APPLICATION OF α-AMINOORGANOSTANNANES TO THE PREPARATION OF β-AMINOALCOHOLS

by

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Abstract

Preparation of non-conjugated dipole-stablilized α-aminoorganolithiums by tin-lithium exchange is explored. The configurational stability of enantiomerically enriched α-aminoorganolithiums is also investigated. These organolithiums can react with aldehydes to provide both racemic and chiral non-racemic β-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 α-aminoorganostannanes are also prepared from stannyl phthalimides. These α-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 α-aminoorganolithiums.

N-*t*-Butylthiomethyl *t*-Boc protected α-aminoorganostannanes transmetalate with *n*-BuLi at –78 °C to give α-aminoorganolithiums which can react with different aldehydes to give β-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 α-aminoorganolithiums racemize very slowly at –95 °C (2-3%) and they react with aldehydes with complete retention of stereochemistry to give β-aminoalcohols in high enantiomeric excess (91-94%). The protected β-aminoalcohols may be converted to oxazolidinones which are then hydrolyzed to primary β-aminoalcohols. Oxazolidinones with straight chains alpha to the nitrogen (R = *n*-C_3H_7, *n*-C_4H_9 and *n*-C_5H_{11}) give low yields of the primary β-aminoalcohols. The β-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

List of Abbreviations

ABq	AB quartet
aq	aqueous
Ar	aryl
BINAL-H	binaphthol-modified lithium aluminum hydride
Bn	benzyl
n-Bu	*n*-butyl
t-Bu	*t*-butyl
Boc, *t*-Boc	*t*-butoxycarbonyl
Calcd	calculated
CBz	benzyloxycarbonyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethyamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
E, E^+	electrophile
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
FABHRMS	fast atom bombardment high resolution mass spectrometry

GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HMPA	hexamethylphosphoric triamide
HOBT	1-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	α-methoxy-α-(trifluoromethyl)phenylacetyl
m/z	mass/charge
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-tolunesulfonate
PHAL	1,3-phthalazinediyl
PNB	*p*-nitrobenzoic acid
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
SET	single electron transfer
S_N2	substitution nucleophilic bimolecular

t	triplet
TBAI	tetra-*n*-butylammonium iodide
TBDMS, TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
UV	ultraviolet
vs	versus
v/v	volume/volume
w/w	weight/weight

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Chapter 1

Introduction

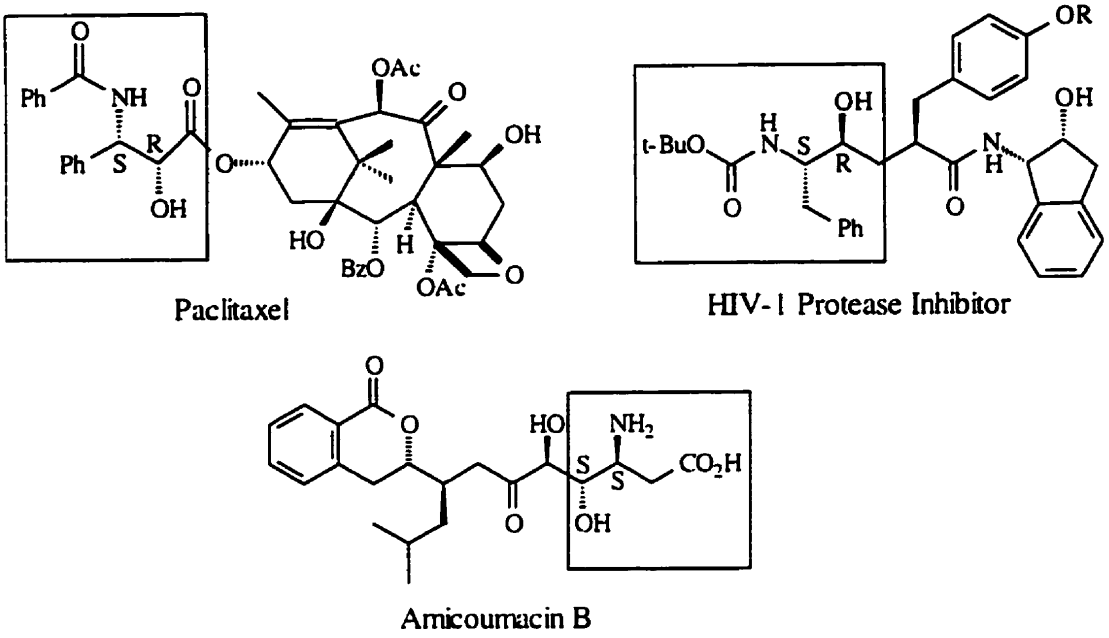
1.0 General: β-Aminoalcohols

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-lympoid 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]

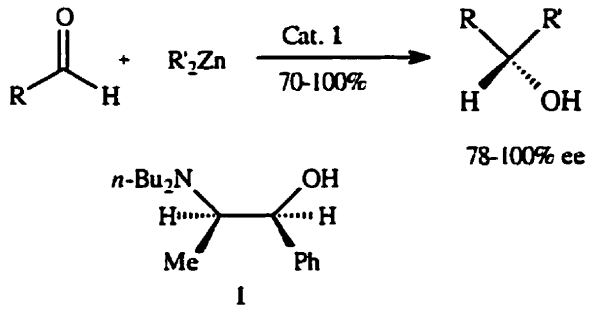
Amicoumacin B is a natural product isolated from the culture broth of *Bacillus pumilus.* It exhibits potent antiulcerogenicity against stress ulcers whilst being non-central suppressive, non-anticholinergic and non-antihistaminergic.[4]

Figure 1: Biologically active β-aminoalcohols



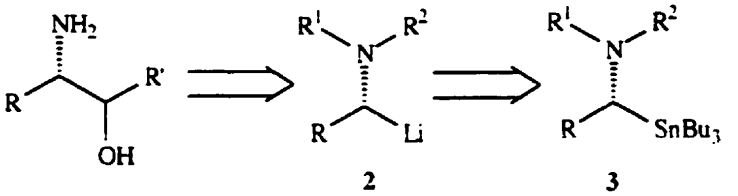
Besides being found in biologically active molecules, β-aminoalcohols are also used as chiral ligands and auxiliaries for asymmetric synthesis. For example, (1S,2R)-(-)-2-(*N*,*N*-dibutylamino)-1-phenylpropan-1-ol **1** (Scheme 1), catalyses the enantioselective addition of dialkylzinc reagents to aliphatic 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, R^1 and R^2 should be easily removed to give either primary or secondary β-aminoalcohols.

Scheme 2



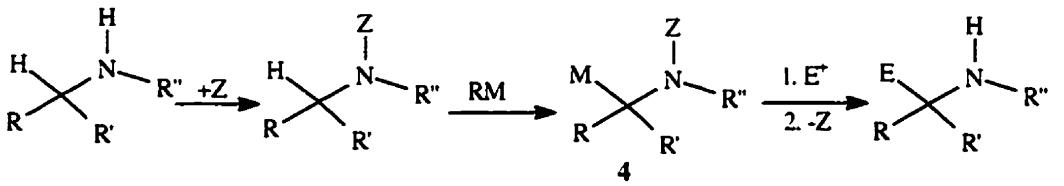
Over the past few years it has been the challenge of organic chemists to find a system that would fulfill all these requirements.

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

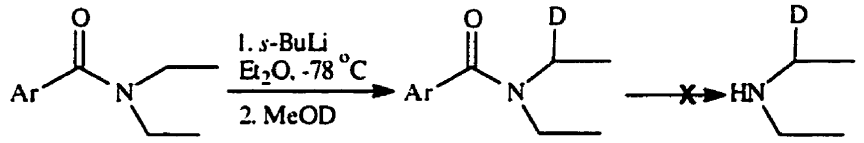


4

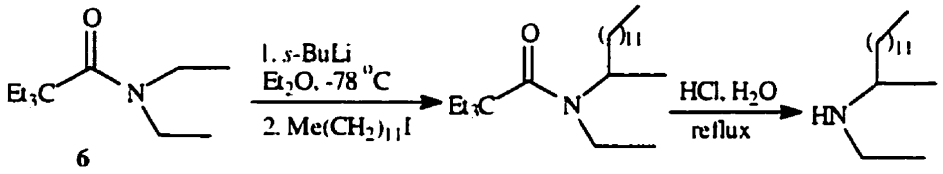
A number of activating groups have been developed; however, some had drawbacks. For example, nitrosoamines first reported by Keefer and Fodor[7] and later extensively studied by Seebach[8] are limited by the hazards in using these substances because they are potential carcinogens. Amides have also been 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 α-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

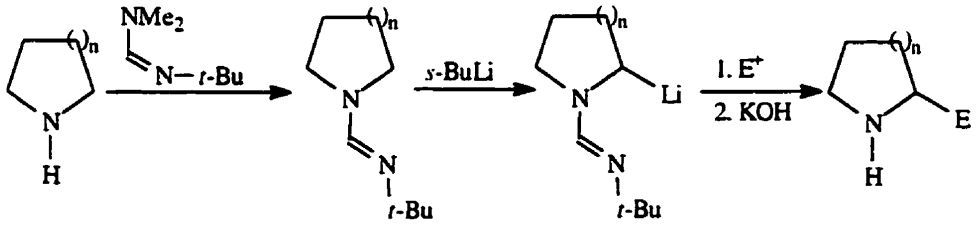


5 Ar = 2,4,6-*i*-$Pr_3C_6H_2$



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

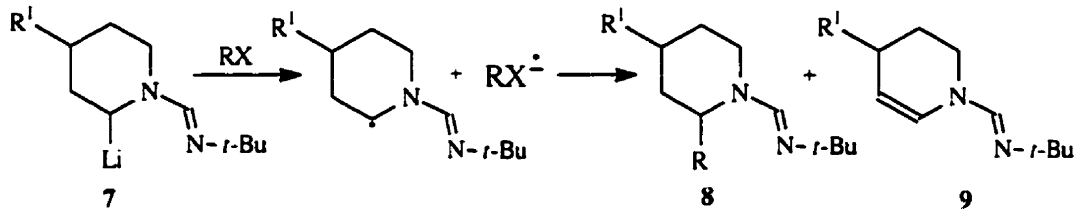


The acidity of the α-protons is considerably enhanced when they are allylic or benzylic, and their chemistry is also somewhat different. The most important difference is

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** (R^1 = Bu^t) 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]

Scheme 6



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 alkylations. 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.

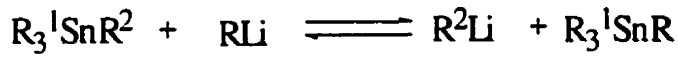
Beak later showed that the *t*-butoxycarbonyl group (*t*-Boc) can also act as a dipole-stabilizing group, which directs α-lithiation.[13]

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.

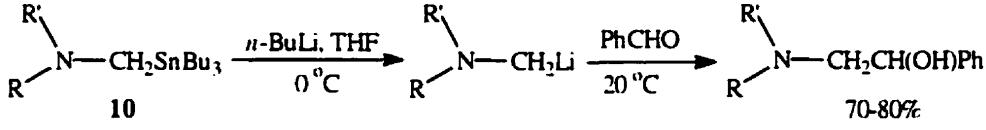
Seyferth discovered the first transmetalation reaction in the late 1950's.[14] The transmetalation reaction is an equilibrium in which the driving force is the relative difference in base strength of the organolithium species RLi and R^2Li (Scheme 7).[15] As a result, alkyl-substituted anionic species would be more difficult to obtain than unsubstituted ones. However, correct choice of solvents and substituents can allow a nearly quantitative shift towards R^2Li. This was shown to be true when R^1 and R are alkyl or aryl groups, and R^2 was allyl[16], benzyl[17], vinyl[18] or even cyclopropyl[19].

Scheme 7



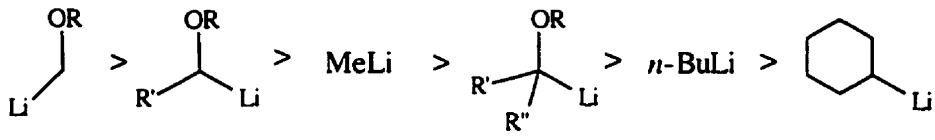
What later became even more useful was the report by Peterson in 1971 that transmetalations were also possible with systems where R^2 was an α-heterosubstituted alkyl[20]. These first transmetalations involved use of *N,N*-dialkylaminomethylstannanes **10** (Scheme 8) which have no destabilizing alkyl substitution at the anionic center.

Scheme 8



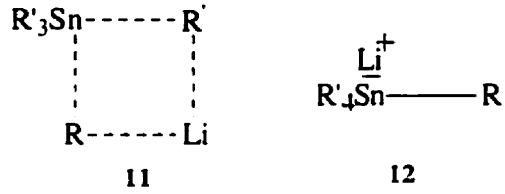
McGarvey later did a study on the relative stability of α-alkoxyorganolithiums and alkyllithiums. As shown in Figure 2, the stability of the α-alkoxyorganolithiums decreases with substitution at the carbanionic center.[21] The α-aminoorganolithiums are believed to follow the same trend.

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).[22] 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.[23] However, McGarvey and coworkers did not observe any of these stannylate complexes in similar NMR experiments with α-alkoxyorganostannanes.[24] They used slightly different conditions than Reich and Philips: THF, Et_2O 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.[23] 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.



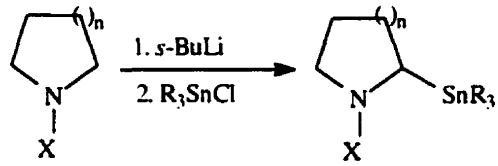
11 12

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 α-Aminoorganostannanes

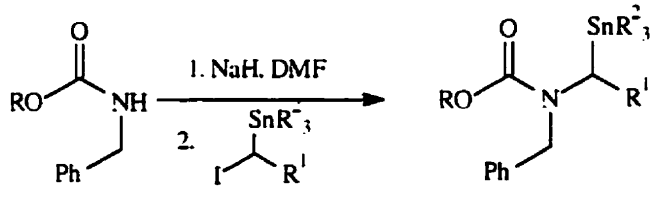
The standard procedure for preparation of cyclic aminoorganostannanes involves deprotonation of the active pyrrolidine or proline and reaction of the organolithium with trialkylstannyl chloride (Scheme 9).[25]

Scheme 9



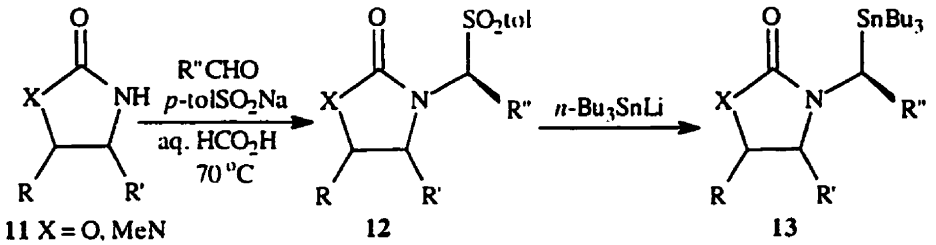
For acyclic systems which can not rely on deprotonation, Pearson and Lindbeck reported a method that involves N-alkylation of carbamates with α-iodoalkylstannanes (Scheme 10).[26] The limitation to this procedure is that α-iodoalkylstannanes other than (iodomethyl)trialkylstannane (R^1 = H) or (iodoethyl)trialkylstannane (R^1 = Me) are not readily available. Elimination of the iodide also occurs instead of alkylation, leading to low yields. In addition, optically active α-iodoalkylstannanes are not available.

Scheme 10



Pearson *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*-toluenesulfonic 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**.[27]

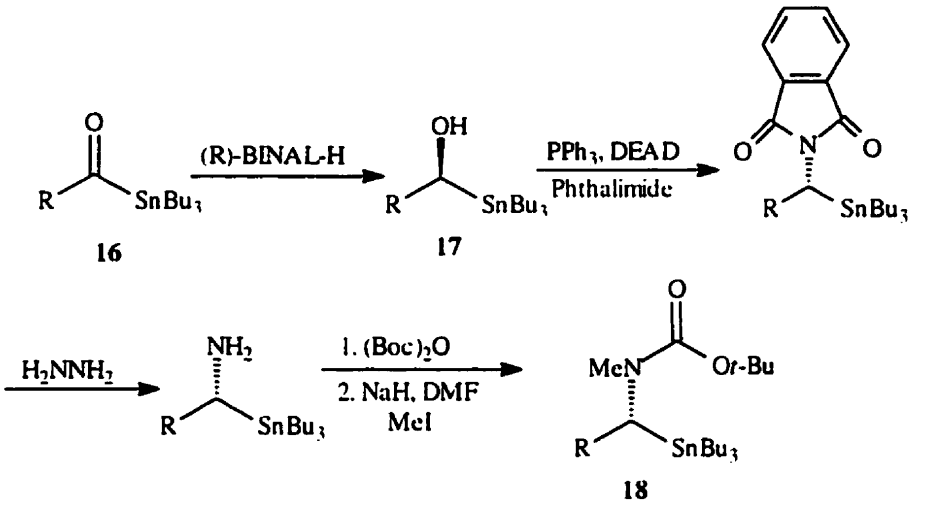
Scheme 11



This method only gives chiral α-aminoorganostannanes when one has a chiral oxazolidinone or chiral imidazolidinone. Simple acyclic protecting groups like *t*-Boc give racemic α-aminoorganostannanes.[28]

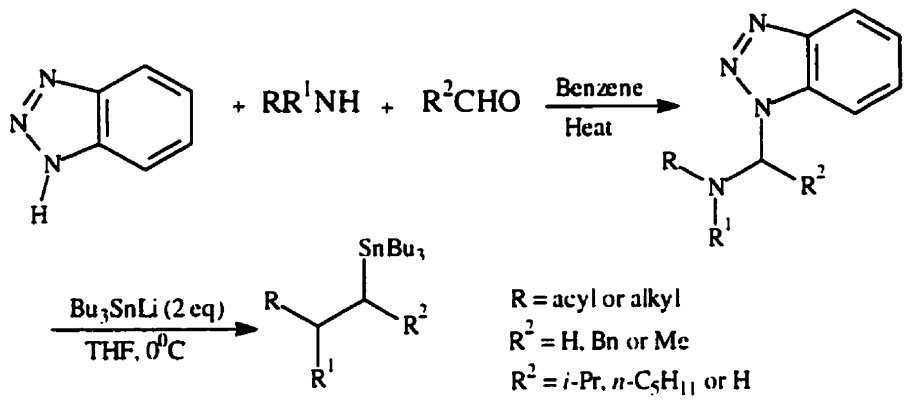
The other method that gave enantiomerically enriched acyclic α-aminoorganostannanes was reported by Chong and Park (Scheme 12).[29] The key step is the enantioselective reduction of acylstannanes **16** with binaphthol modified $LiAlH_4$ (BINAL-H). The resulting α-hydroxystannanes **17** (96% ee) underwent the subsequent steps shown in Scheme 12 and gave α-aminoorganostannanes **18** (94% ee, 42% yield from acylstannanes). The reduction step is the one that contributes most to the poor overall yield.

Scheme 12



Two groups concurrently reported another method to α-aminoorganostannanes.[31,32] 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-aminoorganostannanes. This method is very short and give the products in very high yields. However, it has only been used to make racemic aminoorganostannanes.

Scheme 13



1.3 Configurational Stability of Organolithiums

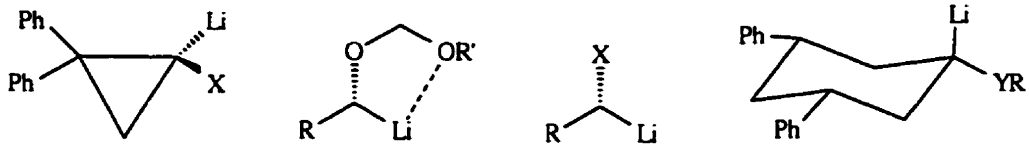
Organolithium species in which the carbanionic center is sp^3 hybridized are isoelectronic with amines and might also undergo pyramidal inversion like the amines. Lestinger and Traynhan prepared the first optically active organolithium, (R)-2-octyllithium, from (R)-2-octyl iodide and *n*-BuLi at –78 °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.[35] 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[36], SPh[37], Br[38]), 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.[39] The equatorial α-aminoorganolithium can also be formed but it is less stable, therefore it quckily 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 is not possible due to steric interactions.

Figure 4: Chiral organolithiums

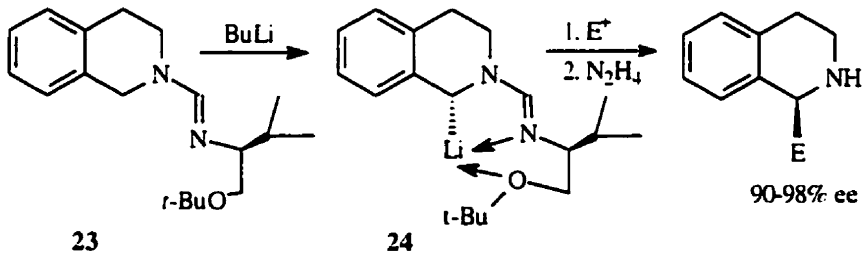


19 **20** **21** **22** Y = S or Se

1.3.1 Configurational stability of α-Aminoorganolithiums

Early studies on configurational stability of aminoorganolithiums were reported by Meyers and coworkers.[40] 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.[40]

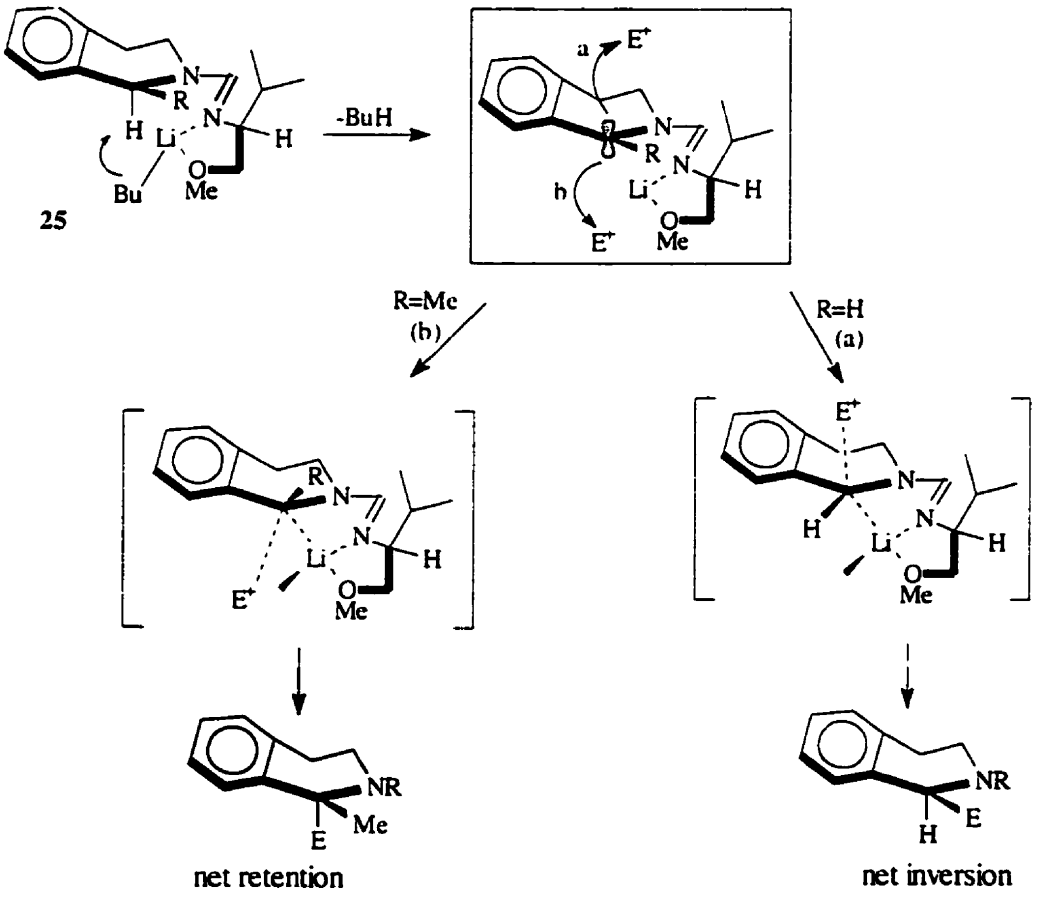
Scheme 14



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.[41]

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



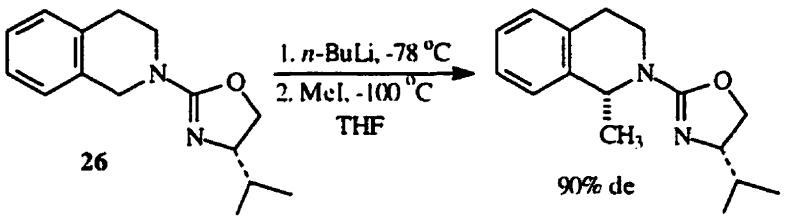
Experiments were also done to investigate the alkylation of 3° carbanions.[42] With all these experiments the authors suggested that the overall mechanism summarized in Scheme 15 occured. The authors showed that all deprotonations take place from the α-

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.

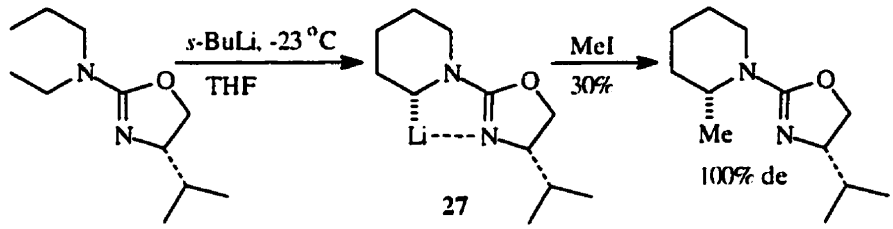
Scheme 16



Experimental evidence later suggested that the β-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.

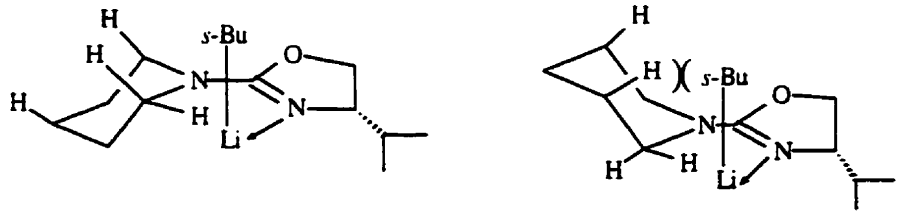
Gawley also studied the non-benzylic piperidinooxazolines (Scheme 17). Alkylation of these systems was found to be 100% stereoselective.[44] Unlike the tetrahydroisoquinolyloxazolines which afford benzylic organolithiums, it was assumed, on both experimental and theoretical grounds, that the organolithium 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.[44]

Scheme 17



The selectivity was rationalized by assuming prior coordination of the alkyllithium to the oxazoline nitrogen, and orientation of the alkyl group to be *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 conlcuded that steric effects must be responsible for the observed selectivity.[44]

Figure 5: Coordination complexes for the deprotonation of piperidinooxazolines.



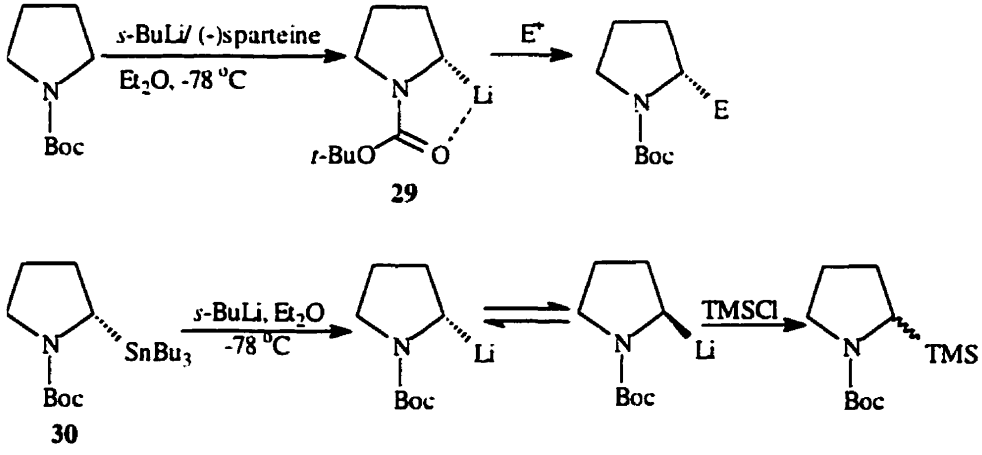
28a **28b**

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

piperidinooxazolines. Although the piperidinooxazolines are configurationally stable,their alkylation give 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 spartein.

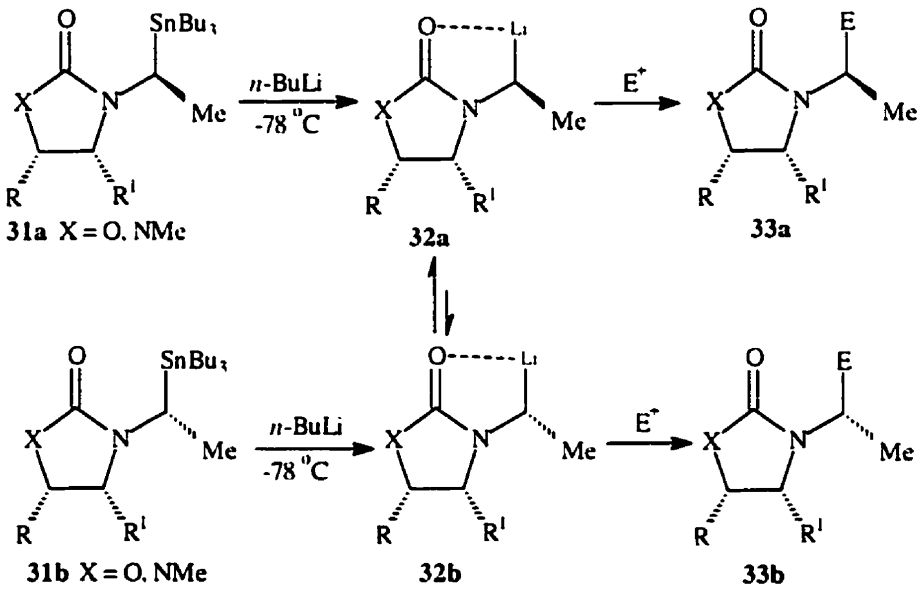
Scheme 18



The first report on configurational stability of nonconjugated, acyclic dipole stabilized α-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



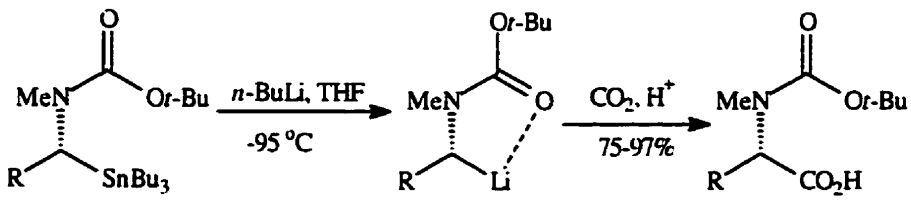
When the oxazolidinones **31** (X = O) were transmetalated, **33a** was the only product isolated even when the starting material was **31b**. Although transmetalation of the two diastereomeric stannanes **31a** and **31b** initially give **32a** and **32b,** respectively, **32b** was found to equilibrate within 40 min at –78 °C to the more stable diastereomer **32a**. The steric hindrance between the *syn* R^1 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).[46]

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.[29]

Scheme 20



34a R = Et, 94% ee
34b R = i-Pr, 92% ee

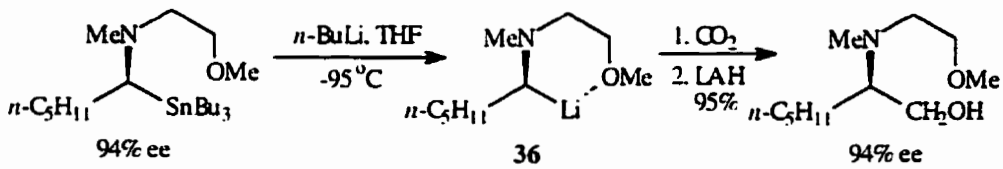
35

R = Et, 94% ee
R = i-Pr, 92% 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.[29] 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.[47] 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.

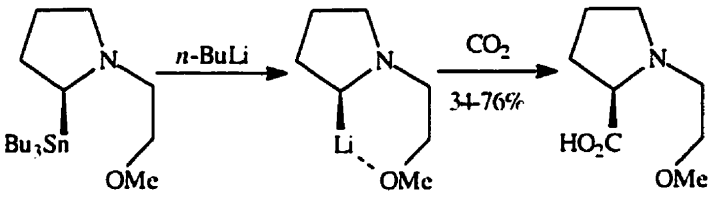
Scheme 21



Gawley and Zhang later prepared the cyclic counterparts, **37** (Scheme 22).[48] 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 °C only in a THF/TMEDA solvent system. In the absence of TMEDA, racemization is faster, especially in DME.

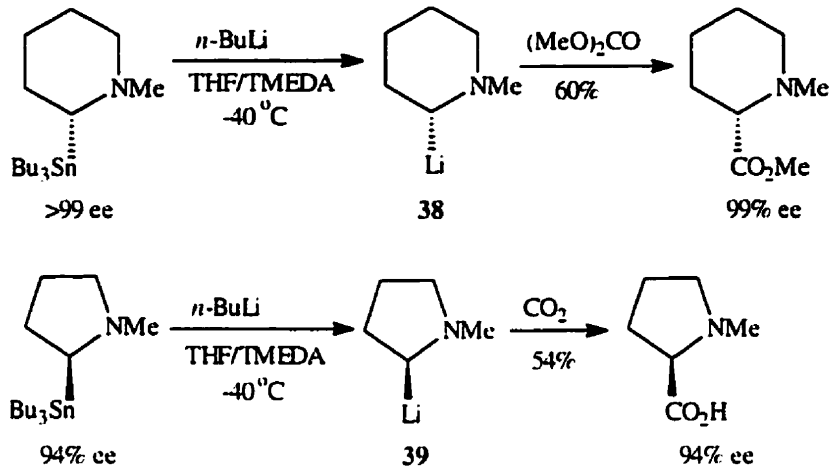
Scheme 22



37

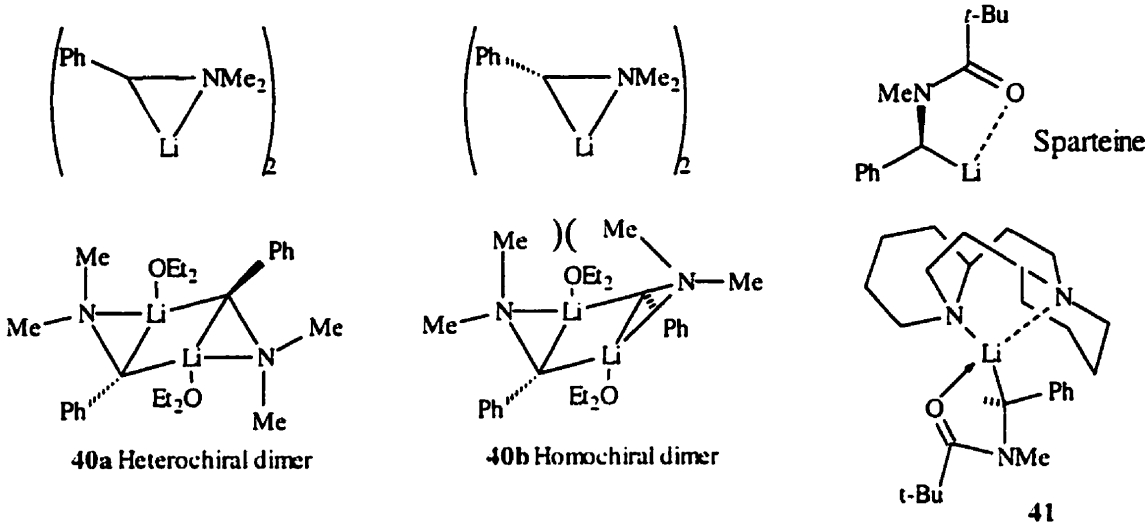
Yamamoto[49] and Chong[47] were not successful in their attempt to obtain unchelated acyclic 2° α-aminoorganolithiums by transmetalation. Surprisingly, Gawley and Zhang were able to prepare *N*-methyl 2-lithiopyrolidines and piperidines (**39** and **38** respectively) which were configurationally stable at temperatures as high as –40 °C in THF in the presence of TMEDA (Scheme 23).[48] 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 α-aminoorganolithiums reported to date.

Scheme 23



Gawley and Zhang explained this unusual configurational stability using the crystal structures of [α-(dimethylamino)benzyllithium.diethyl ether]$_2$ **40** and S-α-(methylpivaloylamino)benzyllithium.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



40a Heterochiral dimer

40b Homochiral dimer

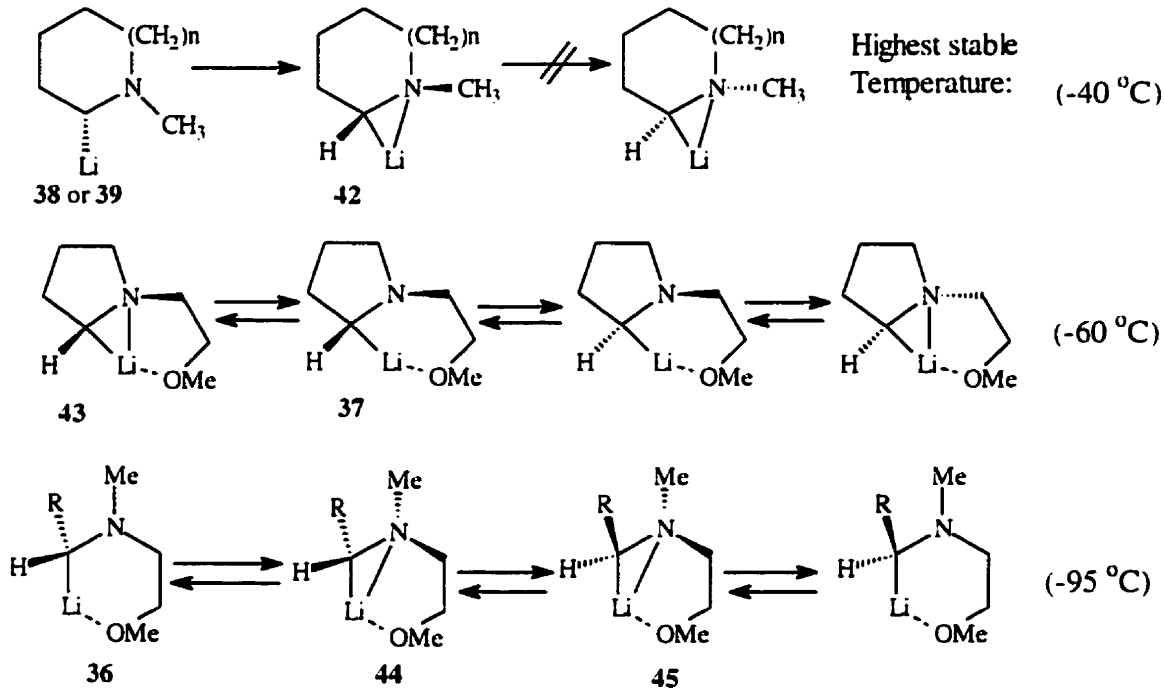
41

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.[49] 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

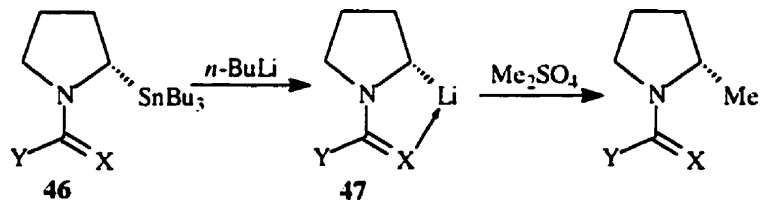


Both *N*-methyl-2-lithiopiperidine and pyrrolidine (**38** and **39**) were found to react with different electrophiles giving 2-substituted heterocycles in very good yields.[51] In the piperidine system, the reaction with carbonyl electrophiles occurred with nearly 100% retention of stereochemistry 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.[52] They compared the transmetalation of the lithioformamidines **46a** and Beak's *t*-Boc system **46b** (Scheme 25).[45] The organolithium **47a** was found to be configurationally stable between –78 °C and –55 °C in THF and also trapped with Me_2SO_4 without any racemization. However, N-*t*-Boc lithiopyrrolidine **47b** showed complete loss of optical activity after 30 min at –78 °C.

Scheme 25



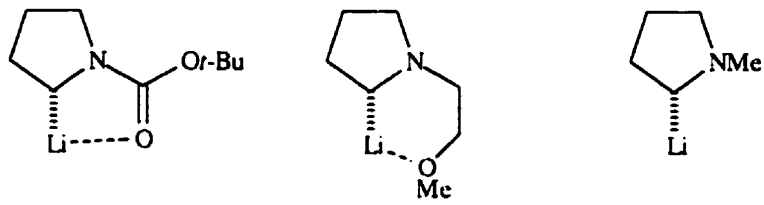
46 **47**

a) X = N-*t*-Bu, Y = H (Formamidine)
b) X = O, Y = O*t*-Bu (*t*-Boc)

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.[52]

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.

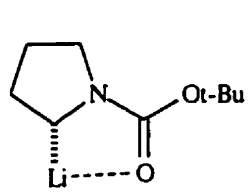
Figure 7: Configurational stability of lithiopyrrolidines



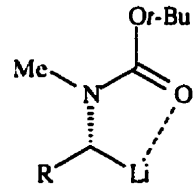
29 Not Stable **37** Stable up to -60 °C **39** Stable up to -40 °C

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-*t*-Boc lithiopyrrolidine **29** (Figure 8), racemizes completely at –78 °C[44] whereas its acyclic cousin **35** underwent only 12% racemization at –78 °C after 3 h.[29]

Figure 8: Cyclic vs. acyclic organolithiums



29



35

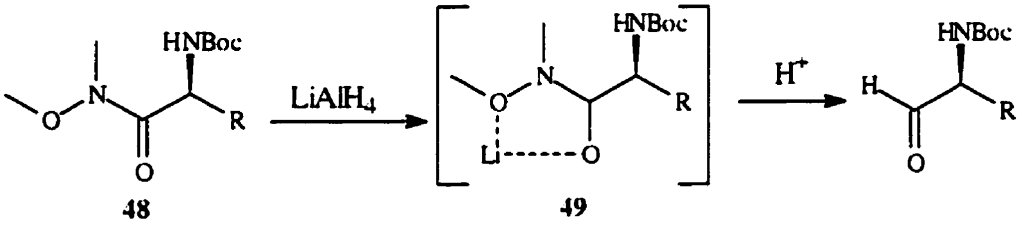
From what is known so far, the addition of coordinating solvents to acyclic α-aminoorganolithiums facilitates racemization. On the other hand, coordinating solvents seem to enhance configurational stability in cyclic organolithiums. This opposite behavior might suggest that the mechanism of inversion 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 $LiAlH_4$ reduction of imidazolides. The resulting aminoalcohols can then be oxidized back to the aminoaldehydes making the

method longer.[53] An efficient method that does not involve racemization or overrreduction was reported by Fehrentz and Castro (Scheme 26).[54] The reduction of N-methoxy-N-methyl carboxamides **48** with $LiAlH_4$ 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.

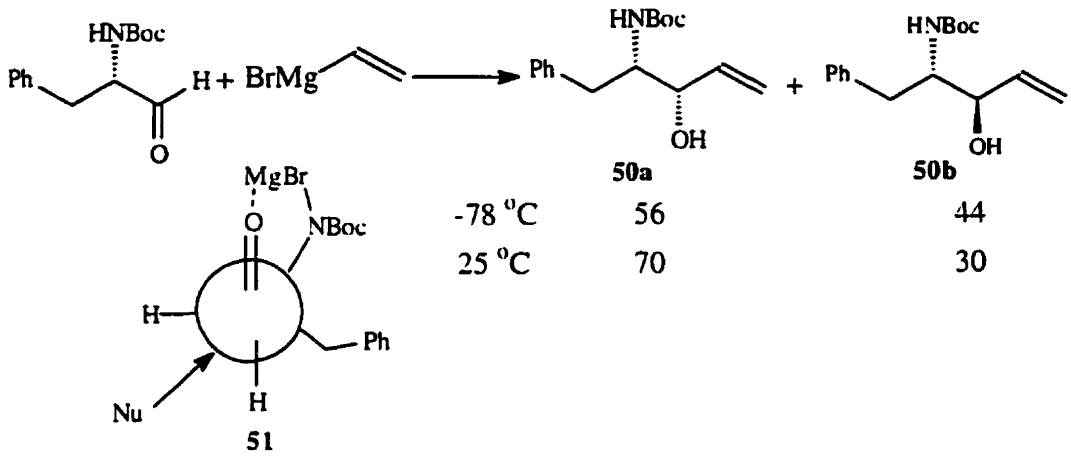
Scheme 26



48 **49**

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.[55] 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.

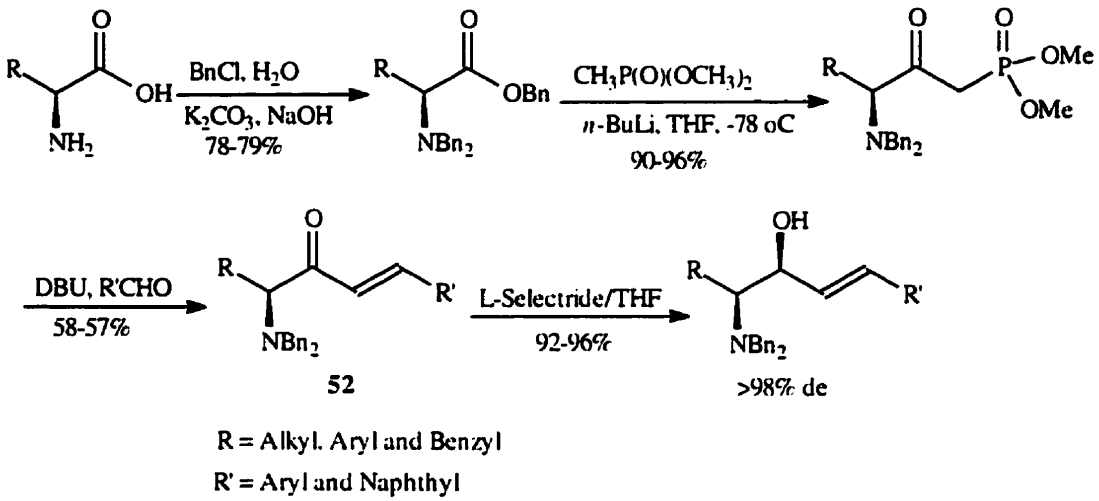
Scheme 27



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.[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 **52** (Scheme 28) derived from α-amino acids. Reduction of the amino enones with lithium tri-*sec*-butylborohydride (L-Selectride®) 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.[57]

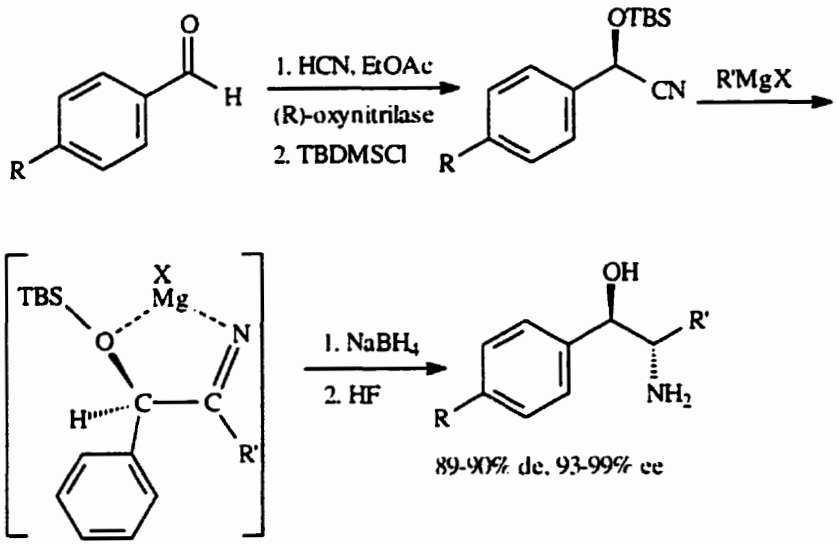
Scheme 28



The major disadvantage of both aminoaldehydes 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).[58] The cyanohydrins are first protected by the *tert*-butyldimethylsilyl (TBDMS) group and then addition of Grignard reagents gives an imine which then undergoes diastereoselective reduction with $NaBH_4$. The β-aminoalcohols were obtained in 93-99% ee and 80-98% de with the *anti* being the major diastereomer due to chelation control.[59]

Scheme 29



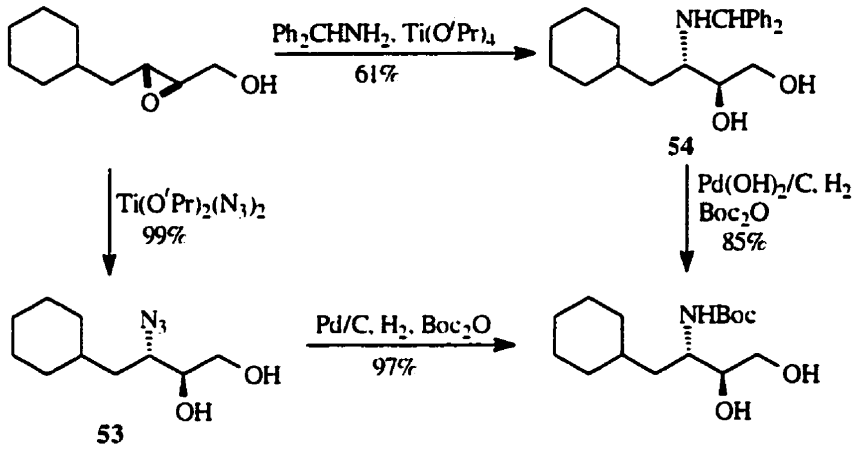
The *syn* β-aminoalcohols are obtained when DIBAL is added to the O-protected cyanohydrin before the organolithium reagent is added. This procedure, however, gives lower diastereoselectivity.[60]

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 β-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 β-aminoalcohol.[63] Riera and coworkers later reported the use of benzhydrylamine in order to avoid the use of

potentially risky azides.[64] 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.

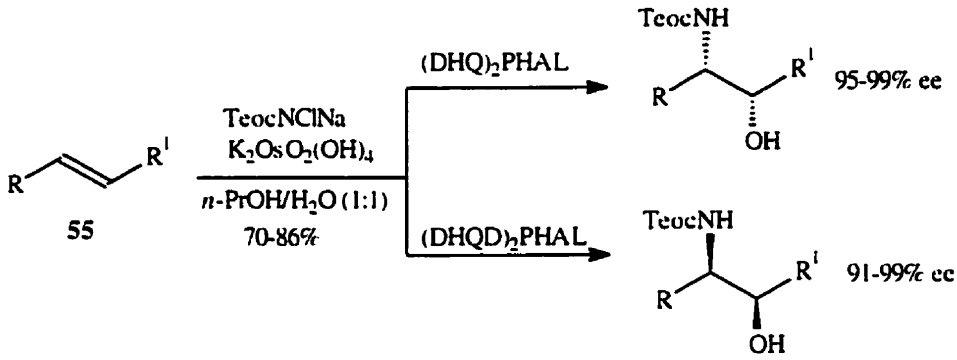
Scheme 30



What might be a more direct route to β-aminoalcohols to date, is the asymmetric aminohydroxylation (AA) recently reported by Sharpless.[65] 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 (TsNClNa) 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 (TeocNClNa) (Scheme 31).[66]

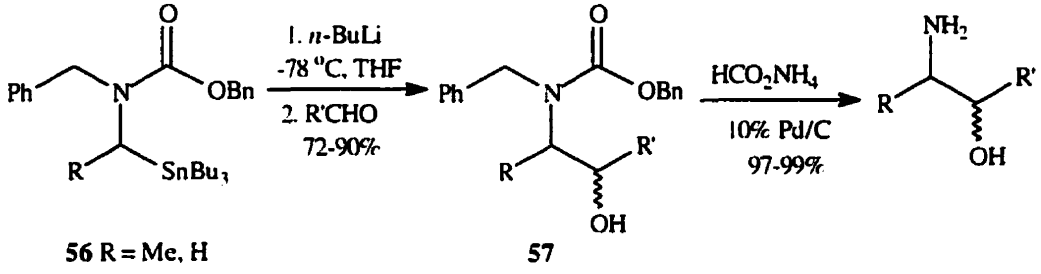
Scheme 31



The examples that the authors reported involve only *E* alkenes **55** with aromatic R groups and R^1 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* β-aminoalcohols.

The only example that involves the use of acyclic α-aminoorganolithiums was reported by Pearson and Lindbeck.[26] This was achieved by transmetalation of α-aminoorganostannanes **56** (Scheme 32) and trapping the resulting organolithiums with different aldehydes to give the β-aminoalcohols **57**. Deprotection by transfer hydrogenolysis gave the primary β-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 β-aminoalcohols.

Scheme 32



56 R = Me, H **57**

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.

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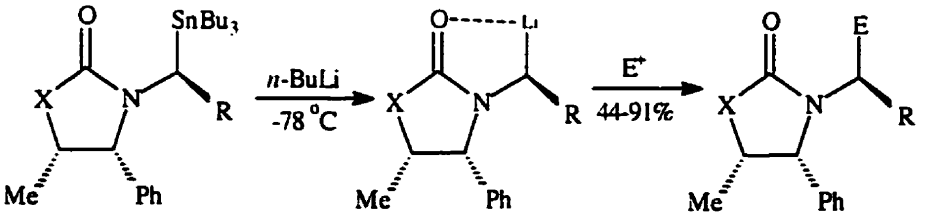
Chapter 2

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.[1] 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



58a X = NMe
58b X = O

59

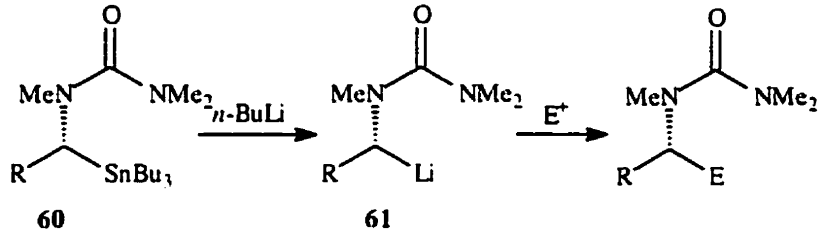
R = Me, Et, *i*-Pr

E = D, $SnBu_3$, $C(OH)(CH_2)_5$, CH(OH)Ph, $CH(OH)^iPr$, CO_2Et

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 α-aminoorganolithiums.

Scheme 34



60 **61**

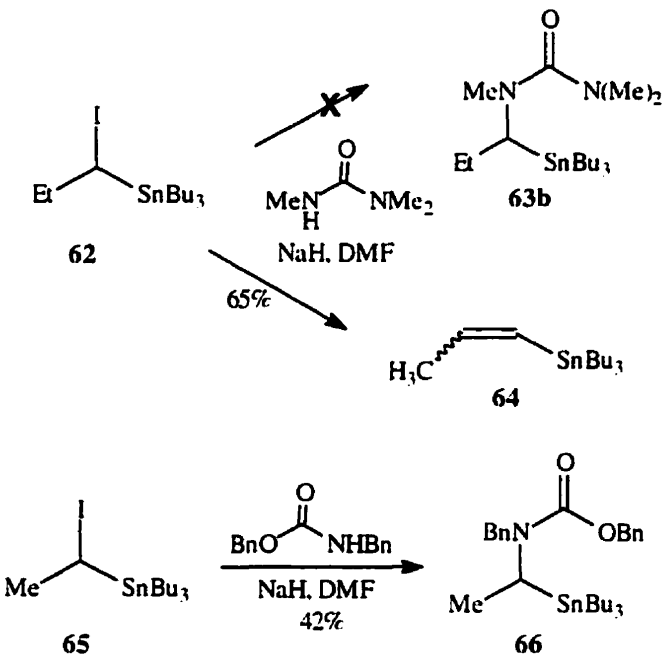
2.2 Results and Discussion

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 α-iodoalkylstannanes, first reported by Pearson and Lindbeck.[2] The α-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 α-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.[2] Perhaps the iodostannane **62** is too sterically hindered to react with the trimethylurea anion.

Scheme 35



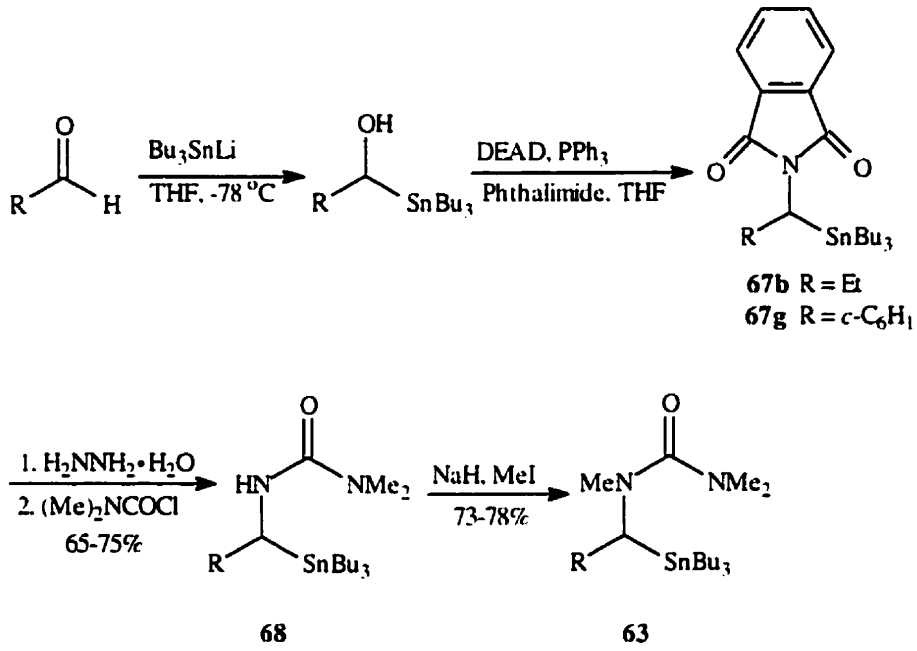
Note: All the compounds with different R groups will be numbered alphabetically as follows:

no.	a	b	c	d	e	f	g
R	Me	Et	*n*-C_3H_7	*n*-C_4H_9	*n*-C_5H_{11}	*i*-Pr	*c*-C_6H_{11}

The most successful method for making tributylstannyl carbamates was reported by Chong and Park.[4] 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

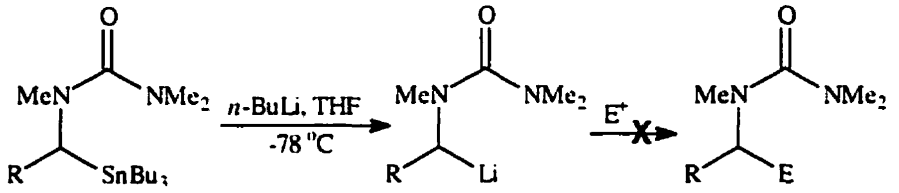


2.2.2 Transmetalation of α-aminoorganostannanes

Transmetalation of **63b** with *n*-BuLi at –78 °C led to >95% transmetalation (based on isolated *n*-Bu_4Sn) in 5 min (Scheme 37). However, attempted trapping of the resulting organolithium with CO_2 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.

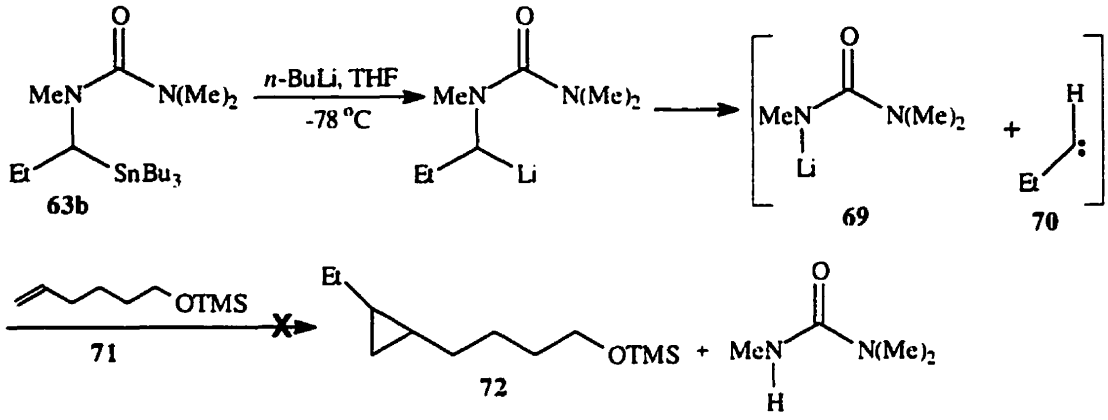
Assuming that we were facing a polarity problem, we tried to circumvent this by using a bigger R group; cyclohexyl. We were hoping that it would give a less polar product that would be easier to isolate. Unfortunately, trasmetalation of **63g** and attempted trapping of the organolithium with either CO_2 or PhCHO also gave no product.

Scheme 37



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 occuring, 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.[5] Hence, we could not obtain any experimental evidence for the proposed decomposition pathway.

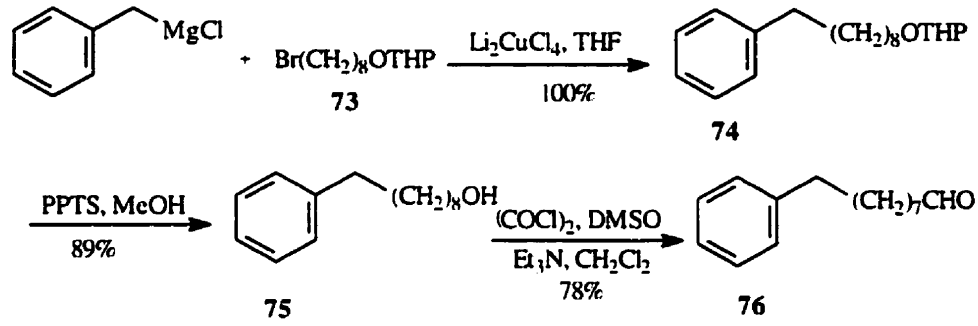
Scheme 38



Attempts were also made to detect the decomposition products by low temperature ^{1}H NMR spectroscopy. *n*-BuLi was added to a solution of α-aminoorganostannane **63b** in THF-d_8 at –78 °C and a ^{1}H NMR experiment was performed immediately. To our disappointment, no useful information was obtained from the spectrum.

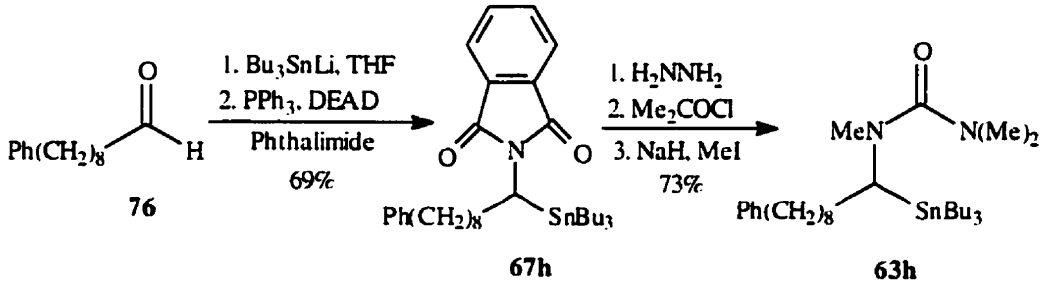
We decided to prepare an aldehyde that had a long chain and was also UV active. The intent here was to make an α-aminoorganostannane which would give a hydrophobic product which might be easier to detect and isolate. Aldehyde **76** was prepared as outlined in Scheme 39. Coupling of the bromide **73**[6] and benzylmagnesium chloride in the presence of dilithium tetrachlorocuprate (Li_2CuCl_4) gave the tetrahydropyranyl (THP) ether **74** in quantitative yield.[7] The THP group was easily removed by pyridinium *p*-toluenesulfonate (PPTS) and gave the alcohol **75**.[8] However, oxidation of the alcohol using pyridinium chlorochromate (PCC) gave a very low yield of **76** (44%).[9] 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.[10]

Scheme 39



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

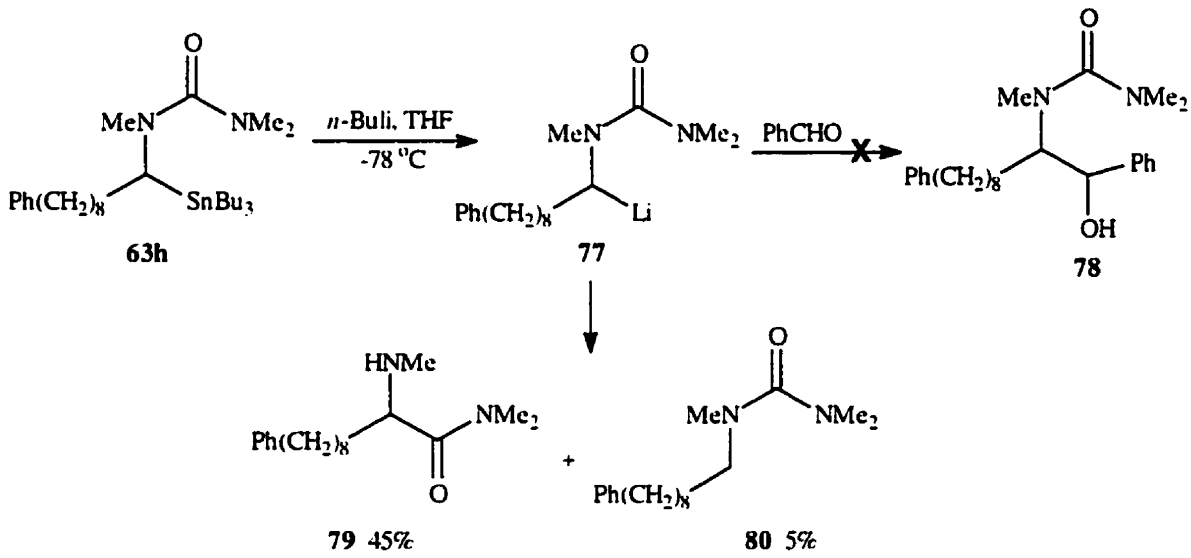
Scheme 40



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-C_6H_{11}), the byproducts would be even more polar and would also be hard to detect because they are not ultraviolet (UV) active.

Scheme 41

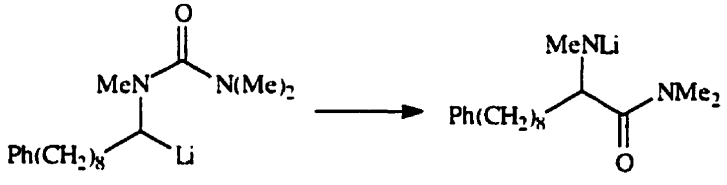


The minor product **80** was due to protonation of the organolithium and the major product **79** was due to 1,2 migration of the amide group (Scheme 42). This was very disappointing, since Pearson and Lindbeck had successfully transmetalated the imidazolidinones **58a** (Scheme 33) and trapped the resulting 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 pK_a of their conjugate acids. Generally, the pK_a of an

amine (N-H) is around 35.[11] The pK_a of an alkane (C-H) is between 47-50. However, the congugate 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**.

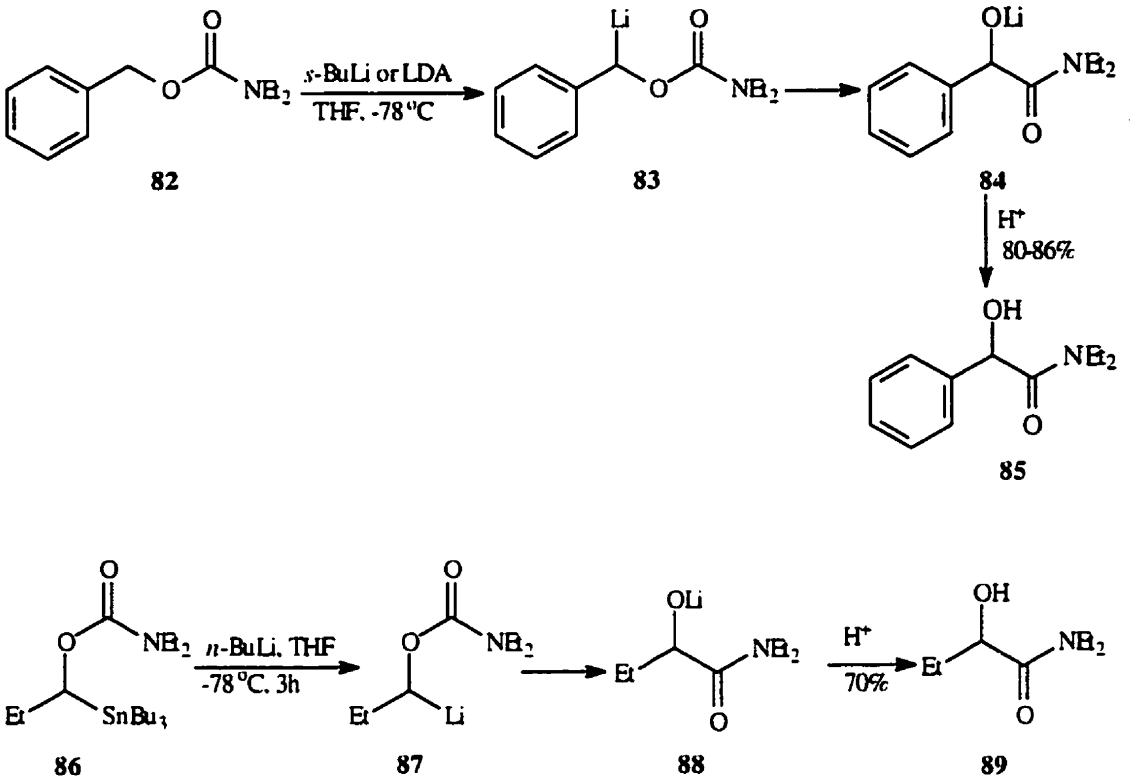
Scheme 42



77 **81**

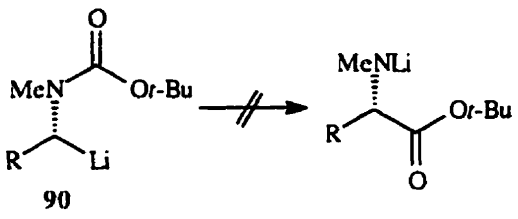
The only anionic 1,2 migrations that have been reported involve migration of the carbonyl from oxygen to carbon (O-C migrations). For example, when Gawley and Zhang lithiated the benzylic carbamate **82** (Scheme 43), the amide group migrated to the benzylic position giving the alkoxide **84** which gave the alcohol **85** in high yield.[12] 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 seem to be sterically controlled because organolithiums from the transmetalation of *N,N*-diisopropyl stannyl carbamates do not undergo migration.[13] Formation of alkoxides is not surprising at all because of the big difference in pK_a of alcohols (pK_a =16) and pK_a ~41 and <48 for the conjugate acids of the carbanions for **83** and **87** respectively.[11]

Scheme 43



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.

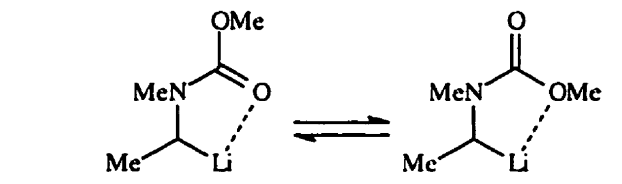
Scheme 44



To try and explain why this migration was being observed in ureas and not in carbamates, we did semi-emperical molecular orbital calculations (MOPAC) using the MNDO Hamilitonian.[14] 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 (ΔH_f). This was expected because the carbonyl oxygen chelates to the lithium atom much more strongly than either nitrogen or ether-type oxygen.

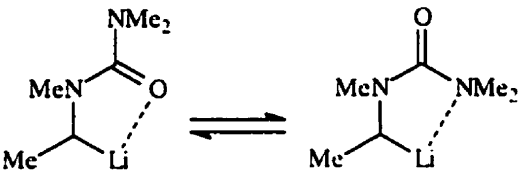
The difference in ΔH_f between **91a** and **91b** ($\Delta\Delta H_f$ = 9.1 kcal/mol) is higher than that between **92a** and **92b** ($\Delta\Delta H_f$ = 6.4 kcal/mol). Due to this big difference in energy between **91a** and **91b**, the carbanion must exist mainly as **91a**. The minor conformations **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.

Scheme 45



$\Delta\Delta H_f$ (kcal/mol): 9:1

91a ΔH_f = -102.61 kcal/mol **91b** ΔH_f = -93.53 kcal/mol



6:4

92a ΔH_f = -50.68 kcal/mol **92b** ΔH_f = -44.26 kcal/mol

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 gylcol/water 30:70 v/v); –78 °C (dry ice-acetone); -95 °C (N_2-MeOH). Diethyl ether, tetrahydrofuran and hexane were distilled from sodium/benzophenone ketyl: CH_2Cl_2 and CH_3CN were distilled over CaH_2. Anhydrous ethanol was distilled from magnesium ethoxide and stored over 3Å molecular sieves. Diisopropylamine and triethylamine were distilled from CaH_2 and stored over 3Å molecular sieves. *N,N*-Dimethylformamide (DMF) was distilled from CaH_2 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] $Br(CH_2)_8OTHP$ 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 F_{254} 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. ^1H

and ^{13}C NMR spectra were recorded using Bruker AC-200 and AM-250 spectrometers using $CDCl_3$ as solvent unless otherwise noted. Tetramethylsilane (^1H, δ 0.0) and $CDCl_3$ (^{13}C, δ 77.0) were used as internal references. ^1H 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 (δ_A-δ_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-tributylstannyl dimethylureas* **68**

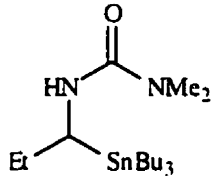
Reaction 1:

To a 0.1 M solution of the corresponding phthalimide in EtOH was added hydrazine hydrate (50 equiv) and H_2O (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_2O 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:

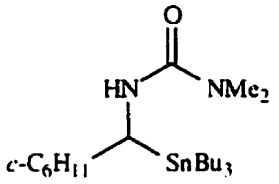
To a cooled (0 °C) 0.2 M solution of the crude amine in CH_2Cl_2 was added Et_3N (1.3 equiv) and dimethylcarbamoyl chloride (1.2 equiv). The solution was warmed to room temperature (rt) and stirred for the specified time. The mixture was washed with water, dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (35 g of silica/g of substrate; 2:1 hexane/Et_2O).

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



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, $N(CH_3)_2$), 1.81-1.60 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.54-1.01 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.97-0.75 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2CHN$); ^{13}C NMR (50 MHz) δ 158.7, 43.4, 36.3, 29.3 (^2J = 20), 28.1, 27.6 (^3J = 55), 13.7, 12.7, 10.1 (^1J = 317, 304); MS, FAB *m/z* (relative intensity) 363 (M^+ - C_4H_9, 100), 289 (8), 249 (15), 207 (25), 129 (40). Anal. Calcd for $C_{18}H_{40}N_2OSn$: C, 51.57; H, 9.62; N, 6.68. Found: C, 51.74; H, 9.59; N, 6.69.

2.3.4 *N-(1-Cyclohexyl-1-tributylstannylmethyl)-N',N'-dimethylurea* **68g**



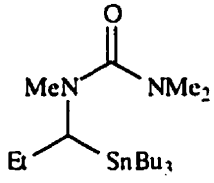
This dimethylurea was prepared from **67g** according to the general procedure described in section 2.3.2 with a reaction time of 24 h for reaction 1, and 5 h for reaction 2. The product was obtained as a white solid in 65% yield: mp 75-79 °C; IR (KBr) 3304, 2901, 1617, 1535, 1452, 1360, 1230, 1069 cm^{-1}; ^1H NMR (250 MHz) δ 4.70 (d, 1 H, J = 7.2 Hz, NH), 3.10 (t, 1 H, J = 7.6 Hz, CHN), 2.87 (s, 6 H, $N(CH_3)_2$), 1.67-1.16 (m, 21 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and *c*-$C\underline{H}(C\underline{H}_2)_2CH_2(C\underline{H}_2)_2$), 0.91-0.71 (m, 17 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and *c*-$CH(CH_2)_2C\underline{H}_2(CH_2)_2$); ^{13}C NMR (63 MHz) δ 158.7, 48.8, 42.1, 36.3, 32.5, 31.8, 29.4 (^2J = 19), 27.7 (^3J = 56), 26.7, 26.5, 26.3, 13.8, 10.3 (^1J = 315, 308); MS, FAB *m/z* (relative intensity) 417 (M^+ - C_4H_9, 28), 377 (10), 305 (12), 235 (26), 185 (100), 119 (30). Anal. Calcd for $C_{22}H_{46}N_2OSn$: C, 55.83; H, 9.80; N, 5.92. Found: C, 56.02; H, 9.64; N, 5.79.

2.3.5 *General procedure for the preparation of 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 rt and stirred for the specified time. The mixture was quenched carefully with saturated NH_4Cl, diluted with Et_2O, washed with H_2O followed

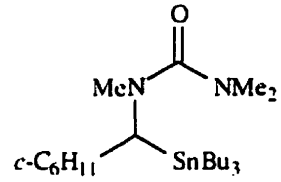
by saturated NaCl. The organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude products were purified by flash chromatography (40 g silica/ g of substrate; 2:1 hexane/Et_2O) to give the stannanes as colorless oils.

2.3.6 *N-(1-Tributylstannylpropyl)-N,N',N'-trimethylurea* **63b**



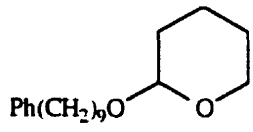
This trimethylurea was prepared from **68b** according to the general procedure described in section 2.3.5 with a reaction time of 48 h in 70% yield: IR (neat) 2904, 1631, 1497, 1459, 1368, 1120, 1067 cm^{-1}; ^1H NMR (200 MHz) δ 3.00 (t, 1 H, J = 8.1, CHN), 2.84 (s, 3 H, CH_3N), 2.74 (s, 6 H, $N(CH_3)_2$), 1.88-1.59 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.55-1.21 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.99-0.69 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2CHN$); ^{13}C NMR (50 MHz) δ 165.2, 54.1, 38.9, 38.3, 29.2 (^2J = 29), 27.6 (^3J = 55), 25.3, 13.6, 12.8, 10.1 (^1J = 309, 297); MS, FAB *m/z* (relative intensity) 377 (M^+-C_4H_9, 85), 291 (10), 221 (18), 177 (25), 143 (100). Anal. Calcd for $C_{19}H_{42}N_2OSn$: 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-tributylstannylmethyl)-N,N',N'-trimethylurea* **63g**



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, CH_3N), 2.73 (6 H, $N(CH_3)_2$), 2.73-2.68 (m, 1 H, CHN), 1.88-1.15 (m, 21 H, *c*-C<u>H</u>(C<u>H</u>$_2$)$_2$CH$_2$(C<u>H</u>$_2$)$_2$ and SnCH$_2$(C<u>H</u>$_2$)$_2$CH$_3$), 0.92-0.68 (m, 17 H, *c*-CH(CH$_2$)$_2$C<u>H</u>$_2$(CH$_2$)$_2$ and SnC<u>H</u>$_2$(CH$_2$)$_2$C<u>H</u>$_3$); ^{13}C NMR (63 MHz) δ 164.8, 60.1, 39.8, 39.3, 38.8, 32.8, 32.1, 29.3 (^2J = 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^+-C_4H_9, 80), 337 (12), 315 (10), 219 (16), 197 (100), 119 (16). Anal Calcd for $C_{23}H_{48}N_2OSn$: C, 56.68; H, 9.93; N, 5.75. Found: C, 56.69; H, 9.79; N, 5.71.

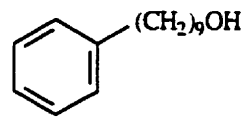
2.3.8 *(9-Phenyl)nonyl tetrahydropyranyl ether* **74**



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(CH$_2$)$_8$OTHP (3.1 g, 10.6 mmol) and Li_2CuCl_4 (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 NH_4Cl (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic solution was washed with 1 N HCl (2 x 80 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (200g silica; 10:1 hexane/Et_2O) 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*-OC<u>H</u>(CH_2)O), 3.91-3.88 (m, 1 H, *c*-OCH(CH_2)$_3$C<u>H</u>$_2$O), 3.78-3.68 (m, 1 H, Ph(CH_2)$_8$C<u>H</u>$_2$O), 3.53-3.45 (m, 1 H, *c*-OCH(CH_2)$_3$C<u>H</u>$_2$O), 3.42-3.33 (m, 1 H, Ph(CH_2)$_8$C<u>H</u>$_2$O, 2.59 (t, 2 H, J = 7.7, PhC<u>H</u>$_2$(CH_2)$_8$), 1.84-1.47 (m, 10 H, PhCH_2C<u>H</u>$_2$(CH_2)$_5$C<u>H</u>$_2$CH_2O and *c*-OCH(C<u>H</u>$_2$)$_3$CH_2O), 1.40-1.15 (m, 10 H, Ph(CH_2)$_2$(C<u>H</u>$_2$)$_5$(CH_2)$_2$O); ^{13}C 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 $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.69; H, 10.39.

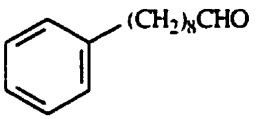
2.3.9 9-Phenylnonan-1-ol 75



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, C<u>H</u>$_2$OH), 2.59 (t, 2 H, J =

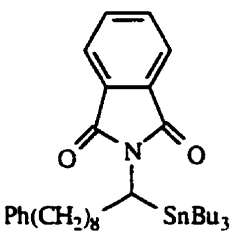
7.7, $PhC\underline{H}_2$), 1.96 (s, 1 H, OH), 1.63-1.50 (m, 4 H, $PhCH_2C\underline{H}_2(CH_2)_5C\underline{H}_2$), 1.29 (m, 10 H, $Ph(CH_2)_2(C\underline{H}_2)_5$); ^{13}C NMR (63) δ 142.8, 128.3, 128.1, 125.5, 62.8, 35.9, 32.7, 31.4, 29.4, 29.3, 29.2, 25.7; MS, EI *m/z* (relative intensity) 220 (M^+, 13), 202 (M^+-H_2O, 5), 104 (94), 91 (100). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.78.

2.3.10 9-Phenylnonanal 76



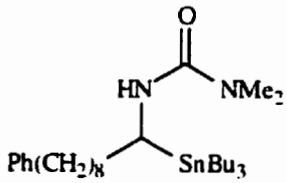
This aldehyde was prepared by the Swern oxidation[10] of **75** as a white solid in 78% yield: mp 31-35 °C; IR (KBr) 3058, 3026, 2927, 2855, 1720, 1602, 1495, 1044 cm^{-1}; ^1H NMR (250 MHz) δ 9.71 (t, 1 H, J = 1.8, CHO), 7.25 (m, 5 H, ArH), 2.59 (t, 2 H, J = 7.7, $PhC\underline{H}_2$), 2.38 (dt, 2 H, J = 7.3, 1.8, $C\underline{H}_2CHO$), 1.62-1.56 (m, 4 H, $PhCH_2C\underline{H}_2(CH_2)_4C\underline{H}_2$), 1.30 (m, 8 H, $Ph(CH_2)_2(C\underline{H}_2)_4$); ^{13}C 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 $C_{15}H_{22}O$: 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[5] as a yellow oil in 69% yield: IR (neat) 2906, 1770, 1705, 1460, 1379, 1065 cm^{-1}; ^1H NMR (250 MHz) δ 7.81 (m, 2 H, ArH), 7.76 (m, 2 H, ArH), 7.27 (m, 5 H, $\underline{Ph}CH_2$), 3.95 (dd, 1 H, J = 6.7, 9.3, CHN), 2.56 (t, 2 H, J = 7.7, $PhC\underline{H}_2$), 1.93-1.87 (m, 1 H, $Ph(CH_2)_7C\underline{H}_2$), 1.79-1.60 (m, 1 H, $Ph(CH_2)_7C\underline{H}_2$), 1.58-1.40 (m, 20 H, $PhCH_2(C\underline{H}_2)_4$ and $SnCH_2(C\underline{H}_2)_2CH_3$), 1.00-0.54 (m, 19 H, $PhCH_2C\underline{H}_2(CH_2)_4C\underline{H}_2CH_2$ and $SnC\underline{H}_2C(CH_2)_2C\underline{H}_3$); ^{13}C NMR (63 MHz) δ 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 (^2J = 57), 13.6, 10.3 (^1J = 326, 310); MS, FAB *m/z* (relative intensity) 582 (M^+ - C_4H_9, 92), 266 (49), 177 (100). Anal. Calcd for $C_{35}H_{53}NO_2Sn$: C, 65.84; H, 8.37; N, 2.19. Found: C, 66.09; H, 8.22; N, 2.10.

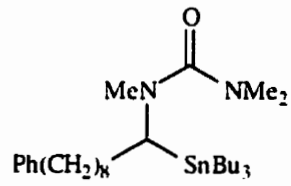
2.3.12 N-[1-Tributylstannyl-(9-phenyl)nonyl]-N',N'-dimethylurea ***63h***



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}; ^1H NMR (250 MHz) δ 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, $PhC\underline{H}_2$), 1.68-1.23 (m, 22 H, $PhCH_2(C\underline{H}_2)_2(CH_2)_2(C\underline{H}_2)_3CHN$ and

$SnCH_2(C\underline{H}_2)_2CH_3$), 0.97-0.72 (m, 19 H, $Ph(CH_2)_3(C\underline{H}_2)_2(CH_2)_3CHN$ and $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{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 (^3J = 55), 13.5, 10.0 (^1J = 316, 303); MS, FAB *m/z* (relative intensity) 523 (M^+ - C_4H_9, 100), 177 (50), 164 (25). Anal. Calcd for $C_{30}H_{56}N_2OSn$: C, 62.18; H, 9.74; N, 4.83. Found: C, 62.35; H, 9.61; N, 4.82.

2.3.13 N-[1-Tributylstannyl-(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}; ^1H 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_3N), 2.72 (s, 6 H, $(CH_3)_2N$), 2.59 (t, 2 H, J = 7.7, $PhC\underline{H}_2$), 1.63-1.23 (m, 24 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $PhCH_2(C\underline{H}_2)_3CH_2(C\underline{H}_2)_3CHN$), 0.95-0.78 (m, 17 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $Ph(CH_2)_4C\underline{H}_2(CH_2)_3CHN$); ^{13}C NMR (63 MHz) δ *165.9, 164.9, 142.6, 128.2, 127.9, 125.3, 52.1 (^1J = 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 (^3J = 60), 13.5, 10.1 (^1J = 308, 296); MS, FAB *m/z* (relative intensity) 537 (M^+ - C_4H_9, 100), 303 (80), 179 (96), 164 (49). Anal. Calcd for $C_{31}H_{58}N_2OSn$: C, 62.74; H, 9.85; N, 4.72. Found: C, 63.00; H, 9.57; N, 4.71.

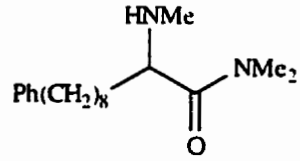
2.3.14 Attempted preparation of carboxylic acids

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 (R_f) due to Bu_4Sn. A stream of CO_2 was bubbled through the reaction flask for 2 min. The reaction mixture was warmed to rt, diluted with Et_2O and extracted with 2 N NH_4OH (several times).The combined base washes were acidified (2 N HCl) and extracted with Et_2O (several times). The combined organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. No acid was isolated for any of the reactions.

2.3.15 Attempted preparation of aminoalcohols

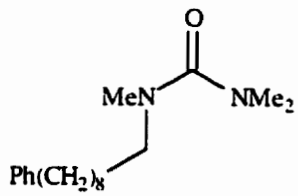
Transmetalation was performed as described in section 2.3.14. Benzaldehyde (1.3 equiv) was added to the resulting solution and the reaction was stirred at –78 °C for another 15 min. The reaction was quenched with saturated NH_4Cl and warmed to rt. The reaction mixture was diluted with Et_2O, washed with water, dried ($MgSO_4$), 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/Et_2O up to 100% MeOH) to give Bu_4Sn (95%), and products **79** (45%) and **80**(15%).

2.3.16 N,N-Dimethyl (2-methylamino)-10-phenyldecanamide ***79***



IR (neat) 3317, 2926, 2853, 1645, 1456, 1259, 1136, 1047 cm^{-1}; ^1H NMR (250 MHz) δ 7.26 (m, 5H, ArH), 4.3 (s, 1 H, $CH_3N\underline{H}$), 3.59 (t, 1 H, J = 6.3, CHN), 3.05 (s, 3 H, $CONCH_3(C\underline{H}_3)$), 2.99 (s, 3 H, $CONC\underline{H}_3(CH_3)$), 2.58 (t, 2 H, J = 7.6, $PhC\underline{H}_2$), 2.39 (s, 3H, $C\underline{H}_3NH$), 1.60 (m, 4H, $PhCH_2C\underline{H}_2(CH_2)_5C\underline{H}_2$), 1.30 (m, 10H, $Ph(CH_2)_2(C\underline{H}_2)_5CH_2$); ^{13}C NMR (JMOD, 63 MHz) δ 173.4, 142.7, (128.2), (128.0), (125.4), (59.3), (36.8), 35.8, (35.6), (34.2), 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 $C_{19}H_{32}N_2O$: 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***



IR (neat) 2925, 2853, 1645, 1494, 1380, 1141, 1045 cm^{-1}; ^1H NMR (250 MHz) δ 7.26 (m, 5 H, ArH), 3.12 (t, 2 H, J = 7.5, CH_2N), 2.78 (s, 9 H, $C\underline{H}_3NCON(C\underline{H}_3)_2$), 2.59 (t, 2 H, J = 7.6, $PhC\underline{H}_2$), 1.63-1.52 (m, 4 H, $PhCH_2C\underline{H}_2(CH_2)_5C\underline{H}_2CH_2$), 1.28-1.20 (m, 10 H, $Ph(CH_2)_2(C\underline{H}_2)_5(CH_2)_2N$); ^{13}C NMR (63 MHz) δ 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

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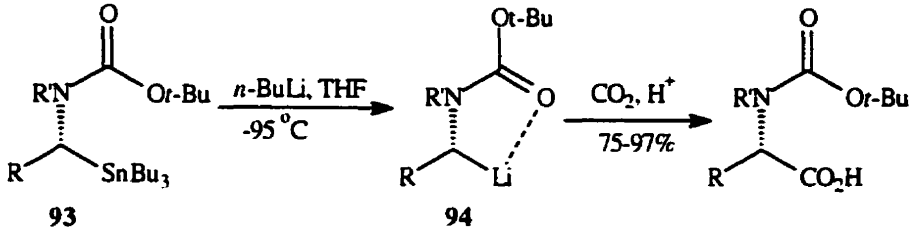
Chapter 3

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 CO_2 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*-C_6H_{11}).[2] This was mainly due to steric hindrance imposed by these bigger groups.

Scheme 46

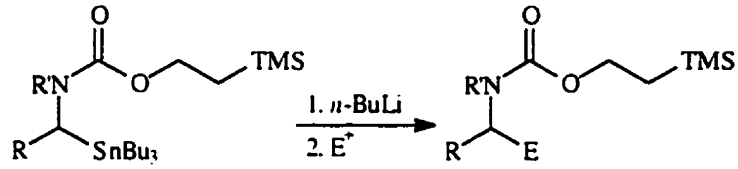


93 **94**

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

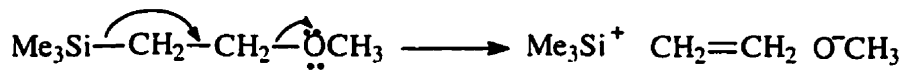
of the final product. In addition, the resulting organolithiums should be chemically and configurationally stable at temperatures higher than –95 °C. Based on this, we decided to use a smaller carbamate, 2-(trimethylsilyl)ethoxycarbonyl (Teoc). Since Teoc is smaller than the *t*-Boc group, we expected 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



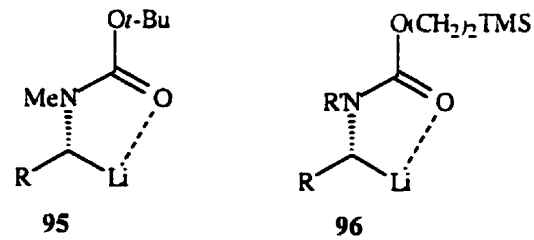
The effect of Teoc on configurational stability of organolithiums compared to the *t*-Boc group is not very clear. This is mainly due to the lack of understanding regarding the mechanism of racemization of these organolithiums as discussed in Chapter 1. However, if the chelation shown in Figure 9 plays 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



However, this hyperconjugation has been shown to be less effective than the electron donation by inductive effect given by the *t*-butyl group in other reactions.[5] Assuming this to be the same in this case, the trimethylsilyl ethyl group would be less electron donating than the *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 α-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 *t*-Boc protected α-aminoorganolithiums



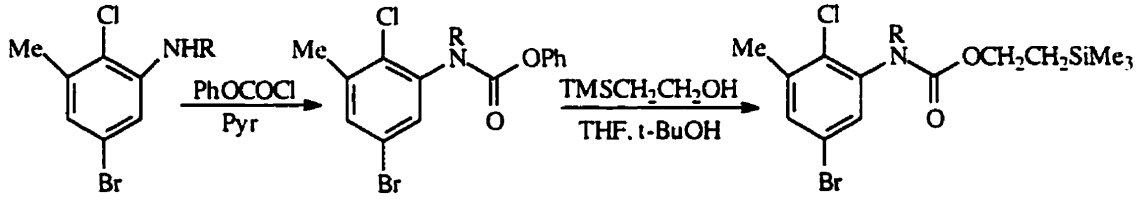
Another advantage of the Teoc group is that it is easily removed using acid or fluoride ion. The byproducts are gases, making the deprotection a very clean reaction.

3.2 Results and Discussion

3.2.1 Protection of amines with the Teoc Group

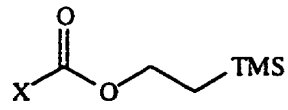
The Teoc group has not been widely used for the protection of amines. Carpino and Tsao first reported the use of this group in 1978.[6] Earlier reports involving its use in peptide and amino acid chemistry suggested that introduction of this group could be troublesome.[7] Meyers used this group in the total synthesis of maytansinoids.[8] 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



97 **98**

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 = N_3).[6] 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.[9] Unfortunately, the use of this reagent is limited by the fact that phosgene, which is very toxic, is required for its preparation.

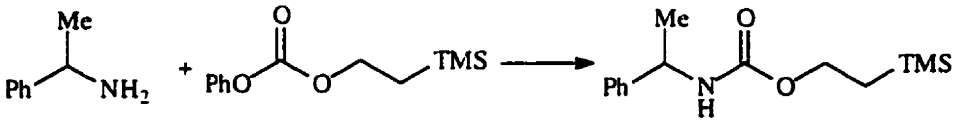


99

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 α-methylbenzylamine because it is sterically similar to our secondary α-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*-dimethylamino)pyridine (DMAP) since it is a good acylation catalyst.[11] The yield increased and the best results were obtained with CH_2Cl_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



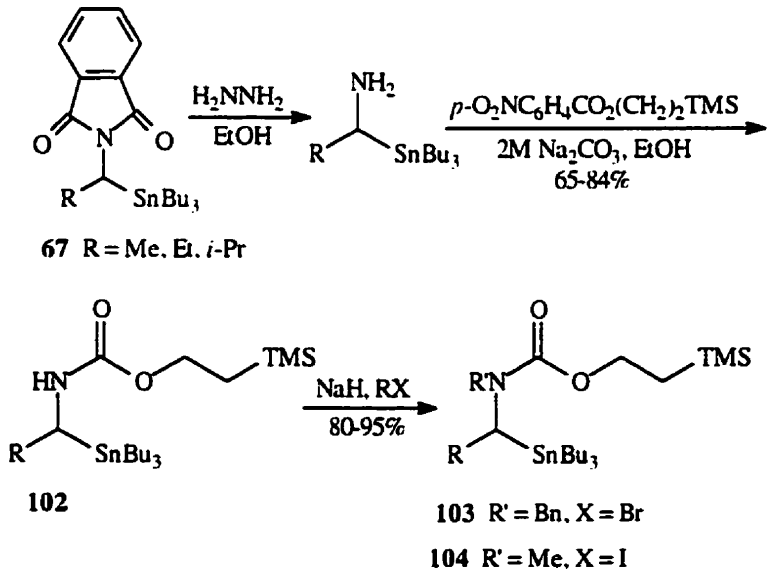
100 **101**

Entry	*Base*	*Solvent/Condition*	*Yield(%)*
1	DBU	THF, reflux (o/n)	<50
2	DBU/DMAP	THF, rt (o/n)-reflux (4 hrs)	56
3	DBU/DMAP	CH_2Cl_2, reflux (o/n)	65
4	DBU/DMAP	CH_2Cl_2, rt (o/n)	81
5	Et_3N/DMAP	CH_2Cl_2, reflux (48 hrs)	55
6	*i*-Pr_2NEt/DMAP	CH_2Cl_2, reflux (o/n)	71

As in Chapter 2, we applied Chong and Park's method for preparing the α-aminoorganostannnes.[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_2Cl_2. We then tried to use the method that was used by Rowosky and Wright.[7] Using 2 M aqueous Na_2CO_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 α-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



3.2.2 Transmetalation of Teoc protected α-aminoorganostannanes

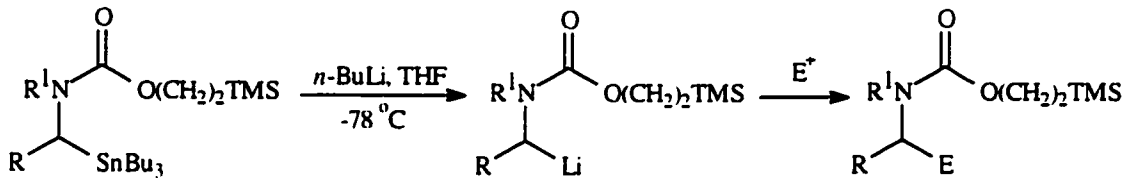
Transmetalation of the α-aminoorganostannanes with *n*-BuLi at –78 °C gave >90% transmetalation based on the amount of tetrabutyltin isolated (Table 2). Unfortunately, trapping of the organolithiums with benzaldehyde (entries 1 and 2) gave lower yield of products than expected. Since transmetalation 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, CO_2. Unfortunately, trapping the organolithiums with CO_2 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



Entry	*R*	*R¹*	*E⁺*	*Product*	*Yield(%)*
1	Me	Bn	PhCHO	**105a**	66
2	Et	"	"	**105b**	69, 81[a]
3	Me	"	CO_2	**106a**	86
4	Et	"	"	**106b**	62
5	i-Pr	"	"	**106f**	56, 63[a]
6	Et	Me	"	**107b**	70

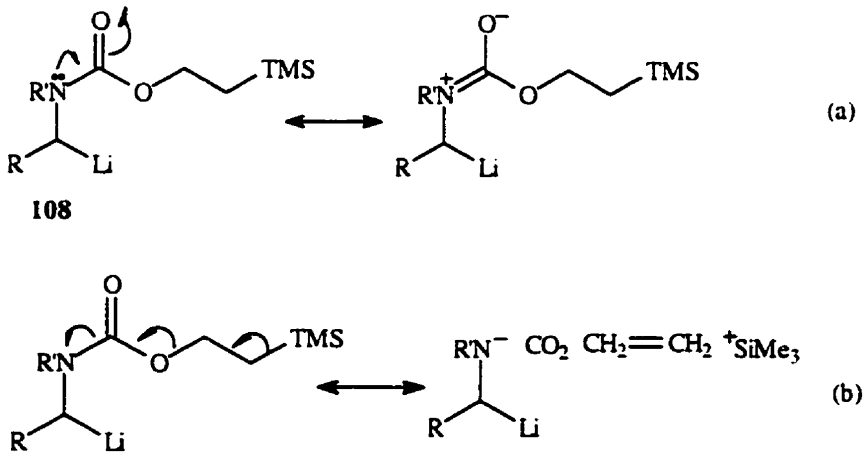
[a] Reaction done at –95 °C

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.[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 hypercongugation, 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.

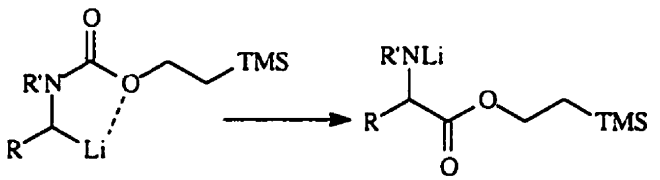
Figure 10: Resonance structures for Teoc protected α-aminoorganolithiums



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



109 **110**

3.2.3 Summary

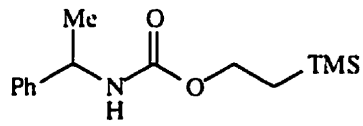
Teoc protected α-aminoorganostannanes were prepared using 2-(trimethylsilyl) ethyl *p*-nitrophenyl carbonate as the protecting reagent. These organostannanes underwent almost complete transmetalation with *n*-BuLi at –78 °C . Unfortunately, trapping with either benzaldehyde or CO_2 gave low yield of products. Thus, Teoc protected α-aminoorganolithiums were found to be chemically less stable than the *t*-Boc α-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***



To a solution of α-methylbenzylamine (213 μL, 1.6 mmol) in CH_2Cl_2 (6 mL) was added DBU (321 μL, 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 Et_2O (30 mL), washed with H_2O and 1 N HCl (20 ml). The organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (20 g silica; 10 : 1 hexane/Et_2O) and gave the product as a colorless oil (354 mg) in 81% yield: IR(neat) 3324, 3031, 2946, 1701, 1518, 1242, 1055 cm^{-1}; ^1H NMR (250 MHz) δ 7.33-7.21 (m, 5 H, ArH), 5.09 (broad, 1 H, NH), 4.82 (m, 1 H, $CH_3C\underline{H}N$), 4.11 (m, 2 H, $OC\underline{H_2}CH_2TMS$), 1.43 (d, 3 H, J = 6.9, $C\underline{H_3}CHN$), 0.93 (m, 2 H, $OCH_2C\underline{H_2}TMS$), 0.0 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz) δ 155.9, 143.7, 128.3, 127.0, 125.8, 62.7, 50.3, 22.3, 17.6, -1.7 ($J_{Si\text{-}C}$ = 51 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 $C_{14}H_{23}NO_2Si$: 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-(tributylstannyl) carbamates

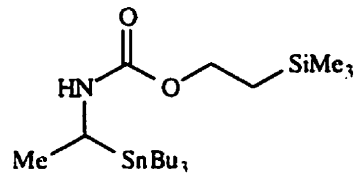
Reaction 1

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

Reaction 2:

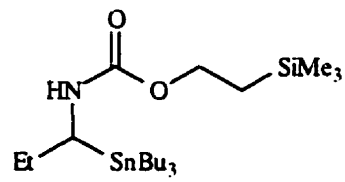
To a solution of the crude stannylamine (1 equiv) in 2 M Na_2CO_3 (10 equiv) at 55 °C was added a 1 M solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (2 equiv) in warm EtOH. The temperature was raised to 75 °C and more ethanol was added (to make a 0.1 M solution of stannylamine in EtOH) over 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_2O. 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_2O) to give the carbamates as colorless oils.

3.3.4 2-(Trimethylsilyl)ethyl N-(1-tributylstannylethyl)carbamate ***102a***



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, $OC\underline{H}_2CH_2TMS$), 3.25 (m, 1 H, CHN), 1.55-1.25 (m, 15 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $C\underline{H}_3CHN$), 0.97-0.84 (m, 17 H, $OCH_2C\underline{H}_2TMS$ and $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$), 0.12 (s, 9 H, $Si(CH_3)_3$); ^{13}C 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^+ - C_4H_9, 52), 394 (100), 322 (25), 176 (54). Anal. Calcd for $C_{20}H_{45}NO_2SiSn$: C, 50.22; H, 9.48; N, 2.93. Found: C, 49.94; H, 9.33; N, 2.94.

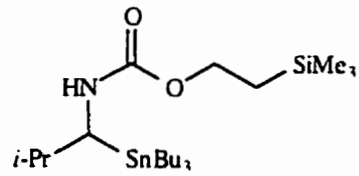
3.3.5 2-(Trimethylsilyl)ethyl N-(1-tributylstannylpropyl)carbamate ***102b***



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, in 75% yield: IR (neat) 3331, 2955, 2923, 1699, 1507, 1459, 1248, 1055 cm^{-1}; ^1H NMR (250 MHz) δ 4.75 (d, 1 H, J = 7.2, HN), 4.09 (t, 2 H, J = 8.4, $OC\underline{H}_2CH_2TMS$), 3.13 (q, 1 H, J = 7.5, CHN), 1.72-1.51 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.49-1.20 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.97-0.78 (m, 20 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$, $OCH_2C\underline{H}_2TMS$ and $C\underline{H}_3CH_2CHN$), 0.0 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz) δ 159.6, 62.9, 43.0, 29.2 (^2J = 19), 27.8, 27.5 (^3J = 52), 17.7, 13.6, 12.6, 9.7 (^1J = 311 Hz), -1.5; MS, FAB *m/z* (relative intensity) 435 (M^+ - C_4H_9, 62), 408 (100), 336 (30), 176 (41). Anal. Calcd for $C_{21}H_{47}NO_2SiSn$: C, 51.22; H, 9.62; N, 2.84. Found: C, 51.42; H, 9.59; N, 2.78.

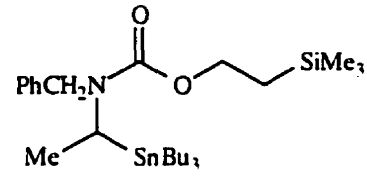
3.3.6 2-(Trimethylsilyl)ethyl N-(2-methyl-1-tributylstannylpropyl)carbamate ***102f***



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, 2924, 1700, 1506, 1462, 1249, 1036 cm^{-1}; ^1H NMR (250 MHz) δ 4.76 (d, 1 H, J = 8.3, HN); 4.09 (t, 2 H, J = 8.4, $OC\underline{H}_2CH_2TMS$), 3.08 (dd, 1 H, J = 7.3, 8.3, CHN), 1.95 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.52-1.20 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.98-0.74 (m, 23 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$, $(C\underline{H}_3)_2CH$ and $OCH_2C\underline{H}_2TMS$), -0.03 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz) δ 158.5, 64.2, 50.9, 34.1, 30.7 (^2J = 19), 29.0 (^3J = 57), 23.1, 22.7, 19.3, 15.1, 11.8 (^1J = 315, 302), 0.0; MS, FAB

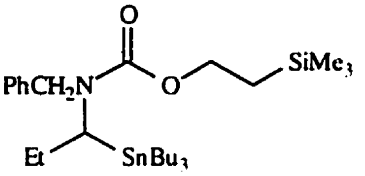
m/z (relative intensity) 449 (M^+ - C_4H_9, 51), 422 (100), 350 (33), 177 (74). Anal. Calcd for $C_{22}H_{49}NO_2SiSn$: 52.18; H, 9.75; N, 2.76. Found: C, 51.92; H, 9.50; N, 2.92.

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



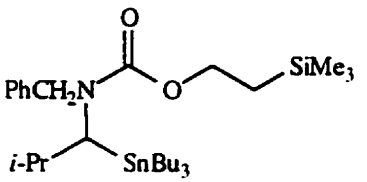
This compound was prepared according to the general procedure described in section 2.3.5 from **102a** and BnBr with a reaction time of 7 h in 85% yield: IR (neat) 3029, 2954, 2921, 1681, 1462, 1316, 1249 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.78 (m, 5 H, ArH), 4.81 (d, 1 H, J = 15.3, PhC$\underline{H}_2$), 4.34-4.20 (m, 2 H, OC$\underline{H}_2$CH$_2$TMS), 4.17 (d, 1 H, J = 15.3, PhC$\underline{H}_2$), 2.85 (q, 1 H, J = 7.3, CHN), 1.78-1.43 (m, 15 H, SnCH$_2$(C$\underline{H}_2$)$_2$CH$_3$ and C$\underline{H}_3$CHN), 1.19-0.92 (m, 17 H, SnC$\underline{H}_2$(CH$_2$)$_2$C$\underline{H}_3$ and OCH$_2$C$\underline{H}_2$TMS), -0.07 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR (50 MHz, C_6D_6) δ 157.0, 138.9, 128.7, 128.5, *128.3, 127.6, 63.8, 51.6, 43.5, 29.7 (^2J = 19), 28.1 (^3J = 57), 18.2, 17.7, 14.0, 11.2 (^1J = 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***



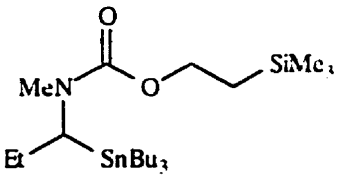
This compound was prepared according to the general procedure described in section 2.3.5 from **102b** and BnBr with a reaction time of 3.5 h in 80% yield: IR (neat) 2955, 2922, 1681, 1429, 1240 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.33-7.13 (m, 5 H, ArH), 4.89 (d, 1 H, J = 15.1, PhC$\underline{H}_2$), 4.34-4.23 (m, 2 H, OC$\underline{H}_2CH_2$TMS), 4.10 (d, 1 H, J = 15.1, PhC$\underline{H}_2$), 2.78 (t, 1 H, J = 7.6, CHN), 2.02-1.95 (m, 2 H, $CH_3C\underline{H}_2$CHN), 1.69-1.41 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 1.06-0.91 (m, 20 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$, $OCH_2C\underline{H}_2$TMS and $C\underline{H}_3CH_2CHN$), -0.05 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (50 MHz, C_6D_6) 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^+ - C_4H_9, 30), 502 (100), 427 (34), 220 (42). Anal. Calcd for $C_{28}H_{53}NO_2SiSn$: 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, C_6D_6) δ 7.50-7.14 (m, 5 H, ArH), 5.10 (d, 1 H, J = 14.7, $PhC\underline{H}_2$), 4.33 (m, 2 H, $OC\underline{H}_2CH_2TMS$), 4.02 (d, 1 H, J = 14.7, $PhC\underline{H}_2$), 2.65 (d, 1 H, J = 3.1, CHN), 1.80-1.34 (m, 13 H, $(CH_3)_2C\underline{H}$ and $SnCH_2(C\underline{H}_2)_2CH_3$), 1.19-0.92 (m, 23 H, $(C\underline{H}_3)_2CH$, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $OCH_2C\underline{H}_2TMS$), 0.0 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (50 MHz, C_6D_6) 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 (^2J = 18), 28.3 (^3J = 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^+ - C_4H_9, 54), 512 (100), 437 (38), 234 (52), 177(35). Anal. Calcd for $C_{29}H_{55}NO_2SiSn$: 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, C_6D_6) δ 4.34-4.24 (m, 2 H, $OC\underline{H}_2CH_2TMS$), 2.98-2.83 (m, 4 H, CH_3N and CHN), 2.00-1.42 (m, 14 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3C\underline{H}_2$), 1.20-0.95 (m, 20 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$, $C\underline{H}_3CH_2$ and $OCH_2C\underline{H}_2TMS$), 0.0 (s, 9

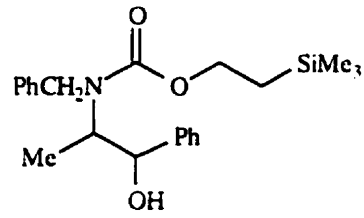
H, $Si(CH_3)_3$); ^{13}C NMR (50 MHz, C_6D_6) δ 157.1, 63.4, 54.3, 36.4, 29.8 (^2J = 18), 28.1 (^3J = 56), *27.9, 25.7, 14.0, 13.0, 11.3 (^1J = 321, 307), 10.0, -1.5; MS, FAB *m/z* (relative intensity) 449 (M^+ - C_4H_9, 100), 350 (48), 188 (84). Anal. Calcd for $C_{22}H_{49}NO_2SiSn$: C, 52.18; H, 9.75; 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_2O).

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

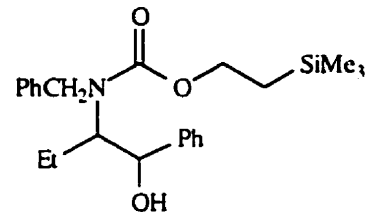
105a



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}; ^1H NMR (250 MHz), δ 7.35-7.12 (m, 10H, ArH), 4.93 (m, 1H, C<u>H</u>(OH)Ph), 4.60 (d, 1 H, J = 16.1, PhC<u>H</u>$_2$), 4.29-4.18 (m, 3 H, PhC<u>H</u>$_2$ and OC<u>H</u>$_2$C<u>H</u>$_2$TMS), 3.48 (m, 1 H, CHN), 1.16 (d, 3 H, J = 7.0, C<u>H</u>$_3$CHN), 1.06 (m, 2 H, OCH$_2$C<u>H</u>$_2$TMS), 0.05 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (50 MHz, C_6D_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 $C_{22}H_{31}NO_3Si$: 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***

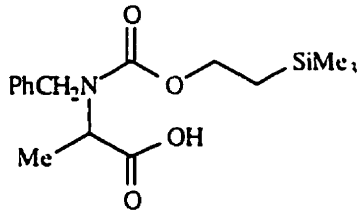


This aminoalcohol was prepared from **103b** according to the general procedure described in section 3.3.11 at –95 °C, as a mixture of diastereomers in 81% yield: IR (neat) 3398, 2952, 1680, 1446, 1248 cm^{-1}; ^1H NMR (250 MHz), δ 7.38-7.09 (m, 10 H, ArH), 5.40 (m, 0.3 H, C<u>H</u>(OH)Ph), 5.22 (m, 0.7 H, C<u>H</u>(OH)Ph), 4.83 (d, 1 H, J = 15.3, PhC<u>H</u>$_2$), 4.34 (m, 2 H, OC<u>H</u>$_2$CH$_2$TMS), 4.03 (d, 1 H, J = 15.3, PhC<u>H</u>$_2$), 3.45-3.40 (m, 1 H, CHN), 2.47-2.45 (m, 1 H, CH$_3$C<u>H</u>$_2$), 1.79-1.70 (m, 1 H, CH$_3$C<u>H</u>$_2$), 1.02 (m, 2 H, OCH$_2$C<u>H</u>$_2$TMS), 0.74 (t, 3 H, J = 7.5, C<u>H</u>$_3$CH$_2$), 0.0 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR (50 MHz, C_6D_6) 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 $C_{23}H_{33}NO_3Si$: 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

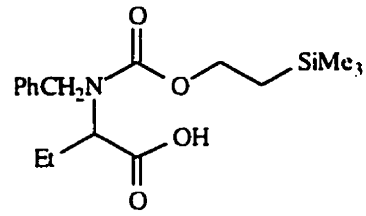
The amino acids were prepared as described in section 2.3.14. The products were obtained as colorless thick oils. Samples for analysis were purified by pipette column (1:1 hexane/Et_2O and 1% AcOH).

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



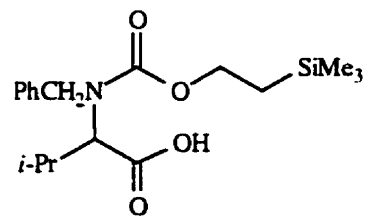
This compound was prepared from **103a** according to the general procedure described in section 3.3.14 in 86 % yield: IR (neat) 3023, 2950, 2896, 1701, 1442, 1245, 1012 cm^{-1}; ^1H NMR (250 MHz) δ 10.61 (broad singlet, 1 H, CO_2H), 7.32-7.27 (m, 5 H, ArH), 4.64 (d, 1 H, J = 16.3, $PhC\underline{H}_2$), 4.40-4.36 (m, 2 H, $PhC\underline{H}_2$ and CHN), 4.20 (t, 2 H, J = 8.7, $OC\underline{H}_2CH_2TMS$), 1.32 (d, 3 H, J = 7.1, $C\underline{H}_3CHN$), 1.00 (m, 2 H, $OCH_2C\underline{H}_2TMS$), -0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C 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 ($J_{Si\text{-}C}$ = 52 Hz); MS, ES *m/z* (relative intensity) 325 (M^+ + 2, 28), 324 (M^+ + 1, 100). Anal. Calcd for $C_{16}H_{25}NO_4Si$: C, 59.41; H, 7.79; N, 4.33. Found: C, 59.20; H, 7.64; N, 4.28.

3.3.16 N-Benzyl-N-[2-(trimethylsilyl)ethoxycarbony]-2-aminobutanoic acid ***106b***



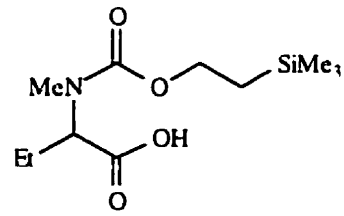
This compound was prepared from **103b** according to the general procedure described in section 3.3.14 at –95 °C in 62% yield: IR(neat) 3069, 2956, 1700, 1441, 1252, 1054 cm^{-1}; ^1H NMR (250 MHz) δ 9.70 (broad singlet, 1 H, CO_2H), 7.28-7.24 (m, 5 H, ArH), 4.61 (m, 1 H, CHN), 4.31(ABq, 2 H, <δ = 0.23, J = 15.8, $PhC\underline{H}_2$), 4.23 (m, 2 H, $OC\underline{H}_2CH_2TMS$), 2.02-1.91 (m, 1 H, $CH_3C\underline{H}_2CHN$), 1.79-1.76 (m, 1 H, $CH_3C\underline{H}_2CHN$), 1.00 (m, 2 H, $OCH_2C\underline{H}_2TMS$), 0.78 (distorted triplet, 3H, J = 6.3, $C\underline{H}_3CH_2CHN$), 0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz) δ *177.2, 176.6, 157.3, 137.7, 128.3, *128.0, 127.7, 127.3, 64.5, 61.8, *60.9, 50.8, *23.3, 22.6, 17.7, 11.1, -1.6 (J_{Si-C} = 51 Hz); MS, ES *m/z* (relative intensity) 339 (M^+ + 2, 22), 338 (M^+ + 1, 100), 310 (M^+ - 28, 44). Anal. Calcd for $C_{17}H_{27}NO_4Si$: C, 60.50; H, 8.06; N, 4.15. Found: C, 60.39; H, 7.87; N, 4.02.

3.3.17 N-Benzyl-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 °C in 63% yield: IR (neat) 3047, 2961, 1697, 1444, 1258 cm^{-1}; ^1H NMR (250 MHz) δ 10.35 (broad singlet, CO_2H), 7.23 (m, 5 H, ArH), 4.51 (m, 2 H, $PhC\underline{H}_2$ and CHN), 4.22 (m, 2 H, $OC\underline{H}_2CH_2TMS$), 4.01 (d, 1 H, J = 10.2, $PhC\underline{H}_2$), 2.34 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.19-1.16 (m, 2 H, $OCH_2C\underline{H}_2TMS$), 0.95 (d, 3 H, J = 6.0, $(C\underline{H}_3)_2CH$), 0.76 (d, 3 H, J = 6.0, $(C\underline{H}_3)_2CH$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz) δ 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_{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 $C_{18}H_{29}NO_4Si$: C, 61.50; H, 8.35; N, 3.98. Found: 61.65; H, 8.19; N, 3.91.

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



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}; ^1H NMR (250 MHz), δ 10.72 (broad singlet, CO_2H), 4.73 (dd, 0.6 H, J = 4.8, 10.6, CHN), 4.55(dd, 0.4 H, J = 4.8, 10.6, CHN), 4.22 (t, 2 H, J = 8.3, $OC\underline{H}_2CH_2TMS$), 2.87 (s, 1 H, CH_3N), 2.85 (s, 2H, CH_3N), 2.10-1.99 (m, 1 H, $CH_3C\underline{H}_2CHN$), 1.80-1.67 (m, 1 H, $CH_3C\underline{H}_2CHN$), 1.07-0.92 (m, 5 H, $C\underline{H}_3CH_2CHN$ and $OCH_2C\underline{H}_2TMS$), 0.05 (s, 9

H, $Si(CH_3)_3$); ^{13}C 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 $C_{11}H_{23}NO_4Si$: C, 50.54; H, 8.87; N, 5.36. Found: C, 50.36; H, 8.64; N, 5.19.

3.4 References

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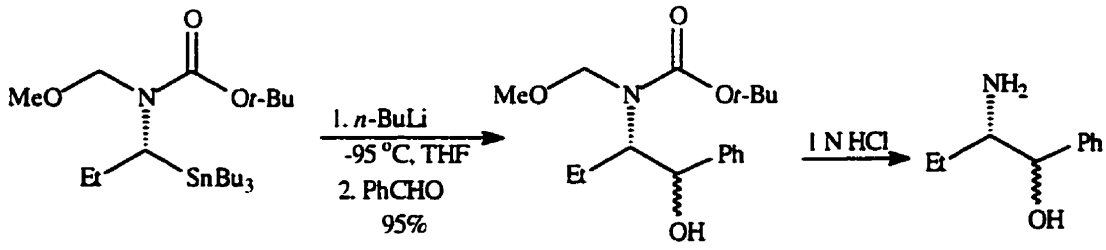
Chapter 4

Preparation and Transmetalation of *N*-*t*-Butylthiomethyl Boc Protected α-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 α-aminoorganostannane **111**.[1] 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 β-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

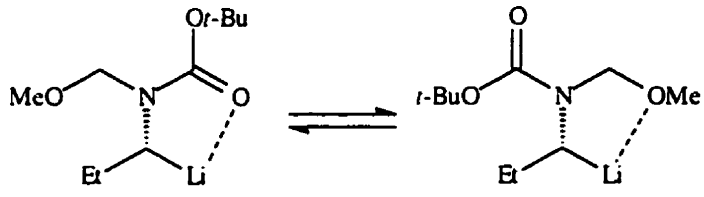


111 94% ee **112** 83% ee

Generally it is believed that carbamate protected α-aminoorganolithiums are stabilized by chelation between the carbonyl oxygen and the Li atom (Scheme 53). Since

racemization was not observed at –95 °C with *N*-Methyl Boc protected α-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 **114** is expected to be weaker than **113**, so the Li is not held as tightly and pyramidal inversion can take place.

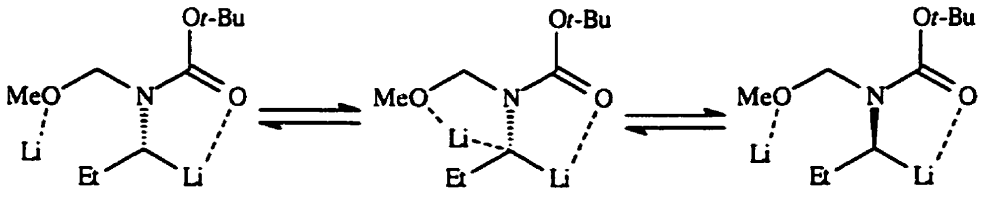
Scheme 53



113 **114**

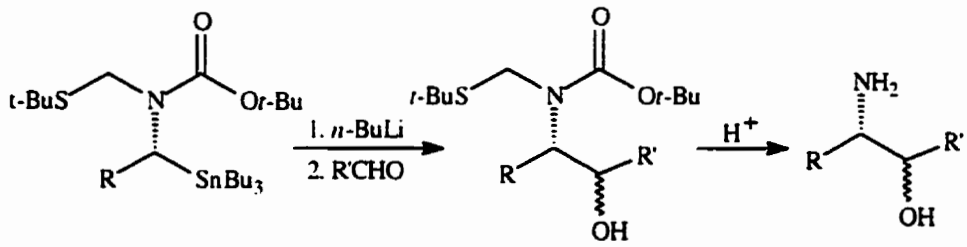
Park also speculated that racemization might be occuring by an inverse S_N2-type process. While the Li ion is chelated to the carbonyl oxygen, a second Li atom can also chelate to the methoxy oxygen. This Li atom would then attack the original Li-C bond from the backside causing inversion as shown in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

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*-*t*-butylthiomethyl group is also expected to be easily removed under acidic conditions.

Scheme 55



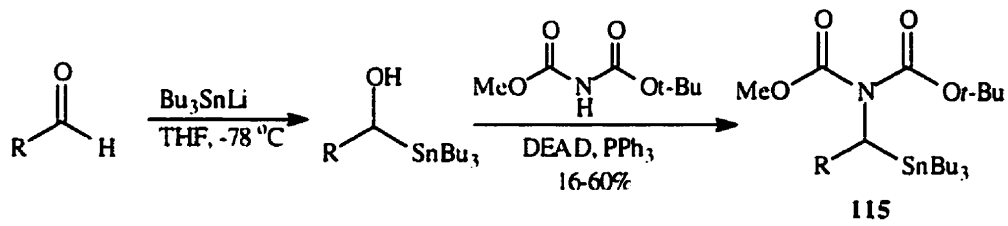
4.2 Results and Discussion

4.2.1 Preparation of α-aminoorganostannanes

Park reported that iminodicarbonates **115** can be prepared by the Mitsunobu reaction of methyl *t*-butyl iminodicarbonate and hydroxystannanes (Scheme 56).[1]

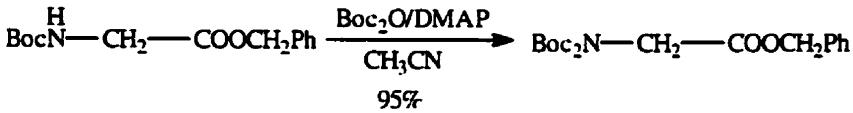
Unfortunately, when we attempted this reaction it gave very low yields especially for branched R groups (R = *i*-Pr and *c*-C_6H_{11}), presumably due to steric hindrance.

Scheme 56



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 Boc_2O/DMAP in acetonitrile and obtained the *N,N*-diacyl compound in very high yields (Scheme 57).[3]

Scheme 57



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 Boc_2O 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 $LiAlH_4$ 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 *t*-BuSH gave the α-aminoorganostannanes **118**. These were obtained in 29-40% overall yield from the aldehydes.

Scheme 58

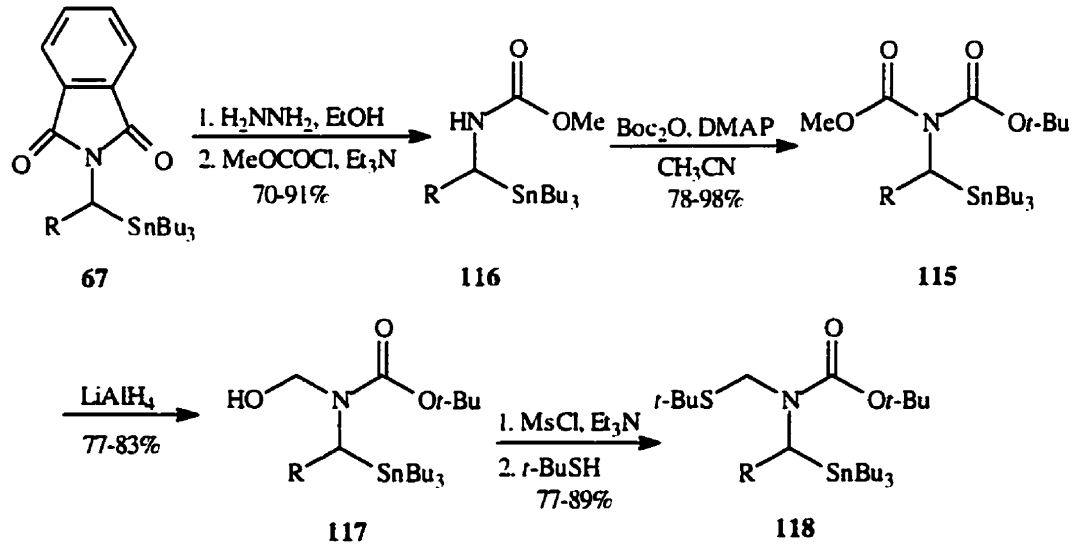


Table 3: Overall yield of the iminodicarbonates **115** from aldehydes

Entry	*R*	*Yield of 115*[a]	*Yield of 115*[b]
1	Me	60	56
2	Et	50	-
3	n-C_5H_{11}	48	51
4	i-Pr	16	48
5	c-C_6H_{11}	21	-

[a] Iminodicarbonate prepared by the method in Scheme 55

[b] Iminodicarbonate Prepared by the method in Scheme 57

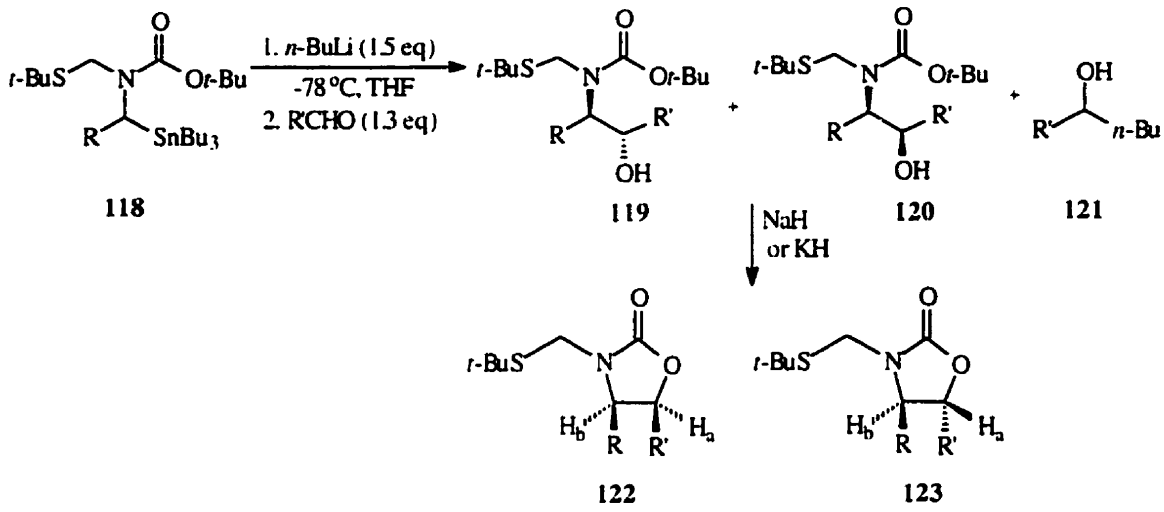
4.2.2 Transmetalation of α-aminoorganostannanes

Treatment of organostannanes **118** with n-BuLi at –78 °C led to >90% transmetalation (based on isolated Bu_4Sn), 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 β-aminoalcohols by ^1H 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 β-aminoalcohols with NaH or KH gave the oxazolidinones **122** and **123** which were easy to analyze by ^1H 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_2H with different R' groups.[4] 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* β-aminoalcohols **119** (Table 4). This indicated that transmetalation of the racemic α-aminoorganostannanes **118** and trapping of the resulting α-aminoorganolithiums with benzaldehyde gave only the *anti* diastereomer **119**.

Table 4: Transmetalation of α-aminoorganostannanes and trapping with aldehydes.



118 119 120 121

122 123

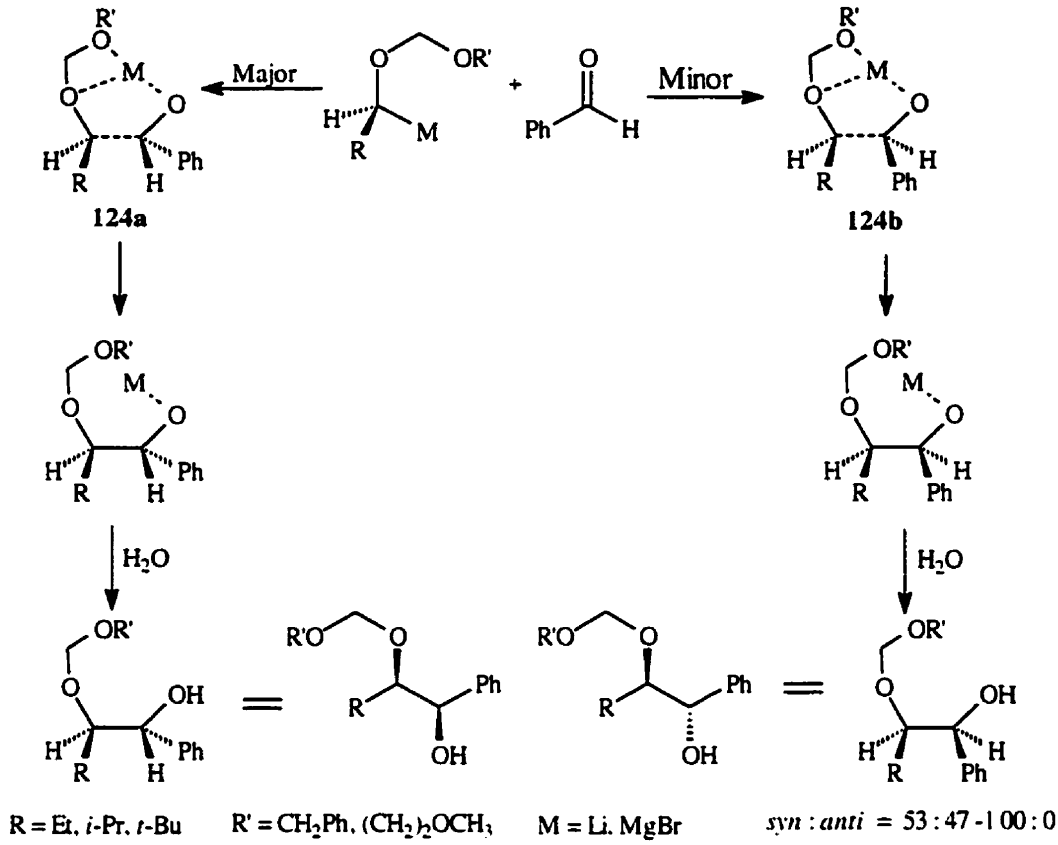
Entry	*R*	*R'*	*Product*	*Yield (%)*	*de (%)*[a]
1	Me	Ph	**119a**	55	>98
2	Et	"	**119b**	54	>98
3	n-C_5H_{11}	"	**119e**	55	nd
4	i-Pr	"	**119f**	35	>98
5	c-C_6H_{11}	"	**119g**	40	>98
6	Et	$CH_3OC_6H_4$	**119h**	50	>98
7	"	c-C_6H_{11}	**119i, 120i**	65	0
8	"	i-Pr	**119j, 120j**	60	0

[a] determined from ^{1}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).[5] 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.

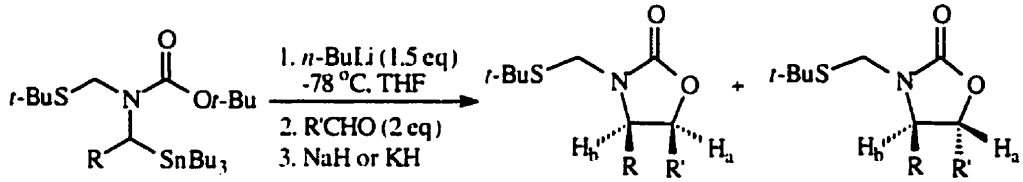
Scheme 59



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



118 **122** **123**

Entry	*R*	*R'*	*Product*	*Yield (%)*[a]	*cis : trans*
1	Me	Ph	**122a,123a**	90	2.5 : 1.0
2	Et	"	**122b, 123b**	77	1.9 : 1.0
3	Et	$CH_3OC_6H_4$	**122h, 123h**	80	2.5 : 1.0
4	*i*-Pr	Ph	**122g, 123g**	68[b]	2.8 : 1.0
5	Et	*c*-C_6H_{11}	**122i, 123i**	70	1.0 : 1.3
6	Et	*i*-Pr	**122j, 123j**	69	1.0 : 1.3

[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 aminoorganostannanes **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* diasereomer 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.

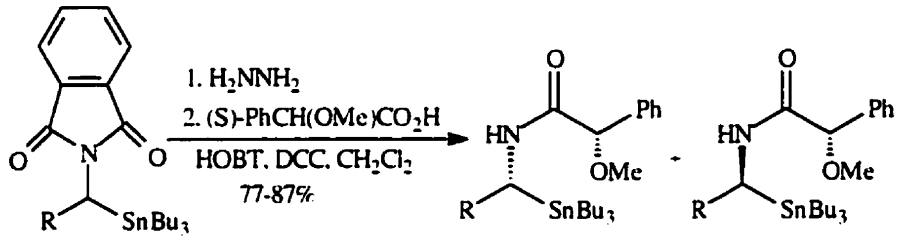
The β-aminoalcohols were converted to the oxazolidinones for two other reasons: the *syn* and *anti* diastereomers and the byproduct **121** had very close R_f values which made separation very difficult. To our great benefit, the *cis* and *trans* oxazolidinones had very different R_f values which were 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.[6] 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

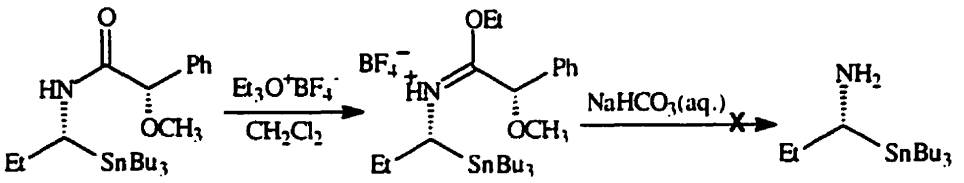


67b R = Et
67e R = *n*-C_5H_{11}

125 **126**

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 triethyloxonium fluoroborate ($Et_3O^+BF_4^-$), a mild agent for hydrolysis of amide bonds.[7] 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 ^1H 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.

Scheme 61



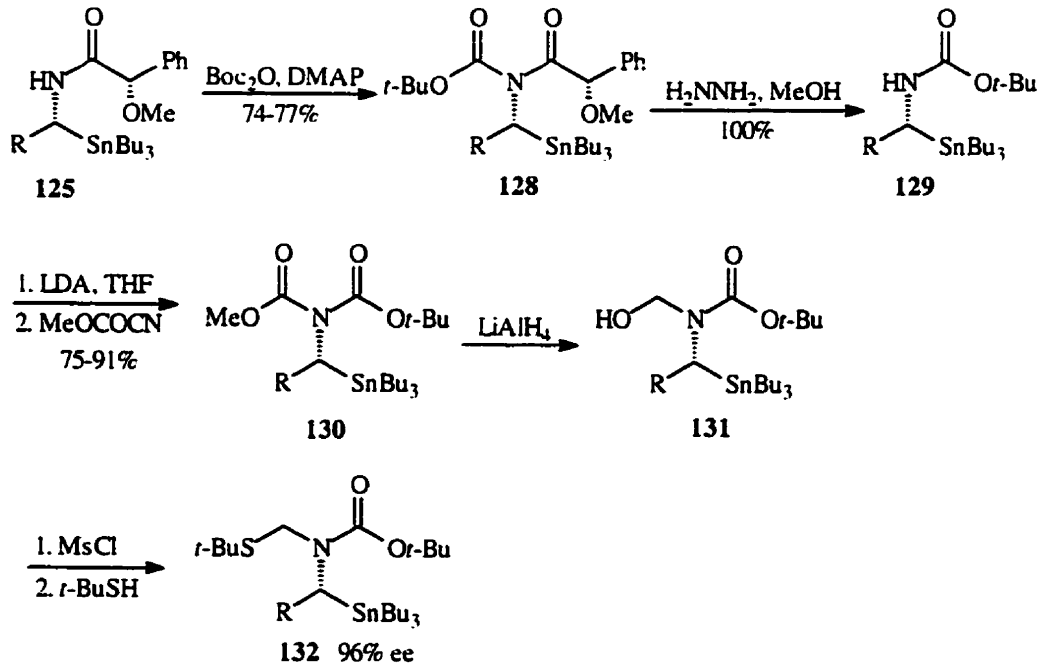
125 **127**

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 Boc_2O 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 Et_3N 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.[8] 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.[9] 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.[10] 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,[6a] 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

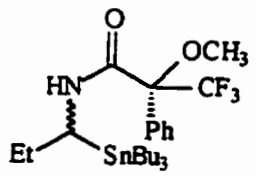


125 **128** **129**

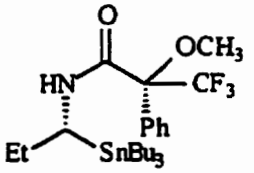
130 **131**

132 96% ee

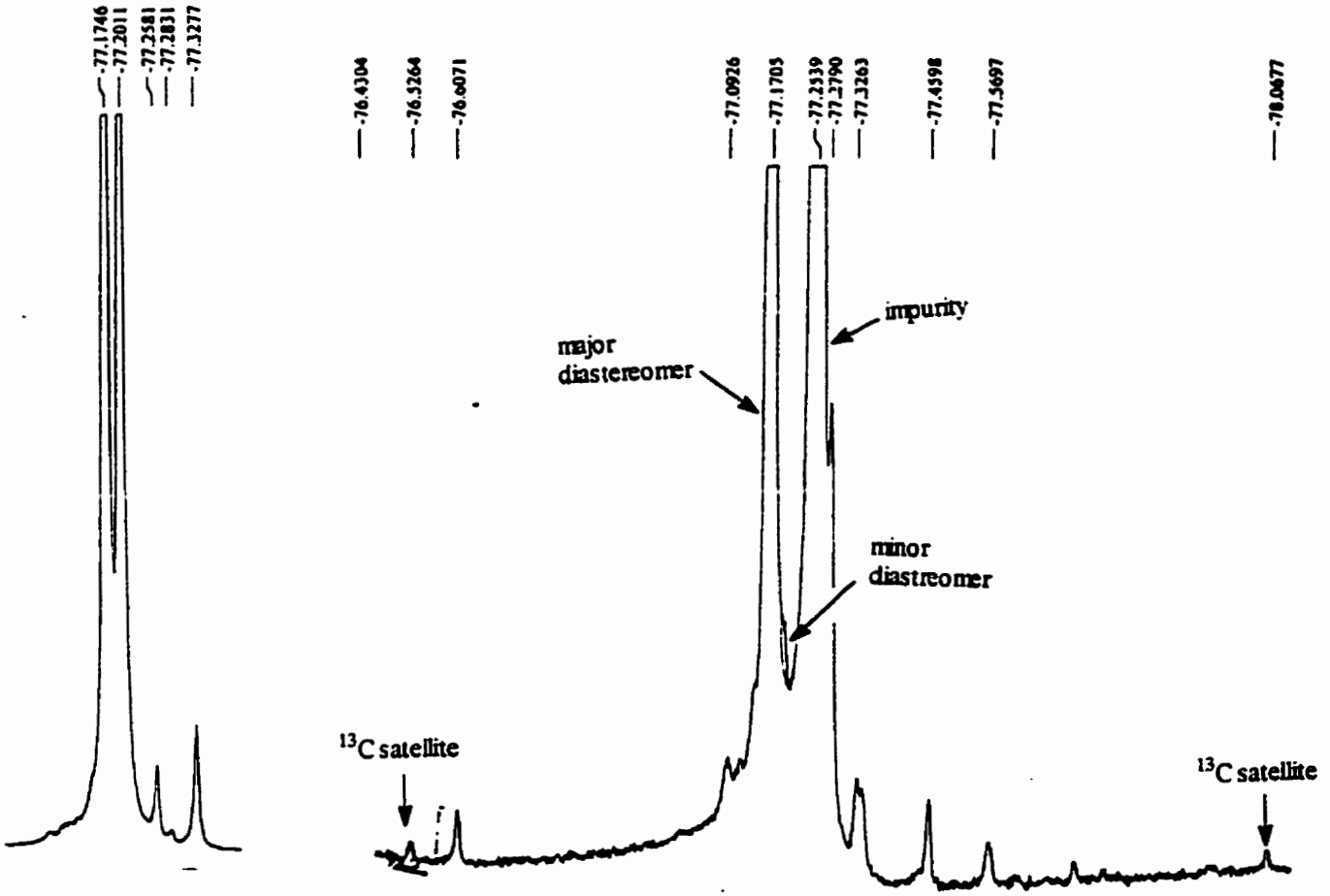
Figure 11: Partial ^{19}F NMR spectra of Mosher amides A and B



A



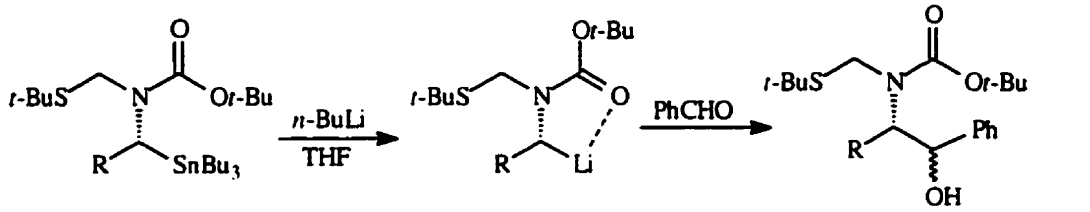
B 96% de



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, intramoleuclar 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_2O; however, it gave only about 5% transmetalation after 15 min. Use of a 1:1 mixture of THF:Et_2O gave almost the same result as using only THF (entry 3).

Table 6: Configurational stability of α-aminoorganolithiums



132 **133** **134** *Anti* : *Syn* = 2 : 1

Entry	*R*	*Temp(°C)*	*Time(min)*	*Yield(%)*	*ee(%)*[a]	
					Anti	*Syn*
1	Et	-78	30	70	84	82
2	"	-95	15	79	94	91
3	"	-78[b]	30	63	82	nd
4	"	-78[c]	30	58	51	48
5	C_5H_{11}	-78	30	68	86	nd
6	"	-95	15	60	93	nd

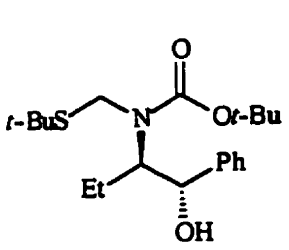
[a] Determined by HPLC analysis (Chiracel OD)

[b] Et_2O-THF mixture used as solvent

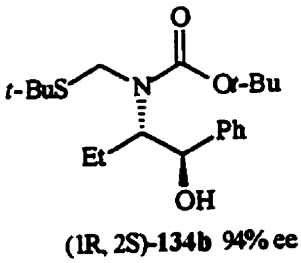
[c] LiBr was added to the stannane solution before transmetalation

nd means the enantiomeric excess was not recorded.

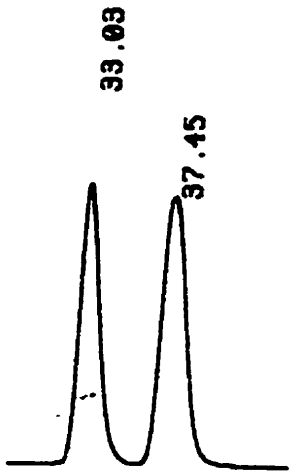
Figure 12: HPLC analysis of β-aminoalcohols **119b** and **134b**[a]

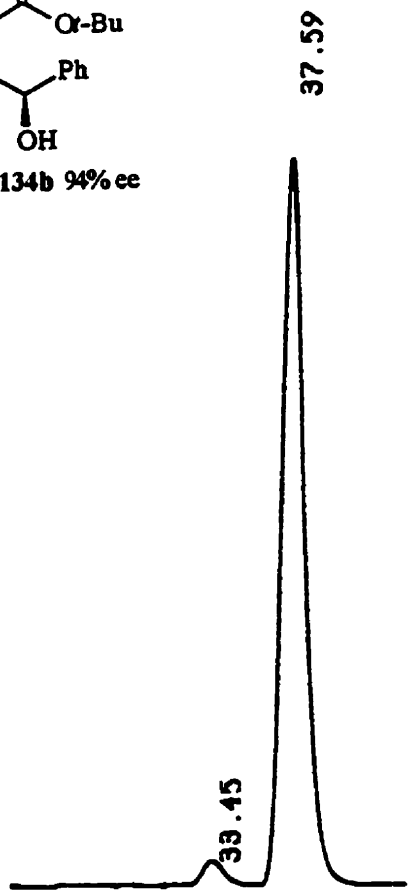


(±) -119b



(1R, 2S)-134b 94% ee

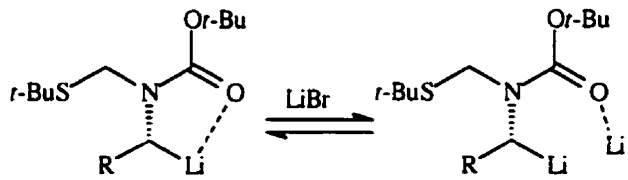




[a] Eluted with hexane/*i*-PrOH 99.5:0.5 (v/v) and a flow rate of 0.25 mL/min.

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.

Scheme 63



133a **133b**

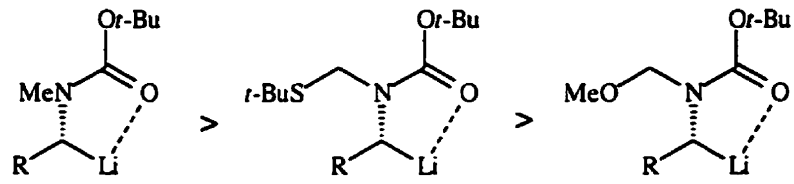
Another interesting observation was the difference in enantiomeric excess between the two diastereomers. The *anti* diastereomer always had a higher ee than the *syn* diastereomer (entries 1, 2 and 4). This confirmed the conclusion we had made earlier concerning the difference in the rate of formation 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, **132e** (R = C_5H_{11}) was also transmetalated (entries 5 and 6). This gave similar results to what was observed with organolithiums derived from **132b** (R = Et).

Although these *N*-*t*-butylthiomethyl Boc protected α-aminoorganolithiums racemize at -78 °C, they can be trapped at -95 °C to give β-aminoalcohols in high enantiomeric purity. This verified Park's proposal that the methoxy oxygen in **113** (Figure 13) was competing with the carbonyl oxygen for chelation to the Li atom leading to racemization. The 2% racemization in **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, *N*-*t*-butylthiomethyl Boc α-aminoorganolithiums **133** fall in-between the *N*-methyl (**94**) and the *N*-methoxymethyl (**113**) Boc α-aminoorganolithiums (Figure 11), in terms of configurational stability.

Figure 13: α-Aminoorganolithiums in decreasing configurational stability

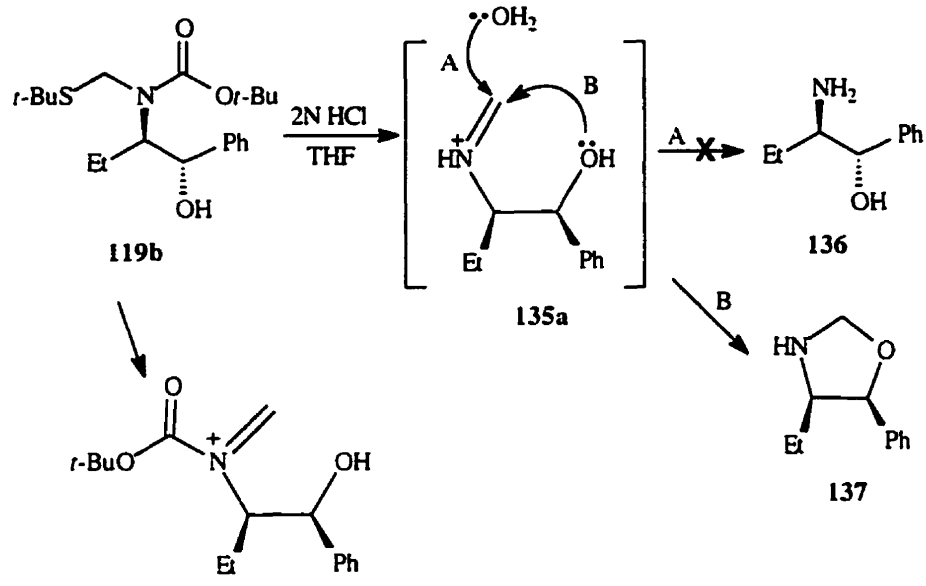


94 **133** **113**

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]

Scheme 64

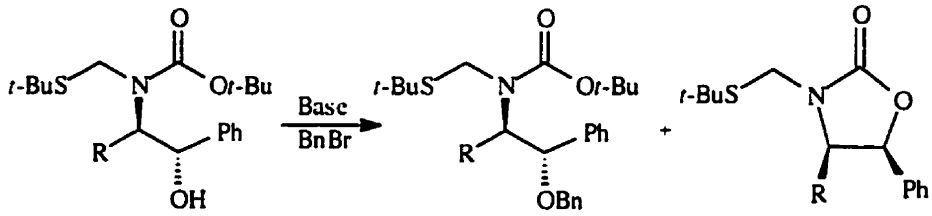


It was clear from these results that deprotection was not possible in the presence of the OH. To get around this problem, one had to protect the alcohol first so that it does not interfere. Since the deprotection was being done with acid, the alcohol protecting group had to be stable under acidic conditions. 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.[12] 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



119 **138** **122**

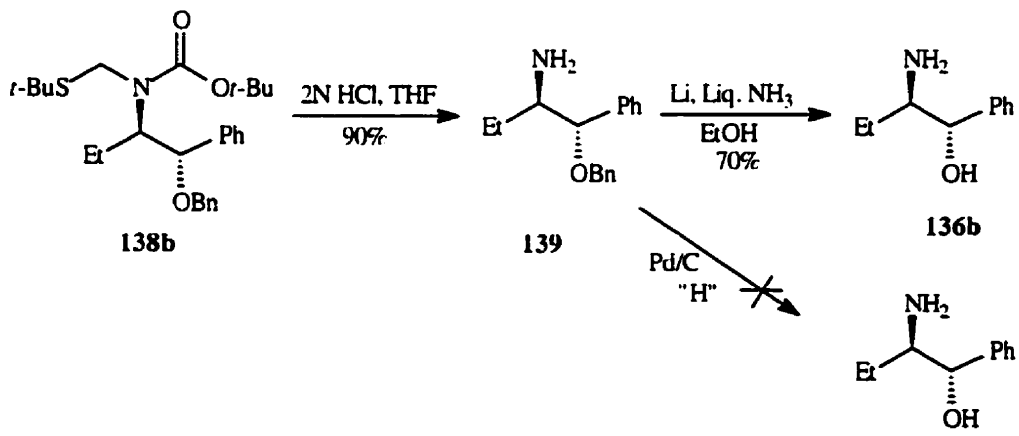
Entry	*R*	*Base*	*Yield(%)*	
			138	*122*
1	Et	NaH	0	70
2[a]	Et	NaOH	67	30
3[a]	c-C_6H_{11}	"	53	23

[a] reaction done using phase transfer catalysis

The product from entry 2, **138b**, 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_2 in the presence of Pd/C catalyst.[13] Starting material was

consumed, but no product was isolated, only unidentifiable byproducts. We then used milder conditions, transfer hydrogenolysis with either cyclohexadiene[14] or ammonium formate[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.[16] Perhaps that is why we were not being successful with our debenzylation. We then tried dissolving metal reduction,[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-debenzylations. Surprisingly, only the required primary benzyl group was removed and gave the product **136b** in good yield.

Scheme 65



138b **139** **136b**

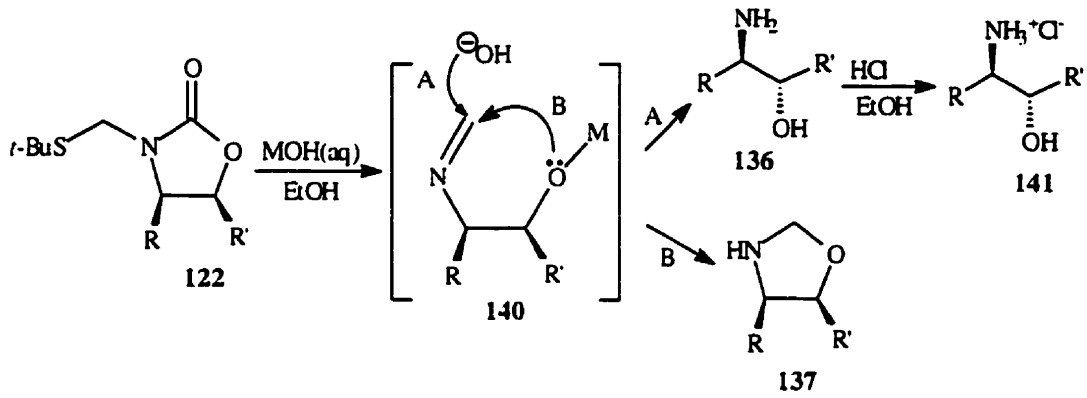
Although we were able to make the primary β-aminoalcohols, this method was not satisfactory. Protection of the alcohol occurred in low yields making the overall process unsuitable. Since the β-aminoalcohols were easily cyclized to oxazolidinones, we decided to hydrolyze the oxazolidinones to primary β-aminoalcohols. Wee and McLeod

had used aqueous KOH to hydrolyze an oxazolidinone which was a precursor to microgin.[18] 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.[19] 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*-C_5H_{11}, 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*-C_5H_{11} representing long chains and the branched chains represented by R= *i*-Pr and *c*-C_6H_{11}. The difference we were observing between R =Et and *n*-C_5H_{11} was suggesting that the straight chains were behaving differently. We were not sure whether the behavior of the oxazolidinones had altered between C_2 and C_5 since we had no data for C_3 and C_4, so

we prepared the oxazolidinones for C_3 and C_4. 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



Entry	*R*	*R'*	*M*	***136* : *137*[a]**	*% Yield of **141**[b]*
1	Et	Ph	K	1.5 : 1	nd
2	Et	$CH_3OC_6H_4$-	K	2 : 1	nd
3	Me	Ph	Li	100 : 0	84
4	Et	"	"	>90 : <10	75
5	*n*-C_3H_7	"	"	1 : 1	nd
6	*n*-C_4H_9	"	"	1 : 1	nd
7	*n*-C_5H_{11}	"	"	0 : 100	84 (**137e**)
8	*i*-Pr	"	"	>90 : <10	76
9	Et	$CH_3OC_6H_4$-	"	>90 : <10	66

[a] ratio determined by ^{1}H NMR spectroscopy

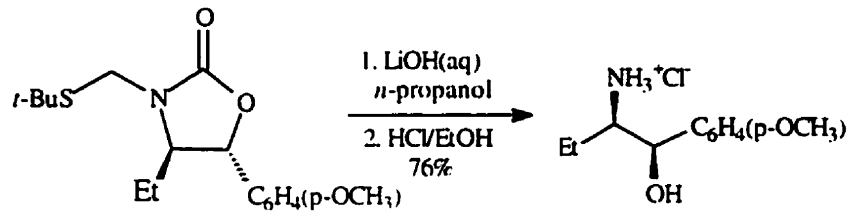
[b] Overall yield from **122**

Consequently, straight chain alkyl groups (C_3 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*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}), might be due to a hydrophobic effect.[20] 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).

Scheme 66

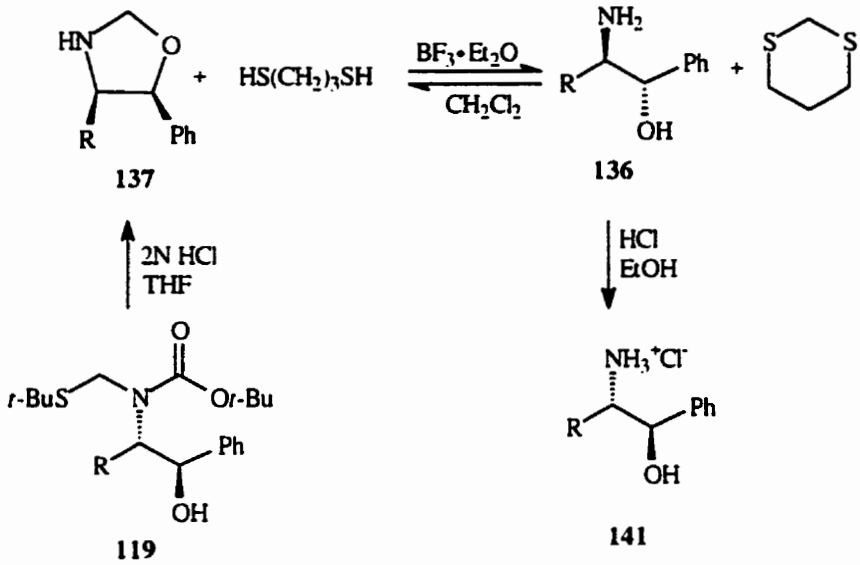


123h **142h**

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.[21] 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 $BF_3 \cdot Et_2O$ 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*-C_5H_{11} (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: Transacetilization of aminoacetals



Entry	*R*	*137* : *136*[a]	*Product*	*Yield (%)*[b]
1	Me	3 : 1	**141a**	nd
2	Et	2.5 : 1	**141b**	nd
3	C_3H_7	10 : 1	**141c**	70
4	C_4H_9	20 : 1	**141d**	75
5	C_5H_{11}	>99 : <1	**141e**	86

[a] Ratio determined by ^{1}H NMR spectroscopy

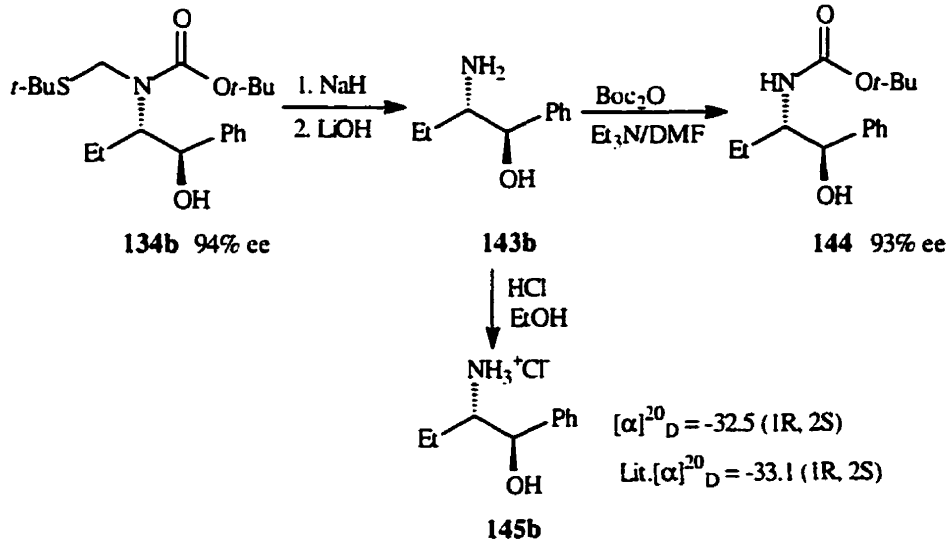
[b] Overall yield from **119**.

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 (C_3, C_4, C_5) 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.

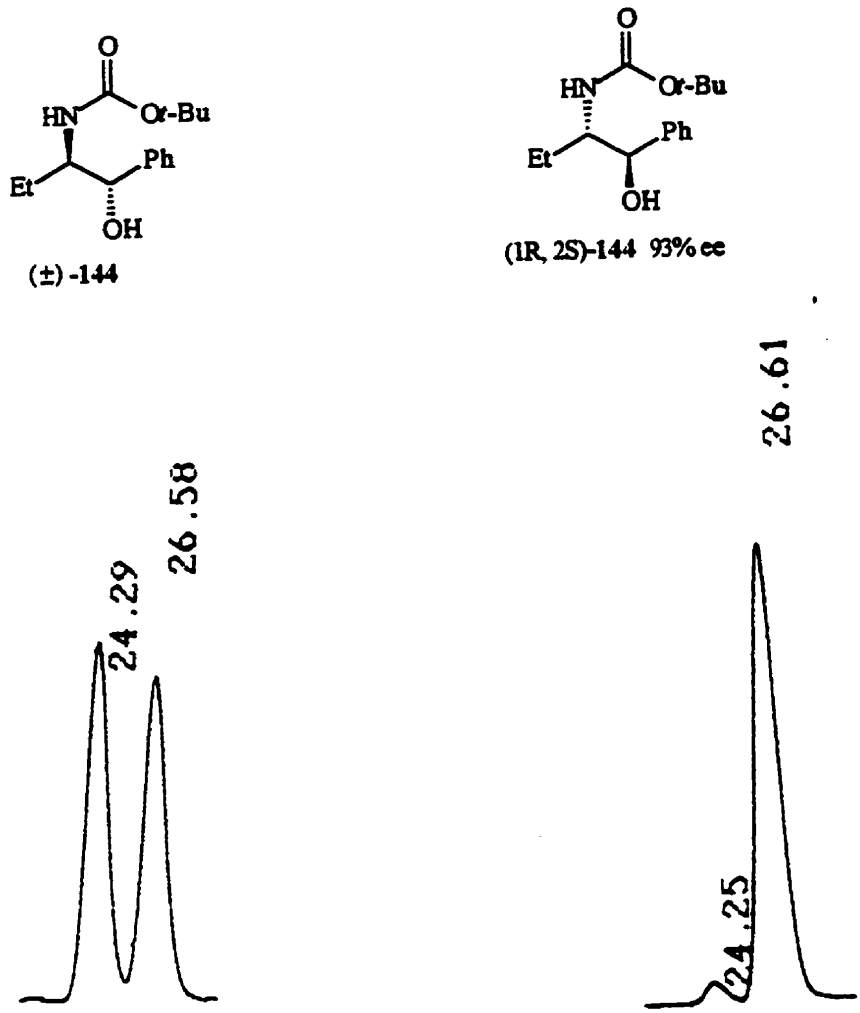
Scheme 67



134b 94% ee **143b** **144** 93% ee

145b

Figure 14: HPLC analysis of carbamate **144**[a]

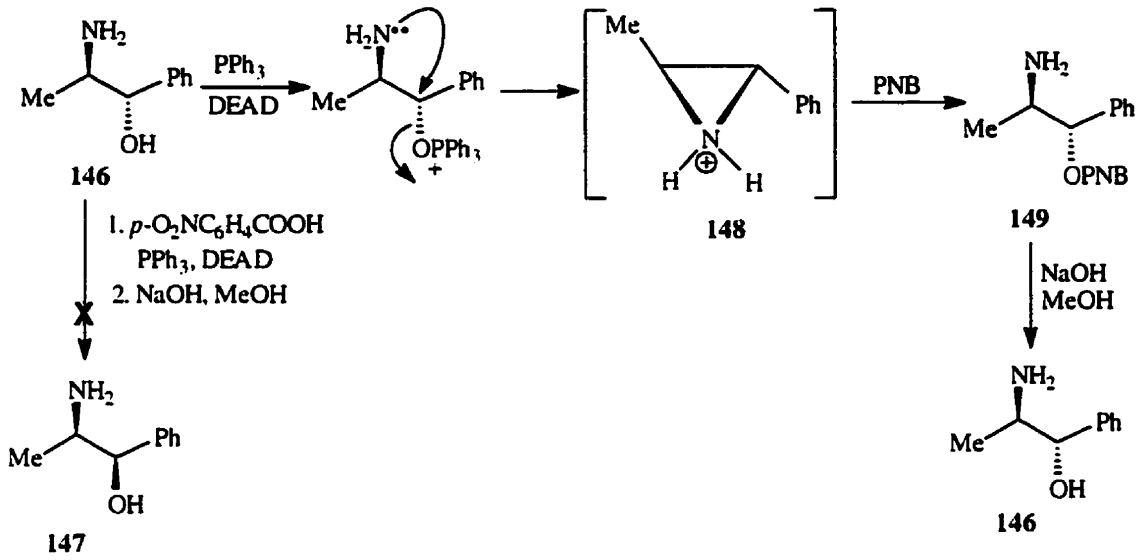


[a] Eluted with hexane/*i*-PrOH 99.5:0.5 (v/v) and a flowrate of 0.35 mL/min

4.2.6 Inversion of stereochemistry for the β-aminoalcohols

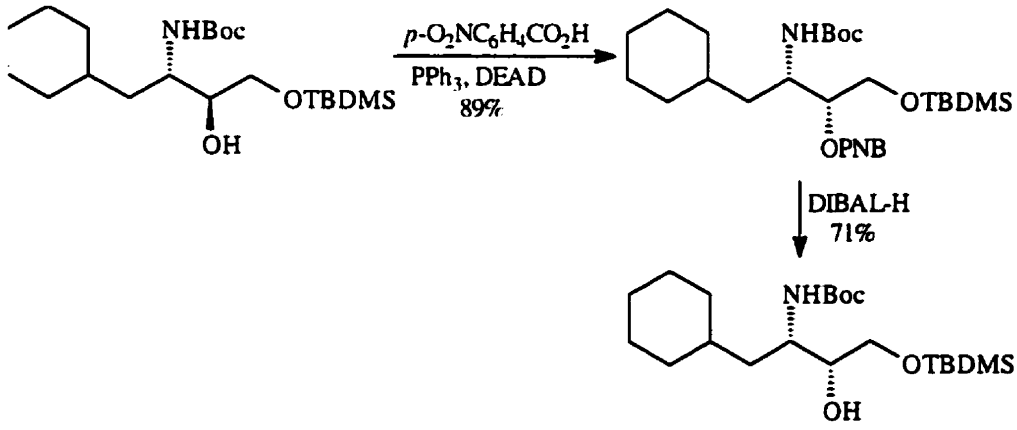
Biologically active molecules with β-aminoalcohol functionality have either the *anti* or the *syn* configuration and not a mixture. In order to make this methodology more useful, we had to find a method for stereochemical inversion, i.e. convert the *anti* to the *syn* diastereomer or *vice versa*. 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 PPh_3 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 NaN_3 as the nucleophile.[23] 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**.

Scheme 68



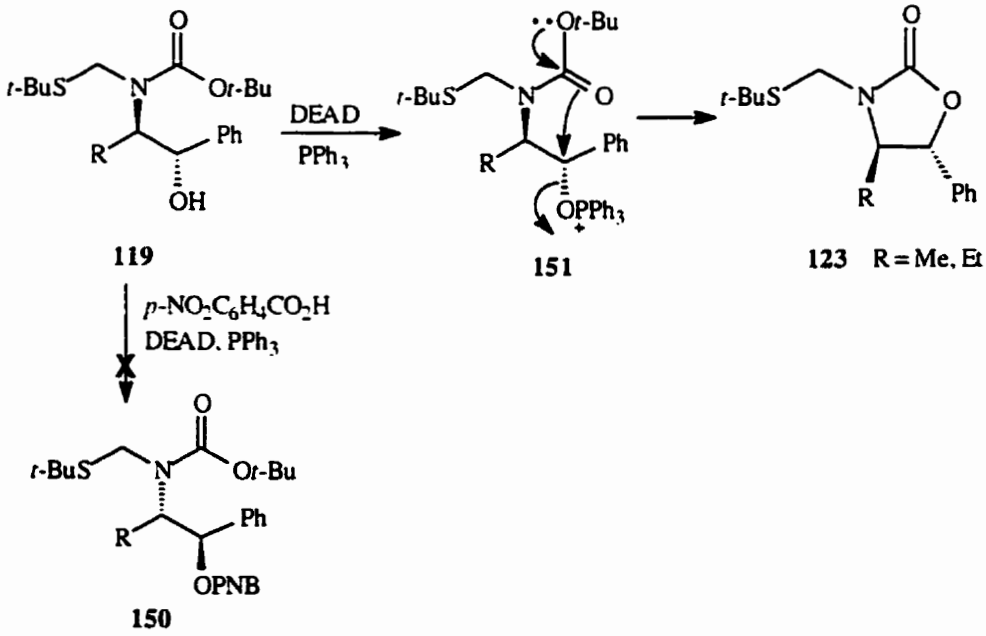
Pericas and coworkers had successfully done Mitsunobu reactions on *N*-Boc protected β-aminoalcohols (Scheme 69).[24]

Scheme 69



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

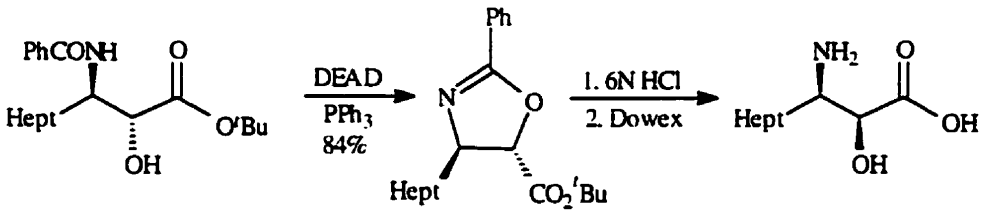


It was not clear whether **119** reacted with *p*-nitrobenzoic acid first to give the ester and then cyclized to the oxazolidinone or whether the oxazolidinone was formed *via* a different route. To probe this mechanism, we performed the reaction in the absence of the

nucleophile, *p*-nitrobenzoic acid, and the *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 β-aminoalcohols using PPh_3 and C_2Cl_6.[25]

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

Scheme 71



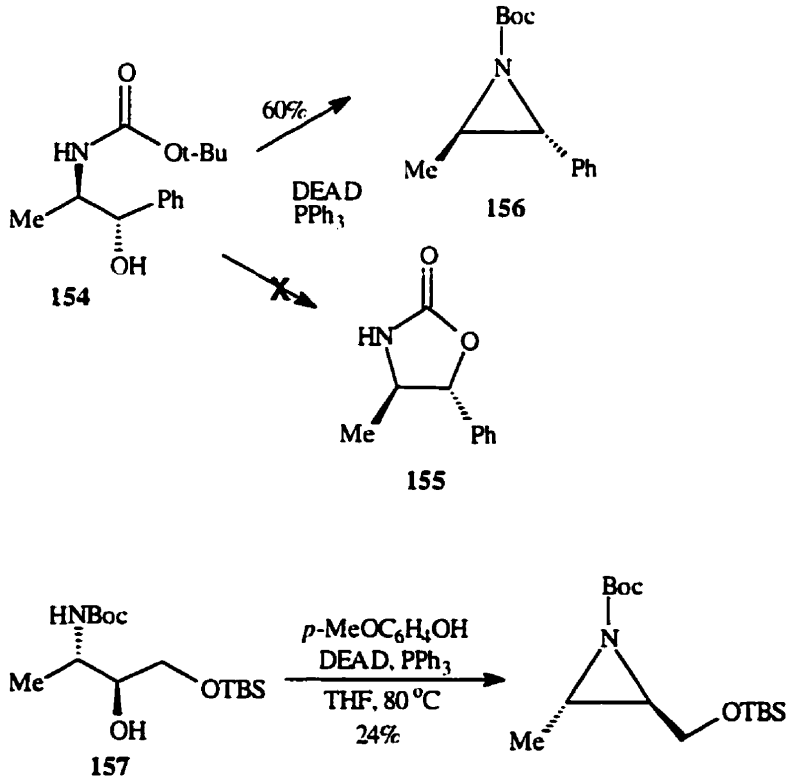
152 **153**

In order to investigate whether this reaction would also work with *N*-Boc β-aminoalcohols, we treated the carbamate **154** with 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 C_2Cl_6 and PPh_3, they isolated the aminochloride because C_2Cl_6 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).[24a] This was because they used a weak nucleophile, *p*-methoxyphenol.

Scheme 72

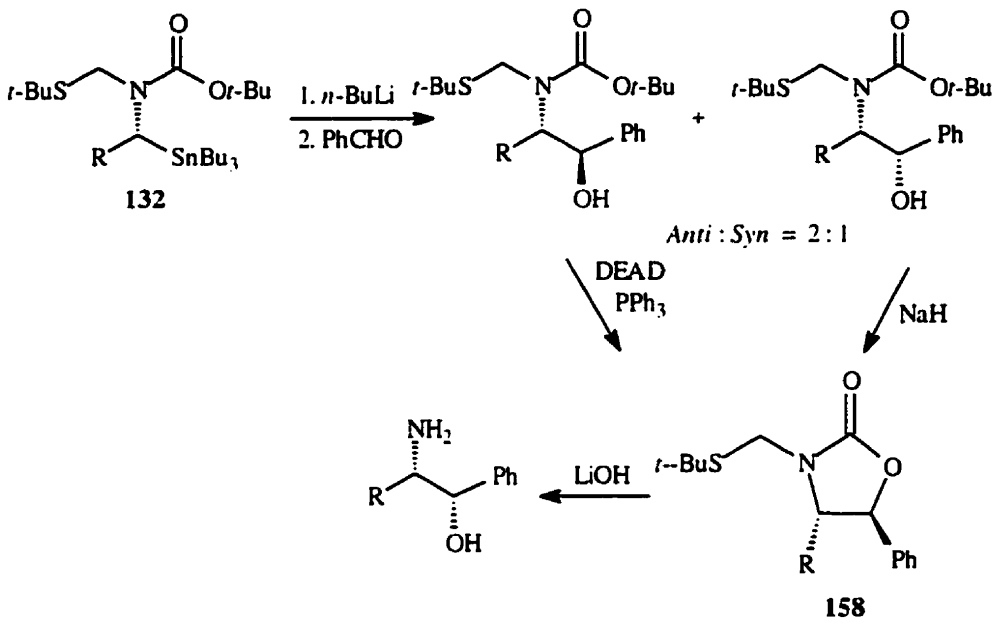


The reason why there is so much difference in Mitsunobu reactions of mono and disubstituted β-aminoalcohols might be due to hydrogen bonding. The monosubstituted β-aminoalcohols **154** and **157** can engage in intermolecular hydrogen bonding between the carbonyl oxygen and the hydrogen atom on nitrogen. 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-aminoorganostannnes **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.

Scheme 73



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*-C_3H_7, *n*-C_4H_9 and *n*-C_5H_{11}), 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*-butylthiomethyl Boc α-aminoorganolithiums, the latter are superior because both protecting groups are removable to give primary β-aminoalcohols.

Anti *N*-*t*-butylthiomethyl 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.*[27] (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) was prepared from the (R)-acid according to the procedure of Sharpless *et al.*[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*, S*) is used to represent a racemic mixture of the (R, S) diastereomer, *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

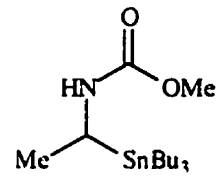
Reaction 1:

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 *in vacuo* and Et_2O was added to the residue. The solution was washed with water, dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo* to yield the crude primary amines which were used without further purification.

Reaction 2:

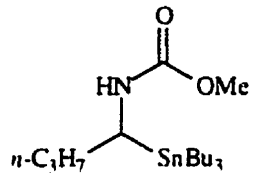
To a cooled (0 °C) 0.2 M solution of amine in CH_2Cl_2 was added Et_3N (1.3 equiv) and then methyl chloroformate (1.5 equiv). The resulting mixture was stirred at rt for 30 min and diluted with CH_2Cl_2. The mixture was washed with water, dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (35 g of silica/g of substrate; 10:1 hexane/Et_2O) to give the carbamates as colorless oils.

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



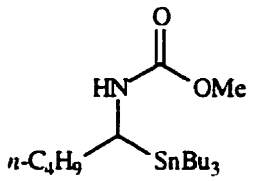
This compound was prepared from **67a** according to the general procedure described in section 4.3.2 with a reaction time of 3 h for reaction 1, in 82% yield: IR (neat) 3339, 2918, 1702, 1520, 1458, 1252 cm^{-1}; ^1H NMR (250 MHz) δ 4.73 (broad , 1 H, HN), 3.64 (s, 3 H, CO_2CH_3), 3.27 (m, 1 H, CHN), 1.64-1.20 (m, 15 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $C\underline{H}_3CHN$), 0.99-0.75 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C 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^+-CO_2Me, 100), 291 (8), 233 (7), 222 (10). Anal. Calcd for $C_{16}H_{35}NO_2Sn$: 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***



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}; ^1H NMR (250 MHz) δ 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, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_2CHN$), 0.98-0.72 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2CHN$). ^{13}C NMR (63 MHz) δ 157.1, 51.7, 40.9, 37.0, 29.0 (^2J = 20), 27.3, (^3J = 55), 21.0, 13.6, 13.5, 9.6 (^1J = 311), *9.0; MS, FAB *m/z* (relative intensity) 364 (M^+- C_4H_9, 100), 306 (7), 281 (8), 235 (12). Anal. Calcd for $C_{18}H_{39}NO_2Sn$: C, 51.45; H, 9.36; N, 3.33. Found: C, 51.58; H, 9.18; N, 3.38.

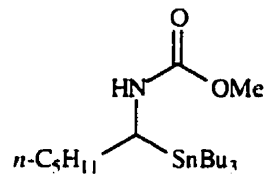
4.3.5 Methyl N-(1-tributylstannylpentyl)carbamate ***116d***



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}; ^1H NMR (250 MHz) δ 4.82

(d, 1 H, J = 7.6, HN), 3.70 (s, 0.5 H, CO_2CH_3), 3.64 (s, 2.5 H, CO_2CH_3), 3.22 (dt, 1 H, J = 7.1, 7.6, CHN), 1.66-1.18 (m, 18 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_3CHN$), 1.0-0.74 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_3CHN$); ^{13}C 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^+-C_4H_9, 100), 320 (11), 289 (8), 264 (10), 235 (12). Anal. Calcd for $C_{19}H_{41}NO_2Sn$: C, 52.55; H, 9.52; N, 3.22. Found: C, 52.40; H, 9.38; N, 3.28.

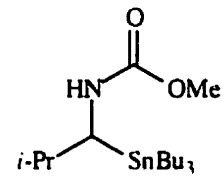
4.3.6 Methyl N-(1-tributylstannylhexyl)carbamate ***116e***



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, CO_2CH_3), 3.23 (dt, 1H, J = 7.6, 6.8, CHN), 1.60 (m, 2 H, $C\underline{H}_2CHN$), 1.48-1.23 (m, 18 H, $CH_3(C\underline{H}_2)_3CH_2$ and $SnCH_2(C\underline{H}_2)_2CH_3$), 1.0-0.64 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_4$); ^{13}C 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^+ - C_4H_9,100), 334 (12), 291 (7), 278 (8),

235 (12). Anal. Calcd for $C_{20}H_{43}NO_2Sn$: C, 53.59; H, 9.67; N, 3.12. Found: C, 53.37; H, 9.42; N, 3.05.

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



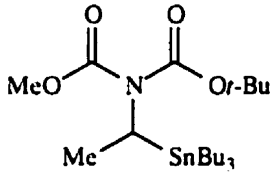
This carbamate was prepared from **67f** according to the general procedure described in section 4.3.2 with a reaction time of 24 h for reaction 1, in 70% yield: IR (neat) 3326, 2914, 1705, 1519, 1459, 1252, 1191 cm^{-1}; ^1H NMR (250 MHz) δ 4.87 (d, 1 H, J = 8.4, HN), 3.69 (s, 0.3 H, CO_2CH_3), 3.64 (s, 2.7 H, CO_2CH_3), 3.12 (dd, 1 H, J = 8.4, 7.4, CHN), 1.98 (m, 1 H, $(CH_3)_2CH$), 1.59-1.24 (m, 12 H, $SnCH_2(CH_2)_2CH_3$), 0.97-0.89 (m, 21 H, $SnCH_2(CH_2)_2CH_3$ and $(CH_3)_2CH$); ^{13}C NMR (63 MHz) δ 157.2, 51.8, 49.5, 32.4, 29 (^2J = 19), 27.4 (^3J = 56), 21.3, 20.6, 13.5, 10.2 (^1J = 314, 304); MS, FAB *m/z* (relative intensity) 364 (M^+ - C_4H_9, 100), 306 (5), 250 (12). Anal. Calcd for $C_{18}H_{44}NO_2Sn$: 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*,-dimethylamino)pyridine (0.1 equiv) and di-*tert*-butyldicarbonate (2 equiv), the solution was stirred at room temperature or sonicated for the specified time. The solvent was

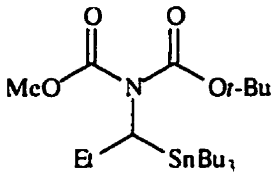
removed *in vacuo* to give a brownish residue which was diluted with Et_2O, washed several times with 1 M $KHSO_4$ followed by saturated $NaHCO_3$. The organic solution was dried (MgSO4), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (38 g of silica/g of substrate; 10:1 hexane/Et_2O) to give the products as colorless oils.

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



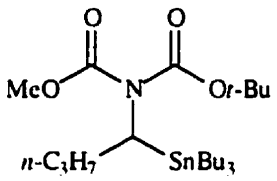
This compound was prepared from **116a** according to the general procedure described in section 4.3.8 with a reaction time of 40 h in 98% yield: IR (neat) 2917, 1744, 1688, 1448, 1272, 1165 cm^{-1}; ^1H NMR (250 MHz) δ 3.87 (q, 1 H, J = 7.4, CHN), 3.78 (s, 3 H, CO_2CH_3), 1.57-1.20 (m, 15 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $C\underline{H}_3CHN$), 1.5 (s, 9 H, $CO_2C(C\underline{H}_3)_3$), 0.98-0.74 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C 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^+-C_4H_9, 55), 380 (100), 334 (70), 274 (55), 233 (48). Anal. Calcd for $C_{21}H_{43}NO_4Sn$: 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-tributylstannylpropyl)iminodicarbonate ***115b***



This compound was prepared according to the method of Park[1] in 50% yield and had the same spectral characteristics as reported.

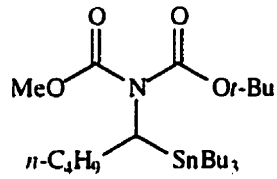
4.3.11 t-Butyl methyl N-(1-tributylstannylbutyl)iminodicarbonate ***115c***



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}; ^1H NMR (250 MHz) δ 3.93 (t, 1 H, J = 8.0, CHN), 3.78 (s, 3 H, CO_2CH_3), 1.85-1.53 (m, 2 H, $CH_3CH_2C\underline{H}_2CHN$), 1.50 (s, 9 H, $CO_2C(CH_3)_3$), 1.47-1.22 (m, 14 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3C\underline{H}_2CH_2CHN$), 0.93-0.71 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2CHN$); ^{13}C NMR (63 MHz) δ 155.5, 153.3, 81.9, 53.1, 47.3 (^1J = 357, 342), 35.2, 28.9 (^2J = 19), 27.8, 27.3 (^3J = 50), 20.7, 13.7, 13.5, 10.0 (^1J = 326, 311); MS, FAB *m/z* (relative intensity) 464 (M^+-C_4H_9, 45), 408

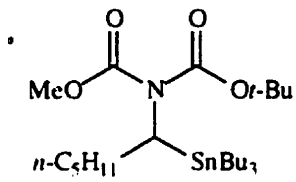
(77), 364 (78), 276 (100), 235 (79). Anal. Calcd for $C_{23}H_{47}NO_4Sn$: C, 53.09; H, 9.11; N, 2.69. Found: C, 52.88; H, 9.04; N, 2.69.

4.3.12 t-Butyl methyl N-(1-tributylstannylpentyl)iminodicarbonate ***115d***



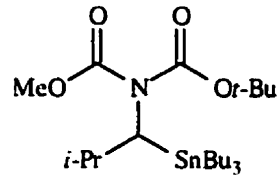
This compound was prepared from **116d** according to the general procedure described in section 4.3.8 with a reaction time of 44 h in 92% yield: IR (neat) 2915, 1743, 1692, 1449, 1342, 1151, 1073 cm^{-1}; ^1H NMR (250 MHz) δ 3.90 (t, 1 H, J = 8.0, CHN), 3.78 (s, 3 H, CO_2CH_3). 2.11-1.57 (m, 2 H, $CH_3(CH_2)_2\underline{CH_2}CHN$), 1.50 (s, 9 H, $CO_2C(CH_3)_3$), 1.57-1.18 (m, 16 H, $SnCH_2(C\underline{H_2})_2CH_3$ and $CH_3(C\underline{H_2})_2CH_2CHN$). 0.92-0.71 (m, 18 H, $SnC\underline{H_2}(CH_2)_2C\underline{H_3}$ and $C\underline{H_3}(CH_2)_3CHN$): ^{13}C 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^+- C_4H_9, 36), 422 (62), 378 (70), 276 (100), 235 (70). Anal. Calcd for $C_{24}H_{49}NO_4Sn$: 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-tributylstannylhexyl)iminodicarbonate ***115e***



This compound was prepared from **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}; ^1H NMR (250 MHz) δ 3.86 (t, 1 H, J = 8.0, CHN), 3.78 (s, 3 H, CO_2CH_3), 1.55 (m, 2 H, $CH_3(CH_2)_3C\underline{H}_2CHN$), 1.49 (s, 9 H, $CO_2C(CH_3)_3$), 1.47-1.17 (m, 18 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_3CH_2CHN$), 0.91-0.77 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_4CHN$); ^{13}C NMR (63 MHz) δ 155.7, 153.4, 82.3, 53.4, 47.8, 33.0, 31.6, 29.1 (^2J = 19), 28.0, 27.5, *27.4, 22.6, 14.0, 13.6, 10.2 (^1J = 326); MS, FAB *m/z* (relative intensity) 492 (M^+-C_4H_9, 66), 436 (70), 392 (74), 276 (100), 235 (59). Anal. Calcd for $C_{25}H_{51}NO_4Sn$: C, 54.76; H, 9.30; N, 2.55. Found: C, 54.88; H, 9.12; N, 2.52.

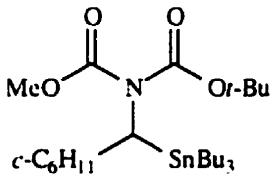
4.3.14 t-Butyl methyl N-(2-methyl-1-tributylstannylpropyl)iminodicarbonate ***115f***



This compound was prepared from **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}; ^1H NMR (250 MHz) δ 3.77 (s, 3 H, CO_2CH_3), 3.69 (d, 0.2 H, J = 11, CHN), 3.60 (d, 0.8 H, J = 11, CHN), 2.0 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.56-1.10 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 1.48 (s, 9 H, $CO_2C(CH_3)_3$), 0.97-0.63 (m, 21 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $(C\underline{H}_3)_3CH$), ^{13}C NMR (63 MHz) δ 155.5, 153.3, 81.8, 55.2, 51.3, 30.0, 28.9, (^2J = 19), 27.7, *27.6, 27.3, 21.3, 20.2, 13.4, 10.4 (^1J = 324, 310); MS, FAB *m/z* (relative intensity) 462 (M^+ - C_4H_9, 70), 408 (82), 364 (100), 323 (60), 291(68), 276 (85), 235 (39). Anal. Calcd for $C_{23}H_{46}NO_4Sn$: C, 53.31; 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***



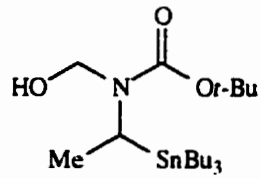
This compound was prepared according to the method of Park[1] with a reaction time of 42 h in 21% yield: IR (neat) 2914, 1742, 1691, 1446, 1346, 1265, 1233, 1150 cm^{-1}; ^1H NMR (250 MHz) δ 3.78 (s, 3 H, CO_2CH_3), 3.7 (d, 0.75 H, J = 11, CHN), 1.85 (d, 0.25 H, J = 11, CHN), 1.5 (s, 9 H, $CO_2C(CH_3)_3$), 1.88-1.10 (m, 23 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and *c*-C_6H_{11}), 0.98-0.73 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C NMR (63 MHz) δ 155.7, 153.5, 82.1, *54.2, 53.3, 39.5, 32.2, 31.1, 29.0 (^2J = 19), 27.9, 27.4, 26.9, 26.5, 25.8, 13.1, 10.5 (^1J = 324, 309); MS, FAB *m/z* (relative intensity) 504 (M^+-C_4H_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. ^1H NMR spectra were recorded using DMSO-d_6 as solvent and DMSO-d_6 (δ 2.49) was used as the internal standard.

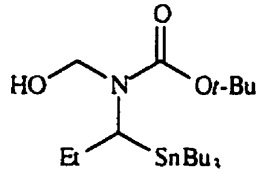
*4.3.17 t-Butyl N-hydroxymethyl-N-(1-tributylstannylethyl)carbamate **117a***



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}; ^1H NMR (200 MHz) δ 5.60 (t, 1 H, J = 6.9, OH), 4.63 (m, 2 H, C<u>H</u>$_2$OH), 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, $SnCH_2(C\underline{H}_2)_2CH_2$ and

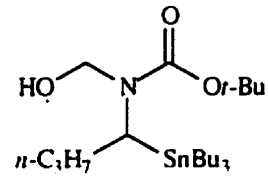
$C\underline{H}_3CHN$), 0.87-0.62 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C NMR (63 MHz) δ 156.1 *154.7, 79.9, 73.3, *71.7, 42.8, *41.3, 29.1 (^2J = 20), 28.3, 27.4 (^3J = 56), *19.5, 18.9, 13.6, 10.0 (^1J = 324 Hz), *9.3; MS, FAB *m/z* (relative intensity) 448 (M^+-OH, 10), 408 (M^+-C_4H_9, 46), 352 (63), 290 (100), 135 (26), 177 (49). Anal. Calcd for $C_{20}H_{43}NO_3Sn$: 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-(1-tributylstannylpropyl)carbamate ***117b***



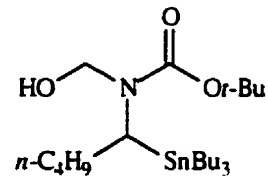
This compound was prepared from **115b** according to the general procedure described in section 4.3.16 in 77% yield: IR (neat) 3345, 2918, 1693, 1595, 1504, 1165 cm^{-1}; ^1H NMR (200 MHz) δ 5.62 (t, 1 H, J = 6.8, OH), 4.72 (m, 1H, $C\underline{H}_2OH$), 4.58 (m, 1 H, $C\underline{H}_2OH$), 2.92 (t, 1 H, J = 7.6, CHN), 1.76 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.4 (s, 9 H, $CO_2C(CH_3)_3$), 1.54-1.12 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.93-0.65 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2CHN$); ^{13}C NMR (50 MHz) δ 154.8, 80.2, *79.9, *74.2, 72.4, 51.2, 39.3, 29.1 (^2J = 20), 28.9, 27.4 (^3J = 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_4H_9, 19), 366 (20), 336 (29), 291 (40), 57 (100). Anal. Calcd for $C_{21}H_{45}NO_3Sn$: C, 52.74; H, 9.48; N, 2.93. Found: C, 52.55; H, 9.23; N, 2.93.

4.3.19 t-Butyl N-hydroxymethyl-N-(1-tributylstannylbutyl)carbamate 117c



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}; ^1H NMR (200 MHz) δ 5.80 (m, 0.15 H, OH), 5.63 (t, 0.85 H, J = 6.9, OH), 4.70 (m, 1 H, $C\underline{H}_2OH$), 4.50 (m, 1 H, $C\underline{H}_2OH$), 3.09 (t, 1 H, J = 7.7, CHN), 1.70- 1.17 (m, 16 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_2CHN$), 1.37 (s, 9 H, $CO_2C(CH_3)_3$), 0.90- 0.65 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2CHN$); ^{13}C NMR (50 MHz) δ 156.4, *154.8, *80.1, 79.9, 74.1, *72.2, 48.9, *46.3, 35.7, 29.1 (^2J = 19), 28.4, 27.5 (^3J = 50), *27.4, 21.3, *20.8, *13.5, 13.6, 10.2 (^1J = 319), *9.4; MS, FAB *m/z* (relative intensity) 476 (M^+- OH, 9), 436 (M^+- C_4H_9, 30), 380 (35), 318 (100), 291 (30), 235 (38). Anal. Calcd for $C_{22}H_{47}NO_3Sn$: C, 53.67; H, 9.62; N, 2.84. Found: C, 53.70; H, 9.49; N, 2.85.

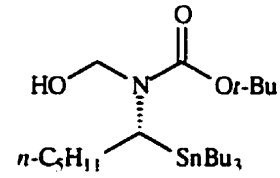
4.3.20 t-Butyl N-hydroxymethyl-N-(1-tributylstannylpentyl)carbamate 117d



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, $C\underline{H}_2OH$), 4.51 (m, 1 H, $C\underline{H}_2OH$), 2.97 (t, 1 H, J = 7.7, CHN), 1.68 (m, 2 H, $CH_3(CH_2)_2C\underline{H}_2CHN$), 1.37 (s, 9 H, $CO_2C(CH_3)_3$), 1.56-1.12 (m, 16 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_2CH_2CHN$), 0.86-0.65 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2CH_2CHN$); ^{13}C 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^+- C_4H_9, 15), 434 (30), 378(40), 332 (100), 235 (42). Anal. Calcd for $C_{23}H_{49}NO_3Sn$: C, 54.56; H, 9.76; N, 2.77. Found: C, 54.70; H, 9.77; N, 2.84.

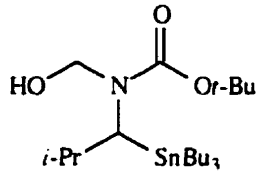
4.3.21 t-Butyl N-hydroxymethyl-N-(1-tributylstannylhexyl)carbamate ***117e***



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, $C\underline{H}_2OH$), 4.51 (m, 1 H, $C\underline{H}_2OH$), 2.97 (t, 1 H, J = 7.8, CHN), 1.60 (m, 2 H, $CH_3(CH_2)_3C\underline{H}_2CHN$), 1.37 (s, 9 H, $CO_2C(CH_3)_3$), 1.50-1.10 (m, 18 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_3CH_2CHN$), 0.86-0.57 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_3CH_2CHN$); ^{13}C 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.

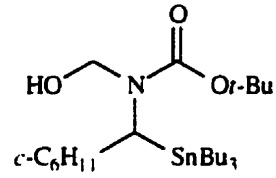
*4.3.22 t-Butyl N-hydroxymethyl-N-(2-methyl-1-tributylstannylpropyl)carbamate **117f***



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, C<u>H</u>$_2$OH), 4.43 (dd, 1 H, J = 7.0, 10.3, C<u>H</u>$_2$OH), 2.67 (d, 1 H, J = 9.8, J_{Sn-H} = 49 Hz, CHN), 2.15 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.37 (s, 9 H, $CO_2C(CH_3)_3$), 1.55-1.27 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.98-0.59 (m, 21 H, $Sn\underline{CH}_2(CH_2)_2C\underline{H}_3$ and $(C\underline{H}_3)_2CH$); ^{13}C 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-hydroxymethyl-N-(1-cyclohexyl-1-tributylstannylmethyl)carbamate

117g



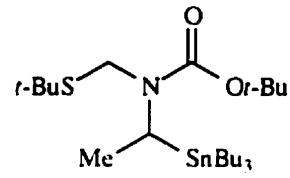
This compound was prepared from **115g** according to the general procedure described in section 4.3.16 in 80% yield: IR (neat) 3425, 2925, 1665, 1366, 1174 cm^{-1}; ^1H NMR (200 MHz) δ 5.67 (t, 0.24 H, J = 7.0, OH), 5.58 (t, 0.76 H, J = 7.0, OH), 4.78 (dd, 1 H, J = 7.0, 10.0, $C\underline{H}_2OH$), 4.37 (dd, 1 H, J = 7.0, 10.0, $C\underline{H}_2OH$), 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, $SnCH_2(C\underline{H}_2)_2CH_3$ and *c*-C_6H_{11}), 1.37 (s, 9 H, $CO_2C(CH_3)_3$), 0.87-0.65 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C NMR (63 MHz) δ *159.0, 155.5, 80.0, 75.5, 57.2, 40.3, 32.4, 32.3, 29.1 (^2J = 17), 28.5, 27.5 (^3J = 58), *27.4, 26.7, *26.2, 26.1, 13.7, *13.6, 10.8, 10.1 (^1J = 310, 290); MS, FAB *m/z* (relative intensity) 416 (M^+-OH, 4), 476 (M^+-C_4H_9, 28), 420 (32), 358 (80), 291 (28), 177 (40), 124 (100). Anal. Calcd for $C_{25}H_{51}NO_3Sn$: 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 carbamates

To a 0.07 M solution of the *N*-hydroxymethyl carbamate **117** in hexane was added Et_3N (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

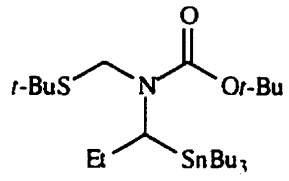
with hexane and washed several times with saturated $NaHCO_3$. The organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (40 g silica/g of substrate; 40:1 hexane/Et_2O) to give the products as colorless oils.

4.3.25 t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylethyl)carbamate ***118a***



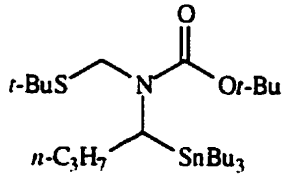
This compound was prepared from **117a** according to the general procedure described in section 4.3.24 in 77% yield: IR (neat) 2921, 1679, 1443, 1237, 1161 cm^{-1}; ^1H NMR (250 MHz) δ 4.50 (ABq, 2 H, Δδ = 0.14, J = 13.7, CH_2S), 2.97 (q, 1 H, J = 7.3, CHN), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.36 (s, 9 H, $SC(CH_3)_3$), 1.55-1.10 (m, 15 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $C\underline{H}_3CHN$), 0.68-0.92 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$); ^{13}C NMR (63 MHz) δ 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^+-C_4H_9, 34), 380 (28), 290 (100), 235 (10). Anal. Calcd for $C_{24}H_{51}NO_2SSn$: 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-(1-tributylstannylpropyl)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}; ^1H NMR (200 MHz) δ 4.49 (ABq, 2 H, Δδ = 0.26, J = 13.6, CH_2S), 3.16 (m, 0.25 H, CHN), 2.82 (dd, 0.75 H, J = 7.5, 7.0, CHN), 1.84 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.50-1.20 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.36 (s, 9 H, $SC(CH_3)_3$), 0.9-0.7 (m, 18 H, $Sn\underline{CH}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2CHN$); ^{13}C NMR (50 MHz) δ 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/z* (relative intensity) 494 (M^+-C_4H_9, 81), 394 (40), 304 (73), 57 (100). Anal. Calcd for $C_{25}H_{53}NO_2SSn$: C, 54.55; H, 9.70; N, 2.54. Found: C, 54.44; H, 9.57; N, 2.55.

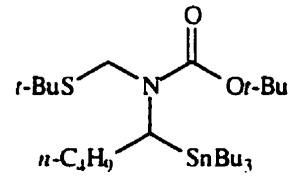
4.3.27 t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylbutyl)carbamate ***118c***



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, CH_2S), 4.50 (ABq, 1.4 H, Δδ = 0.24, J = 13.5, CH_2S), 2.91 (dd, 1 H, J = 7.9, 7.6, CHN), 1.84-1.65 (m, 2 H, $CH_3CH_2C\underline{H}_2CHN$), 1.61-1.10 (m, 14 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3C\underline{H}_2CH_2CHN$), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.36 (s, 9 H, $SC(CH_3)_3$), 0.95-0.70 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2$); ^{13}C 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^+-C_4H_9, 17), 408 (12), 364 (13), 318 (100), 291 (18). Anal. Calcd for $C_{26}H_{55}NO_2SSn$: C, 55.33; H, 9.82; N, 2.48. Found: C, 55.24; H, 9.78; N, 2.40.

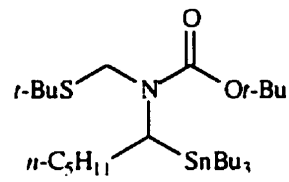
4.3.28 t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylpentyl)carbamate ***118d***



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, SCH_2), 4.50 (ABq, 1.5 H, Δδ = 0.27, J = 13.5, SCH_2), 2.89 (t, 1 H, J = 7.8, CHN), 1.8 (q, 2 H, J = 7.7, $CH_3(CH_2)_2C\underline{H}_2CHN$), 1.58-1.0 (m, 16 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_2CH_2CHN$), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.35 (s, 9 H, $SC(CH_3)_3$), 0.99-0.73 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_2CH_2CHN$); ^{13}C 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

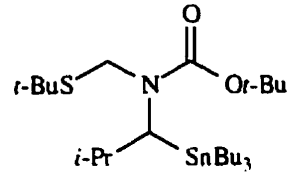
(^1J = 322); MS, FAB *m/z* (relative intensity) 522 (M^+-C_4H_9, 20), 422 (12), 332 (100), 291 (12). Anal. Calcd for $C_{27}H_{57}NO_2SSn$: C, 56.06; H, 9.93; N, 2.41. Found: C, 55.90; H, 9.78; N, 2.40.

4.3.29 t-Butyl N-t-butylthiomethyl-N-(1-tributylstannylhexyl)carbamate ***118e***



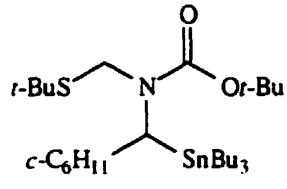
This compound was prepared from **117e** according to the general procedure described in section 4.3.24 in 81% yield: IR (neat) 2957, 2933, 1677, 1451, 1391, 1163 cm^{-1}; ^1H NMR (250 MHz) δ 4.48 (ABq, 2 H, Δδ = 0.48, J = 13.5, SCH_2), 2.89 (t, 1 H, J = 8.0, CHN), 1.8 (m, 2 H, $CH_3(CH_2)_3C\underline{H}_2CHN$), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.35 (s, 9 H, $SC(CH_3)_3$), 1.5-1.2 (m, 18 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_3CH_2CHN$), 0.92–0.71 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_3CH_2CHN$). ^{13}C NMR (63 MHz) δ 154.5, 79.7, 49.2, 49.0, 42.7, 32.3, 32.8, 31.3, 29.2 (^2J = 19), 28.4, 27.6 (^3J= 57), 22.6, 14.0, 13.7, 10.7 (^1J = 322, 307), 10.0; MS, FAB *m/z* (relative intensity) 536 (M^+-C_4H_9, 48), 436 (18), 390 (16), 346 (100), 291 (16), 233 (20). Anal. Calcd for $C_{28}H_{59}NO_2SSn$: 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-butylthiomethyl-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}; ^1H NMR (200 MHz, C_6D_6) δ 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, $(CH_3)_3C\underline{H}$), 1.8 (m, 12 H, $SnCH_2(C\underline{H}_2)CH_3$), 1.42 (s, 9 H, $CO_2C(CH_3)_3$), 1.24, (s, 9 H, $SC(CH_3)_3$), 1.49-0.49 (m, 21 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $(C\underline{H}_3)_2CH$); ^{13}C NMR (63 MHz) δ 154.8, 79.6, 57.4, 50.3, 42.5, 31.3, 31.2, 29.3 (^2J = 19), 28.4, 27.6 (^1J = 59), *21.9, *21.7, 21.6, 21.4, *21.1, 13.7, 11.3 (^1J = 321); MS, FAB *m/z* (relative intensity) 508 (M^+-C_4H_9, 52), 408 (18), 318 (100), 290 (13), 235 (14). Anal. Calcd for $C_{26}H_{55}NO_2SSn$: 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-butylthiomethyl-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, C_6D_6) δ 5.04 (d, 1 H, J = 12.9, SCH_2), 4.10 (d, 1 H, J = 12.9, CH_2S), 2.85 (d, 1 H, J = 9.6, J_{Sn-H} = 49, CHN), 2.3 (m, 1 H, *c*-C<u>H</u>CHN), 1.84 (m, 16 H, *c*-CHC<u>H</u>$_2$$(CH_2)_3$C<u>H</u>$_2$ and $SnCH_2$(C<u>H</u>$_2$$)_2CH_3$), 1.43 (s, 9 H, $CO_2C(CH_3)_3$), 1.26 (s, 9 H, $SC(CH_3)_3$), 1.21-0.94 (m, 21 H, *c*-$CHCH_2$(C<u>H</u>$_2$$)_3CH_2$ and SnC<u>H</u>$_2$$(CH_2)_2$C<u>H</u>$_3$); ^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^+-C_4H_9, 12), 404 (8), 358 (70), 291 (8), 214 (9), 177 (18), 124 (100). Anal. Calcd for $C_{29}H_{59}NO_2SSn$: 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

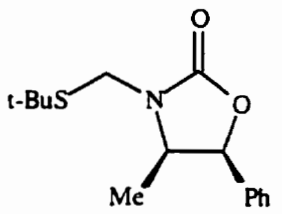
To a cooled (-78 °C) 0.15 M solution of the α-aminoorganostannane **118** was added *n*-BuLi (1.5 equiv) slowly and the solution was stirred for 15 min. The appropriate aldehyde (2.0 equiv) was added and the mixture was stirred for 15 min and quenched at -78 °C with saturated ammonium chloride. The mixture was diluted with Et_2O, washed with water, dried ($MgSO_4$), 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 Et_2O and washed with water. The organic layer was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (100 g

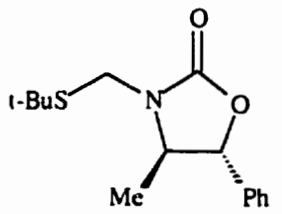
silica/g substrate; 5:1 hexane/Et_2O) to give the oxazolidinones as colorless oils or white solids.

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***



(4R*, 5S*)- **122a**



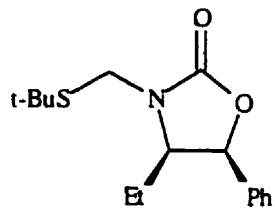
(4R*, 5R*)- **123a**

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

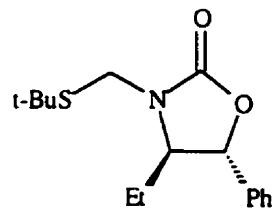
(4R*, 5S*)-**122a** was obtained in 65% yield: mp 98-99 °C; IR (KBr) 2942, 1734, 1404, 1294, 1244, 1173 cm^{-1}; ^1H NMR (250 MHz) δ 7.43–7.26 (m, 5 H, ArH), 5.58 (d, 1 H, J = 8.4, CHO), 5.07 (d, 1 H, J = 14.7, CH_2S), 4.4 (quintet, 1 H, J = 6.6, CHN), 4.01 (d, 1 H, J = 14.7, CH_2S), 1.42 (s, 9 H, $SC(CH_3)_3$), 0.78 (d, 3 H, J = 6.6, $C\underline{H}_3CH$); ^{13}C 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^+-C_4H_9, 13), 190 (44), 146 (94), 105 (100), 57 (22). Anal. Calcd for $C_{15}H_{21}NO_2S$: 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, CH_2S), 4.94 (d, 1 H, J = 8.1, CHO), 4.1 (d, 1 H, J = 14.9, CH_2S), 3.98 (quintet, 1 H, J = 6.2, CHN), 1.37 (m, 12 H, $C\underline{H}_3CH$ and $SC(CH_3)_3$); ^{13}C 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^+-C_4H_9, 13), 190 (31), 146 (100), 105 (85), 91 (18), 57 (18). Anal. Calcd for $C_{15}H_{21}NO_2S$: 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***



(4R*, 5S*)- **122b**



(4R*, 5R*)- **123b**

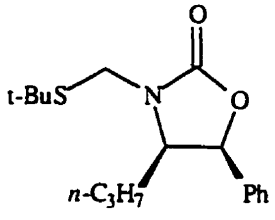
This mixture of diastereomers was prepared from **118b** according to the general procedure described in section 4.3.32 in 77% overall yield.

(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, CH_2S), 4.26 (dt, 1 H, J = 3.8, 8.2, CHN), 4.06 (d, 1 H, J = 14.8, CH_2S), 1.42 (s, 9 H, $SC(CH_3)_3$), 1.47-1.24 (m, 2 H, $CH_3C\underline{H}_2$), 0.55 (t, 3 H, J = 7.5, CH_3CH_2), ^{13}C NMR (63 MHz) δ 156.9, 134.7, 128.6, 128.4, 126.5, 78.9, 58.3,

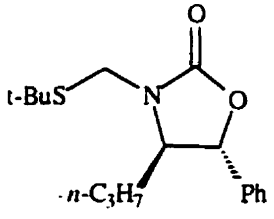
43.5, 42.6, 31.2, 20.6, 9.0; MS, EI *m/z* (relative intensity) 293 (M^+, 0.7), 236 (M^+-C_4H_9, 11), 204 (50), 160 (89), 105 (100), 57 (32). Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.54; H, 7.78; N, 4.88.

(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, CH_2S), 4.04 (d, 1 H, J = 14.9, CH_2S), 3.90 (dt, 1 H, J = 3.1, 6.4, CHN), 1.82-1.66 (m, 2 H, $CH_3\underline{CH_2}$), 1.35 (s, 9 H, $SC(CH_3)_3$), 0.98 (t, 3 H, J = 7.5, $\underline{CH_3}CH_2$); ^{13}C 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^+-C_4H_9, 15), 204 (37), 160 (100), 105 (76), 57 (18). Anal. Calcd for $C_{16}H_{23}NO_2S$: 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***



(4R*, 5S*)- **122c**



(4R*, 5R*)- **123c**

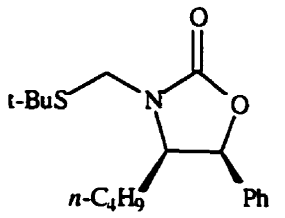
This mixture of diastereomers was prepared from **118c** according to the general procedure described in section 4.3.32 in 86% overall yield.

(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

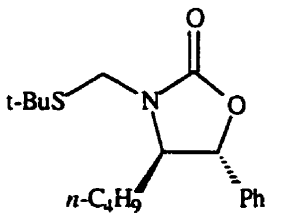
H, J = 8.2, CHO), 5.10 (d, 1 H, J = 14.8, CH_2S), 4.30 (dt, 1 H, J = 8.2, 3.7, CHN), 4.10 (d, 1 H, J = 14.8, CH_2S), 1.42 (s, 9 H, $SC(CH_3)_3$), 1.37-1.00 (m, 2 H, $CH_3CH_2C\underline{H}_2$), 1.2-0.8 (m, 2 H, $CH_3C\underline{H}_2CH_2$), 0.64 (t, 3 H, J = 7.0, $C\underline{H}_3CH_2CH_2$); ^{13}C NMR (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^+-C_4H_9, 12), 218 (45), 174 (66), 132 (81), 91 (100), 57 (50). Anal. Calcd for $C_{17}H_{25}NO_2S$: 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, CH_2S), 4.10 (d, 1 H, J = 14.8, CH_2S), 4.0 (m, 1 H, CHN), 1.84-1.71 (m, 2 H, $CH_3CH_2C\underline{H}_2$), 1.68-1.40 (m, 2 H, $CH_3C\underline{H}_2CH_2$), 1.34 (s, 9 H, $SC(CH_3)_3$), 0.96 (t, 3 H, J = 7.2, $C\underline{H}_3CH_2CH_2$); ^{13}C 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^+-C_4H_9, 16), 218 (49), 174 (95), 132 (100), 91 (87), 57 (51). Anal. Calcd for $C_{17}H_{25}NO_2S$: 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-butylthiomethyl-5-phenyl-2-oxazolidinone ***122/123d***



(4R*, 5S*)- **122d**



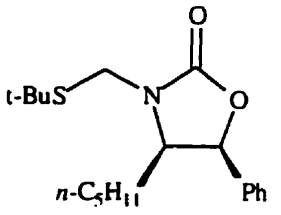
(4R*, 5R*)- **123d**

This mixture of diastereomers was prepared from **118d** according to the general procedure described in section 4.3.32 in 79% overall yield.

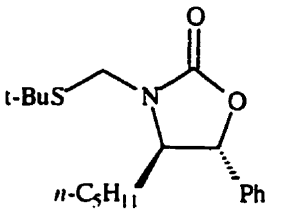
(4R*, 5S*)-**122d** was obtained in 55% yield: mp 48-50 °C; IR (KBr) 2923, 1730, 1461, 1422, 1232, 1174, 1114 cm^{-1}; ^1H NMR (250 MHz) δ 7.41–7.29 (m, 5 H, ArH), 5.56 (d, 1 H, J = 8.2, CHO), 5.10 (d, 1 H, J = 14.9, CH_2S), 4.30 (dt, 1 H, J = 3.7, 8.2, CHN), 4.06 (d, 1 H, J = 14.9, CH_2S), 1.42 (s, 9 H, $SC(CH_3)_3$), 1.44-0.85 (m, 6 H, $CH_3(C\underline{H}_2)_3$), 0.64 (t, 3 H, J = 7.3, $C\underline{H}_3(CH_2)_3$); ^{13}C 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, EI *m/z* (relative intensity) 321 (M^+, 0.2), 264 (M^+-C_4H_9, 7), 232 (38), 188 (61), 132 (100), 91 (68), 57 (38). Anal. Calcd for $C_{18}H_{27}NO_2S$: 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, 1H, J = 14.9, CH_2S), 4.05 (d, 1 H, J = 14.9, CH_2S), 4.04-3.97 (m, 1 H, CHN), 1.83-1.74 (m, 1 H, $CH_3(CH_2)_2C\underline{H}_2$), 1.69-1.57 (m, 1 H, $CH_3(CH_2)_2C\underline{H}_2$), 1.34 (s, 9 H, $SC(CH_3)_3$), 1.46-1.20 (m, 4 H, $CH_3(C\underline{H}_2)_2CH_2$), 0.91 (t, 3 H, J = 6.8, $C\underline{H}_3(CH_2)_3$); ^{13}C 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, EI *m/z* (relative intensity) 321 (M^+, 0.4), 264 (M^+-C_4H_9, 10), 232 (33), 188 (71), 132 (100), 91 (73), 57 (41). Anal. Calcd for $C_{18}H_{27}NO_2S$: 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***



(4R*, 5S*)- **122e**



(4R*, 5R*)- **123e**

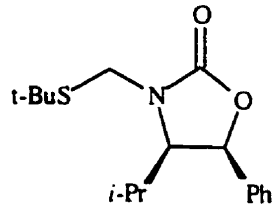
The protected β-aminoalcohols **119/120e** were prepared from **118e** according to the general procedure described in section 4.3.32, in 75% overall yield. The two diastereomers were separated by column chromatography before cyclization to the oxazolidinones.

(4R*, 5S*)-**122e** was prepared in 85% yield from the *anti* β-aminoalcohol **119e**: IR (neat) 2953, 1861, 1754, 1410, 1241, 1169 cm^{-1}; ^1H 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_2S), 4.30 (dt, 1 H, J = 8.2, 3.6), 4.06 (d, 1 H, J = 14.9, CH_2S), 1.42 (s, 9 H, $SC(CH_3)_3$), 1.20-0.84 (m, 8 H, $CH_3(C\underline{H}_2)_4$), 0.71 (t, 3 H, J = 6.7, $C\underline{H}_3(CH_2)_4$): ^{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_4H_9, 5), 246 (16), 202 (52), 132 (100), 105 (35), 91 (63), 57 (34). Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.03; H, 8.71; N, 4.17. Found: C, 67.89; H, 8.67; N, 4.18.

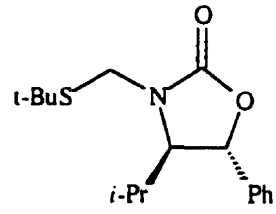
(4R*, 5R*)-**123e** was prepared in 90% yield from the *syn* β-aminoalcohol **120e**: IR (neat) 2938, 2862, 1748, 1430, 1229, 1171 cm^{-1}; ^1H NMR (250 MHz) δ 7.40-7.30 (m, 5 H, ArH), 5.10 (d, 1 H, J = 5.8, CHO), 5.07 (d, 1 H, J = 14.4, CH_2S), 4.06 (d, 1 H, J = 14.4, CH_2S), 3.90 (m, 1 H, CHN), 1.70-1.40 (m, 2 H, $CH_3(CH_2)_3C\underline{H}_2$), 1.35 (s, 9 H,

$SC(CH_3)_3$), 1.30-0.94 (m, 6 H, $CH_3(C\underline{H}_2)_3CH_2$), 0.88 (t, 3 H, J = 6.4, $C\underline{H}_3(CH_2)_4$); ^{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^+-C_4H_9, 8), 246 (25), 202 (64), 132 (100), 105 (38), 91 (68), 37 (38). Anal. Calcd for $C_{19}H_{29}NO_2S$: 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 ***122/123f***



(4R*, 5S*)- **122f**



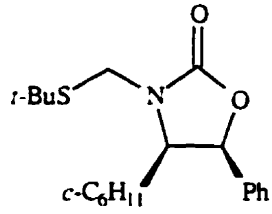
(4R*, 5R*)- **123f**

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, CH_2S), 4.29 (dd, 1 H, J = 2.2, 8.2, CHN), 4.1 (d, 1 H, J = 15.0, CH_2S), 1.74-1.62 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.41 (s, 9 H, $SC(CH_3)_3$), 0.87 (d, 3 H, J = 7.1, $(C\underline{H}_3)_2CH$), 0.68 (d, 3 H, J = 7.1, $(C\underline{H}_3)_2CH$); ^{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^+-C_4H_9, 10), 218 (75), 174

(93), 105 (79), 91 (100), 57 (81). Anal. Calcd for $C_{17}H_{25}NO_2S$: 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, CH_2S), 4 03 (d, 1 H, J = 14.9, CH_2S), 4.00-3.95 (m, 1 H, CHN), 2.14 (m, 1 H, $(CH_3)_2C\underline{H}$), 1.30 (s, 9 H, $SC(CH_3)_3$), 0.99 (t, 6 H, J = 6.7, $(C\underline{H}_3)_2CH$); ^{13}C 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^+-C_4H_9, 15), 218 (59), 174 (100), 105 (79), 91 (82), 57 (60). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.42; H, 8.20; N, 4.55. Found: C, 66.62; H, 8.14; N, 4.60.

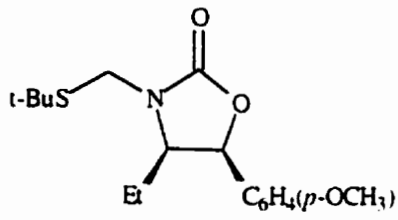
4.3.39 (4R*, 5S*)-*3-t-Butylthiomethyl-4-cyclohexyl-5-phenyl-2-oxazolidinone* ***122g***



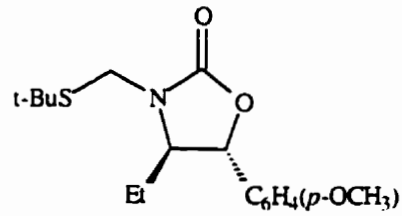
The *anti* β-aminoalcohol **119g** was prepared from **118e** according to the general procedure described in section 4.3.32 using 1.3 equiv of benzaldehyde in 40% yield. The oxazolidinone **122g** was prepared from **119e** in 89% yield: mp 109-110 °C; IR (KBr) 2909, 1738, 1426, 1223, 1170, 1037 cm^{-1}; ^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, CH_2S), 4.2 (m, 1 H, CHN), 4.15 (d, 1 H, J = 14.9, CH_2S), 1.60-1.45 (m, 5 H, *c*-C<u>H</u>C<u>H</u>$_2$(CH_2)$_3$C<u>H</u>$_2$), 1.42 (s, 9 H, SC(CH_3)$_3$), 1.26-0.78 (m, 6 H, *c*-CHC<u>H</u>$_2$(C<u>H</u>$_2$)$_3$C<u>H</u>$_2$); ^{13}C 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, EI *m/z* (relative intensity) 290 (M^+-C_4H_9, 6), 258 (38), 214 (62), 132 (100), 105 (25), 91 (63), 57 (61). Anal. Calcd for $C_{20}H_{29}NO_2S$: 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***



(4R*, 5S*)- **122h**



(4R*, 5R*)- **123h**

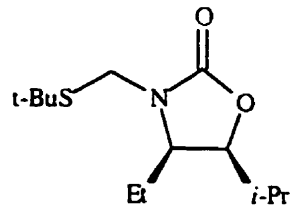
This mixture of diastereomers was prepared from **118b** according to the general procedure described in section 4.3.32 in 80% overall yield.

(4R*, 5S*)-**122h** was obtained in 57% yield: mp 58-62 °C; IR (KBr) 2924, 1739, 1617, 1586, 1432, 1362 cm^{-1}; ^{1}H 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, CH_2S), 4.21 (dt, 1 H, J = 3.6, 8.2, CHN), 4.06 (d, 1 H, J = 14.8, CH_2S), 3.82 (s, 3 H, OCH_3), 1.42 (s, 9 H, SC(CH_3)$_3$), 1.50-1.19 (m, 2 H, CH_3C<u>H</u>$_2$), 0.59 (t, 3 H, J = 7.4, C<u>H</u>$_3$$CH_2$); ^{13}C 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,

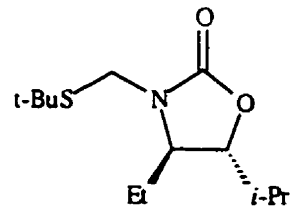
9.2; MS, EI *m/z* (relative intensity) 323 (M^+, 2), 266 (M^+-C_4H_9, 2), 190 (100), 135 (100), 57 (35). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.40; H, 7.53; N, 4.39.

(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, CH_2S), 5.05 (d, 1 H, J = 6.8, CHO), 4.05 (d, 1 H, J = 14.8, CH_2S), 3.98 (dt, 1 H, J = 3.2, 6.8, CHN), 3.81 (s, 3 H, OCH_3), 1.82-1.63 (m, 2 H, $CH_3C\underline{H}_2$), 1.37 (s, 9 H, $SC(CH_3)_3$), 0.94 (t, 3 H, J = 7.4, $C\underline{H}_3CH_2$); ^{13}C 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, EI *m/z* (relative intensity) 323 (M^+, 1), 266 (M^+-C_4H_9, 0.5), 234 (5), 190 (100), 135 (89), 57 (26). Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.06; H, 7.79; N, 4.29.

4.3.41 3-t-Butylthiomethyl-4-ethyl-5-isopropyl-2-oxazolidinone ***122/123i***



(4R*, 5S*)- **122i**



(4R*, 5R*)- **123i**

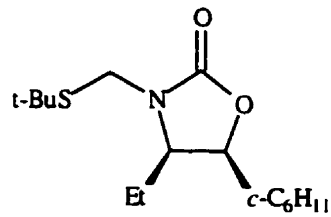
This mixture of diastereomers was prepared from **118b** according to the general procedure described in section 4.3.32, in 69% overall yield.

(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, CH_2S), 4.07-3.94 (m, 2

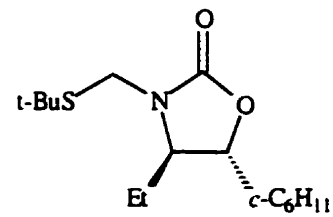
H, CHO and CHN), 3.90 (d, 1 H, J = 14.9, CH_2S), 2.10 (m, 1H, $CH_3C\underline{H}_2$), 1.70 (m, 2 H, $CH_3C\underline{H}_2$ and $(CH_3)_2C\underline{H}$), 1.37 (s, 9 H, $SC(CH_3)_3$), 1.10 (d, 3 H, J = 6.5, $(C\underline{H}_3)_2CH$), 0.95 (m, 6 H, $(C\underline{H}_3)_2CH$ and $C\underline{H}_3CH_2$); ^{13}C 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^+-C_4H_9, 9), 170 (54), 126 (17), 70 (100), 41 (32). Anal. Calcd for $C_{13}H_{25}NO_2S$: 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, CH_2S), 3.98 (d, 1 H, J = 14.9, CH_2S), 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, $CH_3C\underline{H}_2$), 1.68-1.57 (m, 2 H, $CH_3C\underline{H}_2$ and $(CH_3)_2C\underline{H}$), 1.37 (s, 9 H, $SC(CH_3)_3$), 1.00 (d, 3 H, J = 6.5, $(C\underline{H}_3)_2CH$), 0.98 (d, 3 H, J = 6.5, $(C\underline{H}_3)_2CH$), 0.89 (t, 3 H, J = 7.5, $C\underline{H}_3CH_2$); ^{13}C 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^+-C_4H_9, 3), 170 (25), 126 (9), 70 (100), 42 (19). Anal. Calcd for $C_{13}H_{25}NO_2S$: 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***



(4R*, 5S*)- **122j**



(4R*, 5R*)- **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, CH_2S), 3.98 (d, 1 H, J = 14.8, CH_2S), 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, $CH_3C\underline{H}_2$ and *c*-$C\underline{H}C\underline{H}_2(CH_2)_3C\underline{H}_2$), 1.37 (s, 9 H, $SC(CH_3)_3$), 1.48-1.0 (m, 6 H, *c*-$CHCH_2(C\underline{H}_2)_3CH_2$), 0.89 (t, 3 H, J = 7.4, $C\underline{H}_3CH_2$); ^{13}C 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^+-C_4H_9, 9), 210 (56), 166 (26), 70 (100), 57 (36), 41 (37). Anal. Calcd for $C_{16}H_{29}NO_2S$: C, 64.18; H, 9.76; N, 4.68. Found: C, 63.98; H, 9.98; N, 4.75.

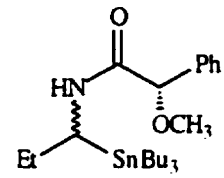
(4R*, 5S*)-**122j** was obtained in 30% yield: mp 66-69 °C; IR (KBr) 2927, 1713, 1423, 1385, 1242 cm^{-1}; ^1H NMR (250 MHz) δ 5.05 (d, 1 H, J = 14.9, CH_2S), 4.07 (m, 2 H, CHN and CHO), 3.94 (d, 1 H, J = 14.9, CH_2S), 2.05 (m, 1 H, $C\underline{H}CHO$), 1.78-1.60 (m, 8 H, *c*-$CH(C\underline{H}_2)_2CH_2(C\underline{H}_2)_2$), 1.37 (s, 9 H, $SC(CH_3)_3$), 1.35-1.31 (m, 2 H, *c*-$CH(CH_2)_2C\underline{H}_2(CH_2)_2$), 1.21 (t, 3 H, J = 7.0, $C\underline{H}_3CH_2$); ^{13}C 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^+-C_4H_9, 1), 210 (16), 166 (8), 70 (100). Anal. Calcd for $C_{16}H_{29}NO_2S$: 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 CH_2Cl_2 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 CH_2Cl_2, 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/Et_2O, 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/Et_2O).

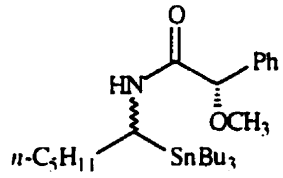
4.3.44 N-(1-Tributylstannylpropyl)-2-methoxy-2-phenylacetamide ***125/126a***



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: $[\alpha]^{20}_D$ = -34.5 (c 1.0, $CHCl_3$); 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, C<u>H</u>Ph), 3.36 (s, 3 H, OCH_3), 3.30 (m, 1 H, CHN), 1.84-1.66 (m, 2 H, $CH_3C\underline{H}_2CHN$), 1.52-1.18 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 0.95-0.67 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2CHN$); ^{13}C (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^+- C_4H_9,

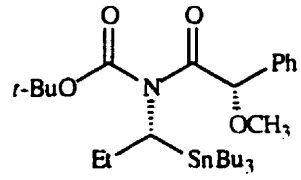
100), 326 (12), 252 (8), 235 (20). Anal. Calcd for $C_{27}H_{49}NO_2Sn$: C, 58.08; H, 8.73; N, 2.82. Found: C, 57.89; H, 8.64; N, 2.92.

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



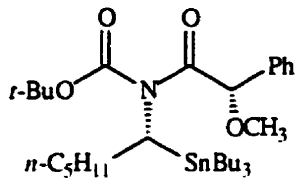
This compound was prepared from **67e** according to the general procedure described in section 4.3.43 as a mixture of diastereomers in 77% overall yield. The less polar diastereomer (1R, 2S)-**125e** exhibited the following: $[\alpha]^{20}_D$ = -33.2 (c 1.0, $CHCl_3$); IR (neat) 3410, 3505, 2955, 2923, 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, PhC<u>H</u>), 3.35 (s, 3 H, OCH_3), 3.35 (m, 1 H, CHN), 1.72-1.10 (m, 20 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(C\underline{H}_2)_4$), 0.90-0.71 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(CH_2)_4$); ^{13}C 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^+ - C_4H_9, 100), 235 (18), 176 (35), 121 (19). Anal. Calcd for $C_{27}H_{49}NO_2Sn$: C, 60.23; H, 9.17; N, 2.60. Found: C, 60.30; H, 9.37; N, 2.77.

4.3.46 (1R, 2S) N-t-Butoxycarbonyl-N-(1-tributylstannylpropyl)-2-methoxy-2-phenylacetamide ***128b***



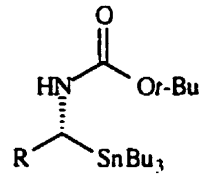
This compound was prepared form **125b** according to the general procedure described in section 4.3.8 with a reaction time of 48 h, in 74% yield: IR (neat) 2938, 1725, 1683, 1461, 1305, 1119, 1070 cm^{-1}; ^1H NMR (250 MHz) δ 7.37-7.28 (m, 5 H, ArH), 5.98 (s, 1 H, C<u>H</u>Ph), 3.62 (t, 1 H, J = 8.0, CHN), 3.41 (s, 3 H, OCH_3), 1.53 (s, 9 H, $CO_2C(CH_3)_3$), 1.63-1.21 (m, 20 H, $Sn(C\underline{H}_2)_3CH_3$ and $CH_3C\underline{H}_2CHN$), 0.88 (t, 9 H, J = 7.2, $Sn(CH_2)_3C\underline{H}_3$), 0.53 (t, 3 H, J = 7.3, $C\underline{H}_3CH_2CHN$); ^{13}C NMR (63 MHz) δ 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_4H_9, 14), 440 (38), 177 (22), 121 (100). Anal. Calcd for $C_{29}H_{51}NO_4Sn$: C, 58.40; H, 8.62; N, 2.35. Found: C, 58.28; H, 8.79; N, 2.38.

4.3.47 (1R, 2S) N-t-Butoxycarbonyl-N-(1-tributylstannylhexyl)-2-methoxy-2-phenylacetamide ***128e***



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}; ^1H NMR (250 MHz) δ 7.35-7.27 (m, 5 H, ArH), 5.98 (s, 1 H, C<u>H</u>Ph), 3.72 (dd, 1 H, J = 8.4, 7.4, CHN), 3.41 (s, 3 H, OCH_3), 1.43 (s, 9 H, $CO_2C(CH_3)_3$), 1.52-1.22 (m, 14 H, $SnCH_2(C\underline{H}_2)_2CH_3$ and $CH_3(CH_2)_3C\underline{H}_2CHN$), 1.06-0.71 (m, 24 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3(C\underline{H}_2)_3CH_2CHN$); ^{13}C NMR (63 MHz) δ 171.1, 154.0, 136.9, 128.3, 128.2, 83.2, 82.8, 57.4, 46.8, 31.4, 29.1 (^2J = 19), 27.8, 27.4 (^3J = 58), 22.5, 13.9, 13.6, 10.4 (^1J = 313, 328); MS, FAB *m/z* (relative intensity) 582 (M^+-C_4H_9, 12), 482 (44), 450 (8), 291 (9), 177 (29), 121 (100). Anal. Calcd for $C_{31}H_{57}NO_4Sn$: C, 60.19; H, 9.00; N, 2.19. Found: C, 60.19; H, 9.03; N, 2.26.

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



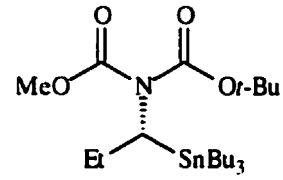
Hydrazine hydrate (10 equiv) was added to a 1 M solution of the stannane **128** in MeOH. The reaction mixture was stirred at reflux for 12-15 h. The solvent was removed *in vacuo*, and the resulting residue was diluted with Et_2O and washed with water (3 times). The organic layer was dried ($MgSO_4$), filtered though Celite and concentrated *in vacuo* to give the carbamates as colorless oils in quantitative yield. The two carbamates

129b (R = Et) and **129e** (R = C_5H_{11}) 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***

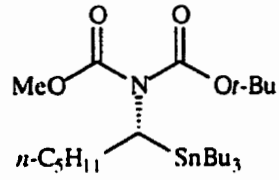
n-BuLi (1.5 equiv, 1.6 M in hexanes) was slowly added to a cooled (0 °C) 0.3 M solution of *i*-Pr_2NH (1.5 equiv) in THF. The solution was stirred for 15 min and cooled to –78 °C. A 0.5 M solution of the stannane **129** in THF was slowly added to provide a bright yellow solution. The solution was stirred for 45 min, quenched with saturated NH_4Cl and warmed to rt. The resulting mixture was diluted with Et_2O, washed with water, the organic layer was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (40 g silica/g of substrate; 10:1 hexane/Et_2O) to give the products as colorless oils.

*4.3.50 (R)-t-Butyl methyl N-(1-tributylstannylpropyl)iminodicarbonate **130b***



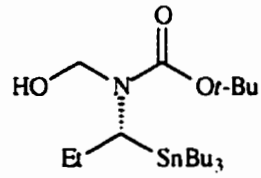
This compound was prepared from **129b** according to the general procedure described in section 4.3.49 in 75% yield: $[\alpha]^{20}_{578}$ = +61.2 (c 1.0, $CHCl_3$); all the other spectral characteristic are as described in section 4.3.10.

4.3.51 (R)-t-Butyl methyl N-(1-tributylstannylhexyl)iminodicarbonate ***130e***



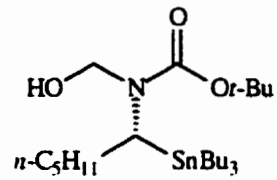
This compound was prepared from **129e** according to the general procedure described in section 4.3.49 in 91% yield: $[\alpha]^{20}_{578}$ = +65.2 (c 1.0, $CHCl_3$); all the other spectral characteristics are as described in section 4.3.13.

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



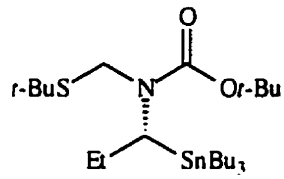
This compound was prepared from **130b** according to the general procedure described in section 4.3.16 in 77% yield: all the spectral characteristics are as described in section 4.3.18.

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



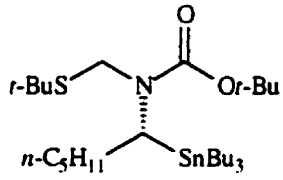
This compound was prepared from **130e** according to the general procedure described in section 4.3.16 in 79% yield: $[\alpha]^{20}_{578}$ = +16.1 (c 1.0, $CHCl_3$); all the other spectral characteristics are as described in section 4.3.21.

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



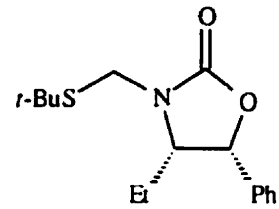
This compound was prepared from **131b** according to the general procedure described in section 4.3.24 in 89% yield: $[\alpha]^{20}_{578}$ = +51.9 (c 1.0, $CHCl_3$); all the other spectral characteristics are as described in section 4.3.26.

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



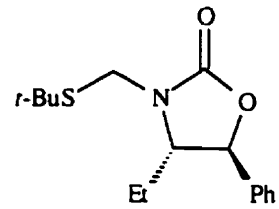
This compound was prepared from **131e** according to the general procedure described in section 4.3.24 in 87% yield: $[\alpha]^{20}_{578}$ = +46.6 (c 1.0, $CHCl_3$); all the other spectral characteristics are as described in section 4.3.29.

*4.3.56 (4S, 5R)-3-t-Butylthiomethyl-4-ethyl-5-phenyl-2-oxazolidinone **122b***



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***



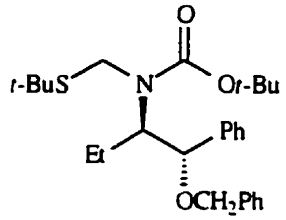
This compound was prepared from *syn* β-aminoalcohol **134b** according to the general procedure described in section 4.3.32 in 96% yield: $[\alpha]^{20}_{578}$ = +61.1 (c 1.0, $CHCl_3$); all the other spectral characteristics are as described in section 4.3.34.

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_2O and washed with water. The organic

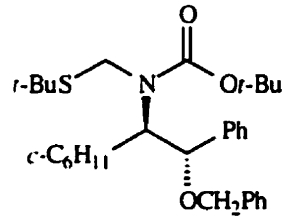
solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (60 g silica/g of substrate; 10:1 hexane/Et_2O) to give products as colorless oils.

4.3.59 (1R, 2S*)-N-t-Butoxycarbonyl-N-t-butylthiomethyl-2-amino-1-phenylbutyl benzyl ether* ***138b***



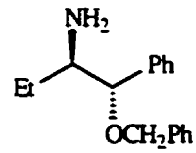
This compound was prepared from **119b** according to the general procedure described in section 4.3.58 with a reaction time of 20 h, in 67% yield: IR (neat) 3030, 2959, 1694, 1452, 1392, 1243, 1163, 1064 cm^{-1}; ^1H NMR (250 MHz) δ 7.42-7.27 (m, 10 H, ArH), 4.78 (d, 0.5 H, J = 7.5, CHO), 4.55-4.21 (m, 4.5 H, CH_2S, $PhC\underline{H}_2$ and CHO), 3.53-3.38 (m, 1 H, CHN), 2.09-1.79 (m, 2 H, $CH_3C\underline{H}_2$), 1.44 (s, 4 H, $CO_2C(CH_3)_3$), 1.38 (s, 5 H, $CO_2C(CH_3)_3$), 1.26 (s, 5 H, $SC(CH_3)_3$), 1.23 (s, 4 H, $SC(CH_3)_3$), 1.00 (t, 3 H, J = 7.3, $C\underline{H}_3CH_2$); ^{13}C 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 $C_{27}H_{39}NO_3S$: 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***



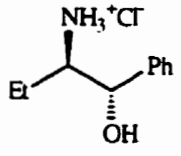
This compound was prepared from **119g** according to the general procedure described in section 4.3.58 with a reaction time of 24 h, in 53% yield: IR (neat) 2925, 2852, 1694, 1450, 1391, 1365, 1240, 1162, 1066 cm^{-1}; ^1H NMR (250 MHz) δ 7.42 –7.25 (m, 10 H, ArH), 4.80-3.96 (m, 5 H, CHO, $PhC\underline{H}_2$ and CH_2S), 3.21-3.04 (m, 1 H, CHN), 2.47-1.53 (m, 5 H, *c*-$C\underline{H}C\underline{H}_2(CH_2)_3C\underline{H}_2$), 1.43-1.06 (m, 24 H, $CO_2C(CH_3)_3$, $SC(CH_3)_3$ and *c*-$CHCH_2(C\underline{H}_2)_3CH_2$): ^{13}C NMR (63 MHz) δ 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 $C_{31}H_{45}NO_3S$: 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***



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 Et_2O (20 mL), extracted with 1 M HCl (3 x 10 mL), the combined acid extracts were basified (2 M NaOH) and extracted with Et_2O (4 x 10 mL). The combined organic solution was dried ($MgSO_4$), 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/Et_2O and 5% Et_3N): 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, PhC$\underline{H}_2$), 4.11 (d, 1 H, J = 11.9, PhC$\underline{H}_2$), 4.03 (d, 1 H, J = 5.9, CHO), 2.90 (m, 1 H, CHN), 1.68 (m, 1 H, $CH_3C\underline{H}_2$), 1.27-1.10 (m, 1 H, $CH_3C\underline{H}_2$), 0.92 (t, 3 H, J = 7.4, $C\underline{H}_3CH_2$), 0.76 (broad s, 2 H, NH_2); ^{13}C NMR (125 MHz, JMOD, C_6D_6) 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 $C_{17}H_{21}NO$: 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***



NH_3 (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). NH_4Cl (1 g) was slowly added, and the reaction mixture was warmed to rt to evaporate NH_3. Et_2O (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 Et_2O (4 x 10 mL). The combined organic solution was dried ($MgSO_4$), 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, NH_3^+), 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, $CH_3C\underline{H}_2$), 0.89 (t, 3 H, J = 7.5, $C\underline{H}_3CH_2$); ^{13}C 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 $C_{10}H_{16}ClNO$: 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 Et_2O and washed with 1 M HCl (4 times). The combined acid extracts were basified (2 M NaOH), extracted with EtOAc, dried ($MgSO_4$), 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.

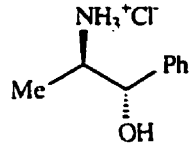
4.3.64 General Procedure for the transacetalization of aminoacetals to primary β-aminoalcohols

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 Et_2O, extracted with 1 M HCl (several times). The combined acid extracts were basified with 2 M NaOH, extracted with EtOAc, dried ($MgSO_4$), 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 CH_2Cl_2 was added 1,3-propanedithiol (10 equiv) followed by $BF_3 \cdot Et_2O$ (3 equiv). The reaction mixture was stirred at room temperature for 24 h. The solution was diluted with CH_2Cl_2, washed with 1 M HCl. The combined acid extracts were basified (2 M NaOH), extracted with EtOAc,

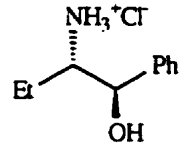
dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo* to give primary β-aminoalcohols as white solids. The β-aminoalcohols were converted to HCl salts as described in section 4.3.62.

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



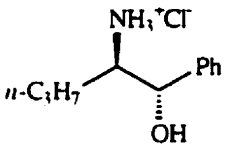
This compound was prepared from the *cis* oxazolidinone **122a** according to the general procedure described in section 4.3.63 with a reaction time of 15 h, in 84% yield: mp 189-191 °C; IR (KBr) 3318, 2980, 1591, 1495, 1205, 1031 cm^{-1}; ^1H NMR (250 MHz) δ 8.37 (broad singlet, 3 H, NH_3^+), 7.40-7.20 (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, $C\underline{H}_3CH$); ^{13}C 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 $C_9H_{24}ClNO$: 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***



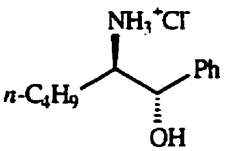
This compound was prepared from the *cis* oxazolidinone *(4S, 5R)-**122b*** according to the general procedure described in section 4.3.63 with a reaction time of 12 h, in 75% yield: $[\alpha]^{20}_{D}$= -32.5 (c 1, MeOH), Lit.[22] $[\alpha]^{20}_{D}$= -33.1 (c 1, H_2O); all other spectral characteristics are as described in section 4.3.62.

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



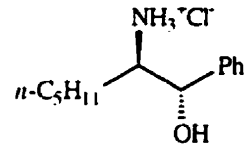
This compound was prepared from the β-aminoalcohol **119e** according to the general procedure described in section 4.3.64 in 70% yield: mp 212-214 °C; IR (KBr) 3308, 2978, 1606, 1494, 1199, 1043 cm^{-1}; ^1H NMR (250 MHz) δ 8.13 (broad singlet, 3 H, NH_3^+), 7.78-7.27 (m, 5 H, ArH), 5.15 (d, 1 H, J = 2.5, CHO), 3.25 (m, 2 H, OH and CHN), 1.54-1.35 (m, 3 H, $CH_3C\underline{H}HC\underline{H}_2$), 1.19-1.11 (m, 1 H, $CH_3CH\underline{H}CH_2$), 0.79 (t, 3 H, J = 6.8, $C\underline{H}_3(CH_2)_2$); ^{13}C NMR (63 MHz) δ 139.1, 126.5, 125.7, 124.5, 70.1, 54.8, 26.8, 17.1, 12.1; MS, ES *m/z* (relative intensity) 180 (M^+-Cl, 100). Anal. Calcd for $C_{11}H_{18}ClNO$: 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-1-hexanol HCl salt **141d***



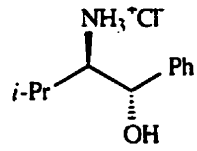
This compound was prepared from the β-aminoalcohol **119d** according to the general procedure described in section 4.3.64 in 75% yield: mp 208-210 °C; IR (KBr) 3335, 2989, 1600, 1497, 1383, 1044 cm^{-1}; ^1H NMR (250 MHz) δ 8.36 (broad singlet, 3 H, NH_3^+), 7.45-7.22 (m, 5 H, ArH), 5.37 (d, 1 H, J = 2.0, CHO), 5.30-5.00 (broad, 1 H, OH), 3.39 (m, 1 H, CHN), 1.63-1.11 (m, 6 H, $CH_3(C\underline{H}_2)_3$), 0.76 (t, 3 H, J = 6.5, $C\underline{H}_3(CH_2)_3$); ^{13}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, 62.73; 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***



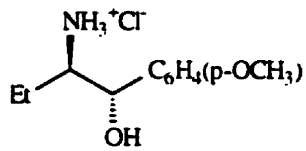
This compound was prepared from the β-aminoalcohol **119e** according to the general procedure described in section 4.3.64 in 86% yield: mp 165-168 °C; IR (KBr) 3326, 2989, 1602, 1487, 1383, 1043 cm^{-1}; ^1H NMR (250 MHz) δ 8.22 (broad singlet, 3 H, NH_3^+), 7.43-7.26 (m, 5 H, ArH), 5.23 (d, 1 H, J = 2.5, CHO), 3.30-3.12 (m, 2 H, CHN and OH), 1.40-1.22 (m, 2 H, $C\underline{H}_2CHN$), 1.19-0.88 (m, 6 H, $CH_3(C\underline{H}_2)_3$), 0.81 (t, 3 H, J = 6.2, $C\underline{H}_3(CH_2)_4$); ^{13}C NMR (63 MHz) δ 139.6, 127.4, 126.6, 125.2. 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***



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, NH_3^+), 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, $(CH_3)_2\underline{C}H$), 1.03 (d, 3 H, J = 6.8, $(C\underline{H}_3)_2CH$), 0.96 (d, 3 H, J = 6.9, $(C\underline{H}_3)_2CH$); ^{13}C 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 $C_{11}H_{18}ClNO$: C, 61.53; H, 7.98; N, 6.52. Found: C, 61.14; H, 8.26; N, 6.23.

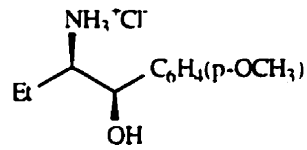
4.3.71 (1R, 2S*)-2-Amino-1-(4-methoxyphenyl)-1-butanol HCl salt* ***141h***



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, $CH_3C\underline{H}_2$), 0.89 (t, 3 H, J = 7.4, $C\underline{H}_3CH_2$); ^{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$0), 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***

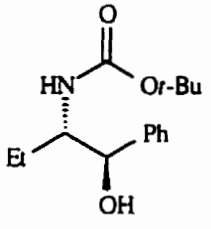


This compound was prepared from the *trans* oxazolidinone **123h** according to the general procedure described in section 4.2.63 using *n*-propanol as solvent. The reaction was stirred for 48 h and the product was obtained in 76 % yield: mp 191-195 °C; IR (KBr) 3345, 2948, 1610, 1503, 1460, 1382, 1240, 1030 cm^{-1}; ^1H 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, $CH_3C\underline{H}_2$), 0.90 (t, 3 H, J = 7.4, $C\underline{H}_3CH_2$); ^{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$0), 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 Et_3N (1.2 equiv) and Boc_2O (1.2 equiv). The reaction mixture was stirred at rt for 1 h. The resulting mixture was diluted with Et_2O, washed with 1 M $KHSO_4$ (3 times) and water. The organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (60 g silica/g of substrate; 2:1 hexane/Et_2O) to give the products as white solids.

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

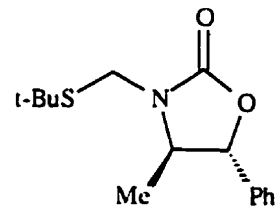


This compound was prepared from **143b** according to the general procedure described in section 4.3.73 in 98% yield: mp 99-102 °C; $[\alpha]^{20}_D$ = -105.7 (c 1.0, $CHCl_3$); IR (KBr) 3375, 1689, 1526, 1173 cm^{-1}; ^1H NMR (200 MHz) δ 7.33 (m, 5 H, ArH), 4.86 (m, 1 H, CHO), 4.48 (broad d, 1 H, J = 8.0, OH), 1.46 (s, 9 H, $CO_2C(CH_3)_3$), 1.24 (m, 2 H, $CH_3C\underline{H}_2$), 0.91 (t, 3 H, J = 7.3, $C\underline{H}_3CH_2$); ^{13}C 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 $C_{15}H_{23}NO_3$: 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

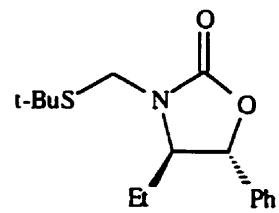
To a 0.1 M solution of aminoalcohol in THF was added *p*-nitrobenzoic acid (1.2 equiv) and PPh_3 (1.2 equiv). The solution was cooled to 0 °C, DEAD (1.2 equiv) was slowly added and the reaction mixture was stirred at rt for the specified time. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (100 g silica/g of substrate; 5:1 hexane/Et_2O).

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



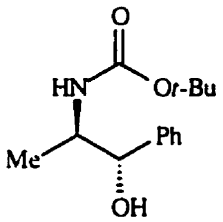
This compound was prepared from the *anti* β-aminoalcohol **119a** according to the general procedure described in section 4.3.75 with a reaction time of 1.5 h. It was obtained as a white solid in 89% yield and exhibited the spectral characteristic described in section 4.3.33.

4.3.77 (4R*, 5R*)-*3-t-Butylthiomethyl-4-ethyl-5-phenyl-2-oxazolidinone* ***123b***



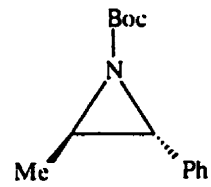
This compound was prepared from the *anti* β-aminoalcohol **119b** according to the general procedure described in section 4.3.75 with a reaction time of 1 h. It was obtained as a white solid in 94% yield (and 92% yield when reaction was done in the absence of *p*-nitrobenzoic acid). The product **123b** 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: $[\alpha]^{20}_{D}$ = +74.8 (c, 1.0, $CHCl_3$); 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, C<u>H</u>(OH) and NH), 3.95 (broad s, 1 H, CHN), 3.65 (broad s, 1 H, OH), 1.44 (s, 9 H, $CO_2C(CH_3)_3$), 0.95 (d, 3 H, J = 6.8, C<u>H</u>$_3$CHN); ^{13}C 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 $C_{14}H_{21}NO_3$: 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-t-Butoxycarbonyl-1-methyl-2-phenylaziridine* ***156***



This compound was prepared from **154** according to the general procedure described in section 4.3.75 in the absence of *p*-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}; ^1H NMR (250 MHz) δ 7.33-7.21 (m, 5 H, ArH), 3.17 (d, 1 H, J = 3.0, PhC<u>H</u>), 2.67-2.59 (m, 1 H, $CH_3C\underline{H}$), 1.42 (s, 9 H, $CO_2C(CH_3)_3$), 1.41 (unresolved d, 3 H, $C\underline{H}_3CH$); ^{13}C NMR (63 MHz) δ 160.3, 137.0, 128.3, 127.6, 126.4, 81.1, 45.9, 42.5, 27.9, 15.9; MS, EI *m/z* (relative intensity) 176 (M^+ -C_4H_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.

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Chapter 5

Synthesis of Chiral α-Aminoorganostannanes

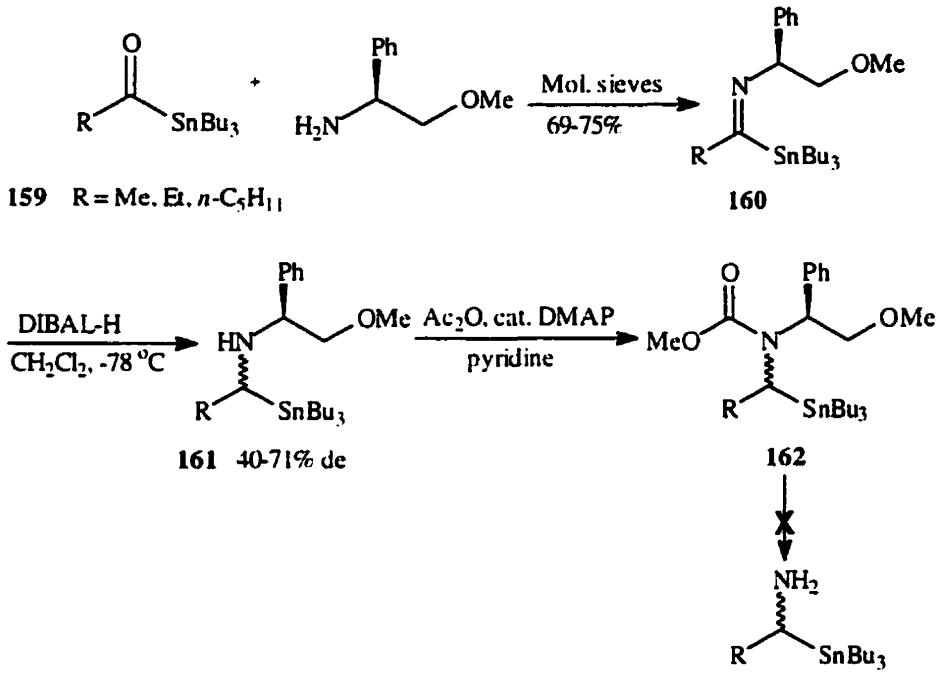
5.1 Introduction

As discussed in chapter one, not many methods have been developed for the asymmetric synthesis of α-aminoorganostannanes. Pearson and Lindbeck have reported the synthesis of enantiomerically enriched α-aminoorganostannanes from chiral sulfones.[1] This method is limited to oxazolidinones and imidazolidinones; one can not obtain enantiomerically enriched α-aminoorganostannnanes with simple protecting groups such as the *t*-Boc group. What seems to be a more versatile method is the enantioselective reduction of ayclstannanes 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 α-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 α-aminoorganostannanes **161**. After investigating a wide variety of reducing agents, the best results were achieved with DIBAL-H at –78 °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 carbamates **162**. Attempts to remove the chiral auxiliary by hydrogenolysis or dissolving metal reduction were not successful.

Scheme 74

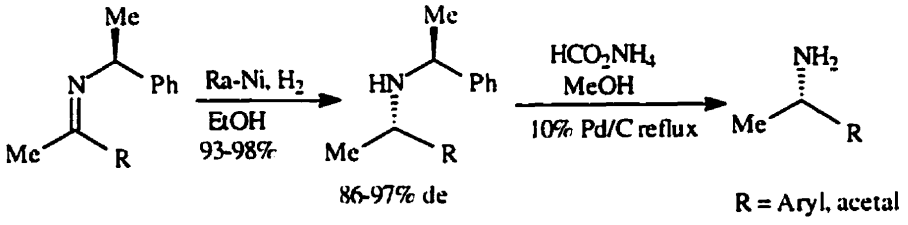


Determined to find a better route to enantiomerically enriched α-aminoorganostannanes and seeing the potential that Bekkali's methodology had, we decided to carry on with this research. Our goal was to investigate the use of other chiral auxiliaries with the hope of finding ones that would give better 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).[4] 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 α-methylbenzylamine as a chiral auxiliary for the reduction of stannylimines.

Scheme 75

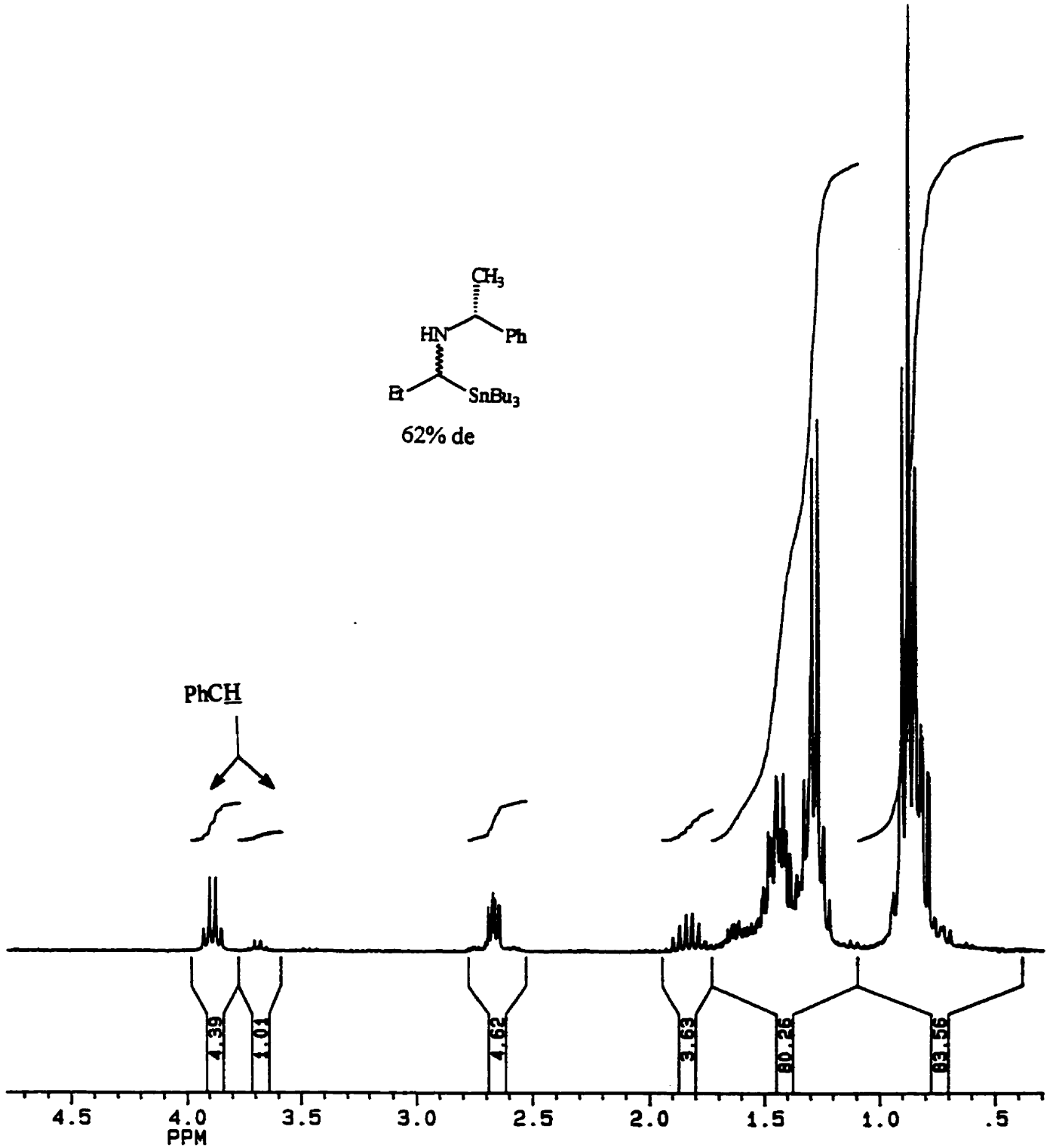


5.2 Results and Discussion

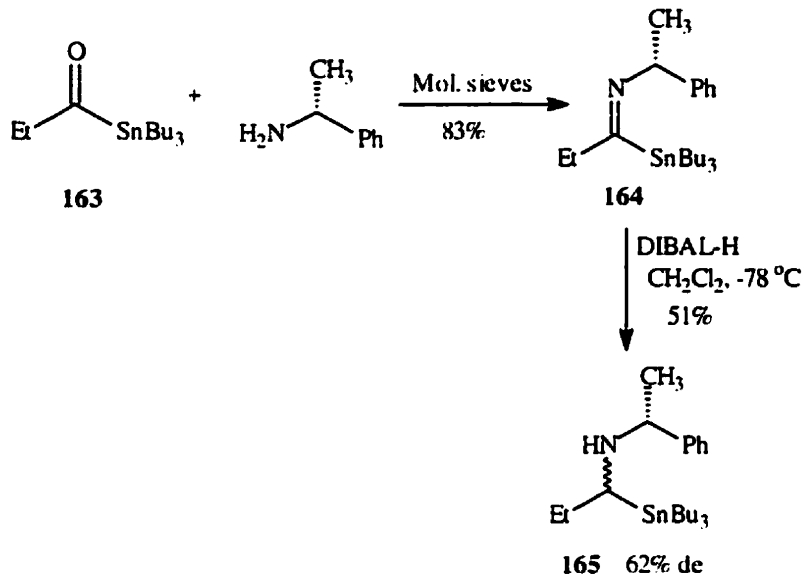
5.2.1 Reduction of stannylimines

The stannylamine **164** was prepared by the condensation of ayclstannanes **163** and (R)-α-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 ^{1}H 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**

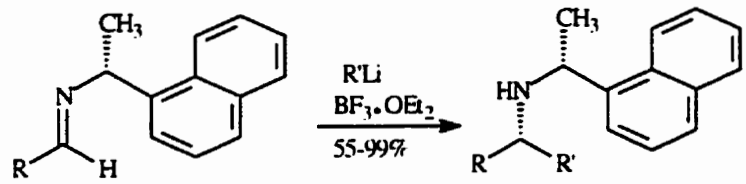


Scheme 76



In their asymmetric additions of alkyllithiums to chiral imines, Nakagawa and coworkers found out that changing the chiral auxiliary from α-methylbenzylamine to α-naphthylethylamine increased the de from 4% to 100% (Scheme 77).[5] 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 π-plane made up of the C-N double bond and the phenyl group. The alkyllithium reagent attacked from the top of the π-plane and gave the observed diastereomer. With (R)-α-methylbenzylamine as the chiral auxiliary, selectivity was low because the phenyl group in the chiral auxiliary could not shield the π-plane as well as the naphthyl group.

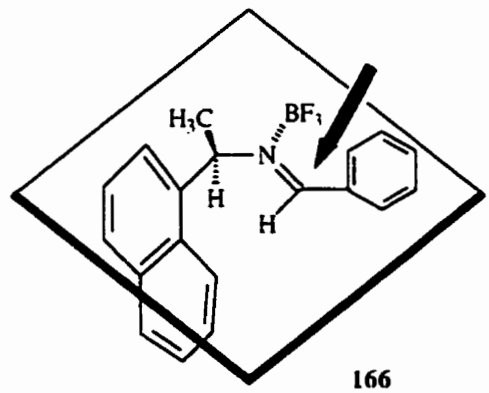
Scheme 77



R = Ph, *t*-Bu

R' = Me, *n*-Bu, *t*-Bu

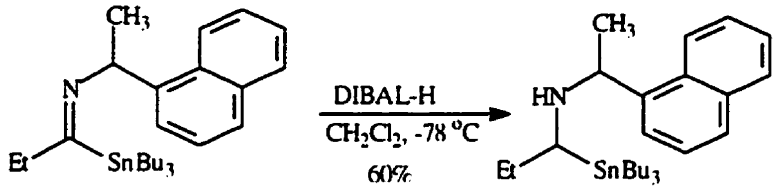
80-100% de



166

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.

Scheme 78



167 **168** 56% de

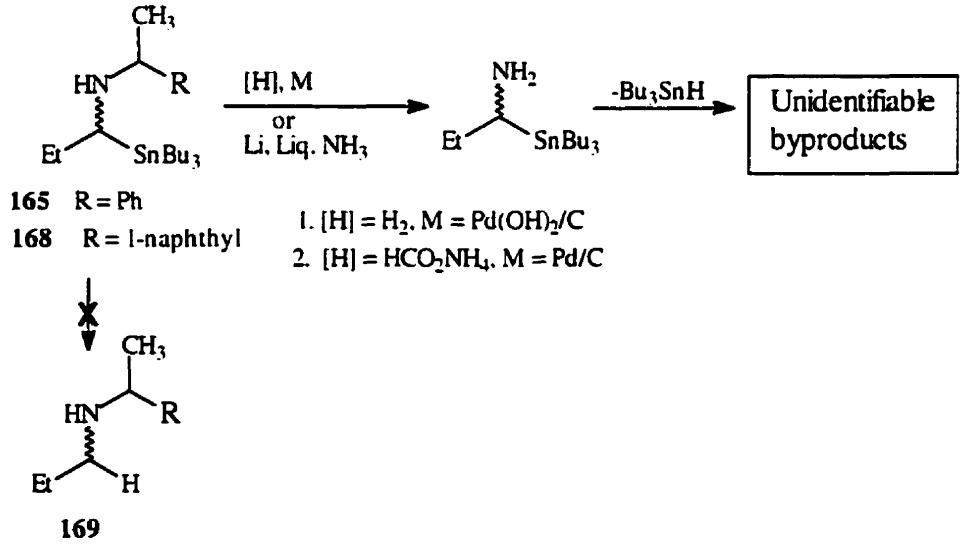
Whereas Bekkali's stannylimines **160** were reduced after 3 h at –78 °C, the reduction of **164** and **167** was very slow (10-12 h). Perhaps the reduction of **160** was enhanced by the ability of the oxygen to bind to the reducing agent. Attempts to perform the reductions at higher temperatures (-40 °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 ($Pd(OH)_2/C/H_2$).[6] 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.[7]

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 Boc_2O to the reaction mixture so that as soon as the primary amine is formed, it could react with Boc_2O 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.

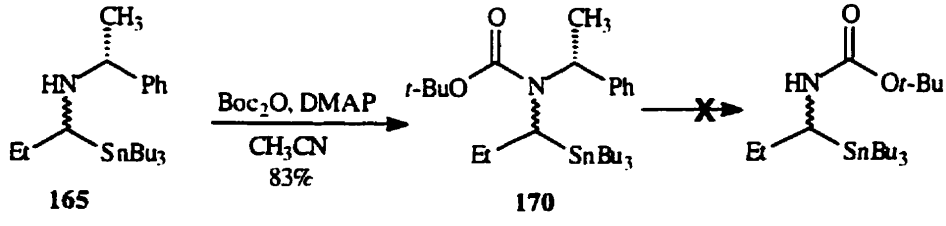
Scheme 79



Perhaps the decomposition was so fast that it occurred before the stannylamine could react with the Boc_2O. 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_2NH_4 and Pd/C led to removal of the carbamate before the chiral auxiliary. This was unexpected because HCO_2NH_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

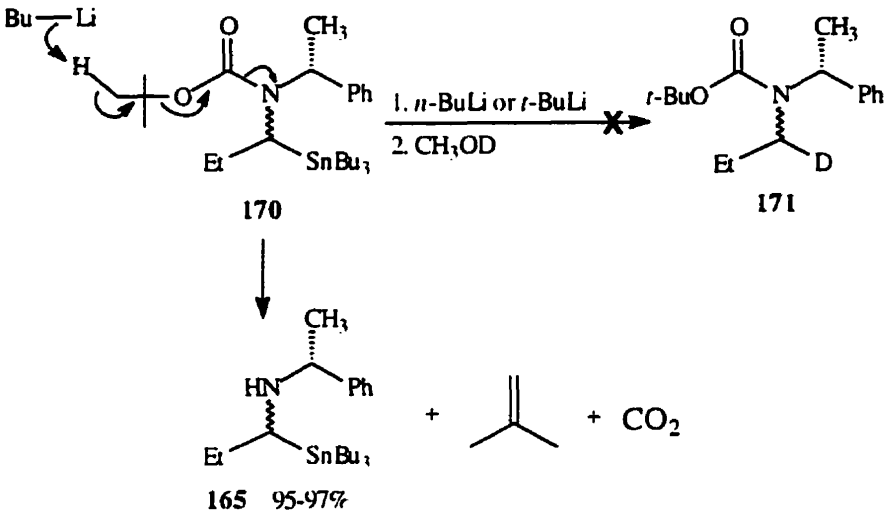


5.2.3 Transmetalation of Boc-protected α-aminoorganostannanes

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 Bu_4Sn to verify that transmetalation had occurred. The reaction mixture was quenched with CH_3OD; 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.

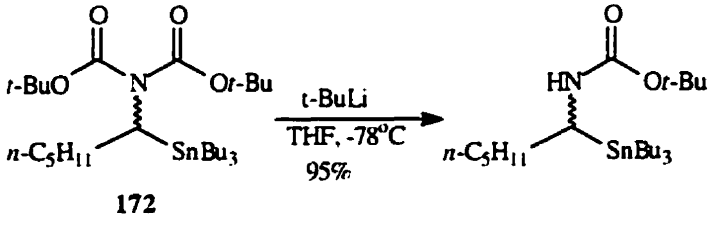
The byproduct **165** had 62% de, verifying that introduction of the Boc group did not occur with racemization. So what we were observing in the ^1H NMR spectrum of **170** were rotamers not diastereomers, and most likely the benzylic proton of the minor diastereomer had the same chemical shift as one of the rotamers.

Scheme 81



Park observed the same reaction when he tried to transmetalate the iminodicarbonate **172** with *t*-BuLi (Scheme 82).[8] Therefore, transmetalation is difficult if one has two sterically hindered N-protecting groups.

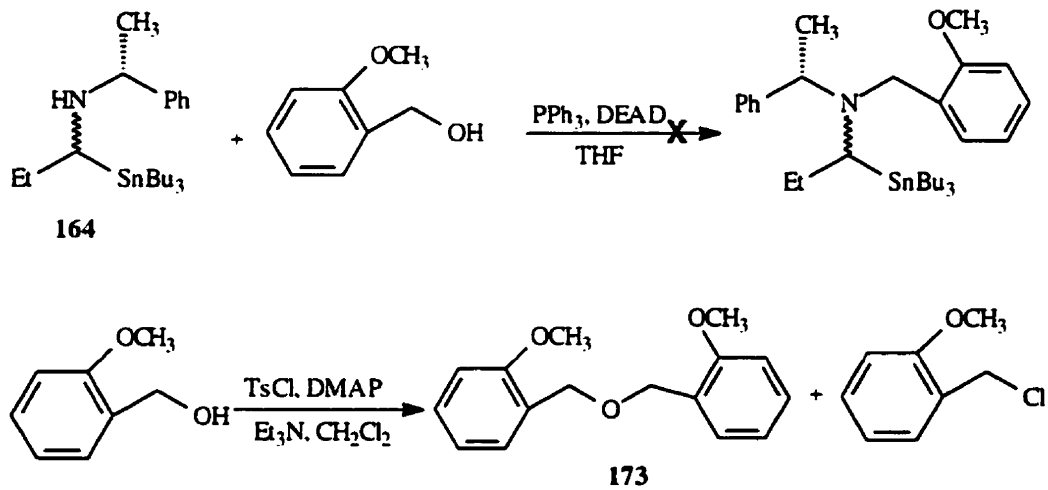
Scheme 82



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.[9] 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

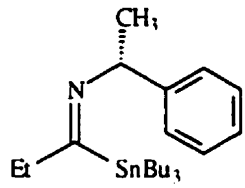
The procedures outlined in section 2.3.1 also apply here with the following addition. The acylstannane **163** was prepared by the method of Chong and Mar.[10]

5.3.2 General procedure for the preparation of stannylimines

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 CH_2Cl_2 and washed with water. The organic solution was dried

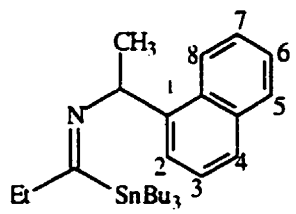
($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude products were purified by distillation, the products remained in the still pots because they had high boiling points (> 140 °C at 0.2 torr). Even after distillation, the stannylimines were not 100% pure, as a result, they could 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: $[\alpha]^{20}_D$ = -21.0 (c 1.0, $CHCl_3$); 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, 1H, J = 6.4, $CH_3C\underline{H}Ph$), 2.45 (q, 2 H, J = 7.4, $CH_3C\underline{H}_2$), 1.61-1.21 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 1.47 (d, 3 H, J = 6.4, $C\underline{H}_3CHPh$), 1.14-0.83 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2$); ^{13}C 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***

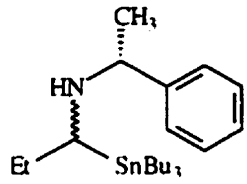


This compound was prepared according to the general procedure described in section 5.3.2, with a reaction time of 60 h as a yellow oil in 71% yield: IR (neat) 2958, 1611, 1509, 1457, 1374, 1073 cm^{-1}; ^1H NMR (250 MHz) δ 8.11 (d, 1 H, J = 8.0, CH(8)), 7.86-7.72 (m, 2 H, CH(4) and CH(5)), 7.70 (d, 1 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, $CH_3C\underline{H}Ar$), 2.53 (q, 1 H, J = 7.4, $CH_3C\underline{H}_2$), 1.65-1.10 (m, 12 H, $SnCH_2(C\underline{H}_2)_2CH_3$), 1.60 (d, 3 H, J = 6.4, $C\underline{H}_3CHAr$), 1.09-0.72 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2$); ^{13}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 (^1J = 299).

5.3.5 General procedure for the preparation of stannylamines

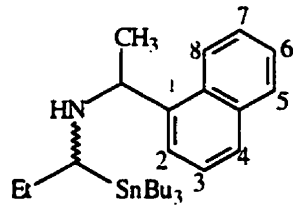
DIBAL (1.1 equiv) was slowly added to a cooled (-78 °C) 0.15 M solution of the stannylimine in CH_2Cl_2 and reaction mixture was stirred at –78 °C for the specified time. The reaction mixture was quenched with saturated NH_4Cl, diluted with CH_2Cl_2 and washed with water. An emulsion formed which separated 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_3N) to give the products as colourless oils.

5.3.6 N-(1-Methylbenzyl)-1-tributylstannylpropylamine ***165***



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, $CH_3C\underline{H}Ph$), 2.65 (m, 1 H, CHN), 1.88-1.76 (m, 1 H, $CH_3CH\underline{H}$), 1.65-1.20 (m, 14 H, $CH_3C\underline{H}H$, NH and $SnCH_2(C\underline{H}_2)_2CH_3$), 1.27 (d, 3 H, J = 6.7, $C\underline{H}_3CHN$), 0.93-0.68 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2$); ^{13}C 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***



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, $CH_3C\underline{H}Ph$), 4.56 (q, 0.2 H, J = 6.5, $CH_3C\underline{H}Ph$), 2.85-2.67 (m, 1 H, CHN), 1.96-1.80 (m, 1 H, $CH_3C\underline{H}H$), 1.77-1.21 (m, 17 H, $CH_3CH\underline{H}$, NH, $C\underline{H}_3CHPh$ and $SnCH_2(C\underline{H}_2)_2CH_3$), 0.97-0.58 (m, 18 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$ and $C\underline{H}_3CH_2$); ^{13}C 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 (^3J = 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 Et_2O and washed with water, the organic solution was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo* to give a cloudy oil which was shown by TLC and ^1H NMR to be mainly Bu_3SnH and other byproducts.

Transfer Hydrogenolysis

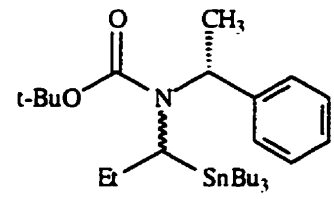
To a 0.1 M solution of the stannylamine in MeOH was added Pd/C (10%) and NH_4CO_2H (5 equiv). The reaction mixture was stirred at rt for 15 h, TLC analysis indicated that no reaction had occurred. The reaction mixture was stirred at reflux for

another 20 h. The product was isolated as outlined above and was also shown to be Bu_3SnH 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 °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_4Cl was slowly added, and the reaction mixture was warmed to rt to evaporate NH_3. The remaining residue was dissolved in Et_2O 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 ^1H NMR and TLC to be starting material and Bu_3SnH.

5.3.10 t-Butyl N-(1-methylbenyzl)-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, $CH_3C\underline{H}Ph$), 5.32 (q, 0.6 H, J = 7.1, $CH_3C\underline{H}Ph$), 2.75-2.66 (m, 1 H, CHN), 1.79-1.63 (m, 1 H, $CH_3C\underline{H}HCHN$), 1.60-1.19 (m, 16 H, $SnCH_2(C\underline{H}_2)_2CH_3$, $CH_3C\underline{H}HCHN$ and $C\underline{H}_3CHPh$), 1.56 (s, 9 H, $CO_2C(CH_3)_3$), 0.98-0.62 (m, 15 H, $SnC\underline{H}_2(CH_2)_2C\underline{H}_3$), 0.43 (unresolved triplet, 3 H, $C\underline{H}_3CH_2CHN$); ^{13}C 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.

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