert them to primary β-aminoalcohols using a method that was reported by Corey and coworkers. Treatment of the aminoacetals with excess 1,3-propanedithiol, led to transacetalization, giving the primary β-aminoalcohol 136 (Table 9). This is an equilibrium reaction and the best results were obtained with BF₃•Et₂O as a Lewis acid. As the chain of the aminoacetal became longer, the equilibrium moved more to the right, giving the β-aminoalcohols in good yields (entries 3 and 4). With R = n-C₅H₁₁ (entry 5), all the aminoacetal was converted to the aminoalcohol. The trend was now opposite to what was observed in the hydrolysis of the oxazolidinones, with Et and Me giving lower conversion. We really have no explanation as to why the equilibrium shifts more to the right when R is a long chain. As was observed with the oxazolidinone hydrolysis, transacetalization of the trans aminoacetals to the corresponding syn aminoalcohols was not successful.
Table 9: Transacetylation of aminoacetals

Therefore, we were able to find two complementary routes to our anti primary β-aminoalcohols: Primary β-aminoalcohols with short and branched R groups can be made...
from hydrolysis of corresponding oxazolidinones. On the other hand, the ones with straight chains (C₃, C₄, C₅) can be obtained from transacetalization of the aminoacetals. Although we do not have a good mechanistic explanation for these results, they are quite encouraging since there really had not been any examples for making primary β-aminoalcohols using this kind of methodology.

In order to determine the enantiomeric excess of the final primary β-aminoalcohols, we deprotected the β-aminoalcohol 134b to its primary β-aminoalcohol 143, which we then converted to the carbamate 144 (Scheme 67). HPLC analysis of 144 showed it had 93% ee (Figure 14). Therefore, deprotection of 134b must have occurred without significant racemization. The enantiomeric excess of 144 went up to 99% after a single recrystallization. Optical rotation of the salt 145b was comparable to the value reported in the literature and also confirmed the predicted stereochemistry.22 Therefore, primary β-aminoalcohols were successfully obtained in very high enantiomeric excess from enantiomerically enriched α-aminoorganolithiums.

Scheme 67

![Scheme 67 Diagram](image-url)
Figure 14: HPLC analysis of carbamate 144

\[ \text{(±)-144} \]

\[ \text{(1R,25)-144} \text{ 93% ee} \]

*Eluted with hexane/i-PrOH 99.5:0.5 (v/v) and a flowrate of 0.35 mL/min*
4.2.6 Inversion of stereochemistry for the β-aminoalcohols

Biologically active molecules with β-aminoalcohol functionality have either the anti or the syn configuration and not a mixture. In order to make this methodology more useful, we had to find a method for stereochemical inversion, i.e. convert the anti to the syn diastereomer or vice versa. Since the anti β-aminoalcohols were always the major diastereomers after trapping with aromatic aldehydes, we decided to start by studying their inversion. When norephedrine 146 was treated with diethyl azodicarboxylate (DEAD) and PPh₃ in the presence of p-nitrobenzoic acid, TLC indicated that reaction had occurred (Scheme 68). Hydrolysis of the crude mixture with NaOH did not give the expected syn β-aminoalcohol 147; instead we isolated the anti β-aminoalcohol 146 that we had started with. Since the TLC had shown that the reaction had occurred, it must have occurred with double inversion. Carboni et al. observed this kind of inversion when they tried to carry out the Mitsunobu reaction with NaN₃ as the nucleophile.³³ Presumably the nitrogen intramolecularly displaced triphenylphosphine oxide by an S_N2 reaction and gave the aziridinium cation 148. The p-nitrobenzoic acid would then have done a second S_N2 attack on the aziridinium cation to give the ester, which was then hydrolyzed to give back the anti β-aminoalcohol 146.
Pericas and coworkers had successfully done Mitsunobu reactions on N-Boc protected β-aminoalcohols (Scheme 69).^{24}
These results suggest that, for a Mitsunobu reaction to be successful, the nitrogen has to be protected. Therefore, we decided to do Mitsunobu reactions on the protected β-aminoalcohol 119 (Scheme 70). However, the reaction did not give the expected ester 150, instead it cyclized to the oxazolidinone 123. $^1$H NMR analysis of the oxazolidinone indicated that it was trans, thus cyclization had occurred with inversion. This result was actually better than what we had expected. The ester 150 would have been 3 steps away from the syn primary β-aminoalcohol. yet hydrolysis of the oxazolidinone 123 would give the product immediately.

Scheme 70

It was not clear whether 119 reacted with $p$-nitrobenzoic acid first to give the ester and then cyclized to the oxazolidinone or whether the oxazolidinone was formed via a different route. To probe this mechanism, we performed the reaction in the absence of the
nucleophile, \( p \)-nitrobenzoic acid, and the \textit{trans} oxazolidinone was again formed under these conditions. Therefore, \( p \)-nitrobenzoic acid was not required for this reaction to occur. The oxazolidinone must have resulted from intramolecular displacement of triphenylphosphine oxide by the carbonyl oxygen (complex 151). van Boom and coworkers also accidentally discovered this reaction when they were attempting a Mitsunobu reaction on \( N \)-benzyl benzyloxycarbonyl (Cbz) protected \( \beta \)-aminoalcohols using \( \text{PPh}_3 \) and \( \text{C}_2\text{Cl}_6 \).\textsuperscript{25}

Davies and coworkers had also reported the cyclization of the aminoalcohol 152 under Mitsunobu conditions to give the oxazoline 153 (Scheme 71).\textsuperscript{26} This method is limited by the harsh conditions required to hydrolyze the oxazoline to the primary \( \beta \)-aminoalcohol. This might be detrimental to acid sensitive groups which might be in the molecule.

\textbf{Scheme 71}

\[ \begin{array}{c}
\text{PhCONH} \\
\text{Hept} \\
\text{OH}
\end{array} \xrightarrow{\text{DEAD}} \xrightarrow{\text{1.6N HCl}} \xrightarrow{\text{2. Dowex}} \begin{array}{c}
\text{NH}_2 \\
\text{CO}_2\text{Bu} \\
\text{OH}
\end{array} \]

In order to investigate whether this reaction would also work with \( N \)-Boc \( \beta \)-aminoalcohols, we treated the carbamate 154 with \( \text{PPh}_3 \) and DEAD (Scheme 72). Surprisingly, we did not isolate any of the expected oxazolidinone 155; instead the aziridine 156 was formed in 60% yield. Evidently the nitrogen had acted as the
nucleophile instead of the carbonyl oxygen. When van Boom and coworkers did the same reaction using C₂Cl₆ and PPh₃, they isolated the aminochloride because C₂Cl₆ provided the Cl⁻ which then displaced the triphenylphosphine oxide.²⁵ Therefore, formation of oxazolidinones only occurs with N-disubstituted aminoalcohols. Monosubstituted β-aminoalcohols undergo normal Mitsunobu inversion by an external nucleophile. However, in the absence of a nucleophile, an aziridine is formed.

Pericas and coworkers had also observed the same kind of reaction in their attempt to do a Mitsunobu reaction on 157 (Scheme 72).²⁴ This was because they used a weak nucleophile, p-methoxyphenol.

**Scheme 72**

![Scheme 72 Diagram](image)
The reason why there is so much difference in Mitsunobu reactions of mono and disubstituted β-aminoalcohols might be due to hydrogen bonding. The monosubstituted β-aminoalcohols 154 and 157 can engage in intermolecular hydrogen bonding between the carbonyl oxygen and the hydrogen atom on nitrogen. This interaction will decrease the nucleophilicity of the carbonyl oxygen, as was shown by their inability to form oxazolidinones. Since we had no nucleophile present in the reaction mixture, the nitrogen was obliged to act as the nucleophile. This might be why Pericas and coworkers were able to successfully obtain the syn β-aminoalcohols (Scheme 68).

In conclusion, one can obtain syn primary β-aminoalcohols as outlined in Scheme 73. Starting from enantiomerically enriched α-aminoorganostannanes 132, transmetalation and trapping with benzaldehyde gives an approximately 2:1 mixture of anti and syn β-aminoalcohols. The anti product can be converted to the trans oxazolidinone 158 by the intramolecular Mitsunobu reaction. The syn product can also be converted to 158 by cyclization with NaH. The resulting trans oxazolidinone can then be hydrolyzed to the syn primary β-aminoalcohol.

Unfortunately, there was no reaction when the Mitsunobu reaction was attempted using the β-aminoalcohol 119g (R = i-Pr), presumably due to steric hindrance. Syn β-aminoalcohols 120 also gave no oxazolidinones under the Mitsunobu conditions. Therefore, anti β-aminoalcohols could not be obtained from the syn diastereomer. This was however not a major drawback because the anti diastereomer was the major product from trapping organolithiums with aromatic aldehydes.
4.2.7 Summary

*N-t*-Butylthiomethyl Boc protected α-aminoorganostannanes were transmetalated at -78 °C with *n*-BuLi and the resulting organolithiums were trapped with different aldehydes. With aromatic aldehydes, formation of the *syn* diastereomer was found to be slower than that of the *anti* diastereomer. Thus, with only 1.3 equiv of aldehyde, only the *anti* diastereomers were isolated, albeit in low yields (35-55%). In order to obtain the *syn* diastereomer, one had to use excess aldehyde (2 equiv) and there was a dramatic increase in yield of the isolated product. Even under these conditions, the *anti* diastereomer still predominated (≈2:1 *anti:*syn ratio).
Enantiomerically enriched α-aminoorganolithiums racemized at -78 °C (12-14% after 30 min). At -95 °C racemization was much slower (2-3%), and trapping of these organolithiums with aldehydes gave β-aminoalcohols in high enantiomeric excess.

The β-aminoalcohols were converted to oxazolidinones, and the cis oxazolidinones were then hydrolyzed to primary β-aminoalcohols. This reaction was not successful for oxazolidinones with straight chains (R = n-C₃H₇, n-C₄H₉ and n-C₅H₁₁), where the aminoacetal byproducts were also isolated. Transacetalization of these aminoacetals gave the required primary β-aminoalcohols. Thus, two routes to primary β-aminoalcohols were established. Hydrolysis of enantiomerically enriched oxazolidinones occurred without any racemization to give primary β-aminoalcohols in very high enantiomeric excess. Although the N-methyl Boc α-aminoorganolithiums are more configurationally stable than N-t-butyliothiomethyl Boc α-aminoorganolithiums, the latter are superior because both protecting groups are removable to give primary β-aminoalcohols.

*Anti* N-t-butyliothiomethyl Boc β-aminoalcohols cyclized under Mitsunobu conditions, with inversion, to give the *trans* oxazolidinones. Hydrolysis of these gave *syn* primary β-aminoalcohols. Attempts to do the same reaction on *N*-t-Boc β-aminoalcohol gave the aziridine.
4.3 Experimental

4.3.1 General

The procedures outlined in section 2.3.1 also apply here with the following additions: methyl t-butyl iminodicarbonate was prepared according to Jones et al.\textsuperscript{27} (S)-(\textpm)-\textalpha-methoxy-\textalpha-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) was prepared from the (R)-acid according to the procedure of Sharpless et al.\textsuperscript{9} Optical rotations were measured on a Perkin Elmer model 241 digital polarimeter. High performance liquid chromatography (HPLC) analyses were conducted on a Waters 600 instrument equipped with a Waters 486 UV-visible detector and a Waters 746 recording integrator. A Chiracel OD column (4.6 x 250 mm) was used and detection was done at 254 nm. The notation (R\textsuperscript{*}, S\textsuperscript{*}) is used to represent a racemic mixture of the (R, S) diastereomer, \textit{i.e.} a mixture of the (R, S) and (S, R) isomer.

4.3.2 General procedure for the preparation of methyl N-tributylstannyl carbamates

\textbf{Reaction 1:}

To a 1.0 M solution of the appropriate phthalimide in ethanol was added hydrazine hydrate (50 equiv) and the resulting mixture was stirred at reflux for the specified time. The mixture was concentrated \textit{in vacuo} and Et\textsubscript{2}O was added to the residue. The solution was washed with water, dried (MgSO\textsubscript{4}), filtered through Celite and concentrated \textit{in vacuo} to yield the crude primary amines which were used without further purification.
**Reaction 2:**

To a cooled (0 °C) 0.2 M solution of amine in CH₂Cl₂ was added Et₃N (1.3 equiv) and then methyl chloroformate (1.5 equiv). The resulting mixture was stirred at rt for 30 min and diluted with CH₂Cl₂. The mixture was washed with water, dried (MgSO₄), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (35 g of silica/g of substrate; 10:1 hexane/Et₂O) to give the carbanates as colorless oils.

### 4.3.3 Methyl N-(1-tributylstannylethyl)carbamate 116a

![Chemical Structure](image)

This compound was prepared from 67a according to the general procedure described in section 4.3.2 with a reaction time of 3 h for reaction 1, in 82% yield: IR (neat) 3339, 2918, 1702, 1520, 1458, 1252 cm⁻¹; ¹H NMR (250 MHz) δ 4.73 (broad, 1 H, HN), 3.64 (s, 3 H, CO₂CH₃), 3.27 (m, 1 H, CHN), 1.64-1.20 (m, 15 H, SnCH₂(CH₂)₂CH₃ and CH₃CHN), 0.99-0.75 (m, 15 H, SnCH₂(CH₂)₂CH₃); ¹³C NMR (63 MHz) δ 157, 51.9, 35.5 (¹J = 339), 29 (²J = 19), 27.5 (³J = 45), 20.7, 13.7, 9.4 (¹J = 320, 305); MS, FAB m/z (relative intensity) 334 (M⁺-CO₂Me, 100), 291 (8), 233 (7), 222 (10). Anal. Calcd for C₁₆H₃₅NO₂Sn: C, 49.00; H, 9.00; N, 3.57. Found: C, 49.16; H, 8.88; N, 3.58.
4.3.4 Methyl N-(1-tributylstannylbutyl)carbamate 116c

\[ \text{HN} \quad \text{OMe} \]
\[ n-C_3H_7 \quad \text{SnBu}_3 \]

This compound was prepared from 67c according to the general procedure described in section 4.3.2 with a reaction time of 5 h for reaction 1, in 78% yield: IR (neat) 3326, 2908, 1704, 1520, 1457, 1253, 1064 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 4.79 (d, 1 H, J = 7.6, HN), 3.67 (s, 0.5 H, OCH\(_3\)), 3.61 (s, 2.5 H, OCH\(_3\)), 3.26 (dt, 1 H, J = 6.5, 7.6, CHN), 1.72-1.24 (m, 16 H, SnCH\(_2\)(CH\(_2\))\(_3\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_3\)CHN), 0.98-0.72 (m, 18 H, SnCH\(_2\)(CH\(_2\))\(_3\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_3\)CHN). \(^1^3\)C NMR (63 MHz) \(\delta\) 157.1, 51.7, 40.9, 37.0, 29.0 (\(^2\)J = 20), 27.3, (\(^3\)J = 55), 21.0, 13.6, 13.5, 9.6 (\(^1\)J = 311), *9.0; MS, FAB m/z (relative intensity) 364 (M\(^+\)- C\(_4\)H\(_9\), 100), 306 (7), 281 (8), 235 (12). Anal. Calcd for C\(_{18}\)H\(_{39}\)NO\(_2\)Sn: C, 51.45; H, 9.36; N, 3.33. Found: C, 51.58; H, 9.18; N, 3.38.

4.3.5 Methyl N-(1-tributylstannylpentyl)carbamate 116d

\[ \text{HN} \quad \text{OMe} \]
\[ n-C_4H_9 \quad \text{SnBu}_3 \]

This carbamate was prepared from 67d according to the general procedure described in section 4.3.2 with a reaction time of 3 h for reaction 1, in 91% yield: IR (neat) 3326, 2913, 1704, 1518, 1460, 1253 1193, 1046 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 4.82
(d, 1 H, J = 7.6, HN), 3.70 (s, 0.5 H, CO₂CH₃), 3.64 (s, 2.5 H, CO₂CH₃), 3.22 (dt, 1 H, J = 7.1, 7.6, CHN), 1.66-1.18 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₃CHN), 1.0-0.74 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₃CHN); ¹³C NMR (63 MHz) δ 157.1, 51.9, 41.3, 34.5, 30.2, 29.1 (²J = 19), 27.4 (³J = 55), 22.4, 13.9, 13.6, 9.7 (¹J = 303, 317); MS, FAB m/z (relative intensity) 378 (M⁺-C₄H₉, 100), 320 (11), 289 (8), 264 (10), 235 (12).


4.3.6 Methyl N-(1-tributylstannylhexyl)carbamate 116e

![Structural formula of 116e](image)

This carbamate was prepared from 67e according to the general procedure described in section 4.3.2 with a reaction time of 10 h for reaction 1. in 88% yield: IR (neat) 3429, 3326, 2956, 2923, 1703, 1517, 1457. 1253 cm⁻¹: ¹H NMR (250 MHz) δ 4.82 (d, 1 H, J = 6.8, HN), 3.63 (s, 3 H, CO₂CH₃), 3.23 (dt, 1H, J = 7.6, 6.8, CHN), 1.60 (m, 2 H, CH₂CHN), 1.48-1.23 (m, 18 H, CH₃(CH₂)₃CH₂ and SnCH₂(CH₂)₂CH₃), 1.0-0.64 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₄); ¹³C NMR (63 MHz) δ 157.2, 52.2, 41.3, *35.1, 34.8, 31.6, 29.2 (²J = 19), 27.7, 27.5 (³J = 55), 22.6, 14.0, 13.6, 9.7 (¹J = 318, 303); MS, FAB m/z (relative intensity) 392 (M⁺ - C₄H₉,100), 334 (12), 291 (7), 278 (8),

4.3.7 Methyl N-(2-methyl-1-tributylstannylpropyl)carbamate 116f

![Chemical structure image]

This carbamate was prepared from 67f according to the general procedure described in section 4.3.2 with a reaction time of 24 h for reaction 1, in 70% yield: IR (neat) 3326, 2914, 1705, 1519, 1459, 1252, 1191 cm$^{-1}$; $^1$H NMR (250 MHz) $\delta$ 4.87 (d, 1 H, J = 8.4, HN), 3.69 (s, 0.3 H, CO$_2$CH$_3$), 3.64 (s, 2.7 H, CO$_2$CH$_3$), 3.12 (dd, 1 H, J = 8.4, 7.4, CHN), 1.98 (m, 1 H, (CH$_3$)$_2$CH), 1.59-1.24 (m, 12 H, SnCH$_2$(CH$_2$)$_2$CH$_3$), 0.97-0.89 (m, 21 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and (CH$_3$)$_2$CH); $^{13}$C NMR (63 MHz) $\delta$ 157.2, 51.8, 49.5, 32.4, 29 ($^2$J = 19), 27.4 ($^3$J = 56), 21.3, 20.6, 13.5, 10.2 ($^1$J = 314, 304); MS, FAB m/z (relative intensity) 364 (M$^+$ - C$_4$H$_9$, 100), 306 (5), 250 (12). Anal. Calcd for C$_{18}$H$_{44}$NO$_2$Sn: C, 51.45; H, 9.36; N, 3.33. Found: C, 51.71; H, 9.12; N, 3.36.

4.3.8 General procedure for the preparation of t-butyl methyl N-tributylstannyl iminodicarbonates

To a 0.1 M solution of the carbamate 116 in acetonitrile was added 4-(N,N,N-dimethylamino)pyridine (0.1 equiv) and di-tert-butyl dicarbonate (2 equiv), the solution was stirred at room temperature or sonicated for the specified time. The solvent was
removed *in vacuo* to give a brownish residue which was diluted with Et₂O, washed several times with 1 M KHSO₄ followed by saturated NaHCO₃. The organic solution was dried (MgSO₄), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (38 g of silica/g of substrate; 10:1 hexane/Et₂O) to give the products as colorless oils.

**4.3.9 t-Butyl methyl N-(1-tributylstannylethyl)iminodicarbonate 115a**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{MeO} & \quad \text{Or-Bu} \\
\text{Me} & \quad \text{SnBu₃}
\end{align*}
\]

This compound was prepared from 116a according to the general procedure described in section 4.3.8 with a reaction time of 40 h in 98% yield: IR (neat) 2917, 1744, 1688, 1448, 1272, 1165 cm⁻¹; ¹H NMR (250 MHz) δ 3.87 (q, 1 H, J = 7.4, CHN), 3.78 (s, 3 H, CO₂CH₃), 1.57-1.20 (m, 15 H, SnCH₂(CH₂)₂CH₃ and CH₃CHN), 1.5 (s, 9 H, CO₂C(CH₃)₃), 0.98-0.74 (m, 15 H, SnCH₂(CH₂)₂CH₃); ¹³C NMR (63 MHz) δ 155.5, 153.3, 82.1, 53.2, 42.3 (¹J = 344, 359), 28.9 (²J = 19), 27.8, 27.3 (³J = 51), 18.6, 13.5, 10.0 (¹J = 330, 314); MS, FAB *m/z* (relative intensity) 436 (M⁺-C₄H₉, 55), 380 (100), 334 (70), 274 (55), 233 (48). Anal. Calcd for C₂₁H₄₃NO₄Sn: C, 51.24; H, 8.81; N, 2.84. Found: C, 51.07; H, 8.87; N, 2.83.
4.3.10 t-Butyl methyl N-((1-tributylstannyl)propyl)iminodicarbonate 115b

![Structure of 115b]

This compound was prepared according to the method of Park\(^1\) in 50% yield and had the same spectral characteristics as reported.

4.3.11 t-Butyl methyl N-((1-tributylstannyl)butyl)iminodicarbonate 115c

![Structure of 115c]

This compound was prepared from 116c according to the general procedure described in section 4.3.8 with a reaction time of 44 h in 94% yield: IR (neat) 2917, 1743, 1692, 1448, 1343, 1292, 1227, 1152, 1073 cm\(^{-1}\): \(^1\)H NMR (250 MHz) \(\delta\) 3.93 (t, 1 H, J = 8.0, CHN), 3.78 (s, 3 H, CO\(_2\)CH\(_3\)), 1.85-1.53 (m, 2 H, CH\(_3\)CH\(_2\)CH\(_2\)CHN), 1.50 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.47-1.22 (m, 14 H, SnCH\(_2\)(CH\(_3\))\(_2\)CH\(_3\) and CH\(_3\)CH\(_2\)CH\(_2\)CHN), 0.93-0.71 (m, 18 H, SnCH\(_2\)(CH\(_3\))\(_2\)CH\(_3\) and CH\(_3\)CH\(_2\)CH\(_2\)CHN); \(^1\)C NMR (63 MHz) \(\delta\) 155.5, 153.3, 81.9, 53.1, 47.3 (\(\text{I}_J = 357, 342\), 35.2, 28.9 (\(\text{I}_J = 19\)), 27.8, 27.3 (\(\text{I}_J = 50\)), 20.7, 13.7, 13.5, 10.0 (\(\text{I}_J = 326, 311\)); MS, FAB \(m/z\) (relative intensity) 464 (M\(^+\)-C\(_4\)H\(_9\), 45), 408
4.3.12 t-Butyl methyl N-((1-tributylstannylpentyl)iminodicarboxylate 115d

This compound was prepared from 116d according to the general procedure described in section 4.3.8 with a reaction time of 44 h in 92% yield: IR (neat) 2915, 1743, 1692, 1449, 1342, 1151, 1073 cm⁻¹; ¹H NMR (250 MHz) δ 3.90 (t, 1 H, J = 8.0, CHN), 3.78 (s, 3 H, CO₂CH₃), 2.11-1.57 (m, 2 H, CH₃(CH₂)₂CH₂CHN), 1.50 (s, 9 H, CO₂C(CH₃)₃), 1.57-1.18 (m, 16 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN), 0.92-0.71 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₃CHN); ¹³C NMR (63 MHz) δ 155.7, 153.4, 82.2, 53.4, 47.7, 32.7, 29.9 (²J = 19), 27.9, 17.4 (³J = 55), 22.4, 13.9, 13.7, 10.2 (¹J = 318); MS, FAB m/z (relative intensity) 478 (M⁺- C₄H₉, 36), 422 (62), 378 (70), 276 (100), 235 (70). Anal. Calcd for C₂₄H₄₉NO₄Sn: C, 53.94; H, 9.24; N, 2.62. Found: C, 53.88; H, 9.12 N, 2.67.
4.3.13 \( t \)-Butyl methyl \( N-(1\text{-tributylstannylhexyl}) \text{iminodicarbonate 115e} \)

\[
\text{MeO} \quad \begin{array}{c}
\text{N} \\
\text{Or-Bu}
\end{array}
\quad n-C_{6}H_{11} \quad \begin{array}{c}
\text{SnBu}_{3}
\end{array}
\]

This compound was prepared from \( \text{116e} \) according to the general procedure described in section 4.3.8 with a reaction time of 60 h in 78% yield: IR (neat) 2913, 1741, 1693, 1449, 1368, 1256, 1152 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \( \delta \) 3.86 (t, 1 H, \( J = 8.0 \), CHN), 3.78 (s, 3 H, CO\(_2\)CH\(_3\)), 1.55 (m, 2 H, CH\(_3\)(CH\(_2\))\(_2\)CH\(_2\)CHN), 1.49 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.47-1.17 (m, 18 H, SnCH\(_3\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_2\)CH\(_2\)CHN), 0.91-0.77 (m, 18 H, SnCH\(_3\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_2\)CH\(_2\)CHN); \(^{13}\)C NMR (63 MHz) \( \delta \) 155.7, 153.4, 82.3, 53.4, 47.8, 33.0, 31.6, 29.1 (\(^2\)J = 19), 28.0, 27.5, *27.4, 22.6, 14.0, 13.6, 10.2 (\(^1\)J = 326); MS, FAB \( m/z \) (relative intensity) 492 (M\(^+\)-C\(_4\)H\(_9\), 66), 436 (70), 392 (74), 276 (100), 235 (59).


4.3.14 \( t \)-Butyl methyl \( N-(2\text{-methyl-1\text{-tributylstannylpropyl}) iminodicarbonate 115f} \)

\[
\text{MeO} \quad \begin{array}{c}
\text{N} \\
\text{Or-Bu}
\end{array}
\quad i\text{-Pr} \quad \begin{array}{c}
\text{SnBu}_{3}
\end{array}
\]

This compound was prepared from \( \text{116f} \) according to general procedure described in section 4.3.8 with a reaction time of 120 h in 86% yield: IR (neat) 2942, 1743, 1692,
14448, 1344, 1246, 1153 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 3.77 (s, 3 H, CO\(_2\)CH\(_3\)), 3.69 (d, 0.2 H, J = 11, CHN), 3.60 (d, 0.8 H, J = 11, CHN), 2.0 (m, 1 H, (CH\(_3\))\(_2\)C), 1.56-1.10 (m, 12 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 1.48 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 0.97-0.63 (m, 21 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and (CH\(_3\))\(_3\)CH), \(^{13}\)C NMR (63 MHz) \(\delta\) 155.5, 153.3, 81.8, 55.2, 51.3, 30.0, 28.9, (\(^2\)J = 19), 27.7, *27.6, 27.3, 21.3, 20.2, 13.4, 10.4 (\(^1\)J = 324, 310); MS, FAB m/z (relative intensity) 462 (M\(^+\) - C\(_4\)H\(_9\), 70), 408 (82), 364 (100), 323 (60), 291(68), 276 (85), 235 (39). Anal. Caled for C\(_{23}\)H\(_{46}\)N\(_2\)O\(_4\)Sn: C, 53.3; H, 9.11; N, 2.69. Found: C, 53.53; H, 8.97; N, 2.65.

4.3.15 t-Butyl methyl N-(1-cyclohexyl-1-tributylstannylmethyl)iminodicarbonate 115g

This compound was prepared according to the method of Park\(^1\) with a reaction time of 42 h in 21% yield: IR (neat) 2914, 1742, 1691, 1446, 1346, 1265, 1233, 1150 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 3.78 (s, 3 H, CO\(_2\)CH\(_3\)), 3.7 (d, 0.75 H, J = 11, CHN), 1.85 (d, 0.25 H, J = 11, CHN), 1.5 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.88-1.10 (m, 23 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and c-C\(_6\)H\(_{11}\)), 0.98-0.73 (m, 15 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)); \(^{13}\)C NMR (63 MHz) \(\delta\) 155.7, 153.5, 82.1, *54.2, 53.3, 39.5, 32.2, 31.1, 29.0 (\(^2\)J = 19), 27.9, 27.4, 26.9, 26.5, 25.8, 13.1, 10.5 (\(^1\)J = 324, 309); MS, FAB m/z (relative intensity) 504 (M\(^+\)-C\(_4\)H\(_9\), 84),
446 (100), 403 (64), 362 (56), 289 (65), 276 (87), 133 (63). Anal. Calcd for C_{26}H_{51}NO_4Sn: C, 55.73; H, 9.17; N, 2.50. Found: C, 55.58; H, 8.96; N, 2.44.

4.3.16 General procedure for the preparation of t-butyl N-hydroxymethyl tributylstannyl carbamates

To a cooled (0 °C) 0.075 M solution of the iminodicarbonate 115 in Et_2O was added lithium aluminum hydride (0.75 equiv). The solution was stirred for 10 min, quenched with Na_2SO_4.10H_2O and stirred at room temperature for 10 min. The mixture was filtered to remove aluminum salts and concentrated in vacuo. The resulting oils were purified by flash chromatography (30 g silica/g of substrate: 5:1 hexane/Et_2O) to give the N-hydroxymethyl carbamates as colorless oils. \(^1\)H NMR spectra were recorded using DMSO-d_6 as solvent and DMSO-d_6 (δ 2.49) was used as the internal standard.

4.3.17 t-Butyl N-hydroxymethyl-N-(1-tributylstannylethyl)carbamate 117a

![Chemical structure](image)

This compound was prepared from 115a according to the general procedure described in section 4.3.16 in 83% yield: IR (neat) 3413, 2916, 1676, 1432, 1367, 1167 cm\(^{-1}\); \(^1\)H NMR (200 MHz) δ 5.60 (t, 1 H, J = 6.9, OH), 4.63 (m, 2 H, CH_2OH), 3.0 (q, 1 H, J = 7.3, CHN), 1.38 (s, 9 H, CO_2C(CH_3)_3), 1.70-1.0 (m, 15 H, SnCH_2(CH_2)_2CH_2 and
(CH$_3$)$_2$N), 0.87-0.62 (m, 15 H, SnCH$_3$(CH$_2$)$_2$CH$_3$); $^{13}$C NMR (63 MHz) δ 156.1, *154.7, 79.9, 73.3, *71.7, 42.8, *41.3, 29.1 ($^2$J = 20), 28.3, 27.4 ($^3$J = 56), *19.5, 18.9, 13.6, 10.0 ($^1$J = 324 Hz), *9.3; MS, FAB m/z (relative intensity) 448 (M$^+$-OH, 10), 408 (M$^+$-C$_4$H$_9$, 46), 352 (63), 290 (100), 135 (26), 177 (49). Anal. Calcd for C$_{20}$H$_{43}$N$_3$O$_3$Sn: C, 51.74; H, 9.34; N, 3.02. Found: C, 52.00; H, 9.12; N, 3.13.

4.3.18 t-Butyl N-hydroxymethyl-N-(t-tributylstannylpropyl)carbamate 117b

![Chemical Structure]

This compound was prepared from 115b according to the general procedure described in section 4.3.16 in 77% yield: IR (neat) 3345, 2918, 1693, 1595, 1504, 1165 cm$^{-1}$; $^1$H NMR (200 MHz) δ 5.62 (t, 1 H, J = 6.8, OH), 4.72 (m, 1H, CH$_2$OH), 4.58 (m, 1 H, CH$_2$OH), 2.92 (t, 1 H, J = 7.6, CHN), 1.76 (m, 2 H, CH$_3$CH$_2$CHN), 1.4 (s, 9 H, CO$_2$C(CH$_3$)$_3$), 1.54-1.12 (m, 12 H, SnCH$_2$(CH$_2$)$_2$CH$_3$), 0.93-0.65 (m, 18 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and CH$_3$CH$_2$CHN); $^{13}$C NMR (50 MHz) δ 154.8, 80.2, *79.9, *74.2, 72.4, 51.2, 39.3, 29.1 ($^2$J = 20), 28.9, 27.4 ($^3$J = 56), 26.7, *26.4, 13.6, *12.8, *10.3, 9.7; MS, FAB m/z (relative intensity) 462 (M$^+$-OH, 3), 422 (M$^+$-C$_4$H$_9$, 19), 366 (20), 336 (29), 291 (40), 57 (100). Anal. Calcd for C$_{21}$H$_{45}$N$_3$O$_3$Sn: C, 52.74; H, 9.48; N, 2.93. Found: C, 52.55; H, 9.23; N, 2.93.
This compound was prepared from 115c according to the general procedure described in section 4.3.16 in 79% yield: IR (neat) 3418, 2920, 1674, 1429, 1367, 1166, 1023; cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 5.80 (m, 0.15 H, OH), 5.63 (t, 0.85 H, J = 6.9, OH), 4.70 (m, 1 H, CH$_2$OH), 4.50 (m, 1 H, CH$_3$OH), 3.09 (t, 1 H, J = 7.7, CHN), 1.70-1.17 (m, 16 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and CH$_3$(CH$_2$)$_2$CHN), 1.37 (s, 9 H, CO$_2$C(CH$_3$)$_3$), 0.90-0.65 (m, 18 H, SnCH$_2$(CH$_2$)$_2$CH$_3$ and CH$_3$(CH$_2$)$_2$CHN); $^{13}$C NMR (50 MHz) $\delta$ 156.4, *154.8, *80.1, 79.9, 74.1, *72.2, 48.9, *46.3, 35.7, 29.1 ($^2$J = 19), 28.4, 27.5 ($^3$J = 50), *27.4, 21.3, *20.8, *13.5, 13.6, 10.2 ($^1$J = 319). *9.4; MS, FAB $m/z$ (relative intensity) 476 (M$^+$ - OH, 9), 436 (M$^+$ - C$_4$H$_9$, 30), 380 (35), 318 (100), 291 (30), 235 (38). Anal. Calcd for C$_{22}$H$_{47}$NO$_3$Sn: C, 53.67; H, 9.62; N, 2.84. Found: C, 53.70; H, 9.49; N, 2.85.

This compound was prepared from 115d according to the general procedure described in section 4.3.16 in 79% yield: IR (neat) 3418, 2920, 1674, 1430, 1367, 1249,
1167. 1021; cm⁻¹; ¹H NMR (200 MHz) δ 5.68 (m. 0.15 H, OH), 5.60 (t, 0.85 H, J = 6.9, OH), 4.60 (m, 1 H, CH₂OH), 4.51 (m, 1 H, CH₃OH), 2.97 (t, 1 H, J = 7.7, CHN), 1.68 (m, 2 H, CH₃(CH₂)₂CH₂CHN), 1.35 (s, 9 H, CO₂C(CH₃)₃), 1.56-1.12 (m, 16 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN), 0.86-0.65 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN); ¹³C NMR (50 MHz) δ *156.4, 154.8, *79.8, 79.6, 74.0, 49.1, *46.6, 33.0, *32.8, 30.4, *29.2, 29.1, 38.4, 27.5 (3J = 57), 22.6, *22.5, *13.9, 13.6, 10.3 (1J = 312), *9.43; MS, FAB m/z (relative intensity) 490 (M⁺-OH, 8), 450 (M⁺- C₄H₉, 15), 434 (30), 378(40), 332 (100), 235 (42). Anal. Calcd for C₂₃H₄₉N₀₃Sn: C 54.56; H, 9.76; N, 2.77. Found: C, 54.70; H, 9.77; N, 2.84.

4.3.21  t-Butyl N-hydroxymethyl-N-(1-tributylstannylhexyl)carbamate 117e

This compound was prepared from 115e according to the general procedure described in section 4.3.16 in 79% yield: IR (neat) 3402, 2911, 1679, 1423, 1259, 1160, 1025 cm⁻¹; ¹H NMR (200 MHz) δ 5.58 (m, 1 H, OH), 4.68 (m, 1 H, CH₂OH), 4.51 (m, 1 H, CH₃OH), 2.97 (t, 1 H, J = 7.8, CHN), 1.60 (m, 2 H, CH₃(CH₂)₃CH₂CHN), 1.37 (s, 9 H, CO₂C(CH₃)₃), 1.50-1.10 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN), 0.86-0.57 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN); ¹³C NMR (63 MHz) δ 156.3, *154.8, *80.0, 79.7, 71.9, 49.2, 33.3, 31.6, *31.3, 29.1 (2J = 19), 28.4, 27.5 (3J =
56), *27.4, 22.6, 13.9, 13.6, 10.2 (^1J = 311), 9.4; MS, FAB m/z (relative intensity) 504 (M^+-OH, 8), 464 (M^+-C_4H_9, 42), 408 (41), 364 (100), 291 (29), 232 (28). Anal. Calcd for C_{24}H_{51}NO_3Sn: C, 55.39; H, 9.88; N, 2.69. Found: C, 55.47; H, 9.77; N, 2.74.

4.3.22 t-Butyl N-hydroxymethyl-N-(2-methyl-1-tributylstannylpropyl)carbamate 117f

![Chemical Structure]

This compound was prepared from 115f according to the general procedure described in section 4.3.16 in 77% yield: IR (neat) 3427, 2923, 1671, 1446, 1367, 1163, 1027 cm^{-1}; ^1H NMR (200 MHz) δ 5.65 (t, 0.25 H, J = 7.0, OH), 5.55 (t, 0.75 H, J = 7.0, OH), 4.82 (dd, 1 H, J = 7.0, 10.3, CH_2OH), 4.43 (dd, 1 H, J = 7.0, 10.3, CH_3OH), 2.67 (d, 1 H, J = 9.8, J_{Sn-H} = 49 Hz, CHN), 2.15 (m, 1 H, (CH_3)_2CH), 1.37 (s, 9 H, CO_2C(CH_3)_3), 1.55-1.27 (m, 12 H, SnCH_2(CH_3)_2CH_3), 0.98-0.59 (m, 21 H, SnCH_2(CH_3)_2CH_3 and (CH_3)_2CH); ^13C NMR (63 MHz) δ 155.1, 88.0, 75.5, 58.3 (^1J = 347), 31.1, 28.6, 28.1, 27.6 (^3J = 56), 21.72, 21.66, 13.7. *10.9 (^1J = 319, 304), 10.23 (^1J = 308, 294); MS, FAB m/z (relative intensity) 476 (M^+-OH, 10), 436 (M^+-C_4H_9, 52), 378 (50), 318 (100), 291 (36), 235 (32). Anal. Calcd for C_{22}H_{47}NO_3Sn: C, 53.67; H, 9.62; N, 2.84. Found: C, 53.53; H, 9.46; 2.84.
4.3.23 t-Butyl N-hydroxyethyl-N-(1-cyclohexyl-1-tributylstannylmethyl)carbamate

\[ \text{HO} \text{N} \text{O} \text{Or-Bu} \]

\[ \text{c-C}_6\text{H}_{11} \text{SnBu}_3 \]

This compound was prepared from 115g according to the general procedure described in section 4.3.16 in 80% yield: IR (neat) 3425, 2925, 1665, 1366, 1174 cm\(^{-1}\);

\(^1\)H NMR (200 MHz) \( \delta \) 5.67 (t, 0.24 H, J = 7.0, OH). 5.58 (t, 0.76 H, J = 7.0, OH), 4.78 (dd, 1 H, J = 7.0, 10.0, CH\(_2\)OH), 4.37 (dd, 1 H, J = 7.0, 10.0, CH\(_2\)OH), 2.76 (d, 0.8 H, J = 10.0, CHN), 1.81 (d, 0.2 H, J = 10.0, CHN), 1.66-1.10 (m, 23 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and c-C\(_6\)H\(_{11}\)), 1.37 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)). 0.87-0.65 (m, 15 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)): \(^{13}\)C NMR (63 MHz) \( \delta \) *159.0, 155.5, 80.0, 75.5, 57.2, 40.3, 32.4, 32.3, 29.1 (*J = 17). 28.5. 27.5 (*J = 58). *27.4, 26.7, *26.2, 26.1, 13.7, *13.6, 10.8, 10.1 (*J = 310). 290); MS, FAB m/z (relative intensity) 416 (M\(^+\)-OH, 4), 476 (M\(^+\)-C\(_4\)H\(_9\), 28), 420 (32), 358 (80), 291 (28), 177 (40), 124 (100). Anal. Calcd for C\(_{25}\)H\(_{31}\)NO\(_3\)Sn: C, 56.40; H, 9.66; N, 2.63. Found: C, 56.23; H, 9.41; N, 2.66.

4.3.24 General procedure for the preparation of t-Butyl N-t-butylthiomethyl tributylstannyl car bamates

To a 0.07 M solution of the N-hydroxymethyl carbamate 117 in hexane was added Et\(_3\)N (0.95 equiv). The solution was cooled (-20 °C) and MsCl (25 equiv) was slowly added. The resulting mixture was stirred for 15 min and 1.3 M solution of t-butylthiol (25 equiv) in hexane was added. The mixture was stirred at room temperature for 2 h. diluted
with hexane and washed several times with saturated NaHCO₃. The organic solution was
dried (MgSO₄), filtered through Celite and concentrated \textit{in vacuo}. The resulting oils were
purified by flash chromatography (40 g silica/g of substrate: 40:1 hexane/Et₂O) to give
the products as colorless oils.

4.3.25 \textit{t-Butyl N-t-butyliothiomethyl-N-(1-tributylstannylethyl)carbamate 118a}

![Chemical Structure](image_url)

This compound was prepared from 117a according to the general procedure
described in section 4.3.24 in 77% yield: IR (neat) 2921, 1679, 1443, 1237, 1161 cm⁻¹;

$^1$H NMR (250 MHz) \( \delta \) 4.50 (ABq, 2 H, \( \Delta \delta = 0.14 \), \( J = 13.7 \)), 2.97 (q, 1 H, \( J = 7.3 \)), 1.46 (s, 9 H, CO₂C(CH₃)₃), 1.36 (s, 9 H, S(CH₃)₃), 1.55-1.10 (m, 15 H, SnCH₂(CH₂)₂CH₃ and CH₃CHN), 0.68-0.92 (m, 15 H, SnCH₂(CH₂)₂CH₃); \(^{13}\)C NMR (63 MHz) \( \delta \) 154.4, 79.7, 48.2, 42.8, 42.1, 32.3, *31.5, 29.2 (\( ^2J = 19 \)), *28.6, 28.4, 27.6 (\( ^3J = 57 \)), 17.6, 13.7, 10.4 (\( ^1J = 318 \)); MS, FAB \( m/z \) (relative intensity) 480 (M⁺-C₄H₉, 34), 380 (28), 290 (100), 235 (10). Anal. Calcd for C₂₄H₅₁NO₂SSn: C, 53.74; H, 9.58; N, 2.61. Found: C, 53.97; H, 9.58; N, 2.69.
4.3.26 t-Butyl N-t-butylthiomethyl-N-(t-butyldistyannylpropyl)carbamate 118b

This compound was prepared from 117b according to the general procedure described in section 4.3.24 in 89% yield: IR (neat) 1680, 1450, 1238, 1163 cm\(^{-1}\); \(^1\)H NMR (200 MHz) \(\delta\) 4.49 (ABq, 2 H, \(\Delta\delta = 0.26, J = 13.6, \text{CH}_2\text{S}\)), 3.16 (m, 0.25 H, CHN), 2.82 (dd, 0.75 H, \(J = 7.5, 7.0, \text{CHN}\)), 1.84 (m, 2 H, \(\text{CH}_3\text{CH}_2\text{CHN}\)), 1.50-1.20 (m, 12 H, \(\text{SnCH}_2\text{(CH}_2)_2\text{CH}_3\)), 1.46 (s, 9 H, \(\text{CO}_2\text{C(CH}_3)_3\)), 1.36 (s, 9 H, \(\text{SC(CH}_3)_3\)), 0.9-0.7 (m, 18 H, \(\text{SnCH}_2\text{(CH}_2)_2\text{CH}_3\) and \(\text{CH}_3\text{CH}_2\text{CHN}\)); \(^13\)C NMR (50 MHz) \(\delta\) 154.6, 79.7, 50.8, 49.2, 42.7, 31.3, 29.2 (\(2J = 19\)), 28.5, 27.6 (\(3J = 57\)), 25.2, 13.7, 12.7, 10.74 (\(1J = 310, 322\)).

*10.0: MS, FAB \(m/\zeta\) (relative intensity) 494 (\(M^+\text{-C}_4\text{H}_9\), 81), 394 (40), 304 (73), 57 (100). Anal. Calcd for \(\text{C}_{25}\text{H}_{53}\text{NO}_2\text{SSn}\): C, 54.55; H, 9.70; N, 2.54. Found: C, 54.44; H, 9.57; N, 2.55.

4.3.27 t-Butyl N-t-butylthiomethyl-N-(t-butyldistyannylbutyl)carbamate 118c

This compound was prepared from 117c according to the general procedure described in section 4.3.24 in 87% yield: IR (neat): 2916, 1680, 1450, 1365, 1237, 1164
cm⁻¹; ¹H NMR (200 MHz) δ 4.51 (ABq, 0.6 H, Δδ = 0.14, J = 13.5, CH₂S), 4.50 (ABq, 1.4 H, Δδ = 0.24, J = 13.5, CH₂S), 2.91 (dd, 1 H, J = 7.9, 7.6, CHN), 1.84-1.65 (m, 2 H, CH₃CH₂CH₂CHN), 1.61-1.10 (m, 14 H, SnCH₂(CH₃)₂CH₃ and CH₃CH₂CH₂CHN), 1.46 (s, 9 H, CO₂C(CH₃)₃), 1.36 (s, 9 H, SC(CH₃)₃). 0.95-0.70 (m, 18 H, SnCH₂(CH₂)₂CH₃, and CH₃(CH₂)₂); ¹³C NMR (63 MHz) δ 154.6, 79.6, 49.1, 48.7, 42.6, 34.7, 31.3, 29.2 (²J = 18), 28.4, 27.5 (³J = 57), 21.3, 14.1, 13.7, 10.7 (¹J = 322, 309); MS, FAB m/z (relative intensity) 508 (M⁺-C₄H₉, 17), 408 (12), 364 (13), 318 (100), 291 (18). Anal. Calcd for C₂₆H₅₅NO₂SSn: C, 55.33; H, 9.82; N, 2.48. Found: C, 55.24; H, 9.78; N, 2.40.

4.3.28 ⁴-Butyl N-⁴-butylthiomethyl-N-(¹-tributylstannylpentyl)carbamate 118d

This compound was prepared from 117d according to the general procedure described in section 4.3.24 in 88% yield: IR (neat): 2917, 1680, 1444, 1366, 1236, 1164 cm⁻¹; ¹H NMR (200 MHz) δ 4.51 (ABq, 0.5 H, Δδ = 0.16, J = 13.5, SCH₂), 4.50 (ABq, 1.5 H, Δδ = 0.27, J = 13.5, SCH₂), 2.89 (t, 1 H, J = 7.8, CHN), 1.8 (q, 2 H, J = 7.7, CH₃(CH₂)₂CH₂CHN), 1.58-1.0 (m, 16 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN), 1.46 (s, 9 H, CO₂C(CH₃)₃), 1.35 (s, 9 H, SC(CH₃)₃). 0.99-0.73 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₂CH₂CHN); ¹³C NMR (63 MHz) δ 154.5, 79.6, 49.1, 48.9, 42.7, 32.0, 31.3, *30.3, 29.2 (²J = 19), 28.4, 27.5 (³J = 57), 22.7, 14.1, 13.7, 10.0
(\textsuperscript{1}J = 322): MS, FAB m/z (relative intensity) 522 (M\textsuperscript{+}-C\textsubscript{4}H\textsubscript{9}, 20), 422 (12), 332 (100), 291 (12). Anal. Calcd for C\textsubscript{27}H\textsubscript{57}NO\textsubscript{2}SSn: C, 56.06; H, 9.93; N, 2.41. Found: C, 55.90; H, 9.78; N, 2.40.

4.3.29 \textit{t-Butyl N-t-butylthiomethyl-N-(\textit{t}-tributylstannylhexyl)carbamate 118e}  

\begin{center}
\begin{tikzpicture}
\draw[thick] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\draw[thick] (0.5,0.5) -- (0.5,1) -- (0,1) -- (0,0.5) -- cycle;
\draw[thick] (0,0.5) -- (1,0.5);
\draw[thick] (0.5,0) -- (0.5,1);
\draw[thick] (0.5,0.5) -- (0.5,1);
\end{tikzpicture}
\end{center}

This compound was prepared from 117e according to the general procedure described in section 4.3.24 in 81\% yield: IR (neat) 2957, 2933, 1677, 1451, 1391, 1163 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (250 MHz) \(\delta\) 4.48 (ABq, 2 H, \(\Delta\delta = 0.48, J = 13.5, \text{SCH}_2\)), 2.89 (t, 1 H, J = 8.0, CHN), 1.8 (m, 2 H, CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{2}CH\textsubscript{3}CHN), 1.46 (s, 9 H, CO\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}), 1.35 (s, 9 H, SC(CH\textsubscript{3})\textsubscript{3}), 1.5-1.2 (m, 18 H, SnCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}CH\textsubscript{3} and CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{2}CHN). \textsuperscript{13}C NMR (63 MHz) \(\delta\) 154.5, 79.7, 49.2, 49.0, 42.7, 32.3, 32.8, 31.3, 29.2 (\textsuperscript{2}J = 19), 28.4, 27.6 (\textsuperscript{3}J = 57), 22.6, 14.0, 13.7, 10.7 (\textsuperscript{1}J = 322, 307). 10.0; MS, FAB m/z (relative intensity) 536 (M\textsuperscript{+}-C\textsubscript{4}H\textsubscript{9}, 48), 436 (18), 390 (16), 346 (100), 291 (16), 233 (20). Anal. Calcd for C\textsubscript{28}H\textsubscript{59}NO\textsubscript{2}SSn: C, 56.76; H, 10.04; N, 2.36. Found: C, 56.80; H, 9.82; N, 2.46.
4.3.30 t-Butyl N-t-butyliothiomethy1-N-(2-methyl-1-tributylstannylpropyl)carbamate 118f

This compound was prepared from 117f according to the general procedure described in section 4.3.24 in 87% yield: IR (neat) 2913, 1681, 1424, 1342, 1289, 1236, 1165 cm\(^{-1}\); \(^1\)H NMR (200 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.02 (d, 1 H, J = 12.9, SCH\(_2\)), 4.1 (d, 1 H, J = 12.9, SCH\(_2\)), 2.76 (d, 1 H, J = 9.2, CHN), 2.5 (m, 1 H, (CH\(_3\))\(_2\)CH), 1.8 (m, 12 H, SnCH\(_2\)(CH\(_2\))CH\(_3\)), 1.42 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.24 (s, 9 H, SC(CH\(_3\))\(_3\)), 1.49-0.49 (m, 21 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and (CH\(_3\))\(_2\)CH); \(^{13}\)C NMR (63 MHz) \(\delta\) 154.8, 79.6, 57.4, 50.3, 42.5, 31.3, 31.2, 29.3 (\(^2\)J = 19), 28.4, 27.6 (\(^3\)J = 59), *21.9, *21.7, 21.6, 21.4, *21.1, 13.7, 11.3 (\(^1\)J = 321); MS, FAB \(m/z\) (relative intensity) 508 (M\(^+\)-C\(_4\)H\(_9\), 52), 408 (18), 318 (100), 290 (13), 235 (14). Anal. Calcld for C\(_{26}\)H\(_{55}\)NO\(_2\)SSn: C, 55.33; H, 9.82; N, 2.48. Found: C, 55.19; H, 9.77; N, 2.39.

4.3.31 t-Butyl N-t-butyliothiomethy1-N-(1-cyclohexyl-1-tributylstannylmethyl)carbamate

118g
This compound was prepared from 117g according to the general procedure described in section 4.3.24 in 83% yield: IR (neat) 2911, 1681, 1451, 1365, 1237, 1164 cm⁻¹: ¹H NMR (200 MHz, C₆D₆) δ 5.04 (d, 1 H, J = 12.9, SCH₂), 4.10 (d, 1 H, J = 12.9, CH₂S), 2.85 (d, 1 H, J = 9.6, J₁ = 49. CHN), 2.3 (m, 1 H, c-CHHN), 1.84 (m, 16 H, c-CH₂(CH₂)₃CH₂ and SnCH₂(CH₂)₂CH₃), 1.43 (s, 9 H, CO₂C(CH₃)₃), 1.26 (s, 9 H, SC(CH₃)₃), 1.21-0.94 (m, 21 H, c-CHCH₂(CH₂)₃CH₂ and SnCH₂(CH₂)₂CH₃); ¹H NMR (63 MHz) δ 154.8, 79.6, 56.4, 50.4, 42.4, *40.1, 32.4, *32.3, 31.3, 29.2, *29.1, 28.4, 27.6 (²J = 59), 26.8, 26.4, 26.2, 13.7, 11.2 (¹J = 320, 306); MS. FAB m/z (relative intensity) 548 (M⁺-C₄H₉, 12), 404 (8), 358 (70), 291 (8), 214 (9), 177 (18), 124 (100). Anal. Calcd for C₃₉H₅₉NO₂SSn: C, 57.62; H, 9.84; N, 2.32. Found: C, 57.95; H, 9.87, 2.38.

4.3.32 General procedure for the preparation of oxazolidinones

To a cooled (-78 °C) 0.15 M solution of the α-aminoorganostannane 118 was added n-BuLi (1.5 equiv) slowly and the solution was stirred for 15 min. The appropriate aldehyde (2.0 equiv) was added and the mixture was stirred for 15 min and quenched at -78 °C with saturated ammonium chloride. The mixture was diluted with Et₂O, washed with water, dried (MgSO₄), filtered through Celite and concentrated in vacuo to give β-aminoalcohols which were used without purification in most cases.

To a 0.1 M solution of β-aminoalcohol in THF was added NaH (2 equiv), the mixture was stirred for 30 min-1 h. quenched with water, diluted with Et₂O and washed with water. The organic layer was dried (MgSO₄), filtered through Celite and concentrated in vacuo. The resulting oils were purified by flash chromatography (100 g
silica/g substrate: 5:1 hexane/Et₂O) to give the oxazolidinones as colorless oils or white solids.

For the systems where R = n-butyl or n-pentyl, it was easier to separate the two diastereomers as the protected β-aminoalcohols, that is before cyclization. However the syn diastereomer was still contaminated with 1-phenyl-1-butanol 121 which was then removed after cyclization.

4.3.33 3-t-Butylthiomethyl-4-methyl-5-phenyl-2-oxazolidinone 122/123a

This mixture of diastereomers was prepared from 118a according to general procedure described in section 4.3.32 in 90% overall yield.

(4R*, 5S*)-122a was obtained in 65% yield: mp 98-99 °C; IR (KBr) 2942, 1734, 1404, 1294, 1244, 1173 cm⁻¹; ¹H NMR (250 MHz) δ 7.43–7.26 (m, 5 H, ArH), 5.58 (d, 1 H, J = 8.4, CHO), 5.07 (d, 1 H, J = 14.7, CH₂S), 4.4 (quintet, 1 H, J = 6.6, CHN), 4.01 (d, 1 H, J = 14.7, CH₂S), 1.42 (s, 9 H, SC(CH₃)₃), 0.78 (d, 3 H, J = 6.6, CH₃CH); ¹³C NMR (63 MHz) δ 156.4, 134.5, 128.4, 126, 78.6, 53.0, 43.4, 42.1, 31.2, 13.9; MS, EI m/z (relative intensity) 279 (M⁺, 1), 222 (M⁺-C₄H₉, 13), 190 (44), 146 (94), 105 (100), 57 (22). Anal. Calcd for C₁₅H₂₁NO₂S: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.67; H, 7.72; N, 5.02.
(4R*, 5R*)-123a was obtained in 25% yield: mp 60-62 °C; IR (KBr) 2964, 1750, 1460, 1411, 1274, 1227, 1175 cm⁻¹; ¹H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.06 (d, 1 H, J = 14.9, CH₂S), 4.94 (d, 1 H, J = 8.1, CHO), 4.1 (d, 1 H, J = 14.9, CH₂S), 3.98 (quintet, 1 H, J = 6.2, CHN), 1.37 (m, 12 H, CH₃CH and SC(CH₃)₂); ¹³C NMR (63 MHz) δ 156.3, 137.4, 128.9, 128.8, 125.9, 82.6, 57.3, 43.3, 41.9, 31.1, 16.8; MS, EI m/z (relative intensity) 279 (M⁺, 0.8), 222 (M⁺-C₄H₉, 13), 190 (31), 146 (100), 105 (85), 91 (18), 57 (18). Anal. Calcd for C₁₅H₂₁NO₂S: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.47; H, 7.67; N, 4.88.

4.3.34 3-t-Butylthiomethyl-4-ethyl-5-phenyl-2-oxazolidinone 122/123b

This mixture of diastereomers was prepared from 118b according to the general procedure described in section 4.3.32 in 77% overall yield.

(4R*, 5S*)-122b was obtained in 51% yield: mp 43-45 °C; IR (KBr) 2942, 1744, 1417, 1283, 1226, 1172 cm⁻¹; ¹H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.56 (d, 1 H, J = 8.2, CHO), 5.12 (d, 1 H, J = 14.8, CH₂S), 4.26 (dt, 1 H, J = 3.8, 8.2, CHN), 4.06 (d, 1 H, J = 14.8, CH₂S), 1.42 (s, 9 H, SC(CH₃)₃), 1.47-1.24 (m, 2 H, CH₃CH₂), 0.55 (t, 3 H, J = 7.5, CH₃CH₂), ¹³C NMR (63 MHz) δ 156.9, 134.7, 128.6, 128.4, 126.5, 78.9, 58.3, ...
43.5, 42.6, 31.2, 20.6, 9.0; MS. EI m/z (relative intensity) 293 (M+ 0.7), 236 (M+ - C4H9, 11), 204 (50), 160 (89), 105 (100), 57 (32). Anal. Calcd for C16H23NO2S: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.54; H, 7.78; N, 4.88.

(4R*, 5R*)-123b was obtained in 26% yield: mp 45-49 °C; IR (KBr) 2929, 1742, 1413, 1259, 1222, 1170 cm⁻¹; 1H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.12 (d, 1 H, J = 6.4, CHO), 5.10 (d, 1 H, J = 14.9, CH₂S), 4.04 (d, 1 H, J = 14.9, CH₂S), 3.90 (dt, 1 H, J = 3.1, 6.4, CHN), 1.82-1.66 (m, 2 H, CH₃CH₂), 1.35 (s, 9 H, SC(CH₃)₃), 0.98 (t, 3 H, J = 7.5, CH₃CH₂); 13C NMR (63 MHz) δ 156.3, 138.6, 128.7, 125.9, 79.2, 61.4, 43.4, 41.9, 31.1, 23.2, 7.8; MS, EI m/z (relative intensity) 293 (M+ 0.8), 236 (M+ - C4H9, 15), 204 (37), 160 (100), 105 (76), 57 (18). Anal. Calcd for C16H23NO2S: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.69; H, 7.82; N, 4.88.

4.3.35 3-t-Butylthiomethyl-5-phenyl-4-propyl-2-oxazolidinone 122/123c

This mixture of diastereomers was prepared from 118c according to the general procedure described in section 4.3.32 in 86% overall yield.

(4R*, 5S*)-122c was obtained in 57% yield: mp 45-47 °C; IR (KBr) 2924, 1733, 1457, 1418, 1366, 1226, 1175 cm⁻¹; 1H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.45 (d, 1
H, J = 8.2, CHO), 5.10 (d, 1 H, J = 14.8, CH₂S). 4.30 (dt, 1 H, J = 8.2, 3.7, CHN), 4.10 (d, 1 H, J = 14.8, CH₂S), 1.42 (s, 9 H, SC(CH₃)₃), 1.37-1.00 (m, 2 H, CH₃CH₂CH₂), 1.2-0.8 (m, 2 H, CH₃CH₂CH₂), 0.64 (t, 3 H, J = 7.0, CH₃CH₂CH₂); ¹³C NMR (63 MHz) δ 156.7, 134.7, 128.5, 128.2, 126.4, 78.9, 56.9, 43.3, 42.5, 31.1, 29.7, 18.0, 13.8; MS, EI m/z (relative intensity) 307 (M⁺, 0.4), 250 (M⁺-C₄H₉, 12), 218 (45), 174 (66), 132 (81), 91 (100), 57 (50). Anal. Calcd for C₁₇H₂₅N₀₂S: C, 66.42; H, 8.20; N, 4.55. Found: C, 66.67; H, 8.23; N, 4.67.

(4R*, 5R*)-123c was obtained in 29% yield: mp 63-66 °C; IR (KBr) 2931, 1741, 1432, 1309, 1227, 1111 cm⁻¹; ¹H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.10 (d, 1 H, J = 6.1, CHO), 5.10 (d, 1 H, J = 14.8, CH₂S), 4.10 (d, 1 H, J = 14.8, CH₂S), 4.0 (m, 1 H, CHN), 1.84-1.71 (m, 2 H, CH₃CH₂CH₂), 1.68-1.40 (m, 2 H, CH₃CH₂CH₂), 1.34 (s, 9 H, SC(CH₃)₃), 0.96 (t, 3 H, J = 7.2, CH₃CH₂CH₂); ¹³C NMR (63 MHz) δ 156.2, 138.5, 128.7, 126.0, 79.9, 60.4, 43.3, 41.9, 33.0, 31.1, 17.2, 14.0; MS, EI m/z (relative intensity) 307 (M⁺, 0.4), 250 (M⁺-C₄H₉, 16), 218 (49), 174 (95), 132 (100), 91 (87), 57 (51). Anal. Calcd for C₁₇H₂₅N₀₂S: C, 66.42; H, 8.20; N, 4.55. Found: C, 66.54; H, 8.25; N, 4.56.

4.3.36 4-Butyl-3-t-butyliothiomethyl-5-phenyl-2-oxazolidinone 122/123d
This mixture of diastereomers was prepared from 118d according to the general procedure described in section 4.3.32 in 79% overall yield.

(4R*, 5S*)-122d was obtained in 55% yield: mp 48-50 °C; IR (KBr) 2923, 1730, 1461, 1422, 1232, 1174, 1114 cm⁻¹; ¹H NMR (250 MHz) δ 7.41-7.29 (m, 5 H, ArH), 5.56 (d, 1 H, J = 8.2, CHO), 5.10 (d, 1 H, J = 14.9, CH₂S), 4.30 (dt, 1 H, J = 3.7, 8.2, CHN), 4.06 (d, 1 H, J = 14.9, CH₂S), 1.42 (s, 9 H, SC(CH₃)₃), 1.44-0.85 (m, 6 H, CH₃(CH₂)₃), 0.64 (t, 3 H, J = 7.3, CH₃(CH₂)₃); ¹³C NMR (63 MHz) δ 156.8, 134.8, 128.6, 128.3, 126.6, 79.0, 57.2, 43.5, 42.6, 31.2, 27.2, 26.9, 22.4, 13.4; MS, El m/z (relative intensity) 321 (M⁺, 0.2), 264 (M⁺-C₄H₉, 7), 232 (38), 188 (61), 132 (100), 91 (68), 57 (38). Anal. Calcd for C₁₈H₂₇N₂O₂S: C, 67.26; H, 8.47; N, 4.43. Found: C, 67.33; H, 8.45; N, 4.39.

(4R*, 5R*)-123d was obtained in 24% yield: IR (neat) 2924, 1753, 1415, 1229, 1172 cm⁻¹; ¹H NMR (250 MHz) δ 7.43-7.27 (m, 5 H, ArH), 5.11 (d, 1 H, J = 5.8, CHO), 5.07 (d, 1 H, J = 14.9, CH₂S), 4.05 (d, 1 H, J = 14.9, CH₂S), 4.04-3.97 (m, 1 H, CHN), 1.83-1.74 (m, 1 H, CH₃(CH₂)₂CH₂), 1.69-1.57 (m, 1 H, CH₃(CH₂)₂CH₂), 1.34 (s, 9 H, SC(CH₃)₃), 1.46-1.20 (m, 4 H, CH₃(CH₂)₂CH₂), 0.91 (t, 3 H, J = 6.8, CH₃(CH₂)₃); ¹³C NMR (63 MHz) δ 156.3, 138.6, 128.7, 125.9, 79.9, 60.6, 43.4, 42.0, 31.1, 30.5, 25.9, 22.5, 13.8; MS, El m/z (relative intensity) 321 (M⁺, 0.4), 264 (M⁺-C₄H₉, 10), 232 (33), 188 (71), 132 (100), 91 (73), 57 (41). Anal. Calcd for C₁₈H₂₇N₂O₂S: C, 67.26; H, 8.47; N, 4.43. Found: C, 67.06; H, 8.30; N, 4.52.
4.3.37 3-t-Butylthiomethyl-4-pentyl-5-phenyl-2-oxazolidinone 122/123e

The protected β-aminoalcohols 119/120e were prepared from 118e according to the general procedure described in section 4.3.32. in 75% overall yield. The two diastereomers were separated by column chromatography before cyclization to the oxazolidinones.

(4R*, 5S*)-122e was prepared in 85% yield from the anti β-aminoalcohol 119e: IR (neat) 2953, 1861, 1754, 1410, 1241, 1169 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 7.36-7.40 (m, 5 H, ArH), 5.56 (d, 1 H, J = 8.2, CHO), 5.10 (d, 1 H, J = 14.9, CH\(_2\)S), 4.30 (dt, 1 H, J = 8.2, 3.6), 4.06 (d, 1 H, J = 14.9, CH\(_2\)S). 1.42 (s, 9 H, SC(CH\(_3\))\(_3\)), 1.20-0.84 (m, 8 H, CH\(_3\)(CH\(_2\))\(_4\)), 0.71 (t, 3 H, J = 6.7, CH\(_3\)(CH\(_2\))\(_4\)); \(^13\)C NMR (63 MHz) δ 156.9, 134.7, 128.6, 128.4, 126.6, 79.1, 57.5, 43.5, 42.6, 31.5, 31.3, 27.6, 24.3; MS, EI m/z (relative intensity) 335 (M\(^+\), 0.1), 278 (M\(^+\)-C\(_4\)H\(_9\), 5), 246 (16), 202 (52), 132 (100), 105 (35), 91 (63), 57 (34). Anal. Calcd for C\(_{19}\)H\(_{29}\)NO\(_2\)S: C, 68.03; H, 8.71; N, 4.17. Found: C, 67.89; H, 8.67; N, 4.18.

(4R*, 5R*)-123e was prepared in 90% yield from the syn β-aminoalcohol 120e: IR (neat) 2938, 2862, 1748, 1430, 1229, 1171 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.10 (d, 1 H, J = 5.8, CHO), 5.07 (d, 1 H, J = 14.4, CH\(_2\)S), 4.06 (d, 1 H, J = 14.4, CH\(_2\)S), 3.90 (m, 1 H, CHN), 1.70-1.40 (m, 2 H, CH\(_3\)(CH\(_2\))\(_3\)CH\(_2\)), 1.35 (s, 9 H,
SC(CH₃)₃. 1.30-0.94 (m, 6 H, CH₃(CH₂)₂CH₂), 0.88 (t, 3 H, J = 6.4, CH₃(CH₂)₄); $^{13}$C NMR (63 MHz) δ 156.3, 138.6, 126.6, 126.0, 79.0, 60.7, 43.4, 42.1, 31.6, 31.2, 27.6, 23.4, 2.6, 13.6; MS, EI m/z (relative intensity) 335 (M⁺, 0.3), 278 (M⁺-C₄H₉, 8), 246 (25), 202 (64), 132 (100), 105 (38), 91 (68), 37 (38). Anal. Calcd for C₁₉H₂₉N₀₂S: C, 68.03; H, 8.71; N, 4.17. Found: C, 68.14; H, 8.61; N, 3.96.

4.3.38 3-t-Butylthiomethyl-4-isopropyl-5-phenyl-2-oxazolidinone 122f/123f

This mixture of diastereomers was prepared from 118f according to the general procedure described in section 4.3.32 using 5 equiv n-BuLi, 5 equiv benzaldehyde and KH as the base for cyclization. The diastereomers were obtained in 68% overall yield.

(4R*, 5S*)-122f was obtained in 50% yield: mp 95-98 °C; IR (KBr), 2933, 1727, 1418, 1333, 1289, 1227, 1175, 1115 cm⁻¹; ¹H NMR (250 MHz) δ 7.43-7.21 (m, 5 H, ArH), 5.58 (d, 1 H, J = 8.2, CHO), 5.22 (d, 1 H, J = 15.0, CH₂S), 4.29 (dd, 1 H, J = 2.2, 8.2, CHN), 4.1 (d, 1 H, J = 15.0, CH₂S), 1.74-1.62 (m, 1 H, (CH₃)₂CH), 1.41 (s, 9 H, SC(CH₃)₃), 0.87 (d, 3 H, J = 7.1, (CH₃)₂CH), 0.68 (d, 3 H, J = 7.1, (CH₃)₂CH); $^{13}$C NMR (63 MHz) δ 157, 134.5, 128.3, 128.1, 125.9, 79.7, 61.6, 44.3, 43.5, 31.3, 28.2, 21.2, 16.3; MS, EI m/z (relative intensity) 307 (M⁺, 0.1), 250 (M⁺-C₄H₉, 10), 218 (75), 174
(93), 105 (79), 91 (100), 57 (81). Anal. Calcd for C₁₇H₂₅N₂O₂S: C, 66.42; H, 8.20; N, 4.55. Found: C, 66.60; H, 8.17; N, 4.62.

(4R*, 5R*)-123f was obtained in 18% yield: mp 60-69 °C; IR (KBr) 2933, 1733, 1417, 1333, 1279, 1170 cm⁻¹: ¹H NMR (250 MHz) δ 7.43-7.21 (m, 5 H, ArH), 5.18 (d, 1 H, J = 4.9, CHO), 5.10 (d, 1 H, J = 14.9, CH₂S), 4.03 (d, 1 H, J = 14.9, CH₂S), 4.00-3.95 (m, 1 H, CHN), 2.14 (m, 1 H, (CH₃)₂CH), 1.30 (s, 9 H, SC(CH₃)₃), 0.99 (t, 6 H, J = 6.7, (CH₃)₂CH); ¹³C NMR (63 MHz) δ 156.5, 139.7, 128.7, 128.5, 125.3, 75.4, 65.1, 49.4, 31.1, 27.2, 17.7, 15.0. MS, EI m/z (relative intensity) 307 (M⁺, 1), 250 (M⁺-C₄H₉, 15), 218 (59), 174 (100), 105 (79), 91 (82), 57 (60). Anal. Calcd for C₁₇H₂₅N₂O₂S: C, 66.42; H, 8.20; N, 4.55. Found: C, 66.62; H, 8.14; N, 4.60.

4.3.39 (4R*, 5S*)-3-t-Butylthiomethyl-4-cyclohexyl-5-phenyl-2-oxazolidinone 122g

The anti β-aminoalcohol 119g was prepared from 118e according to the general procedure described in section 4.3.32 using 1.3 equiv of benzaldehyde in 40% yield. The oxazolidinone 122g was prepared from 119e in 89% yield: mp 109-110 °C; IR (KBr) 2909, 1738, 1426, 1223, 1170, 1037 cm⁻¹: ¹H NMR (250 MHz) δ 7.40-7.27 (m, 5 H,
ArH), 5.60 (d, 1 H, J = 8.0, CHO). 5.21 (d, 1 H, J = 14.9, CH₂S). 4.2 (m, 1 H, CHN). 4.15 (d, 1 H, J = 14.9, CH₂S). 1.60-1.45 (m, 5 H, c-CHCH₂(CH₃)₃CH₂), 1.42 (s, 9 H, SC(CH₃)₃). 1.26-0.78 (m, 6 H, c-CHCH₂(CH₃)₃CH₂); ¹³C NMR (63 MHz) δ 157.1, 134.7, 128.3, 125.9, 80.1, 61.5, 44.5, 43.6, 38.8, 31.4, 31.3, 27.2, 26.8, 26.0, 25.7; MS, El m/z (relative intensity) 290 (M⁺-C₄H₉, 6), 258 (38), 214 (62), 132 (100), 105 (25), 91 (63), 57 (61). Anal. Calcd for C₂₀H₂₉NO₂S: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.35; H, 8.43; N, 4.03.

4.3.40 3-t-Butylthiomethyl-4-ethyl-5-(4-methoxyphenyl)-2-oxazolidinone 122/123h

This mixture of diastereomers was prepared from 118b according to the general procedure described in section 4.3.32 in 80% overall yield.

(4R*, 5S*)-122h was obtained in 57% yield: mp 58-62 °C; IR (KBr) 2924, 1739, 1617, 1586, 1432, 1362 cm⁻¹; ¹H NMR (250 MHz) δ 7.25 (d, 2 H, J = 8.6, ArH), 6.90 (d, 2 H, J = 8.6, ArH), 5.52 (d, 1 H, J = 8.2, CHO), 5.10 (d, 1 H, 14.8, CH₂S), 4.21 (dt, 1 H, J = 3.6, 8.2, CHN), 4.06 (d, 1 H, J = 14.8, CH₂S), 3.82 (s, 3 H, OCH₃), 1.42 (s, 9 H, SC(CH₃)₃), 1.50-1.19 (m, 2 H, CH₂CH₂), 0.59 (t, 3 H, J = 7.4, CH₃CH₂); ¹³C NMR (63 MHz) δ 159.7, 156.9, 128.9, 126.7, 114.7, 78.7. 58.4, 55.2, 43.3, 42.5, 31.2, 20.6,
9.2; MS, El m/z (relative intensity) 323 (M⁺, 2), 266 (M⁺-C₄H₉, 2), 190 (100), 135 (100), 57 (35). Anal. Calcd for C₁₇H₂₅NO₃S: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.40; H, 7.53; N, 4.39.

(4R*, 5R*)-123h was obtained in 23% yield: IR (neat) 2944, 1750, 1613, 1515, 1251, 1175 cm⁻¹; ¹H NMR (250 MHz) δ 7.26 (d, 2 H, J = 8.8, ArH), 6.9 (d, 2 H, J = 8.8, ArH), 5.08 (d, 1 H, J = 14.8, CH₂S), 5.05 (d, 1 H, J = 6.8, CHO), 4.05 (d, 1 H, J = 14.8, CH₂S), 3.98 (dt, 1 H, J = 3.2, 6.8, CHN), 3.81 (s, 3 H, OCH₃), 1.82-1.63 (m, 2 H, CH₃CH₂), 1.37 (s, 9 H, SC(CH₃)₃), 0.94 (t, 3 H, J = 7.4, CH₃CH₂); ¹³C NMR (63 MHz) δ 159.9, 156.3, 130.3, 127.5, 114.79.4, 61.2, 55.1, 43.3, 41.9, 31.1, 23.2, 7.9; MS, El m/z (relative intensity) 323 (M⁺, 1), 266 (M⁺-C₄H₉, 0.5), 234 (5), 190 (100), 135 (89), 57 (26). Anal. Calcd for C₁₇H₂₅NO₃S: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.06; H, 7.79; N, 4.29.

4.3.4.1 3-t-Butylthiomethyl-4-ethyl-5-isopropyl-2-oxazolidinone 122/123i

This mixture of diastereomers was prepared from 118b according to the general procedure described in section 4.3.32, in 69% overall yield.

(4R*, 5S*)-122i was obtained in 30% yield: IR (neat) 2933, 1750, 1412, 1366, 1254, 1220, 1171 cm⁻¹; ¹H NMR (250 MHz) δ 5.06 (d, 1 H, J = 14.9, CH₂S), 4.07-3.94 (m, 2
H, CHO and CHN), 3.90 (d, 1 H, J = 14.9, CH₂S), 2.10 (m, 1H, CH₃CH₂), 1.70 (m, 2 H, CH₃CH₂ and (CH₃)₂CH), 1.37 (s, 9 H, SC(CH₃)₃), 1.10 (d, 3 H, J = 6.5, (CH₃)₂CH), 0.95 (m, 6 H, (CH₃)₂CH and CH₃CH₂); ¹³C NMR (63 MHz) δ 157.2, 83.7, 55.7, 43.5, 42.4, 31.2, 27.3, 19.3, 19.2, 19.1, 9.2; MS: EI m/z (relative intensity) 259 (M⁺, 1), 202 (M⁺-C₄H₉, 9), 170 (54), 126 (17), 70 (100), 41 (32). Anal. Calcd for C₁₃H₂₅NO₂S: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.01; H, 9.59; N, 5.31.

(4R*, 5R*)-123i was obtained in 39% yield: mp 60-62 °C; IR (KBr) 2956, 1749, 1462, 1422, 1230, 1175 cm⁻¹; ¹H NMR (250 MHz) δ 5.01 (d, 1 H, J = 14.9, CH₂S), 3.98 (d, 1 H, J = 14.9, CH₂S), 3.84 (dd, 1 H, J = 5.3, 6.2, CHO), 3.80 (q, 1 H, J = 4.9, CHN), 1.86-1.73 (m, 1 H, CH₃CH₂), 1.68-1.57 (m, 2 H, CH₃CH₂ and (CH₃)₂CH), 1.37 (s, 9 H, SC(CH₃)₃), 1.00 (d, 3 H, J = 6.5, (CH₃)₂CH), 0.98 (d, 3 H, J = 6.5, (CH₃)₂CH), 0.89 (t, 3 H, J = 7.5, CH₃CH₂); ¹³C NMR (63 MHz) δ 156.4, 82.4, 56.1, 43.4, 41.5, 32.4, 31.1, 23.7, 17.7, 17.0, 7.4; MS, EI m/z (relative intensity) 259 (M⁺, 1), 202 (M⁺-C₄H₉, 3), 170 (25), 126 (9), 70 (100), 42 (19). Anal. Calcd for C₁₃H₂₅NO₂S: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.40; H, 9.55; N, 5.40.

4.3.42 3-t-Butylthiomethyl-4-ethyl-5-cyclohexyl-2-oxazolidinone 122/123j
This mixture of diastereomers was prepared from 118b according to general procedure described in section 4.3.32 in 70% overall yield:

(4R*, 5R*)-123j was obtained in 40% yield: IR (neat) 2928, 2856, 1748, 1427, 1240 cm⁻¹

¹H NMR (250 MHz) δ 5.0 (d, 1 H, J = 14.8, CH₂S), 3.98 (d, 1 H, J = 14.8, CH₂S), 3.91 (dd, 1 H, J = 5.4, 6.0, CHO), 3.82 (q, 1 H, J = 5.0, CHN), 1.90-1.56 (m, 7 H, CH₃CH₃ and c-CHCH₂(CH₂)₃CH₂), 1.37 (s, 9 H, SC(CH₃)₃), 1.48-1.0 (m, 6 H, c-CHCH₂(CH₂)₃CH₂), 0.89 (t, 3 H, J = 7.4, CH₃CH₂); ¹³C NMR (63 MHz) δ 156.5, 81.7, 55.9, 43.3, 42.0, 41.6, 31.1, 28.1, 27.3, 26.0, 25.7, 25.4, 23.6, 7.4; MS, EI m/z (relative intensity) 299 (M⁺, 1), 242 (M⁺-C₄H₉, 9), 210 (56), 166 (26), 70 (100), 57 (36), 41 (37). Anal. Calcd for C₁₆H₂₉NO₂S: C, 64.18; H, 9.76; N, 4.68. Found: C, 63.98; H, 9.98; N, 4.75.

(4R*, 5S*)-122j was obtained in 30% yield: mp 66-69 °C; IR (KBr) 2927. 1713. 1423. 1385. 1242 cm⁻¹; ¹H NMR (250 MHz) δ 5.05 (d, 1 H, J = 14.9, CH₂S), 4.07 (m, 2 H, CHN and CHO), 3.94 (d, 1 H, J = 14.9, CH₂S), 2.05 (m, 1 H, CHCHO), 1.78-1.60 (m, 8 H, c-CH(CH₂)₂CH₂(CH₂)₂), 1.37 (s, 9 H, SC(CH₃)₃), 1.35-1.31 (m, 2 H, c-CH(CH₂)₂CH₂(CH₂)₂), 1.21 (t, 3 H, J = 7.0, CH₃CH₂); ¹³C NMR (63 MHz) δ 157.8, 82.5, 55.7, 43.4, 42.4, 36.8, 29.4, 29, 26.1, 25.3, 25.2, 19.4, 9.4; MS, EI m/z (relative intensity) 242 (M⁺-C₄H₉, 1), 210 (16), 166 (8), 70 (100). Anal. Calcd for C₁₆H₂₉NO₂S: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.45; H, 9.57; N, 4.96.

4.3.43 General procedure for the preparation of O-methylmandelates

The phthalimides were converted to the primary stannylamines as described in section 4.3.2. To a 0.2 M solution of HOBT (1.1 equiv) in CH₂Cl₂ was added O-
methylmandelic acid (1.1 equiv) and DCC (1.1 equiv) and the mixture was cooled (0 °C). The crude primary stannylamine was added as a 0.4 M solution in CH₂Cl₂, and the reaction mixture was stirred at room temperature for 15 h. The mixture was concentrated in vacuo, and the resulting residue was extracted with 3:1 hexane/Et₂O, filtered through a plug of silica and concentrated in vacuo. The two diastereomers were separated by flash chromatography (60g silica/g of substrate; 10:1 hexane/Et₂O).

4.3.44 N-(1-Tributylstannylpropyl)-2-methoxy-2-phenylacetamide 125/126a

This compound was prepared from 67b according to the general procedure described in section 4.3.43 as a mixture of diastereomers in 87% overall yield. The less polar diastereomer (1R, 2S)-125a exhibited the following: [α]²⁰D = -34.5 (c 1.0, CHCl₃); IR (neat) 3407, 3310, 3032, 2906, 1661, 1518, 1450, 1104, 1074 cm⁻¹; ¹H NMR (200 MHz) δ 7.4-7.3 (m, 5 H, ArH), 6.93 (d, 1 H, J = 7.2, HN), 4.58 (s, 1 H, CHPh), 3.36 (s, 3 H, OCH₃), 3.30 (m, 1 H, CHN), 1.84-1.66 (m, 2 H, CH₃CH₁CHN), 1.52-1.18 (m, 12 H, SnCH₂(CH₂)₂CH₃), 0.95-0.67 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂CHN); ¹³C (63 MHz) δ 169.4, 137.2, 128.3, 128.0, 126.8, 83.9, 57.0, 41.1, 29.0 (²J = 19), 27.4 (³J = 56), 27.2, 13.6, 12.8, 9.7 (¹J = 318, 305); MS, FAB m/z (relative intensity) 440 (M⁺- C₄H₉,
100), 326 (12), 252 (8), 235 (20). Anal. Calcd for C27H49NO2Sn: C, 58.08; H, 8.73; N, 2.82. Found: C, 57.89; H, 8.64; N, 2.92.

4.3.45 N-(1-Tributylstannylhexyl)-2-methoxy-2-phenylacetamide 125/126e

This compound was prepared from 67e according to the general procedure described in section 4.3.43 as a mixture of diastereomers in 77% overall yield. The less polar diastereomer (1R, 2S)-125e exhibited the following: [α]20°D = -33.2 (c 1.0, CHCl3); IR (neat) 3410, 3505, 2955, 2923, 1660, 1516, 1074 cm⁻¹; ¹H NMR (200 MHz) δ 7.3 (m, 5 H, ArH), 6.90 (d, 1 H, J = 7.6, NH), 4.58 (s, 1 H, PhCH), 3.35 (s, 3 H, OCH₃), 3.35 (m, 1 H, CHN), 1.72-1.10 (m, 20 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₄), 0.90-0.71 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃(CH₂)₄); ¹³C NMR (50 MHz) δ 169.3, 137.3, 128.3, 128.2, 126.9, 83.9, 57.1, 39.2, 34.2, 31.4, 29.1 (²J = 19), 27.9, 27.4 (³J = 56), 22.5, 13.9, 13.6, 9.8 (¹J = 304, 318); MS, FAB m/z (relative intensity), 482 (M⁺ - C₄H₉, 100), 235 (18), 176 (35), 121 (19). Anal. Calcd for C₂₇H₄₉NO₂Sn: C, 60.23; H, 9.17; N, 2.60. Found: C, 60.30; H, 9.37; N, 2.77.
4.3.46 (1R, 2S) \textit{N-t-Butoxycarbonyl-\textit{N-(1-tributylstannylpropyl)}}-2-methoxy-2-phenylacetamide 128b

![Chemical structure](image)

This compound was prepared from 125b according to the general procedure described in section 4.3.8 with a reaction time of 48 h. in 74% yield: IR (neat) 2938, 1725, 1683, 1461, 1305, 1119, 1070 cm$^{-1}$; \textit{\textit{1H NMR}} (250 MHz) $\delta$ 7.37-7.28 (m, 5 H, ArH), 5.98 (s, 1 H, CHPh), 3.62 (t, 1 H, $J = 8.0$, CHN), 3.41 (s, 3 H, OCH$_3$), 1.53 (s, 9 H, CO$_2$C(CH$_3$)$_3$), 1.63-1.21 (m, 20 H, Sn(CH$_2$)$_3$CH$_3$ and CH$_3$CH$_2$CHN), 0.88 (t, 9 H, $J = 7.2$, Sn(CH$_2$)$_3$CH$_3$), 0.53 (t, 3 H, $J = 7.3$, CH$_3$CH$_2$CHN); \textit{\textit{13C NMR}} (63 MHz) $\delta$ 173.9, 153.8, 146.5, 136.7, 128.2, 128.0, 83.0, 82.6, 57.1, 48.5, 28.8 ($^2J = 19$), 27.5, 27.2 ($^3J = 57$), 24.3, 14.9, 13.4, 12.1, 10.2 ($^1J = 312$, 328); MS. FAB $m/z$ (relative intensity) 540 (M$^+$-C$_4$H$_9$, 14), 440 (38), 177 (22), 121 (100). Anal. Caled for C$_{29}$H$_{51}$NO$_4$Sn: C. 58.40; H. 8.62; N. 2.35. Found: C. 58.28; H. 8.79; N. 2.38.

4.3.47 (1R, 2S) \textit{N-t-Butoxycarbonyl-\textit{N-(1-tributylstannyhexyl)}}-2-methoxy-2-phenylacetamide 128e

![Chemical structure](image)
This compound was prepared from 125 according to the general procedure described in section 4.3.8 with a reaction time of 36 h, in 77% yield: IR (neat) 2956, 2924, 1724, 1684, 1458, 1370, 1292, 1141 cm\(^{-1}\): \(^1\)H NMR (250 MHz) \(\delta\) 7.35-7.27 (m, 5 H, ArH), 5.98 (s, 1 H, CHPh), 3.72 (dd, 1 H, J = 8.4, 7.4, CHN), 3.41 (s, 3 H, OCH\(_3\)), 1.43 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.52-1.22 (m, 14 H, SnCH\(_3\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_2\)CH\(_2\)CHN), 1.06-0.71 (m, 24 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_3\)(CH\(_2\))\(_2\)CH\(_2\)CHN; \(^1\)C NMR (63 MHz) \(\delta\) 171.1, 154.0, 136.9, 128.3, 128.2, 83.2, 82.8, 57.4, 46.8, 31.4, 29.1 (\(^2\)J = 19), 27.8, 27.4 (\(^3\)J = 58), 22.5, 13.9, 13.6, 10.4 (\(^1\)J = 313, 328); MS, FAB \(m/z\) (relative intensity) 582 (M\(^+\)-C\(_4\)H\(_9\), 12), 482 (44), 450 (8), 291 (9), 177 (29), 121 (100).


4.3.48 General procedure for the preparation of (R)-\(t\)-butyl carbamates 129

Hydrazine hydrate (10 equiv) was added to a 1 M solution of the stannane 128 in MeOH. The reaction mixture was stirred at reflux for 12-15 h. The solvent was removed \textit{in vacuo}, and the resulting residue was diluted with Et\(_2\)O and washed with water (3 times). The organic layer was dried (MgSO\(_4\)), filtered though Celite and concentrated \textit{in vacuo} to give the carbamates as colorless oils in quantitative yield. The two carbamates
129b (R = Et) and 129e (R = C₅H₁₁) exhibited the same spectral characteristics as the ones reported in the literature.⁶ᵃ

4.3.49 General procedure for the preparation of (R)-iminodicarbonates 130

ₙ-BuLi (1.5 equiv, 1.6 M in hexanes) was slowly added to a cooled (0 ᵒC) 0.3 M solution of i-Pr₂NH (1.5 equiv) in THF. The solution was stirred for 15 min and cooled to -78 ᵒC. A 0.5 M solution of the stannane 129 in THF was slowly added to provide a bright yellow solution. The solution was stirred for 45 min, quenched with saturated NH₄Cl and warmed to rt. The resulting mixture was diluted with Et₂O, washed with water, the organic layer was dried (MgSO₄), filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography (40 g silica/g of substrate: 10:1 hexane/Et₂O) to give the products as colorless oils.

4.3.50 (R)-t-Butyl methyl N-(t-tributylstanny1propyl)iminodicarbonate 130b

This compound was prepared from 129b according to the general procedure described in section 4.3.49 in 75% yield: [α]₂⁰⁻⁵₇₈ = +61.2 (c 1.0, CHCl₃); all the other spectral characteristic are as described in section 4.3.10.
4.3.51 (R)-t-Butyl methyl N-(1-tributylstannyhexyl)iminodicarbonate 130e

![Chemical structure](image)

This compound was prepared from 129e according to the general procedure described in section 4.3.49 in 91% yield: \([\alpha]_{D}^{20} = +65.2 (c 1.0, \text{CHCl}_3)\); all the other spectral characteristics are as described in section 4.3.13.

4.3.52 (R)-t-Butyl N-hydroxymethyl-N-(1-tributylstannypropyl)carbamate 131b

![Chemical structure](image)

This compound was prepared from 130b according to the general procedure described in section 4.3.16 in 77% yield: all the spectral characteristics are as described in section 4.3.18.

4.3.53 (R)-t-Butyl N-hydroxymethyl-N-(1-tributylstannyhexyl)carbamate 131e

![Chemical structure](image)
This compound was prepared from 130e according to the general procedure described in section 4.3.16 in 79% yield: \([\alpha]_{578}^{20} = +16.1 \text{ (c 1.0, CHCl}_3)\); all the other spectral characteristics are as described in section 4.3.21.

4.3.54 (R)-t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylpropyl)carbamate 132b

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{r-BuS} \\
\text{Br} \\
\text{SnBu}_3
\end{array}
\]

This compound was prepared from 131b according to the general procedure described in section 4.3.24 in 89% yield: \([\alpha]_{578}^{20} = +51.9 \text{ (c 1.0, CHCl}_3)\); all the other spectral characteristics are as described in section 4.3.26.

4.3.55 (R)-t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylhexyl)carbamate 132e

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{r-BuS} \\
n-C_{5}H_{11} \\
\text{SnBu}_3
\end{array}
\]

This compound was prepared from 131e according to the general procedure described in section 4.3.24 in 87% yield: \([\alpha]_{578}^{20} = +46.6 \text{ (c 1.0, CHCl}_3)\); all the other spectral characteristics are as described in section 4.3.29.
4.3.56 (4S, 5R)-3-t-Butylthiomethyl-4-ethyl-5-phenyl-2-oxazolidinone 122b

![Chemical structure](attachment:image_122b)

This compound was prepared from *anti* β-aminoalcohol 134b according to the general procedure described in section 4.3.32 in 98% yield: $[\alpha]^20_{578} = +58.0$ (c 1.0, CHCl$_3$); all the other spectral characteristics are as described in section 4.3.34.

4.3.57 (4S, 5S)-3-t-Butylthiomethyl-4-ethyl-5-phenyl-2-oxazolidinone 123b

![Chemical structure](attachment:image_123b)

This compound was prepared from *syn* β-aminoalcohol 134b according to the general procedure described in section 4.3.32 in 96% yield: $[\alpha]^20_{578} = +61.1$ (c 1.0, CHCl$_3$); all the other spectral characteristics are as described in section 4.3.34.

4.3.58 General procedure for the preparation of benzyl ethers

To a 0.04 M solution of β-aminoalcohol 119 in THF was added NaOH (5 equiv, 12.5 M), TBAI (0.01 equiv) and BnBr (1.5 equiv). The reaction mixture was stirred at reflux for the specified time, diluted with Et$_2$O and washed with water. The organic
solution was dried (MgSO₄), filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography (60 g silica/g of substrate; 10:1 hexane/Et₂O) to give products as colorless oils.

4.3.59 (1R*, 2S*)-N-t-Butoxycarbonyl-N-t-butythiomethyl-2-amino-1-phenylbutyl

*benzyl ether 138b*

This compound was prepared from **119b** according to the general procedure described in section 4.3.58 with a reaction time of 20 h, in 67% yield: IR (neat) 3030, 2959, 1694, 1452, 1392, 1243, 1163, 1063 cm⁻¹; ¹H NMR (250 MHz) δ 7.42-7.27 (m, 10 H, ArH), 4.78 (d, 0.5 H, J = 7.5, CHO), 4.55-4.21 (m, 4.5 H, CH₃S, PhCH₂ and CHO), 3.53-3.38 (m, 1 H, CHN), 2.09-1.79 (m, 2 H, CH₃CH₂), 1.44 (s, 4 H, CO₂C(CH₃)₃), 1.38 (s, 5 H, CO₂C(CH₃)₃), 1.26 (s, 5 H, SC(CH₃)₃), 1.23 (s, 4 H, SC(CH₃)₃), 1.00 (t, 3 H, J = 7.3, CH₃CH₂); ¹³C NMR (63 MHz) δ 154.8, 140.1, 138.1, 128.2, 128.0, 127.9, *127.7, 127.6, 127.5, 127.3, 83.3, 82.4, 80.1, *79.9, 70.9, *70.5, 42.7, 42.4, 31.0, 28.3, 22.5, 11.9, *11.8; MS, ES m/z (relative intensity) 458 ([M⁺ +1, 100], 368 (50). Anal. Calcd for C₂₇H₃₉NO₅S: C, 70.87; H, 8.59; N, 3.06. Found: C, 71.04; H, 8.44; N, 3.15.
4.3.60 (1R*, 2S*)-N-t-Butoxycarbonyl-N-t-butylthiomethyl-2-amino-2-cyclohexyl-1-
phenylethyl benzyl ether 138g

![Chemical Structure](image)

This compound was prepared from 119g according to the general procedure described in section 4.3.58 with a reaction time of 24 h. in 53% yield: IR (neat) 2925, 2852, 1694, 1450, 1391, 1365, 1240, 1162, 1066 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 7.42 - 7.25 (m, 10 H, ArH), 4.80 - 3.96 (m, 5 H, CHO, PhCH\(_2\) and CH\(_2\)S), 3.21 - 3.04 (m, 1 H, CHN), 2.47 - 1.53 (m, 5 H, c-CHCH\(_3\)(CH\(_2\))\(_3\)CH\(_3\)), 1.43 - 1.06 (m, 24 H, CO\(_2\)C(CH\(_3\))\(_3\), SC(CH\(_3\))\(_3\) and c-CHCH\(_3\)(CH\(_2\))\(_3\)CH\(_2\)): \(^1\)C NMR (63 MHz) \(\delta\) 154.8, 140.3, 138.5, 128.2, 128.1, 127.9, 127.8, 127.7, *127.6, 127.5, *127.4, 127.3, *82.9, 82.4, *80.3, 79.8, 70.6, 70.2, *42.6, 42.4, 41.3, 33.3, 31.7, 31.0, 28.3, 29.9, 26.8, 25.5, 15.2; MS, ES m/z (relative intensity) 512 (M\(^+\) + 1, 98), 422 (100). Anal. Calcd for C\(_{31}\)H\(_{45}\)NO\(_3\)S: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.71; H, 8.63; N, 2.80.

4.3.61 (1R*, 2S*)-2-Amino-1-phenylbutyl benzyl ether 139

![Chemical Structure](image)
Benzyl ether 138b (200 mg, 0.43 mmol) was dissolved in a 1:1 mixture of THF (3 mL) and HCl (3 mL, 2 M). The reaction mixture was stirred at reflux for 45 h. The resulting mixture was diluted with Et₂O (20 mL), extracted with 1 M HCl (3 x 10 mL), the combined acid extracts were basified (2 M NaOH) and extracted with Et₂O (4 x 10 mL). The combined organic solution was dried (MgSO₄), filtered through Celite and concentrated *in vacuo* to give the product as a colorless oil in 90% yield which was used without further purification. The sample for analysis was purified by pipette column (1:1 hexane/Et₂O and 5% Et₃N): IR (neat) 3364, 3061, 3029, 2926, 2869, 1494, 1453, 1090 cm⁻¹; ¹H NMR (250 MHz) δ 7.27-7.09 (m, 10 H, ArH), 4.38 (d, 1 H, J = 11.9, PhCH₂), 4.11 (d, 1 H, J = 11.9, PhCH₂), 4.03 (d, 1 H, J = 5.9, CHO). 2.90 (m, 1 H, CHN), 1.68 (m, 1 H, CH₃CH₂), 1.27-1.10 (m, 1 H, CH₃CH₂), 0.92 (t, 3 H, J = 7.4, CH₃CH₂), 0.76 (broad s, 2 H, NH₂); ¹³C NMR (125 MHz, JMOD, C₆D₆) δ 140.2, 139.2, (128.5), (128.4), (128.3), (127.8), (127.6), (86.1), 70.8, (58.2), 26.4, (10.9); MS, ES m/z (relative intensity) 257 (M⁺ + 2, 28), 256 (M⁺ + 1, 100). Anal. Calcd for C₁₇H₂₁NO: C, 79.96; H, 8.29; N, 5.48. Found: C, 79.74; H, 8.10; N, 5.40.

4.3.62 (1R*, 2S*)-2-Amino-1-phenyl-1-butanol HCl salt 141b

NH₃ (approx. 25 mL) was condensed in a 3 neck round bottomed flask fitted with a KOH drying tube and a dry ice/acetone condenser at -78 °C. Small pieces of Li wire (4
mg, 1.3 equiv) were added and the mixture was stirred for 1 min, during which time the solution turned blue. A solution of the amine 139b (117 mg, 0.46 mmol) in anhydrous EtOH (269 μL, 10 equiv) and THF (5 mL) was added and the reaction mixture was stirred until the blue color disappeared (40 min). NH₄Cl (1 g) was slowly added, and the reaction mixture was warmed to rt to evaporate NH₃. Et₂O (20 mL) was added to the remaining residue and the organic layer was extracted with 1 M HCl (4 x 10 mL). The combined acid extracts were basified (2 M NaOH) and extracted with Et₂O (4 x 10 mL). The combined organic solution was dried (MgSO₄), filtered through Celite and concentrated in vacuo to give the product 136 as a white solid (49 mg) in 65% yield. To a solution of the aminoalcohol in EtOH (2 mL) was added conc. HCl (3 drops) and the mixture was stirred for 30 min. The reaction mixture was concentrated in vacuo to give a white solid which was recrystallized from isopropanol to give the salt as a white solid (60 mg) in 98% yield: mp 243-245 °C; IR (KBr) 3312, 3018, 1590, 1499, 1198, 1040 cm⁻¹; ¹H NMR (250 MHz) δ 8.16 (broad singlet, 3 H, NH₃⁺), 7.42-7.27 (m, 5 H, ArH), 5.78 (d, 1 H, J = 3.7, CHO), 5.16 (s, 1 H, OH), 3.17 (m, 1 H, CHN), 1.51-1.31 (m, 2 H, CH₃CH₂), 0.89 (t, 3 H, J = 7.5, CH₃CH₂); ¹³C NMR (63 MHz) δ 139.5, 127.1, 126.4, 125.1, 70.7, 57.6, 18.5, 9.5; MS, ES m/z (relative intensity) 166 (M⁺-Cl, 100). Anal. Calcd for C₁₀H₁₆ClNO: C, 59.55; H, 8.00; N, 6.94. Found: C, 59.55; H, 7.84; N, 6.90.
4.3.63 **General procedure for the hydrolysis of oxazolidinones to primary β-aminoalcohols**

To a 0.1 M solution of the oxazolidinone 122/123 in EtOH was added 2 M LiOH (5 equiv) and the reaction mixture was stirred at reflux for the specified time. The solvent was removed *in vacuo* and the remaining residue was diluted with Et₂O and washed with 1 M HCl (4 times). The combined acid extracts were basified (2 M NaOH), extracted with EtOAc, dried (MgSO₄), filtered through Celite and concentrated *in vacuo* to give primary β-aminoalcohols as yellowish solids. The β-aminoalcohols were converted to HCl salts as described in section 4.3.62.

4.3.64 **General Procedure for the transacetalization of aminoacetals to primary β-aminoalcohols**

A 1.0 M solution of the β-aminoalcohol 119/120 in 1:1 2 M HCl/THF was stirred at reflux overnight. The reaction mixture was diluted with Et₂O, extracted with 1 M HCl (several times). The combined acid extracts were basified with 2 M NaOH, extracted with EtOAc, dried (MgSO₄), filtered through Celite and concentrated *in vacuo* to give aminoacetals 137 as yellowish oils. The aminoacetals seemed to decompose when exposed to silica gel, hence, they were used without purification.

To a 1 M solution of the appropriate aminoacetal in CH₂Cl₂ was added 1,3-propanedithiol (10 equiv) followed by BF₃•Et₂O (3 equiv). The reaction mixture was stirred at room temperature for 24 h. The solution was diluted with CH₂Cl₂, washed with 1 M HCl. The combined acid extracts were basified (2 M NaOH), extracted with EtOAc,
dried (MgSO₄), filtered through Celite and concentrated in vacuo to give primary β-aminoalcohols as white solids. The β-aminoalcohols were converted to HCl salts as described in section 4.3.62.

4.3.65 (1R*, 2S*)-2-Amino-1-phenyl-1-propanol HCl salt 141a

This compound was prepared from the cis oxazolidinone 122a according to the general procedure described in section 4.3.63 with a reaction time of 15 h, in 84% yield: mp 189-191 °C; IR (KBr) 3318, 2980, 1591, 1495, 1205, 1031 cm⁻¹; ¹H NMR (250 MHz) δ 8.37 (broad singlet, 3 H, NH₃¹), 7.40-7.20 (m, 5 H, ArH), 5.38 (broad singlet, 1H, OH), 5.27 (d, 1 H, J = 2.0, CHO), 3.49 (m, 1 H, CHN), 1.11 (d, 3 H, J = 6.7, CH₂CH); ¹³C NMR (63 MHz) δ 139.7, 127.0, 126.3, 124.8, 70.5, 51.9, 10.2; MS. ES m/z (relative intensity) 152 (M⁺-Cl, 100). Anal. Calcd for C₉H₂₄ClNO: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.70; H, 7.25; N, 7.28.

4.3.66 (1R, 2S)-2-Amino-1-phenyl-1-butanol HCl salt 145
This compound was prepared from the cis oxazolidinone (4S, 5R)-122b according to the general procedure described in section 4.3.63 with a reaction time of 12 h. in 75% yield: [α]\textsubscript{D}^{20} = -32.5 (c 1, MeOH), Lit.\textsuperscript{32} [α]\textsubscript{D}^{20} = -33.1 (c 1, H₂O); all other spectral characteristics are as described in section 4.3.62.

4.3.67 (1R\*, 2S\*)-2-Amino-1-phenyl-5-pentanol HCl salt 141c

This compound was prepared from the β-aminoalcohol 119e according to the general procedure described in section 4.3.64 in 70% yield: mp 212-214 °C; IR (KBr) 3308, 2978, 1606, 1494, 1199, 1043 cm\(^{-1}\); \(\text{^1}H\) NMR (250 MHz) \(\delta\) 8.13 (broad singlet, 3 H, NH₃\(^+\)), 7.78-7.27 (m, 5 H, ArH), 5.15 (d, 1 H, J = 2.5, CHO), 3.25 (m, 2 H, OH and CHN), 1.54-1.35 (m, 3 H, CH\textsubscript{3}CHHCH\textsubscript{2}), 1.19-1.11 (m, 1 H, CH\textsubscript{3}CHHCH\textsubscript{2}), 0.79 (t, 3 H, \(J = 6.8\), CH\textsubscript{3}(CH\textsubscript{2})\textsubscript{3}); \(\text{^13}C\) NMR (63 MHz) \(\delta\) 139.1, 126.5, 125.7, 124.5, 70.1, 54.8, 26.8, 17.1, 12.1; MS. ES \(m/\text{z}\) (relative intensity) 180 (M\textsuperscript{+}\textsuperscript{-}Cl. 100). Anal. Calcd for C\textsubscript{11}H\textsubscript{18}ClNO: C, 61.24; H, 8.41; N, 6.40. Found: C, 60.97; H, 8.40; N, 6.44.

4.3.68 (1R\*, 2S\*)-2-Amino-1-phenyl-6-hexanol HCl salt 141d
This compound was prepared from the β-aminoalcohol 119d according to the general procedure described in section 4.3.64 in 75% yield: mp 208-210 °C; IR (KBr) 3335, 2989, 1600, 1497, 1383, 1044 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 8.36 (broad singlet, 3 H, NH\(_3^+\)), 7.45-7.22 (m, 5 H, ArH), 5.37 (d, 1 H, J = 2.0, CHO), 5.30-5.00 (broad, 1 H, OH), 3.39 (m, 1 H, CHN), 1.63-1.11 (m, 6 H, CH\(_3\)(CH\(_2\))\(_3\)), 0.76 (t, 3 H, J = 6.5, CH\(_3\)(CH\(_2\))\(_3\)); \(^1\)C NMR (63 MHz) δ 139.1, 126.3, 125.6, 124.3, 69.9, 54.9, 25.7, 24.1, 20.3, 11.9; MS, ES m/z (relative intensity) 194 (M\(^+\)-Cl, 100). Anal. Calcd for C\(_{12}\)H\(_{20}\)ClNO: C, 61.73; H, 8.77; N, 6.09. Found: C, 63.00; H, 8.79; N, 6.29.

4.3.69 (1R\(^*\), 2S\(^*\))-2-Amino-1-phenyl-1-heptanol HCl salt 141e

![Diagram of 141e]

This compound was prepared from the β-aminoalcohol 119e according to the general procedure described in section 4.3.64 in 86% yield: mp 165-168 °C; IR (KBr) 3326, 2989, 1602, 1487, 1383, 1043 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 8.22 (broad singlet, 3 H, NH\(_3^+\)), 7.43-7.26 (m, 5 H, ArH), 5.23 (d, 1 H, J = 2.5, CHO), 3.30-3.12 (m, 2 H, CHN and OH), 1.40-1.22 (m, 2 H, CH\(_3\)CHN), 1.19-0.88 (m, 6 H, CH\(_3\)(CH\(_2\))\(_3\)), 0.81 (t, 3 H, J = 6.2, CH\(_3\)(CH\(_2\))\(_4\)); \(^1\)C NMR (63 MHz) δ 139.6, 127.4, 126.3, 125.6, 71.0, 56.6, 30.4, 25.4, 24.4, 21.2, 13.0; MS, ES m/z (relative intensity) (M\(^+\)-Cl, 100). Anal. Calcd for C\(_{13}\)H\(_{22}\)ClNO: C, 64.05; H, 9.10; N, 5.74. Found: C, 63.84; H, 8.91; N, 5.66.
4.3.70 (1R*, 2S*)-2-Amino-3-methyl-1-phenyl-1-butanol HCl salt 141f

![Chemical structure of 141f]

This compound was prepared from the cis oxazolidinone 122f according to the general procedure described in section 4.3.63 with a reaction time of 20 h, in 76% yield: mp 233-235 °C; IR (KBr) 3294, 2955, 1607, 1570, 1498, 1200, 1041 cm⁻¹; ¹H NMR (250 MHz) δ 8.08 (broad singlet, 3 H, NH₃⁺), 7.72-7.25 (m, 5 H, ArH), 5.20 (d, 1 H, J = 3.7, CHO), 5.10 (broad singlet, 1 H, OH), 3.18 (m, 1 H, CHN), 1.89-1.79 (m, 1 H, (CH₃)₂CH), 1.03 (d, 3 H, J = 6.8, (CH₃)₂CH), 0.96 (d, 3 H, J = 6.9, (CH₃)₂CH); ¹³C NMR (63 MHz) δ 139.4, 127.3, 126.5, 125.5, 70.6, 60.9, 25.1, 20.0, 17.2; MS, ES m/z (relative intensity) 180 (M⁺-Cl, 100). Anal. Calcd for C₁₁H₁₈ClNO: C, 61.53; H, 7.98; N, 6.52. Found: C, 61.14; H, 8.26; N, 6.23.

4.3.71 (1R*, 2S*)-2-Amino-1-(4-methoxyphenyl)-1-butanol HCl salt 141h

![Chemical structure of 141h]

This compound was prepared from the cis oxazolidinone 122h according to the general procedure described in section 4.3.63 with a reaction time of 20 h, in 66% yield: mp 200-202 °C; IR (KBr) 3346, 2980, 1610, 1509, 1462, 1303, 1252, 1040 cm⁻¹; ¹H
NMR (250 MHz) δ 8.15 (broad singlet, 3 H, NH$_3^+$), 7.32 (d, 2 H, J = 8.6, ArH), 6.9 (d, 2 H, J = 8.6, ArH), 5.74 (broad singlet, 1 H, OH), 5.10 (m, 1 H, CHO), 3.79 (s, 3 H, OCH$_3$), 3.18 (m, 1 H, CHN), 1.50 (m, 2 H, CH$_3$CH$_2$), 0.89 (t, 3 H, J = 7.4, CH$_3$CH$_2$); $^{13}$C NMR (63 MHz) δ 157.6, 131.4, 126.2, 112.5, 70.3, 57.8, 54.0, 18.5, 9.5; MS, ES $m/z$ (relative intensity) 196 (M$^+$-Cl, 100), 178 (M$^+$-(Cl+H$_2$O), 30). Anal. Calcd for C$_{11}$H$_{18}$ClNO$_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 56.86; H, 7.77; N, 6.11.

4.3.72 (1R*, 2R*)-2-Amino-1-(4-methoxyphenyl)-1-butanol HCl salt 142h

![Chemical structure](image)

This compound was prepared from the trans oxazolidinone 123h according to the general procedure described in section 4.2.63 using n-propanol as solvent. The reaction was stirred for 48 h and the product was obtained in 76 % yield: mp 191-195 °C; IR (KBr) 3345, 2948, 1610, 1503, 1460, 1382, 1240, 1030 cm$^{-1}$; $^1$H NMR (250 MHz) δ 8.05 (broad singlet, 3 H, NH$_3^+$), 7.30 (d, 2 H, J = 8.6, ArH), 6.90 (d, 2 H, J = 8.6, ArH), 6.01 (d, 1 H, J = 3.6, OH), 4.56 (dd, 1 H, J = 6.0, 3.6, CHO), 3.80 (s, 3 H, OCH$_3$), 3.06 (m, 1 H, CHN), 1.52-1.45 (m, 2 H, CH$_3$CH$_2$), 0.90 (t, 3 H, J = 7.4, CH$_3$CH$_2$); $^{13}$C NMR (MHz) δ 157.6, 131.4, 126.2, 112.5, 70.3, 57.8, 54.0, 18.5, 9.5; MS, ES $m/z$ (relative intensity) 196 (M$^+$-Cl, 95), 178 (M$^+$-(Cl+H$_2$O), 100). Anal. Calcd for C$_{11}$H$_{18}$ClNO$_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 56.94; H, 7.59; N, 5.88.
4.3.73 General Procedure for the preparation of N-Boc β-aminoalcohols

To a 0.25 M solution of aminoalcohol in THF was added Et₃N (1.2 equiv) and Boc₂O (1.2 equiv). The reaction mixture was stirred at rt for 1 h. The resulting mixture was diluted with Et₂O, washed with 1 M KHSO₄ (3 times) and water. The organic solution was dried (MgSO₄), filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography (60 g silica/g of substrate; 2:1 hexane/Et₂O) to give the products as white solids.

4.3.74 (1R, 2S)-N-t-Butoxycarbonyl-2-amino-1-phenylbutanol 144

This compound was prepared from 143b according to the general procedure described in section 4.3.73 in 98% yield: mp 99-102 °C; [α]D⁰₂₀ = -105.7 (c 1.0, CHCl₃); IR (KBr) 3375, 1689, 1526, 1173 cm⁻¹: ¹H NMR (200 MHz) δ 7.33 (m, 5 H, ArH), 4.86 (m, 1 H, CHO), 4.48 (broad d, 1 H, J = 8.0, OH), 1.46 (s, 9 H, CO₂C(CH₃)₃), 1.24 (m, 2 H, CH₃CH₂), 0.91 (t, 3 H, J = 7.3, CH₃CH₂); ¹³C NMR (50 MHz) δ 147.1, 140.8, 128.1, 127.4, 126.5, 79.8, 76.8, 58.2, 28.3, 22.6, 10.7; MS, ES m/z (relative intensity) 267 (M⁺+2, 18), 266 (M⁺+1. 100), 210 (52). Anal. Calcd for C₁₅H₂₃NO₃: C. 67.98; H. 8.74; N, 5.28. Found: C, 68.04; H, 8.61; N, 5.22.
4.3.75 General procedure for the Mitsunobu reaction of β-aminoalcohols

To a 0.1 M solution of aminoalcohol in THF was added p-nitrobenzoic acid (1.2 equiv) and PPh₃ (1.2 equiv). The solution was cooled to 0 °C, DEAD (1.2 equiv) was slowly added and the reaction mixture was stirred at rt for the specified time. The solvent was removed in vacuo and the crude product was purified by flash chromatography (100 g silica/g of substrate; 5:1 hexane/Et₂O).

4.3.76 (4R*, 5R*)-3-t-Butyliothiomethyl-4-methyl-5-phenyl-2-oxazolidinone 123a

This compound was prepared from the anti β-aminoalcohol 119a according to the general procedure described in section 4.3.75 with a reaction time of 1.5 h. It was obtained as a white solid in 89% yield and exhibited the spectral characteristic described in section 4.3.33.

4.3.77 (4R*, 5R*)-3-t-Butyliothiomethyl-4-ethyl-5-phenyl-2-oxazolidinone 123b
This compound was prepared from the anti β-aminoalcohol 119b according to the general procedure described in section 4.3.75 with a reaction time of 1 h. It was obtained as a white solid in 94% yield (and 92% yield when reaction was done in the absence of p-nitrobenzoic acid). The product 123b exhibited the spectral characteristics described in section 4.3.34

4.3.78 (1S, 2R)-N-t-Butoxycarbonyl-2-amino-1-phenyl-1-propanol 154

This compound was prepared from norephedrine according to general procedure described in section 4.3.73 in 85% yield: [α]_D^20 = +74.8 (c, 1.0, CHCl₃); mp 83-86 °C; IR (KBr) 3357, 2969, 1685, 1342, 1034 cm⁻¹; ¹H NMR (250 MHz) δ 7.33-7.24 (m, 5 H, ArH), 4.83 (m, 2 H, CH(OH) and NH), 3.95 (broad s, 1 H, CHN), 3.65 (broad s, 1 H, OH), 1.44 (s, 9 H, CO₂C(CH₃)₃), 0.95 (d, 3 H, J = 6.8, CH₃CHN); ¹³C NMR δ 156.1, 141.1, 128.0, 127.3, 126.2, 79.6, 76.5, 52.0, 28.3, 14.4; MS, ES m/z (relative intensity) 252 (M⁺+1, 100), 196 (40) Anal. Calcd for C₁₄H₂₁NO₃: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.06; H, 8.66; N, 5.69.
4.3.79 \((1R^*, 2R^*)-N\text{-}t\text{-}Butoxycarbonyl\text{-}l\text{-}methyl\text{-}2\text{-}phenylaziridine 156\)

This compound was prepared from 154 according to the general procedure described in section 4.3.75 in the absence of \(p\text{-}nitrobenzoic\) acid with a reaction time of 2 h. It was obtained as a colorless oil in 60\% yield: IR (neat) 2980, 1714, 1458, 1367, 1311, 1159, 1048 cm\(^{-1}\); \(^1\)H NMR (250 MHz) \(\delta\) 7.33-7.21 (m, 5 H, ArH), 3.17 (d, 1 H, \(J = 3.0\), PhCH\(_3\)), 2.67-2.59 (m, 1 H, CH\(_3\)CH\(_2\)), 1.42 (s, 9 H, CO\(_2\)C(CH\(_3\))\(_3\)), 1.41 (unresolved d, 3 H, CH\(_3\)CH\(_3\))\(^{13}\)C NMR (63 MHz) \(\delta\) 160.3, 137.0, 128.3, 127.6, 126.4, 81.1, 45.9, 42.5, 27.9, 15.9; MS, EI \(m/\text{z}\) (relative intensity) 176 (M\(^+\) - C\(_4\)H\(_9\), 2), 132 (93), 57 (100). Anal. Calcd for C\(_{14}\)H\(_{19}\)NO\(_2\): C, 72.07; H, 8.21; N, 6.00. Found: C, 71.97; H, 8.09; N, 5.97.
4.4 References

Chapter 5

Synthesis of Chiral $\alpha$-Aminoorganostannanes

5.1 Introduction

As discussed in chapter one, not many methods have been developed for the asymmetric synthesis of $\alpha$-aminoorganostannanes. Pearson and Lindbeck have reported the synthesis of enantiomerically enriched $\alpha$-aminoorganostannanes from chiral sulfones.\(^1\) This method is limited to oxazolidinones and imidazolidinones; one can not obtain enantiomerically enriched $\alpha$-aminoorganostannanes with simple protecting groups such as the $t$-Boc group. What seems to be a more versatile method is the enantioselective reduction of acylstannanes using BINAL-H reported by Chong and Park.\(^2\) Unfortunately, this method gives low yields of product and special conditions are required to obtain high enantiomeric excess.

In an effort to find a better route to enantiomerically enriched $\alpha$-aminoorganostannanes, Bekkali made chiral stannylimines 160 from acylstannanes 159, with (R)-(1-phenyl-2-methoxy)ethylamine as the chiral auxiliary (Scheme 74).\(^3\) His intention was to diastereoselectively reduce the stannylimines to give enantiomerically enriched $\alpha$-aminoorganostannanes 161. After investigating a wide variety of reducing agents, the best results were achieved with DIBAL-H at $-78\, ^\circ$C. Other reducing agents such as LiAlH$_4$ led to tin cleavage, and NaBH$_4$ gave very low diastereomeric excess (22%).
Due to their instability, the stannylamines 161 were converted to the carbanates 162. Attempts to remove the chiral auxiliary by hydrogenolysis or dissolving metal reduction were not successful.

Scheme 74

\[
\begin{align*}
R \text{SnBu}_3 + \text{PhMe}_2 \text{OMe} & \xrightarrow{\text{Mol. sieves, 69-75\%}} \text{R}\text{SnBu}_3 \\
\text{DIBAL-H, CH}_2\text{Cl}_2, -78^\circ\text{C} & \xrightarrow{} \text{R}\text{SnBu}_3
\end{align*}
\]

Determined to find a better route to enantiomerically enriched α-aminoorganostannanes and seeing the potential that Bekkali’s methodology had, we decided to carry on with this research. Our goal was to investigate the use of other chiral auxiliaries with the hope of finding ones that would give better diastereoselectivity and would also be removed easily.

(S)-α-Methylbenzylamine had been successfully used as a chiral auxiliary in the diastereoselective reduction of imines (Scheme 75). This chiral auxiliary was very appealing to us because it gave good diastereoselectivity and it was also easily removed.
As a result we decided to use \( \alpha \)-methylbenzylamine as a chiral auxiliary for the reduction of stannylamines.

**Scheme 75**

5.2 Results and Discussion

5.2.1 Reduction of stannylamines

The stannylamine 164 was prepared by the condensation of acylstannanes 163 and (R)-\( \alpha \)-methylbenzylamine using the method that was established by Bekkali (Scheme 76). Reduction of 164 with DIBAL-H (Bekkali's protocol), gave the stannylamine 165 in 51% yield and 62% de. The de was determined by \( ^1H \) NMR spectroscopy (Figure 15). The diastereoselectivity was almost the same as what Bekkali had reported with the 1-(1-phenyl-2-methoxy)ethylamine chiral auxiliary.
Figure 15: Partial $^1$H NMR spectrum of 165

62% de
In their asymmetric additions of alkylolithiums to chiral imines, Nakagawa and coworkers found out that changing the chiral auxiliary from \(\alpha\)-methylbenzylamine to \(\alpha\)-naphthylethylamine increased the de from 4% to 100% (Scheme 77). By using semi-empirical molecular orbital calculations (MOPAC), they showed that the lowest energy conformation of the BF\(_3\)-complexed imines was 166. In this model the naphthyl group is perpendicular to the \(\pi\)-plane made up of the C-N double bond and the phenyl group. The alkylolithium reagent attacked from the top of the \(\pi\)-plane and gave the observed diastereomer. With (R)-\(\alpha\)-methylbenzylamine as the chiral auxiliary, selectivity was low because the phenyl group in the chiral auxiliary could not shield the \(\pi\)-plane as well as the naphthyl group.
Since we already had higher diastereoselectivity with (R)-α-methylbenzylamine, we were motivated to use α-naphthylethylamine. We used the racemic amine because the enantiomerically pure one is expensive, and it was not going to affect the outcome of the reaction with respect to diastereoselectivity. If high de were observed, enantiomerically pure amine would be used to obtain stannylamines of high ee. To our great disappointment, reduction of the stannylimine 167 gave the amine 168 with only 56% de (Scheme 78). The size of the R group seemed to have had no effect at all on the selectivity. The only difference between Nakagawa’s method and ours is that we did not add any BF$_3$·OEt$_2$ in our reductions since we had obtained reasonable selectivity with (R)-α-methylbenzylamine without the BF$_3$·OEt$_2$. 
Whereas Bekkali's stannylimines 160 were reduced after 3 h at -78 °C, the reduction of 164 and 167 was very slow (10-12 h). Perhaps the reduction of 160 was enhanced by the ability of the oxygen to bind to the reducing agent. Attempts to perform the reductions at higher temperatures (-40 °C) led to tin cleavage, as was indicated by the presence of tributyltin hydride in the reaction mixture and also very low yields of isolated product. At 0 °C no product was isolated; all the starting material was cleaved.

5.2.2 Attempted cleavage of the chiral auxiliaries

Before we expended our effort in trying to optimize the reduction conditions to improve both the yields and selectivity, we had to make sure that we could remove the chiral auxiliaries. In addition to being removed by transfer hydrogenolysis, 1-methylbenzylamine has also been removed by standard hydrogenolysis (Pd(OH)$_2$/C/H$_2$). However, attempts to remove the chiral auxiliaries from both 165 and 168 using catalytic amounts of Pd(OH)$_2$/C and H$_2$ led to no reaction after 3 days (Scheme 79). When the amount of catalyst was increased to 1.2 equiv. the tin was cleaved and no product was isolated. Attempts to use transfer hydrogenolysis also led to tin cleavage. Dissolving metal conditions (Li/NH$_3$) also gave byproducts due to tin cleavage.
During all these hydrogenolysis reactions, we were unable to isolate the amine 169 which would have resulted from the cleavage of tin from 165 and 168. The only byproduct that we could identify was tributyltin hydride. Perhaps the required primary stannylamine might have been formed and then decomposed under the conditions used. In order to investigate this possibility, we added Boc₂O to the reaction mixture so that as soon as the primary amine is formed, it could react with Boc₂O and give the Boc protected stannylamine which is known to be more stable than the primary stannylamine. Unfortunately, no product was isolated under these conditions either.

**Scheme 79**

![Scheme 79 Diagram]

Perhaps the decomposition was so fast that it occurred before the stannylamine could react with the Boc₂O. If this was the problem, we decided to get around it by introducing the Boc group before removal of the auxiliary. Thus, 165 was converted to the carbamate 170 in good yield (Scheme 80). Although we had used a diastereomeric
mixture of the stannane 165, the TLC of 170 showed only one spot. The \(^1\)H NMR spectrum showed two peaks due to the benzylic proton which were 0.3 ppm apart. The ratio of these two peaks suggested that the product had only 27% de. This was surprising because the starting material had 62% de and the reaction was not affecting any of the stereocenters. Perhaps these two peaks might have been due to rotamers since carbamates show rotamers. In order to verify that we were not encountering racemization, we had to find the ee of the final product after removal of the chiral auxiliary. Attempts to introduce the carbamate group to 168 were not successful; this was not too surprising because of steric hindrance caused by the naphthyl group. Attempts to remove the chiral auxiliary from 170 using HCO\(_2\)NH\(_4\) and Pd/C led to removal of the carbamate before the chiral auxiliary. This was unexpected because HCO\(_2\)NH\(_4\) was thought to be too weak an acid to remove the Boc group. As we had observed previously, attempts to remove the chiral auxiliary under dissolving metal conditions led to tin cleavage.

Scheme 80
5.2.3 Transmetalation of Boc-protected α-aminoorganostannanes

It was clear from these results that removal of the chiral auxiliary in the presence of tin was not possible. In our attempts to avoid this problem, we decided to transmetalate the carbamate 170 and then remove the chiral auxiliary at the end of the reaction sequence. We were also interested in how the chiral auxiliary was going to affect the configurational stability of the resulting organolithium. When 170 was treated with \( n\)-BuLi, TLC analysis after 15 min indicated that starting material was consumed but there was no \( \text{Bu}_4\text{Sn} \) to verify that transmetalation had occurred. The reaction mixture was quenched with CH\(_3\)OD; and as the TLC had indicated, no deuterated product 171 was obtained. Instead, we isolated the stannylamine 165 (Scheme 81). The \( n\)-BuLi had attacked the Boc group instead of performing the tin-lithium exchange. If the \( n\)-BuLi was attacking the carbonyl group, then use of \( t\)-BuLi, a hindered base, would discourage this reaction. However, transmetalation with \( t\)-BuLi also led to removal of the Boc group. Since the size of the base did not affect the outcome of this reaction, the mechanism shown in Scheme 80 best explains these results. The driving force for this reaction must be the formation of the isobutene gas and CO\(_2\). Attack of the carbonyl group would have resulted in the formation of \( t\)-butyl or \( n\)-butyl pentanoate; since these two compounds were not isolated, this also supports the proposed mechanism.

The byproduct 165 had 62\% de, verifying that introduction of the Boc group did not occur with racemization. So what we were observing in the \(^1\)H NMR spectrum of 170 were rotamers not diastereomers, and most likely the benzylic proton of the minor diastereomer had the same chemical shift as one of the rotamers.
Park observed the same reaction when he tried to transmetalate the iminodicarbonate 172 with t-BuLi (Scheme 82). Therefore, transmetalation is difficult if one has two sterically hindered N-protecting groups.

We had to find a protecting group that was not going to react with the alkyllithiums but would be able to stabilize the resulting organolithium. Burchat had shown that the use of the 2-methoxybenzyl protecting group gave better transmetalation than using just an ordinary benzyl group. The oxygen coordinates to the Li atom of the
organolithium and helps stabilize it. Our first attempt to introduce this group by the Mitsunobu reaction of the stannylamine 165 with 2-methoxybenzyl alcohol was not successful (Scheme 83). No reaction occurred after stirring the reaction mixture for 2 days. We tried to convert the 2-methoxybenzyl alcohol to its tosylate, which is more reactive; unfortunately, we isolated the ether 173 and 2-methoxybenzyl chloride (Scheme 83). Presumably the tosylate was being formed, but was too reactive, and subsequently reacted with the chloride ion and the alcohol to give the chloride and the ether, respectively.

Scheme 83

Due to shortage of time, we could not investigate other ways of introducing this group. We were also unable to find ways of improving the diastereoselectivity of the stannylimines.
5.2.4 Summary

Stannylamines were made by the condensation of acylstannanes and (R)-α-methylbenzylamine and α-naphthylethylamine as chiral auxiliaries. Diastereoselective reduction of the stannylamines with Dibal-H at −78 °C gave the stannylamines in moderate diastereomeric excess (56-62%). Attempts to remove the chiral auxiliaries by hydrogenolysis or dissolving metal conditions led to tin cleavage. The stannylamine 165 was protected by the Boc group, and attempts to remove the chiral auxiliary from the Boc protected organostannanes were not successful. Attempted transmetalation of the Boc-protected organostannane 170 led to attack of the Boc group by the alkyllithium instead of tin-lithium exchange. Due to shortage of time, we were unable to find other protecting groups which would not react with the alkyllithiums.

5.3 Experimental

5.3.1 General

The procedures outlined in section 2.3.1 also apply here with the following addition. The acylstannane 163 was prepared by the method of Chong and Mar.10

5.3.2 General procedure for the preparation of stannylamines

A mixture of the acylstannane 163 and the amine (1 equiv) was stirred at rt under nitrogen (glove box), in the presence of 3Å molecular sieves (30% w/w) for the specified time. The reaction mixture was filtered to remove molecular sieves, and the resulting solution was diluted with CH2Cl2 and washed with water. The organic solution was dried
(MgSO₄), filtered through Celite and concentrated in vacuo. The crude products were purified by distillation, the products remained in the still pots because they had high boiling points (> 140 °C at 0.2 torr). Even after distillation, the stannylimines were not 100% pure. as a result, they could not be fully characterized. The products were stored under argon at -4 °C.

5.3.3 1-(1-Methylbenzylimino)-1-tributylstannylpropane 164

This compound was prepared according to the general procedure described in section 5.3.2, with a reaction time of 72 h as a yellow oil in 83% yield: [α]²⁰_D = -21.0 (c 1.0, CHCl₃); IR (neat) 2912, 1613, 1492, 1455, 1374, 1071 cm⁻¹: ¹H NMR (250 MHz) δ 7.37-7.19 (m, 5 H, ArH), 4.04 (q, 1 H, J = 6.4, CH₃CHPh), 2.45 (q, 2 H, J = 7.4, CH₃CH₂), 1.61-1.21 (m, 12 H, SnCH₂(CH₂)₂CH₃), 1.47 (d, 3 H, J = 6.4, CH₃CHPh), 1.14-0.83 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂); ¹³C NMR (63 MHz) δ 187.8, 145.6, 128.0, 126.2, 126.1, 71.7, 38.0, 29.1, 28.0, 27.2 (³J = 47), 16.2, 13.3, 11.2 (¹J = 288).

5.3.4 1-(1-Naphthylethylimino)-1-tributylstannylpropane 167
This compound was prepared according to the general procedure described in section 5.3.2, with a reaction time of 60 h as a yellow oil in 71% yield: IR (neat) 2958, 1611, 1509, 1457, 1374, 1073 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 8.11 (d, 1 H, J = 8.0, CH(8)), 7.86-7.72 (m, 2 H, CH(4) and CH(5)), 7.70 (d, 1 H, J = 8.0, CH(2)), 7.50-7.39 (m, 3 H, CH(3), CH(6) and CH(7)). 4.80 (q, 1 H, J = 6.4, CH\(_2\)CHAr), 2.53 (q, 1 H, J = 7.4, CH\(_3\)CH\(_2\)), 1.65-1.10 (m, 12 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 1.60 (d, 3 H, J = 6.4, CH\(_3\)CHAr), 1.09-0.72 (m, 18 H, SnCH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_3\)CH\(_2\)); \(^1^3\)C NMR (50 MHz) δ 188.2, 142.1, 133.8, 130.2, 128.8, 126.8, 125.5, 125.3, 124.9, 123.4, 123.1, 68.3, 38.3, 29.2, 27.2, 25.3, 13.6, 13.4, 11.2 (\(^1\)J = 299).

5.3.5 General procedure for the preparation of stannylamines

DIBAL (1.1 equiv) was slowly added to a cooled (-78 °C) 0.15 M solution of the stannylamine in CH\(_2\)Cl\(_2\) and reaction mixture was stirred at -78 °C for the specified time. The reaction mixture was quenched with saturated NH\(_4\)Cl, diluted with CH\(_2\)Cl\(_2\) and washed with water. An emulsion formed which separated after the mixture was allowed to stand for a few min. The organic solution was dried (MgSO\(_4\)), filtered through Celite and concentrated in vacuo. The products were purified by flash chromatography (100 g silica/g of substrate; 100% hexane and 5% Et\(_3\)N) to give the products as colourless oils.
5.3.6  *N-(1-Methylbenzyl)-1-tributylstannylpropylamine 165*

![Structure of compound 165](image)

This compound was prepared from 164 according to the general procedure described in section 5.3.5, with a reaction time of 10 h, as a 4:1 mixture of diastereomers in 51% yield. The less polar and major diastereomer exhibited the following: IR (neat) 3025, 2956, 1455, 1010 cm⁻¹; ¹H NMR (250 MHz) δ 7.30-7.19 (m, 5 H, ArH), 3.87 (q, 1 H, J = 6.4, CH₃CHPh), 2.65 (m, 1 H, CHN), 1.88-1.76 (m, 1 H, CH₃CHH), 1.65-1.20 (m, 14 H, CH₃CHH, NH and SnCH₂(CH₂)₂CH₃), 1.27 (d, 3 H, J = 6.7, CH₃CHN), 0.93-0.68 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CH₂); ¹³C NMR (63 MHz) δ 146.1, 128.2, 126.9, 126.6, 55.9, 49.0, 29.3, 27.6, 25.8, 24.8, 13.6, 12.4, 9.01 (¹J = 293).

5.3.7  *N-(1-Naphthylethyl)-1-tributylstannylpropylamine 168*

![Structure of compound 168](image)

This compound was prepared from 167 according to the general procedure described in section 5.3.5, with a reaction time of 12 h, as a 3.6:1 mixture of diastereomers in 60% yield. The diastereomers could not be separated by column chromatography: IR (neat) 3049, 2956, 2923, 1456, 1375, 1120, 1072 cm⁻¹; ¹H NMR
(250 MHz) δ 8.24 (dd, 1 H, J = 2.1, 8.1. CH(8)), 7.8-7.71 (m, 3 H, CH(2). CH(4) and CH(5)), 7.51-7.42 (m, 3 H, CH(3). CH(6) and CH(7)), 4.76 (q, 0.8 H, J = 6.5, CH₃CHPh), 4.56 (q, 0.2 H, J = 6.5, CH₃CHPh), 2.85-2.67 (m, 1 H, CHN). 1.96-1.80 (m, 1 H, CH₃CHH), 1.77-1.21 (m, 17 H, CH₃CHH, NH, CH₃CHPh and SnCH₂(CH₂)₂CH₃), 0.97-0.58 (m, 18 H, SnCH₂(CH₂)₂CH₃ and CH₃CHH); ¹³C NMR (50 MHz) δ 142.0, 133.8, 130.2, 128.7, 126.7, 125.5, 125.2, 124.8, 123.4, 123.1, 68.3, *65.3, 38.2, 29.1, 27.1 (¹J = 58), 25.3, 16.2, 13.5, 13.2, 11.1 (¹J = 297), *11.0.

5.3.8 Attempted removal of the chiral auxiliaries by hydrogenolysis

Hydrogenolysis

Pd(OH)₂/C (20%) was added to a 0.1 M solution of stannylamine in EtOH, and the reaction mixture was stirred under 1 atmosphere of hydrogen (balloon) at rt for 72 h. TLC analysis of the reaction mixture showed that no reaction had occurred. More Pd(OH)₂/C (to make a total of 1.2 equiv) was added and the reaction mixture was stirred for 5 h. The reaction mixture was filtered through a plug of silica and solvent was removed in vacuo. The resulting residue was diluted with Et₂O and washed with water, the organic solution was dried (MgSO₄), filtered through Celite and concentrated in vacuo to give a cloudy oil which was shown by TLC and ¹H NMR to be mainly Bu₃SnH and other byproducts.

Transfer Hydrogenolysis

To a 0.1 M solution of the stannylamine in MeOH was added Pd/C (10%) and NH₄CO₂H (5 equiv). The reaction mixture was stirred at rt for 15 h. TLC analysis indicated that no reaction had occurred. The reaction mixture was stirred at reflux for
another 20 h. The product was isolated as outlined above and was also shown to be Bu$_3$SnH and some other byproducts.

5.3.9 Attempted removal of the chiral auxiliaries by dissolving metal reduction

NH$_3$ (approx. 25 mL/0.5 mmol of amine) was condensed in a 3 N round bottomed flask fitted with a KOH drying tube and a dry ice/acetone condenser at $-78^\circ$C. Small pieces of Li wire (10 equiv) were added and the mixture was stirred for 1 min, during which time the solution turned blue. A 0.1 M solution of the stannylamine in THF and anhydrous EtOH (10 equiv) was added and the reaction mixture was stirred until the blue color disappeared (20 min). NH$_4$Cl was slowly added, and the reaction mixture was warmed to rt to evaporate NH$_3$. The remaining residue was dissolved in Et$_2$O and washed with water. The organic solution was dried (MgSO$_4$), filtered through Celite and concentrated in vacuo to give a product that was shown by $^1$H NMR and TLC to be starting material and Bu$_3$SnH.

5.3.10 t-Butyl N-(1-methylbenzyl)-N-(1-tributylstannylpropyl)carbamate 170

This compound was prepared from stannane 165 (mixture of diastereomers) according to the procedure described in section 4.3.8 with a reaction time of 20 h. It was obtained in 83% yield, as a mixture of diastereomers which could not be separated by
column chromatography: IR (neat) 2923, 1786, 1716, 1456, 1372, 1225, 1144 cm⁻¹; ¹H NMR (250 MHz) δ 7.45-7.26 (m, 5 H, ArH), 5.63 (q, 0.4 H, J = 7.1, CH₃C₆H₅), 5.32 (q, 0.6 H, J = 7.1, CH₃C₆H₅), 2.75-2.66 (m, 1 H, CHN), 1.79-1.63 (m, 1 H, CH₃CHHCHN), 1.60-1.19 (m, 16 H, SnCH₂(CH₂)₂CH₃, CH₃CHHCHN and CH₃C₆H₅), 1.56 (s, 9 H, CO₂C(CH₃)₃), 0.98-0.62 (m, 15 H, SnCH₂(CH₂)₂CH₃), 0.43 (unresolved triplet, 3 H, CH₃CH₂CHN); ¹³C NMR (50 MHz) δ 159.4, 141.9, 128.0, 127.6, 127.2, 79.0, 54.8, 46.5, 29.3 (²J = 18), 28.6, 27.6 (³J = 57), 25.6, 16.8, 13.7, 12.1, 10.6.
5.4 References


