PREPARATION AND SYNTHETIC APPLICATIONS OF α-ALKOXYSTANNANES AS PRECURSORS TO α-ALKOXYORGANOLITHIUMS

by

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Abstract

The preparation of α-alkyl and α,α-dialkyl α-alkoxystannanes is described, and their synthetic utility as precursors of α-alkoxyorganolithium reagents is demonstrated.

N,N-Diethyl-, *N,N*-diisopropyl- and *N*-phenylcarbamate protected α-hydroxy-trimethylstannanes are prepared (34-83% yields). These compounds are shown to undergo tin-lithium exchange to provide stable α-alkoxyorganolithium species that trap aliphatic and aromatic aldehydes to provide protected 1,2-diols in good yields (53-93%). In contrast, prepared MOM-protected derivatives (75-78% yield) do not undergo tin-lithium exchange as cleanly as their tributyl-analogues do. Removal of the *N,N*-dialkyl-, and *N*-phenylcarbamate protecting groups is accomplished with alane and $LiAlH_4$, respectively. An enantiomerically enriched (>97% ee) *N,N*-diethylcarbamate protected α-alkoxyorganolithium is trapped using benzaldehyde with complete retention of configuration (HPLC).

The addition of *N,N*-diethylcarbamate protected α-alkoxyorganolithiums to benzaldehyde provides the protected 1,2-diols in approximately 1:1 ratios. Organo-magnesium species prepared from α-alkoxyorganolithiums using $MgBr_2 \bullet OEt_2$ give high selectivities (87:13), while other organometallic species incorporating metals such as Al, B, and Zn show no reactivity.

The addition of organomagnesium reagents to acylstannanes provides one route to α,α-dialkyl α-alkoxystannanes. Other organometallic reagents resulted in complex reaction mixtures. The enantioselective addition of simple alkyl organometallic reagents to (1-tributylstannyl)propan-1-one and (1-tributylstannyl)ethan-1-one provides α,α-dialkyl α-alkoxystannanes with low levels of enantioselectivity (<56% ee) and poor reproducibility.

Finally, the chromatographic separation of diastereomeric carbamates prepared from (*S*)-α-naphthylethylamine is a useful method of obtaining α,α-dialkyl α-alkoxystannanes in high levels of diastereomeric purity (91-97% de). Cleavage of the (*S*)-α-naphthylethyl-carbamate group (alane) and protection of the enantiomerically enriched α-hydroxystannane as the *N,N*-diethylcarbamate provides access to configurationally stable α,α-dialkyl α-alkoxyorganolithium reagents. Trapping with benzaldehyde is shown to proceed with complete retention of configuration.

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To Dyanne

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List of Abbreviations and Tradenames

ABq	AB quartet
aq	aqueous
Ar	aryl
Aux	auxiliary
b	broad
BINAL-H	2,2′-dihydroxy-1,1′-binaphthyl-modified lithium aluminum hydride
bm	broad multiplet
Bn	benzyl
BOM	benzyloxymethyl
bp	boiling point
bs	broad singlet
Bu	*n*-butyl
BuLi	*n*-butyllithium
Calcd	calculated
Chirald®	(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol
d	doublet
DBNE	(1*S*,2*R*)-*N*,*N*-di-*n*-butyl-norephedrine
DCBC	2,6-dichlorobenzoyl chloride
dd	doublet of doublets
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIPC	1,3-diisopropylcarbodiimide
DIPS	diisopropyl sulfide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DPMPM	(*S*)-(+)-diphenyl(*N*-methylpyrrolidin-2-yl)methanol
dr	diastereomeric ratio
ds	diastereoselectivity
dq	doublet of quartets
E	electrophile
ee	enantiomeric excess
EE	α-ethoxyethyl
er	enantiomeric ratio
Et	ethyl
ether	diethyl ether
EI	electron ionization
equiv	equivalent
ES	electrospray
GCMS	gas chromatography mass spectrometry
h	hour(s)
[H]	reduction
HMMPMP	(2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography

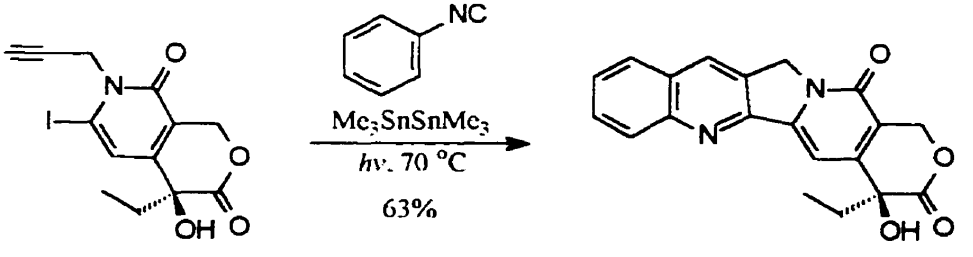
Hz	hertz
i-Pr	isopropyl
IR	infrared
LAH	lithium aluminum hydride
LC	liquid chromatography
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
MeLi	methyllithium
MenOM	menthoxymethyl
MOM	methoxymethyl
mp	melting point
MPLC	medium-pressure liquid chromatography
MS	mass spectrometry
MTPA	α-methoxy-α-trifluoromethylphenylacetate
m/z	mass to charge
NMR	nuclear magnetic resonance
n-Pent	*n*-pentyl
PG	protecting group
Ph	phenyl
PPL	porcine pancreatic lipase
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
SAMP	(*S*)-1-amino-2-(methoxymethyl)-pyrrolidine
SEM	β-(trimethylsilyl)ethoxymethyl
SM	starting material
t	triplet
TADDOL	α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-BOC	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
Temp	temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
Un	unsaturated group
UV	ultraviolet

CHAPTER 1

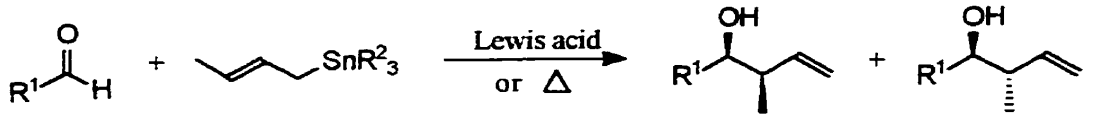
INTRODUCTION

One of the great challenges that synthetic organic chemists face today is the task of developing stereoselective routes to complex organic molecules. The past two decades have seen a dramatic increase in the synthetic application of organostannane chemistry in meeting these goals.[1] This class of chemistry has proven invaluable as a source of new reagents and selective transformations.[2] Recent advances in organotin chemistry include the development of fluorous tin reagents (e.g., azide,[3a] halide,[3b] and hydride[3c]); water soluble tin hydride;[4] and tin-functionalized polymer supports.[5] In particular, two areas have benefited greatly, and illustrate the synthetic impact organostannane chemistry has made. The generation of carbon radicals for C-H and C-C bond formation from a multitude of functional groups has permitted access to numerous natural products (e.g., camptothecin,[6] Scheme 1).[7] The relative weakness of the C-Sn bond enables organostannanes to be excellent precursors to carbon nucleophiles. This type of reaction may be promoted by Lewis acids, e.g., the reaction of allylstannanes with aldehydes (Scheme 2)[8] or via transmetalation to form other more reactive organometallic reagents (e.g., organolithiums,[9] Scheme 3).[10] Also of importance is the role that transition metals have played in transferring carbon nucleophiles from tin to electrophilic reaction sites, e.g., the palladium catalyzed cross-coupling reaction of organostannanes with electrophiles (Scheme 4).[11]

Scheme 1[6]

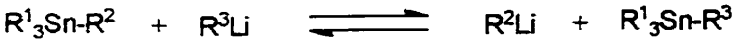


Scheme 2



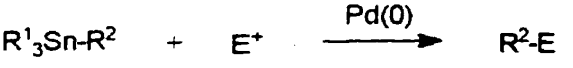
R^1 = alkyl, aryl
R^2 = Me, Bu, Ph

Scheme 3



R^1 = alkenyl, α-alkoxy, allyl
R^2, R^3 = Me, Bu

Scheme 4



R^1 = Me, Bu
R^2 = H, alkyl, alkenyl, alkynyl, allyl, aryl, benzyl
E^+ = acid chlorides, allyl and benzyl halides
aryl and vinyl halides and triflates

This thesis will focus on only one aspect of organostannane chemistry mentioned above; specifically, on the preparation of α-alkoxystannanes and their use as precursors to α-alkoxyorganolithium reagents.

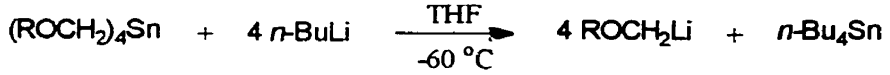
The following sections of this Chapter provide a review of α-alkoxystannane chemistry with emphasis on their application as precursors to α-alkoxyorganolithium reagents.

1.1 α-Alkoxystannanes as Precursors of α-Alkoxyorganolithium Reagents

1.1.1 Unsubstituted α-Alkoxystannanes

In 1970, Schöllkoph reported the first tin-lithium exchange of an α-alkoxystannane.[12] This involved the transmetalation of tetrakis(alkoxymethyl)stannanes (**1**) with *n*-butyllithium to yield α-alkoxymethyllithiums (**2**) (Scheme 5).

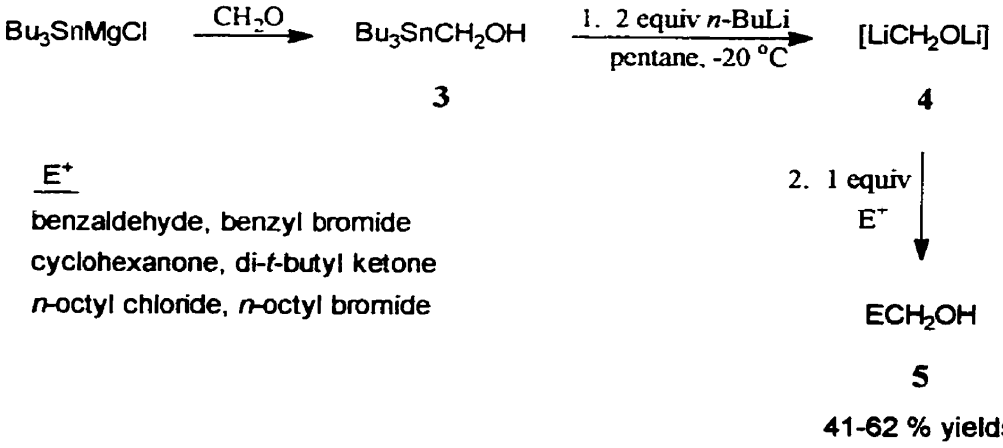
Scheme 5



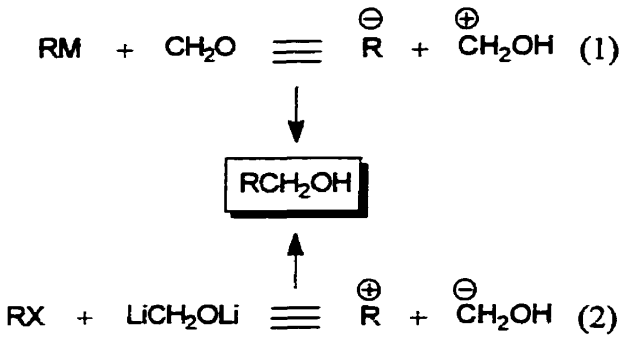
1 **2**

Seebach and Meyer later reported the preparation of "doubly metalated methanol" (**4**) from the tin-lithium exchange of stannyl alcohol **3**.[13] The intermediate dianion **4** was trapped with various electrophiles to provide alcohols **5** (Scheme 6). Typically, primary alcohols were prepared from the reaction of an organometallic reagent with formaldehyde (equation 1, Scheme 7). This alternative method represented a reversed mode of reactivity ("umpolung") for preparing such substrates (equation 2).

Scheme 6[13]

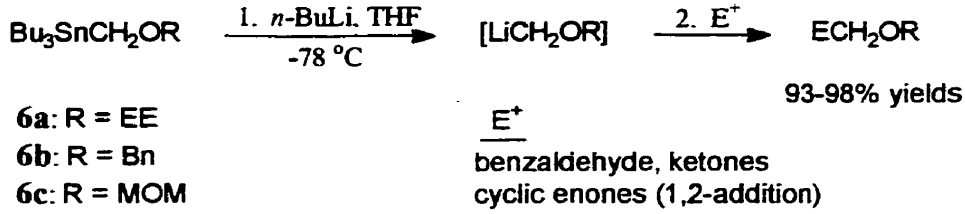


Scheme 7

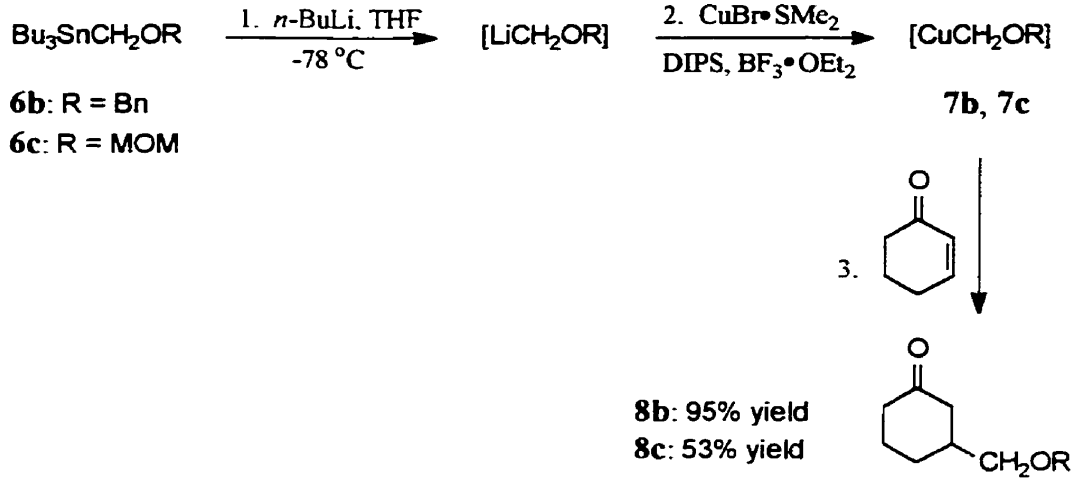


To increase on the moderate yields observed for alcohol **5**, and to improve the stability of α-hydroxystannanes, protected derivatives (**6a**,[14] **6b** and **6c**[15]) of **3** were prepared (Scheme 8). Subsequent tin-lithium exchange and trapping gave substantially higher (93-98%) yields. Addition of the α-alkoxymethyllithium reagent to an enone resulted in the exclusive formation of the 1,2-addition product (Scheme 8). To allow access to the 1,4-addition product, Hutchinson and Fuchs[16] as well as Johnson and Medich[15] prepared α-alkoxymethyl copper reagents **7b** and **7c**, respectively (Scheme 9). When reagents **7b** and **7c** were reacted with cyclohexenone, the 1,4-addition products **8b** and **8c**, respectively, were isolated (Scheme 9). The α-alkoxymethyl copper reagents were found to be susceptible to dimerization in the presence of trace copper (II) salts; hence only sources of high quality copper (I) can be used. One additional drawback was that reaction of these reagents with sterically hindered enones was found to be sluggish. Aside from these concerns, Hutchinson and Fuchs demonstrated the synthetic utility of these reagents by performing the addition of **7b** to the ammonium salt **9** to yield **10**, an intermediate in the total synthesis of (+)-carbacyclin (Scheme 10).[16]

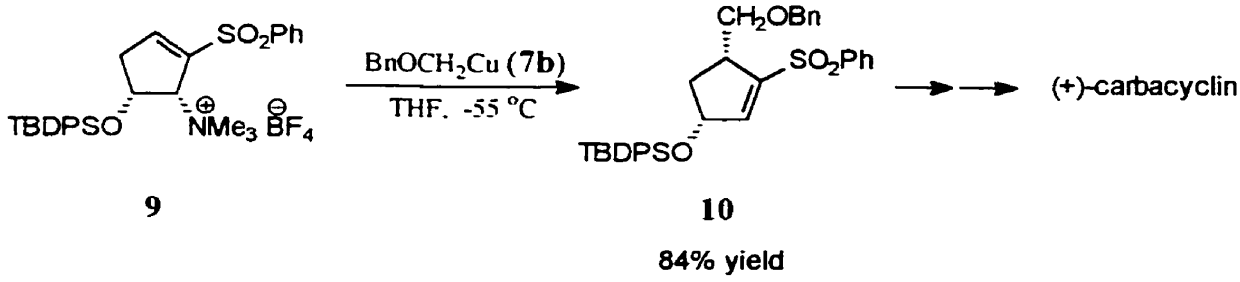
Scheme 8[14,15]



Scheme 9[16]

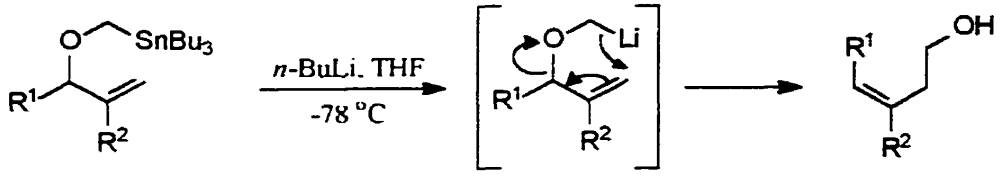


Scheme 10[16]



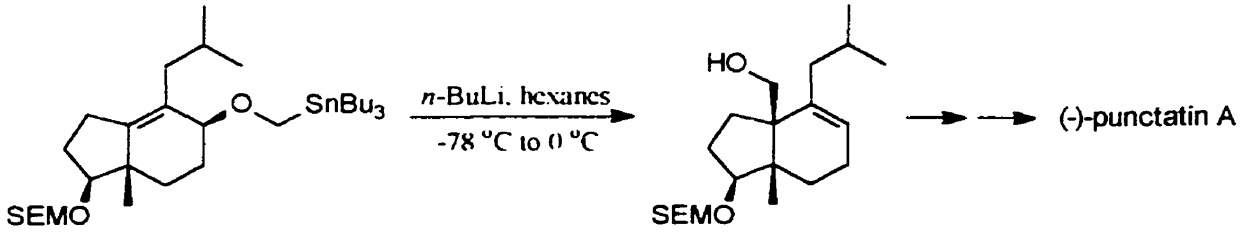
In 1978, Still and Mitra reported a novel application of α-alkoxymethyllithium reagents derived from allylstannyl methyl ethers (**11**).[17a] The allyloxy carbanion **12**, which was obtained from the transmetalation of **11** with *n*-butyllithium, undergoes a [2,3]-sigmatropic rearrangement[17b] producing Z-trisubstituted homoallylic alcohols **13** (Scheme 11). The synthetic utility of this "Wittig-Still" rearrangement was demonstrated during the total synthesis of (-)-punctatin A (Scheme 12).[18]

Scheme 11



11 **12** **13**

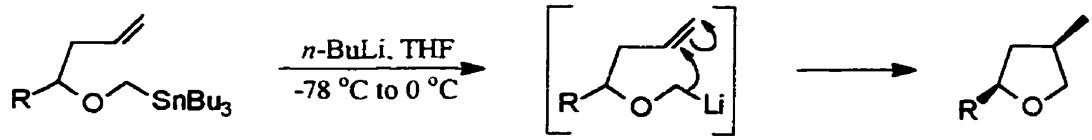
Scheme 12[18]



In 1988, Broka and coworkers reported the preparation of *cis*-2,4-disubstituted tetrahydrofurans from homoallyl stannylmethyl ethers (**14**).[19] Transmetalation of **14** with an excess of *n*-butyllithium yields α-alkoxymethyllithium **15**, which then undergoes anionic cyclization. The resultant tetrahydrofurans (**16**) are obtained with cis:trans ratios ranging from 11:1 to >15:1 (Scheme 13). A novel feature of this chemistry is the use of methoxy-substituted stannanes (**17**), which yield tetrahydrofurans (**18**) containing an olefinic substituent suitable for further chemical manipulation (Scheme 14). Lautens and Kumanovic

have recently employed this methodology to access bicyclo[5.3.0]decenes (**20**).[20] The anionic intramolecular ring opening of allyloxy ethers (**19**) provides the desired 5,7-fused ring system of **20**, which is found in many natural products, e.g., sesquiterpenes (Scheme 15).

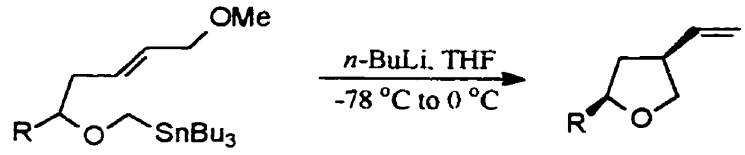
Scheme 13[19]



14 **15** **16**

R = *n*-C_6H_{13}: 54 % yield, cis:trans = 11:1
R = *c*-C_6H_{11}: 49 % yield, cis:trans = >15:1

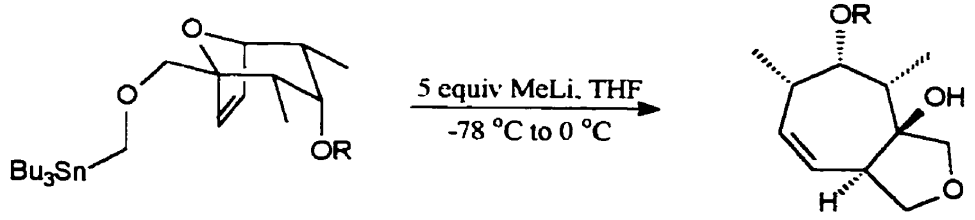
Scheme 14[19]



17 **18**

R = *n*-C_6H_{13}: 85 % yield, cis:trans = 13:1
R = *c*-C_6H_{11}: 78 % yield, cis:trans = >15:1

Scheme 15[20]



19

R = H, Me, Bn, TBDMS

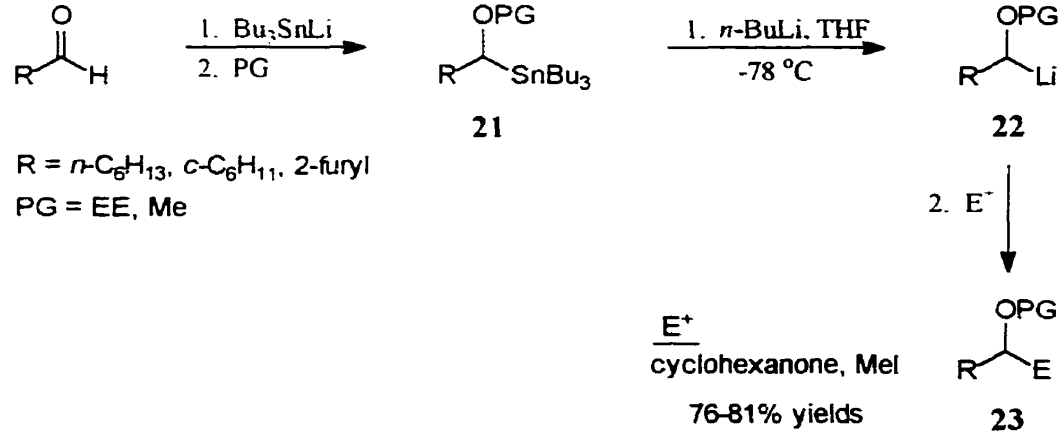
20

80-85% yield

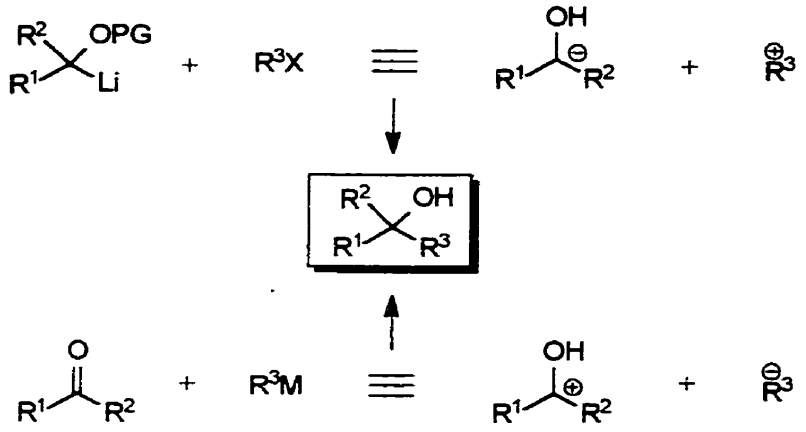
1.1.2 α-Substituted α-Alkoxystannanes

In 1978, Still reported the transmetalation of α-substituted α-alkoxystannanes (**21**) to obtain α-substituted α-alkoxyorganolithiums (**22**).[14] These intermediates were trapped with electrophiles to provide the protected alcohols **23** (Scheme 16). This addition of a masked carbinyl carbanion to a carbonyl compound represented yet another example of umpolung reactivity. The equivalent and conventional approach to preparing an alcohol would involve the addition of an organometallic reagent to an aldehyde or ketone (Scheme 17). The synthetic potential of this reverse polarity approach was demonstrated by a simple synthesis of dendrolasin.[14] The conventional approach would have involved the addition of an allyl organometallic, which may undergo isomerization, to furan-3-carboxaldehyde resulting in a potential mixture of regio- and stereoisomers (Scheme 18). Alternatively, the addition of the α-alkoxyorganolithium generated from transmetalation of **24** to an allyl chloride (geranyl chloride) provided the product with retention of the geometry of the central trisubstituted double bond.

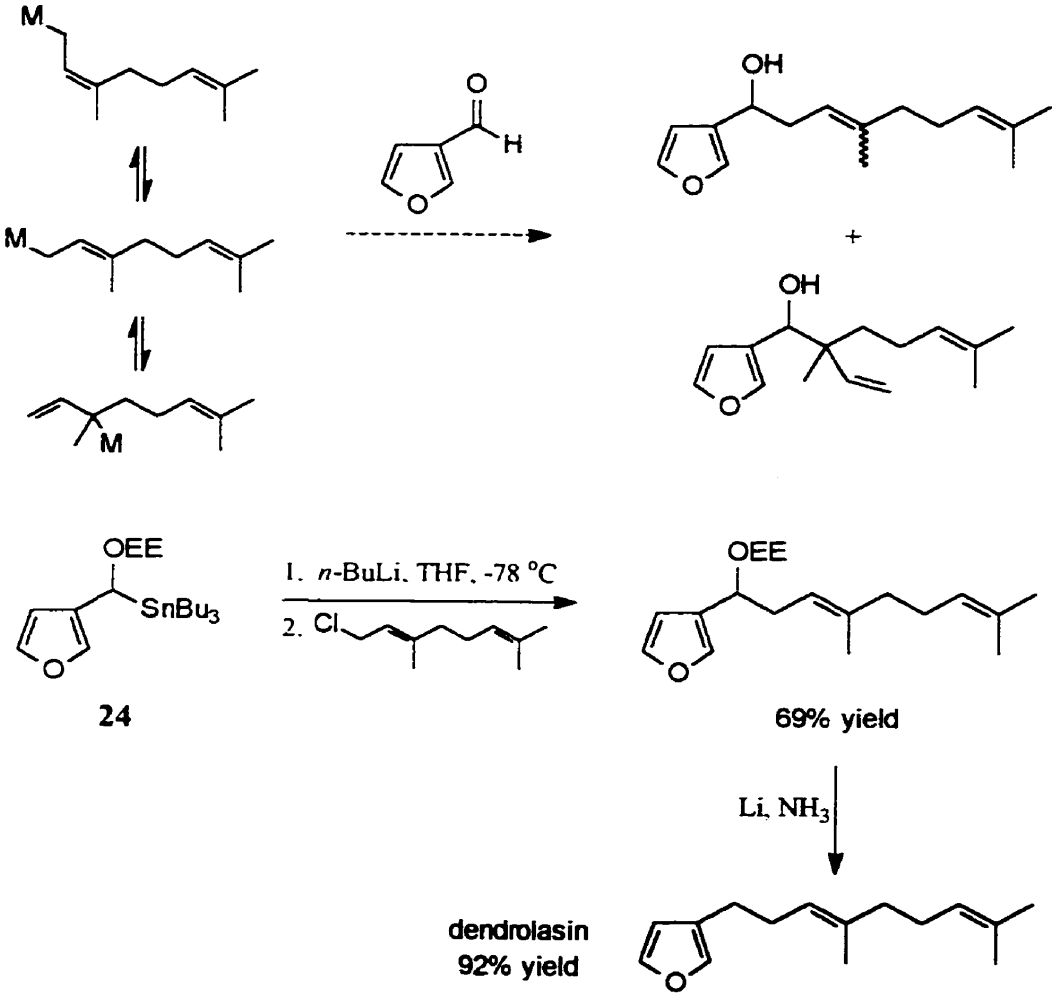
Scheme 16[14]



Scheme 17

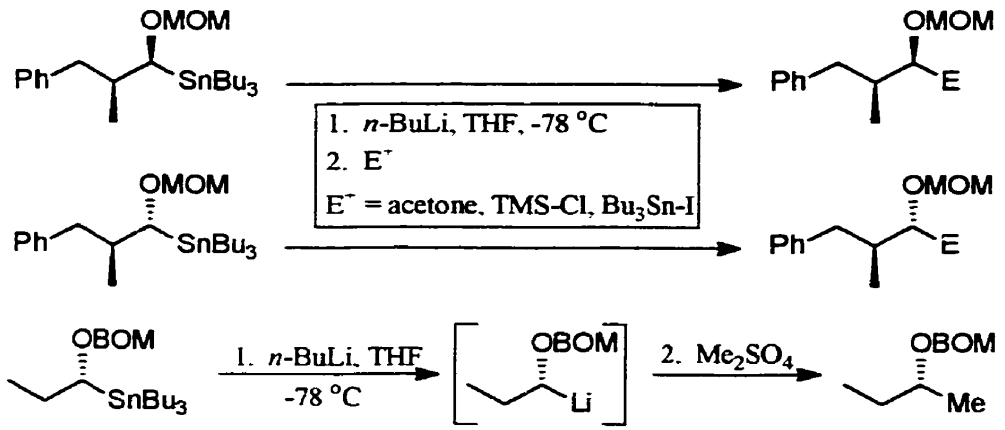


Scheme 18[14]



Quite possibly one of the greatest contributions pertaining to the configurational stability of α-alkoxyorganolithium reagents was made by Still. In 1980, he demonstrated that both diastereomerically and enantiomerically pure α-alkoxystannanes could undergo transmetalation and trapping with electrophiles to provide adducts with no detectable loss of stereochemical purity; hence, the transmetalation-trapping sequence takes place with overall retention of configuration (Scheme 19).[21]

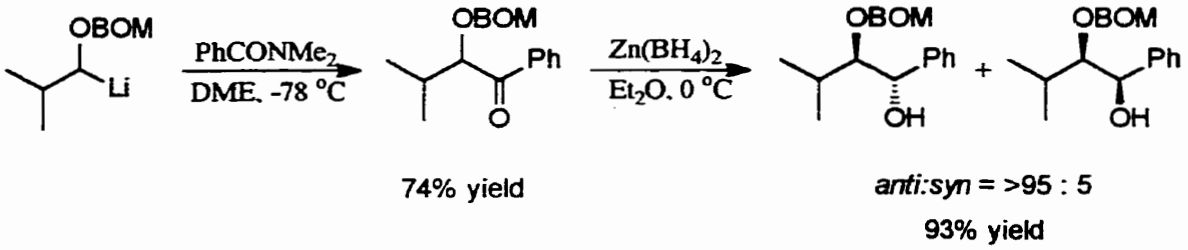
Scheme 19[21]



In light of Still's contribution to the understanding of α-alkoxyorganolithium reagents, several research groups have applied these reagents for other selective transformations. The following examples highlight some of the more important applications of α-alkoxystannane reagents.

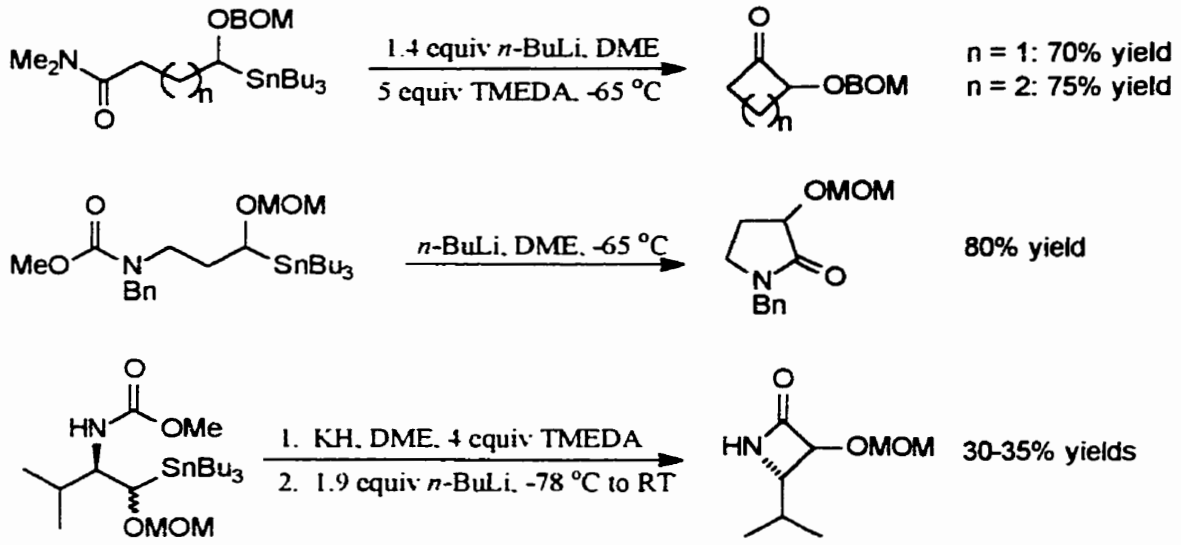
McGarvey and Kimura reported a stereoselective route to *anti*-1,2-diols using α-alkoxyorganolithium reagents obtained from the transmetalation of α-alkoxystannanes.[22] Reaction of the α-alkoxyorganolithiums with amides provided α-alkoxy ketones that were reduced stereoselectively with zinc borohydride to yield the 1,2-diols (Scheme 20).[22]

Scheme 20[22]



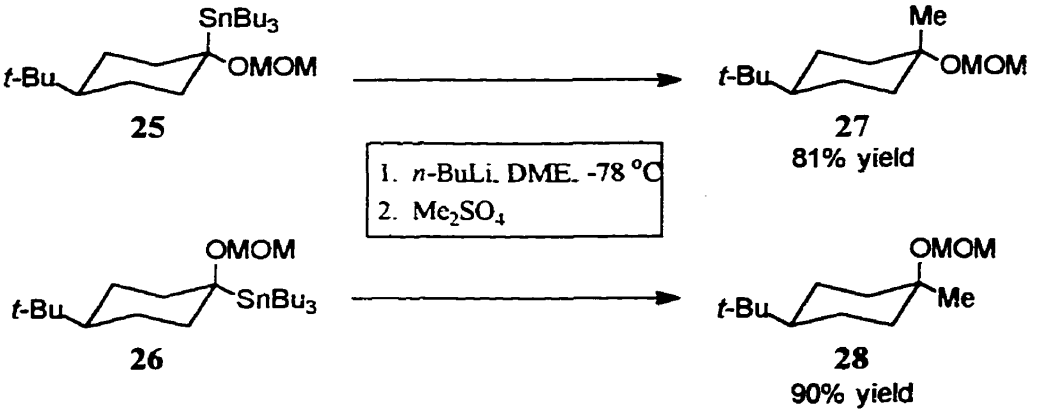
Extension of this methodology, by McGarvey and Kimura, to include intramolecular cyclization of stannyl amides allowed access to carbocycles and heterocycles (Scheme 21).[23]

Scheme 21[23]



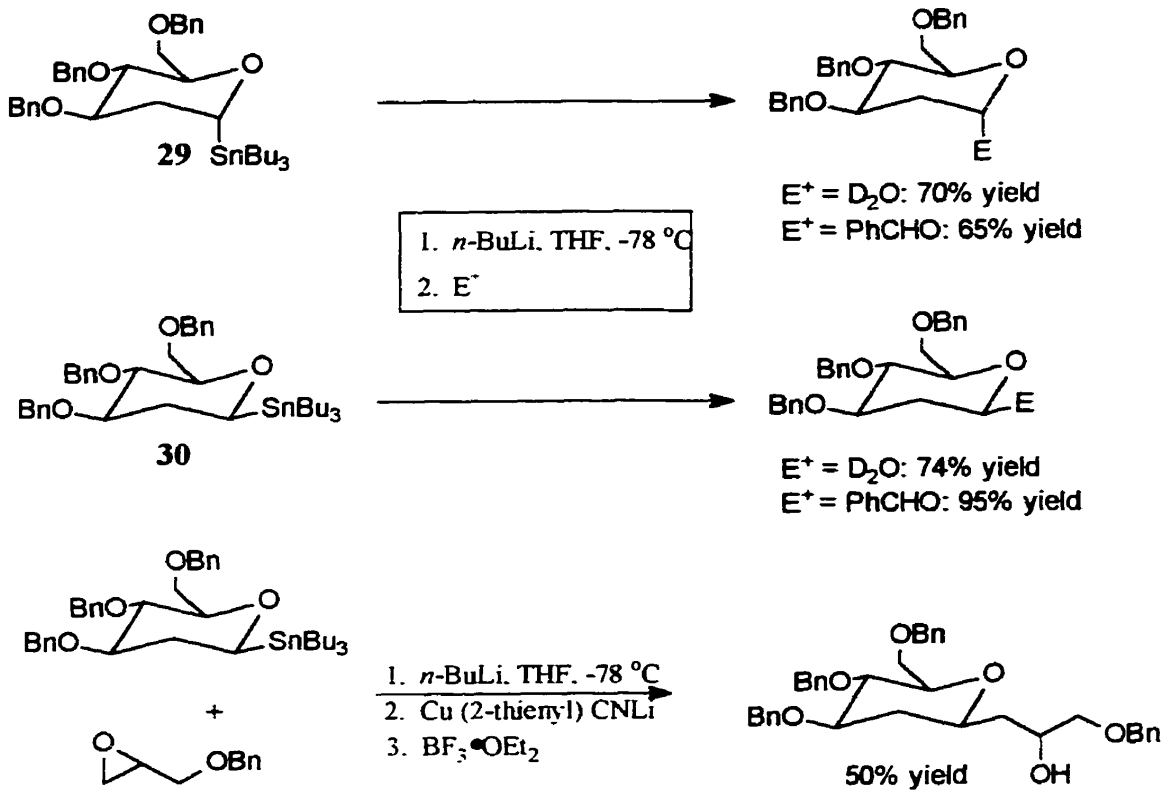
In subsequent studies, McGarvey and coworkers provided additional evidence for the configurational stability of α-alkoxyorganolithium reagents.[24] When α-alkoxystannanes **25** and **26** were transmetalated and trapped with Me_2SO_4, the resultant methylated products **27** and **28** were obtained with complete retention of configuration (Scheme 22). This methodology has proved invaluable, as axially substituted cyclohexanes such as **27** cannot be prepared in the conventional manner due to the propensity of equatorial attack by nucleophilic carbanions on the carbonyl of the selected cyclohexanone.

Scheme 22[24]



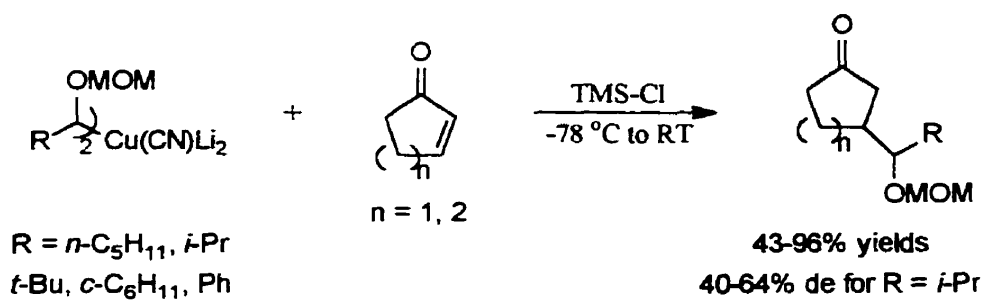
Similar results were reported by Beau and coworkers who examined the transmetalation of α- and β-D-glucosylstannanes **29** and **30** (Scheme 23).[25] The α- and β-D-glucosyllithium reagents prepared from **29** and **30** were trapped with deuterium oxide and benzaldehyde with complete retention of configuration. These organolithium reagents were subsequently converted into the α- and β-D-glucosyl copper reagents by Hutchinson and Fuchs and shown to add to enones in a 1,4-manner, producing *C*-glycosides stereospecifically.[16] Beau and coworkers extended this methodology by examining the ring opening of epoxides in the presence of boron trifluoride diethyl etherate, with the higher order cuprate reagent prepared from the α- and β-D-glucosyllithiums with 2-thienylcyano-cuprate (Scheme 23).[26] The cuprates were shown to be configurationally stable at low temperatures (-78 °C) and the coupling reactions proceeded with retention of configuration.

Scheme 23[25,26]



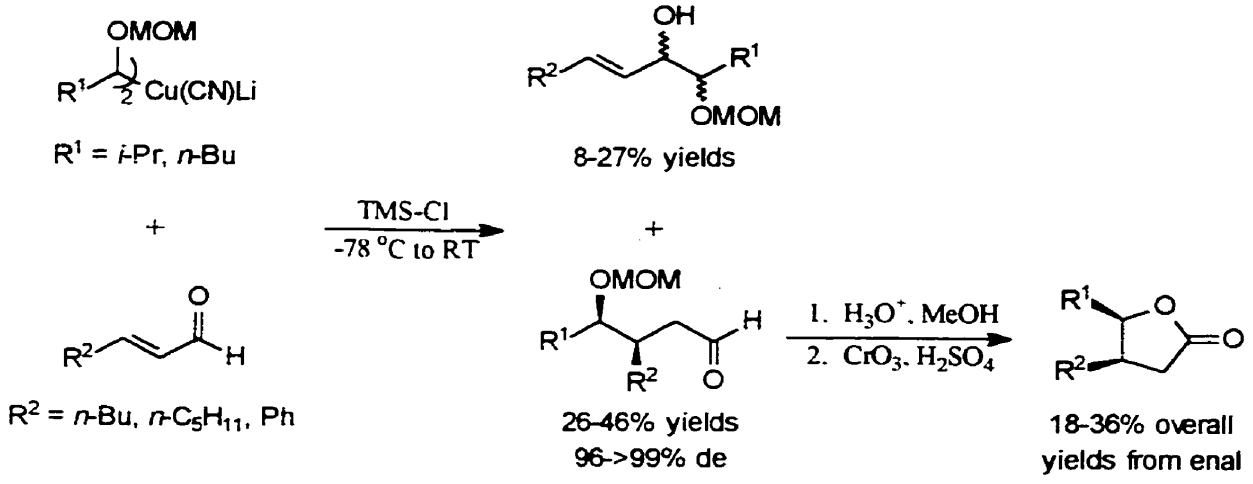
Linderman and coworkers reported on the preparation of α-alkoxyorganocuprates and their addition to unhindered cyclic enones, in the presence of trimethylsilyl chloride (TMS-Cl).[27] The best results were obtained with the higher order cyanocuprates, which gave moderate to excellent yields of 1,4-adducts; however, only modest diastereoselectivity was observed (Scheme 24).

Scheme 24[27]



Linderman and coworkers further demonstrated the synthetic utility of α-alkoxy-organocuprates by examining their addition to enals in the presence of trimethylsilyl chloride.[28] This reaction sequence provided a convenient route to *cis*-3,4-disubstituted butyrolactones (Scheme 25). The diastereoselectivity in the formation of the intermediate γ-alkoxy aldehydes was found to be exceptionally high (45:1 to >250:1), while the yields were relatively poor (26-46%). Small quantities of the 1,2-addition products (8-27%) were also isolated from the reaction. However, treatment of the intermediate γ-alkoxy aldehydes with acid followed by oxidation, provided the desired *cis*-3,4-disubstituted butyrolactones in 18-36% overall yields.

Scheme 25[28]

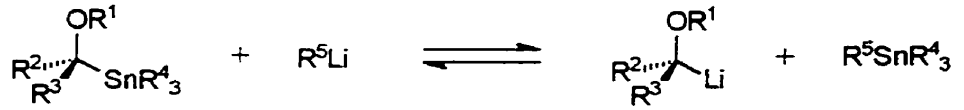


This section has highlighted some of the various synthetic applications of α-alkoxy-stannanes. The impact that these reagents have made since their introduction is noted by their creative use in C-C bond formation.

1.2 Transmetalation of Organostannanes

The transmetalation reaction of α-alkoxystannanes (as well as allyl and vinyl stannanes) and alkyllithiums is actually an equilibrium process in which the position of the equilibrium is determined by the relative thermodynamic stabilities of the organolithium species involved (Scheme 26).[24b,29] McGarvey and coworkers developed a relative ordering of α-alkoxyorganolithium species (generated by tin-lithium exchange) and alkyllithium reagents (Figure 1, presented in decreasing order from left to right).[24b] The ordering of the various organolithium species was determined by ^{1}H NMR and chromatographic analyses of competition experiments between two α-alkoxystannanes for an alkyllithium reagent. It was approximated that at least 1.5 pKa units separates the individual organolithium species with regards to relative acidity.

Scheme 26



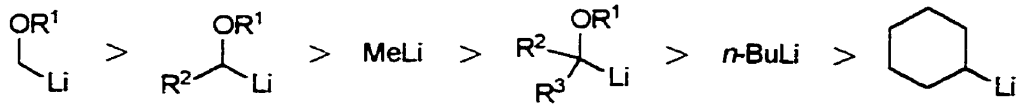


Figure 1. Relative stabilities of α-alkoxyorganolithium and alkyllithium reagents generated via tin-lithium exchange.[24b]

The difference in thermodynamic stability between the various organolithium species depicted in Figure 1 was mainly attributed to the σ-inductive effect of the adjacent α-alkoxy functionality.[24b] Other contributing factors included intramolecular coordination of the lithium cation to the lone pair of electrons on oxygen and the aggregation state of the α-alkoxyorganolithium species in solution.[24b] The rate of transmetalation between an α-alkoxystannane and alkyllithium reagent is also influenced by the size of the trialkylstannyl moiety (relative rate: Me >> *n*-Bu >> *c*-C_6H_{11}) and the solvent (relative rate: DME > THF > Et_2O).[24b]

The transmetalation reaction has been postulated to proceed through a four-centered transition state. However, stannylate intermediates have also been proposed to explain the mechanism of organostannane transmetalation (Figure 2). Still was unable to find any evidence to support the stannylate postulate, after examining competition experiments of α-alkoxystannanes.[14] Spectroscopic evidence supporting their existence was reported by Reich and Phillips; however, tetralkylstannanes and not α-alkoxystannanes were the focus of this study.[30] NMR studies undertaken by McGarvey and coworkers on the transmetalation of α-alkoxystannanes,[24b] and by Linderman and Ghannam on the transmetalation of α-silyloxy-stannanes[31] concluded that stannylate intermediates were not detected. It was suggested by McGarvey that they may be too short-lived to be seen on the NMR time scale.

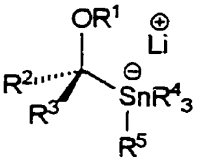


Figure 2. Proposed stannylate intermediate.

1.3 Preparation of Enantiomerically and Diastereomerically Enriched α-Alkoxystannanes

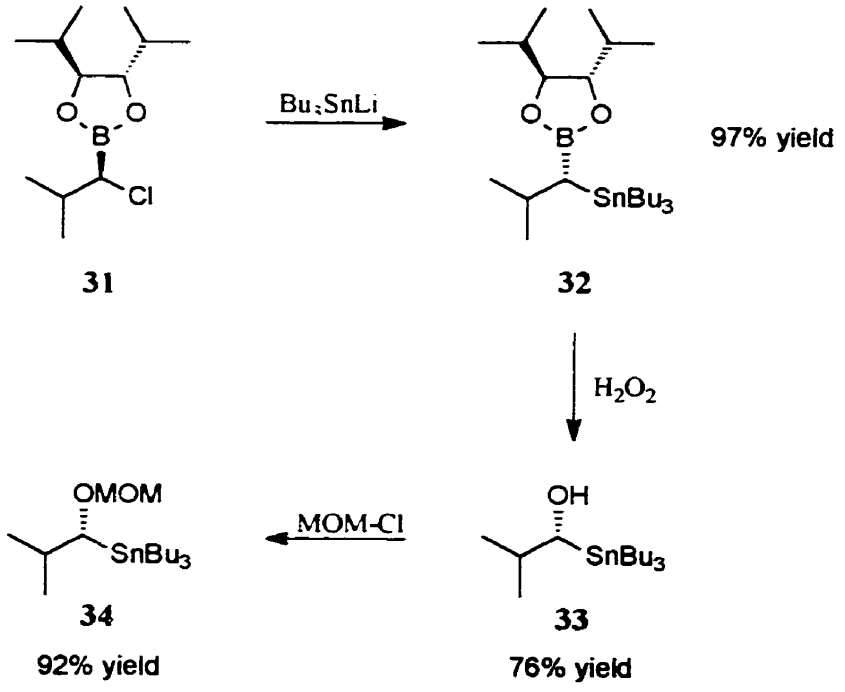
Developing routes for the generation of enantiomerically and diastereomerically enriched α-alkoxystannanes has become increasingly important for two reasons. First, these reagents act as convenient precursors to homochiral α-alkoxyorganolithiums for synthesis. Secondly, by having access to these intermediates it allows an opportunity to study and understand the factors that influence their configurational stability. Initially, synthetic routes allowing access to enriched α-alkoxystannanes were not convenient. As a result, extensive studies on the configurational stability of α-alkoxyorganolithium species were lacking in the literature. For this reason, these reagents were thought to react stereospecifically with all types of electrophiles. In 1988, the asymmetric reduction of acylstannanes[32,33] using Noyori's[34] 2,2'-dihydroxy-1,1'-binaphthyl-modified lithium aluminum hydride (BINAL-H) reagent (see Chapter 4, page 130, for a detailed discussion) to obtain enantiomerically enriched α-alkoxystannanes was reported and for the first time factors such as the nature of the electrophile could be fully studied. Subsequently, it was determined that α-alkoxyorganolithium reagents (generated from tin-lithium exchange) actually react with certain electrophiles, such as alkyl iodides, allyl bromides, and benzyl bromides, to give racemic products.[24b,35] This observed racemization was believed to occur through lithium-halogen exchange via a single electron transfer, resulting in an intermediate α-alkoxy radical and loss of the original chirality. Griedel and Linderman reported that the reaction of a higher order cyanocuprate, prepared from an enantiomerically enriched α-alkoxystannane, with an enone gives the 1,4-addition product in nearly racemic form.[36] It is possible in this case that racemization may be occurring by a single electron transfer mechanism despite the fact that reaction conditions were chosen to disfavor this pathway.

A continued effort directed towards the development of new routes to enantiomerically enriched α-alkoxystannanes ensures that limitations surrounding current methods are minimized. The following section will discuss current methods of preparing enriched α-alkoxystannanes, excluding the chromatographic resolution of diastereomeric intermediates, which will be discussed in Chapter 5.

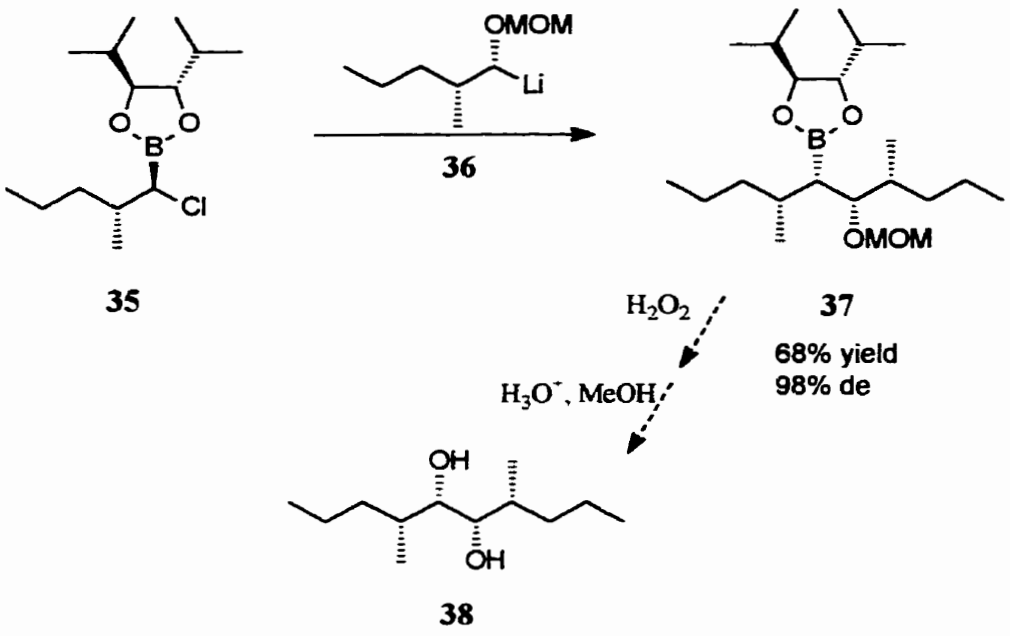
1.3.1 Asymmetric Synthesis

In 1989, Matteson and coworkers reported the use of enantiomerically pure diisopropylethanediol (DIPED)-derived α-chloro boronic esters (**31**) for the preparation of enantiomerically enriched α-alkoxystannanes **34** (Scheme 27).[37] The α-chloro boronic esters (**31**), available as either enantiomer (>90% ee), are reacted with tributyltinlithium with inversion of configuration to yield α-tributylstannyl boronic ester **32**. Ester **32** is oxidized to the intermediate α-hydroxystannane **33** and then protected to provide **34**. A very novel application of this chemistry is the ability to couple two aliphatic chains containing several chiral centers. For example, coupling of chiral boronic ester **35** with the chiral α-alkoxy organolithium **36**, derived from the α-alkoxystannane, yields **37** that now contains four contiguous chiral centers (Scheme 28). The symmetrical diol **38** would be accessible after oxidation followed by hydrolysis.

Scheme 27[37]



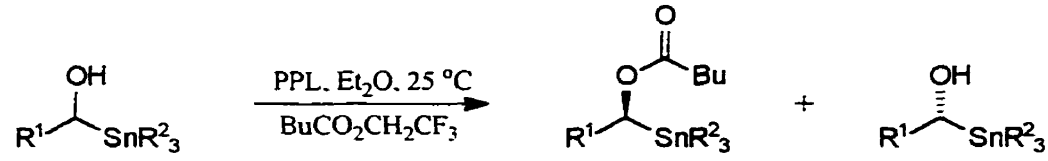
Scheme 28[37]



1.3.2 Enzymatic Resolution

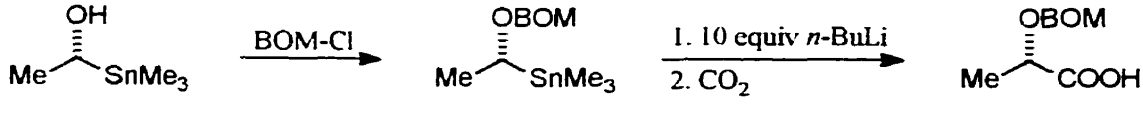
In 1991, Chong and Mar reported the porcine pancreatic lipase (PPL) catalyzed esterification of α-hydroxystannanes (Table 1).[38] Excellent enantioselectivities of the product ester were obtained (94-99% ee). The rate of the enantioselective esterification was found to be very sensitive to the size of the alkyl side chain (R^1) and the size of the trialkylstannyl moiety (R^2). The fastest reaction was obtained with trimethylstannylethanol (entry 1), while no reaction was observed from tributylstannylethanol (entry 6). The product alcohols and their esters were shown to be useful homochiral building blocks. Alcohol **39** (>98% ee) was protected as the benzyloxymethyl (BOM) ether **40** and then transmetalated and trapped with carbon dioxide to yield acid **41** in 46% yield, of >98% ee (Scheme 28).[38] Therefore, the transmetalation-carboxylation proceeds with complete retention of configuration.

Table 1. Porcine pancreatic lipase (PPL) catalyzed esterification of α-hydroxystannanes.[38]



Entry	α-Hydroxystannane		Time (h)	Product Ester	
	R^1	R^2		Yield (%)	ee (%)
1	Me	Me	48	31	97
2	Et	Me	64	36	99
3	Pr	Me	129	7	97
4	Me	Et	84	35	99
5	Et	Et	85	14	97
6	Me	Bu	111	0	-:-

Scheme 28[38]



(*R*)-**39**

(*R*)-**40**
>98% ee
59% yield

(*S*)-**41**
>98% ee
46% yield

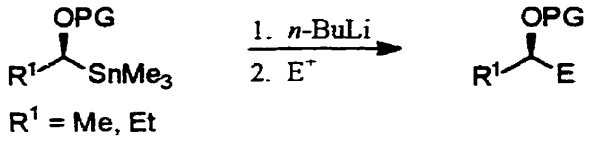
1.4 Scope of Thesis

The synthetic utility of α-alkoxyorganolithium reagents, as generated from organostannanes by tin-lithium exchange, has been illustrated with several examples cited within Sections 1.1 and 1.3. In light of these accomplishments, this thesis will present several shortcomings of α-alkoxystannane chemistry, the methodology used to address these challenges, and new applications of these compounds as reagents for organic synthesis. The predominant focus of this thesis will be the preparation of chemically, as well as configurationally, stable α-substituted and α,α-disubstituted α-alkoxyorganolithium reagents.

1.4.1 Preparation of α-Substituted α-Alkoxyorganolithium Reagents

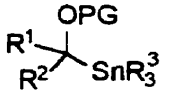
Mar[38] within our laboratory, has demonstrated a novel method of obtaining enantiomerically enriched α-alkoxystannanes using the PPL catalyzed esterification of α-hydroxystannanes (Table 1). Subsequent transmetalation and trapping of these α-alkoxystannanes demonstrated the retention of configuration of the derived α-alkoxyorganolithium species (Scheme 28). However, what should be stressed is that ten equivalents of *n*-butyllithium were required to obtain sufficient α-alkoxyorganolithium intermediate to provide trapped adduct **41** in a mediocre 46% yield. Variables such as the choice of protecting group have been shown to play a large role in improving the synthetic yields of the desired trapped products (compare Schemes 6 and 8). Therefore, it was with precedent that a study be conducted on the selection of protecting groups for organotrimethylstannanes so that the full utility of these enantiomerically enriched compounds, as precursors to α-alkoxyorganolithium reagents, may be realized (Scheme 29). This study will be presented in Chapter 2 with applications directed towards the synthesis of 1,2-diols described in Chapter 3.

Scheme 29



1.4.2 Preparation of α,α-Disubstituted α-Alkoxyorganolithium Reagents

The literature review provided in this Chapter predominately focused on unsubstituted and α-substituted α-alkoxystannanes. As will be shown in Chapter 4, examples of α,α-disubstituted α-alkoxystannanes are rare (Figure 3). With the exception of a few α,α-dialkyl (**42a**) examples, most compounds within this description are benzylic α-alkoxystannanes (**42b**).



42a R^1, R^2 = alkyl, R^3 = Me, Bu

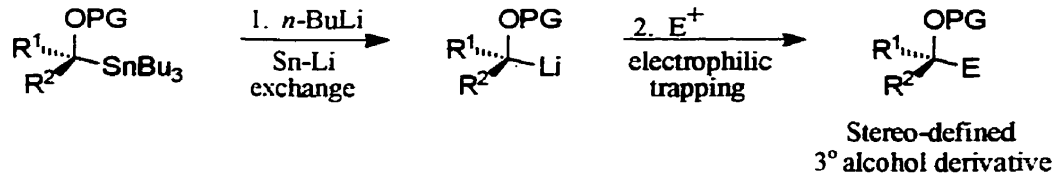
42b R^1 = alkyl, R^2 = Ph, R^3 = Me, Bu

Figure 3. α,α-Disubstituted α-alkoxystannanes.

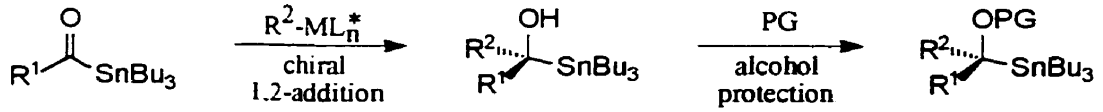
Currently there are no examples of enantiomerically enriched α,α-dialkyl α-alkoxystannanes in the literature. This is surprising because these organostannanes would serve as convenient precursors of enantiomerically enriched α,α-dialkyl α-alkoxyorganolithium reagents. Their application towards synthesis is significant because they would potentially allow the construction of masked tertiary alcohols with complete control of stereochemistry (Scheme 30). Therefore, this thesis will also describe our efforts in preparing these compounds as outlined by the following two approaches: (1) the enantioselective 1,2-addition of organometallic reagents to acylstannanes in Chapter 4 (Scheme 31); and (2) the chromatographic separation of diastereomeric α-alkoxystannanes in Chapter 5 (Scheme 32). Upon obtaining a successful synthetic route to enantiomerically enriched α,α-dialkylalkoxy-

stannanes, a study on the configurational stability of the derived α-alkoxyorganolithium intermediates will be initiated.

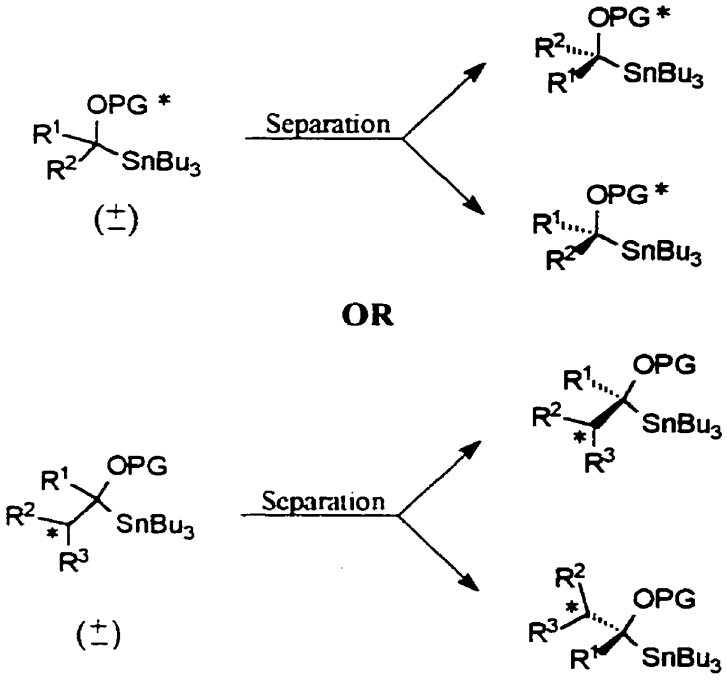
Scheme 30



Scheme 31



Scheme 32



OR

* ≡ chiral center

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CHAPTER 2

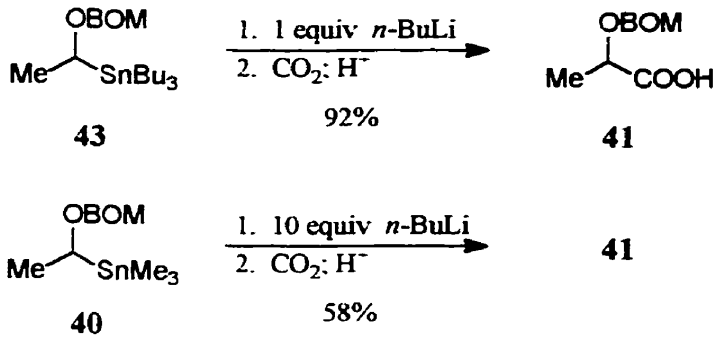
PREPARATION AND TRANSMETALATION OF α-ALKOXY TRIMETHYLSTANNANES [1]

2.1 Introduction

Since their original introduction by Still,[2,3] α-alkoxyorganostannanes have been exploited in numerous chemical applications.[4] That initial report described the use of α-alkoxyorganostannanes as precursors to α-alkoxyorganolithium species via tin-lithium exchange. As with Still's original study, the tributylstannyl group has been predominately chosen throughout the literature for the preparation of α-alkoxyorganolithium reagents and other related chemistry. Factors such as; availability, ease of handling and lower toxicity, as well as the quantity of literature reporting the use of these reagents, have all contributed to the predominant use of the tributylstannyl group. However, other trialkylstannyl groups, particularly trimethylstannyl, offer certain advantages over the analogous tributylstannyl group.[5] The formation of a volatile transmetalation by-product (Me_4Sn, bp 77 °C/760 mmHg *vs* 145°C/10 mmHg for Bu_4Sn), which can be easily removed via work-up of the reaction, simplifies the isolation and quantification of reaction mixtures.[5d] The primary advantage gained is perhaps the simplicity of their ^1H NMR spectra: trimethylstannyl compounds display a singlet for the Me_3Sn group near δ 0.1 while the tributylstannyl compounds produce several multiplets for the Bu_3Sn group ranging from δ 0.70 to 1.50.[6] Within organotin chemistry, the trimethylstannyl group has seen extensive applications in Stille couplings,[7] reactions of vinylstannanes[6,8] and stannyl cuprates.[9] Chong and Mar have reported on the preparation of enantiomerically enriched (>98% ee) α-hydroxytrimethylstannanes via kinetic resolution using porcine pancreatic lipase (PPL) as an acylation catalyst.[10] The synthetic value of this methodology was further highlighted by the inability to achieve similar results with the sterically more hindered tributylstannyl analogues. Simple elaboration of these compounds to α-alkoxytrimethylstannanes provides very valuable

synthetic intermediates. The transmetalation of these intermediates provide α-alkoxy-organolithiums in high enantiomeric excess. Unfortunately, there is literature precedent which suggests that the transmetalation of α-alkoxytrimethylstannanes does not proceed as well as the analogous tributylstannanes.[10.11] This has been demonstrated by the example in Scheme 33.[10.12]

Scheme 33



The transmetalation of tributylstannane **43** with 1 equivalent of *n*-BuLi proceeds smoothly to generate the corresponding α-alkoxyorganolithium species, which is then trapped with CO_2 to give the desired acid **41** in 92% yield. Alternatively, the trimethylstannane **40** required 10 equivalents of *n*-BuLi to generate sufficient quantity of the same α-alkoxyorganolithium, which when trapped with CO_2 gave a 58% yield of product **41**. From this example, it can be noted that there is an inherent benefit in employing the tributylstannane over the trimethylstannane for this particular chemistry. This reactivity may explain the lack of literature describing the transmetalation of trimethylstannanes.[5.13]

The efficiency of the transmetalations of **40** and **43** might be explained by examining the relative stability of the organolithium species involved. The relative stability of α-alkoxyorganolithium and alkyllithium species classified according to McGarvey[14] and co-workers, follows the order: $R^1OCH_2Li > R^1OCH(R^2)Li > MeLi > R^1OCR^2R^3Li > n\text{-BuLi} > c\text{-HexLi}$ (R^1 = MOM, see Figure 1, page 15). It can be reasoned that the treatment of organostannane **40** with *n*-BuLi should yield organolithium BOMOCH(Me)Li selectively

over MeLi. The fact that 10 equivalents of *n*-BuLi must be employed suggests that the intermediate organolithium is actually less stable than MeLi. Therefore, if the stability of PGOCH(Me)Li could be increased over MeLi through the judicious screening of different protecting groups, the trimethylstannyl group could be employed for the transmetalation of α-alkoxystannanes. A detailed study of the factors surrounding the transmetalation of α-alkoxytrimethylstannanes is lacking in the literature.

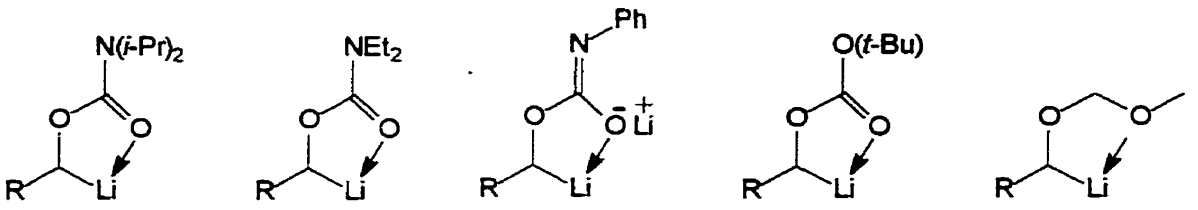
A survey of protecting groups for the stabilization of α-alkoxyorganolithium species, obtained through the tin-lithium exchange of α-alkoxytrimethylstannanes and alkyllithiums, was undertaken. Once the best protecting group was determined on racemic stannanes, further studies on enantiomerically enriched compounds were performed. Enantiomerically enriched α-alkoxytrimethylstannanes were obtained in a general manner by kinetic resolution using PPL,[10] and were protected as best determined from the initial study on racemic stannanes. Finally, the transmetalation and trapping of these protected α-alkoxytrimethyl-stannanes were carried out to assess whether this transformation proceeds with retention of configuration. The following section details our results in pursuing this chemistry.

2.2 Results and Discussion

2.2.1 Selection of Protecting Groups for α-Hydroxystannanes

The protecting groups that were chosen for the initial study included carbamates **44-46**, carbonate **47** and the methoxymethyl ether **48** (Figure 4). These groups were selected because of literature precedent for their stabilization of organolithiums.[3,11,15] All of these protecting groups offer stabilization through the σ-inductive effect of the α-alkoxy group as well as through intramolecular chelation of an oxygen lone pair to the lithium cation. In the case of the carbamates **44** and **45**, the maximum amount of chelation could be realized via donation of the nitrogen lone pair onto the carbonyl group of the amide functionality. In one example, the *N*-phenylcarbamate **46**, a dianion was employed for the stabilization of the organolithium species.[16] In this case, an anion would be generated first, placing the maximum negative charge on the carbonyl oxygen via resonance. It was speculated that this

scenario might offer the highest level of stabilization for the organolithium species. The carbonate **47** was postulated to behave in the same manner as the carbamates. Finally, the study included the MOM protecting group as a control to compare with the original chemistry performed by McGarvey[11,14] and Still.[3]



44 **45** **46** **47** **48**

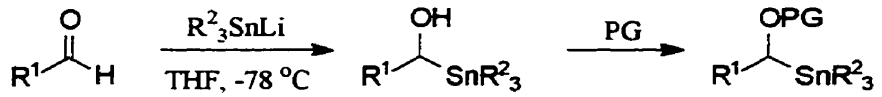
Figure 4. Potential protecting groups for α-alkoxyorganolithiums.

2.2.2 Preparation of O-Protected α-Hydroxystannanes

The preparation of (±)-α-hydroxystannanes for the initial study followed typical literature procedures, these compounds were obtained by the reaction of an aldehyde with either tributyltinlithium (Bu_3SnH/LDA)[3] or trimethyltinlithium (Me_3SnCl/Li[17] or $Me_3SnSnMe_3$/ MeLi[18]). Due to the higher toxicity of Me_3SnCl *vs* Bu_3SnH,[5e] tributylstannyl derivatives were prepared for each type of protecting group, with the exception of **47**, in order to assess and minimize potential problems prior to the preparation of the trimethylstannyl derivatives (Table 2). The MOM derivatives were readily prepared from MOMCl (*i*-Pr_2NEt, CH_2Cl_2) in good yields. The carbamates were prepared either from *i*-Pr_2NCOCl (Et_3N, CH_2Cl_2) or PhNCO (CH_2Cl_2) in low to moderate yields. Attempts to prepare the diethylcarbamates directly from Et_2NCOCl failed; their preparation and use will be discussed later in this Chapter. Efforts to prepare *t*-butylcarbonates under typical conditions [$(BOC)_2O$, DMAP, Et_3N, CH_2Cl_2] initially proved to be very difficult. This protecting group was finally accessed in good yield through the addition of $MgBr_2 \bullet OEt_2$ [$(BOC)_2O$, *i*-Pr_2NEt, CH_2Cl_2] (Table 2).[19]

Overall, each of the desired stannanes, with the exception of the diethylcarbamates, were prepared in sufficient quantity to proceed with the desired study. The transmetalation and trapping of these organostannanes will be discussed in the next section.

Table 2. Preparation of *O*-protected α-hydroxystannanes **49-57**.



49-57

Entry	R^1	R^2	PG	Stannane	Yield[a] (%)
1	*n*-Pent	Me	MOM	**49**	78
2	*n*-Pent	*n*-Bu		**50**	75
3	Me	Me	*i*-Pr_2NCO	**51**	45
4	*i*-Pr	Me		**52**	34
5	*n*-Pent	Me		**53**	34
6	*n*-Pent	*n*-Bu		**54**	36
7	*n*-Pent	Me	PhN(H)CO	**55**	36
8	*n*-Pent	*n*-Bu		**56**	60
9	*n*-Pent	Me	*t*-BOC	**57**	65

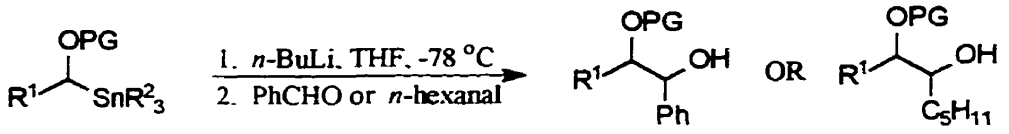
[a] Isolated yields of chromatographically-pure products.

2.2.3 *Transmetalation and Trapping Experiments of O-Protected α-Hydroxystannanes*

Results obtained from the transmetalation and trapping of stannanes **49-57** are presented in Table 3. Initially, the study used two types of electrophiles: PhCHO, an aromatic aldehyde; and *n*-hexanal, an aliphatic enolizable aldehyde. All tin-lithium (Sn-Li) exchanges were carried out with 1.05 equivalents of *n*-BuLi, with the exception of *N*-phenylcarbamates **55** and **56**, which required 2.5 equivalents of *n*-BuLi to generate the dianion intermediates.

Preliminary transmetalation and trapping results obtained from the α-methoxy-methoxy stannanes proceeded as expected. The trimethylstannyl derivative **49** gave mediocre yields (40 and 49%), while the tributylstannyl derivative **50** gave much higher yields (78 and 81%) of the expected adducts, under identical reaction conditions. The trimethylstannyl derivatives of the *N,N*-diisopropylcarbamates **51** and **52**, gave good yields (80 and 93%) when trapped with PhCHO. When *n*-hexanal was employed as the electrophile for the same carbamates, the yields were moderate to good (66 and 74%), which might be a reflection of enolization of the aldehyde. The use of stannanes **53** and **54**, (R^1 = *n*-Pent), resulted in lower then expected yields of product **61**. These results may be explained by problems associated with either the titer of *n*-BuLi or with the purification of the product by column chromatography for these individual experiments. The *N*-phenylcarbamate **55** gave comparable product yields to the *N,N*-diisopropylcarbamates. Transmetalation and trapping of the *t*-butylcarbonate **57** resulted in the complete consumption of the starting material but failed to yield the desired product. This result potentially reflects the difference in electrophilicity between the carbonate and carbamate carbonyl group: attack of the alkyllithium reagent on the carbonate carbonyl is a more favored reaction. Similar results were obtained when either *t*-BuLi or MeLi were employed for the Sn-Li exchange.

Table 3. Transmetalation and trapping of *O*-protected α-hydroxystannanes **49-57**.



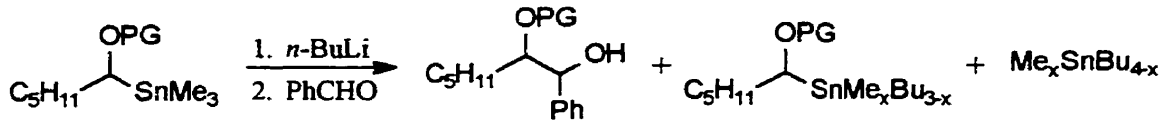
49-57 **58-62** **63-67**

Stannane	PG	R^1	R^2	% yield (**58-62**)	% yield (**63-67**)
49	MOM	*n*-Pent	Me	40 (**58**)	49 (**63**)
50		*n*-Pent	*n*-Bu	78 (**58**)	81 (**63**)
51	*i*-Pr_2NCO	Me	Me	80 (**59**)	66 (**64**)
52		*i*-Pr	Me	93 (**60**)	74 (**65**)
53		*n*-Pent	Me	65 (**61**)	68 (**66**)
54		*n*-Pent	*n*-Bu	56 (**61**)	nd[a]
55	PhN(H)CO	*n*-Pent	Me	77 (**62**)	53 (**67**)
56		*n*-Pent	Bu	87 (**62**)	nd[a]
57	*t*-BOC	*n*-Pent	Me	0	nd[a]

[a] Not determined.

The MOM, *i*-Pr_2NCO and PhN(H)CO protecting groups were further assayed to determine their ability to stabilize the α-alkoxyorganolithiums obtained from Sn-Li exchange. The transmetalation of stannanes **49**, **51** and **55** were performed under various conditions, followed by trapping with PhCHO. The crude reaction mixtures were then analyzed by GCMS. The scrambled organostannane species, $Me_xSnBu_{(4-x)}$ and $C_5H_{11}CH(OPG)SnMe_{(3-x)}Bu_x$, were identified by comparison to standard samples and recorded as the percent area for the corresponding peak (Table 4).

Table 4. Scrambling of organostannane species under various conditions.[a]

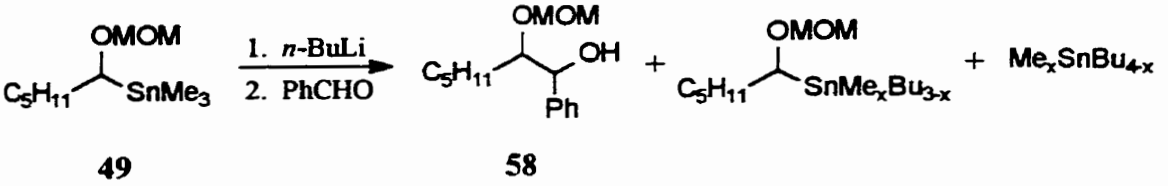


49 PG = MOM **58**
51 PG = *i*-Pr_2NCO **61**
55 PG = PhN(H)CO **62**

Entry (Stannane)	Organostannane Species (% Area)[b,c]						
	Me_2SnBu_2	$MeSnBu_3$	$SnBu_4$	$RSnMe_3$	$RSnMe_2Bu$	$RSnMeBu_2$	$RSnBu_3$
1 (**49**)	13.7	8.5	1.7	16.3	8.7	4.1	0.5
2 (**49**)[d]	11.5	5.4	1.3	13.7	15.1	5.8	0.5
3 (**49**)[e]	10.1	2.8	0.7	13.6	16.6	6.3	1.0
4 (**49**)[f]				36.2			
5 (**51**)	1.4	0	0	13.2	0.6	0	0
6 (**55**)[g]	31.7	23.5	4.6	1.4	0	0	0

[a] Transmetalations were performed in THF with 1.05 equiv of *n*-BuLi at –78 °C for 15 minutes, unless otherwise noted.
[b] Determined by GCMS analysis of the crude reaction mixtures.
[c] Where R ≡ $C_5H_{11}C(H)OPG$.
[d] Time of Sn-Li exchange was 120 minutes.
[e] Transmetalation performed at –95 °C for 3 minutes.
[f] MeLi was used for transmetalation.
[g] Stannane was treated initially with 1.05 equiv of NaH at 0 °C for 15 minutes.

When the transmetalation of stannane **49** was performed using the MOM protecting group (Table 4, entry 1, see Figure 5), the desired adduct **58** was obtained as a 1:1 mixture of diastereomers. Also present in the product mixture was a considerable amount of organostannane **49** as well as scrambled derivatives of **49** where the trialkyltin moiety contained butyl groups (i.e. $C_5H_{11}CH(OMOM)SnMe_xBu_{(3-x)}$, x = 0,1,2). It is also worth noting the presence of 1-phenylethanol, which was formed from MeLi addition to PhCHO. The presence of three distinct $Me_xSnBu_{(4-x)}$ species may have arisen from scrambling due to *n*-BuLi present in solution (Figure 6).



49 **58**

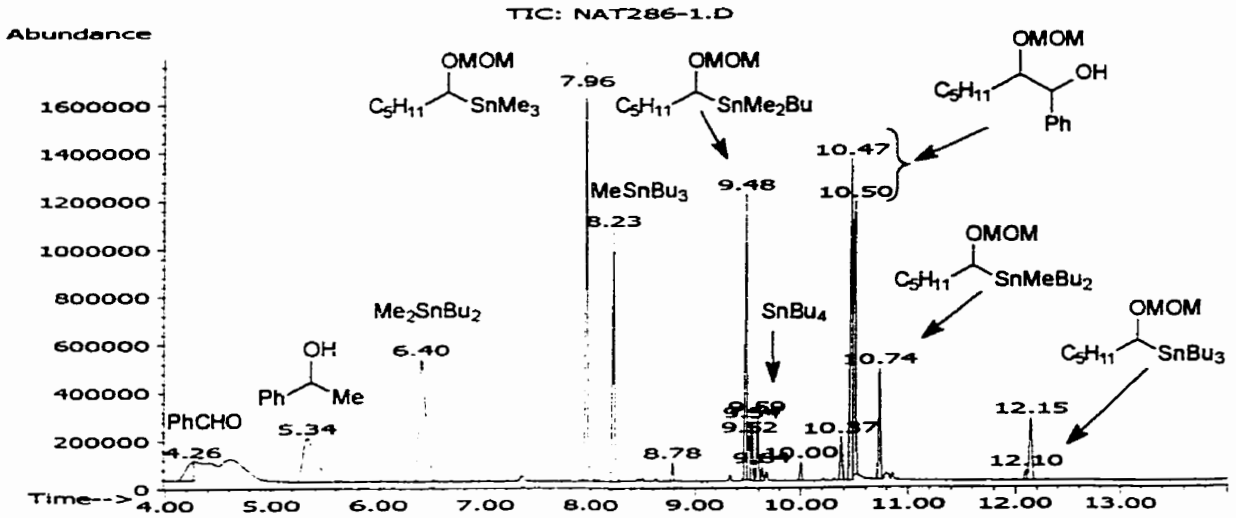


Figure 5. GCMS analysis: Transmetalation and trapping of organostannane **49**.

$$Me_3SnBu + n\text{-BuLi} \rightleftharpoons Me_2SnBu_2 + MeLi$$

$$Me_2SnBu_2 + n\text{-BuLi} \rightleftharpoons MeSnBu_3 + MeLi$$

$$MeSnBu_3 + n\text{-BuLi} \rightleftharpoons SnBu_4 + MeLi$$

Figure 6. Scrambling of $Me_xSnBu_{(4-x)}$ species in the presence of *n*-BuLi.

These results suggested that the formation of the expected α-alkoxyorganolithium **68** and methyllithium was a competitive process; therefore, these species must be comparable in stability as represented in Figure 7. The presence of *n*-BuLi leads to further scrambling of the trialkyltin moiety within $C_5H_{11}CH(OMOM)SnMe_xBu_{(3-x)}$, generating additional MeLi.

This initial experiment was performed under typical conditions for a transmetalation and trapping sequence (-78°C, 15 min, Table 4, entry 1). To gain further insight into the rate of the Sn-Li exchange and the relative equilibrium of the various species, reactions were performed at -78°C for 120 minutes and at -95°C for 3 minutes (entries 2 and 3, Table 4). The results obtained were almost identical to those of entry 1 (-78°C for 15 min) and suggest that the rate of the Sn-Li exchange of stannane **49** is very rapid. The equilibrium between the various $Me_xSnBu_{(4-x)}$ and $C_5H_{11}CH(OMOM)SnMe_{(3-x)}Bu_x$ species is established in less than 3 minutes at -95°C.

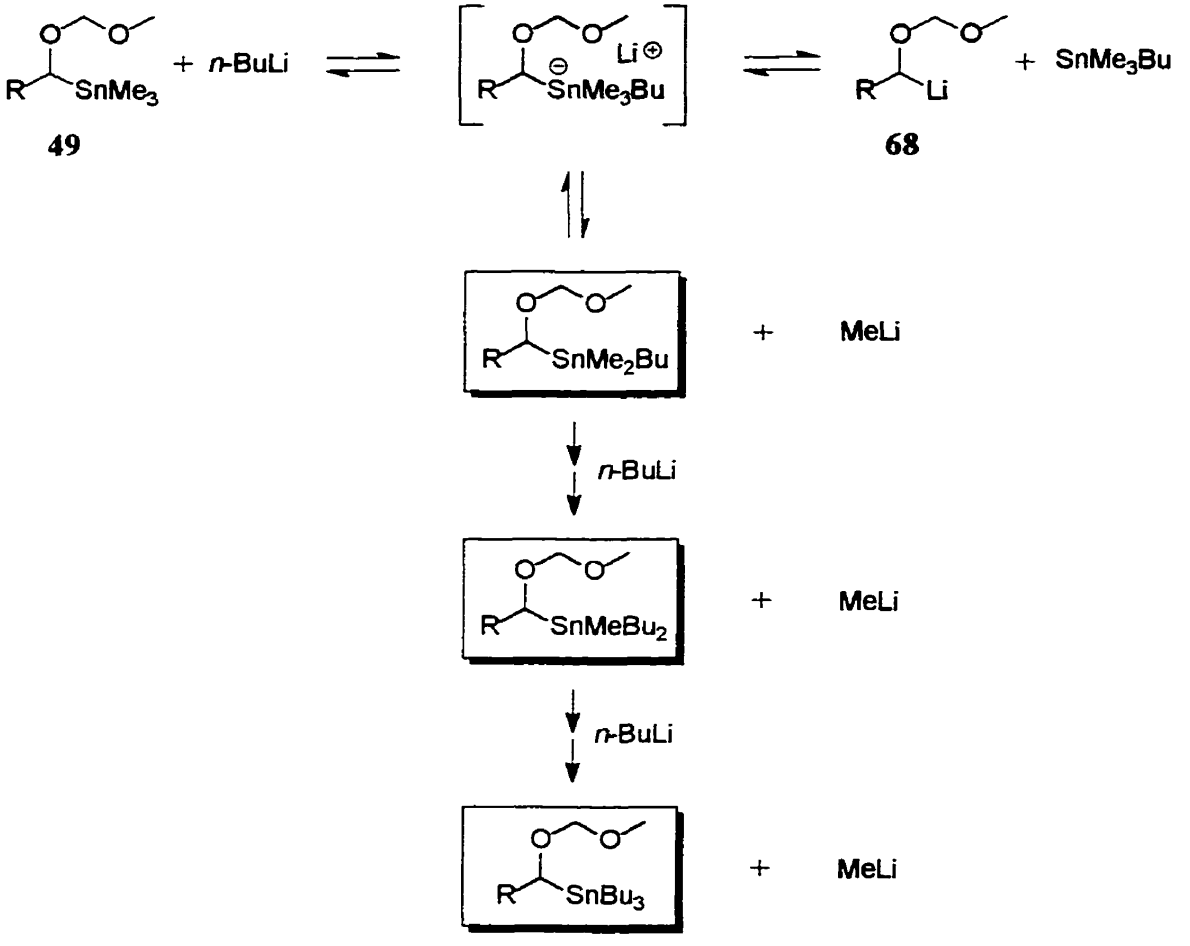
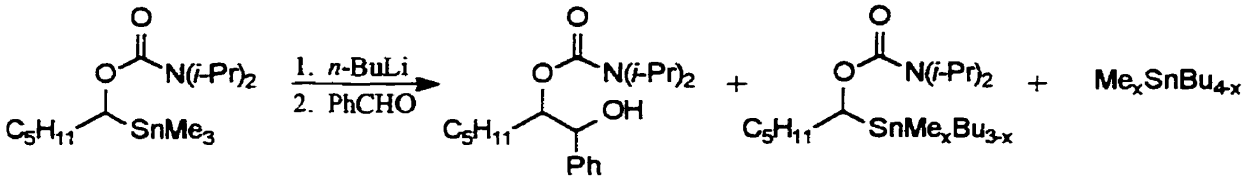


Figure 7. Mechanistic rationale: Scrambling of $C_5H_{11}CH(OMOM)SnMe_xBu_{(3-x)}$.

The substitution of the *i*-Pr_2NCO protecting group in place of the MOM group gave very different results (Table 4, entry 5, see Figure 8). Only a single scrambled-derivative of stannane **51** was detected where one methyl group was exchanged for a single butyl group. Again the desired adduct **61** was present; however, no 1-phenylethanol was detected by GCMS. The stabilization offered by the *i*-Pr_2NCO protecting group is evidently superior to that of the MOM group for the transmetalation of trimethylalkylorganostannanes. Therefore, the derived organolithium **69** is more stable than MeLi and is preferentially formed, resulting in higher yields of intermediate **69** available for electrophilic trapping (Figure 9).



51 **61**

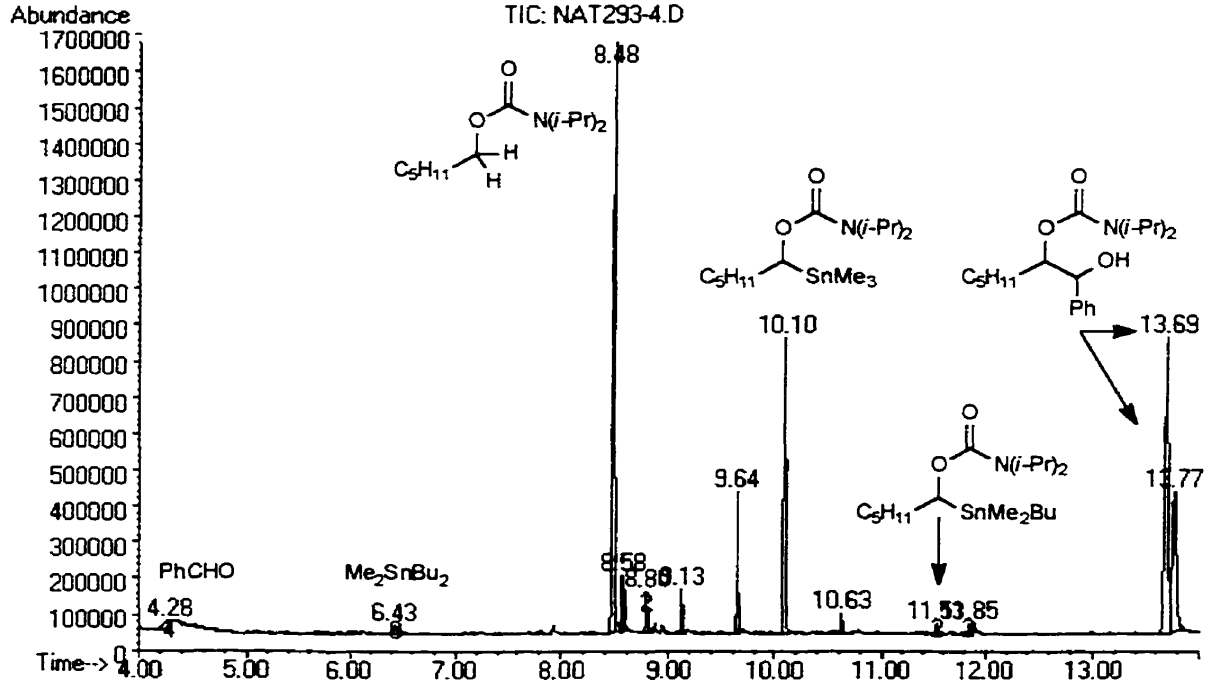


Figure 8. GCMS analysis: Transmetalation and trapping of organostannane **51**.

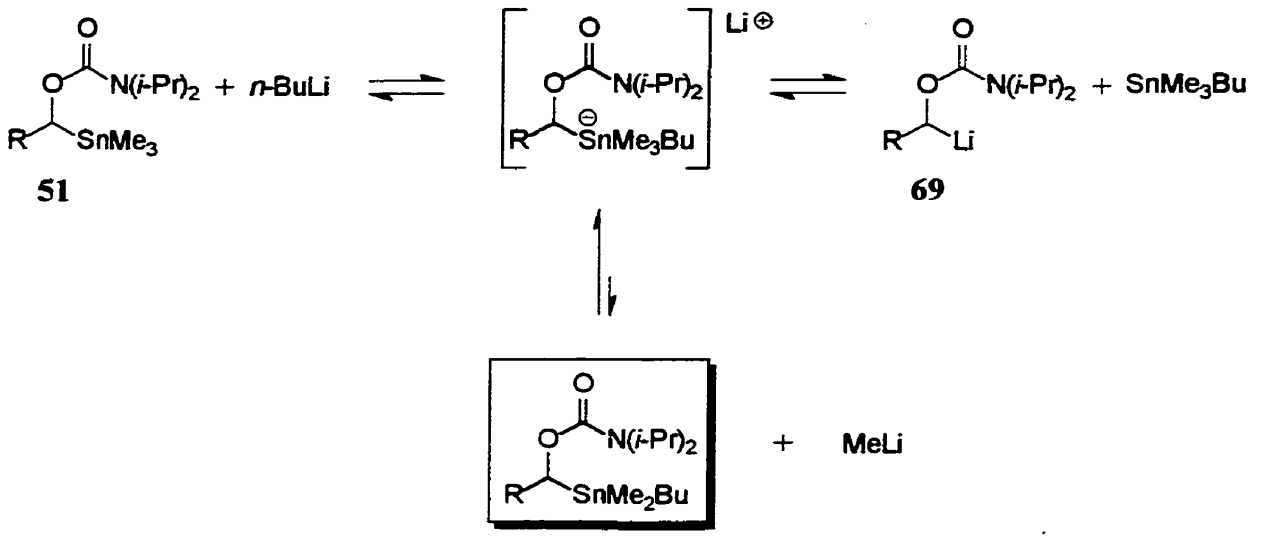


Figure 9. Mechanistic rationale: Scrambling of $C_5H_{11}CH[OC(O)N(i\text{-}Pr)_2]SnMe_xBu_{(3-x)}$.

The PhN(H)CO protecting group also gave surprisingly good results (Table 4, entry 6). Only trace amounts of starting material **55** were detected by GCMS analysis, and there was no evidence for scrambling of the trialkyltin moiety. Employing the dianion approach to assist in stabilizing the intermediate α-alkoxyorganolithium proved to be very successful.

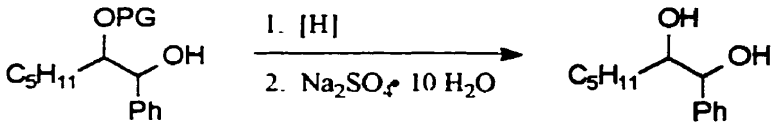
The i-Pr_2NCO and PhN(H)CO protecting groups gave very good results from this study as reflected by the yields of the protected diols. To obtain the free 1,2-diols from these products, the removal of the protecting groups was next investigated.

2.2.4 Reduction of Carbamate Protecting Groups

To determine conditions for the removal of the i-Pr_2NCO and PhN(H)CO protecting groups, compounds **61** and **62** were selected and treated with a selection of reagents. The *N,N*-diisopropylcarbamate group was removed with the use of AlH_3 (2 equiv, Table 5).[20] This same reaction was extremely slow when $LiAlH_4$ was employed as an alternative to AlH_3. By thin-layer chromatography (TLC) analysis the reaction never proceeded beyond 50% completion when performed in Et_2O (rt, 12 h). Other reagents such as $LiEt_3BH$ or

$Me_2S{\bullet}BH_3$ (THF, rt, 12 h) gave no reaction as indicated by TLC analysis. The *N*-phenylcarbamate group, on the other hand, was easily removed with $LiAlH_4$.[21] This protecting group was resistant to hydrolysis (1M HCl or NaOH) and to hydrolytic cleavage with LiOOH (THF/H_2O, 3:1). In summary, both protecting groups could be easily removed, affording the free diol products in high yields.

Table 5. Reduction of carbamate protecting groups.



61-62 **70**

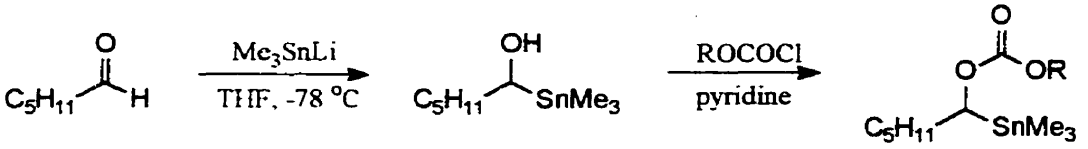
Protected Diol	PG	Reagent/ Conditions	Time (min)	Yield of **70** (%)
61	$(i\text{-Pr})_2NCO$	AlH_3, THF, rt	10	86
62	PhN(H)CO	LAH, THF, rt	10	64
62	PhN(H)CO	LAH, Et_2O, Δ	120	83

The *N,N*-diisopropylcarbamate protecting group was very effective for the transmetalation of trimethylalkylorganostannanes (yields as high as 93%), but unfortunately, the protected stannanes (**51-54**) could only be prepared in mediocre yields (<45%). Therefore, a significant effort was undertaken to improve the yields of these precursor stannanes; the results of these efforts will be presented in the following section.

2.2.5 *Attempts to Access Improved Yields of N,N-Diisopropylcarbamate Protected α-Hydroxystannanes*

Preliminary efforts focused on the synthesis of carbonate-protected analogues of α-hydroxystannanes as intermediates to the desired carbamates. These carbonates would contain stabilized alkoxy-leaving groups that might facilitate displacement with $(i\text{-Pr})_2NH$ or lithium diisopropylamide (LDA). Thus, initial studies employed carbonates of 1-trimethylstannylhexanols (Table 6, **71-73**), which were obtained from the reaction of the respective chloroformate and the α-hydroxystannane in pyridine.

Table 6. Preparation of trimethylstannyl carbonates **71-73**.



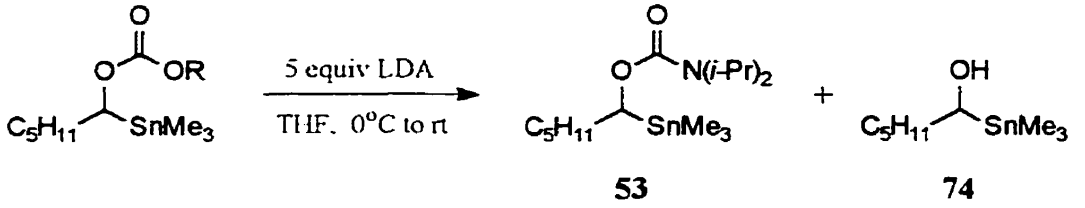
71-73

R	Carbonate	Yield of Carbonate (%)
Cl_3C	**71**	51
Ph	**72**	84
$p\text{-}NO_2C_6H_4$	**73**	86

Direct attempts to displace the alkoxide leaving group (i.e. Cl_3CO, PhO and $p\text{-}NO_2C_6H_4O$) from carbonates **71-73** with $(i\text{-Pr})_2NH$ (DMAP, pyridine, rt) failed. In each example, the reactant stannane was re-isolated from the reaction mixture after work-up. Efforts to perform the displacement with $(i\text{-Pr})_2NH$ in the presence of Na_2CO_3,[22] using EtOH at reflux, also failed to generate the desired carbamate. This substitution was also attempted using the more nucleophilic LDA (1.0 equiv, THF, 0°C). In all trials, no reactivity of the amine as a nucleophile was observed at 0°C. Only after the addition of 5 equivalents of LDA followed by warming to room temperature was there evidence of displacement, as monitored

by TLC analysis alongside authentic material. When R = Cl_3C or *p*-$NO_2C_6H_4$, the starting material was consumed but none of the expected product was obtained. When R = Ph, a 2:1 ratio of **53** and **74** was obtained as determined by ^1H NMR analysis of the crude reaction mixture (Scheme 34). This very modest chemoselectivity gave a 37% yield of **53**.

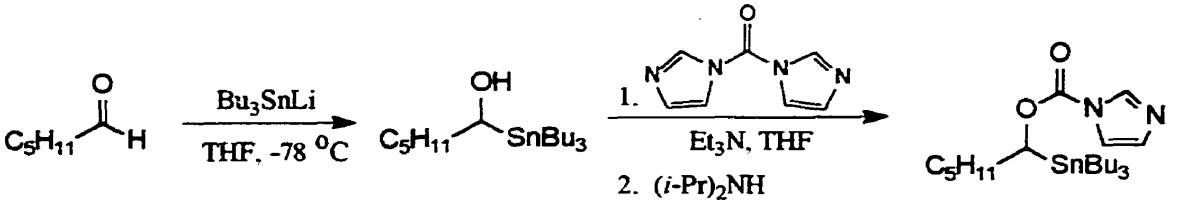
Scheme 34



53 **74**

The next approach towards the preparation of *N,N*-diisopropylcarbamates involved the *in situ* activation of the α-hydroxystannane using 1,1′-carbonyldiimidazole (THF, Et_3N, rt) (Scheme 35). After complete derivatization to carbamate **75**, $(i\text{-Pr})_2NH$ would then be added to perform the displacement and liberate imidazole. Derivatization of the α-hydroxystannane using 1,1′-carbonyldiimidazole was complete within 3 hours. The addition of $(i\text{-Pr})_2NH$ gave none of the desired adduct after 4 hours at room temperature. Further warming to reflux for a period of 12 hours resulted in no change in the reaction mixture by TLC. Addition of *N*-butylamine to the reaction, followed by an additional 18 hours of stirring at room temperature provided none of the corresponding *N*-butylcarbamate. Only carbamate **75** was isolated by column chromatography and characterized by ^1H NMR analysis. It appears that the imidazole-derived carbamate **75** is quite stable to nucleophilic attack, even in the presence of a primary amine; this lack of reactivity may be due to the steric hindrance surrounding the carbonyl, which prevents approach of nucleophiles and thus displacement of imidazole (Scheme 35).

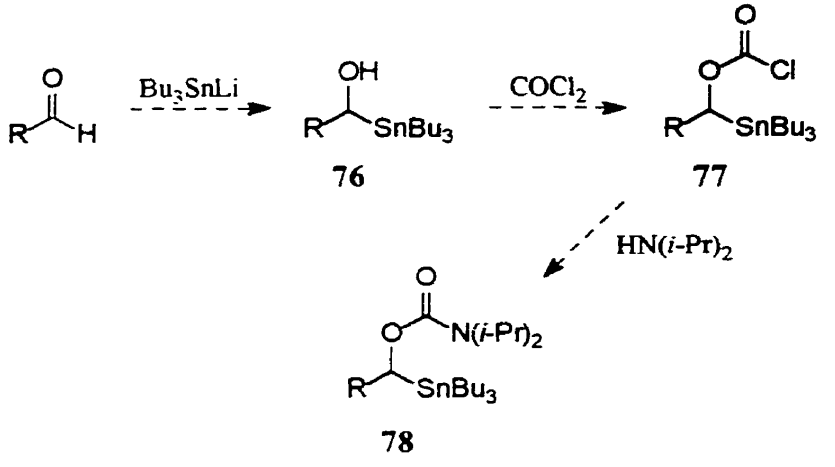
Scheme 35



75

Still and Sreekumar have reported the optical resolution of 1-tributylstannyl-1-propanol via the formation of a urethane with (-)-(α)-phenylethylamine [1. $COCl_2$, *i*-Pr_2NEt; 2. (-)-$PhCH(CH_3)NH_2$].[3,23] In light of this report, the preparation of (1-tributylstannyl)hexyl-1-chloroformate (77) was investigated as an intermediate for the synthesis of *N,N*-diisopropyl carbamates. We envisioned the plan illustrated in Scheme 36.

Scheme 36



76 **77**

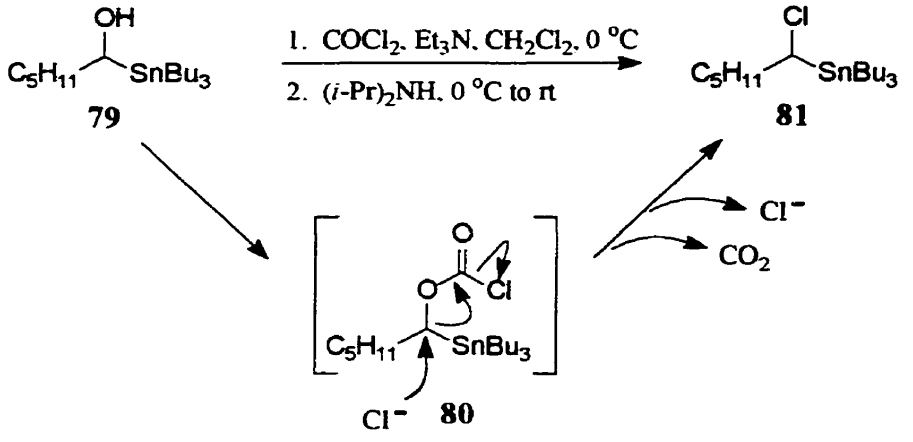
78

Thus, *in situ* preparation of the chloroformate 77 followed by the addition of (*i*-$Pr)_2NH$ should afford carbamate **78**. The reaction of α-hydroxystannane **79** with $COCl_2$ (Et_3N, CH_2Cl_2, 0°C) produced a light yellow solution after 30 minutes. Addition of (*i*-$Pr)_2NH$ followed by warming to room temperature, yielded one major product with a higher R_f value than the anticipated product. Column chromatography yielded a colorless oil, which was identified as 1-chloro-1-tributylstannyl hexane (**81**) by GCMS [M^+-(C_4H_9 + Cl^-) = 317], ^1H NMR (doublet of doublets at δ 3.70 for the methine proton) and ^{13}C NMR

(peak at δ 48.53 for the tertiary carbon) (Scheme 37). The chlorostannane **81** may arise by S_N2 attack of Cl^- on the intermediate chloroformate **80** as shown in Scheme 37.

Performing the addition of $COCl_2$ at –78°C (pyridine, CH_2Cl_2 or Et_2O) followed after 30 minutes by the addition of $(i\text{-Pr})_2NH$ in an effort to inhibit nucleophilic attack of the counter ion on chloroformate **80** was also unsuccessful, giving rise to chlorostannane **81**. Similar results were obtained using either LDA (THF, –78°C) or *N*-butylamine (Et_2O, –78°C). Hence, it appears that reaction of Cl^- with chloroformate **80** is very fast, and this route does not allow access to the desired carbamate **78**. This result is contrary to the findings obtained by Still and Sreekumar.

Scheme 37

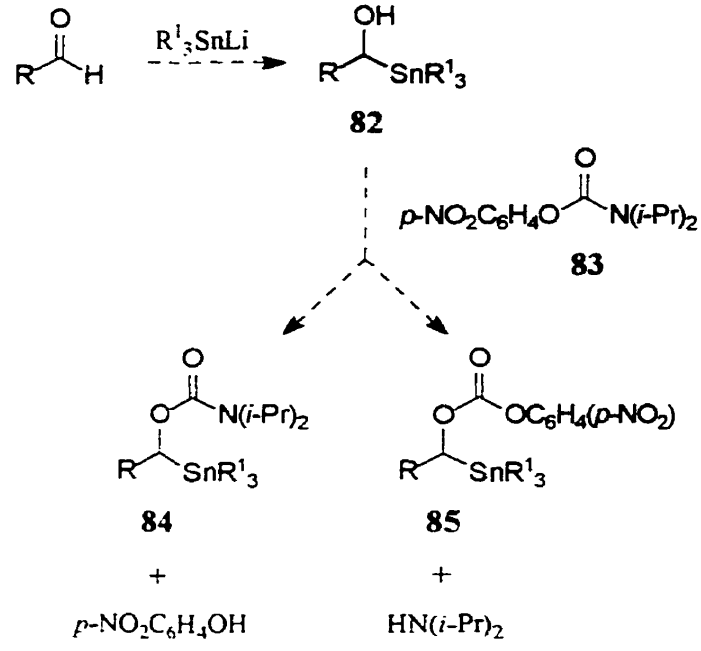


The lack of success that had been obtained with carbonate substrates **71-73** and combination with amine nucleophiles prompted us to reinvestigate methods that would employ the α-hydroxystannane as a nucleophile. The *N,N*-diisopropylcarbamates **51-54** had been prepared through the reaction of $(i\text{-Pr})_2NCOCl$ with the corresponding α-hydroxy-stannane (Table 2). Therefore, we speculated that an alternative derivative of $(i\text{-Pr})_2NCOX$, where X represented some type of leaving group, might offer superior yields of the desired carbamates. For this purpose *N,N*-diisopropyl-4-nitrophenylcarbamate (**83**) was prepared,[24] where $X = p\text{-}NO_2C_6H_4O^-$. Scheme 38 shows two alternate pathways for the derivatization of

the α-hydroxystannane **82**, where either the desired carbamate **84** is formed, displacing *p*-$NO_2C_6H_4O^-$, or the carbonate **85** is formed, eliminating $(i\text{-Pr})_2N^-$. Due to the differences in pKa values for $(i\text{-Pr})_2NH$ and *p*-$NO_2C_6H_4OH$ (36 *vs* 7), preferential formation of carbamate **84** should occur, as *p*-$NO_2C_6H_4O^-$ should be the better leaving group.

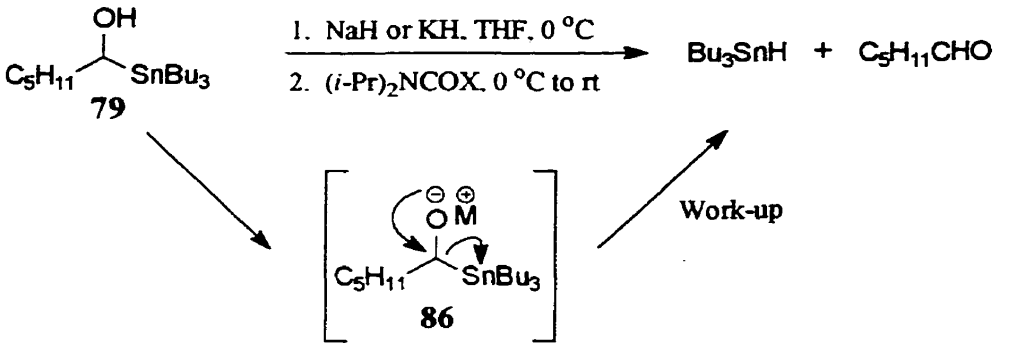
Our attempts to pursue this method ended abruptly as no reactivity was observed between the α-hydroxystannane and *N,N*-diisopropyl-4-nitrophenylcarbamate (pyridine or DMAP, Et_3N, CH_2Cl_2, rt).

Scheme 38



As a final effort to prepare these carbamates, the α-hydroxystannane was treated with a metal hydride reagent to generate the respective metal alkoxide. This intermediate should offer superior nucleophilicity towards derivatization with $(i\text{-Pr})_2NCOX$ type reagents. Treatment of α-hydroxystannane **79** with either NaH or KH (THF, 0°C) followed by the addition of $(i\text{-Pr})_2NCOX$ (where X = Cl or *p*-$NO_2C_6H_4O$), and then warming to room temperature gave none of the desired product (Scheme 39).

Scheme 39



TLC analysis of the reaction mixture indicated complete consumption of alcohol **79**, with the generation of a spot at the solvent front. Analysis of the reaction by GCMS revealed the generation of Bu_3SnH. Therefore, it seems that attempts to generate a hard anion, for increased nucleophilicity, are thwarted by the instability of these metal alkoxides (**86**), which undergo loss of Bu_3SnM to provide Bu_3SnH and the free aldehyde after work-up.[25]

Although the results from our efforts to improve the synthetic yields of *N,N*-diisopropylcarbamates had been discouraging, the option of pursuing an alternative dialkylcarbamate was available. The next section details the preparation of *N,N*-diethyl-carbamates.

2.2.6 Preparation of N,N-Diethylcarbamate Protected α-Hydroxystannanes

Initial attempts to prepare *N,N*-diethylcarbamates of α-hydroxystannanes directly from Et_2NCOCl had failed. This result was puzzling because the diisopropyl derivative had been accessible through the use of $(i\text{-Pr})_2NCOCl$, which is presumably the more sterically hindered reagent of the two chloroformates. In spite of the lack of success in preparing *N,N*-diisopropylcarbamates from carbonates **71-73** and $(i\text{-Pr})_2NH$, this method was once again attempted using Et_2NH. The smaller alkyl chains (Et *vs* *i*-Pr) should cause less shielding of the nitrogen lone pair. Consequently, it was expected that this secondary amine should be more reactive towards addition to carbonate-carbonyls and ultimately lead to substitution.

Preparation of the desired *p*-nitrophenylcarbonate **87** was facile, but purification by column chromatography gave evidence of decomposition of the product on silica gel (Scheme 40). Sufficiently pure carbonate was obtained by flash chromatography on silica gel and treated with neat Et_2NH. Within minutes, yellow, solid (p-$NO_2C_6H_4O^-{}^+NH_2Et_2$) was liberated in the reaction. The desired *N,N*-diethylcarbamate **93** was isolated from the reaction in a 73% yield. To circumvent decomposition of the *p*-nitrophenylcarbonate precursor, α-hydroxystannane **79** was derivatized completely to carbonate **87** in pyridine as solvent and then treated *in situ* with a 5-fold excess of Et_2NH. This one-pot synthesis produced the *N,N*-diethylcarbamates in much higher yields (Table 7).

Scheme 40

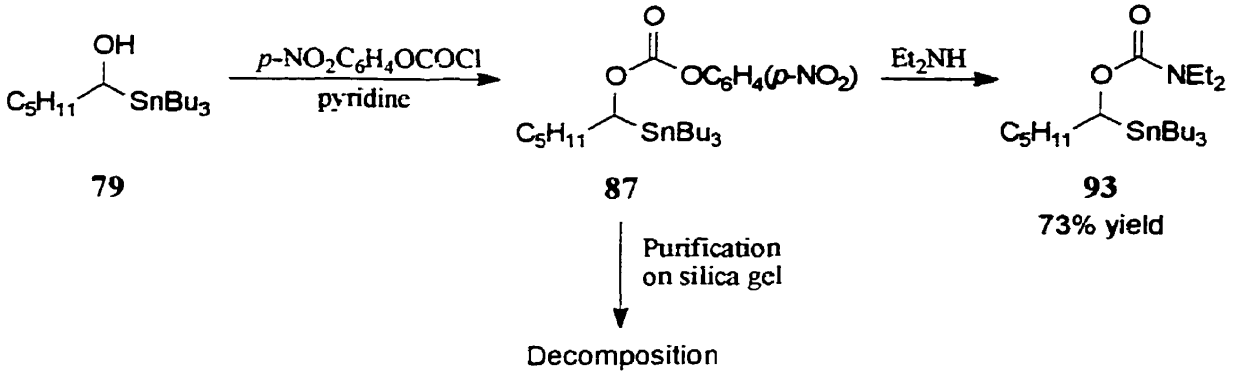
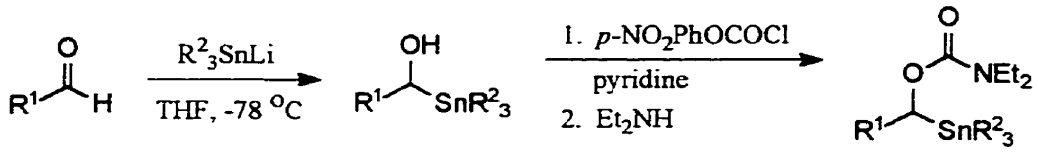


Table 7. Preparation of *N,N*-diethylcarbamate-*O*-protected α-hydroxystannanes **88-94**.



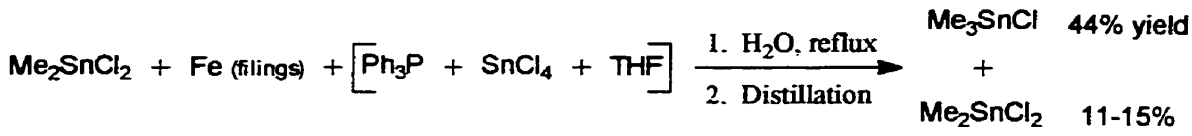
88-94

Entry	R^1	R^2	Stannane	Yield[a] (%)
1	Me	Me	**88**	74
2	*n*-Pent		**89**	57
3	*i*-Pr		**90**	80[b]
4	*c*-Hex		**91**	83[b]
5	Me	*n*-Bu	**92**	35
6	*n*-Pent		**93**	73
7	*i*-Pr		**94**	59

[a] Isolated yields of chromatographically-pure products.
[b] Me_3SnLi generated from $(Me_3Sn)_2$ and MeLi.

This method of preparing *N,N*-diethylcarbamates allowed access to these stannanes in higher yields than the analogous *N,N*-diisopropyl systems. Higher yields of the trimethylstannanes were observed when Me_3SnLi was generated from $(Me_3Sn)_2$ and MeLi (entries 3 and 4, Table 7). This result is in part due to the superior generation of Me_3SnLi by this method as compared to its generation from Me_3SnCl and Li. Typically, Me_3SnCl was prepared as described by Lipshutz and Reuter[26] from the relatively inexpensive Me_2SnCl_2 ($15.50/g,[27] Scheme 41). However, even after multiple fractional distillations, the desired product was always contaminated with approximately 11-15% of the starting Me_2SnCl_2. Alternatively, commercially available $(Me_3Sn)_2$ ($38.70/g)[27] can be distilled prior to use to achieve higher levels of purity and results in a near quantitative generation of Me_3SnLi when treated with MeLi at -20°C (15 min).[18] The next section describes the initial transmetalation and trapping of stannane **93**.

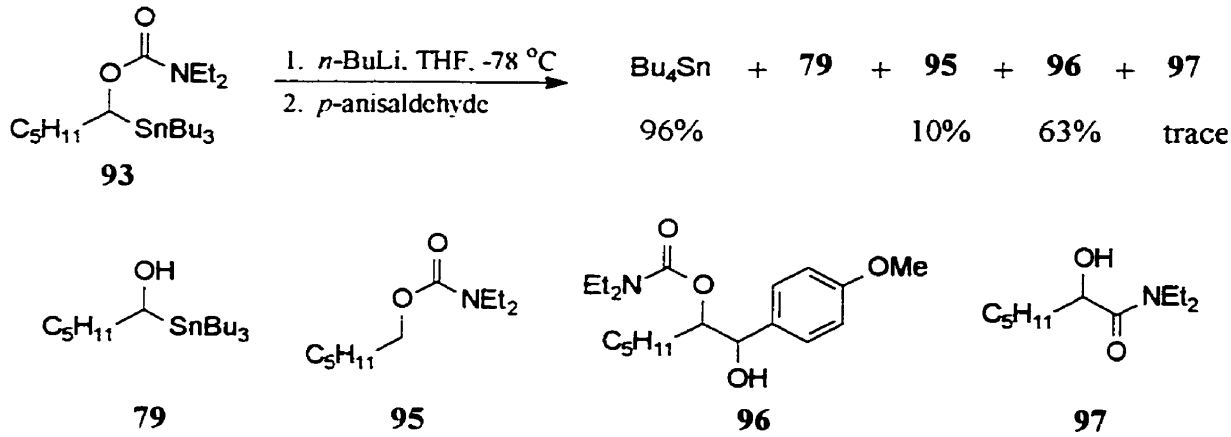
Scheme 41



2.2.7 Transmetalation of N,N-Diethylcarbamate Protected α-Hydroxystannanes

The transmetalation of *N,N*-diethylcarbamate protected α-hydroxystannanes had not been previously attempted in our laboratory. As such, many elements of the chemistry were unknown: the rate of transmetalation, the stability of the derived α-alkoxyorganolithiums, the possibility of 1,2-carbamoyl migration of the *N,N*-diethylcarbamate protecting group, and the susceptibility of the carbamate group towards nucleophilic attack by alkyllithium reagents. As an initial trial, stannane **93** was sequentially treated with *n*-BuLi and *p*-anisaldehyde (Scheme 42).

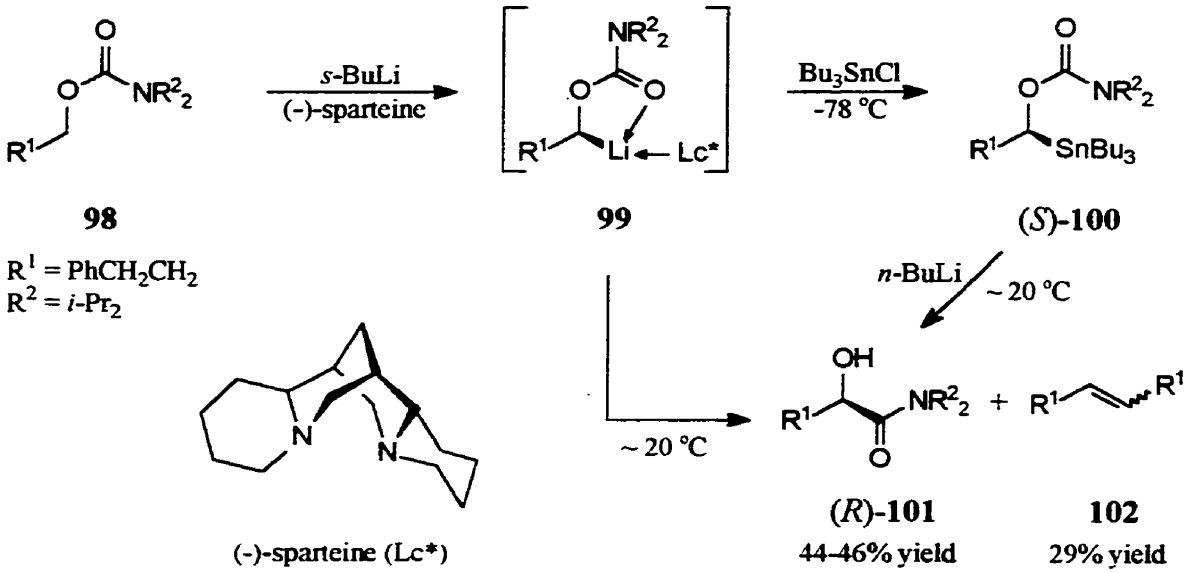
Scheme 42



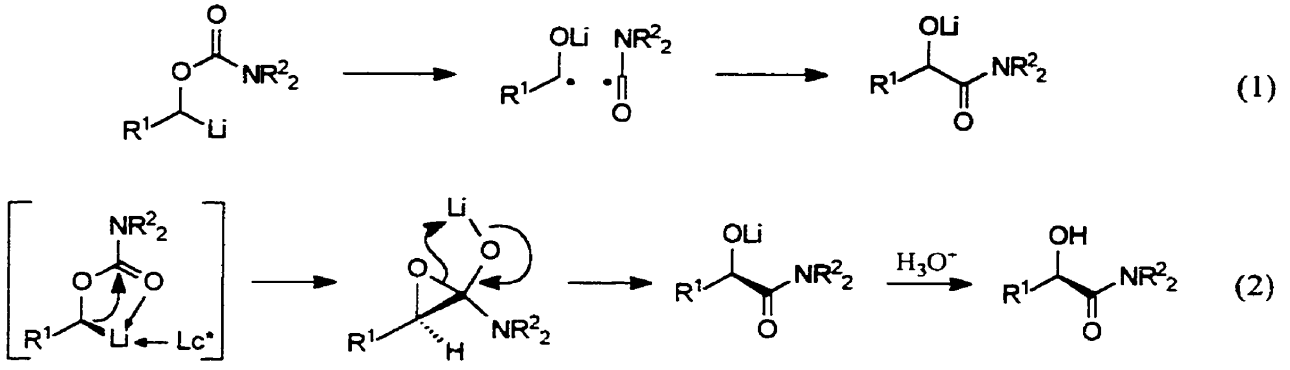
The Sn-Li exchange was almost quantitative (96% isolated yield of Bu_4Sn). However, the trapped adduct **96** was only obtained in 63% yield. TLC analysis of the reaction mixture gave evidence that stannane **93** had undergone nucleophilic attack by the *n*-BuLi reagent. This was evident from the presence of α-hydroxystannane **79** by TLC, resulting from attack and loss of the *N,N*-diethylamide protecting group. Trace amounts of the very polar 1,2-carbamoyl migration product **97** were also isolated by column chromatography.

The 1,2-carbamoyl migration of α-lithiated alkyl, allylic and benzylic carbamates have been reported in the literature.[23,28] Nakai and co-workers[28c] have examined the 1,2-carbamoyl migration of enantiomerically enriched α-lithioalkyl carbamate **99** generated from the enantioselective deprotonation of **98** with *s*-butyllithium/sparteine (Scheme 43). Their findings have provided mechanistic evidence for the migration pathway. When intermediate **99** was trapped with Bu_3SnCl (-78°C), stannane (*S*)-**100** was obtained in 97% ee. Since the stannylation is known to proceed with retention of configuration,[29] the lithio species **99** must have the (*S*)-configuration. When (*S*)-**99** was generated in the same manner (-78°C) and gradually warmed to room temperature, the (*R*)-α-hydroxy amide **101** was isolated in 46% yield and 96% ee, as well as the olefin **102** (29%) as an *E/Z* mixture (*E/Z* = 86/14). Alternatively, when stannane (*S*)-**100** (>95% ee) was transmetalated with *n*-BuLi (THF, -78°C) in the absence of sparteine and allowed to warm to room temperature, (*R*)-**101** was obtained in 44% and >95% ee. Therefore, the 1,2-carbamoyl migration actually occurs with retention of configuration, thus ruling out a radical cleavage-recombination mechanism (equation 1, Scheme 44). An addition-elimination mechanism in which the intramolecular addition of the Li-bearing carbon to the carbamoyl-carbonyl occurs with retention of configuration was proposed by Nakai (equation 2, Scheme 44).[30]

Scheme 43[28c]

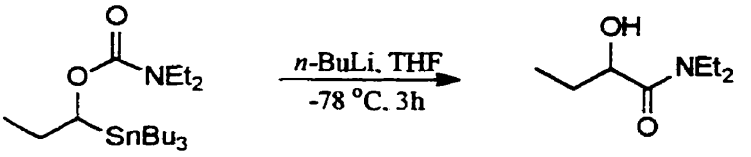


Scheme 44[28c]



Gawley and Zhang have documented the 1,2-carbamoyl migration of *N,N*-diethyl-carbamate **103**. Tin-lithium exchange of **103** with *n*-BuLi (-78°C) resulted in a 70% yield of the α-hydroxy amide **104** after 3 hours (Scheme 45).[23]

Scheme 45[23]



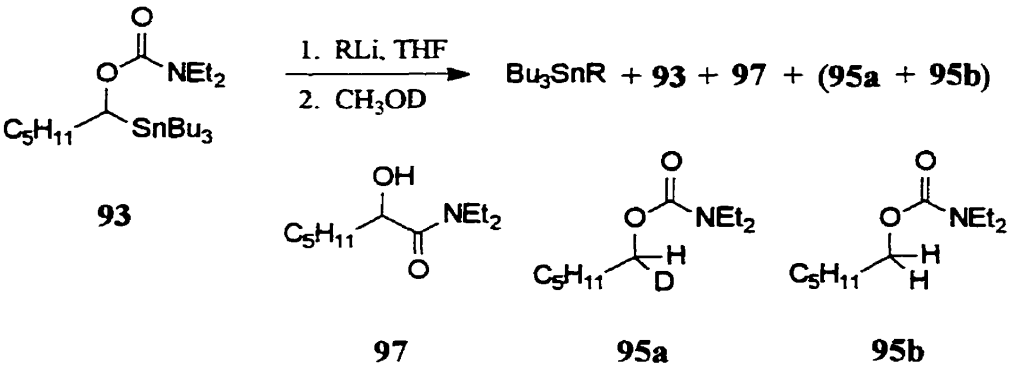
103 **104**
70% yield

In order to develop conditions for the transmetalation of the *N,N*-diethylcarbamates that would circumvent problems such as 1,2-carbamoyl migration and attack of the alkyllithium on the carbamoyl-carbonyl, stannane **93** was treated under varying reaction conditions, which included: choice of alkyllithium, varied reaction temperature, and time of tin-lithium exchange (Table 8). The α-alkoxyorganolithium intermediate obtained from these trials was quenched using CH_3OD. The use of CH_3OD was found to be useful as a means of examining for extraneous proton sources. The level of deuterium incorporation was approximately assessed by ^1H NMR analysis of the product **95**.

From entry 1 of Table 8, it's evident that transmetalation under typical conditions (*n*-BuLi, -78°C, 15 min) gave almost quantitative Sn-Li exchange. The 63% yield of the expected product was in agreement with previous results (Scheme 42). A 9% yield of the 1,2-migration product **97** confirmed the unstable nature of the α-alkoxyorganolithium species. This instability became more evident when the Sn-Li exchange was allowed to proceed for 120 minutes (-78°C, entry 2) A 41% yield of **97** was isolated along with an 18% yield of adduct **95**. Decreasing the Sn-Li exchange time to 2 minutes gave an incomplete exchange (85% complete, entry 3) Isolation of **97** in 23% yield indicated that the α-alkoxy-organolithium derived from **93** can undergo migration very rapidly at –78°C. This result seemed contradictory to entry 1 (9% of **97** after 15 min), but may be due to isolation problems by chromatography because of its high polarity. Also obtained from this trial was an approximate 2% yield of both $C_5H_{11}CH(OH)SnBu_3$ and $C_4H_9CONEt_2$, which gave evidence that the *N,N*-diethylcarbamate protecting group was being attacked by the alkyllithium reagent. This reaction was not observed when the more sterically hindered *N,N*-

diisopropylcarbamate protecting group had been employed. An attempt to prevent 1,2-migration by using a lower temperature (-95°C, 5 min, entry 4) was successful.

Table 8. Conditions for the transmetalation of *N,N*-diethylcarbamate **93**.[a]



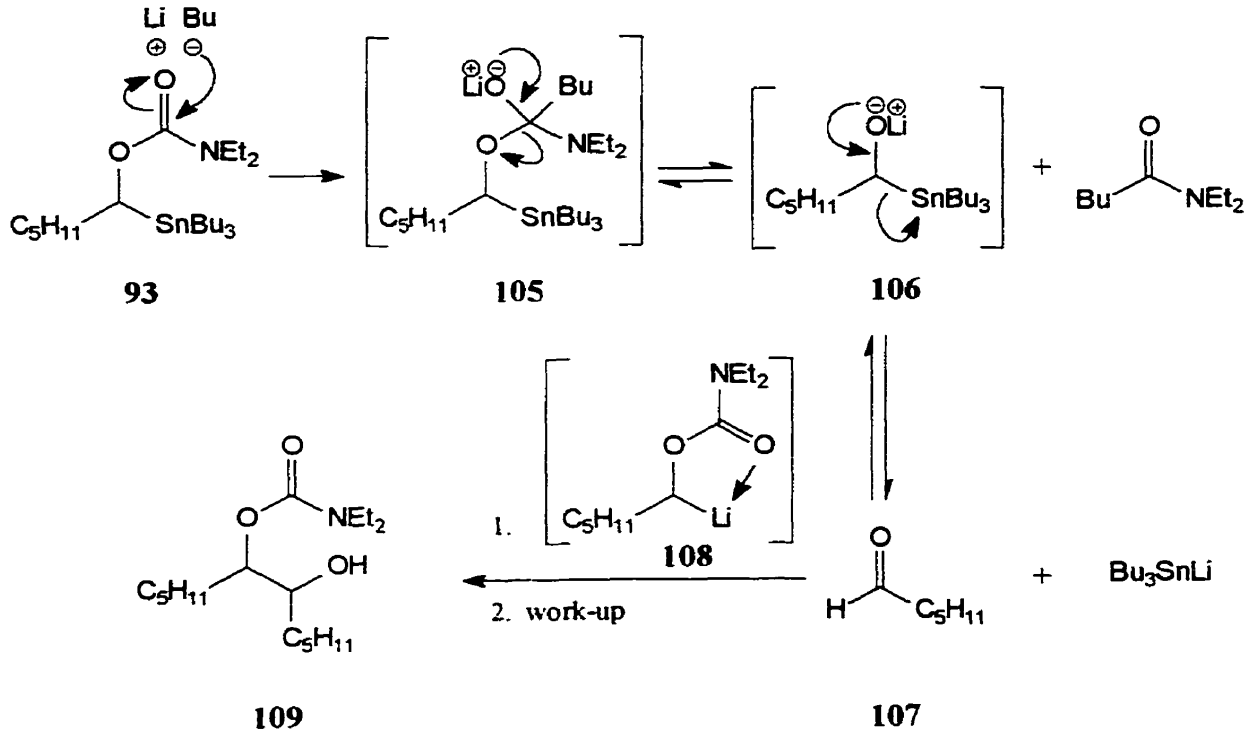
93 **97** **95a** **95b**

Entry	RLi	Temp (°C)	Time (min)	Bu_3SnR (%)	**93** (%)	**97** (%)	**95a** + **95b** (%)
1	*n*-Bu	-78	15	96	0	9	63
2	*n*-Bu	-78	120	96	2	41	18
3[b]	*n*-Bu	-78	2	85	12	23	60
4[b]	*n*-Bu	-95	5	75	14	0	69
5	*s*-Bu	-95	15	96	0	0	64
6	*t*-Bu	-95	15	63	20	0	59

[a] Results are based on the mass recovery of the individual species obtained after column chromatography.
[b] Approximately 2% each of $C_5H_{11}CH(OH)SnBu_3$ and $C_4H_9CONEt_2$ were isolated.

None of the 1,2-migration product **97** was isolated. As expected the Sn-Li exchange was slower at the reduced temperature, and attack by *n*-BuLi was still evident. Interestingly, compound **109** was isolated from the reaction mixture and its structure confirmed by ^1H NMR when compared to a standard sample. This compound may arise by the pathway outlined in Scheme 46. Attack of *n*-BuLi on the carbamate carbonyl of **93** generates α-alkoxystannane **105**, which can undergo retro-addition to liberate alkoxide **106**. Elimination of Bu_3SnLi, generates hexanal (**107**) which may be trapped by intermediate **108**, to generate adduct **109** (Scheme 46).

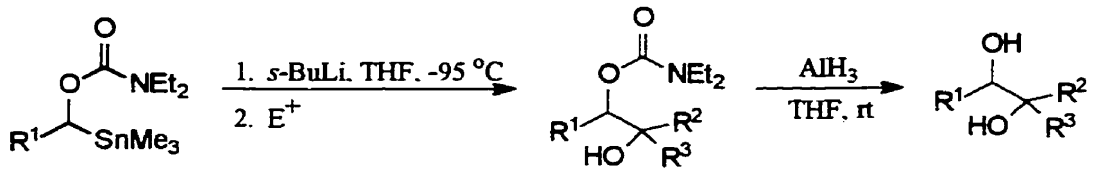
Scheme 46



Entries 5 and 6 (Table 8), display the outcome when *s*-BuLi and *t*-BuLi, two more sterically hindered alkyllithiums, were employed. These reaction conditions did not give the products resulting from attack of alkyllithium on the protecting group. The best conditions for the transmetalation of *N,N*-diethylcarbamates were determined to be as follows: *s*-BuLi, THF, –95°C, 15 min.

With the transmetalation conditions of *N,N*-diethylcarbamate derivatives of tributylstannanes in hand, the similar derivatives of trimethylstannanes were investigated (Table 9). Overall, good yields (65-81%) of the desired adducts were obtained. Lower yields were observed with stannane **88** (R^1 = Me), probably due to difficulty in isolation of the polar water-soluble products. Electrophilic trapping with cyclohexanone also resulted in lower yields, presumably due to competing enolization (entry 14). Transmetalations attempted at higher temperatures (-78°C) resulted in the formation of α-hydroxy amides due to 1,2-migration (compare entries 7 and 8). The final 1,2-diols were easily obtained by reduction with AlH_3 (2 equiv, THF, rt, 15 min). The reduction was also carried out with $LiAlH_4$ but reaction times were significantly longer (i.e., 1-2 h).

Table 9. Transmetalation of *N,N*-diethylcarbamate-protected α-hydroxytrimethylstannanes.



88-91 **110-125** **126-134**

Entry	Stannane	R^1	E^+	R^2	R^3	% yield[a] (110-125)	% yield[a] (126-134)
1	**88**	Me	benzaldehyde	Ph	H	60 (**110**)	nd[c]
2			*p*-anisaldehyde	4-$CH_3OC_6H_4$	H	70 (**111**)	nd[c]
3			tolualdehyde	4-$CH_3C_6H_4$	H	72 (**112**)	nd[c]
4	**89**	*n*-C_5H_{11}	benzaldehyde	Ph	H	79 (**113**)	80 (**126**)
5			*p*-anisaldehyde	4-$CH_3OC_6H_4$	H	75 (**96**)	83 (**127**)
6			tolualdehyde	4-$CH_3C_6H_4$	H	77 (**114**)	nd[c]
7	**90**	*i*-Pr	benzaldehyde	Ph	H	85 (**115**)	79 (**128**)
8			benzaldehyde	Ph	H	62 (**115**)[b]	—
9			*p*-anisaldehyde	4-$CH_3OC_6H_4$	H	83 (**116**)	nd[c]
10			tolualdehyde	4-$CH_3C_6H_4$	H	77 (**117**)	80 (**129**)
11			1-naphthaldehyde	1-naphthyl	H	84 (**118**)	91 (**130**)
12			pivaldehyde	$(CH_3)_3C$	H	78 (**119**)	nd[c]
13			piperonal	piperonyl	H	88 (**120**)	84 (**131**)
14			cyclohexanone	-$(CH_2)_5$-		63 (**121**)	69 (**132**)
15			hexanal	*n*-C_5H_{11}	H	81 (**122**)	nd[c]
16	**91**	*c*-C_6H_{11}	benzaldehyde	Ph	H	83 (**123**)	82 (**133**)
17			*p*-anisaldehyde	4-$CH_3OC_6H_4$	H	75 (**124**)	nd[c]
18			tolualdehyde	4-$CH_3C_6H_4$	H	76 (**125**)	80 (**134**)

[a] Isolated yields of chromatographically-pure products (1:1 mixture of diastereomers except **121**).
[b] Transmetalation using *n*-BuLi, THF, -78 °C.
[c] Not determined.

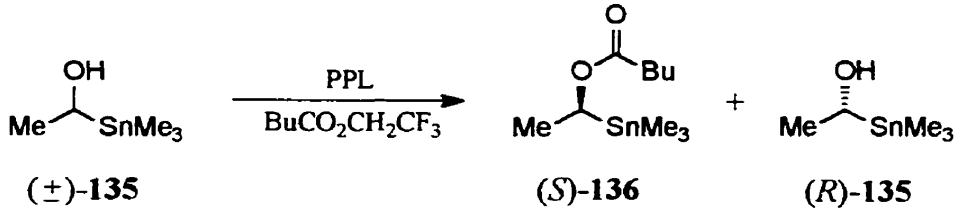
Results obtained from the transmetalation and trapping of *N,N*-diethylcarbamates proved that the use of dialkylcarbamates provided sufficient stabilization for the intermediate α-alkoxyorganolithiums to be trapped by electrophiles in very good yields. A study to

determine whether this methodology could be performed with complete retention of configuration using enantiomerically enriched α-alkoxyorganostannanes is described in the following section.

2.2.8 Configurational Stability of Carbamate-Protected α-Alkoxyorganolithiums

Chong and Mar[10] have demonstrated the enzymatic esterification of α-hydroxystannanes to provide esters of high enantiomeric purity (>98% ee) (Scheme 47). It was decided that these esters could serve as convenient precursors of carbamate protected α-hydroxystannanes. The configurational stability of *N,N*-diethylcarbamate-protected α-alkoxyorganolithium species could then be investigated.

Scheme 47



(±)-**135** (*S*)-**136** (*R*)-**135**

A quantity of ester (*S*)-**136** was available from the original work carried out by Mar[9] within our laboratories. The enantiomeric excess of (*S*)-**136** (>97% ee) had been originally determined by ^{1}H NMR analysis of its derived (+)-MTPA ester. To confirm that (*S*)-**136** had not undergone racemization during storage, the ester was first reduced with DIBAL-H and the resulting α-hydroxystannane (*S*)-**135** was derivatized to its (*R*)-(-)-MTPA ester **137** (Scheme 48). The ^{1}H NMR spectrum of **137** displayed methyl singlets for the Me_3Sn group at δ 0.12 for the (*S*)-enantiomer and δ 0.10 for the (*R*)-enantiomer (see Figure 10). By comparison of the ^{13}C satellites (0.55% per peak) of the (*S*)-enantiomer at δ 0.37 and δ -0.13 and the Me_3Sn peak for the (*R*)-enantiomer, the contribution of the (*R*)-enantiomer can be qualitatively assigned as less than 0.5%. Therefore, the enantiomeric excess of **136** is

actually higher than the conservative value reported by Mar of >97% ee and confirms the stability of these stannanes during long periods of storage. The *N,N*-diethylcarbamate (*S*)-**138** was prepared from ester (*S*)-**136** in 73% yield (Scheme 48). The enantiomeric excess of this compound was assigned > 97% ee based on the results obtained from (*R*)-MTPA ester **137**. Transmetalation of (*S*)-**138** (*s*-BuLi, THF –95°C) and treatment of the resulting α-alkoxyorganolithium with PhCHO gave alcohol **139** in 60% yield, as a 1:1 mixture of diastereomers (Scheme 48).

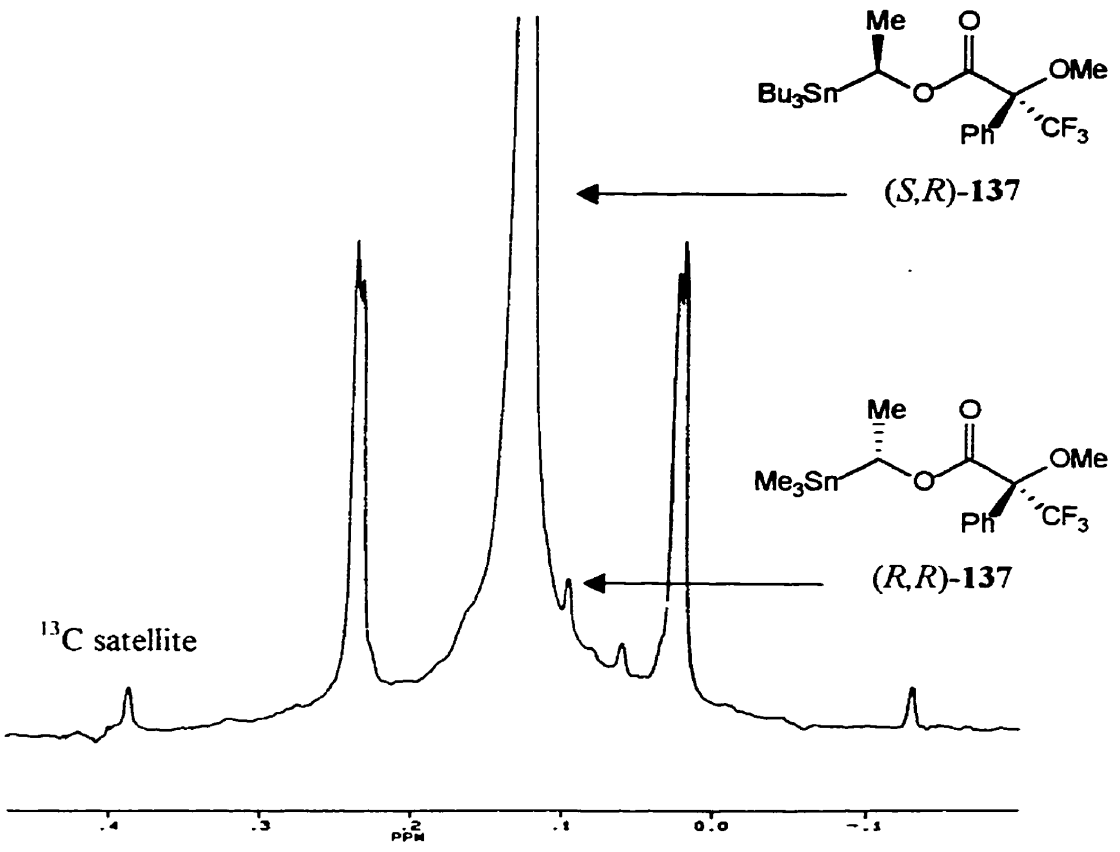
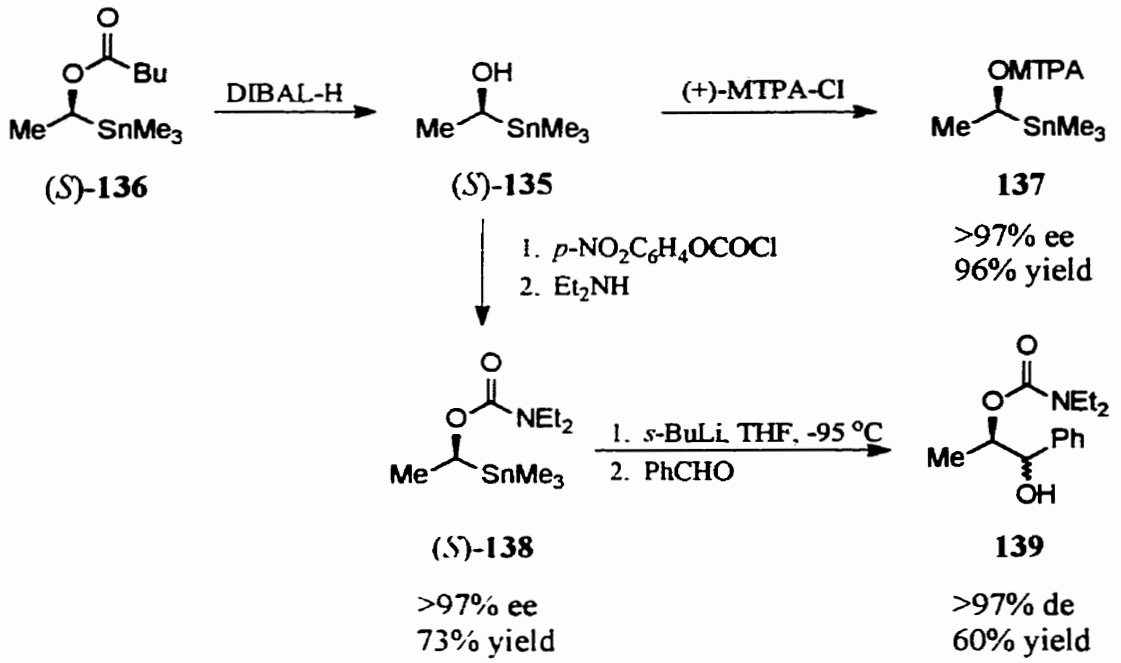


Figure 10. 250 MHz ^{1}H NMR spectra (δ 0.45 to δ -0.15 region) of (*R*)-(-)-MTPA ester of (*S*)-hydroxystannane **137**.

Scheme 48



The enantiomeric excess of alcohol **139** was subsequently determined by chiral HPLC (Figure 11). Retention times for (*R**,*R**),(*R**,*S**)-**139** were recorded at 37.93, 42.25, 45.01 and 48.56 minutes. The HPLC results obtained for adduct **139** recorded retention times of 42.47 and 49.35 minutes There was no evidence of racemization as the peaks corresponding to the opposite enantiomer (retention time: 37.93 and 45.01 min) were not detected. Therefore, this reaction proceeded with complete retention of configuration.

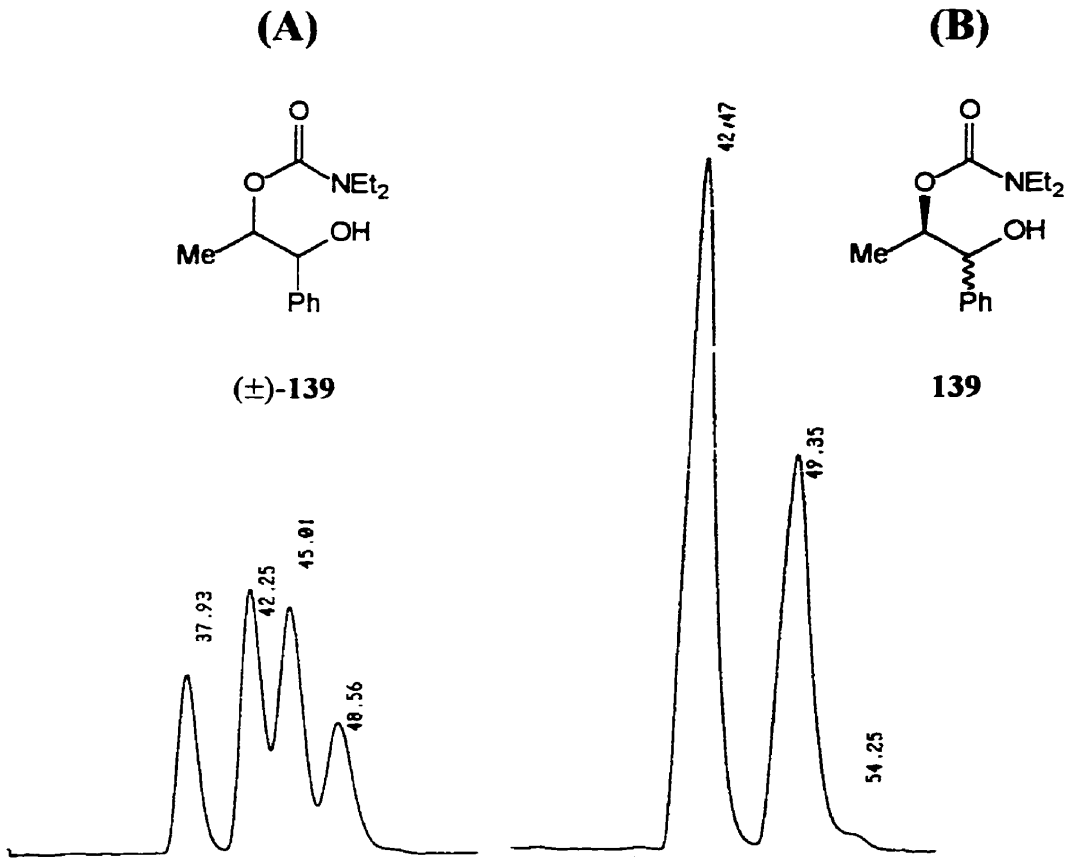


Figure 11. HPLC traces: (A) (±)-**139** and (B) enriched carbamate **139** of >97% de. Conditions: Chiracel-OD column, hexanes-*i*-PrOH, 99:1 as eluent, flow rate of 1.0 mL/min, and detection at 254 nm. Numbers on traces represent the elution time in minutes.

2.2.9 Summary

The successful transmetalation of trimethylalkoxyorganostannanes was performed using *N,N*-dialkylcarbamate and *N*-phenylcarbamate protecting groups. *N,N*-Diisopropyl-carbamates could be prepared in only mediocre yields (34-45%), but provided stable α-alkoxyorganolithiums (1.05 equiv *n*-BuLi, THF –78°C), which could be trapped with aromatic or aliphatic aldehydes in good yields (65-93%). The *N*-phenylcarbamates were obtained in low to moderate yields (36 and 60%). Transmetalation (2.5 equiv *n*-BuLi, THF, -78°C) and trapping provided the expected adducts in moderate yields (53 and 77%).

GCMS experiments gave further evidence that MOM-protected α-alkoxyorgano-trimethylstannanes do not undergo transmetalation as efficiently as their tributylstannyl analogues. In addition, MOM-protected α-alkoxyorganolithiums are comparable in stability to MeLi. This finding is contrary to the relative ordering proposed by McGarvey (Figure 1, page 15). In comparison the *N,N*-diisopropylcarbamate protected derivatives gave highly stabilized α-alkoxyorganolithiums after Sn-Li exchange, which undergo trapping with aldehydes to provide higher overall yields of the expected adducts.

Our attempts to access *N,N*-diisopropylcarbamoylstannanes in higher yields (>45%) by the reaction of amine nucleophiles with carbonate-protected α-hydroxystannanes were unsuccessful. However, this same methodology allowed access to *N,N*-diethylcarbamates in high yields (57-83%). Transmetalation of these stannanes required the use of *s*-BuLi to prevent attack on the carbamate carbonyl and lower temperatures (-95°C) to eliminate 1,2-carbamoyl migration of the diethylamide functionality and thus formation of α-hydroxy amides. Overall, yields of the desired adducts were satisfactory (60-88%).

Finally, the *N,N*-diethylcarbamate protected α-alkoxyorganolithium derived from stannane (*S*)-**138** was shown to be configurationally stable at -95°C. Trapping with PhCHO gave alcohol **139** with no detectable racemization (HPLC).

This study determined that the best protecting group for α-alkoxytrimethylstannanes was the *N,N*-diethylcarbamate. α-Hydroxystannanes could be easily protected with this group in good yields. The derived protected stannanes underwent Sn-Li exchange to provide stabilized α-alkoxyorganolithiums, which could be trapped with a variety of electrophiles to provide the desired adducts in excellent yields. The 1,2-diols from these products were easily accessed by the facile removal of the diethylcarbamate group with AlH_3. This protecting group was also shown to allow the transmetalation and trapping of an enantiomerically enriched sample with complete retention of configuration. In conclusion, the synthetic utility of α-alkoxyorganotrimethylstannanes should increase from the information acquired in this study.

2.3 Experimental

2.3.1 General

All reactions were performed using flame dried glassware under an inert atmosphere of argon unless otherwise noted. Diethyl ether, dimethoxyethane and tetrahydrofuran were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane was distilled from CaH_2 immediately prior to use. Diethylamine, diisopropylamine, diisopropylethylamine and pyridine were distilled from CaH_2 and stored over 4 Å molecular sieves. Aldehydes were usually chromatographed on activated basic aluminum oxide or distilled before use. Tributyltin hydride was prepared according to Szammer and Otvos and was freshly distilled before use.[31] Trimethyltinlithium was prepared following the procedure of Tamborski and coworkers.[17] Other reagents were purchased (Aldrich) or prepared by modification of literature methods.

Melting points were taken on a MEL-TEMP apparatus and are uncorrected. Infrared spectra were obtained either as neat liquids or in solution ($CHCl_3$) between sodium chloride plates on a Michelson MB-100 FTIR spectrophotometer. Absorption positions are given in cm^{-1}. NMR spectra were recorded using either a Bruker AC-200, AM-250, or AMX-300 spectrometer in $CDCl_3$ with tetramethylsilane (TMS, $\delta = 0.0$ for ^1H) or chloroform ($\delta = 7.24$ for ^1H, 77.0 for ^{13}C) as an internal standard. ^1H NMR data are presented as follows: chemical shift (multiplicity, integration, J in Hz). For ^{13}C NMR signals, coupling constants for satellites due to $^{117/119}Sn$ are reported in parentheses. Mass spectra were recorded in ES mode using a VG Quattro II mass spectrometer or in EI mode using a Hewlett Packard G1800A GCD system fitted with a 30 m × 0.25 mm HP5 column. The GCMS temperature program was as follows: initial temperature 70°C, for 10 min; rate of heating 20°C/min, for 10 min; final temperature 270°C, for 10 min. Data are reported in the form *m z* (intensity relative to base = 100). For compounds containing tin, masses indicated are those for ^{120}Sn. High pressure liquid chromatography were recorded on a Waters 600 instrument using a Chiracel OD column (4.6 × 150 mm). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

2.3.2 *General Procedure for the Preparation of Trimethyltinlithium*[17]

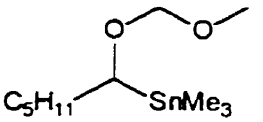
A general procedure for the preparation of trimethyltinlithium is given below.

The procedure of Tamborski *et al.*[17] was essentially followed. A 250 mL three-necked round bottom flask is equipped with a glass stopper, a dropping funnel (25 mL) and Schlenk filter tube which is connected to another 250 mL two-necked flask. The three-necked flask is charged with THF (50 mL) and lithium wire (1.58 g, 0.23 mol), which is cut into fine pieces (~ 5 mm, with the aid of parafilm oil) and washed with hexanes (3 × 5 mL). After the above stirred suspension is cooled to –5°C, a solution of trimethyltin chloride (4.13 g, 0.021 mol) in THF (10 mL) is added slowly over 30 min. The reaction is allowed to stir overnight at –5°C and then filtered through the Schlenk tube into the two-necked flask. This solution of trimethyltinlithium (~ 0.35 M) is subsequently cooled to –78°C and then treated with an aldehyde (1.2 equiv).

2.3.3 *Representative Procedure for the Preparation of Methoxymethyl Protected α-Hydroxystannanes*

A representative procedure for the preparation of ether **49** is given below, followed by spectral data of ethers **49** and **50**. The yields of these ethers can be found in Table 2.

1-Methoxymethoxy-1-(trimethylstannyl)hexane (49)

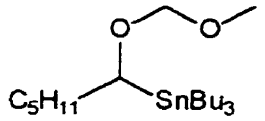


To a cooled (-78°C) solution of trimethyltinlithium (0.015 mol in 50 mL of THF) was added *n*-hexanal (2.19 mL, 0.018 mol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide 4.05 g of crude α-hydroxystannane.

This material was cooled to 0°C and then CH_2Cl_2 (2 mL), $(i\text{-Pr})_2NEt$ (5.31 mL, 0.030

mol), DMAP (~0.5 equiv), and chloromethyl methyl ether (1.74 mL, 0.023 mol) were added. The reaction was stirred at 0°C for 10 min and was then allowed to warm to room temperature. The reaction was monitored by TLC until complete (0.5-1.0 h). The solution was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 4.13 g of orange oil. Purification by flash chromatography (30 g of silica/g of substrate; 40:1 hexanes:ethyl acetate) provided 3.71 g (78%) of the title compound: IR (neat film) 2917, 1458, 1147, 1097, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 [s, 9 H, $J_{H\text{-}Sn}$ = 50.2, 52.3 Hz, $Sn(C\underline{H}_3)_3$], 0.80-0.95 [m, 3 H, $CH_2(CH_2)_3C\underline{H}_3$], 1.15-1.45 [m, 6 H, $CH_2(C\underline{H}_2)_3CH_3$], 1.70-1.95 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 3.32 (s, 3 H, $OC\underline{H}_3$), 3.96 (t, 1 H, J = 6.5 Hz, C<u>H</u>OMOM), 4.57 (ABq, 2 H, J = 6.6 Hz, $\Delta\nu_{AB}$ = 10.5 Hz, $OC\underline{H}_2O$); ^{13}C NMR (63 MHz, $CDCl_3$) δ -10.00 [^1J = 297, 311 Hz, $Sn(\underline{C}H_3)_3$], 13.99 ($\underline{C}H_3CH_2$), 22.60 ($CH_3\underline{C}H_2$), 27.31 (^2J = 33 Hz, $CH_2\underline{C}H_2CH$), 31.86 ($CH_3CH_2\underline{C}H_2$), 34.61 ($\underline{C}H_2CH_2CH$), 55.35 ($O\underline{C}H_3$), 73.94 (^1J = 454, 476 Hz, <u>C</u>HSn), 96.40 ($O\underline{C}H_2O$); MS (EI) ***m/z*** 295 (3, M^+-CH_3), 265 (12), 165 (100), 150 (10), 135 (20), 45 (63); Anal. Calcd for $C_{11}H_{26}O_2Sn$: C, 42.76; H, 8.48. Found: C, 42.87; H, 8.41.

*1-Methoxymethoxy-1-(tributylstannyl)hexane(**50**)* [32]

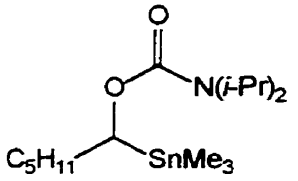


IR (neat film) 2909, 1584, 1460, 1376, 1146, 1033, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.70-1.05 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $CH_2(CH_2)_3C\underline{H}_3$], 1.15-1.65 (m, 18 H,$CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_2(C\underline{H}_2)_3CH_3$], 1.70-1.90 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 3.32 (s, 3 H, $OC\underline{H}_3$), 4.04 (t, 1 H, J = 6.5 Hz, C<u>H</u>OMOM), 4.55 (ABq, 2 H, J = 6.6 Hz, $\Delta\nu_{AB}$ = 14.3 Hz, $OC\underline{H}_2O$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.04 (^1J = 289, 303 Hz, $\underline{C}H_2Sn$), 13.43 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.82 ($\underline{C}H_3CH_2$), 22.50 ($CH_3\underline{C}H_2$), 27.33 ($^2J$ = 51 Hz, $\underline{C}H_2CH_2Sn$), 27.68 ($CH_2\underline{C}H_2CH$), 29.05 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.74 ($CH_3CH_2\underline{C}H_2$), 34.93 ($\underline{C}H_2CH_2CH$), 55.13 ($O\underline{C}H_3$), 73.90 (<u>C</u>HSn), 96.22 ($O\underline{C}H_2O$); MS (EI) ***m/z*** 379 (6, M^+-C_4H_9), 291 (16), 235 (28), 179 (44), 121 (29), 45 (100); Anal. Calcd for $C_{20}H_{44}O_2Sn$: C, 55.32; H, 10.21. Found: C, 55.50; H, 9.92.

2.3.4 *Representative Procedure for the Preparation of N,N-Diisopropylcarbamate Protected α-Hydroxystannanes*

A representative procedure for the preparation of carbamate **53** is given below, followed by spectral data of carbamates **51-54**. The yields of these carbamates can be found in Table 2.

1-(Trimethylstannyl)hexyl N,N-Diisopropylcarbamate (53)

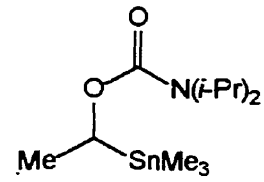


To a cooled (-78°C) solution of trimethyltinlithium (0.021 mol in 50 mL of THF) was added *n*-hexanal (3.03 mL, 0.025 mol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide 5.54 g of crude α-hydroxystannane.

This material was cooled to 0°C and then CH_2Cl_2 (5 mL), triethylamine (4.37 mL, 0.031 mol), *N,N*-diisopropylcarbamoyl chloride (4.11 g, 0.025 mol) and DMAP (100 mg) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated no further consumption of starting material (6-12 h). The solution was diluted with ethyl acetate (75 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 6.53 g of yellow oil. Purification by flash chromatography (30 g of silica/g of substrate; 40:1, hexanes:ethyl acetate) provided 2.76 g (34%) of the title compound: IR (neat film) 2935, 1674, 1438, 1315, 1148, 1050, 769 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 [s, 9 H, $J_{H\text{-}Sn}$ = 51.0, 53.3 Hz, $Sn(C\underline{H}_3)_3$], 0.80-0.95 (m, 3 H, $CH_2(CH_2)_3C\underline{H}_3$), 1.17 [d, 12 H, J = 6.7 Hz $CH(C\underline{H}_3)_2$], 1.05-1.45 (m, 6 H, $CH_2(C\underline{H}_2)_3CH_3$), 1.65-1.95 (m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$), 3.50-3.85 [bs, 1 H, $C\underline{H}(CH_3)_2$], 3.90-4.20 [bs, 1 H, $C\underline{H}(CH_3)_2$], 4.43 (dd, 1 H, J = 6.2, 8.2 Hz, $C\underline{H}Sn$) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ -9.23 [^1J = 316, 330 Hz, $Sn(\underline{C}H_3)_3$] 13.86 ($\underline{C}H_3CH_2$), 20.96 [b, $CH(\underline{C}H_3)_2$], 22.45 ($CH_3\underline{C}H_2$), 27.36 (^2J=34 Hz, $CH_2\underline{C}H_2CH$), 31.49, 33.69 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 45.65 [b, $\underline{C}H(CH_3)_2$], 71.99 (^1J= 441, 463 Hz, $\underline{C}HSn$), 156.36 ($\underline{C}O$); MS (EI) *m/z* 378 (3, M^+-CH_3), 294 (9), 228 (19), 165 (36), 135 (14),

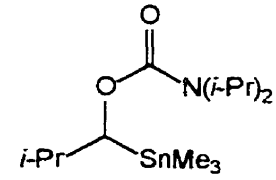
86 (50), 43 (100); Anal. Calcd for $C_{16}H_{35}NO_2Sn$: C, 49.01; H, 9.00; N, 3.57. Found: C, 49.18; H, 8.91; N, 3.60.

*1-(Trimethylstannyl)ethyl N,N-Diisopropylcarbamate (**51**)*



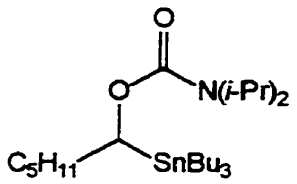
IR (neat film) 2936, 1674, 1447, 1323, 1146, 1052, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 [s, 9 H, $J_{H\text{-}Sn}$ = 51.2, 53.4 Hz, $Sn(C\underline{H}_3)_3$], 1.17 [d, 12 H, J = 6.8 Hz, $CH(C\underline{H}_3)_2$], 1.50 (d, 3 H, J = 7.6 Hz, $C\underline{H}_3CH$), 3.45-4.30 [bm, 2H, $C\underline{H}(CH_3)_2$], 4.50 (q, 1 H, J = 7.6 Hz, $CH_3C\underline{H}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ -9.87 [^1J = 318, 332 Hz, $Sn(\underline{C}H_3)_3$], 19.14 ($\underline{C}H_3CH$), 20.74 [$CH(\underline{C}H_3)_2$], 45.32 [$\underline{C}H(CH_3)_2$], 66.63 (^1J = 446, 461 Hz, $CH_3\underline{C}H$), 156.11 ($\underline{C}O$); MS (EI) ***m/z*** 322 (50, M^+-CH_3), 294 (33), 165 (92), 150 (14), 135 (35), 100 (27), 86 (82), 58 (28), 43 (100); Anal. Calcd for $C_{12}H_{27}NO_2Sn$: C, 42.89; H, 8.09; N, 4.16. Found: C, 43.00; H, 7.97; N, 4.34.

*(1-Trimethylstannyl-2-methyl)propyl N,N-Diisopropylcarbamate (**52**)*



IR (neat film) 2936, 1675, 1450, 1330, 1170, 1043, 923, 768 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.08 [s, 9 H, $J_{H\text{-}Sn}$ = 50.8, 53.0 Hz, $Sn(C\underline{H}_3)_3$], 0.96 [d, 6 H, J = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.18 [d, 12 H, J = 6.5 Hz, $N(CH(C\underline{H}_3)_2)_2$], 2.10-2.25 [m, 1 H, $C\underline{H}(CH_3)_2$], 3.55-3.85 [bm, 1 H, $NC\underline{H}(CH_3)_2$], 3.95-4.25 [bm, 1 H, $NC\underline{H}(CH_3)_2$], 4.29 [d, 1 H, J = 6.7 Hz $C\underline{H}Sn$]; ^{13}C NMR (63 MHz, $CDCl_3$) δ -8.51 [^1J = 316, 330 Hz, $Sn(\underline{C}H_3)_3$], 19.98 [^3J = 27 Hz, $CH(\underline{C}H_3)_2$], 20.5 [b, overlapping, $N(CH(\underline{C}H_3)_2)_2$], 20.62 [$^3J$ = 27 Hz, $CH(\underline{C}H_3)_2$], 31.64 [$\underline{C}H(CH_3)_2$], 44.86 [b, $N\underline{C}H(CH_3)_2$], 45.69 [b, $N\underline{C}H(CH_3)_2$] 78.90 (^1J = 443, 463 Hz, $\underline{C}HSn$), 155.97 ($\underline{C}O$); MS (EI) ***m/z*** 350 (14, M^+-CH_3), 294 (26), 200 (60), 165 (75), 135 (30), 100 (41), 86 (62), 57 (27), 43 (100); Anal. Calcd for $C_{14}H_{31}NO_2Sn$: C, 46.18; H, 8.58; N, 3.84. Found: C, 45.91; H, 8.37; N, 3.68.

1-(Tributylstannyl)hexyl N,N-Diisopropylcarbamate (54)

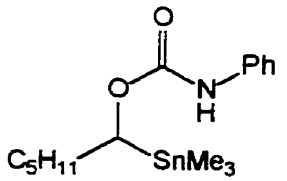


IR (neat film) 2915, 1676, 1449, 1301, 1046 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.05 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $CH_2(CH_2)_3C\underline{H}_3$), 1.17 [d, 12 H, J = 6.8 Hz, $N(CH(C\underline{H}_3)_2)_2$], 1.10-1.65 [m, 18 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_2(C\underline{H}_2)_3CH_3$], 1.65-2.00 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 3.55-4.20 [bm, 2 H, $N(C\underline{H}(CH_3)_2)_2$], 4.64 (dd, 1 H, J = 5.8, 8.7 Hz, $C\underline{H}Sn$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.77 (^1J = 305, 319 Hz, $\underline{C}H_2Sn$), 13.67 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.99 ($\underline{C}H_3CH_2$), 21.10 [b, $N(CH(\underline{C}H_3)_2)_2$], 22.59 ($CH_3\underline{C}H_2$), 27.56 ($^2J$ = 56 Hz, $\underline{C}H_2CH_2Sn$), 27.64 ($CH_2\underline{C}H_2CH$), 29.16 (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.62 ($CH_3CH_2\underline{C}H_2$), 34.55 ($\underline{C}H_2CH_2CH$), 45.50 [b, $N(\underline{C}H(CH_3)_2)_2$], 71.55 ($\underline{C}HSn$), 156.27 ($\underline{C}O$); MS (ES) *m/z* 520 (61, M+1), 462 (100); Anal. Calcd for $C_{25}H_{53}NO_2Sn$: C, 57.92; H, 10.30; N, 2.70. Found: C, 57.70; H, 10.46; N, 2.98.

2.3.5 *Representative Procedure for the Preparation of N-Phenylcarbamate Protected α-Hydroxystannanes*

A representative procedure for the preparation of carbamate **55** is given below, followed by spectral data of carbamates **55** and **56**. The yields of these carbamates can be found in Table 2.

1-(Trimethylstannyl)hexyl N-Phenylcarbamate (55)

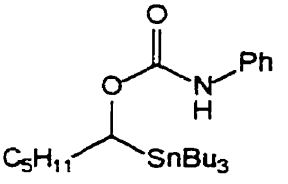


To a cooled (-78°C) solution of trimethyltinlithium (0.020 mol in 50 mL of THF) was added *n*-hexanal (2.88 mL, 0.024 mol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water

bath at rt) to provide 5.22 g of crude α-hydroxystannane.

This material was cooled to 0°C and then CH_2Cl_2 (10 mL), triethylamine (4.11 mL, 0.030 mol), and phenyl isocyanate (2.56 mL, 0.024 mol) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (0.5-2.0 h). The solution was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 8.79 g of orange oil. Purification by flash chromatography (30 g of silica/g of substrate; 40:1, hexanes:ethyl acetate) provided 2.69 g (36%) of the title compound as a light yellow oil: IR (neat film) 3325, 2918, 1703, 1602, 1527, 1443, 1225, 1045, 748 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 [s, 9 H, $J_{H\text{-}Sn}$ = 51.6, 53.6 Hz, $Sn(C\underline{H}_3)_3$], 0.89–1.00 [m, 3 H, $CH_2(CH_2)_3C\underline{H}_3$], 1.15-1.50 [m, 6 H, $CH_2(C\underline{H}_2)_3CH_3$], 1.70-2.00 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 4.60 (dd, 1 H, J = 6.5, 8.2 Hz, C<u>H</u>Sn), 6.64 (s, 1 H, N<u>H</u>), 7.03 (t, 1 H, J = 7.2 Hz, Ar<u>H</u>), 7.28 (t, 2 H, J = 7.3 Hz, Ar<u>H</u>), 7.35 (t, 2 H, J = 7.8 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ -9.45 [^1J = 319, 334 Hz, $Sn(\underline{C}H_3)_3$], 13.98 ($\underline{C}H_3CH_2$), 22.55 ($CH_3\underline{C}H_2$), 27.03 (^2J = 31 Hz, $CH_2\underline{C}H_2CH$), 31.60 ($CH_3CH_2\underline{C}H_2$), 33.81 ($\underline{C}H_2CH_2CH$), 72.82 (^1J = 416, 435 Hz, <u>C</u>HSn), 118.71, 123.17, 128.97, 138.14 (Ar-<u>C</u>'s), 154.40 (<u>C</u>O); MS (EI) *m/z* 370 (16, M^+-CH_3), 286 (13), 242 (28), 212 (18), 165 (100), 135 (41), 120 (20); Anal. Calcd for $C_{16}H_{27}NO_2Sn$: C, 50.03; H, 7.09; N, 3.65. Found: C, 50.20; H, 6.99; N, 3.55.

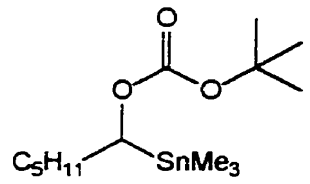
*1-(Tributylstannyl)hexyl N-Phenylcarbamate (**56**)*



IR (neat film) 3328, 2912, 2350, 1705, 1601, 1527, 1442, 1217, 1024 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.10 [m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $CH_2(CH_2)_3C\underline{H}_3$], 1.20-1.65 [m, 18 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_2(C\underline{H}_2)_3CH_3$], 1.70-2.05 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 4.83 (dd, 1 H, J = 5.7, 8.6 Hz, C<u>H</u>Sn), 6.49 (s, 1 H, N<u>H</u>), 7.04 (t, 1 H, J = 7.0 Hz, Ar<u>H</u>), 7.20-7.45 (m, 4 H, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.55 (^1J = 307, 322 Hz, $\underline{C}H_2Sn$), 13.50 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.87 ($\underline{C}H_3CH_2$), 22.48 ($CH_3\underline{C}H_2$), 27.15 ($CH_2\underline{C}H_2CH$), 27.33 ($^2J$ = 55 Hz, $\underline{C}H_2CH_2Sn$), 29.00 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.51 ($CH_3CH_2\underline{C}H_2$), 34.38 ($\underline{C}H_2CH_2CH$), 72.48 ($^1J$ = 352, 363

Hz, CHSn), 118.69, 122.87, 128.70, 138.22 (Ar-C's), 154.40 (CO); MS (EI) *m/z* 511 (M^+, 29), 454 (100), 326 (38), 235 (32), 212 (42), 177 (48), 119 (59); Anal. Calcd for $C_{25}H_{45}NO_2Sn$: C, 58.84; H, 8.88; N, 2.74. Found: C, 58.72; H, 9.06; N, 2.96.

2.3.6 *1-(Trimethylstannyl)hexyl t-Butylcarbonate (57)*



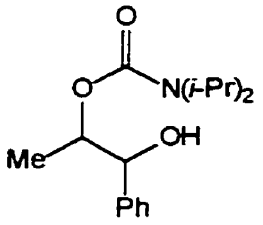
To a cooled (-78°C) solution of trimethyltinlithium (5.63 mmol in 12 mL of THF) was added *n*-hexanal (0.68 mL, 6.75 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (50 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide 1.49 g of crude 1-trimethylstannyl-1-hexanol.

This material was cooled to 0°C and then CH_2Cl_2 (5 mL), $(i\text{-}Pr)_2NEt$ (2.94 mL, 16.8 mmol), $MgBr_2 \bullet OEt_2$ (1.45 g, 11.3 mmol in 5 mL of CH_2Cl_2), and di-*tert*-butyl dicarbonate (2.46 g, 11.3 mmol) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (12 h). The solution was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 2.54 g of brown oil. Purification by flash chromatography (30 g of silica/g of substrate; 40:1 hexanes:ethyl acetate) provided 1.33 g (65%) of the title compound as a colorless oil: IR (neat film) 2960, 2927, 2859, 1722, 1463, 1368, 1339, 1275, 1167, 771 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 [s, 9 H, $J_{H\text{-}Sn}$ = 51.5, 53.9 Hz, $Sn(CH_3)_3$], 0.80-1.00 [m, 3 H, $CH_2(CH_2)_3CH_3$], 1.15-1.40 [m, 6 H, $CH_2(CH_2)_3CH_3$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.65-1.95 [m, 2 H, $CH_2(CH_2)_3CH_3$], 4.60 (dd, 1 H, J = 6.6, 8.4 Hz, CHSn); ^{13}C NMR (63 MHz, $CDCl_3$) δ -9.63 [^1J = 319, 333 Hz, $Sn(CH_3)_3$], 13.96 (CH_3CH_2), 22.50 (CH_3CH_2), 26.88 (^2J = 31 Hz, CH_2CH_2CH), 27.76 [$C(CH_3)_3$], 31.55 (CH_2CH_2CH), 33.52 ($CH_3CH_2CH_2$), 74.73 (^1J = 413, 433 Hz, CHSn), 81.22 [$C(CH_3)_3$], 154.21 (CO); MS (EI) *m/z* 310 (1, M^+-CH_3), 227 (14), 211 (19), 165 (100), 135 (19), 57 (32); Anal. Calcd for $C_{14}H_{30}O_3Sn$: C, 46.05; H, 8.28. Found: C, 45.88; H, 8.10.

2.3.7 *Representative Procedure for the Transmetalation and Trapping of N,N-Diisopropylcarbamate and Methoxymethyl, O-Protected α-Hydroxystannanes*

A representative procedure for the transmetalation of *N,N*-diisopropylcarbamate **51** and trapping with PhCHO is given below, followed by spectral data of carbamates **59-61**, **64-66** and ethers **58** and **63**. The yields of these adducts can be found in Table 3. All products were isolated as a 1:1 mixture of diastereomers unless otherwise noted.

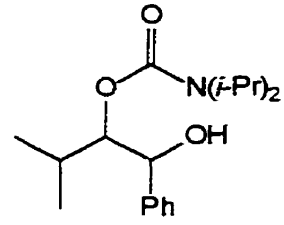
(1R,2R*),(1R*,2S*)-2-(N,N-Diisopropylcarbamoyloxy)-1-phenyl-1-propanol (59)*



To a cold (-78°C) stirred solution of 1-(trimethylstannyl)ethyl *N,N*-diisopropylcarbamate (**51**) (227.3 mg, 0.68 mmol, 1 equiv) in THF (5 mL) was added dropwise *n*-BuLi (0.54 mL of a 1.31 M solution in hexanes, 1.05 equiv). After 15 min, benzaldehyde (75.6 μL, 0.74 mmol, 1.1 equiv) was added. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (30 g of silica/g of substrate; initially 40:1, hexanes:ethyl acetate, with gradual increase in solvent polarity to 5:1) affording 150.4 mg (80% yield) of product as a colorless oil; IR ($CHCl_3$) 3603, 3373, 2989, 1667, 1449, 1303, 1136, 1059, 911, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.45 [m, 15 H, CH_3CH and $N(CH(CH_3)_2)_2$], 3.55-4.20 [bm, 3 H, $N(CH(CH_3)_2)_2$ and OH], 4.61 (bd, 0.5 H, J = 6.2 Hz, PhCHOH), 4.85 (bs, 0.5 H, PhCHOH), 5.03 (dq, 0.5 H, J = 6.5, 7.2 Hz, CHOCO), 5.13 (dq, 0.5 H, J = 2.9, 6.6 Hz, CHOCO), 7.14-7.50 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.23, 17.00 (CH_3CH), 20.86 [b, $N(CH(CH_3)_2)_2$], 45.53 [b, $N(CH(CH_3)_2]$], 46.20 [b, $N(CH(CH_3)_2]$], 75.24, 75.75, 76.58, 78.29 (PhCHOH and CHOCO), 126.75, 127.06, 127.42, 127.90, 127.94, 128.32 (Ar-C's), 140.12, 140.98 (*ipso*-Ar-C), 155.87, 156.25 (CO); MS (EI) *m/z* 173 (22, M^+-PhCHO), 158 (23), 128 (75), 86 (100), 43

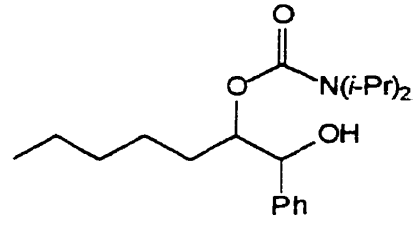
(70); Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.00; H, 9.22; N, 5.13.

(1R,2R*),(1R*,2S*)-2-(N,N-Diisopropylcarbamoyloxy)-3-methyl-1-phenyl-1-butanol* ***(60)***



colorless wax; IR ($CHCl_3$) 3601, 3380, 2971, 1668, 1446, 1380, 1311, 1135, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.35 [m, 18 H, $N(CH(C\underline{H}_3)_2)_2$ and $CH(C\underline{H}_3)_2$], 1.75 [dseptets, 0.5 H, J = 4.2, 7.6 Hz, $C\underline{H}(CH_3)_2$], 1.88-2.00 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 3.60-4.00 [m, 3 H, O<u>H</u> and $N(C\underline{H}(CH_3)_2)_2$], 4.70-4.90 (m, 2 H, PhC<u>H</u>OH and C<u>H</u>OCO), 7.20-7.45 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.84, 18.38, 20.05, 20.16 [$CH(C\underline{H}_3)_2$], 20.30, 20.79, 21.16, 21.36 [$N(CH(C\underline{H}_3)_2)_2$], 28.45, 28.94 [$C\underline{H}(CH_3)_2$], 45.65, 45.83, 46.16 [$N(C\underline{H}(CH_3)_2)_2$], 74.48, 75.36, 82.54, 83.35, 126.72, 127.18, 127.43, 127.68, 127.85, 128.38 (Ar-<u>C</u>'s), 140.84, 141.70 (*ipso*-Ar-<u>C</u>), 155.58, 156.68 (<u>C</u>O); MS (EI) *m/z* 201 (11, M^+-PhCHO), 128 (98), 86 (100), 43 (59); Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.42; H, 9.74; N, 4.76.

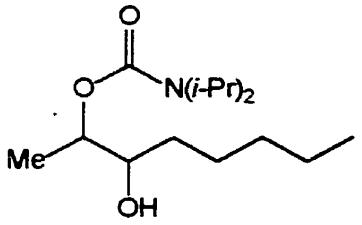
(1R,2R*),(1R*,2S*)-2-(N,N-Diisopropylcarbamoyloxy)-1-phenyl-1-heptanol* ***(61)***



colorless oil; IR ($CHCl_3$) 3602, 3379, 2949, 1665, 1450, 1370, 1306, 1141, 1060, 909, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.60-1.80 [m, 23 H, n-$C_5\underline{H}_{11}$ and $N(CH(C\underline{H}_3)_2)_2$], 3.55-4.15 [bm, 2 H, $N(C\underline{H}(CH_3)_2)_2$], 3.82 (d, 0.5 H, J = 5.2 Hz, O<u>H</u>), 4.28 (d, 0.5 H, J = 4.9 Hz, O<u>H</u>), 4.66 (dd, 0.5 H, J = 5.2, 7.1 Hz, PhC<u>H</u>OH), 4.83 (dd, 0.5 H, J = 2.8, 4.9 Hz, PhC<u>H</u>OH), 4.90-5.05 (m, 1 H, C<u>H</u>OCO), 7.15-7.45 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.79, 13.82 ($\underline{C}H_3CH_2$), 20.46 [b, $N(CH(\underline{C}H_3)_2)_2$], 22.32, 22.38 ($CH_3\underline{C}H_2$), 25.02, 25.53 ($CH_2\underline{C}H_2CH$), 29.88, 30.60 ($\underline{C}H_2CH_2CH$), 31.41, 31.45 ($CH_3CH_2\underline{C}H_2$), 45.75, 46.09 [b, $N(\underline{C}H(CH_3)_2)_2$], 76.12, 76.71, 78.90, 79.12 (Ph<u>C</u>HOH and <u>C</u>HOCO), 126.77, 126.85, 127.20, 127.59, 127.76, 128.16 (Ar-<u>C</u>'s),

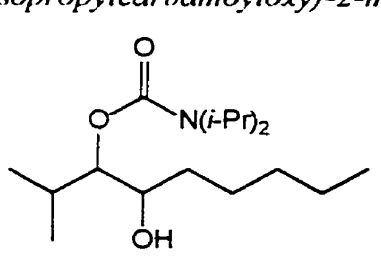
140.39, 141.34 (*ipso*-Ar-C), 156.09, 156.26 (CO); MS (EI) *m/z* 258 (4, M^+-C_6H_5), 214 (32), 146 (39), 128 (42), 102 (29), 86 (100), 55 (40), 43 (75); Anal. Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.18. Found: C, 71.60; H, 10.11; N, 4.27.

(2R,3R*),(2R*,3S*)-2-(N,N-Diisopropylcarbamoyloxy)-3-octanol (64)*



yellow oil; IR ($CHCl_3$) 3603, 3411, 2934, 1669, 1451, 1372, 1301, 1137, 1061, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.00 [m, 3 H, $CH_2(CH_2)_3CH_3$], 1.10-1.60 [m, 23 H, CH_3CH, $N(CH(CH_3)_2)_2$, and $CH_2(CH_2)_5CH_3$], 2.50-2.65 (bs, 0.5 H, OH), 2.73-2.90 (bs, 0.5 H, OH), 3.55-4.20 (bm, 3 H, CHOH and $N(CH(CH_3)_2)_2$], 4.75-4.95 (m, 1 H, CHOCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92 (CH_3CH_2), 14.97, 16.47 (CH_3CH), 20.88 [b, $N(CH(CH_3)_2)_2$], 22.48 (CH_3CH_2), 24.99, 25.56 (CH_2CH_2CH), 31.77, 31.79 (CH_2CH_2CH), 32.12, 33.19 ($CH_3CH_2CH_2$), 45.33 [b, $N(CH(CH_3)_2)_2$], 74.03, 74.17, 74.33, 74.81 (CHOH and CHOCO), 155.68 (CO); MS (EI) *m/z* 258 (5, M^+-CH_3), 158 (31), 130 (55), 86 (100); Anal. Calcd for $C_{15}H_{31}NO_3$: C, 65.89; H, 11.43; N, 5.12. Found: C, 65.92; H, 11.66; N, 5.11.

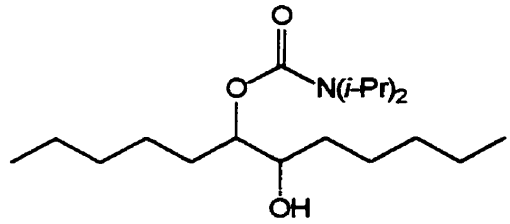
(3R,4R*),(3R*,4S*)-3-(N,N-Diisopropylcarbamoyloxy)-2-methyl-4-nonanol (65)*



yellow oil; IR ($CHCl_3$) 3414, 2966, 1668, 1449, 1370, 1305, 1142, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.65 [m, 29 H, *n*-C_5H_{11}, $CH(CH_3)_2$ and $N(CH(CH_3)_2)_2$], 1.95-2.14 [m, 1 H, $CH(CH_3)_2$], 2.25-2.50 (bs, 0.5 H, OH), 3.00-3.30 (bs, 0.5 H, OH), 3.65-3.79 (bm, 1 H, CHOH), 3.80-4.10 [bm, 2 H, $N(CH(CH_3)_2)_2$], 4.54 (dd, 0.5 H, J = 4.9, 6.5 Hz, CHOCO), 4.64 (dd, 0.5 H, J = 3.9, 6.4 Hz, CHOCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96 (CH_3CH_2), 17.85, 18.47, 19.55, 19.58 [$CH(CH_3)_2$], 20.40, 21.42 [$N(CH(CH_3)_2)_2$], 22.51, 22.55 (CH_3CH_2), 25.06, 25.58

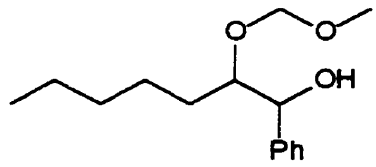
($CH_2\underline{C}H_2CH$), 28.82, 29.39 [$\underline{C}H(CH_3)_2$], 31.78, 31.86 ($\underline{C}H_2CH_2CH$), 32.31, 34.24 ($CH_3CH_2\underline{C}H_2$), 45.46, 45.63, 46.26 [$N(\underline{C}H(CH_3)_2)_2$], 71.64, 72.00, 81.89, 83.13 ($\underline{C}$HOCO and $\underline{C}$HOH), 156.11, 156.39 ($\underline{C}$O); MS (EI) *m/z* 286 (2, M^+-CH_3), 186 (29), 128 (54), 86 (100), 43 (69); Anal. Calcd for $C_{17}H_{35}NO_3$: C, 67.73; H, 11.70; N, 4.65. Found: C, 67.53; H, 11.47; N, 4.54.

(6R,7R*),(6R*,7S*)-7-(N,N-Diisopropylcarbamoyloxy)-6-dodecanol* ***(66)***



colorless oil; IR ($CHCl_3$) 3405, 2959, 2933, 1667, 1450, 1303, 1139, 1059, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.70 [m, 34 H, $HOCH\underline{C}H_2(C\underline{H}_2)_3C\underline{H}_3$, $C\underline{H}_3(C\underline{H}_2)_3C\underline{H}_2CHO$ and $N(CH(C\underline{H}_3)_2)_2$], 2.05-2.30 (bs, 0.5 H, O$\underline{H}$), 2.87-3.15 (bs, 0.5 H, O$\underline{H}$), 3.50-3.69 (m, 1 H, C$\underline{H}$OH), 3.60-4.10 [bm, 2 H, $N(C\underline{H}(CH_3)_2)_2$], 4.65-4.80 (m, 1 H, C$\underline{H}$OCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93, 14.01 ($\underline{C}H_3CH_2$), 20.56, 21.47 [b, $N(CH(\underline{C}H_3)_2)_2$], 22.47, 22.55, 22.58 ($CH_3\underline{C}H_2$), 25.17, 25.67, 25.72 ($CH_2\underline{C}H_2CH$), 30.15, 30.82, 31.64, 31.72, 31.82, 31.92, 32.10, 33.84 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 45.47, 46.39 [b, $N(\underline{C}H(CH_3)_2)_2$], 73.21, 73.95, 77.56, 79.24 (O$\underline{C}$H$\underline{C}$HOH), 155.95, 156.34 ($\underline{C}$O); MS (EI) *m/z* 314 (1, M^+-CH_3), 214 (33), 146 (37), 128 (41), 86 (100), 55 (37), 43 (70); Anal. Calcd for $C_{19}H_{39}NO_3$: C, 69.25; H, 11.93; N, 4.25. Found: C, 69.41; H, 12.12; N, 4.35.

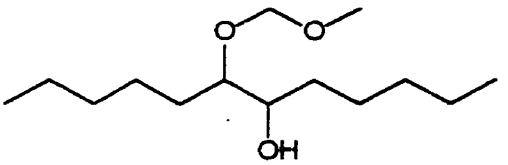
(1R,2R*),(1R*,2S*)-2-Methoxymethoxy-1-phenyl-1-heptanol* ***(58)***



colorless oil; IR ($CHCl_3$) 3570, 3451, 2936, 1457, 1035, 914, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 [t, 3 H, J = 7.0 Hz, $CH_2(CH_2)_3C\underline{H}_3$], 1.10-1.55 [m, 8 H, $C\underline{H}_2(C\underline{H}_2)_3CH_3$], 3.07 (d, 1 H, J = 3.8 Hz, O$\underline{H}$), 3.36 (s, 1.5 H, $OC\underline{H}_3$), 3.39 (s, 1.5 H, $OC\underline{H}_3$), 3.55-3.80 (m, 1 H, C$\underline{H}$OMOM), 4.50-4.85 (m, 3 H, $OC\underline{H}_2O$ and PhC$\underline{H}$OH), 7.20-7.45 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR (75

MHz, $CDCl_3$) δ 13.93, 13.94 ($\underline{C}H_3CH_2$), 22.47, 22.50 ($CH_3\underline{C}H_2$), 24.85, 25.35 ($CH_2\underline{C}H_2CH$), 29.42, 31.33, 31.71 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 55.81 ($O\underline{C}H_3$), 74.95, 76.33 (<u>C</u>HOMOM), 83.02, 85.12 (Ph<u>C</u>HOH), 96.73, 97.44 ($O\underline{C}H_2O$), 126.63, 126.90, 127.29, 127.67, 128.03, 128.26 (Ar-<u>C</u>'s), 140.64, 141.27 (*ipso*-Ar-<u>C</u>); MS (EI) *m/z* 207 (2, M^+-CH_3OCH_2), 152 (6), 107 (100), 79 (18), 45 (56); Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.34.

(6R,7R*),(6R*,7S*)-7-Methoxymethoxy-6-dodecanol (63)*

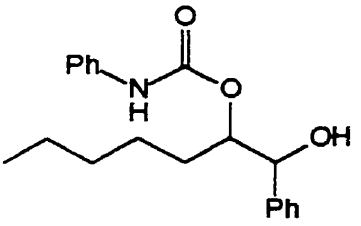


colorless oil; IR ($CHCl_3$) 3578, 3443, 2940, 1462, 1379, 1143, 1097, 1035, 914 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.05 [m, 6 H, $C\underline{H}_3(CH_2)_3CH_2CHO$ and $HOCHCH_2(CH_2)_3C\underline{H}_3$], 1.15-1.70 [m, 16 H, $CH_3(C\underline{H}_2)_3C\underline{H}_2CHO$ and $HOCHC\underline{H}_2(C\underline{H}_2)_3CH_3$], 2.77 (bs, 1 H, O<u>H</u>), 3.30-3.70 (m, 2 H, C<u>H</u>OMOM and C<u>H</u>OH), 3.41 (s, 1.5 H, $OC\underline{H}_3$), 3.42 (s, 1.5 H, $OC\underline{H}_3$), 4.65-4.80 (m, 2 H, $OC\underline{H}_2O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.95, 13.98 ($\underline{C}H_3CH_2$), 22.52, 22.56, 22.58 ($CH_3\underline{C}H_2$), 24.82, 25.27, 25.64, 25.85 ($CH_2\underline{C}H_2CH$), 30.09, 30.94, 31.52, 31.80, 31.90, 31.94, 33.20 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 55.67, 55.72 ($OC\underline{H}_3$), 72.68, 72.96 (<u>C</u>HOMOM), 83.23, 84.05 (C<u>H</u>OH), 96.99, 97.10 ($O\underline{C}H_2O$); MS (EI) *m/z* 201 (5, M^+-CH_3OCH_2), 145 (10), 101 (25), 83 (37), 45 (100); Anal. Calcd for $C_{14}H_{30}O_3$: C, 68.25; H, 12.27. Found: C, 68.09; H, 12.43.

2.3.8 *Representative Procedure for the Transmetalation and Trapping of N-Phenylcarbamate, O-Protected α-Hydroxystannanes*

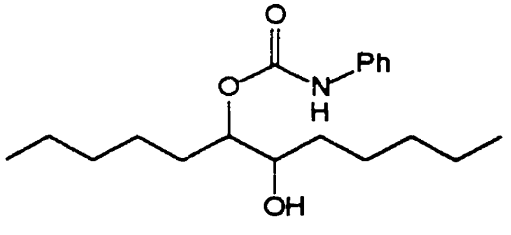
A representative procedure for the transmetalation of *N*-phenylcarbamate **55** and trapping with PhCHO is given below, followed by spectral data of carbamates **62** and **67**. The yields of these carbamates can be found in Table 3. Carbamates **62** and **67** were isolated as a 1:1 mixture of diastereomers.

(1R,2R*),(1R*,2S*)-2-(N-Phenylcarbamoyloxy)-1-phenyl-1-heptanol (62)*



To a cold (-78°C) stirred solution of 1-(trimethylstannyl)hexyl *N*-phenylcarbamate (257.4 mg, 0.67 mmol, 1 equiv) in THF (5 mL) was added dropwise *n*-BuLi (1.45 mL of a 1.15 M solution in hexanes, 2.5 equiv). After 15 min, benzaldehyde (76.3 μL, 0.75 mmol, 1.1 equiv) was added neat. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (20 g of silica/g of substrate; initially 20:1, hexanes:ethyl acetate, with gradual increase in solvent polarity to 5:1) affording 168.4 mg (77% yield) of the product as a yellow oil; IR ($CHCl_3$) 3601, 3432, 2957, 2931, 1725, 1600, 1525, 1443, 1314, 1065, 908, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.70 [m, 11 H, *n*-$C_5\underline{H}_{11}$], 3.11 (bs, 1 H, O<u>H</u>), 4.68 (d, 0.5 H, J = 6.6 Hz, PhC<u>H</u>OH), 4.96 (d, 0.5 H, J = 2.9 Hz, PhC<u>H</u>OH), 5.00-5.15 (m, 1 H, C<u>H</u>OCO), 6.70-7.50 (m, 11 H, N<u>H</u> and Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93 ($\underline{C}H_3CH_2$), 22.39, 22.41 ($CH_3\underline{C}H_2$), 24.91, 25.11 ($CH_2\underline{C}H_2CH$), 28.21, 30.66, 31.52, 31.60 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 75.42, 76.07, 78.62, 78.98 (<u>C</u>HOCO and <u>C</u>HOH), 118.74, 123.45, 123.51, 126.51, 126.80, 126.98, 127.65, 128.20, 128.48, 128.96 (Ar-<u>C</u>'s), 137.70, 137.76, 139.86, 140.53 (*ipso*-Ar-<u>C</u>), 153.84 (<u>C</u>O); MS (EI) *m/z* 234 (8, M^+-C_6H_5NH), 133 (13), 107 (51), 90 (100), 77 (18), 55 (15), 41 (18); Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28 Found: C, 73.22; H, 7.80; N, 4.44.

(6R,7R*),(6R*,7S*)-7-(N-Phenylcarbamoyloxy)-6-dodecanol (67)*



yellow oil; IR ($CHCl_3$) 3599, 3433, 2932, 1725, 1600, 1525, 1443, 1312, 1205, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.00 [m, 6 H, $C\underline{H}_3(CH_2)_3CH_2$ and $HOCHCH_2(CH_2)_3C\underline{H}_3$], 1.05-

1.75 [m, 16 H, $CH_3(C\underline{H}_2)_3C\underline{H}_2$ and $HOCHC\underline{H}_2(C\underline{H}_2)_3CH_3$], 2.15-2.40 (bs, 0.5 H, O<u>H</u>), 2.45-2.73 (bs, 0.5 H, O<u>H</u>), 3.55-3.69 (bm, 0.5 H, C<u>H</u>OH), 3.70-3.85 (bm, 0.5 H, C<u>H</u>OH), 4.64-4.90 (m, 1 H, C<u>H</u>OCO), 6.95-7.50 (m, 6 H, N<u>H</u> and Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.95 ($\underline{C}H_3CH_2$), 22.45, 22.52 ($CH_3\underline{C}H_2$), 25.06, 25.29, 25.36, 25.64 ($CH_2\underline{C}H_2CH$), 28.77, 30.90, 31.66, 31.68, 31.71, 31.77, 32.14, 33.61 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 72.76, 73.37, 77.43, 78.76 (<u>C</u>HOCO and <u>C</u>HOH), 118.61, 123.31, 123.40, 128.96 (Ar-<u>C</u>'s), 137.85, 137.97 (*ipso*-Ar-<u>C</u>), 153.70, 153.86 (<u>C</u>O); MS (EI) *m/z* 207 (3, M^+-C_5H_{11}, -C_3H_7), 113 (13), 95 (60), 81 (25), 69 (61), 55 (63), 43 (100), 29 (41); Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.16; H, 9.90; N, 4.52.

2.3.9 General Procedure for the Transmetalation and Trapping of O-Protected α-Hydroxystannanes; Analysis of Organostannane Scrambled Mixtures by GCMS

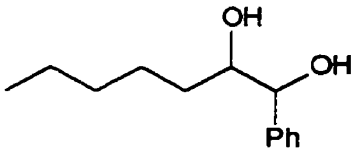
A general procedure for the transmetalation and trapping of *O*-protected α-hydroxystannanes for the purpose of analyzing organostannane scrambling by GCMS is given below. The results from this study can be found in Table 4.

To a cold (-78°C) stirred solution of *O*-protected α-hydroxystannanes (0.15 M in THF, 1.0 equiv) was added dropwise *n*-BuLi (1.05 equiv). After 15 min, benzaldehyde (1.1 equiv) was added. After a further 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was passed through a short pipet of silica (~1 g of silica; 2:1 hexanes:ethyl acetate), to eliminate trace salts, affording the product as a colorless oil, after concentration *in vacuo*. Samples for GCMS analysis were prepared in diethyl ether.

*2.3.10 Alane Reduction of N,N-Diisopropylcarbamate **61** in THF*

To a cold (0°C), stirred solution of $LiAlH_4$ (0.72 mL of a 1.0 M solution in THF, 0.72

mmol) in 2 mL of THF was added H_2SO_4 (0.36 mL of a 1 M solution in Et_2O, 0.36 mmol). This solution was allowed to warm to room temperature and was stirred for 30 min. The solution was then cooled (0°C), and *N,N*-diisopropylcarbamate **61** (119.5 mg, 0.36 mmol) was added. The reaction was allowed to warm to room temperature. A TLC taken 10 min later showed that no starting material was present. The reaction was quenched with solid $Na_2SO_4 \bullet 10\ H_2O$. After 20 min of stirring, all solid material was removed by filtration through Celite® using warm ethyl acetate as eluent. Removal of all volatiles *in vacuo* provided 63.7 mg (86%) of 1-phenyl-1,2-heptanediol (**70**).[34]



This latter material exhibited: IR ($CHCl_3$) 3589, 3440, 3010, 2940, 2863, 1493, 1456, 1384, 1258, 1049 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-0.95 (m, 3 H, $CH_2C\underline{H}_3$), 1.00-1.55 (m, 8 H, $C\underline{H}_2(C\underline{H}_2)_3CH_3$), 1.65-2.30 (bs, 2H, O<u>H</u>), 3.65-3.75 (m, 0.5 H, $CH_2C\underline{H}OH$), 3.80-3.90 (bm, 0.5 H, $CH_2C\underline{H}OH$), 4.44 (d, 0.5 H, J = 6.8 Hz, PhC<u>H</u>OH), 4.68 (d, 0.5 H, J = 4.5 Hz, PhC<u>H</u>OH), 7.20-7.50 (m, 5 H, Ar<u>H</u>).

*2.3.11 Lithium Aluminum Hydride Reduction of N-Phenylcarbamate **62** in THF*

To a cold (0°C), stirred solution of *N*-phenylcarbamate **62** (195.7 mg, 0.60 mmol) in 5 mL of THF was added $LiAlH_4$ (1.20 mL of a 1.0 M solution in THF, 1.20 mmol). The reaction was allowed to warm to room temperature. A TLC taken 10 min later showed that no starting material was present. The reaction was quenched with solid $Na_2SO_4 \bullet 10\ H_2O$. After 20 min of stirring, all solid material was removed by filtration through Celite® using warm ethyl acetate as eluent. Removal of all volatiles *in vacuo* provided 109.8 mg of crude orange oil. Chromatography of this oil on silica gel (4 g) using hexanes/ethyl acetate (5:1) as eluent afforded 79.4 mg (64%) of 1-phenyl-1,2-heptanediol (**70**).

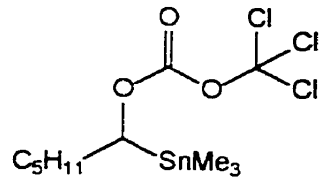
2.3.12 Lithium Aluminum Hydride Reduction of N-Phenylcarbamate 62 in Et_2O

To a cold (0°C), stirred solution of *N*-phenylcarbamate **62** (525.9 mg, 1.60 mmol) in 10 mL of Et_2O was added $LiAlH_4$ (182.2 mg, 4.80 mmol). The cooling bath was removed and the reaction was warmed to reflux for a period of 2 h. The reaction was cooled (0°C) and quenched with solid $Na_2SO_4 \bullet 10\ H_2O$. After 20 min of stirring at room temperature, all solid material was removed by filtration through Celite® using warm ethyl acetate as eluent. Removal of all volatiles *in vacuo* provided 424.3 mg of crude orange oil. Chromatography of this oil on silica gel (17 g) using hexanes/ethyl acetate (5:1) as eluent afforded 278.1 mg (83%) of 1-phenyl-1,2-heptanediol (**70**).

2.3.13 Representative Procedure for the Preparation of Carbonate Protected α-Hydroxystannanes

A representative procedure for the preparation of carbonate **71** is given below, followed by ^1H NMR spectral data of carbonates **71-73**. The yields of these carbonates can be found in Table 6.

1-(Trimethylstannyl)hexyl Trichloromethylcarbonate (71)

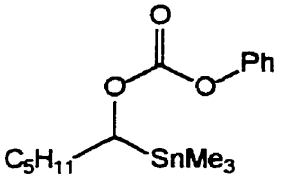


To a cooled (-78°C) solution of trimethyltinlithium (3.89 mmol in 10 mL of THF) was added *n*-hexanal (0.56 mL, 4.67 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide 1.05 g of crude α-hydroxystannane.

This material was cooled to 0°C and then pyridine (10 mL), and trichloromethyl

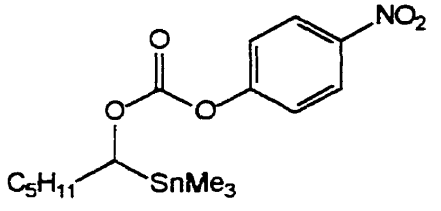
chloroformate (0.46 mL, 3.89 mmol) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (2 h). The solution was diluted with ether (50 mL), washed with 1 M HCl (2 × 20 mL), 10% $NiCl_{2\,aq}$ (3 × 20 mL), $NaHCO_3$ (50 mL), H_2O (25 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 1.127 g of crude orange oil. Chromatography of the resulting oil on silica gel (17 g) using hexanes/ethyl acetate (40:1) as eluent provided 842.5 mg (51%) of the title compound as a colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.17 [s, 9 H, $J_{H\text{-}Sn}$ = 51.9, 53.6 Hz, $Sn(C\underline{H}_3)_3$], 0.87 (t, 3 H, J = 6.7 Hz, $CH_2C\underline{H}_3$), 1.15-1.50 (m, 6 H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.75-2.00 (m, 2 H, $C\underline{H}_2CH$), 3.64 (dd, 1 H, J = 6.4, 8.2 Hz, $CH_2C\underline{H}$).

1-(Trimethylstannyl)hexyl Phenylcarbonate (72)



^{1}H NMR (250 MHz, $CDCl_3$) δ 0.17 (s, 9 H, $J_{H\text{-}Sn}$ = 51.9, 54.3 Hz, $Sn(C\underline{H}_3)_3$, 0.90 (t, 3 H, J = 6.6 Hz, $CH_2C\underline{H}_3$), 1.15-1.50 (m, 6 H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.75-2.10 (m, 2 H, $C\underline{H}_2CH$), 4.68 (dd, 1 H, J = 6.3, 8.4 Hz, $CH_2C\underline{H}$), 6.78-7.00 (m, 1 H, Ar$\underline{H}$), 7.10-7.50 (m, 4 H, Ar$\underline{H}$); MS (EI) *m/z* 371 (3, M^+-CH_3), 243 (15), 211 (13), 165 (100), 135 (23), 117 (12).

1-(Trimethylstannyl)hexyl 4-Nitrophenylcarbonate (73)



^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 [s, 9 H, $J_{H\text{-}Sn}$ = 50.1, 52.3 Hz, $Sn(C\underline{H}_3)_3$], 0.90 (t, 3 H, J = 6.3 Hz, $CH_2C\underline{H}_3$), 1.15-1.50 (m, 6 H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.75-2.00 (m, 2 H, $C\underline{H}_2CH$), 4.03 (dd, 1 H, J = 6.5, 8.1 Hz, $CH_2C\underline{H}$), 7.26-7.35 (AA′ of AA′XX′, 2 H, Ar$\underline{H}$), 8.24-8.30 (XX′ of AA′XX′, 2 H, Ar$\underline{H}$).

2.3.14 Reaction of 72 with (i-Pr)$_2$NH and DMAP in Pyridine

To 214.2 mg (0.56 mmol) of **72** in pyridine (5 mL) was added DMAP (catalytic) and (*i*-Pr)$_2$NH (0.10 mL, 0.79 mmol). The reaction was stirred initially at room temperature for 1 h and then at reflux for an additional 1 h. TLC indicated no progress in the reaction. The reaction was allowed to stir for 24 h at room temperature. The mixture was diluted with ether (20 mL) and washed with 1 M HCl (2 × 25 mL), 10% $NiCl_2$ (2 × 25 mL), H_2O (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 198.1 mg (92%) of starting material **72**.

2.3.15 Reaction of 72 with (i-Pr)$_2$NH and Na_2CO_3 in EtOH[22]

To a warm (50°C) solution of (i-Pr)$_2$NH (62.5 μL, 0.48 mmol) and Na_2CO_3 (3.23 mL of a 2 M solution, 6.48 mmol) was added **72** (153.0 mg, 0.40 mmol) as a solution in EtOH (1 mL). This mixture was warmed to reflux and an additional 3 mL of EtOH was added. The reaction was allowed to reflux for a further 2 h. TLC indicated no substitution had taken place. The reaction was cooled to room temperature, diluted with ether (25 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 124.6 mg (81%) of starting material **72**.

2.3.16 Reaction of 72 with LDA in THF

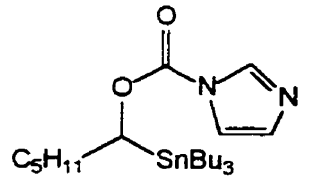
To a cold (0°C) solution of (i-Pr)$_2$NH (85.1 μL, 0.65 mmol) in THF (5 mL) was added *n*-BuLi (0.56 mL of a 1.15 M solution in hexanes, 0.65 mmol). After 15 min of stirring, carbonate **72** (250.0 mg, 0.65 mmol) was added (neat) via syringe. After 1 h at 0°C, an additional 5 equiv of LDA (3.25 mmol) were added. The reaction was quenched after an additional 1 h of stirring at 0°C, with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with 1 M HCl (2 × 20 mL), Na_2CO_3 (20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was

dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 143.1 mg of oil. ^1H NMR analysis of the crude oil gave a 2:1 ratio of the desired product **53** (37%) and α-hydroxystannane **72** (18%).

2.3.17 Reaction of 1-Tributylstannyl-1-hexanol with 1,1'-Carbonyldiimidazole and (i-Pr)$_2$NH

To a cooled (-78°C) solution of tributyltinlithium (0.64 mmol in 10 mL of THF) was added *n*-hexanal (92.1 μL, 0.76 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt).

To a cold (0°C) solution of 1,1'-carbonyldiimidazole (103.6 mg, 0.64 mmol) and Et_3N (0.18 mL, 1.28 mmol) in THF (7 mL) was added a solution of the α-hydroxystannane in THF (3 mL). The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the derivatization was complete (3 h). (*i*-Pr)$_2$NH (0.42 mL, 3.20 mmol) was added at room temperature and the reaction allowed to stir for 4 h. The reaction was further heated at reflux for a period of 12 h. TLC indicated no substitution taking place. The reaction was cooled to room temperature and *N*-butylamine (126 μL, 1.28 mmol) was added with further stirring for a period of 18 h at room temperature. The reaction was diluted with ethyl acetate (25 mL), washed with 1 M HCl (2 × 15 mL), $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 445.4 mg of crude orange oil. ^1H NMR analysis of the crude oil, revealed only the imidazole-protected carbamate **75** (>100%).



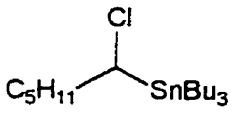
This material exhibited: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.50-1.00 (m, 18 H, $C\underline{H}_3CH_2$ and $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$), 1.05-1.65 [m, 20 H, $CH_3(C\underline{H}_2)_3C\underline{H}_2$ and $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$], 5.07 (dd, 1

H, J = 5.6, 8.9 Hz, $CH_2C\underline{H}O$), 7.00 (s, 1 H, OCNCHC<u>H</u>N), 7.33 (s, 1 H, OCNC<u>H</u>CHN), 8.04 (s, 1 H, NC<u>H</u>N).

*2.3.18 Attempted preparation of carbamate **54** via in situ generation of (1-Tributylstannyl)hexyl-1-chloroformate (**81**)*

To a cooled (-78°C) solution of tributyltinlithium (1.94 mmol in 10 mL of THF) was added *n*-hexanal (0.30 mL, 2.33 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt).

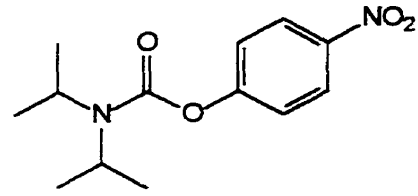
This material was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. To this solution was added Et_3N (0.68 mL, 4.85 mmol) and $COCl_2$ (0.97 mL of a 2.0 M solution in toluene, 1.94 mmol) with stirring. The reaction stirred for 30 min at 0°C and then $(i\text{-Pr})_2NH$ (0.31 mL, 2.33 mmol) was added dropwise. The reaction was allowed to stir at 0°C for a further 30 min before warming to room temperature. The reaction was quenched with H_2O (2 mL) and concentrated *in vacuo*. The remaining residue was dissolved in ether (30 mL) and washed with 1 M HCl (2 × 15 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 1.57 g of crude oil. Chromatography of the resulting oil on silica gel (15 g) using 40:1, hexanes:ethyl acetate provided 684 mg (86%) of 1-chloro-1-tributylstannyl hexane (**81**).



This material exhibited: IR (neat) 2905, 1459, 1376, 1073, 870, 672 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.65-1.05 (m, 18 H, $C\underline{H}_3CH_2$ and $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$), 1.15-1.65 [m, 18 H, $CH_3(C\underline{H}_2)_3CH_2$ and $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$], 1.80-2.00 (m, 2 H, $CH_3(CH_2)_3C\underline{H}_2$) 3.70 (dd, 1 H, J = 6.1, 8.5 Hz, $CH_2C\underline{H}O$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.58 (^1J = 313, 328 Hz, $\underline{C}H_2Sn$), 13.63 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.01 ($\underline{C}H_3$), 22.64 ($CH_3\underline{C}H_2$), 27.46 ($^2J$ = 56 Hz, $\underline{C}H_2CH_2Sn$), 28.28 ($CH_2\underline{C}H_2CH$), 29.07 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.32 ($CH_3CH_2\underline{C}H_2$), 37.85 ($\underline{C}H_2CH_2CH$),

48.53 (CHCl).

2.3.19 N,N-Diisopropyl-4-nitrophenyl carbamate (83) [24]



To a cold (0°C) solution of 4-nitrophenyl chloroformate (971.0 mg, 4.82 mmol) in CH_2Cl_2 (5 mL) was added DMAP (catalytic), Et_3N (1.34 mL, 9.63 mmol) and $(i\text{-Pr})_2NH$ (0.63 mL, 4.82 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with 1 M HCl (2 × 25 mL), $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 1.187 g of crude brown oil. Chromatography on silica gel (24 g) using hexanes/ethyl acetate, 20:1, afforded 946.3 mg of the title compound as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 [bs, 12 H, $N(CH(C\underline{H}_3)_2)_2$], 4.05 [bs, 2 H, $N(C\underline{H}(CH_3)_2)_2$] , 7.25-7.35 (AA' of AA'XX', 2 H, Ar<u>H</u>), 8.20-8.30 (XX' of AA'XX', 2 H, Ar<u>H</u>).

2.3.20 Reaction of 1-Trimethylstannyl-1-hexanol with N,N-Diisopropyl-4-nitrophenyl carbamate (83)

To a cooled (-78°C) solution of trimethyltinlithium (1.84 mmol in 10 mL of THF) was added *n*-hexanal (0.27 mL, 2.21 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt).

This material was dissolved in pyridine (5 mL) and cooled to 0°C. *N,N*-Diisopropyl-4-nitro- phenyl carbamate (587.4 mg, 2.21 mmol) was added and the reaction mixture was warmed to room temperature. After 12 h of stirring the reaction was diluted in ether (30 mL) and washed

with 1 M HCl (2 × 15 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 703.3 mg of crude oil. ^1H NMR analysis of the crude oil confirmed the absence of product **53**.

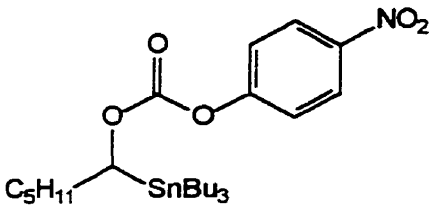
2.3.21 Reaction of 1-Tributylstannyl-1-hexanol with NaH and N,N-Diisopropylcarbamoyl chloride

To a cooled (-78°C) solution of tributyltinlithium (1.02 mmol in 10 mL of THF) was added *n*-hexanal (0.15 mL, 1.22 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt).

This material was dissolved in THF (5 mL) and cooled to 0°C. *N,N*-Diisopropyl-carbamoyl chloride (250.1 mg, 1.53 mmol) and NaH (61.1 mg, 1.53 mmol, washed in hexanes) were added and the reaction mixture was warmed to room temperature. TLC after 2 h revealed the absence of both starting material and product. The reaction was quenched with H_2O and diluted with ether (20 mL). After separation of the phases, the organic layer was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 402.4 mg of crude oil. ^1H NMR analysis of the crude oil confirmed the absence of product **54**.

An identical reaction was performed as above with KH instead of NaH as the metal hydride. ^1H NMR analysis of the crude mixture revealed, as expected, the absence of product **54**.

2.3.22 1-(Tributylstannyl)hexyl 4-Nitrophenylcarbonate (87)



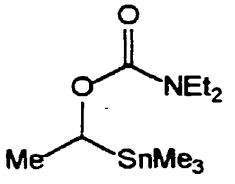
To a cooled (0°C) solution of $(i\text{-Pr})_2NH$ (0.81 mL, 6.16 mmol) was added *n*-BuLi (4.03 mL of a 1.53 M solution in hexanes). After the solution stirred for 15 min Bu_3SnH (1.79 g, 6.16 mmol) was added and stirring was continued for a further 20 min. The mixture was then cooled (-78 °C), and *n*-hexanal (0.89 mL, 7.40 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (50 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide crude 1-tributylstannyl-1-hexanol.

This material was cooled to 0°C and then pyridine (5 mL), and *p*-nitrophenyl chloroformate (1.49 g, 7.40 mmol) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (2-4 hrs). The solution was diluted with ether (50 mL), washed with 1 M HCl (2 × 25 mL), 10% $NiCl_{2\,aq}$ (50 mL), $NaHCO_3$ (50 mL), H_2O (25 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography of the resulting yellow oil (5.32 g) on silica gel (160 g) using hexanes/ethyl acetate (30:1) as eluent provided 1.77 g (52%) of the title compound as a colorless oil; IR (neat film) 2915, 1755, 1528, 1215, 860 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.15 [m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $CH_2(CH_2)_3C\underline{H}_3$], 1.20-1.65 [m, 18 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_2(C\underline{H}_2)_3CH_3$], 1.70-2.10 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 4.90 (dd, 1 H, J = 5.7, 8.8 Hz, C<u>H</u>OCO), 7.26-7.38 (AA′ of AA′XX′, 2 H, Ar<u>H</u>), 8.18-8.30 (XX′ of AA′XX′, 2 H, Ar<u>H</u>); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.53 (^1J = 312, 326 Hz, <u>C</u>H_2Sn), 13.65 (<u>C</u>$H_3CH_2CH_2CH_2Sn$), 14.01 (<u>C</u>H_3CH_2), 22.55 (CH_3<u>C</u>H_2), 27.12 (CH_2<u>C</u>H_2CH), 27.41 (^2J = 56 Hz, <u>C</u>H_2CH_2Sn), 28.97 (^3J = 20 Hz, <u>C</u>$H_2CH_2CH_2Sn$), 31.49 (CH_3CH_2<u>C</u>H_2), 34.18 (<u>C</u>H_2CH_2CH), 78.27 (<u>C</u>HOCO), 121.74, 125.27, 145.25, 152.82 (Ar-<u>C</u>'s), 155.91 (<u>C</u>O); MS (EI) *m/z* 500 (100, M^+-C_4H_9), 372 (77), 291 (63), 269 (87), 235 (70), 177 (97), 121 (59); Anal. Calcd for $C_{25}H_{43}NO_5Sn$: C, 53.97; H, 7.79; N, 2.51. Found: C, 53.76; H, 7.64; N, 2.56.

2.3.23 *Representative Procedure for the Preparation of N,N-Diethylcarbamate Protected α-Hydroxystannanes*

A representative procedure for the preparation of carbamate **88** is given below, followed by spectral data of carbamates **89-94**. The yields of these carbamates can be found in Table 7.

1-(Trimethylstannyl)ethyl N,N-Diethylcarbamate (88)

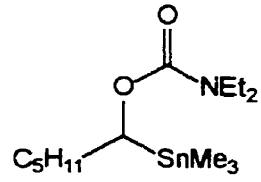


To a cooled (-78°C) solution of trimethyltinlithium (0.019 mol in 50 mL of THF) was added acetaldehyde (1.18 mL, 0.021 mol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (100 mL), washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at rt) to provide 4.50 g of crude α-hydroxystannane.

This material was dissolved in pyridine (10 mL) and cooled to 0°C. To this solution was added *p*-nitrophenyl chloroformate (4.63 g, 0.023 mol) with stirring. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (2-4 h). The reaction was cooled (0°C) and Et_2NH (9.92 mL, 0.096 mol) was added dropwise. The ice bath was removed, and the mixture stirred at room temperature until TLC indicated the complete consumption of carbonate (UV active) (0.5-1.0 h). The solution was diluted with ether (100 mL), washed with 2 M HCl (2 × 50 mL), H_2O (50 mL), 3 M NaOH (3 × 50 mL), H_2O (50 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 6.57 g of orange oil. Purification by flash chromatography (30 g of silica/g of substrate; 30:1, hexanes:ethyl acetate) provided 4.34 g (74%) of the title compound as a colorless oil: IR (neat film) 2953, 1683, 1475, 1427, 1276, 1174, 770 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 [s, 9 H, $J_{H\text{-}Sn}$ = 51.3, 53.5 Hz, $Sn(C\underline{H}_3)_3$], 1.08 (t, 6 H, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.48 (d, 3 H, J = 7.6 Hz, $C\underline{H}_3CH$), 3.23 (bq, 4 H, J = 7.0 Hz, $NC\underline{H}_2CH_3$), 4.48 (q, 1 H, J = 7.6 Hz, $CH_3C\underline{H}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ -9.97 [^1J = 319, 333 Hz, $Sn(\underline{C}H_3)_3$], 13.56 ($NCH_2\underline{C}H_3$), 19.24

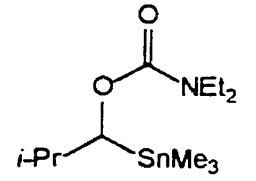
(C̲H₃CH), 41.21 (NC̲H₂CH₃), 67.02 (^1J = 434, 455 Hz, CH₃C̲H), 156.37 (C̲O); MS (EI) *m/z* 294 (29, M^+-CH₃), 266 (11), 165 (34), 144 (36), 100 (44), 72 (100); Anal. Calcd for $C_{10}H_{23}NO_2Sn$: C, 38.99; H, 7.52; N, 4.54. Found: C, 39.17; H, 7.38; N, 4.60.

*1-(Trimethylstannyl)hexyl N,N-Diethylcarbamate (**89**)*



IR (neat film) 2922, 1638, 1445, 1378, 1275, 1175, 1099, 1066, 984, 899, 769 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 [s, 9 H, J_{Sn-H} = 51.1, 53.3 Hz, Sn(C̲H₃)₃], 0.80-0.95 [m, 3 H, CH₂(CH₂)₃C̲H₃] 1.08 (t, 6 H, J = 7.1 Hz, NCH₂C̲H₃), 1.10-1.40 [m, 6 H, CH₂(C̲H₂)₃CH₃], 1.70-1.95 [m, 2 H, C̲H₂(CH₂)₃CH₃], 3.15-3.30 (m, 4 H, NC̲H₂CH₃), 4.40 (dd, 1 H, J = 6.3, 8.0 Hz, C̲HOCO); ^{13}C NMR (63 MHz, $CDCl_3$) δ -9.34 [^1J = 316, 332 Hz, Sn(C̲H₃)₃], 13.8 (b, NCH₂C̲H₃), 13.84 (C̲H₃CH₂), 22.45 (CH₃C̲H₂), 27.11 (^2J = 33 Hz, CH₂C̲H₂CH), 31.51 (CH₃CH₂C̲H₂), 33.75 (C̲H₂CH₂CH), 41.34 (b, NC̲H₂CH₃), 72.30 (^1J = 439, 458 Hz, C̲HOCO), 156.55 (C̲O); MS (EI) *m z* 350 (32, M^+-CH₃), 266 (41), 200 (24), 165 (47), 135 (21), 100 (56), 72 (100); Anal. Calcd for $C_{14}H_{31}NO_2Sn$: C, 46.18; H, 8.58; N, 3.85. Found: C, 46.24; H, 8.44; N, 3.86.

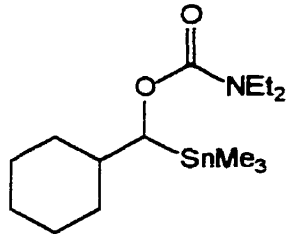
*(1-Trimethylstannyl-2-methyl)propyl N,N-Diethylcarbamate (**90**)*



IR (neat film) 2967, 2350, 1684, 1475, 1426, 1272, 988, 770 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08 [s, 9 H, J_{H-Sn} = 50.7, 53.2 Hz, Sn(C̲H₃)₃], 0.94 [d, 6 H, J = 7.4 Hz, CH(C̲H₃)₂], 1.09 (t, 6 H, J = 7.1 Hz, NCH₂C̲H₃), 2.10-2.20 [m, 1 H, C̲H(CH₃)₂], 3.24 (bq, 4 H, J = 6.8 Hz, NC̲H₂CH₃), 4.26 (d, 1 H, J = 6.7 Hz, C̲HOCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ -8.81 [^1J = 317, 332 Hz, Sn(C̲H₃)₃], 13.29, 13.62 (b, NCH₂C̲H₃), 19.52 [^3J = 27 Hz, CH(C̲H₃)₂], 20.62 [^3J = 27 Hz, CH(C̲H₃)₂], 31.53 [C̲H(CH₃)₂], 41.00 (b, NC̲H₂CH₃), 78.76 (^1J = 442, 460 Hz, C̲HOCO), 156.03

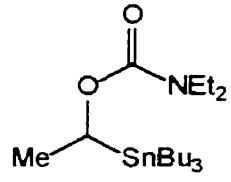
(CO); MS (EI) *m/z* 322(18, M^+-CH_3), 266 (21), 165 (33), 135 (16), 116 (22), 100 (39), 72 (100); Anal. Calcd for $C_{12}H_{27}NO_2Sn$: C, 42.89; H, 8.09; N, 4.16. Found: C, 43.05; H, 7.99; N, 3.90.

*(1-Cyclohexyl-1-trimethylstannyl)methyl N,N-Diethylcarbamate (**91**)*



IR (neat film) 2924, 1683, 1425, 1272, 1175, 1059, 983, 887, 769 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 [s, 9 H, $J_{H\text{-}Sn}$ = 50.9, 53.0 Hz, $Sn(CH_3)_3$], 1.09 (t, 6 H, J = 7.1 Hz, NCH_2CH_3), 0.95-1.90 (bm, 11 H, *c*-C_6H_{11}), 3.10-3.35 (bq, 4 H, J = 6.8 Hz, NCH_2CH_3), 4.28 (d, 1 H, J = 6.7 Hz, CHOCO); ^{13}C NMR (63 MHz, $CDCl_3$) δ -8.56 [^1J = 316, 330 Hz, $Sn(CH_3)_3$], 13.95 (b, NCH_2CH_3), 26.04, 26.17, 26.42 (-$CH_2CH_2CH_2$-), 30.55 (^3J = 27 Hz, -$CH_2CHCHSn$), 31.28 (^3J = 27 Hz, -$CH_2CHCHSn$), 41.6 (b, NCH_2CH_3), 41.60 (CHCHSn), 78.23 (^1J = 439, 460 Hz, CHOCO), 156.52 (CO); MS (EI) *m/z* 362 (15, M^+-CH_3), 266 (38), 165 (37), 100 (46), 72 (100); Anal. Calcd for $C_{15}H_{31}NO_2Sn$: C, 47.90; H, 8.30; N, 3.72. Found: C, 47.63; H, 7.99; N, 3.57.

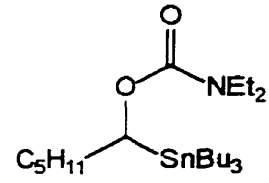
*1-(Tributylstannyl)ethyl N,N-Diethylcarbamate (**92**)*



IR (neat film) 2923, 1684, 1468, 1426, 1275, 1173 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.65-1.00 (m, 15 H, $CH_3CH_2CH_2CH_2Sn$), 1.08 (t, 6 H, J = 7.1 Hz, NCH_2CH_3), 1.05-1.65 (m, 12 H, $CH_3CH_2CH_2CH_2Sn$), 1.49 (d, 3 H, J = 7.5 Hz, CH_3CH), 3.10-3.40 (bm, 4 H, NCH_2CH_3), 4.72 (q, 1 H, J = 7.5 Hz, CHOCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.29 (^1J = 306, 321 Hz, CH_2Sn), 13.69 ($CH_3CH_2CH_2CH_2Sn$), 13.7 (b, overlapping, NCH_2CH_3), 20.44 (CH_3CH), 27.50 (^2J = 55 Hz, CH_2CH_2Sn), 29.12 (^3J = 20 Hz, $CH_2CH_2CH_2Sn$), 41.40 (b, NCH_2CH_3), 66.85 (CHOCO), 156.56 (CO); MS (EI) *m/z* 378 (100, M^+-C_4H_9), 350 (12), 236 (33), 177 (41), 144 (31), 121 (31), 100 (38), 72 (46); Anal. Calcd for $C_{19}H_{41}NO_2Sn$: C, 52.55; H, 9.51; N, 3.22. Found: C, 52.65; H,

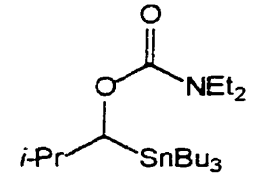
9.48; N, 3.02.

*1-(Tributylstannyl)hexyl N,N-Diethylcarbamate (**93**)*



IR (neat film) 2915, 1684, 1467, 1425, 1274, 1174, 1067, 983 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.70-1.05 [m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $CH_2(CH_2)_3C\underline{H}_3$], 1.08 (t, 6 H, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.15-1.60 [m, 18 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_2(C\underline{H}_2)_3CH_3$], 1.65-2.00 [m, 2 H, $C\underline{H}_2(CH_2)_3CH_3$], 3.10-3.40 (m, 4 H, $NC\underline{H}_2CH_3$), 4.65 (dd, 1 H, J = 5.8, 8.6 Hz, C<u>H</u>OCO); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.48 (^1J = 306, 321 Hz, $\underline{C}H_2Sn$), 13.27 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.5 (b, overlapping, $NCH_2\underline{C}H_3$), 13.60 ($\underline{C}H_3CH_2$), 22.30 ($CH_3\underline{C}H_2$), 27.12 ($CH_2\underline{C}H_2CH$), 27.20 (^2J = 55 Hz, $\underline{C}H_2CH_2Sn$), 28.85 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.30 ($CH_3CH_2\underline{C}H_2$), 34.23 ($\underline{C}H_2CH_2CH$), 41.13 (b, $N\underline{C}H_2CH_3$), 71.61 (^1J = 369, 387 Hz, <u>C</u>HOCO), 156.12 (<u>C</u>O); MS (EI) *m/z* 434 (46, M^+-CH_3), 350 (31), 236 (34), 192 (17), 177 (52), 121 (42), 100 (75), 72 (100); Anal. Calcd for $C_{23}H_{49}NO_2Sn$: C, 56.33; H, 10.07; N, 2.85. Found: C, 56.50; H, 9.96; N, 2.95.

*1-(Tributylstannyl-2-methyl)propyl N,N-Diethylcarbamate (**94**)*



IR (neat film) 2958, 1686, 1467, 1424, 1271, 1173, 986 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.65-1.00 (m, 15 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$), 0.92 [d, 6 H, J = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.09 (t, 6 H, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.15-1.65 (m, 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 2.05-2.20 [m, 1 H, $C\underline{H}(CH_3)_2$], 3.10-3.40 (bm, 4 H, $NC\underline{H}_2CH_3$), 4.51 (d, 1 H, J = 6.8 Hz, C<u>H</u>OCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.20 (^1J = 304, 319 Hz, $\underline{C}H_2Sn$), 13.67 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.7 (b, overlapping, $NCH_2\underline{C}H_3$), 20.23, 20.83 [$CH(\underline{C}H_3)_2$], 27.54 (^2J = 57 Hz, $\underline{C}H_2CH_2Sn$), 29.16 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 32.47 [$\underline{C}H(CH_3)_2$], 41.26 (b, $N\underline{C}H_2CH_3$), 78.76 (<u>C</u>HOCO), 156.44 (<u>C</u>O); MS (EI) *m/z* 406 (100, M^+-C_4H_9), 350 (82), 236 (67), 177 (90), 121 (51), 100 (82), 72 (91); Anal.

Calcd for $C_{21}H_{45}NO_2Sn$: C, 54.56; H, 9.81; N, 3.02. Found: C, 54.34; H, 9.61; N, 2.94.

2.3.24 General Procedure for the Transmetalation of N,N-Diethylcarbamates and Trapping with CH_3OD

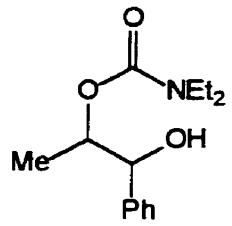
A general procedure for the transmetalation of carbamate **93**, employing a CH_3OD quench is given below. The results from this study can be found in Table 8.

To a cold (-78 or –95 °C) stirred solution of carbamate **93** (0.15 M in THF, 1.0 equiv) was added dropwise RLi (1.05 equiv). After 15 min, CH_3OD (5 equiv) was added. After a further 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (20 g of silica/g of substrate) using hexanes:ethyl acetate (initially 20:1, with a gradual gradient to 5:1).

2.3.25 Representative Procedure for the Transmetalation and Trapping of N,N-Diethyl-carbamate Protected α-Hydroxystannanes

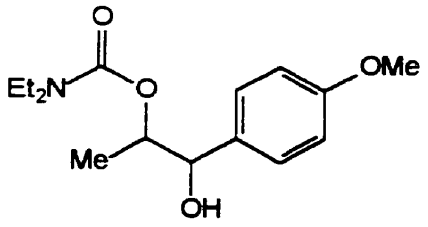
A representative procedure for the transmetalation of *N,N*-diethylcarbamate **88** and trapping with PhCHO is given below, followed by spectral data of carbamates **96, 110-125**. The yields of these carbamates can be found in Table 9. All products were isolated as a 1:1 mixture of diastereomers except compound **121**.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-phenyl-1-propanol* ***(110)***



To a cold (-95°C) stirred solution of 1-(trimethylstannyl)ethyl *N,N*-diethylcarbamate (441.8 mg, 1.43 mmol, 1 equiv) in THF (5 mL) was added dropwise *s*-BuLi (1.50 mL of a 1.14 M solution in hexanes, 1.2 equiv). After 15 min, benzaldehyde (0.18 mL, 1.72 mmol, 1.2 equiv) was added neat. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (40 g of silica/g of substrate; initially 10:1, hexanes:ethyl acetate, with gradual increase in solvent polarity to 5:1) affording 198.5 mg (60% yield) of product as a colorless oil; IR (neat film) 3414, 2958, 1680, 1453, 1276, 1176, 1052, 763, 702 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95-1.30 (m, 9 H, $C\underline{H}_3CH$ and $NCH_2C\underline{H}_3$), 3.10-3.45 (bm, 5 H, $NC\underline{H}_2CH_3$ and O<u>H</u>), 4.60 (d, 0.5 H, J = 7.5 Hz, PhC<u>H</u>OH), 4.85 (d, 0.5 H, J = 3.2 Hz, PhC<u>H</u>OH), 4.99 (dq, 0.5 H, J = 6.5, 13.3 Hz, $CH_3C\underline{H}$), 5.09 (dq, 0.5 H, J = 3.3, 6.6 Hz, $CH_3C\underline{H}$), 7.20-7.40 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.59 (b, $NCH_2\underline{C}H_3$), 14.96, 16.75 ($\underline{C}H_3CH$), 41.56 (b, $N\underline{C}H_2CH_3$), 75.12, 75.66, 76.30, 77.75 [O<u>C</u>H<u>C</u>H(OH)Ph], 126.67, 126.97, 127.42, 127.82, 127.94, 128.23 (Ar-<u>C</u>'s), 140.19, 140.83 (*ipso*-Ar-<u>C</u>), 155.89, 156.26 (<u>C</u>O); MS (EI) *m/z* 207 (1, M^+-CO_2), 145 (22), 134 (14), 116 (33), 100 (100), 72 (42); Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.17; H, 8.36; N, 5.69.

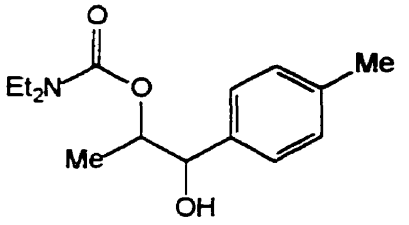
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-(4-methoxyphenyl)-1-propanol* ***(111)***



yellow oil; IR ($CHCl_3$) 3602, 3405, 2994, 1678, 1613, 1513, 1477, 1430, 1260, 1176, 1069, 1034, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 1.5 H, J = 6.4 Hz, $C\underline{H}_3CH$), 1.10 (t, 6 H,

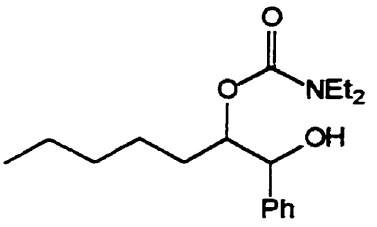
J = 7.1 Hz, $NCH_2\underline{C}H_3$), 1.15 (d, 1.5 H, J = 6.5 Hz, $\underline{C}H_3CH$), 3.10-3.35 (m, 4 H, $NC\underline{H}_2CH_3$), 3.75, (s, 1.5 H, $OC\underline{H}_3$), 3.76 (s, 1.5 H, $OC\underline{H}_3$), 3.70-3.85 (m, 1 H, O<u>H</u>), 4.55 (dd, 0.5 H, J = 3.9, 7.1 Hz, PhC<u>H</u>OH), 4.70 (t, 0.5 H, J = 3.7 Hz, PhC<u>H</u>OH), 4.88-5.05 (m, 1 H, C<u>H</u>OCO), 6.80-6.90 (AA′ of AA′XX′, 2 H, Ar<u>H</u>), 7.20-7.30 (XX′ of AA′XX′, 2 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.17, 13.59 ($NCH_2\underline{C}H_3$), 14.96, 16.35 ($\underline{C}H_3CH$), 41.00, 41.49 ($N\underline{C}H_2CH_3$), 54.87 ($O\underline{C}H_3$), 74.78, 75.52 (Ph<u>C</u>HOH), 75.27, 76.59 (<u>C</u>HOCO), 113.08, 113.32, 127.66, 127.88, 132.50, 132.82 (Ar-<u>C</u>'s), 155.59, 155.93 (*ipso*-Ar-<u>C</u>), 158.65, 158.91 (<u>C</u>O); MS (EI) *m/z* 165 (4, M^+-Et_2NCOO), 137 (26), 116 (59), 100 (27), 72 (25); Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.28; H, 8.22; N, 5.05.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-(4-methylphenyl)-1-propanol (**112**)*



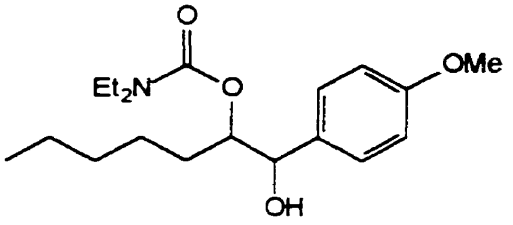
yellow oil; IR ($CHCl_3$) 3603, 3404, 2997, 1678, 1478, 1430, 1277, 1177, 1069, 977 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 1.5 H, J = 6.5 Hz, $\underline{C}H_3CH$), 1.09 (t, 6 H, J = 7.1 Hz, $NCH_2\underline{C}H_3$), 1.14 (d, 1.5 H, J = 6.6 Hz, $\underline{C}H_3CH$), 2.31 (s, 3 H, $ArC\underline{H}_3$), 3.10-3.35 (m, 4 H, $NC\underline{H}_2CH_3$), 3.65-3.80 (m, 1 H, O<u>H</u>), 4.55 (d, 0.5 H, J = 6.9 Hz, PhC<u>H</u>OH), 4.74 (bs, 0.5 H, PhC<u>H</u>OH), 4.90-5.05 (m, 1 H, C<u>H</u>OCO), 7.05-7.30 (m, 4 H, Ar<u>H</u>) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.21, 13.64 ($NCH_2\underline{C}H_3$), 14.81, 16.45 ($\underline{C}H_3CH$), 20.84, 20.86 ($Ar\underline{C}H_3$), 41.05, 41.55 ($N\underline{C}H_2CH_3$), 74.91, 75.82 (Ph<u>C</u>HOH), 75.31, 77.04 (<u>C</u>HOCO), 126.45, 126.72, 128.41, 128.68, 136.67, 137.13, 137.27, 137.70 (Ar-<u>C</u>'s), 155.67, 156.03 (<u>C</u>O); MS (EI) *m/z* 221 (1, M^+-CO_2), 148 (51), 145 (24), 121 (23), 116 (91), 100 (100), 72 (55); Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.88; H, 8.93; N, 5.41.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-phenyl-1-heptanol (113)*



yellow oil; IR ($CHCl_3$) 3597, 3392, 2947, 1676, 1477, 1431, 1278, 1176, 1073, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.60 [m, 11 H, *n*-$C_5\underline{H}_{11}$], 1.09 (t, 6 H, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 3.10-3.40 (m, 4 H, $NC\underline{H}_2CH_3$), 3.90 (d, 0.5 H, J = 5.2 Hz, O<u>H</u>), 4.08 (d, 0.5 H, J = 4.4 Hz, O<u>H</u>), 4.65 (t, 0.5 H, J = 5.4 Hz, PhC<u>H</u>OH), 4.81 (t, 0.5 H, J = 3.7 Hz, PhC<u>H</u>OH), 4.85-5.05 (m, 1 H, C<u>H</u>OCO), 7.15-7.40 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.17 ($NCH_2C\underline{H}_3$), 13.71, 13.73 ($\underline{C}H_3CH_2$), 13.87 ($NCH_2C\underline{H}_3$), 22.23, 22.27 ($CH_3\underline{C}H_2$), 24.86, 25.23 ($CH_2\underline{C}H_2CH$), 29.44, 30.32 ($CH_3CH_2\underline{C}H_2$), 31.34, 31.36 ($\underline{C}H_2CH_2CH$), 41.03, 41.68 ($N\underline{C}H_2CH_3$), 75.76, 76.27 (PhCHOH), 78.88 (CHOCO), 126.68, 126.74, 127.13, 127.45, 127.69, 128.02 (Ar-C's), 140.32, 141.14 (*ipso*-Ar-C), 156.34, 156.55 (CO); MS (EI) *m/z* 207 (4, M^+-Et_2NCO), 116 (14), 100 (55), 72 (15); Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.30; H, 9.31; N, 4.59.

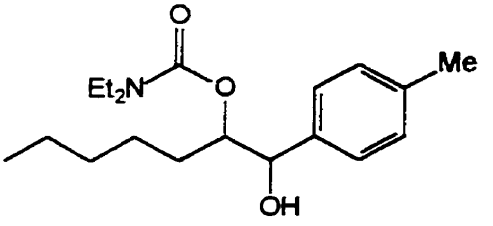
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-(4-methoxyphenyl)-1-heptanol (96)*



yellow oil; IR (neat film) 3601, 3393, 2945, 1676, 1514, 1478, 1431, 1278, 1249, 1072, 1036, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-1.55 (m, 17 H, *n*-$C_5\underline{H}_{11}$ and $NCH_2C\underline{H}_3$), 3.15-3.40 (m, 4 H, $NC\underline{H}_2CH_3$), 3.63 (d, 0.5 H, J = 4.9 Hz, O<u>H</u>), 3.78 (s, 1.5 H, $OC\underline{H}_3$), 3.79 (s, 1.5 H, $OC\underline{H}_3$), 3.82 (d, 0.5 H, J = 4.2 Hz, O<u>H</u>), 4.59 (dd, 0.5 H, J = 4.8, 7.3 Hz, PhC<u>H</u>OH), 4.77 (t, 0.5 H, J = 3.5 Hz, PhC<u>H</u>OH), 4.85-5.00 (m, 1 H, C<u>H</u>OCO), 6.80-6.90 (AA′ of AA′XX′, 2 H, Ar<u>H</u>), 7.20-7.30 (XX′ of AA′XX′, 2 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.30 ($NCH_2C\underline{H}_3$), 13.82, 13.85 ($\underline{C}H_3CH_2$), 13.92 ($NCH_2C\underline{H}_3$), 22.34, 22.38 ($CH_3\underline{C}H_2$), 24.91, 25.35 ($CH_2\underline{C}H_2CH$), 29.71, 30.62 ($CH_3CH_2\underline{C}H_2$), 31.44, 31.48 ($\underline{C}H_2CH_2CH$), 41.17, 41.82 ($N\underline{C}H_2CH_3$), 55.10 ($O\underline{C}H_3$),

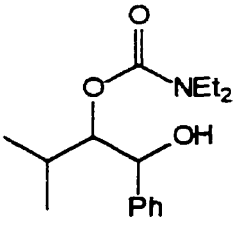
75.62, 76.36 (PhCHOH), 78.98, 79.19 (CHOCO), 113.24, 113.64, 127.97, 128.01, 132.39, 133.37 (Ar-C's), 156.56, 156.83 (*ipso*-Ar-C), 158.87, 159.11 (CO); MS (EI) *m/z* 220 (12, M^+-Et_2NCO, CH_3CH_2), 163 (16), 150 (15), 147 (12), 137 (22), 121 (23), 116 (37), 100 (41), 72 (24), 28 (100); Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.71; H, 9.36; N, 4.22.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-(4-methylphenyl)-1-heptanol* ***(114)***



yellow oil; IR ($CHCl_3$) 3599, 3396, 2943, 1676, 1477, 1431, 1278, 1176, 1074, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.60 [m, 11 H, *n*-C_5H_{11}], 1.10 (t, 6 H, *J* = 7.1 Hz, NCH_2CH_3), 2.32 (s, 3 H, $ArCH_3$), 3.05-3.40 (m, 4 H, NCH_2CH_3), 3.72 (d, 0.5 H, *J* = 5.1 Hz, OH), 3.90 (d, 0.5 H, *J* = 4.3 Hz, OH), 4.60 (dd, 0.5 H, *J* = 5.3, 6.8 Hz, PhCHOH), 4.77 (t, 0.5 H, *J* = 3.6 Hz, PhCHOH), 4.85-5.05 (m, 1 H, CHOCO), 7.05-7.30 (m, 4 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.20 (NCH_2CH_3), 13.74, 13.76 (CH_3CH_2), 13.83 (NCH_2CH_3), 20.91, 20.93 ($ArCH_3$), 22.27, 22.32 (CH_3CH_2), 24.87, 25.28 (CH_2CH_2CH), 29.44, 30.43 ($CH_3CH_2CH_2$), 31.38, 31.41 (CH_2CH_2CH), 41.05, 41.70 (NCH_2CH_3), 75.66, 76.29 (PhCHOH), 78.91 (CHOCO), 126.64, 126.70, 128.41, 128.77, 136.68, 137.09, 137.28, 138.16 (Ar-C's), 156.40, 156.65 (CO); MS (EI) *m/z* 204 (9, M^+-Et_2NCOOH), 121 (19), 116 (55), 100 (100), 72 (35); Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.26; H, 9.71; N, 4.39.

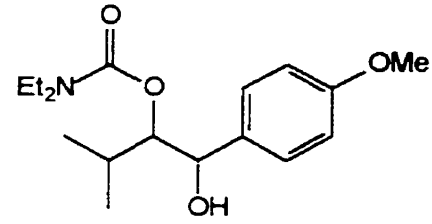
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-3-methyl-1-phenyl-1-butanol* ***(115)***



yellow oil; IR (neat film) 3427, 2961, 1683, 1477, 1428, 1276, 1176, 1065, 999, 762, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.20 [m, 12 H, $CH(CH_3)_2$ and NCH_2CH_3], 1.68 [dseptets,

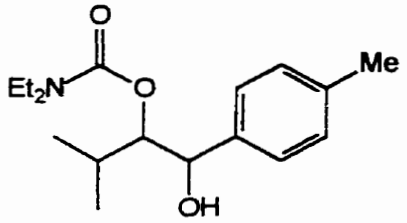
0.5 H, J = 3.8, 6.8 Hz, C<u>H</u>$(CH_3)_2$], 1.82-1.97 [m, 0.5 H, C<u>H</u>$(CH_3)_2$], 3.05-3.45 (m, 2 H, NC<u>H</u>$_2$CH$_3$), 3.27 (q, 2 H, J = 7.1 Hz, NC<u>H</u>$_2$CH$_3$), 3.86 (bs, 1 H, O<u>H</u>), 4.73 (d, 0.5 H, J = 7.7 Hz, PhC<u>H</u>OH), 4.80 (d, 0.5 H, J = 3.8 Hz, PhC<u>H</u>OH), 4.81-4.90 (m, 1 H, C<u>H</u>OCO), 7.15-7.45 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.23, 13.79, 13.97 (NCH$_2$<u>C</u>H$_3$), 16.30, 17.96, 19.95, 20.17 [CH(<u>C</u>H$_3$)$_2$], 28.43, 28.81 [<u>C</u>H$(CH_3)_2$], 40.93, 41.24, 41.75, 41.92 (N<u>C</u>H$_2$CH$_3$), 74.29, 75.36 (Ph<u>C</u>HOH), 82.56, 83.30 (<u>C</u>HOCO), 126.71, 127.11, 127.43, 127.70, 127.82, 128.35 (Ar-<u>C</u>'s), 140.72, 141.49 (*ipso*-Ar-<u>C</u>), 156.38, 157.16 (<u>C</u>O); MS (EI) ***m/z*** 207 (1, M$^+$-Et$_2$N), 173 (11), 116 (20), 100 (100), 72 (31); Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 69.00; H, 8.86; N, 4.87.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-1-(4-methoxyphenyl)-3-methyl-1-butanol (**116**)*



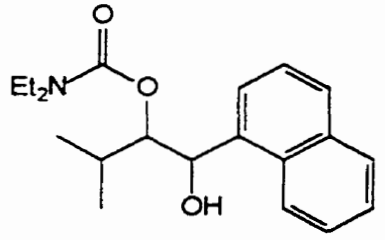
yellow oil; IR ($CHCl_3$) 3602, 3400, 2971, 1676, 1514, 1476, 1431, 1260, 1177, 1070, 1036, 999, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-1.20 [m, 12 H, CH(C<u>H</u>$_3$)$_2$ and NCH$_2$C<u>H</u>$_3$], 1.55-1.70 [m, 0.5 H, C<u>H</u>$(CH_3)_2$], 1.90-2.02 [m, 0.5 H, C<u>H</u>$(CH_3)_2$], 3.00-3.45 (m, 4 H, NC<u>H</u>$_2$CH$_3$), 3.75 (s, 1.5 H, OC<u>H</u>$_3$), 3.76 (s, 1.5 H, OC<u>H</u>$_3$), 3.82 (d, 0.5 H, J = 5.2 Hz, O<u>H</u>), 3.89 (d, 0.5 H, J = 3.9 Hz, O<u>H</u>), 4.60-4.90 [m, 2 H, OC<u>H</u>C<u>H</u>(OH)Ph], 6.75-6.90 (AA' of AA'XX', 2 H, Ar<u>H</u>), 7.20-7.35 (XX' of AA'XX', 2 H, Ar<u>H</u>), ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.94, 13.07, 13.68, 13.83 (NCH$_2$<u>C</u>H$_3$), 16.05, 17.33, 19.73, 19.97 [CH(<u>C</u>H$_3$)$_2$], 28.29, 28.59 [<u>C</u>H$(CH_3)_2$], 40.71, 41.03, 41.49, 41.69 (N<u>C</u>H$_2$CH$_3$), 54.88 (O<u>C</u>H$_3$), 73.46, 74.59 (Ph<u>C</u>HOH), 81.75, 82.87 (<u>C</u>HOCO), 113.02, 113.54, 127.72, 128.17, 132.99, 133.47 (Ar-<u>C</u>'s), 155.96, 156.91 (*ipso*-Ar-<u>C</u>), 158.74, 158.91 (<u>C</u>O); MS (EI) ***m z*** 236 (1, M$^+$-Et$_2$NH), 192 (26), 137 (42), 116 (81), 100 (59), 72 (37); Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.00; H, 8.61; N, 4.51.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-3-methyl-1-(4-methylphenyl)-1-butanol (117)*



yellow oil; IR ($CHCl_3$) 3601, 3396, 2973, 1675, 1477, 1431, 1277, 1178, 1070, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.30 (m, 6 H, $NCH_2C\underline{H}_3$), 0.93 [d, 3 H, J = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.01 [d, 3 H, J = 6.8 Hz, $CH(C\underline{H}_3)_2$], 1.65 [dseptet, 0.5 H, J = 3.4, 6.8 Hz, $C\underline{H}(CH_3)_2$], 1.85-2.00 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 2.32 (s, 1.5 H, $ArC\underline{H}_3$), 2.33 (s, 1.5 H, $ArC\underline{H}_3$), 3.05-3.45 (m, 4 H, $NC\underline{H}_2CH_3$), 3.55-3.70 (bm, 1 H, O<u>H</u>), 4.65-4.90 [m, 2 H, $OC\underline{H}C\underline{H}$(OH)Ph], 7.05-7.35 (m, 4 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.16, 13.29, 13.86, 14.04 ($NCH_2\underline{C}H_3$), 16.14, 18.07, 19.99, 20.27 [$CH(\underline{C}H_3)_2$], 21.04, 21.07 ($\underline{C}H_3$), 28.48, 28.87 [$\underline{C}H(CH_3)_2$], 40.96, 41.28, 41.77, 41.98 ($N\underline{C}H_2CH_3$), 74.25, 75.40 (Ph<u>C</u>HOH), 82.62, 83.28 (<u>C</u>HOCO), 126.71, 127.10, 128.57, 129.12, 137.09, 137.47, 137.62, 138.50 (Ar-<u>C</u>'s), 156.51, 157.32 (<u>C</u>O); MS (EI) *m/z* 250 (1, M^+-$(CH_3)_2CH$), 173 (12), 121 (21), 116 (44), 100 (100), 72 (36); Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.77. Found: C, 69.43; H, 9.17; N, 4.82.

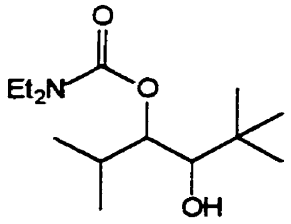
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-3-methyl-1-(1-naphthyl)-1-butanol (118)*



yellow oil; IR ($CHCl_3$) 3602, 3399, 2972, 1680, 1477, 1429, 1276, 1176, 1068, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.35 [m, 12 H, $CH(C\underline{H}_3)_2$ and $NCH_2C\underline{H}_3$], 1.65-1.80 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 2.05-2.20 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 2.80-3.40 (bm, 4.5 H, $NC\underline{H}_2CH_3$ and O<u>H</u>), 3.94 (d, 0.5 H, J = 5.2 Hz, O<u>H</u>), 5.10 (dd, 0.5 H, J = 3.9, 5.9 Hz, <u>C</u>HOCO), 5.18 (dd, 0.5 H, J = 4.3, 7.1 Hz, <u>C</u>HOCO), 5.47 (t, 0.5 H, J = 6.1 Hz, ArC<u>H</u>OH), 5.72 (d, 0.5 H, J = 4.3 Hz, ArC<u>H</u>OH), 7.35-7.95 (m, 6 H, Ar<u>H</u>), 8.23 (dd, 1 H, J = 4.9, 8.0 Hz, Ar<u>H</u>) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ

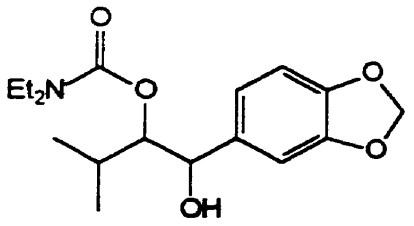
13.04, 13.28, 13.79, 14.07 ($NCH_2\underline{C}H_3$), 16.74, 17.04, 20.31, 20.64 [$CH(\underline{C}H_3)_2$], 28.34, 28.82 [$\underline{C}H(CH_3)_2$], 40.80, 41.32, 41.53, 41.96 ($N\underline{C}H_2CH_3$), 70.57, 72.93 (Ar$\underline{C}$HOH), 80.78, 82.75 (C$\underline{H}$OCO), 123.39, 123.47, 124.34, 125.15, 125.17, 125.29, 125.47, 125.98, 126.11, 128.00. 128.44, 128.59, 128.88, 130.86, 131.15, 133.49, 133.96, 136.99, 137.06 (Ar-$\underline{C}$'s), 155.49, 157.07 ($\underline{C}$O); MS (EI) *m/z* 257 (1, M^+-Et_2NH), 212 (33), 157 (17), 129 (16), 116 (27), 100 (100), 72 (41); Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.15; H, 8.15; N, 4.21.

(3R,4R*),(3R*,4S*)-4-(N,N-Diethylcarbamoyloxy)-2,2,5-trimethyl-3-hexanol* ***(119)***



white solid; IR ($CHCl_3$) 3440, 2965, 1683, 1476, 1428, 1276, 1177, 1067, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.25 [m, 12 H, $NCH_2C\underline{H}_3$ and $CH(C\underline{H}_3)_2$], 0.91 [s, 4.5 H, $C(C\underline{H}_3)_3$], 0.96 [s, 4.5 H, $C(C\underline{H}_3)_3$], 2.00-2.25 [m, 1 H, $C\underline{H}(CH_3)_2$], 3.15-3.45 [m, 6 H, $NC\underline{H}_2CH_3$, $(CH_3)_3CC\underline{H}O\underline{H}$], 4.78 (d, 0.5 H, J = 7.4 Hz, C$\underline{H}$OCO), 4.84 (dd, 0.5 H, J = 3.7, 6.7 Hz, C$\underline{H}$OCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.27, 14.15 ($NCH_2\underline{C}H_3$), 16.53, 18.36, 18.93, 20.02 [$CH(\underline{C}H_3)_2$], 25.89, 26.35 [$C(\underline{C}H_3)_3$], 29.69, 31.12 [$\underline{C}H(CH_3)_2$], 34.91, 34.98 [$\underline{C}(CH_3)_3$], 40.85, 41.16, 41.65, 42.00 ($N\underline{C}H_2CH_3$), 77.15 [$(CH_3)_3C\underline{C}HOH$], 78.10, 78.64 ($\underline{C}$HOCO), 154.88, 155.63 ($\underline{C}$O); MS (EI) *m/z* 244 (1, M^+-CH_3), 173 (6), 118 (38), 116 (34), 100 (100), 72 (30); Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.83; H, 11.27; N, 5.40. Found: C, 64.95; H, 11.14; N, 5.20.

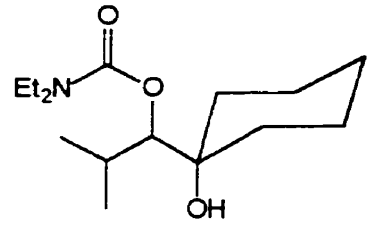
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-3-methyl-1-(3,4-methylenedioxyphenyl)-1-butanol* ***(120)***



yellow oil; IR ($CHCl_3$) 3595, 3392, 2964, 1676, 1483, 1436, 1277, 1246, 1178, 1042, 937 cm^{-1};

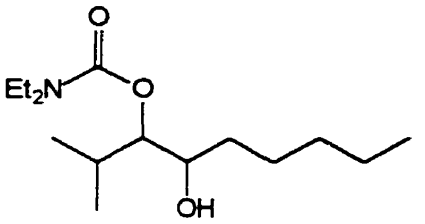
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75-1.30 [m, 12 H, $NCH_2C\underline{H}_3$ and $CH(C\underline{H}_3)_2$], 1.67 [dseptets, 0.5 H, J = 3.5, 6.8 Hz, $C\underline{H}(CH_3)_2$], 1.84-1.96 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 3.10-3.45 (bm, 4 H, $NC\underline{H}_2CH_3$), 3.70-3.90 (bm, 1 H, O<u>H</u>), 4.60-4.90 [m, 2 H, OC<u>H</u>C<u>H</u>(OH)Ar], 5.91 (s, 1 H, $OC\underline{H}_2O$), 5.93 (s, 1 H, $OC\underline{H}_2O$), 6.70-6.90 (m, 3 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.27, 13.89, 14.03 ($NCH_2\underline{C}H_3$), 16.16, 18.00, 19.95, 20.27, [$CH(\underline{C}H_3)_2$], 28.49, 28.87 [$\underline{C}H(CH_3)_2$], 41.01, 41.29, 41.82, 41.99 ($N\underline{C}H_2CH_3$), 74.14, 75.35 (Ph<u>C</u>HOH), 82.54, 83.34 (<u>C</u>HOCO), 100.81, 100.95 ($O\underline{C}H_2O$), 107.13, 107.58, 107.71, 108.09, 120.30, 120.57, 134.71, 135.48, 146.87, 147.13, 147.36, 147.75 (Ar-<u>C</u>'s), 156.47, 157.30 (<u>C</u>O); MS (EI) *m/z* 250 (1, M^+-Et_2NH), 206 (66), 191 (52), 151 (37), 135 (14), 116 (67), 100 (100), 72 (66); Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.11; H, 8.01; N, 4.39.

(1R),(1S*)-1-(1-N,N-Diethylcarbamoyloxy-2-methyl)propyl-1-cyclohexanol (121)*



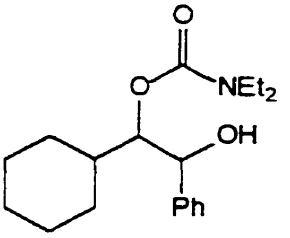
yellow oil; IR ($CHCl_3$) 3597, 2937, 1684, 1475, 1427, 1274, 1174, 1064, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 [d, 3 H, J = 6.9 Hz, $CH(C\underline{H}_3)_2$], 1.00 [d, 3 H, J = 6.8 Hz, $CH(C\underline{H}_3)_2$], 1.05-1.75 (bm, 16 H, *c*-$C_6\underline{H}_{10}$ and $NCH_2C\underline{H}_3$), 1.79 (s, 1 H, O<u>H</u>), 2.12 [dseptets, 1 H, J = 2.8, 6.8 Hz, $C\underline{H}(CH_3)_2$], 3.32 (q, 4 H, J = 7.1 Hz, $NC\underline{H}_2CH_3$), 4.64 (d, 1 H, J = 2.8 Hz, C<u>H</u>OCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.41, 14.36 ($NCH_2\underline{C}H_3$), 17.38, 21.55 [$CH(\underline{C}H_3)_2$], 21.76, 22.05, 25.72 (-$\underline{C}H_2\underline{C}H_2\underline{C}H_2$-), 28.02 [$\underline{C}H(CH_3)_2$], 33.43, 35.67 [-$\underline{C}H_2C(OH)\underline{C}H_2$-], 41.18, 41.96 ($N\underline{C}H_2CH_3$), 73.85 (<u>C</u>OH), 82.93 (<u>C</u>HOCO), 156.19 (<u>C</u>O); MS (EI) *m/z* 271 (1, M^+), 173 (12), 116 (100), 100 (36), 72 (25); Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.31; H, 10.90; N, 5.24.

(3R,4R*),(3R*,4S*)-3-(N,N-Diethylcarbamoyloxy)-2-methyl-4-nonanol (122)*



yellow oil; IR ($CHCl_3$) 3418, 2964, 2933, 1677, 1477, 1429, 1381, 1278, 1068, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-1.75 [bm, 23 H, *n*-$C_5\underline{H}_{11}$, $CH(C\underline{H}_3)_2$ and $NCH_2C\underline{H}_3$], 1.91-2.13 [m, 1 H, $C\underline{H}(CH_3)_2$], 3.20-3.45 (bm, 4 H, $NC\underline{H}_2CH_3$), 3.65-3.80 (bm, 2 H, *n*-$C_5H_{11}C\underline{H}O\underline{H}$), 4.48 (dd, 0.5 H, J = 5.1, 6.1 Hz, C<u>H</u>OCO), 4.56 (dd, 0.5 H, J = 4.1, 6.5 Hz, C<u>H</u>OCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.30, 14.08 ($NCH_2\underline{C}H_3$), 13.91 ($\underline{C}H_3CH_2$),17.52, 18.14, 19.56 [$CH(\underline{C}H_3)_2$], 22.49, 22.53 ($CH_3\underline{C}H_2$), 25.04, 25.49 ($CH_2\underline{C}H_2CH$), 28.81, 29.22 [$\underline{C}H(CH_3)_2$], 31.74, 31.82, 31.92, 34.10 ($CH_3CH_2\underline{C}H_2\underline{C}H_2$), 41.20, 41.89 ($N\underline{C}H_2CH_3$), 71.53, 71.72 (<u>C</u>HOH), 82.18, 83.24 (<u>C</u>HOCO), 156.48, 156.77 (<u>C</u>O); MS (EI) *m/z* 258 (1, M^+-CH_3), 173 (13), 116 (82), 100 (100), 72 (35); Anal. Calcd for $C_{15}H_{31}NO_3$: C, 65.89; H, 11.40; N, 5.11. Found: C, 65.79; H, 11.20; N, 5.21.

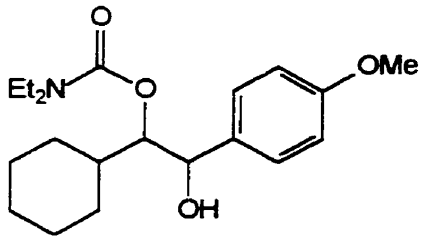
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-2-cyclohexyl-1-phenyl-1-ethanol (123)*



yellow oil; IR ($CHCl_3$) 3602, 3395, 2932, 1676, 1477, 1431, 1277, 1176, 1078, 995, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.90 (m, 17 H, *c*-$C_6\underline{H}_{11}$ and $NCH_2C\underline{H}_3$), 2.90-3.40 (m, 4 H, $NC\underline{H}_2CH_3$), 3.87 (bs, 0.5 H, O<u>H</u>), 4.04 (d, 0.5 H, J = 3.7 Hz, O<u>H</u>), 4.70-4.90 [m, 2 H, OC<u>H</u>C<u>H</u>(OH)Ph], 7.15-7.40 (m, 5 H, Ar<u>H</u>), ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.02, 13.67, 13.85 ($NCH_2\underline{C}H_3$), 25.67, 25.81, 26.09, 26.12, 27.13, 27.61, 29.99, 30.07 [-($C\underline{H}_2$)$_5$-], 38.00, 38.17 (<u>C</u>HCHO), 40.70, 40.99, 41.51, 41.63 ($N\underline{C}H_2CH_3$), 73.42, 74.00 (Ph<u>C</u>HOH), 81.44, 82.61 (<u>C</u>HOCO), 126.38, 126.99, 127.13, 127.29, 127.60, 128.03 (Ar-<u>C</u>'s), 140.88, 141.49 (*ipso*-Ar-<u>C</u>), 156.05, 156.61 (<u>C</u>O); MS (EI) *m/z* 213 (4, M^+-PhCHO), 116 (11), 100 (52), 72 (12); Anal.

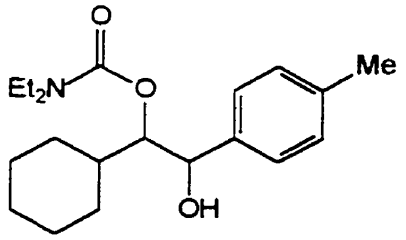
Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.67; H, 9.46; N, 4.57.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-2-cyclohexyl-1-(4-methoxyphenyl)-1-ethanol (**124**)*



yellow oil; IR ($CHCl_3$) 3594, 3399, 2932, 1675, 1513, 1431, 1277, 1249, 1176, 1071, 1036, 991, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.90 [m, 17 H, *c*-$C_6\underline{H}_{11}$ and $NCH_2C\underline{H}_3$], 3.00-3.45 (m, 4 H, $NC\underline{H}_2CH_3$), 3.70 (d, 0.5 H, J = 5.1 Hz, O<u>H</u>), 3.76 (s, 1.5 H, $OC\underline{H}_3$), 3.77 (s, 1.5 H, $OC\underline{H}_3$), 3.83 (d, 0.5 H, J = 4.3 Hz, O<u>H</u>), 4.65-4.90 [m, 2 H, OC<u>H</u>C<u>H</u>(OH)Ph], 6.75-6.90 (AA′ of AA′XX′, 2 H, Ar<u>H</u>), 7.15-7.30 (XX′ of AA′XX′, 2 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.10, 13.77, 13.87, 13.92 ($NCH_2C\underline{H}_3$), 25.70, 25.74, 25.85, 25.88, 26.13, 26.16, 26.89, 27.57, 30.08, 30.12 [-($C\underline{H}_2$)$_5$-], 38.11, 38.23(C<u>H</u>CHO), 40.74, 41.04, 41.52, 41.68 ($NC\underline{H}_2CH_3$), 54.91 ($OC\underline{H}_3$), 73.02, 73.78 (PhC<u>H</u>OH), 81.32, 82.64 (C<u>H</u>OCO), 113.06, 113.53, 127.62, 128.02, 133.01, 133.60 (Ar-C's), 156.11, 156.78 (*ipso*-Ar-C), 158.75, 158.85 (<u>C</u>O); MS (EI) *m/z* 232 (4, M$^+$-Et_2NCOOH), 203 (18), 121 (97), 150 (9), 28 (100); Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.56; H, 8.75; N, 3.81.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-2-cyclohexyl-1-(4-methylphenyl)-1-ethanol (**125**)*



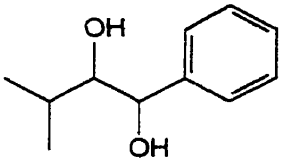
yellow oil; IR ($CHCl_3$) 3596, 3400, 2931, 1677, 1477, 1430, 1277, 1176, 1075, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.95 (m, 17 H, *c*-$C_6\underline{H}_{11}$ and $NCH_2C\underline{H}_3$), 2.32 (s, 1.5 H, $ArC\underline{H}_3$), 2.33 (s, 1.5 H, $ArC\underline{H}_3$), 3.00-3.40 (m, 4 H, $NC\underline{H}_2CH_3$), 3.55 (d, 0.5 H, J = 4.6 Hz, O<u>H</u>), 3.67 (d,

0.5 H, J = 3.1 Hz, OH), 4.60-4.95 [m, 2 H, OCHCH(OH)Ph], 7.05-7.30 (m, 4 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.15, 13.24, 13.88, 14.05 (CH_3CH_2N), 21.03, 21.05 ($ArCH_3$), 25.75, 25.87, 25.90, 26.00, 26.26, 27.01, 28.04, 30.22, 30.32 [-(CH_2)$_5$-], 38.21, 38.33 (CHCHO), 40.91, 41.22, 41.71, 41.87 (NCH_2CH_3), 73.68, 74.37 (PhCHOH), 81.87, 82.92 (CHOCO), 126.53, 127.09, 128.54, 129.03, 136.97, 137.24, 137.70, 138.56 (Ar-C's), 156.51, 157.04 (CO); MS (EI) *m/z* 250 (1, M^+ - *c*-C_6H_{11}), 221 (10), 162 (7), 116 (43), 105 (44), 100 (100), 72 (34); Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.04; H, 9.37; N, 4.20. Found: C, 72.10; H, 9.07; N, 4.30.

2.3.26 Representative Procedure for the AlH_3 Reduction of N,N-Diethylcarbamate Protected Diols

A representative procedure for the alane reduction of *N,N*-diethylcarbamate **115** is given below, followed by spectral data of diols **126-134**. The yields of these diols can be found in Table 9.

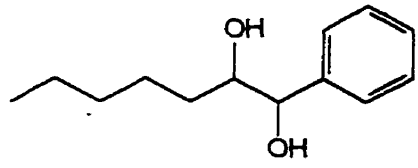
(1R,2R*),(1R*,2S*)-3-Methyl-1-phenyl-1,2-butanediol (**128**)* [33]



To a cold (0°C) stirred solution of 2-(*N,N*-diethylcarbamoyloxy)-3-methyl-1-phenyl-1-butanol (264.5 mg, 0.95 mmol, 1 equiv) in THF (5 mL) was added dropwise AlH_3 (5.68 mL of a 0.5 M solution in THF, 3 equiv). After 15 min the reaction was quenched with solid Na_2SO_4•10 H_2O (915.1 mg, 2.84 mmol, 3 equiv). All solid material was removed by filtration through Celite®, using warm ethyl acetate as eluent. This solution was concentrated *in vacuo*. The resulting oil was passed through a short pipet of silica (~1 g of silica; 2:1 hexanes:ethyl acetate), to eliminate trace salts. After concentration *in vacuo*, 134.4 mg (79% yield) of the product was obtained as a white solid; m.p.: 63-65°C, lit. m.p.: 73.6-74.2°C (*threo*),[34] 103.2-103.9°C (*erythro*);[34] IR ($CHCl_3$) 3595, 3442, 2966, 1460, 1388, 1237, 1056, 1000 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90-1.02 [m, 6 H, $CH(CH_3)_2$], 1.50-1.80 [m, 2 H, $CH(CH_3)_2$ and OH], 2.18 (bs,

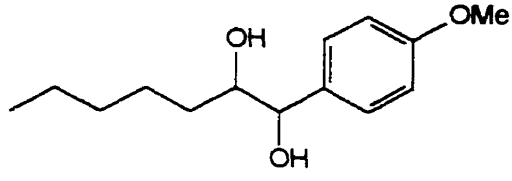
1 H, OH), 3.51 (t, 0.5 H, J = 5.0 Hz, CHOH), 3.60 (t, 0.5 H, J = 5.4 Hz, CHOH), 4.65 (d, 0.5 H, J = 6.1 Hz, PhCHOH), 4.71 (d, 0.5 H, J = 5.7 Hz, PhCHOH), 7.25-7.45 (m, 5 H, ArH).

(1R,2R*),(1R*,2S*)-1-Phenyl-1,2-heptanediol (126)* [35]



yellow oil; IR ($CHCl_3$) 3589, 3440, 2940, 1493, 1456, 1384, 1258, 1049 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-0.95 (m, 3 H, CH_3CH_2), 1.00-1.90 (m, 8.7 H, $CH_2(CH_2)_3CH_3$ and OH), 2.34 (bs, 1 H, OH), 2.61 (bs, 0.3 H, OH), 3.65-3.75 (m, 0.3 H, *n*-C_5H_{11}CHOH), 3.80-3.91 (bm, 0.7 H, *n*-C_5H_{11}CHOH), 4.44 (d, 0.3 H, J = 6.8 Hz, ArCHOH), 4.68 (d, 0.7 H, J = 4.5 Hz, ArCHOH), 7.20-7.50 (m, 5 H, ArH).

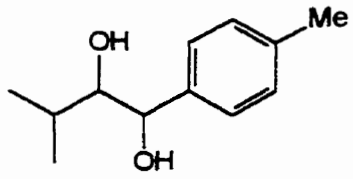
(1R,2R*),(1R*,2S*)-1-(4-Methoxyphenyl)-1,2-heptanediol (127)*



yellow solid; m.p.: 70-71°C; IR ($CHCl_3$) 3591, 3436, 2938, 1612, 1513, 1462, 1248, 1177, 1036, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-0.90 (m, 3 H, CH_3CH_2), 1.15-1.55 (m, 8 H, $CH_2(CH_2)_3CH_3$), 2.15-2.54 (bs, 1 H, OH), 2.76-3.15 (bs, 1 H, OH), 3.52-3.64 (m, 0.5 H, CHOH), 3.66-3.90 (m, 0.5 H, CHOH), 3.78 (s, 3 H, OCH_3), 4.30 (d, 0.5 H, J = 7.3 Hz, ArCHOH), 4.54 (d, 0.5 H, J = 4.3 Hz, ArCHOH), 6.85 (AA′ of AA′XX′, 2 H, ArH), 7.23 (XX′ of AA′XX′, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96 (CH_3CH_2), 22.49, 22.54 (CH_3CH_2), 25.26, 25.52 (CH_2CH_2CH), 31.61, 31.68, 31.76, 32.53 ($CH_3CH_2CH_2CH_2$), 55.15 (OCH_3), 75.12, 75.94, 76.55, 77.53 (HOCHCHOH), 113.62, 113.76, 128.02, 132.51, 133.36, 159.07, 159.21

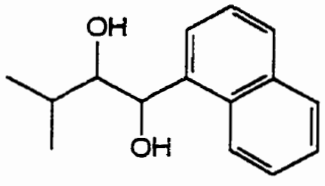
(Ar-C's); MS (EI) *m/z* 238 (20, M), 220 (25), 137 (100), 121 (65), 109 (39), 94 (28), 77 (32); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.29; H, 9.33.

(1R,2R*),(1R*,2S*)-1-(4-Methylphenyl)-3-methyl-1,2-butanediol (129)*



yellow solid; m.p.: 61-63°C; IR ($CHCl_3$) 3591, 3449, 2966, 1514, 1467, 1385, 1237, 1177, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73-1.00 [m, 6 H, $CH(CH_3)_2$], 1.47-1.70 [m, 1 H, $CH(CH_3)_2$], 1.99 (bs, 0.5 H, OH), 2.33 (s, 3 H, $ArCH_3$), 2.55-2.75 (bm, 1 H, OH), 3.02 (bs, 0.5 H, OH), 3.41 (dd, 0.5 H, J = 4.2, 6.6 Hz, CHOH), 3.45-3.55 (m, 0.5 H, CHOH), 4.50 (d, 0.5 H, J = 6.7 Hz, ArCHOH), 4.57 (d, 0.5 H, J = 5.5 Hz, ArCHOH), 7.10-7.26 (m, 4 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.04, 17.10, 19.65, 20.12 [$CH(CH_3)_2$], 21.06 ($ArCH_3$), 28.98, 29.30 [$CH(CH_3)_2$], 74.84, 74.98 (CHOH), 79.47, 80.21 (ArCHOH), 126.54, 127.24, 129.01, 129.09, 137.47, 137.60, 137.83, 138.52 (Ar-C's); MS (EI) *m/z* 194 (7, M), 133 (28), 122 (100), 107 (95), 93 (90), 77 (85), 65 (42), 55 (37); Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.30; H, 9.30.

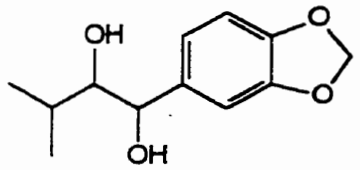
(1R,2R*),(1R*,2S*)-3-Methyl-1-(1-naphthyl)-1,2-butanediol (130)*



yellow solid; m.p.: 49-51°C; IR ($CHCl_3$) 3596, 2964, 1511, 1467, 1394, 1240, 1169, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76-1.04 [m, 6 H, $CH(CH_3)_2$], 1.60-1.85 [m, 1 H, $CH(CH_3)_2$ and OH], 1.97 [dseptets, 0.5 H, J = 3.6, 6.8 Hz, $CH(CH_3)_2$], 2.29 (bs, 0.5 H, OH), 2.61 (bs, 0.5 H, OH), 3.04 (bs, 0.5 H, OH), 3.54-3.60 (m, 0.5 H, CHOH), 3.75-3.82 (m, 0.5 H, CHOH), 5.30-5.45 (m, 1 H, ArCHOH), 7.30-7.55 (m, 3.5 H, ArH), 7.60-7.85 (m, 2.5 H, ArH), 7.90-7.96 (m, 0.5 H, ArH), 8.00-8.15 (m, 0.5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.62, 17.52, 19.80, 20.36 [$CH(CH_3)_2$], 28.86, 30.06 [$CH(CH_3)_2$], 70.91, 72.23 (CHOH), 78.65, 79.02 (ArCHOH),

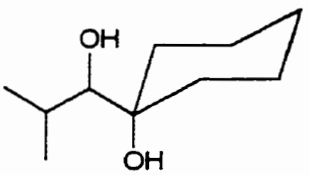
122.82, 123.46, 124.18, 124.70, 125.22, 125.33, 125.50, 125.57, 126.05, 128.17, 128.40, 128.79, 128.98, 130.39, 131.26, 133.72, 133.81, 137.37 (Ar-C's); MS (EI) *m/z* 230 (10, M), 158 (100), 141 (33), 129 (98); Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.39; H, 8.00.

(1R,2R*),(1R*,2S*)-1-(1,3-Benzodioxol-5-yl)-3-methyl-1,2-butanediol (131)* [36]



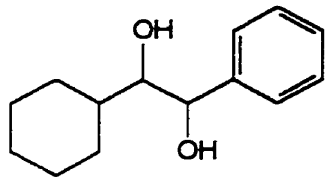
yellow solid; m.p.: 72-74°C; IR ($CHCl_3$) 3588, 2962, 1504, 1487, 1443, 1246, 1095, 1043, 936 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85-1.05 [m, 6 H, $CH(C\underline{H}_3)_2$], 1.50-1.80 [m, 2 H, $C\underline{H}(CH_3)_2$ and O<u>H</u>], 2.22 (t, 0.5 H, *J* = 3.8 Hz, O<u>H</u>), 2.59 (d, 0.5 H, *J* = 3.8 Hz, O<u>H</u>), 3.45 (dt, 0.5 H, *J* = 4.0, 6.6 Hz, C<u>H</u>OH), 3.53 (q, 0.5 H, *J* = 5.7 Hz, C<u>H</u>OH), 4.54 (dd, 0.5 H, *J* = 3.6, 6.7 Hz, ArC<u>H</u>OH), 4.60 (t, 0.5 H, *J* = 3.8 Hz, ArC<u>H</u>OH), 5.96 (s, 2 H, $OC\underline{H}_2O$), 6.75-7.00 (m, 3 H, Ar<u>H</u>).

(1R),(1S*)-1-(1-Hydroxy-2-methyl)propyl-1-cyclohexanol (132)* [37]



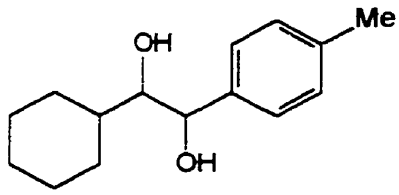
yellow solid; m.p.: 30°C, lit. m.p.:48°C; IR ($CHCl_3$) 3547, 2939, 1457, 1380, 1254, 1168, 1004, 980 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 [d, 3 H, *J* = 6.8 Hz, $CH(C\underline{H}_3)_2$], 1.00 [d, 3 H, *J* = 6.9 Hz, $CH(C\underline{H}_3)_2$], 1.05-1.75 (m, 11 H, *c*-$C_6\underline{H}_{10}$, O<u>H</u>), 1.95 [dseptets, 1 H, *J* = 2.5, 6.9 Hz, $C\underline{H}(CH_3)_2$], 3.23 (d, 1 H, *J* = 2.1 Hz, O<u>H</u>), 3.32 (q, 1 H, *J* = 7.2 Hz, C<u>H</u>OH).

(1R,2R*),(1R*,2S*)-1-Cyclohexyl-2-phenyl-1,2-ethanediol (133)* [38]



yellow solid; m.p.: 111-112°C, lit. m.p.:95-96°C;[39] IR ($CHCl_3$) 3586, 3456, 2928, 1450, 1375, 1251, 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00-1.95 (m, 11.7 H, O<u>H</u> and *c*- $C_6\underline{H}_{11}$), 2.11 (bs, 0.3 H, O<u>H</u>), 2.24 (bs, 0.7 H, O<u>H</u>), 2.55 (bs, 0.3 H, O<u>H</u>), 3.48 (bs, 0.3 H, C<u>H</u>OH), 3.61 (q, 0.7 H, J = 4.5 Hz, C<u>H</u>OH), 4.73 (t, 1 H, J = 5.4 Hz, PhC<u>H</u>OH), 7.20-7.45 (m, 5 H, Ar<u>H</u>).

(1R,2R*),(1R*,2S*)-1-Cyclohexyl-2-(4-methylphenyl)-1,2-ethanediol (134)*

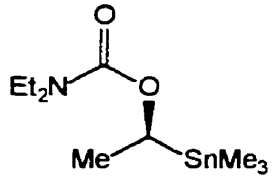


white solid; m.p.: 88-89°C; IR ($CHCl_3$) 3590, 2929, 1513, 1450, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.97 (bm, 11 H, *c*-$C_6\underline{H}_{11}$), 2.33 (s, 3 H, Ar$C\underline{H}_3$), 2.48 (bs, 0.5 H, O<u>H</u>), 2.64 (bs, 0.5 H, O<u>H</u>), 2.92 (bs, 0.5 H, O<u>H</u>), 3.34-3.44 (bm, 0.5 H, C<u>H</u>OH), 3.46-3.58 (bm, 0.5 H, C<u>H</u>OH), 4.60 (dd, 1 H, J = 5.1, 9.9 Hz, ArC<u>H</u>OH), 7.06-7.34 (m, 4 H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.07 (Ar$C\underline{H}_3$), 25.83, 25.95, 26.04, 26.20, 26.30, 26.38, 26.94, 27.36, 29.87, 30.13 [-($\underline{C}H_2$)$_5$-], 38.99, 39.07 (-$CH_2\underline{C}HCH_2$-), 74.09, 74.35 (*c*-$C_6H_{11}\underline{C}$HOH), 78.87, 79.87 (Ar<u>C</u>HOH), 126.43, 127.21, 129.03, 129.09, 137.35, 137.56, 137.84, 138.72 (Ar-<u>C</u>'s); MS (EI) *m/z* 234 (11, M), 134 (28), 122 (100), 107 (94), 91 (85), 77 (82), 65 (37), 55 (64); Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.74; H, 9.60.

2.3.27 Reduction of Acetate [(S)-136] and Preparation of N,N-Diethylcarbamate [(S)-138]

To a cold (-78°C) solution of acetate (*S*)-**136** (591.1 mg, 2.017 mmol) in ether (5 mL) was added DIBAL-H (4.04 mL of a 1.0 M solution in hexanes, 4.04 mmol). The reaction was stirred at –78°C for 15 min and a TLC was taken to ensure complete consumption of acetate. The reaction was quenched (under argon) with NH_4Cl (saturated solution) and was allowed to warm to room temperature. The reaction mixture was diluted with Et_2O (30 mL) and washed with 1 M HCl (5 mL), $NaHCO_3$ (10 mL) H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to afford a colorless oil.

This material was then treated under the same conditions as described for carbamate **88** (Section 2.3.23). Employing 488 mg (2.42 mmol) of *p*-nitrophenyl chloroformate and 1.05 mL (10.1 mmol) of Et_2NH there was obtained 446 mg (73%) of (*S*)-1-(trimethylstannyl)ethyl *N,N*-diethyl- carbamate [(*S*)–**138**].



$[\alpha]_D^{25}$ +80.3° (*c* 0.242, hexanes); ^1H NMR spectrum was identical to that described for (±)-1-(trimethylstannyl)ethyl *N,N*-diethylcarbamate (**88**) (Section 2.3.23).

2.3.28 Transmetalation of (S)-138 and Trapping with Benzaldehyde

The transmetalation of stannane (*S*)–**138** was performed in an identical manner as that previously described for the racemic stannane **88** (Section 2.3.23). From 142 mg (0.461 mmol) of (*S*)–**138** and 56.0 μL (0.551 mmol) of PhCHO there was obtained 69 mg (60%) of the expected product **139**. A ^1H NMR spectrum (250 MHz, $CDCl_3$) of **139** revealed the same 1:1 ratio of diastereomers as observed previously (Section 2.3.25).

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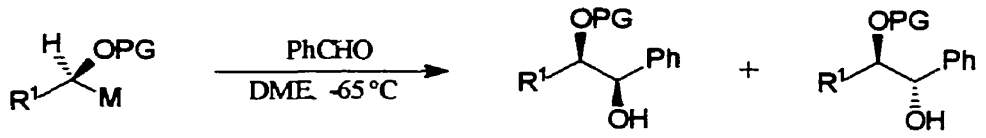
CHAPTER 3

DIASTEREOSELECTIVE 1,2-ADDITIONS OF ORGANOMETALLICS TO BENZALDEHYDE

3.1 Introduction

As a continuation of the work described in Chapter 2, the diastereoselective addition of *N,N*-diethylcarbamate protected α-alkoxyorganometallics to benzaldehyde was investigated as a route towards the stereoselective synthesis of 1,2-diols. (A discussion on the synthesis of 1,2-diols can be found in Chapter 1, Section 1.1.2). In 1982, McGarvey[1] and Kimura demonstrated the diastereoselective 1,2-addition of α-alkoxyorganometallic reagents that were obtained from the transmetalation of α-alkoxyorganostannanes to benzaldehyde (Table 10). The observed *syn:anti* ratios from this study varied from 50:50 to 100:0, and were found to be dependent on the α-alkyl substituent (R^1), the protecting group (PG), and the metal (M). McGarvey attributed the observed diastereoselectivity to the steric demands of the organometallic reagent (compare entries 2, 7 and 11, where R^1 = Et, *i*-Pr, *t*-Bu). The protecting group also influenced the outcome of the reaction. Better selectivities were observed when the protecting group incorporated an acetal oxygen (compare entries 3 and 4). Transmetalation of the organolithium reagent to the corresponding organomagnesium derivative also gave profoundly improved selectivities. Addition of catalytic amounts of copper salts to the reaction only modestly increased the selectivity of the addition (entry 9). Attempts by McGarvey to perform 1,2-additions to benzaldehyde using α-alkoxyorgano-aluminum, boron and zinc reagents as well as in the presence of stoichiometric amounts of copper salts failed due to the lack of reactivity of the organometallic reagents.

Table 10. Diastereoselective additions of α-alkoxyorganometallics to benzaldehyde.[1]



140 *syn* **141** *anti* **141**

Entry	R^1	PG	M[a]	(%) yield[b] (**141**)	*syn*:*anti*[c] (**141**)
1	Et	BOM	Li[d]	75	53 : 47
2		BOM	MgBr	77	63 : 37
3	*i*-Pr	Me	Li	96	50 : 50
4		BOM	Li	95	63 : 37
5		MEM	Li	81	55 : 45
6		Me	MgBr	82	67 : 33
7		BOM	MgBr	84	82 : 18
8		MEM	MgBr	78	79 : 21
9		BOM	MgBr/$Cu(OAc)_2$	79	87 : 13
10	*t*-Bu	BOM	Li[d]	65	92 : 8
11		BOM	MgBr	65	100 : 0

Modified from table in reference 1

[a] M = Li obtained from transmetalation of organostannane. M = MgBr is prepared by the addition of anhydrous $MgBr_2$ to M = Li and stirring for 15 min at –65 °C.

[b] Yields after chromatography.

[c] Ratios determined by ^1H NMR spectroscopy.

[d] Reaction performed in THF at –78 °C

The predominant *syn*-selectivity observed in these reactions was rationalized by considering the diastereomeric transition states **143a** and **143b** (Figure 12). The unfavorable steric interaction between R^1-R^2 present in **143b** (minor), but absent in **143a** (major), dictates the preferred approach of the electrophile to the organometallic reagent and thus the outcome of the reaction. McGarvey speculated that the metal center might play a role in lowering the ground-state energy of **142** as well as determining the geometry of transition states **143a/143b**.[2]

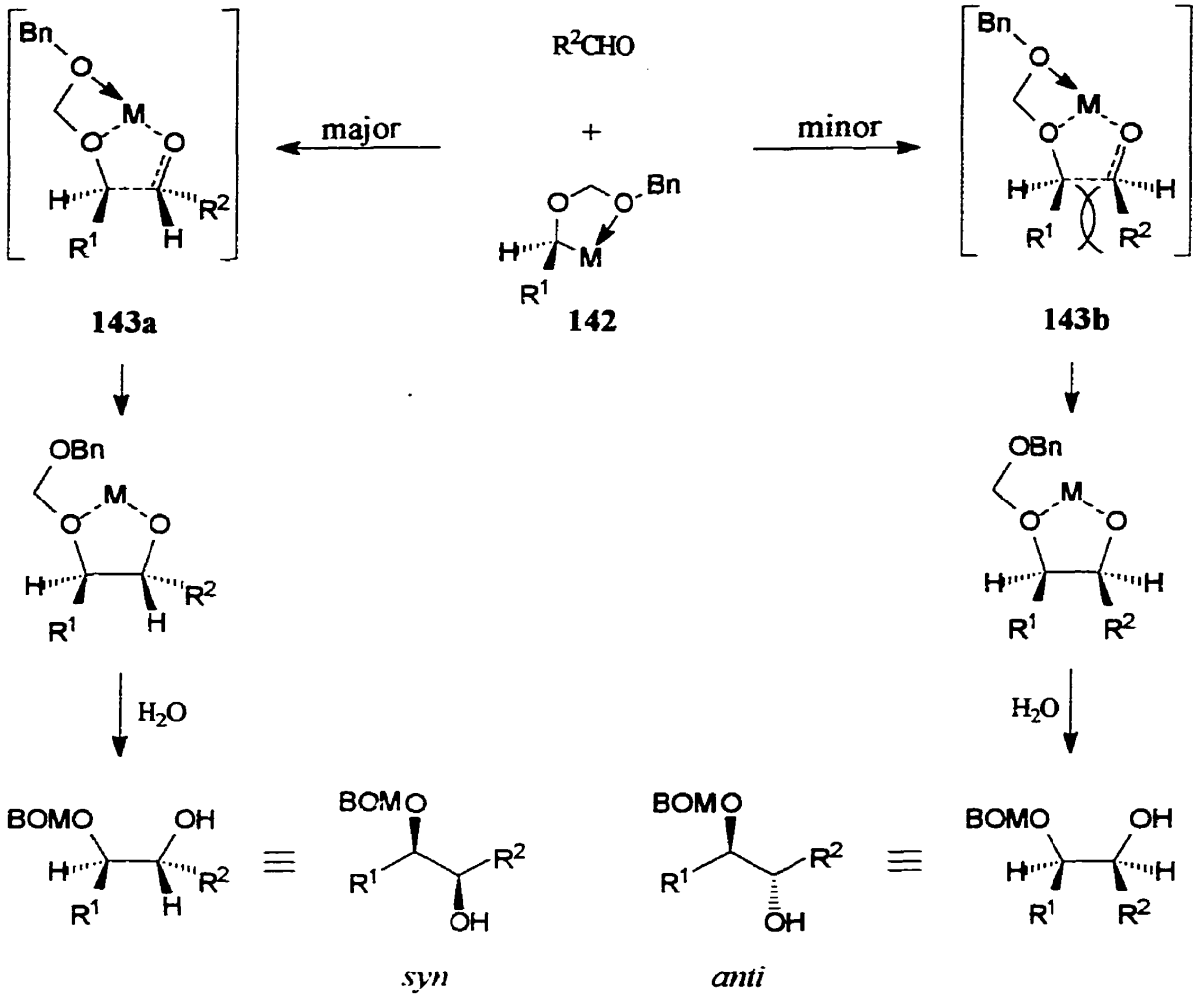
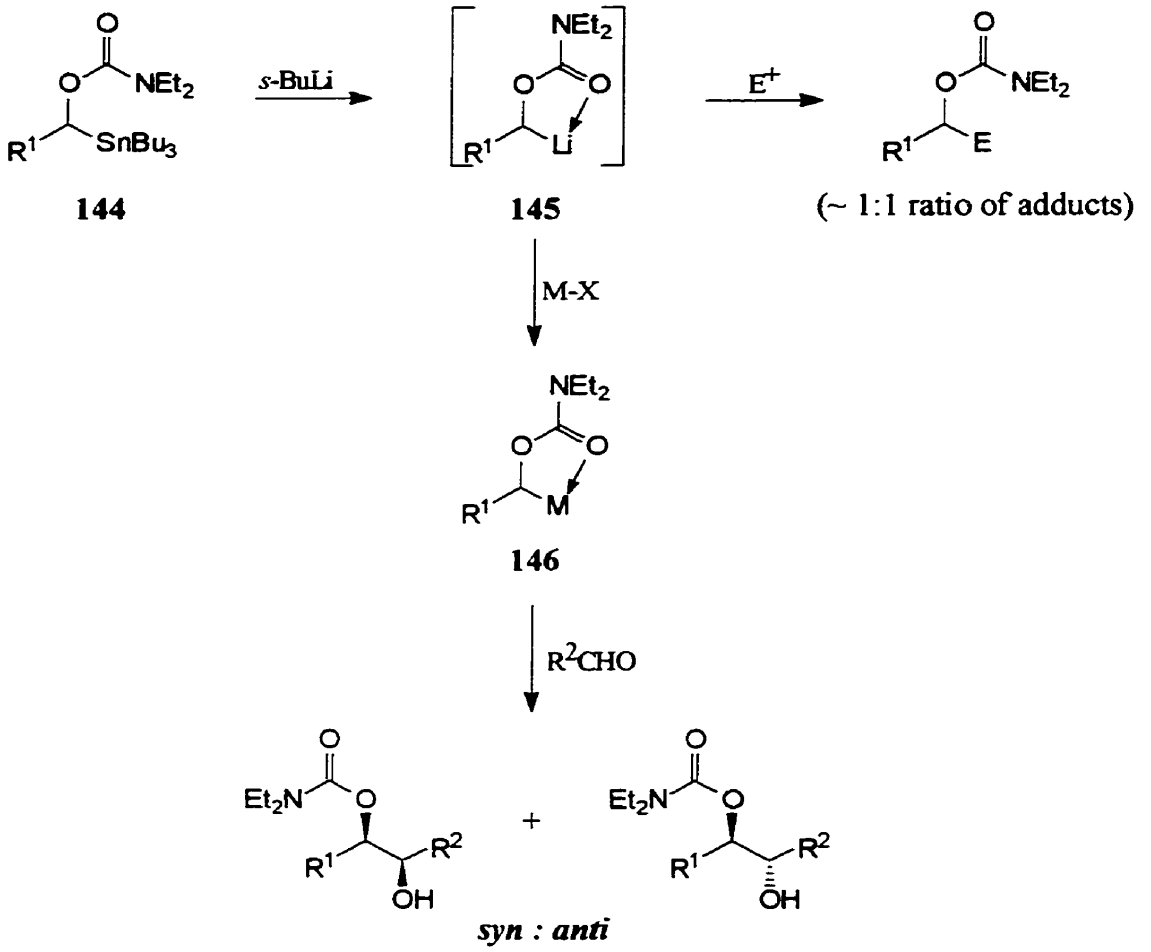


Figure 12. Rationale for the observed *syn*:*anti* selectivity.

In Chapter 2, the transmetalation of *N,N*-diethylcarbamates and trapping of the organolithium intermediates with aldehydes had predominately provided 1:1 mixtures of the desired adducts. In order to enhance stereoselectivities, we sought to examine these additions in the presence of modified organometallic reagents. The *N,N*-diethylcarbamate protecting group had provided highly stabilized organolithium intermediates when compared to MOM-acetals for the transmetalation of trimethylstannanes (Chapter 2). We speculated that *N,N*-diethylcarbamate protected α-alkoxystannanes **144** would also provide stabilized organometallic reagents **146**, after transmetalation of organolithium species **145**, which might

perform highly diastereoselective additions to selected aldehydes (Scheme 49). The *syn:anti* selectivity from these additions is expected to follow the same model proposed by McGarvey in Figure 12, and favor the formation of the *syn*-isomer. Formation of the *anti*-isomer is disfavored due to steric interactions between the R^1 and R^2 substituents (**143b**, Figure 12). The following Section details our efforts in this area.

Scheme 49



144 **145** (~ 1:1 ratio of adducts)

146

3.2 Results and Discussion

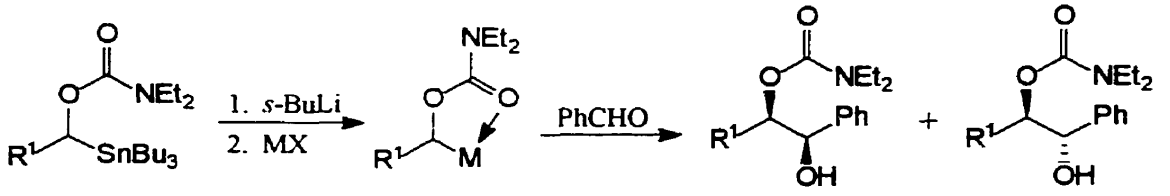
3.2.1 Diastereoselective Additions of Organometallics to Benzaldehyde

The *N,N*-diethylcarbamates that were chosen for this study contained either methyl or isopropyl α-alkyl substituents (R^1, Table 11). McGarvey had shown that high diastereoselectivities (92:8, 100:0) could be obtained when the *t*-butyl substituent was employed even with the corresponding organolithium species (Table 10, entry 10).[1] However, the *t*-butyl substituent was not investigated for this study because it was felt that the large steric bulk of this group would conceal the more subtle stereoregulating effects (i.e. the directing effect of the protecting group) of organometallic reagent **146**, which were of interest in McGarvey's study. Benzaldehyde was chosen as the electrophile for the study.[1] The products from these condensations were easily analyzed by GCMS analysis. Retention times of the diastereomers when R^1 = Me were 16.29 and 16.41 minutes. When R^1 = *i*-Pr, acetylation of the alcohol (acetic anhydride, pyridine and DMAP) was required to achieve optimum separation on the GCMS column. The isomers of acetate **147** eluted at 17.62 and 17.75 minutes. The peak percent area gave the ratio of the respective diastereomers. The results of this study are provided in Table 11.

Regardless of the solvent chosen for the condensation, the organolithium reagents give near equimolar mixtures of diastereomers. One noticeable trend is the higher yields achieved in diethyl ether vs THF or DME (compare entries 1 and 2). This result may arise due to the lower polarity of diethyl ether resulting in less product loss through aqueous work-up. The best selectivities were acquired with the use of the corresponding organomagnesium reagent (compare entries 6 and 10). The highest selectivity with these reagents was realized by performing the reaction in THF (entry 11). McGarvey found identical results with the organomagnesium reagent in the presence of catalytic $Cu(OAc)_2$ when employing the BOM protecting group in DME (Table 10, entry 9).[1] The organoboron reagent, prepared by the addition of $BF_3{\bullet}OEt_2$ (1 equiv, -65°C), showed no reactivity (entry 4). The addition of 2 equivalents of $BF_3{\bullet}OEt_2$ gave a 60% yield of the desired adduct, but with essentially no diastereoselectivity (entry 13). Consistent with the findings of McGarvey, attempts to

increase the selectivity through the use of organoaluminum and organozinc reagents failed due to lack of reactivity.

Table 11. Diastereoselective additions of organometallics to benzaldehyde.[a]



88 R^1 = Me
90 R^1 = *i*-Pr

syn **110** *anti* **110**
syn **115** *anti* **115**

Entry	R^1	M[a]	Equiv	Solvent	Temp (°C)	% yield[b] **(110, 115)**	dr[c] **(110, 115)**
1	Me	Li	1	Et_2O	-95	90	52:48
2		Li	1	THF	-95	55	58:42
3		MgBr	2	THF	-65	62	79:21
4		BF_2	1	THF	-40	0	-:-
5		ZnCl	1	THF	0	0	-:-
6	*i*-Pr	Li	1	Et_2O	-95	95	54:46
7		Li	1	THF	-95	85	53:47
8		Li	1	DME	-78	83	49:51
9		MgBr	2	Et_2O	-65	79	73:27
10		MgBr	2	Et_2O	-95	64	79:21
11		MgBr	2	THF	-65	62	87:13
12		MgBr	2	DME	-65	50	76:24
13		BF_2	2	THF	-40	60	53:47
14		CH_3AlCl	2	THF	0	0	-:-

[a] M = Li obtained from transmetalation of organostannane. M = MgBr or ZnCl is prepared by the addition of ethereal solutions of $MgBr_2$ or $ZnCl_2$. M = BF_2 or CH_3AlCl is prepared by the addition of $BF_3 \bullet OEt_2$ (neat) or CH_3AlCl_2 (1 M in hexanes).

[b] Isolated yields after chromatography.

[c] Diastereomeric ratios were determined by GCMS analysis.

3.2.2 Summary

The results obtained from this study nicely complement those obtained from McGarvey's work.[1] The organolithiums obtained from tin-lithium exchange of *N,N*-diethylcarbamoyl stannanes added to benzaldehyde to give approximately 1:1 mixtures of diastereomers. The importance of optimising the various reaction conditions was demonstrated. The transmetalations and trappings gave much higher yields of the protected 1,2-diols when performed in diethyl ether as compared to THF. Increased diastereoselectivity was obtained when organomagnesium reagents were employed. Optimum diastereoselectivity (87:13) was achieved for the addition of *N,N*-diethylcarbamate protected α-alkoxyorganomagnesium reagents (THF) to benzaldehyde. This level of selectivity was obtained by McGarvey only in the presence of catalytic $Cu(OAc)_2$.[1] The use of an organoboron reagent gave a 60% yield of the desired adduct but with essentially no diastereoselectivity. Organoaluminum and organozinc reagents showed no reactivity towards condensation with benzaldehyde. In conclusion, the *N,N*-diethylcarbamate protected α-alkoxyorganometallics added to benzaldehyde to give protected 1,2-diols with comparable diastereoselectivities to those obtained by McGarvey using the benzyloxymethyl protecting group.

3.3 Experimental

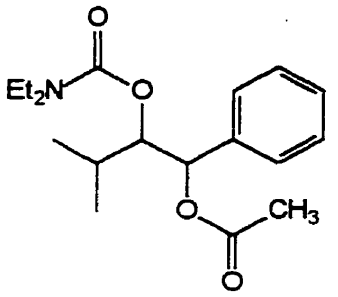
3.3.1 General

The general procedures described in Section 2.3.1 are applicable here with the following additions. Ethereal solutions of $MgBr_2$ were prepared according to the methods of Seebach[3] (Et_2O) and Wakefield[4] (THF). Ethereal solutions of $ZnCl_2$ were prepared according to House *et al.*[5] $BF_3{\bullet}OEt_2$ was distilled prior to use and stored under argon at 0°C. Solutions of CH_3AlCl_2 (1 M in hexanes) were purchased from Aldrich. The ^1H NMR spectra of alcohols **110** and **115** were identical to those previously reported in Section 2.3.25.

*3.3.2 Addition of N,N-Diethylcarbamate Protected Organolithium Reagents to Benzaldehyde in THF and Derivatization to Acetate **147** for Analysis*

To a cold (-95°C) stirred solution of (1-trimethylstannyl-2-methyl)propyl-*N,N*-diethylcarbamate (**90**) (199.7 mg, 0.43 mmol) in THF (5 mL) was added dropwise *s*-BuLi (0.41 mL of a 1.26 M solution in hexanes, 0.52 mmol). After 15 min PhCHO (87.8 μL, 0.86 mmol) was added neat. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil (303 mg) was purified by column chromatography on silica gel (6 g) using hexanes/ethyl acetate (initially 10:1 with a gradual gradient to 5:1) affording 102 mg (85%) of the product as a colorless oil. A portion (18 mg) of this material was acetylated (acetic anhydride, pyridine, DMAP, rt, 1 h). Concentration of this mixture *in vacuo* followed by chromatography on silica gel (2 g) using hexanes/ethyl acetate (2:1) afforded the acetate **147** for GCMS analysis (Table 11, entry 7). Similar experiments were carried out in Et_2O (-95°C) and DME (-78°C).

(1R,2R*), (1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-3-methyl-1-phenylbutyl acetate (147)*



yellow oil; IR ($CHCl_3$) 2967, 1735, 1692, 1475, 1428, 1373, 1276, 1241, 1173, 1068, 1026 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80-1.20 [m, 12 H, $CH(C\underline{H}_3)_2$ and $NCH_2C\underline{H}_3$], 1.58 [dseptet, 0.5 H, $J = 3.3$, 6.8 Hz, $C\underline{H}(CH_3)_2$], 1.80-2.14 [m, 0.5 H, $C\underline{H}(CH_3)_2$], 2.02 (s, 1.5 H, $C\underline{H}_3CO$), 2.07 (s, 1.5 H, $C\underline{H}_3CO$), 2.92-3.52 (m, 4 H, $NC\underline{H}_2CH_3$), 5.11 (dd, 0.5 H, $J = 5.0$, 6.8 Hz, C<u>H</u>OCO), 5.17 (dd, 0.5 H, $J = 3.4$, 8.7 Hz, C<u>H</u>OCO), 5.90 (d, 0.5 H, $J = 1.7$ Hz, ArC<u>H</u>OAc), 5.93 (d, 0.5 H, $J = 3.7$ Hz, ArC<u>H</u>OAc), 7.15-7.55 (m, 5 H, Ar<u>H</u>); MS (EI) *m/z* 204 (6, M^+-Et_2NCOO), 162 (4), 100 (100), 72 (18), 43 (13).

3.3.3 Addition of N,N-Diethylcarbamate Protected Organomagnesium Reagents to Benzaldehyde in Et_2O

To a cold (-95°C) stirred solution of (1-trimethylstannyl-2-methyl)propyl-*N,N*-diethylcarbamate (**90**) (150.1 mg, 0.32 mmol) in Et_2O (5 mL) was added dropwise *s*-BuLi (0.31 mL of a 1.26 M solution in hexanes, 0.39 mmol). After 15 min, $MgBr_2 \bullet OEt_2$ (0.24 mL of a 2.67 M solution in Et_2O, 0.65 mmol) was added and the reaction mixture was allowed to warm to –65°C over a period of 30 min. To the reaction was added PhCHO (66.0 μL, 0.65 mmol) followed by a further 15 min of stirring at –65°C. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica gel (5 g) using hexanes/ethyl acetate (initially 10:1 with a gradual gradient to 5:1) affording 72 mg (79%) of the product as a colorless oil. A portion (13 mg) of this material was acetylated as described in Section 3.3.2

to afford acetate **147** for GCMS analysis (Table 11, entry 9). Similar experiments were carried out in Et_2O (-95°C), THF (-65°C) and DME (-65°C).

3.3.4 Addition of N,N-Diethylcarbamate Protected Organoboron Reagents to Benzaldehyde in THF

To a cold (-95°C) stirred solution of (1-trimethylstannyl-2-methyl)propyl-*N,N*-diethylcarbamate (**90**) (189.1 mg, 0.41 mmol) in THF (5 mL) was added dropwise *s*-BuLi (0.39 mL of a 1.26 M solution in hexanes, 0.49 mmol). After 15 min, $BF_3 \bullet OEt_2$ (100 μL, 0.82 mmol) was added and the reaction mixture was allowed to warm to –40°C over a period of 30 min. To the reaction was added PhCHO (83.2 μL, 0.82 mmol) followed by a further 15 min of stirring at –40°C. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil (242 mg) was purified by column chromatography on silica gel (5 g) using hexanes/ethyl acetate (initially 10:1 with a gradual gradient to 5:1) affording 69 mg (60%) of the product as a colorless oil. A portion (16 mg) of this material was acetylated as described in Section 3.3.2 to afford acetate **147** for GCMS analysis (Table 11, entry 13).

3.3.5 Addition of N,N-Diethylcarbamate Protected Organozinc Reagents to Benzaldehyde in THF

To a cold (-95°C) stirred solution of (1-trimethylstannyl)ethyl-*N,N*-diethylcarbamate (**88**) (193.3 mg, 0.45 mmol) in THF (5 mL) was added dropwise *s*-BuLi (0.42 mL of a 1.26 M solution in hexanes, 0.53 mmol). After 15 min, $ZnCl_2$ (0.61 mL of a 0.73 M solution in THF, 0.45 mmol) was added and the reaction mixture was allowed to warm to 0°C over a period of 30 min. To the reaction was added PhCHO (90.5 μL, 0.89 mmol) followed by a further 15 min of stirring at 0°C. The reaction was quenched with saturated aqueous NH_4Cl.

The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil (164 mg) was purified by column chromatography on silica gel (4 g) using hexanes/ethyl acetate (initially 10:1 with a gradual gradient to 5:1). None of the desired alcohol **110** was isolated (Table 11, entry 5).

3.3.6 Addition of N,N-Diethylcarbamate Protected Organoaluminum Reagents to Benzaldehyde in THF

To a cold (-95°C) stirred solution of 1-trimethylstannyl-2-methyl)propyl-*N,N*-diethylcarbamate (**90**) (203.4 mg, 0.44 mmol) in THF (5 mL) was added dropwise *s*-BuLi (0.42 mL of a 1.26 M solution in hexanes, 0.53 mmol). After 15 min, CH_3AlCl_2 (0.88 mL of a 1.0 M solution in hexanes, 0.88 mmol) was added and the reaction mixture was allowed to warm to -40°C over a period of 30 min. To the reaction was added PhCHO (89.4 μL, 0.88 mmol) followed by a further 15 min of stirring at -40°C. TLC indicated the absence of product; therefore, the reaction was warmed to 0°C over a period of 30 min. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. TLC analysis of the resulting oil (206 mg) indicated the absence of the desired alcohol **115** (Table 11, entry 14).

3.4 References

1. McGarvey, G.J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422.

2. For a review, see: Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917.

3. Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420.

4. Wakefield, B.J. *Organomagnesium Methods in Organic Synthesis;* Academic Press: Toronto, 1995, p. 62.

5. Auerbach, A.; Crumrine, D.S.; Ellison, D.L.; House, H.O. *Org. Synth.* **1988**, *6*, 692.

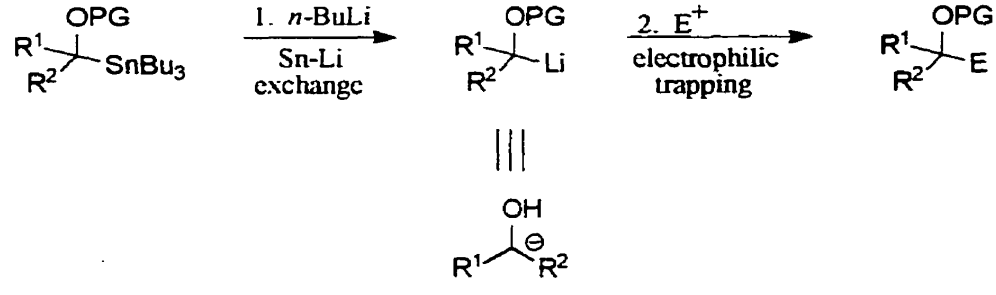
CHAPTER 4

PREPARATION OF ENANTIOMERICALLY ENRICHED α-ALKOXY STANNANES VIA ORGANOMETALLIC ADDITION TO ACYLSTANNANES

4.1 Introduction

The preparation and study of α-alkoxylithio species, generated from tin-lithium exchange of α-alkoxyorganostannanes, has received considerable attention in the literature (Scheme 50).[1-5] As a result, α-alkoxyorganolithium reagents have become popular intermediates for the synthesis of new C-C bonds.[6-9] Predominantly, the literature examples of α-alkoxystannanes tend to be either of unsubstituted (R^1, R^2 = H) or α-substituted ($R^1 \neq R^2$ = H) materials. Few examples of α,α-disubstituted (R^1,$R^2 \neq$ H) exist and those that do are quite often benzylic α-alkoxystannanes, while dialkyl examples are extremely rare.

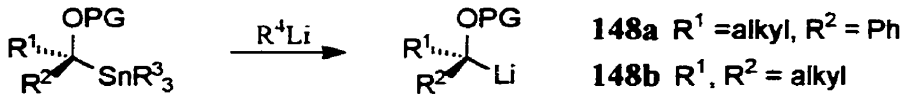
Scheme 50



The configurational stability of chiral, hetero-substituted carbanions has attracted much attention since Still's discovery of non-racemic α-oxy-substituted organolithium compounds, which were generated from α-substituted α-alkoxyorganostannanes (Chapter 1, Scheme 19, page 10). The configurational stability of α,α-disubstituted α-alkoxyorganolithiums has focused entirely on enantioenriched α-oxy-α-alkylbenzyllithiums **148a** (Scheme 51). Currently, there are no published examples of enantiomerically enriched α,α-dialkyl

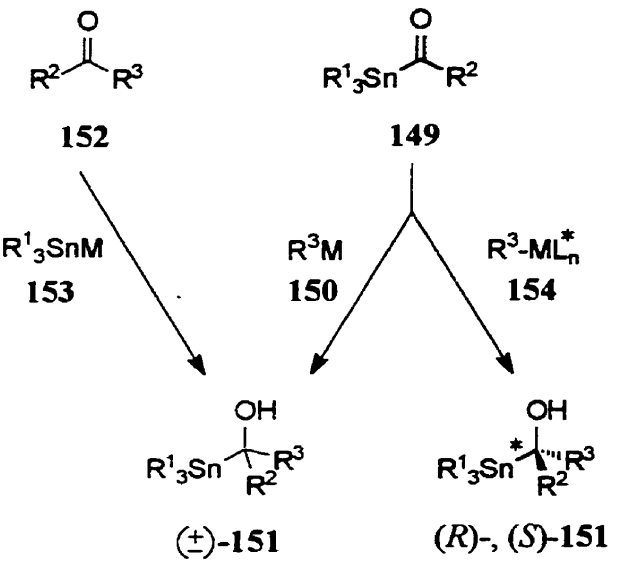
α-alkoxyorganolithiums **148b**. The underlying reason for this shortage in the literature is that no routes currently exist for preparing the precursor α,α-dialkyl α-alkoxystannanes in enantiomerically enriched form.

Scheme 51



The synthetic studies described herein arose from a convergence of several considerations. It was intended to explore the feasibility of performing organometallic (**150**) 1,2-additions to acylstannanes (**149**) (Scheme 52). These reactions would not only provide much needed insight into the chemical reactivity of the relatively obscure acylstannanes, but would hopefully provide a novel method for preparing α,α-dialkyl α-alkoxystannanes [(±)-**151**]. These stannanes have traditionally been prepared as racemates by the condensation of ketones (**152**) with trialkyltin anions (**153**). We anticipated the extension of this process to a method of preparing enantiomerically enriched α,α-dialkyl α-alkoxystannanes [(*R*)-,(*S*)-**151**] by performing these additions in the presence of a chiral auxiliary-modified organometallic species (**154**). These enriched stannanes [(*R*)-,(*S*)-**151**] would allow for the first time, studies to be performed on the configurational stability of non-racemic α,α-dialkyl α-alkoxyorganolithium compounds generated through tin-lithium exchange. The following sections provide a short overview of acylstannane and α,α-disubstituted α-alkoxyorganostannane chemistry.

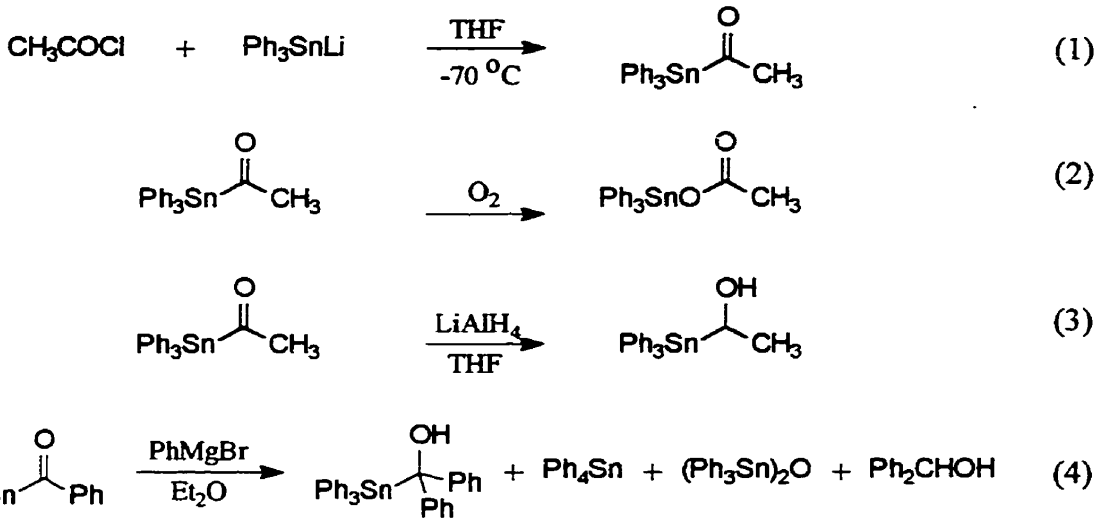
Scheme 52



4.1.1 The Chemistry of Acylstannanes

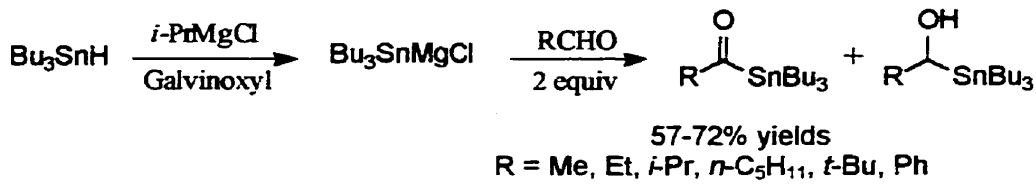
The first acylstannane synthesis was reported in 1966 by Peddle.[10] He prepared acetyl triphenyltin from the addition of triphenyltinlithium to acetyl chloride at –70°C (Scheme 53, equation 1). Peddle noted that acetyl triphenyltin was extremely labile as it was completely converted to triphenyltin acetate on exposure to air for 5 to 10 minutes (Scheme 53, equation 2).[10] The first reactions with this new class of compounds were also documented by Peddle.[10-12] The reduction of acetyl triphenyltin with lithium aluminum hydride ($LiAlH_4$) gave (1-triphenylstannyl)ethanol in 72% yield (Scheme 53, equation 3).[11] The addition of phenylmagnesium bromide to benzoyltriphenyltin gave a complex mixture, which consisted of (triphenylstannyl)diphenylmethanol (9%), tetraphenyltin (16%), hexaphenylditin oxide (47%) and benzhydrol (43%) (Scheme 53, equation 4).[11] However, most of these compounds were characterized only by their melting points.

Scheme 53



Since these early publications, several reports detailing the preparation of acylstannanes have been made.[13-17] They include: (1) stannylation of lithiated conjugated vinyl ethers followed by hydrolysis;[13] (2) treatment of tributylstannylmagnesium chloride with two equivalents of an aldehyde;[14] (3) hydrolysis of stannyl-1,3-dioxans;[15] (4) addition of tributyltin lithium to acid halides;[16] and (5) addition of trialkyltin lithium to carboxylate esters or thioesters.[17] Perhaps the most reliable route is an adaptation of a method originally reported by Quintard *et al.*[14] and developed further within our laboratory.[18,19] Chan found that acylstannanes could be prepared as described by Quintard. However, Galvinoxyl was required for the successful generation of tributylstannylmagnesium chloride from tributyltin hydride and isopropylmagnesium chloride. Explanations regarding the role of Galvinoxyl have been varied. Kosugi suggested that the function of Galvinoxyl was simply to inhibit autoxidation of the acylstannane.[16] However, Chan found that without the addition of Galvinoxyl, as also noted by Neuman,[20] the outcome of the reaction was unpredictable. Treatment of tributylstannylmagnesium chloride with two equivalents of aldehyde normally provides a mixture of acylstannane and stannyl carbinol, which are separable by fractional distillation under high vacuum (Scheme 54).

Scheme 54 [18,19]



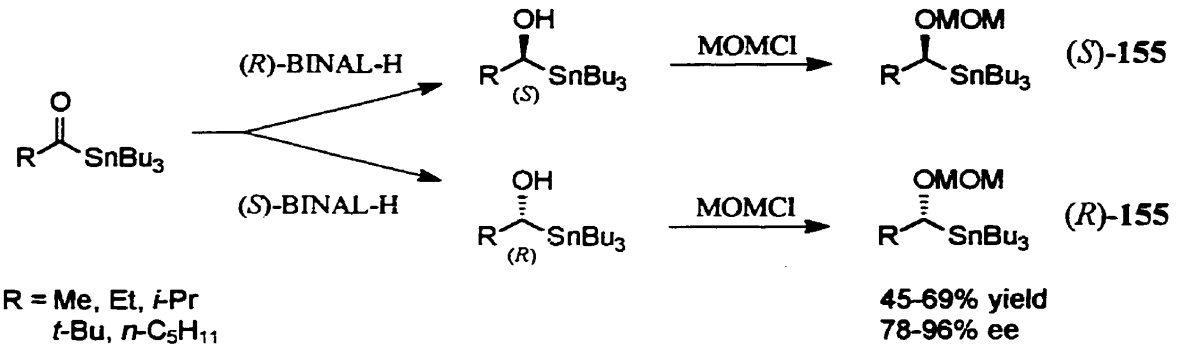
57-72% yields
R = Me, Et, *i*-Pr, *n*-C_5H_{11}, *t*-Bu, Ph

Despite numerous reports describing methods of preparing acylstannanes, this class of compounds remains relatively obscure as seen by the lack of literature describing their chemistry. As suggested by Chan,[18] this may in part be due to difficulties encountered in their preparation and handling. To our knowledge only five separate areas of acylstannane chemistry have ever been investigated: (1) reduction, (2) organometallic addition, (3) palladium-catalyzed coupling, (4) preparation of imidoylstannanes, and (5) preparation of SAMP-hydrazones. Each of these areas will be briefly outlined in the following sections.

Reduction of Acylstannanes

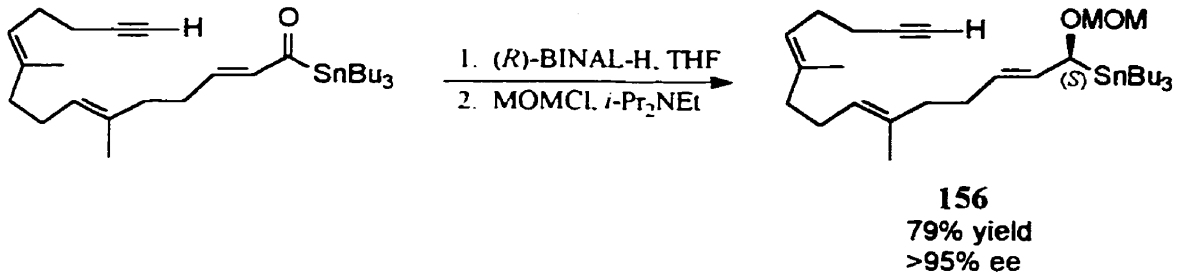
As discussed above, the reduction of acetyl triphenyltin with $LiAlH_4$ was originally reported by Peddle.[10,11] The reduction of acylstannanes with BH_3•THF to yield stannyl carbinols has also been documented within our laboratory.[21] The asymmetric reduction of acylstannanes using Noyori's[22,23] 2,2′-dihydroxy-1,1′-binaphthyl-modified lithium aluminum hydride (BINAL-H) reagent has been demonstrated in two instances. The asymmetric reduction of acylstannanes with BINAL-H to obtain α-alkoxystannanes [(*S*)-, (*R*)-**155**] of 78-96% ee in 45-69% yield was reported by Chan and Chong (Scheme 55).[21] Both enantiomers of **155** could be selectively obtained by judicious choice of the chiral BINAL-H reagent.

Scheme 55 [21]



Marshall and Gung obtained α-alkoxyallylstannane **156** in >95% ee (79% yield) from the (*R*)-BINAL-H reduction of the precursor acylstannane (Scheme 56).[24-27]

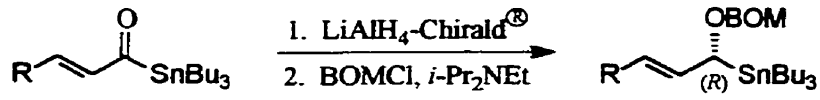
Scheme 56 [24-27]



156
79% yield
>95% ee

Marshall and Gung have also reported the reduction of acylstannanes with the complex derived from lithium aluminum hydride and (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Chirald® or Darvon alcohol) (Scheme 57).[26] However, the observed enantiomeric purity (60-62%) of **157** was much lower than that obtained with BINAL-H.

Scheme 57 [26]



157
60-62% ee
R = Me, *n*-Bu, *c*-C_6H_{11}

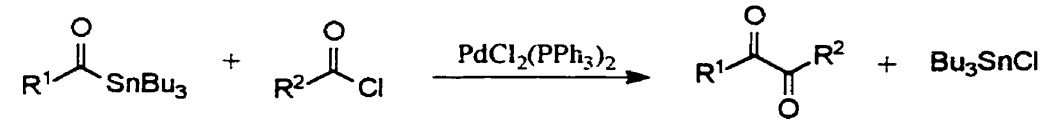
Organometallic Additions to Acylstannanes

Peddle has documented the only addition of an organometallic reagent to an acylstannane as highlighted earlier in Scheme 53 (equation 4).[11] The addition of phenylmagnesium bromide to benzoyltriphenyltin gave the expected alcohol, (triphenylstannyl)diphenylmethanol, in low yield (9%).

Palladium-Catalyzed Coupling

Quintard *et al.* reported on the palladium-catalyzed couplings of acylstannanes with acyl chlorides to yield unsymmetrical and symmetrical α-diketones (**158**) in 41-65% yields (Scheme 58).[28]

Scheme 58 [28]

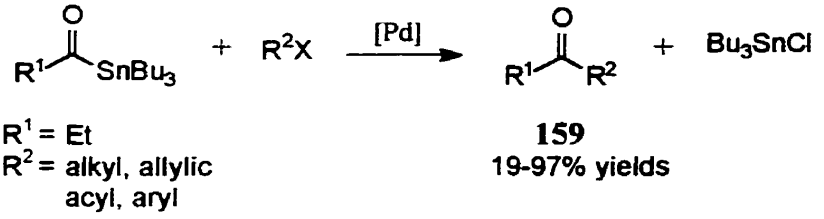


R^1 = Et, *i*-Pr
R^2 = *n*-C_6H_{13}, aryl

158
41-65% yields

Kosugi and co-workers investigated the palladium-catalyzed couplings of acylstannanes with alkyl and aryl halides to yield ketone **159** in 19-97% yields (Scheme 59).[29,30]

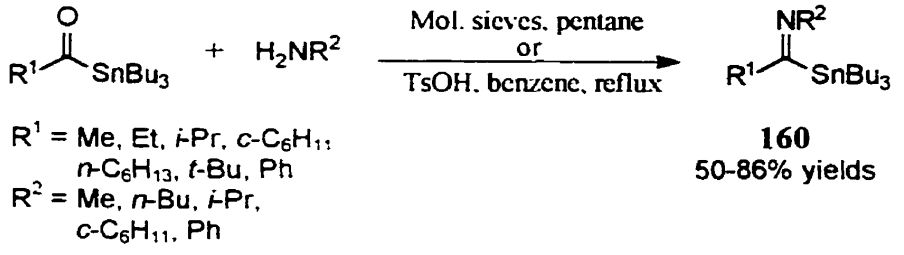
Scheme 59 [29,30]



Preparation of Imidoylstannanes

Ahlbrecht and Baumann reacted acylstannanes with primary aliphatic and aromatic amines to prepare imidoylstannanes (**160**) in 50-86% yields.[31,32] Only a single stereoisomer of **160** could be detected and was assigned as the *Z*-isomer based on an X-ray diffraction (Scheme 60).[32]

Scheme 60 [31,32]

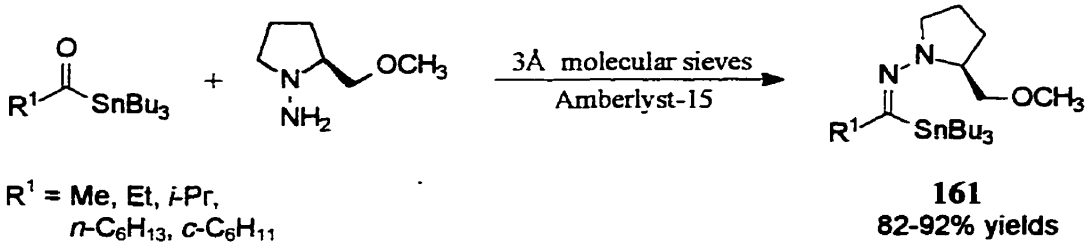


Preparation of SAMP-Hydrazones

Bekkali,[33] within our laboratory, prepared SAMP-hydrazone (**161**) derivatives of acylstannanes by acid catalyzed condensation with (*S*)-1-amino-2-(methoxymethyl)-

pyrrolidine (SAMP). These SAMP-hydrazones could be prepared in 82-92% yields (Scheme 61).

Scheme 61 [33]



R^1 = Me, Et, *i*-Pr, *n*-C_6H_{13}, *c*-C_6H_{11}

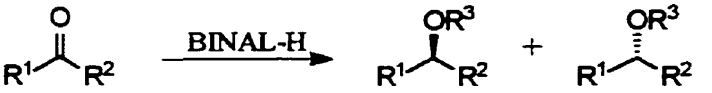
161
82-92% yields

This brief summary highlights the reactivity of acylstannanes. In particular, the main focus has been on the chemistry of the carbonyl and the trialkyltin moiety. The acylstannane carbonyl exhibits similar reactivity to that of a normal ketone. It is susceptible to reduction with alumino- and borohydride reagents. The addition of amines to acylstannanes yields imines. Acylstannanes are also susceptible to palladium insertion to allow coupling with alkyl, aryl and acyl halides.

4.1.2 Structure and Properties of Acylstannanes

The trialkylstannyl group has a strong influence on the spectroscopic properties of acylstannanes as evidenced by the carbonyl absorption in their IR spectrum and the position of the signal for the carbonyl-carbon in their ^{13}C NMR spectrum. The IR absorption is shifted from 1710 cm^{-1} for a dialkyl ketone to 1640 cm^{-1} by replacement of one alkyl with the trialkylstannyl group. This shift is even greater than for an alkyl aryl ketone, which is located at 1690 cm^{-1} for acetophenone. The ^{13}C NMR carbonyl peak is shifted from 210 ppm for a dialkyl ketone to 250 ppm for acylstannanes. This strong electronic effect has played a role in defining their similar chemical behavior to alkyl aryl ketones. For instance, the BINAL-H reduction of acylstannanes performed by Chan demonstrated the chemical similarity between these stannanes and the related alkyl aryl ketones, which had been reduced by Noyori and co-workers under similar conditions (Table 12).[21,22]

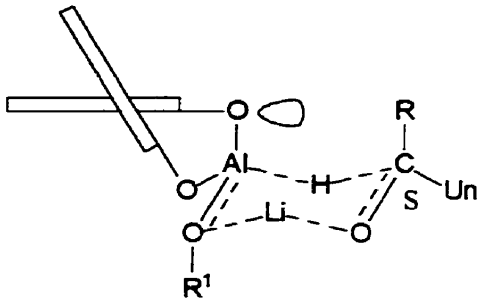
Table 12. Asymmetric reduction of alkyl aryl ketones and acylstannanes with BINAL-H.[21,22]



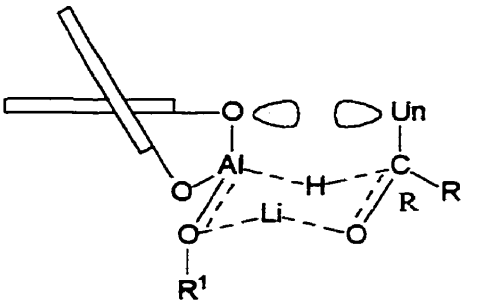
R^1	Product			
	$R^2 = Ph$[22]		$R^2 = SnBu_3$[21]	
	Yield (%)[a]	ee (%)[b]	Yield (%)[c]	ee (%)[d]
Me	61	95	58	94
Et	62	98	69	96
i-Pr	68	71	60	97
t-Bu	80	44	55	80

[a] Determined by GC analysis.
[b] Determined by ^{1}H NMR and HPLC analysis of MTPA esters from (*S*)-(+)-MTPA-Cl.
[c] Isolated yield of chromatographed ether, where R^3 ≡ MOM or BOM.
[d] Determined by ^{1}H NMR analysis of the MTPA esters derived from the crude reaction products.

The enantioselectivities obtained by Noyori *et al.* were rationalized by examining the favored (**162**) and disfavored (**163**) transition state models of the (*S*)-BINAL reduction (Figure 13).[22] The electronic repulsion expected between the oxygen atom on the binaphthol and the unsaturated group (Un) on the ketone substrate, raises the transition state energy of model **163**, hence, making transition state **163** less favorable in comparison to **162**. Arguments supporting simple steric approach were found to be implausible. The reduction of acylstannanes performed by Chan[18] gave comparable (R^1 = Me or Et) and in some instances superior selectivities (R^1 = *i*-Pr or *t*-Bu) than the analogous reduction of alkyl aryl ketones. These results were explained by taking into account the larger electronic repulsion exerted by the trialkyltin moiety as compared to the aryl group. The trialkyltin moiety is often viewed as an unsaturated group due to its strong resonance effect.[21]



162



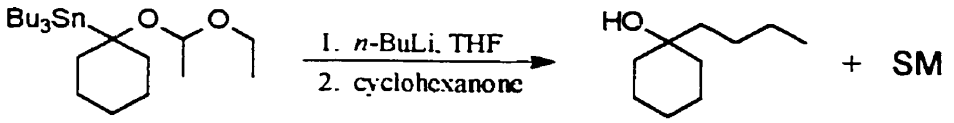
163

Figure 13. Favored (**162**) and disfavored (**163**) transition state of (*S*)-BINAL-H reduction proposed by Noyori.[22]

4.1.3 Transmetalation and Trapping of α,α-Disubstituted α-Alkoxyorganostannanes

The transmetalation of α,α-disubstituted α-alkoxyorganostannanes has been an area of interest since the seminal work of Still.[1] In 1978, he attempted the tin-lithium exchange of stannane **164** which yielded 1-butylcyclohexanol and starting α-alkoxystannane as the only products (Scheme 62). Still speculated that the absence of tin-lithium exchange products might reflect the lower stability of the α,α-disubstituted α-alkoxylithium intermediate or that the result may be purely kinetic.

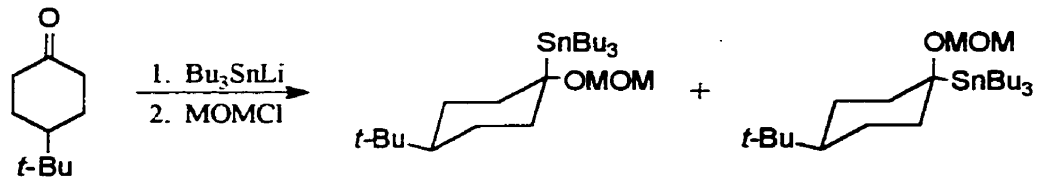
Scheme 62 [1]



164

McGarvey has observed that the addition of tributyltinlithium to 4-*tert*-butylcyclohexanone gives high levels of stereoselection in favor of axial addition (Scheme 63).[2,34] The acetal **165** is obtained as a 93:7 mixture of axial to equatorial.

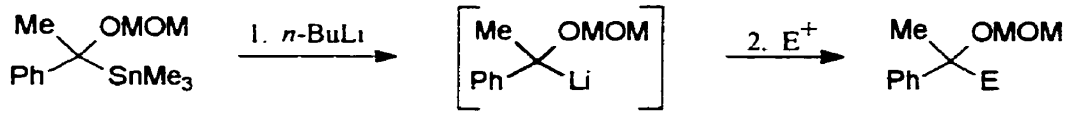
Scheme 63 [2,34]



165
(93:7)

Transmetalation of stannane **165** could only be done in 1,2-dimethoxyethane (DME).[2,34] In contrast, stannane **166** underwent transmetalation in a variety of solvents (DME, THF, Et_2O) when the trimethylstannyl moiety was employed over the tributylstannyl group (Scheme 64). This benzylic-stabilized α-alkoxylithium species was trapped with a variety of electrophiles to yield product **167**.[34] McGarvey rationalized these results by considering the greater thermodynamic stability of the benzylic carbanion of **166** versus the α,α-dialkyl α-alkoxylithium expected from **165**.[34]

Scheme 64 [34]



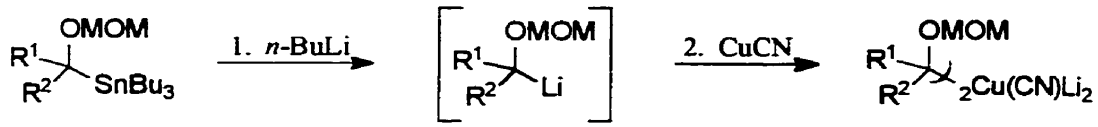
166

167
82-92% yields

Linderman and co-workers also investigated α,α-disubstituted α-alkoxyorganostannane **168** as a precursor to α-alkoxyorganolithium **169** for the eventual preparation of

α-alkoxyorganocuprate reagent **170** (Scheme 65).[8] Interestingly, stannane **168**, where R^1, R^2 = Me, underwent tin-lithium exchange in THF at -78°C. This process could also be carried out in DME. However, when R^1 = Me and $R^2 = n\text{-}C_5H_{11}$, transmetalation of this stannane did not occur in THF, but was accomplished in DME. As shown earlier by McGarvey,[2] generation of benzylic-stabilized α-alkoxyorganolithio species, where R^1 = Me and R^2 = Ph, could be performed in THF. The introduction of a phenyl group for R^2 into **168** enhances the stability of the carbanion by resonance.

Scheme 65[8]



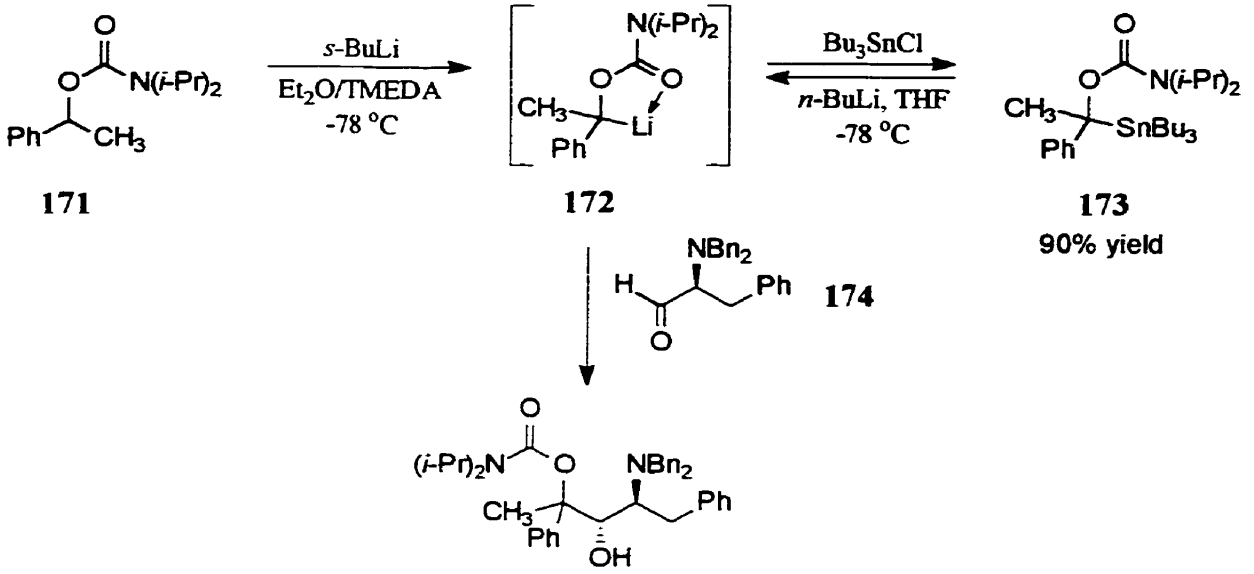
168 **169** **170**

The stability of α-hetero-substituted α-methylbenzyllithium compounds generated from tin-lithium exchange has been undertaken by several research groups. As discussed above, Linderman and co-workers prepared **169** from **168**, where R^1 = Me and R^2 = Ph.[8] Hoffmann *et al.* prepared stannane **173** from deprotonation of *N,N*-diisopropylcarbamate **171** and trapping of α-alkoxyorganolithium **172** with tributyltin chloride in 90% yield (Scheme 66).[3] Stannane **173** was transmetalated and trapped with aldehyde **174** to yield β-amino alcohol **175** in 92% yield as a 50:50 mixture of isomers.

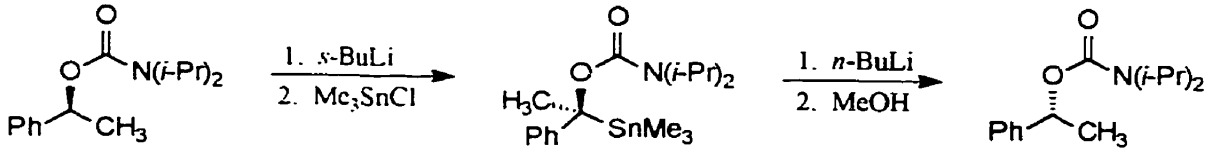
Hoppe and co-workers have prepared enantiomerically enriched α,α-alkylphenyl α-alkoxystannanes from lithiation and trapping of (*R*)- or (*S*)-1-phenylethyl *N,N*-diisopropyl-carbamate (**171**) (Scheme 67).[4] Deprotonation of (*S*)-**171** (≥ 99% ee) with *s*-butyllithium/ TMEDA at –78°C in diethyl ether and trapping with trimethyltin chloride provided (*S*)-**176** in 92% yield. Transmetalation of (*S*)-**176** (*n*-BuLi, Et_2O, -78°C) and trapping with methanol gave (*R*)-**171** of ≥ 95% ee in 65% yield. Hoppe noted that all lithiodestannylation reactions are expected to proceed with stereoretention;[35] therefore, the stannylation of (*S*)-**171** must

occur with inversion of stereochemistry. Similar results have been noted by Hammerschmidt and Hanninger.[5]

Scheme 66[3]



Scheme 67[4]



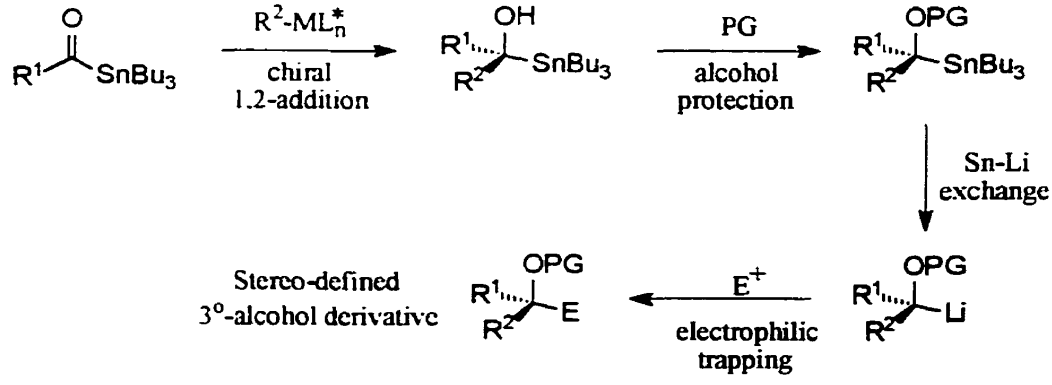
The reactions of acylstannanes with organometallic reagents has been inadequately investigated.[11] Current preparations of α,α-disubstituted α-alkoxyorganostannanes rely either on the condensation of trialkyltin anions with ketone substrates or the deprotonation of

secondary alcohols and trapping with trialkyltin halides.[1,4] Except for isolated examples,[2] only the second method allows for the preparation of enantiomerically enriched stannanes, but this method is dependent on the availability of chiral benzylic alcohols.[4] Unfortunately, examples of enantiomerically enriched α,α-dialkyl α-alkoxystannanes do not exist in the literature.

It is proposed that a judicious survey of organometallic reagents and their addition chemistry with acylstannanes would provide further insight into their reactivity. Modification of organometallic reagents, that show good chemoselectivity for 1,2-additions, with a chiral auxiliary may lead to a new route to enantiomerically enriched α,α-disubstituted α-alkoxystannanes. These enriched alcohols would serve as convenient precursors to homochiral α,α-disubstituted carbanions that would provide useful chiral building blocks for constructing stereo-defined tertiary alcohol derivatives (Scheme 68).

The preparation of α,α-dialkyl α-alkoxystannanes has been demonstrated previously.[2,8] The transmetalation and trapping of these substrates has also been documented.[2,6,8] However, the transmetalation of enantiomerically enriched acyclic α,α-dialkyl α-alkoxystannanes and trapping of the derived α-alkoxyorganolithium species has never been reported. It is not known whether this transformation proceeds with retention of configuration or leads to racemization. The following section details our efforts in addressing these questions.

Scheme 68



4.2 Results and Discussion

4.2.1 The Selection, Preparation, Purification and Characterization of Acylstannanes

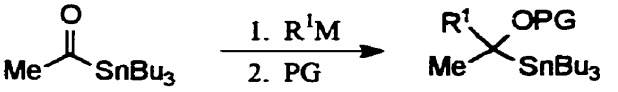
The selection of acylstannanes for this study was based on the following criteria for the α-substituent. It should: (i) allow 1,2-addition of nucleophiles to the carbonyl; (ii) tolerate a variety of nucleophiles, which would ultimately provide mixtures of enantiomers after addition; and (iii) permit enrichment of enantiomers by potential resolution. The acylstannane immediately considered for this study was (1-tributylstannyl)ethan-1-one (**177**) (Scheme 69). It was felt that by choosing an α-alkyl substituent such as methyl, all the above criteria would be met. The methyl substituent should also provide the minimal steric hindrance for the approach of nucleophiles.

Acylstannane **177** was prepared according to literature procedure,[19] and obtained in 47% yield after high vacuum distillation. Characterization of **177** by ^{1}H NMR spectroscopy gave a distinct singlet at δ 2.35 ($^3J_{H\text{-}Sn}$ = 12 Hz, $C\underline{H}_3CO$), which is downfield of a normal methyl ketone (δ 2.09 for CH_3COCH_3). Stannane **177** was stored in an aluminum foil wrapped vial, within a glove box. All dispensing of this material was performed within the same environment. These precautionary measures were necessary to eliminate contact with oxygen, moisture and ultraviolet light (as discussed in Section 4.1.1).[11]

4.2.2 Organometallic Additions to Acylstannanes

The primary objective of this study was to determine whether protected α,α-disubstituted α-alkoxystannanes could be synthesized by the addition of organometallic reagents to acylstannanes (Scheme 69).

Scheme 69



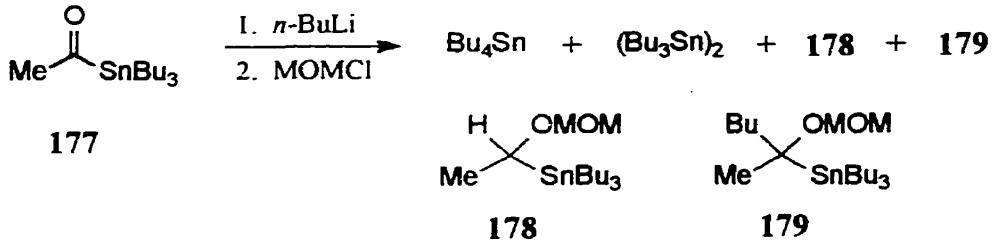
177

A study was undertaken with stannane **177** to determine its general reactivity with various classes of organometallic reagents. The organometallics that were investigated included organo-: aluminum, cerium, lithium, magnesium, and zinc reagents. The additions were performed under literature conditions typical of 1,2-addition chemistry.[36-38] The crude reaction mixtures obtained from these trials were immediately treated with chloromethyl methyl ether (*i*-Pr_2NEt, CH_2Cl_2), to protect any alcohol species formed. The immediate derivatization of α-hydroxystannanes is necessary to prevent their decomposition to Bu_3SnH and the reactant aldehyde.

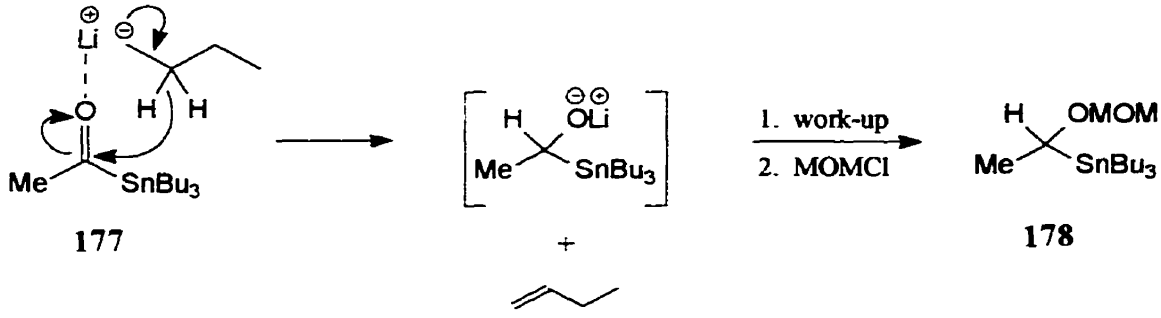
The addition of alkyllithium reagents was investigated first. Stannane **177** was treated with 1 equivalent of *n*-BuLi (THF, -78°C, Scheme 70). The bright yellow-green solution of **177** was essentially titrated colorless with the addition of each drop of *n*-BuLi to the reaction. This technique gave a good indication of how quickly the addition proceeded. Analysis of the reaction mixture by TLC indicated the formation of several different products. Protection of the alcohol species formed in the reaction proceeded in a straight forward manner with chloromethyl methyl ether. Complete separation of the individual components became tedious as their polarities were very similar. Fortunately, partial separation by column chromatography allowed their identification by GCMS analysis. The predominant reaction pathway resulting from the addition of *n*-BuLi was tin-lithium exchange, as $SnBu_4$ was the most abundant species detected by GCMS analysis. The quantitation of this species, to determine the percent transmetalation was hampered by the presence of $Bu_3SnSnBu_3$ in this same fraction. The acylstannane **177** also appeared to undergo 1,2-reduction to form ether **178**, after protection with chloromethyl methyl ether. This reaction pathway may arise from β-hydride transfer from the alkyllithium reagent as indicated in Scheme 71. The desired product **179** was formed in very low quantities as determined by TLC and GCMS analysis. Isolation and quantitation of ether **179** was

impossible due to presence of the secondary ether **178**. The R_f difference between **178** and **179** was less than 0.1 in hexanes/ethyl acetate (10:1).

Scheme 70



Scheme 71



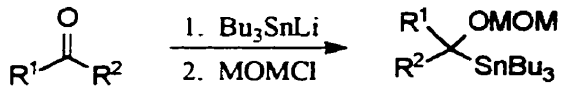
To investigate the generality of alkyllithium additions in different solvents, stannane **177** was treated with *n*-BuLi in diethyl ether and in hexanes. Once again the reactions yielded complex mixtures. A qualitative analysis by GCMS revealed that transmetalation was more prominent in ether solvents, while 1,2-addition was favored in hexanes. However, 1,2-reduction of the acylstannane substrate was a major pathway regardless of solvent choice.

The highly reactive nature of alkyllithium reagents is well documented.[39] The examination of other organometallic species, which may be more chemoselective for 1,2-addition, was pursued taking the following factors into consideration: (i) organometallics with β-hydrogens may be problematic; (ii) complete quantitation of reaction components

may not be possible; (iii) analysis of crude reaction mixtures by GCMS might facilitate a direct comparison of organometallic species; (iv) successful reagents should provide the highest percentage of the desired product while minimizing products arising from competing side-reactions.

A great number of nucleophilic methylating reagents are available. 1,2-Addition of these reagents to stannane **177** would simply produce α,α-dimethylalkoxystannanes, which are achiral. Therefore, (1-tributylstannyl)propan-1-one (**180**) was prepared so that methylating reagents could be included in the study. Standards were prepared of the anticipated products to allow for their identification by GCMS analysis. These compounds were prepared by the addition of Bu_3SnLi (LDA, THF, -78°C) to the appropriate ketone, followed by work-up and then protection with chloromethyl methyl ether. The yield and retention time of these standards are given in Table 13.

Table 13. GCMS analysis of prepared standards.



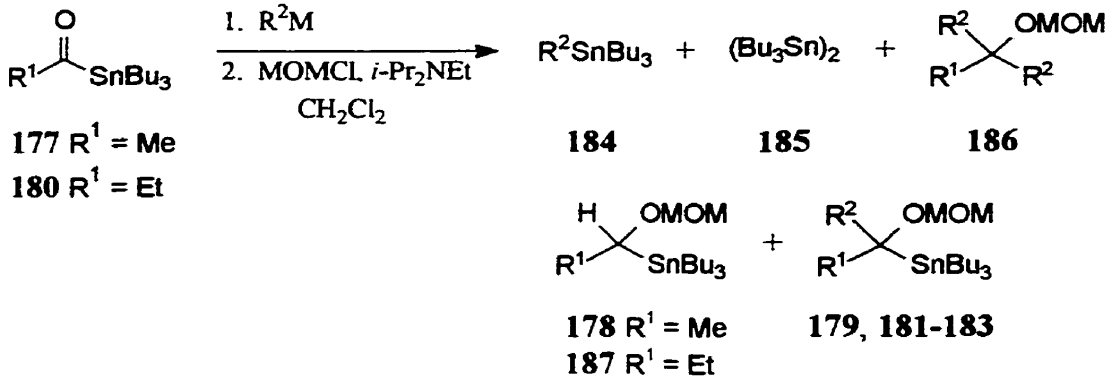
179, 181-183

Entry	R^1	R^2	Stannane	% yield	GCMS [a] (min)
1	Me	*n*-Bu	**179**	51	18.09
2	Me	Me	**181**	40	16.22
3	Me	Et	**182**	57	16.20
4	Et	*n*-Bu	**183**	42	17.85

[a] GCMS temperature program: initial temp 70°C, for 10 min; rate of heating 20°C/min, for 10 min; final temp 270°C, for 10 min.

A summary of the results obtained from the addition of various organometallics to stannanes **177** and **180** is provided in Table 14. The observed reaction patterns for each class of reagent is described in the following sections.

Table 14. Organometallic additions to acylstannanes. [a]



			Various Species (% Peak Area)[a]				
Entry	R^1	R^2M	**184**	**185**	**186**	**178, 187**	**179, 181-183**
1	Me	MeLi	61.2	2.0	0	0	11.2
2		MeMgBr	19.1	0	0	0	45.6
3		Et_2Zn	33.6	0	0	0	0
4		*n*-BuLi	49.1	1.1	10.2	0	4.3
5		*n*-BuMgBr	25.7	0	0	20.4	26.7
6	Et	MeMgBr	8.2	0	0	0	87.8
7		$MeCeCl_2$	19.4	0	0	0	58.4
8		$AlMe_3$	85.1	0	0	0	0
9		$LiAlMe_4$	91.5	0	0	0	0
10		*n*-BuLi	29.3	9.2	4.2	2.1	0.4
11		*n*-BuMgBr	8.5	0	0.6	54.9	29.0
12		*n*-$BuCeCl_2$	15.5	0	14.7	2.0	37.2

[a] Results are recorded as % peak area, determined by GCMS analysis of crude reaction mixtures. Areas have not been normalized. In many cases, other minor products were also observed.

Organolithium Reagents

The use of organolithium reagents predominately provides tetraalkyltin species as the result of tin-lithium exchange chemistry (entries 1 and 4). Thus with stannane **177**, the major

products observed with MeLi and *n*-BuLi were Bu_3SnMe and Bu_4Sn (**184**), respectively. The formation of hexabutylditin (**185**) is unique and was observed only when using alkyllithium reagents. Di-addition of the alkyl moiety, resulting in the formation of **186** is also observed for these reagents. The percent peak area of the desired addition products **179**, **181** and **183** is very low when compared to the analogous Grignard or cerium reagent (compare entries 1 and 2). In short, the use of organolithium reagents does not provide synthetically useful yields of the desired compound.

Organomagnesium Reagents

The occurrence of transmetalation (Sn-Mg) chemistry, resulting in the formation of tetraalkyltin **184** is much less for organomagnesium reagents when compared to the other organometallic reagents. In all examples studied, no hexabutylditin (**185**) was observed by GCMS. Of the four classes of reagents examined that contained β-hydrides, the organomagnesium reagents gave the highest levels of reduction products **178** and **187** (compare entries 10, 11 and 12). The use of Grignard reagents produced lower levels of the di-addition product **186** (compare entries 10 and 11). Grignard reagents give the highest overall levels of the desired product (entries 2, 5 and 6).

Organocerium Reagents

Organocerium and organomagnesium reagents give comparable percent peak areas of the desired product (compare entries 11 and 12). Reduction of the acylstannane resulting in product **187** is greatly minimized when compared to the corresponding organomagnesium reagents; however, the di-addition product **186** is obtained in higher levels. These reagents gave intermediate levels of the corresponding tetraalkyltin species **184**, as a result of transmetalation.

Organozinc Reagents

Stannane **177** was virtually unreactive with diethylzinc at room temperature, as none of the desired addition product **182** was observed (entry 3). The formation of $EtSnBu_3$ (**184**) provides evidence that diethylzinc is able to transmetalate this acylstannane.

Organoaluminum Reagents

The availability of both electrophilic ($AlMe_3$) and nucleophilic ($LiAlMe_4$) aluminum reagents provided an opportunity to study the chemoselectivity of these reagents (entries 8 and 9). Ironically, independent of their mode of reactivity, both of these reagents lead exclusively to the formation of $MeSnBu_3$ (**184**). Stannane **180** was consumed within 20 minutes, after the addition of $AlMe_3$ at –78°C, followed by warming to –5°C. The $LiAlMe_4$ reagent, prepared *in situ* from MeLi and $AlMe_3$ showed no reactivity after 30 minutes at –5°C, but transmetalated stannane **180** upon warming to room temperature.

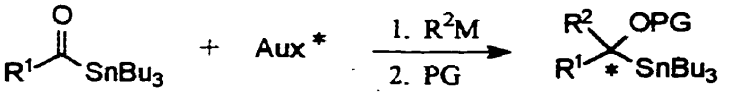
This study of organometallic additions to acylstannanes revealed that organolithium reagents were highly reactive and led primarily to the transmetalation of acylstannanes **177** and **180**. Organomagnesium reagents gave cleaner reaction mixtures and promoted more of the desired 1,2-addition chemistry. Organocerium reagents gave comparable results to the Grignard species; however, they lead to higher levels of transmetalation chemistry. Both the organozinc and organoaluminum reagents failed to perform the 1,2-addition chemistry and were chemoselective in transmetalating the acylstannane substrates.

Organomagnesium reagents were chosen from this study as the best reagents for pursuing the enantioselective synthesis of α,α-dialkyl α-hydroxystannanes. However, we also recognized that organometallic reagents modified by chiral auxiliaries can show both increased and moderated reactivity depending on the electronic nature and degree of substitution surrounding the active metal site. Therefore, selected organometallic reagents, such as $AlMe_3$, $LiAlMe_4$ and Et_2Zn, which had previously shown these characteristics were also used in the following study. The next section details our efforts in this area.

4.2.3 Enantioselective Addition of Organometallic Reagents to Acylstannanes

The enantioselective 1,2-addition of organomagnesium reagents to acylstannanes was pursued as a method of preparing protected α,α-dialkyl α-hydroxystannanes in enantiomerically enriched form (Scheme 72).

Scheme 72



A brief survey[36,37,40] of ligands that have been used in conjunction with Grignard reagents for performing 1,2-additions to carbonyl compounds illustrates that the following were commonly used: (1*S*,2*R*)-*N*,*N*-di-*n*-butyl-norephedrine (DBNE),[41] (*S*)-(+)-diphenyl-(*N*-methylpyrrolidin-2-yl)methanol (DPMPM),[42] (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methyl-pyrrolidin-2-yl)methyl]pyrrolidine (HMMPMP),[43] α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL),[40,44,45] and binaphthol (BINOL)[46] (Figure 14).

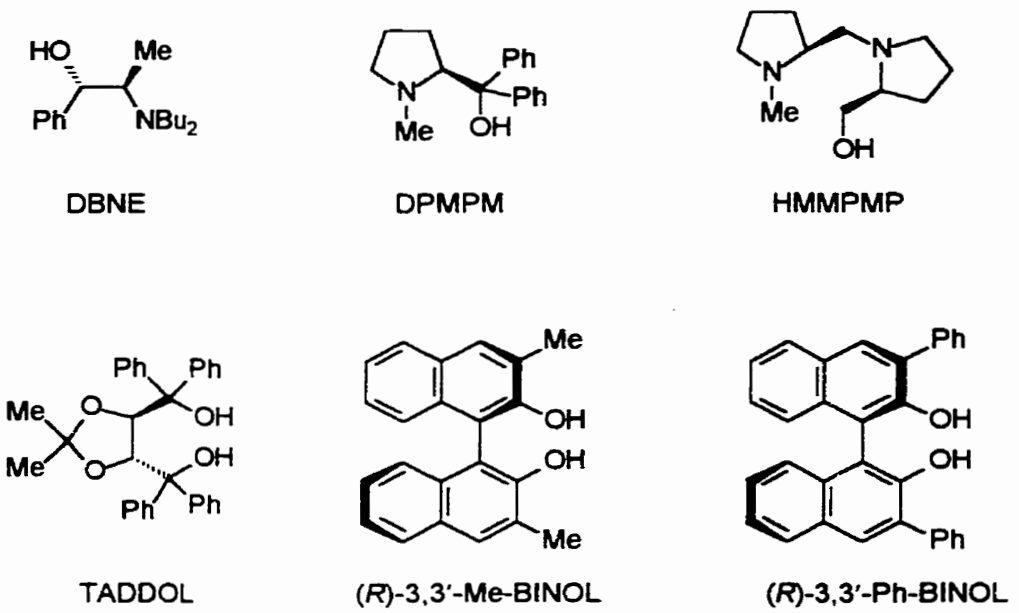
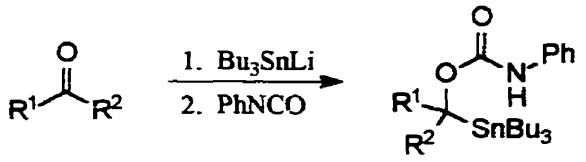


Figure 14. Structures of chiral ligands used with organomagnesium reagents.

These ligands were either available in our laboratory or readily prepared by literature protocols.[41-43,47] The enantioselectivity of the organometallic additions was determined by chiral HPLC on a Chiracel OD column Since MOM derivatives of α,α-dialkyl α-hydroxy-stannanes were non-UV active, derivatization of the alcohols was performed using PhNCO (CH_2Cl_2) to generate the corresponding urethane, which enabled detection at λ = 254 nm. Standards were prepared of the desired products to allow for their identification by HPLC analysis. These compounds were prepared by the addition of Bu_3SnLi (LDA, THF, -78°C) to the appropriate ketone substrate. The yield and retention time (HPLC) of these standards are given in Table 15.

Table 15. HPLC analysis of prepared standards.[a]



(±)-**188-190**

Entry	R^1	R^2	Stannane	Yield (%)	HPLC [b] (min)
1	Me	Et	**188**	50	11.17, 12.58
2	Me	*n*-Bu	**189**	44	8.48, 13.40
3	Me	$C{\equiv}CCH_2CH_3$	**190**	40	12.02, 15.55

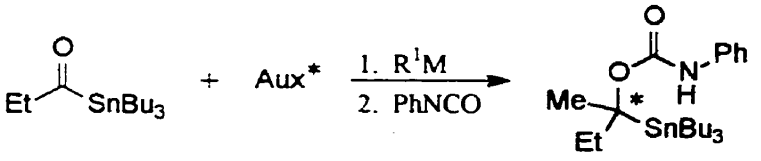
[a] Determined by HPLC analysis using a Chiracel OD column (1% *i*-PrOH/Hex, 0.5 mL/min).
[b] Elution times for the two enantiomers.

The inherent problem of 1,2-reduction chemistry by certain organometallic reagents led us to select organomagnesium reagents which contained no β-hydrogens. Initially, MeMgBr additions to (1-tributylstannyl)propan-1-one were examined. The yield of these reactions were not determined because the goal of this study was to perform a preliminary screening of the reactivity and selectivity of chosen organometallic species in the presence of a chiral auxiliary. If reagents and conditions could be found that would provide selectivities in better than 80% enantiomeric excess, then further effort would be extended to optimize these conditions. Reactions were typically carried out using 2-3 equivalents of chiral ligand per equivalent of acylstannane substrate. The *N*-methylaminoalcohols were treated with either 2 equivalents of Grignard or 1 equivalent of *n*-BuLi followed by 1 equivalent of Grignard. The chiral diols, TADDOL and BINOL, were treated with either 3 equivalents of Grignard or alternatively, 2 equivalents of *n*-BuLi followed by 1 equivalent of Grignard reagent.

The addition of MeMgBr was examined in the presence of DBNE, DPMPM, HMMPMP, TADDOL, and (*R*)-3,3′-Ph-BINOL (Table 16). The reaction conditions used for these chiral additions followed those described in literature references.[40-43,46] The best selectivity achieved for the addition of MeMgBr, employed the DPMPM ligand in Et_2O,

which gave an enantiomeric ratio of 60:40. The use of DBNE failed to give any of the desired product. The employment of other ligands failed to give better results than those obtained with DPMPM (Table 16, entries 1-5). The use of dialkylmagnesium reagents has been shown to promote higher selectivities over the analogous Grignard species. For this reason, Me_2Mg was prepared and reacted with the HMMPMP ligand.[43] Unfortunately, a racemic product was obtained when the reaction was conducted in either toluene or CH_2Cl_2 (entry 6). The organoaluminum reagent $AlMe_3$ was assessed using DPMPM and (*R*)-3,3′-Ph-BINOL. Both trials gave a poor selectivity of the final product: 52:48 and 59:41, respectively (entry 7 and 8). The $LiAlMe_4$ reagent was also used in the presence of (*R*)-3,3′-Me-BINOL, but failed to give any of the desired product (entry 9).

Table 16. Organometallic additions to (1-tributylstannyl)propan-1-one (**180**).



180 **188**

Entry	R^1M	Auxiliary	Solvent	Temp (°C)	er[a] **188**
1	MeMgBr	DBNE	hexane	0	NP[b]
2	MeMgBr	DPMPM	Et_2O	-5	60:40
3	MeMgBr	HMMPMP	Et_2O	0	44:56
4	MeMgBr	TADDOL	THF	-78	53:47
5	MeMgBr	(*R*)-3,3′-Ph-BINOL	THF	-78	NP[b]
6	Me_2Mg	HMMPMP	CH_2Cl_2	-78	49:51
7	$AlMe_3$	DPMPM	CH_2Cl_2	0	52:48
8	$AlMe_3$	(*R*)-3,3′-Ph-BINOL	CH_2Cl_2	0	59:41
9	$LiAlMe_4$	(*R*)-3,3′-Me-BINOL	THF	0	NP[b]
10	$MeTi(i\text{-}PrO)_3$	TADDOL	toluene	-78 to 25	NP[b]

[a] Enantiomeric ratio determined by HPLC, using a Chiracel OD column (1% *i*-PrOH/Hex, 0.5 mL/min).
[b] No product isolated.

In all experiments examined to date, the reactivity of the organometallic reagent followed one of two trends: the additions to the acylstannane were rapid, completed within 15 minutes and yielded a near racemic product; or the reactions were overly sluggish and never reached completion. The rapid consumption of the acylstannane by the organometallic reagent suggested that the reagents might be adding without complexation by the chiral ligand. The slow reaction times possibly suggested that the chiral reagents are formed properly, but steric hindrance about the carbonyl of the acylstannane may impede approach of the nucleophile to perform the 1,2-addition.

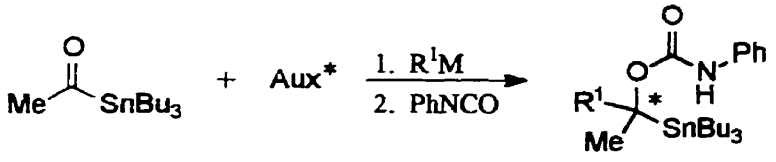
Although the 1,2-reduction chemistry had been a factor in the initial study when using reagents containing β-hydrogens, it was decided to investigate other nucleophiles such as ethyl- and butylmagnesium bromide. Perhaps in the presence of a chiral ligand containing alkoxide substituents, the highly reactive nature of these Grignards may be moderated to prevent the 1,2-reduction of the acylstannane substrates.

To help alleviate problems associated with slow reaction times, possibly caused by steric hindrance between the organometallic reagent and the tributylstannyl moiety, it was postulated that a smaller side-chain on the acylstannane (i.e., Me) might facilitate an easier approach for the nucleophile, thus increasing the relative rate of addition. Likewise, the rapid consumption of the acylstannane yielding an overall racemic product, may be due in part to inadequate quantities of chiral alkoxide (derived from the chiral ligand and alkyllithium) to fully complex the Grignard reagent. Free Grignard in solution would add non-stereoselectively yielding the racemic product. This potential problem was addressed by employing 10 equivalents of chiral ligand and 3 equivalents of Grignard, with respect to acylstannane.

Preliminary results obtained from EtMgBr and *n*-BuMgBr additions to (1-tributyl-stannyl)ethan-1-one (**177**), using the DPMPM ligand in hexanes, were very promising (Table 17, entries 1 and 3). An enantiomeric ratio of 78:22 was obtained with EtMgBr, and 70:30 with *n*-BuMgBr. High selectivity was also found with EtMgBr in the presence of the TADDOL ligand, but only trace amounts of the product were obtained (entry 2). Unfortunately, the results obtained in conjunction with the DPMPM ligand proved very difficult to reproduce. Perhaps the only explanation is the delicate sensitivity of these chiral environments to varying levels of alkoxide. These anomalies may be caused in part to

varying levels of alkoxide within commercial bottles of alkyllithium and Grignard solutions. Difficulties in obtaining reproducibility, when combating anomalous alkoxide concentrations in commercial materials, has also been noted in cuprate chemistry.[48]

Table 17. Organometallic additions to (1-tributylstannyl)ethan-1-one (**177**).



177 **188-190**

Entry	R^1M	Auxiliary	Solvent	Temp (°C)	er[a] **188-190**
1	EtMgBr	DPMPM	hexane	-5	78:22
2	EtMgBr	TADDOL	THF	-5	76:24
3	*n*-BuMgBr	DPMPM	hexane	0	70:30
4	Et_2Mg	(*R*)-BINOL	THF	-78	48:52
5	Et_2Zn	DBNE	hexane	25	NP[b]
6	Et_2Zn	DPMPM	hexane	0	NP[b]
7	$LiC{\equiv}CCH_2CH_3$	DPMPM	THF	-5	49:51
8	$BrMgC{\equiv}CCH_2CH_3$	HMMPMP	THF	-95	44:56

[a] Enantiomeric ratio determined by HPLC, using a Chiracel OD column (1% *i*-PrOH/Hex, 0.5 mL/min).
[b] No product isolated.

Additions of Et_2Mg and Et_2Zn to acylstannane **177** were also examined. The diethylmagnesium reagent gave the product in poor selectivity (48:52) in the presence of (*R*)-BINOL (entry 4). The organozinc reagent failed to give the desired product, when either DBNE or DPMPM were employed as the chiral ligand (entries 5 and 6). Other examples of organometallic reagents that contain no β-hydrogens include anions of 1-alkynes. 1-Butynyllithium and 1-butynylmagnesium bromide were prepared and tested in the presence of DPMPM and HMMPMP, respectively. The selectivities were relatively poor at 49:51 for the alkynyllithium and 44:56 for the Grignard reagent (entries 7 and 8).

4.2.4 Summary

Attempts to develop a route to enantiomerically enriched, α,α-dialkyl α-hydroxy-stannanes, through the enantioselective addition of organometallic reagents to acylstannanes, were unsuccessful. This methodology was hampered by both low selectivities and reactivity. Addition of simple organometallic reagents resulted in complex mixtures.

The addition of methyl nucleophiles to (1-tributylstannyl)propan-1-one (**180**) never produced selectivities higher than 18% ee of the desired product.

The best selectivity observed for the ethylation of (1-tributylstannyl)ethan-1-one (**177**) was 56% ee, with EtMgBr in the presence of DPMPM. However, this result proved very difficult to reproduce. Varying levels of alkoxide within the reaction mixture, which may be introduced through the alkyllithium and Grignard reagents, may interfere with the chiral environment surrounding the nucleophilic site of the metal/ligand complex. Competition between alkoxides and the chiral ligands for the organometallic reagent would change the environment of the active metal site between each separate reaction trial. This in turn would lead to different enantiomeric ratios of the product. Alkynyllithium and alkynyl-Grignard reagents, which contained no β-hydrogens, gave near racemic products.

4.3 Experimental

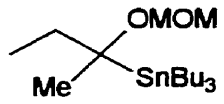
4.3.1 General

The general procedures described in Section 2.3.1 are applicable here with the following additions. Acylstannanes **177** and **180** were prepared following the procedure of Chong and Mar[19]and provided satisfactory analysis by ^{1}H NMR spectroscopy. Solutions of alkynylmagnesium bromide were prepared as described by Brandsma and Verkruijsse.[49] Organocerium reagents were prepared as outlined by Takeda and Imamoto.[50] Dialkylmagnesium reagents were prepared following the procedure of Mukaiyama *et al.*[43] Solutions of $MgBr_2 \bullet OEt_2$ were obtained as described by Seebach and co-workers.[51] Chiral amino alcohols, DBNE and DPMPM, were prepared according to the methodology of Soai and co-workers,[41,42] and HMMPMP was obtained from the procedure described by Mukaiyama *et al.*[43] The optical rotation of the chiral amino alcohols was checked prior to their use and compared to literature values.

4.3.2 Representative Procedure for the Preparation of Methoxymethyl Protected α,α-Dialkyl α-Hydroxystannanes

A representative procedure for the preparation of ether **182** is given below, followed by spectral data of ethers **179**, **181-183** The yields of these ethers can be found in Table 13.

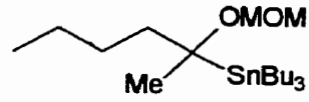
2-Methoxymethoxy-2-tributylstannyl butane (182)



To a cold (0°C) solution of *i*-Pr_2NH (0.24 mL, 1.8 mmol) was added *n*-BuLi (1.31 mL of a 1.41 M solution in hexanes, 1.8 mmol). After the solution was stirred for 15 min, Bu_3SnH (0.5 mL, 1.8 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 2-butanone (0.18 mL, 2.0 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 2-tributylstannyl-2-butanol.

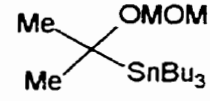
This material was cooled (0°C) and then CH_2Cl_2 (2 mL), *i*-Pr_2NEt (0.78 mL, 4.5 mmol) and chloromethyl methyl ether (0.21 mL, 2.7 mmol) were added. The ice bath was removed, and the mixture was stirred at room temperature until TLC indicated the reaction was complete (0.5-1 h). Excess chloromethyl methyl ether was hydrolyzed using 0.1 M NaOH solution (2 mL). The crude mixture was diluted with ether (75 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 741 mg of crude yellow oil. Column chromatography of this material on silica gel (22 g) using hexanes/ethyl acetate (30:1) afforded 416 mg (57 %) of the title compound as a colorless oil; IR (neat film) 2913, 1458, 1375, 1141, 1033, 917, 867, 645 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.00 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2C$), 1.24-1.60 (m, 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 1.40 (s, 3 H, $C\underline{H}_3$), 1.74 (q, 2 H, J = 7.4 Hz, $CH_3C\underline{H}_2C$), 3.36 (s, 3 H, $C\underline{H}_3O$), 4.65 (ABq, 2 H, J_{AB} = 7.0 Hz, Δν = 13.8 Hz, $OC\underline{H}_2O$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.84 ($\underline{C}H_3CH_2C$), 10.04 (^1J = 282.2, 293.5 Hz, $\underline{C}H_2Sn$), 13.56 ($\underline{C}H_3CH_2$), 25.90 ($CH_3\underline{C}H_2C$), 27.62 (^2J = 55.5 Hz, $\underline{C}H_2CH_2Sn$), 29.29 (^3J = 18.9 Hz, $CH_3\underline{C}H_2$), 34.75 ($\underline{C}H_3C$), 55.43 ($\underline{C}H_3O$), 82.58 ($\underline{C}OMOM$), 93.64 (^3J = 22.6 Hz, $O\underline{C}H_2O$); MS (EI) *m/z* 363 (0.5, M^+-MOM), 351 (0.9, M^+-C_4H_9), 291 (7), 235 (14), 177 (33), 117 (23), 45 (100); Anal. Calcd for $C_{18}H_{40}O_2Sn$: C, 53.09; H, 9.90. Found: C, 52.99; H, 9.85.

2-Methoxymethoxy-2-tributylstannyl hexane (179)



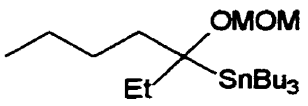
IR (neat) 2956, 1464, 1376, 1140, 1093, 1038, 916, 663, 593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.00 (m, 18 H, $C\underline{H_3}CH_2CH_2C\underline{H_2}Sn$ and $CH_2C\underline{H_3}$), 1.15-1.60 (m, 16 H, $CH_3C\underline{H_2}C\underline{H_2}CH_2Sn$ and $C\underline{H_2}C\underline{H_2}CH_3$), 1.40 (s, 3 H, $C\underline{H_3}C$), 1.64-1.72 (m, 2 H, $C\underline{H_2}C$), 3.35 (s, 3 H, $C\underline{H_3}O$), 4.64 (ABq, 2 H, J_{AB} = 7.0 Hz, Δν = 18.5 Hz, $OC\underline{H_2}O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.31 (^1J = 281, 294 Hz, $\underline{C}H_2Sn$), 13.64 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.12 ($\underline{C}H_3CH_2$), 23.27 ($\underline{C}H_3C$), 26.48 ($CH_3\underline{C}H_2$), 27.64 ($^2J$ = 56 Hz, $\underline{C}H_2CH_2Sn$), 28.04 ($\underline{C}H_2CH_2C$), 29.30 (^3J = 20 Hz, $\underline{C}H_2CH_2CH_2Sn$), 42.37 ($CH_2\underline{C}H_2C$), 55.52 ($\underline{C}H_3O$), 82.11 ($CH_3\underline{C}Sn$), 93.70 ($O\underline{C}H_2O$); MS (EI) *m/z* 391 (1, M^+-MOM), 379 (1, M^+-C_4H_9), 291 (10), 235 (15), 179 (29), 121 (15), 45 (100); Anal. Calcd for $C_{20}H_{44}O_2Sn$: C, 55.19; H, 10.19. Found: C, 55.29; H, 10.01.

2-Methoxymethoxy-2-tributylstannyl propane (181) [8]



^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.80 (m, 33 H, $C\underline{H_3}C\underline{H_2}C\underline{H_2}C\underline{H_2}Sn$ and $C\underline{H_3}$), 3.36 (s, 3 H, $C\underline{H_3}O$), 4.65 (ABq, 2 H, J_{AB} = 7.0 Hz, Δν = 13.8 Hz, $OC\underline{H_2}O$); MS (EI) *m/z* 349 (3, M^+-MOM), 337 (5, M^+-C_4H_9), 291 (17), 235 (29), 179 (46), 121 (31), 103 (13), 73 (30), 45 (100).

3-Methoxymethoxy-3-tributylstannyl heptane (183)



IR ($CHCl_3$) 2959, 2927, 1465, 1378, 1224, 1144, 1077, 1032, 927, 877 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.75-0.95 (m, 21 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$, $\underline{C}H_3CH_2CH_2$ and $C\underline{H}_3CH_2C$), 1.15-1.50 (m, 16 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_3C\underline{H}_2C\underline{H}_2$), 1.65-1.74 (m, 2 H, $CH_3CH_2CH_2C\underline{H}_2$), 1.77 (q, 2 H, J = 7.2 Hz, $CH_3C\underline{H}_2C$), 3.33 (s, 3 H, $C\underline{H}_3O$), 4.61 (s, 2 H, $OC\underline{H}_2O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.75 ($\underline{C}H_3CH_2CH_2$), 10.57 (^1J = 277, 289 Hz, $\underline{C}H_2Sn$), 13.61 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.12 ($\underline{C}H_3CH_2C$), 23.38 ($CH_3\underline{C}H_2CH_2$), 27.65 ($^2J$ = 58 Hz, $\underline{C}H_2CH_2Sn$), 27.97 ($\underline{C}H_2CH_2C$), 29.32 (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 31.73 ($CH_3\underline{C}H_2C$), 38.74 ($CH_2\underline{C}H_2C$), 55.63 ($\underline{C}H_3O$), 88.09 ($CH_3\underline{C}Sn$), 93.91 ($O\underline{C}H_2O$); MS (EI) *m/z* 405 (1, M^+-MOM), 391 (1, M^+-C_4H_9), 291 (4), 235 (8), 179 (16), 121 (12), 45 (100); Anal. Calcd for $C_{21}H_{46}O_2Sn$: C, 56.14; H, 10.32. Found: C, 56.31; H, 10.13.

4.3.3 Reaction of n-BuLi with (1-tributylstannyl)ethan-1-one (177)

To a cooled (-78°C) solution of stannane **177** (233 mg, 0.70 mmol) in THF (5 mL) was added *n*-BuLi (0.50 mL of a 1.40 M solution in hexanes, 0.70 mmol). After 15 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature).

This material was cooled to 0°C and then CH_2Cl_2 (2 mL), *i*-Pr_2NEt (0.30 mL, 1.75 mmol), and chloromethyl methyl ether (80 μL, 1.05 mmol) were added. The reaction was stirred at 0°C for 10 min and was then allowed to warm to room temperature. The reaction was monitored by TLC until complete (0.5-1.0 h). The solution was diluted with ether, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was passed through a short column of silica (~1 g of silica; hexanes/ethyl acetate, 2:1), to eliminate trace salts, affording the crude product as a colorless

oil, after concentration *in vacuo*. Samples for GCMS analysis were prepared in diethyl ether (Table 14, entry 4). A similar experiment was performed using MeLi (0°C).

4.3.4 Reaction of n-BuMgBr with (1-tributylstannyl)ethan-1-one (177)

To a cooled (0°C) solution of stannane **177** (490 mg, 1.47 mmol) in Et_2O (5 mL) was added *n*-BuMgBr (1.47 mL of a 1.0 M solution in Et_2O, 1.47 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). Derivatization and analysis are as described in Section 4.3.3 (Table 14, entry 5). A similar experiment was performed using MeMgBr.

*4.3.5 Reaction of n-BuCeCl$_2$ with (1-tributylstannyl)propan-1-one (**180**)*

To a cooled (-78°C) slurry of $CeCl_3$ (659.1 mg, 1.77 mmol) in THF (5 mL) was added *n*-BuLi (1.81 mL of a 0.98 M solution in hexanes, 1.77 mmol). After 30 min of stirring at -78°C, stannane **180** (511 mg, 1.47 mmol) was added as a solution in THF (2 mL). The pale yellow reaction was stirred at -78°C for a further 30 min. The cooling bath was removed and the reaction allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (20 mL), washed with aqueous 5% acetic acid (5 mL), $NaHCO_3$ (10 mL), H_2O (15 mL), and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). Derivatization and analysis are as described in Section 4.3.3 (Table 14, entry 12). A similar experiment was performed using $MeCeCl_2$.

4.3.6 Reaction of Et_2Zn with (1-tributylstannyl)ethan-1-one (177)

To a cold (0°C) stirred solution of stannane **177** (463 mg, 1.39 mmol) in hexanes (5 mL) was added dropwise Et_2Zn (1.39 mL of a 1.0 M solution in hexanes, 1.39 mmol). After 15 min of stirring at 0°C, the cooling bath was removed and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). Derivatization and analysis are as described in Section 4.3.3 (Table 14, entry 3).

4.3.7 Reaction of $AlMe_3$ with (1-tributylstannyl)propan-1-one (180)

To a cold (-78°C) stirred solution of $AlMe_3$ (0.55 mL of a 2.0 M solution in hexanes, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise stannane **180** (190.1 mg, 0.55 mmol). Once the addition of acylstannane was complete the reaction was warmed to -5°C. After 15 min of stirring at this temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). Derivatization and analysis are as described in Section 4.3.3 (Table 14, entry 8).

4.3.8 Reaction of $LiAlMe_4$ with (1-tributylstannyl)propan-1-one (180)

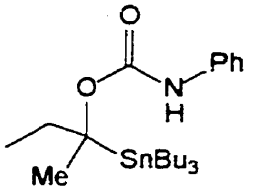
To a stirred solution of $AlMe_3$ (0.45 mL of a 2.0 M solution in hexanes, 0.91 mmol) in hexanes (5 mL) was added dropwise MeLi (0.67 mL of a 1.35 M solution in hexanes, 0.91 mmol) and the mixture stirred for 15 min at room temperature. The reaction was concentrated under high vacuum at room temperature, and the remaining white residue was redissolved in THF (5 mL). The solution was cooled to -5°C and stannane **180** (104.9 mg, 0.30 mmol) was added as a solution in THF (5 mL). After 30 min of stirring at -5°C, the reaction was allowed to warm to room temperature and then quenched with saturated

aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). Derivatization and analysis are as described in Section 4.3.3 (Table 14, entry 9).

4.3.9 Representative Procedure for the Preparation of N-Phenylcarbamate Protected α,α-Dialkyl α-Hydroxystannanes

A representative procedure for the preparation of carbamate **188** is given below, followed by spectral data of carbamates **188-190**. The yields of these carbamates can be found in Table 15.

*2-N-Phenylcarbamoyloxy-2-tributylstannyl butane (**188**)*

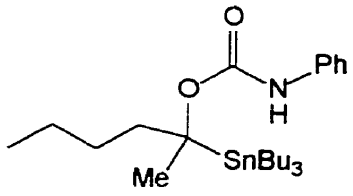


To a cold (0°C) solution of *i*-Pr_2NH (0.23 mL, 1.72 mmol) was added *n*-BuLi (1.68 mL of a 1.02 M solution in hexanes, 1.72 mmol). After the solution stirred for 15 min Bu_3SnH (0.46 mL, 1.72 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 2-butanone (0.18 mL, 2.06 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 2-tributylstannyl-2-butanol.

This material was cooled (0°C) and then CH_2Cl_2 (2 mL) and phenyl isocyanate (0.37 mL, 3.44 mmol) were added. The ice bath was removed, and the mixture was stirred at room

temperature until TLC indicated the reaction was complete (0.5-1 h). The reaction mixture was concentrated and then partitioned between acetonitrile (30 mL) and hexanes (30 mL). The layers were separated, and the acetonitrile fraction was re-extracted with hexanes (3 × 20 mL). The combined hexane fractions were washed with H_2O (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 710 mg of crude yellow oil. Column chromatography of this material on silica gel (22 g) using hexanes/ethyl acetate (60:1) afforded 418 mg (50%) of the title compound as a colorless oil: IR (neat) 3443, 3333, 2956, 1715, 1601, 1523, 1442, 1376, 1312, 1229, 1048, 1028, 750, 691 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75-1.10 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2$), 1.20-1.67 (m, 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$) 1.47 (s, 3 H, $C\underline{H}_3C$), 1.72-1.90 (m, 2 H, $CH_3C\underline{H}_2$), 6.49 (s, 1 H, N$\underline{H}$), 7.00-7.10 (m, 1 H, Ar$\underline{H}$), 7.20-7.40 (m, 4 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.83 ($\underline{C}H_3CH_2C$), 11.11 (^1J = 306, 317 Hz, $\underline{C}H_2Sn$), 13.66 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 25.80 ($\underline{C}H_3C$), 27.62 ($^2J$ = 58 Hz, $\underline{C}H_2CH_2Sn$), 29.12 (^3J = 18 Hz, $\underline{C}H_2CH_2CH_2Sn$), 34.07 ($CH_3\underline{C}H_2C$), 73.20 ($CH_3\underline{C}Sn$), 118.63, 123.05, 128.93, 138.15 (Ar-$\underline{C}$'s), 154.36 ($\underline{C}O$); MS (FAB) *m/z* 426 (100, M^+-C_4H_9), 370 (55), 326 (34), 287 (26), 256 (19), 211 (51), 176 (69), 121 (40), 73 (62); Anal. Calcd for $C_{23}H_{41}NO_2Sn$: C, 57.28; H, 8.56; N, 2.90. Found: C, 57.34; H, 8.63; N, 2.70.

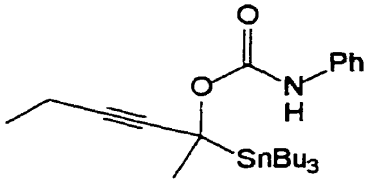
2-N-Phenylcarbamoyloxy-2-tributylstannyl hexane ***(189)***



IR (neat) 3436, 2958, 2927, 1718, 1602, 1521, 1441, 1376, 1311, 1259, 1226, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-1.10 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2CH_2$), 1.15-1.70 (m, 18 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $C\underline{H}_2C\underline{H}_2C\underline{H}_2C$), 1.49 (s, 3 H, $C\underline{H}_3C$), 6.47 (s, 1 H, N$\underline{H}$), 7.00-7.10 (m, 1 H, Ar$\underline{H}$), 7.20-7.40 (m, 4 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.10 (^1J = 309, 324 Hz, $\underline{C}H_2Sn$), 13.64 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.03 ($\underline{C}H_3CH_2CH_2$), 23.08

($CH_3\underline{C}H_2CH_2$), 26.31 ($\underline{C}H_3C$), 27.39 (^2J = 55 Hz, $\underline{C}H_2CH_2Sn$), 28.97 ($\underline{C}H_2CH_2C$), 29.04 (^3J = 18 Hz, $\underline{C}H_2CH_2CH_2Sn$), 41.44 ($CH_2\underline{C}H_2C$), 66.98 ($CH_3\underline{C}Sn$), 118.58, 123.08, 128.92 (Ar-$\underline{C}$'s), 138.16 (*ipso*-Ar-$\underline{C}$), 154.32 ($\underline{C}O$); MS (FAB) ***m/z*** 454 (21, M^+-C_4H_9), 389 (58), 363 (20), 342 (12), 208 (23), 173 (35), 121 (21), 82 (100); Anal. Calcd for $C_{25}H_{45}NO_2Sn$: C, 58.84; H, 8.88; N, 2.74. Found: C, 58.72; H, 8.68; N, 2.55.

2-N-Phenylcarbamoyloxy-2-tributylstannyl hex-4-yne ***(190)***



IR (neat) 3433, 2958, 2921, 1719, 1603, 1522, 1442, 1312, 1226, 1201, 1047, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.20 (m, 15 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$), 1.14 (t, 3 H, J = 7.4 Hz, $C\underline{H}_3CH_2$), 1.25-1.80 (m, 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 1.71 (s, 3 H, $C\underline{H}_3C$), 2.29 (q, 2 H, J = 7.4 Hz, $CH_3C\underline{H}_2$), 6.58 (s, 1 H, N$\underline{H}$), 7.00-7.10 (m, 1 H, Ar$\underline{H}$), 7.20-7.40 (m, 4 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.00 (^1J = 318, 333 Hz, $\underline{C}H_2Sn$), 12.83 ($CH_3\underline{C}H_2$), 13.70 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.11 ($\underline{C}H_3CH_2$), 26.91 ($\underline{C}H_3C$), 27.50 ($^2J$ = 60 Hz, $\underline{C}H_2CH_2Sn$), 28.96 (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 70.24 ($CH_3\underline{C}Sn$), 82.71 ($C\underline{C}CSn$), 89.77 ($\underline{C}CCSn$), 118.57, 123.23, 128.97, 137.91 (Ar-$\underline{C}$'s), 153.54 ($\underline{C}O$); MS (FAB) ***m/z*** 452 (66, M^+-C_4H_9), 342 (88), 231 (22), 173 (27), 100 (62), 82 (100); Anal. Calcd for $C_{25}H_{41}NO_2Sn$: C, 59.30; H, 8.16; N, 2.76. Found: C, 59.35; H, 8.22; N, 2.86.

4.3.10 Reaction of MeMgBr and DBNE with (1-tributylstannyl)propan-1-one ***(180)***

To a cooled (0°C) solution of DBNE (79.3 mg, 0.30 mmol) in hexanes (10 mL) was added MeMgBr (0.20 mL of a 3.0 M solution in Et_2O, 0.60 mmol) and the reaction was warmed to room temperature for 20 min. Then the reaction was cooled (0°C), and

acylstannane **180** (104.5 mg, 0.30 mmol) was added as a solution in hexanes (2 mL). The mixture was stirred for 1 h at 0°C, and then quenched with saturated aqueous NH_4Cl. The organic phase was washed with 1 M HCl (5 mL). The bottom acidic layer was drained and collected to allow recovery of the auxiliary. The organic layer was washed with $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL) and phenyl isocyanate (65 μL, 0.60 mmol)) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). The reaction mixture was concentrated and then partitioned between acetonitrile (10 mL) and hexanes (10 mL). The layers were separated, and the acetonitrile fraction was re-extracted with hexanes (3 × 10 mL). The combined hexane fractions were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Samples for HPLC analysis were prepared in hexanes (Table 16, entry 1).

4.3.11 Reaction of MeMgBr and DPMPM with (1-tributylstannyl)propan-1-one (180)

To a cooled (0°C) solution of DPMPM (1.10 g, 4.17 mmol) in hexanes (18 mL) was added *n*-butyllithium (4.25 mL of a 0.98 M solution in hexanes, 4.17 mmol) and then allowed to warm to room temperature. After the mixture stirred for 10 min, MeMgBr (0.42 mL of a 3.0 M solution in Et_2O, 1.25 mmol) was added with vigorous stirring, and the reaction was warmed to reflux for 30 min. Then the reaction was cooled (-5°C), and acylstannane **180** (145 mg, 0.42 mmol) was added as a solution in Et_2O (2 mL). The mixture was stirred for 1 h at -5°C, and then quenched with saturated aqueous NH_4Cl. The organic phase was washed with 1 M HCl (10 mL). The bottom acidic layer was drained and collected to allow recovery of the auxiliary. The organic layer was washed with $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (91 μL, 0.84 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10

(Table 16, entry 2). Similar experiments were carried out using EtMgBr and *n*-BuMgBr with acylstannane **177** (Table 17, entries 1 and 3).

4.3.12 Reaction of MeMgBr and HMMPMP with (1-tributylstannyl)propan-1-one (180)

The procedure of Mukaiyama *et al.*[43] was essentially followed. To a cooled (0°C) solution of HMMPMP (510.0 mg, 2.57 mmol) in Et_2O (10 mL) was added *n*-butyllithium (2.62 mL of a 0.98 M solution in hexanes, 2.57 mmol). The mixture was warmed to room temperature for 15 min and then MeMgBr (0.86 mL of a 3.0 M solution in Et_2O, 2.57 mmol) was added. The reaction was stirred for a further 30 min at room temperature and then cooled to -78°C. A solution of acylstannane **180** (223.2 mg, 0.64 mmol) in Et_2O (2 mL) was added. The reaction was quenched after 1 h at -78°C, with a saturated solution of NH_4Cl. The mixture was diluted with ether, washed with 1 M HCl, $NaHCO_3$, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.14 mL, 1.28 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 3).

4.3.13 Reaction of EtMgBr and TADDOL with (1-tributylstannyl)propan-1-one (180)

The procedure of Weber and Seebach[40] was essentially followed. To a cooled (-78°C) solution of TADDOL (2.24 g, 4.80 mmol) in THF (20 mL) was added MeMgBr (4.16 mL of a 3.0 M solution in Et_2O, 12.5 mmol). The cooling bath was removed and the reaction mixture warmed to room temperature. The colorless solution was then cooled to -78°C, and a solution of acylstannane **180** (333 g, 0.96 mmol) in Et_2O (2 mL) was added. The reaction was quenched after 1 h with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was

cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.21 mL, 1.92 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 4). A similar experiment was carried out using EtMgBr and TADDOL with acylstannane **177** (Table 17, entry 2).

4.3.14 Reaction of MeMgBr and (R)-3,3'-Ph-BINOL with (1-tributylstannyl)propan-1-one (180)

To a cooled (-78°C) solution of (*R*)-3,3'-Ph-BINOL (78.5 mg, 0.18 mmol) in THF (5 mL) was added MeMgBr (0.17 mL of a 3.0 M solution in Et_2O, 0.52 mmol). The cooling bath was removed and the reaction mixture warmed to room temperature. The colorless solution was then cooled to -78°C, and a solution of acylstannane **180** (58.6 mg, 0.17 mmol) in THF (2 mL) was added. The reaction was quenched after 1 h with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (37 μL, 0.34 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 5).

4.3.15 Reaction of Me_2Mg and HMMPMP with (1-tributylstannyl)propan-1-one (180)

The procedure of Mukaiyama *et al.*[43] was essentially followed. To an ether (10 mL) solution of HMMPMP (487.2 mg, 2.46 mmol) was added *n*-butyllithium (2.51 mL of a 0.98 M solution in hexanes, 2.46 mmol), followed by Me_2Mg (4.91 mL of a 0.5 M solution in Et_2O, 2.46 mmol) at 0°C. The reaction was stirred for 30 min and then was concentrated under high vacuum at room temperature. The remaining solid was redissolved in CH_2Cl_2 (10 mL), and cooled to –78°C. A solution of acylstannane **180** (213.2 mg, 0.61 mmol) was

added. The reaction was quenched after 1 h at -78°C, with a saturated solution of NH_4Cl. The mixture was diluted with ether, washed with 1 M HCl, $NaHCO_3$, H_2O, and brine. The ether layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.13 mL, 1.23 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 6).

4.3.16 Reaction of $AlMe_3$ and DPMPM with (1-tributylstannyl)propan-1-one (180)

To a solution of DPMPM (163.8 mg, 0.62 mmol) in CH_2Cl_2 (4 mL) was added Me_3Al (0.31 mL of a 2.0 M solution in hexanes, 0.62 mmol) at room temperature. The reaction was stirred for 1 h and then cooled to -5°C, and a solution of acylstannane **180** (107.9 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was quenched after 1 h with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL) and phenyl isocyanate (67.6 μL, 0.62 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 7).

4.3.17 Reaction of Me_3Al and (R)-3,3'-Ph-BINOL with (1-tributylstannyl)propan-1-one (180)

To a solution of (*R*)-3,3'-Ph-BINOL (293.1 mg, 0.67 mmol) in CH_2Cl_2 (4 mL) was added Me_3Al (0.33 mL of a 2.0 M solution in hexanes, 0.67 mmol) at room temperature. The reaction was stirred for 1 h and then cooled to -5°C, and a solution of acylstannane **180** (116.0 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was quenched after 1 h with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O, washed with

H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL) and phenyl isocyanate (0.18 mL, 1.67 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 8).

4.3.18 Reaction of $LiAlMe_4$ and (R)-3,3'-Me-BINOL with (1-tributylstannyl)propan-1-one (180)

To a stirred solution of $AlMe_3$ (0.81 mL of a 2.0 M solution in hexanes, 1.61 mmol) in hexanes (5 mL) was added dropwise MeLi (1.19 mL of a 1.35 M solution in hexanes, 1.61 mmol) and the mixture stirred for 15 min at room temperature. The reaction was concentrated under high vacuum at room temperature, and the remaining white residue was redissolved in THF (5 mL). A solution of 3,3'-Me-BINOL (506.5 mg, 1.61 mmol) in THF (2 mL) was added and the mixture stirred for 1.5 h at room temperature. The solution was cooled to -78°C and acylstannane **180** (186.4 mg, 0.53 mmol) was added as a solution in THF (2 mL). After 1 h of stirring at -78°C, the reaction was allowed to warm to 0°C and then quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL) and phenyl isocyanate (0.41 mL, 1.07 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation are as described Section 4.3.10 (Table 16, entry 9).

4.3.19 Reaction of $MeTi(i\text{-}PrO)_3$ and TADDOL with (1-tributylstannyl)propan-1-one (180)

The procedure of Weber and Seebach[45] was essentially followed. To a cooled (-78°C) solution of $ClTi(i\text{-}PrO)_3$ (1.86 mL of a 1.0 M solution in hexanes, 1.86 mmol) in

toluene (4 mL) was added MeLi (1.21 mL of a 1.53 M solution in Et_2O, 1.86 mmol). The yellow solution was warmed to 0°C with vigorous stirring for a period of 30 min.

A separate solution of TADDOL (72.1 mg, 0.15 mmol) and Ti(*i*-PrO)$_4$ (55.2 μL, 0.19 mmol) in toluene (14 mL) was prepared and stirred for 15 min at room temperature before being cooled to -78°C. The previously prepared solution of MeTi(*i*-PrO)$_3$ was added with continued stirring at -78°C for 1 h. A solution of acylstannane **180** (515.0 mg, 1.48 mmol) in toluene (2 mL) was added. The reaction was allowed to warm to room temperature overnight without removal of the cooling bath. The reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O, washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL) and phenyl isocyanate (0.32 mL, 2.96 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 16, entry 10).

4.3.20 Reaction of Et_2Mg and (R)-BINOL with (1-tributylstannyl)ethan-1-one (177)

To a cooled (-78°C) solution of (*R*)-BINOL (243.5 mg, 0.85 mmol) in THF (10 mL) was added *n*-butyllithium (0.76 mL of a 2.2.5 M solution in hexanes, 1.70 mmol) with stirring. After 10 min, Et_2Mg (1.70 mL of a 0.5 M solution in Et_2O, 0.85 mmol) was added to the reaction. Following a further 10 min, a solution of acylstannane **177** (283.2 mg, 0.85 mmol) in THF (2 mL) was added. The reaction temperature was maintained at –78°C for 10 h and then quenched with a saturated solution of NH_4Cl. The reaction was warmed to room temperature and then diluted with Et_2O (20 mL). The organic phase was washed with H_2O (30 mL) and brine (30 mL). The ether layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.37 mL, 3.40 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 17, entry 4).

4.3.21 Reaction of Et_2Zn and DBNE with (1-tributylstannyl)ethan-1-one (177)

The procedure of Soai *et al.*[41] was essentially followed. To a solution of acylstannane **177** (306 mg, 0.92 mmol) in hexanes (5 mL) was added DBNE (14.5 mg, 0.05 mmol, 6 mol %), at room temperature. The mixture was stirred for 20 min and then was cooled to 0°C. Et_2Zn (0.92 mL of a 1.0 M solution in hexanes, 0.92 mmol) was added. The reaction was quenched after 96 h at room temperature, with 1 M HCl. TLC analysis of the crude reaction mixture revealed the absence of the desired α,α-dialkyl α-hydroxystannane. Work-up and derivatization of the reaction mixture was not performed. (Table 17, entry 5).

4.3.22 Reaction of Et_2Zn and DPMPM with (1-tributylstannyl)ethan-1-one (177)

The procedure of Soai *et al.*[42] was essentially followed. To a cooled (0°C) solution of DPMPM (216.7 mg, 0.82 mmol) in hexanes (18 mL) was added *n*-butyllithium (0.37 mL of a 2.25 M solution in hexanes, 0.82 mmol), followed by Et_2Zn (1.81 mL of a 1.0 M solution in hexanes, 1.81 mmol). The clear solution was warmed to reflux for 20 min and then cooled to 0°C. A solution of acylstannane **177** (274.0 mg, 0.82 mmol) in hexanes (2 mL) was added. The reaction was allowed to warm to room temperature overnight. TLC analysis taken 16 h after the addition of acylstannane revealed the absence of the desired α,α-dialkyl α-hydroxystannane. Work-up and derivatization of the reaction mixture was not performed. (Table 17, entry 6).

4.3.23 Reaction of $LiC{\equiv}CCH_2CH_3$ and HMMPMP with (1-tributylstannyl)ethan-1-one (177)

To a cooled (-10°C) mixture of HMMPMP (652.4 mg, 3.29 mmol) and 1-butyne (2.25 mL of a 1.2 M solution in hexanes, 2.70 mmol) in Et_2O (15 mL) was added *n*-butyllithium (4.10 mL of a 1.56 M solution in hexanes, 6.40 mmol). The reaction stirred for 30 min, and then was cooled to –95°C. A solution of acylstannane **177** (309.7 mg, 0.89 mmol) in Et_2O (2 mL) was added. The mixture was stirred for 1 h at -95°C, and then

quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O and washed with 1 M HCl, $NaHCO_3$, H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.19 mL, 1.78 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 17, entry 7).

4.3.24 Reaction of $BrMgC{\equiv}CCH_2CH_3$ and DPMPM with (1-tributylstannyl)ethan-1-one (177)

To a cooled (-78°C) solution of 1-butyne (4.92 mL of a 1.2 M solution in hexanes, 5.90 mmol) was added *n*-butyllithium (3.78 mL of a 1.56 M solution in hexanes, 5.90 mmol). The reaction stirred for 10 min, and then $MgBr_2{\bullet}OEt_2$ (9.67 mL of a 0.61 M solution in Et_2O, 5.90 mmol) was added. The reaction was allowed to warm to 0°C over 30 min. A solution of DPMPM (932.5 mg, 3.54 mmol) in Et_2O (5 mL) was added slowly. The reaction mixture was then warmed to reflux for a period of 30 min. The contents of the reaction vessel were then cooled to -20°C, and a solution of acylstannane **177** (409.3 mg, 1.18 mmol) in Et_2O (2 mL) was added. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The reaction mixture was diluted with Et_2O and enough 1 M HCl to produce a clear bottom layer. The bottom acidic layer was drained and collected to allow recovery of the auxiliary. The organic layer was washed with 1 M HCl, $NaHCO_3$, H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* (water bath at rt). This material was cooled to 0°C and then CH_2Cl_2 (2 mL), and phenyl isocyanate (0.26 mL, 2.36 mmol) were added. The reaction was then allowed to warm to room temperature, and was monitored by TLC until complete (0.5-1.0 h). Work-up and sample preparation was as described in Section 4.3.10 (Table 17, entry 8).

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CHAPTER 5

PREPARATION OF ENANTIOMERICALLY ENRICHED α-ALKOXY-STANNANES VIA CHROMATOGRAPHIC RESOLUTION

5.1 Introduction

To realize the goals discussed in Chapter 4 and obtain a method of accessing enantiomerically enriched α,α-disubstituted α-alkoxystannanes, we focused on chromatographic resolution of diastereomeric mixtures of these compounds. New synthetic strategies were employed to obtain the α,α-disubstituted α-alkoxystannanes, which would be subsequently resolved by column chromatography. Resolution of this type is often viewed as the last resort due to the sometimes tedious separation of isomers by silica gel chromatography and the expensive nature of resolving agents. However, this method has frequently allowed access to functionalized stannanes which are not available through enantioselective synthesis.

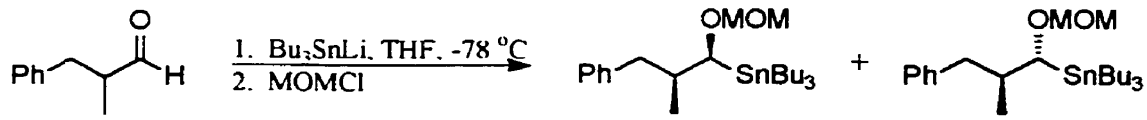
In liquid chromatography (LC), the separation of enantiomers relies on the interactions between the stationary phase and the solute enantiomers.[1] Enantiomers are related by a reflection symmetry, and possess the same physical and chemical properties. If the stationary phase is an optically active material it may interact preferentially with one enantiomer over the other. Interactions which cause a difference in retention time between the stationary phase and the enantiomers, result in separation. However, if the stationary phase is achiral, identical interactions are expected and there is no difference in retention time between enantiomers. Therefore, chromatographic separation of enantiomers on an achiral stationary phase (e.g., silica gel) is limited to diastereomeric derivatives accessed from the reaction of a mixture of enantiomers with an optically pure reagent. Diastereomers are not related by reflection symmetry and possess different physical and chemical properties. These diastereomers are chromatographically separable on a non-chiral stationary phase (Scheme 73).[2]

Scheme 73

Enantiomers	Optically pure reagent	Diastereomers
(*R*)-AX	(*R*)-B*Y	(*RR*)-AB*
(*S*)-AX	-XY	(*RS*)-AB*
(non-separable)		(separable)

The separation of α-alkoxyorganostannane diastereomers was first demonstrated by Still and Sreekumar in 1980.[3] Their preparation of diastereomers followed two different methods. In the first method, the reaction of tributyltinlithium with 2-benzylpropanal (**191**) followed by protection with chloromethyl methyl ether gave a 1:1 mixture of diastereomers **192a** and **192b** (75% yield) which could be separated by medium-pressure liquid chromatography (MPLC) on silica gel (Scheme 74). In this case the chosen aldehyde contained a stereo-center, which produced a mixture of diastereomeric alcohols on reaction with tributyltinlithium. Isomers **192a** and **192b** were shown to undergo tin-lithium exchange and trapping with retention of configuration.[3]

Scheme 74

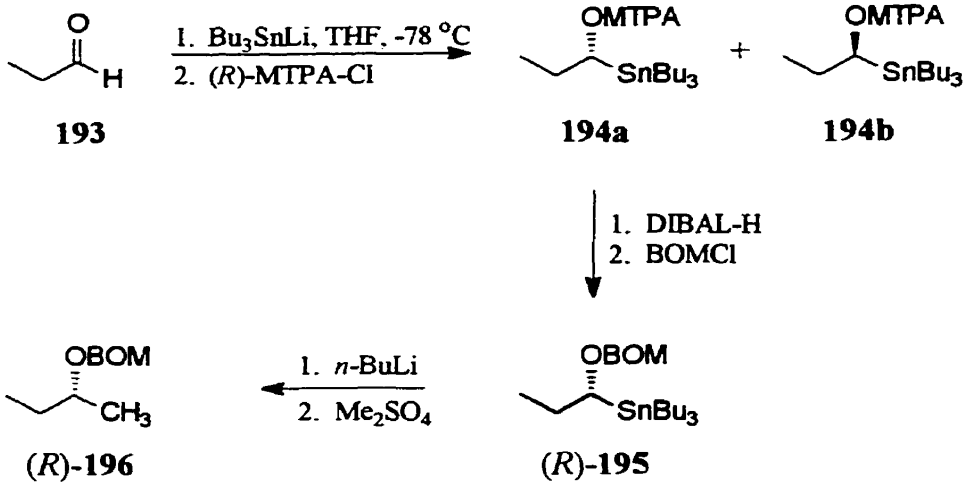


191 **192a** **192b**

The second approach reported by Still and Sreekumar involved the reaction of tributyltinlithium with propanal (**193**) to give a mixture of enantiomers (Scheme 75). Esterification with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(*R*)-MTPA-Cl] gave a quantitative yield of diastereomeric esters **194a** and **194b**, which were also separated by MPLC (Scheme 75).[3] The MTPA ester **194a** was reduced with diisobutylaluminum hydride and reprotected with benzyl chloromethyl ether to give acetal (*R*)-**195**. This sequence was necessary in order to provide (*R*)-**195** in enantiomerically pure form and to

demonstrate that transmetalation and trapping with dimethyl sulfate to provide acetal (*R*)-**196**, proceeded with retention of configuration.

Scheme 75

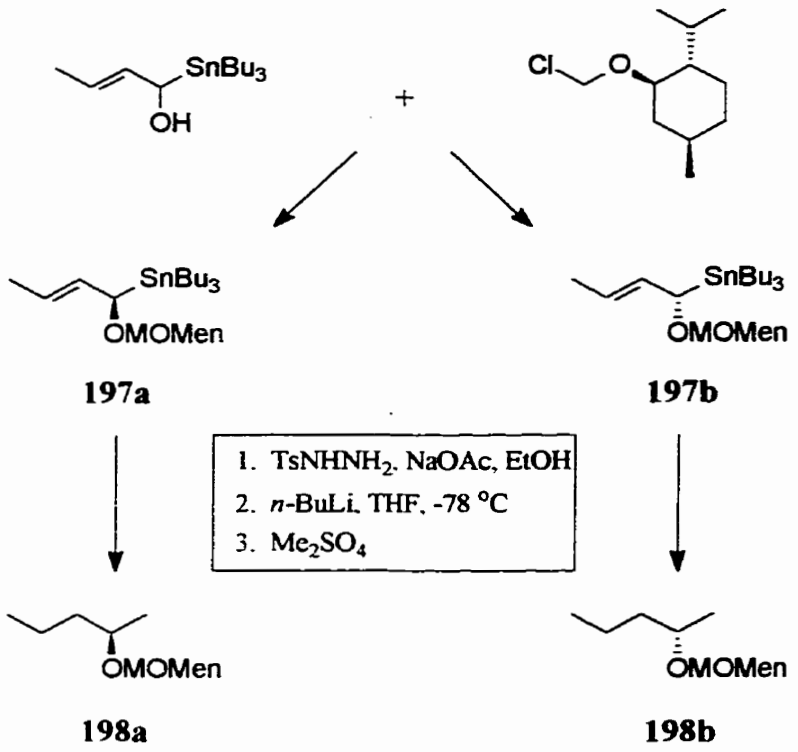


193 **194a** **194b** (*R*)-**196** (*R*)-**195**

The resolution of α,α-disubstituted α-alkoxyorganostannanes has never been reported. However, there are a number of resolving agents which have demonstrated the resolution of α-substituted α-alkoxyorganostannanes. Such agents could be used to obtain non-racemic α,α-disubstituted α-alkoxyorganostannanes that, in turn, would serve as convenient precursors to homochiral α,α-disubstituted carbanions.

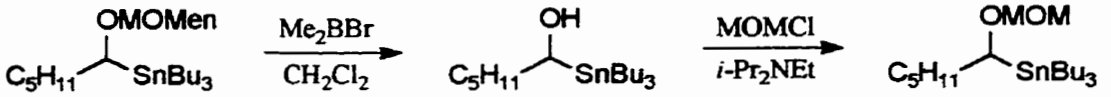
Thomas and Linderman have independently examined the resolution of α-substituted α-alkoxyorganostannanes with acetals prepared from chloromethyl (-)-menthyl ether. Thomas *et al.* prepared 1-[(-)-menthoxymethoxy]-*E*-but-2-enyl tributylstannanes **197a** and **197b** as a mixture and separated the diastereomeric stannanes using column chromatography (Scheme 76).[4,5] Diimide reduction of isomers **197a** and **197b** with *p*-toluenesulfonhydrazide (NaOAc, EtOH) followed by transmetalation and trapping with dimethyl sulfate provided acetals **198a** and **198b**. The (-)-menthoxymethyl protecting group provides sufficient stabilization to the intermediate α-alkoxyorganolithium to allow Sn-Li exchange and trapping with dimethyl sulfate.

Scheme 76



Linderman and co-workers also demonstrated that acetals prepared with chloromethyl (-)-menthyl ether could be resolved by either MPLC or column chromatography.[6] The diastereomeric excess of the examples prepared in this study varied from 82-96% de. Cleavage of acetals (*R*)- or (*S*)-**199** with bromodimethylborane provided α-hydroxy-stannanes. Reprotection with chloromethyl methyl ether gave the desired ethers (*R*)- and (*S*)-**200** in 50 and 66% overall yields with virtually no loss of optical activity (Scheme 77).

Scheme 77



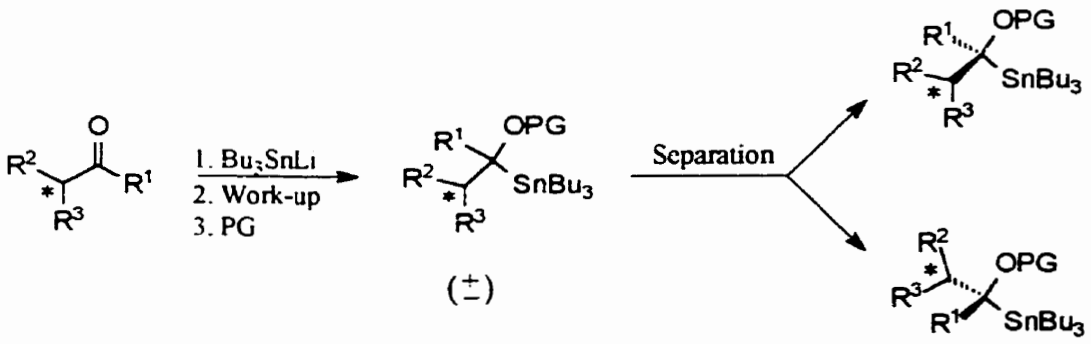
199 **200**

% de	% yield	% ee	% yield
(*R*) 93	75	91	66
(*S*) 91	78	90	84

Gung and co-workers performed an identical resolution of allylstannanes **197a** and **197b** as outlined by Thomas;[4,5] however, the chiral auxiliary employed was 8-(phenyl)-menthyl.[7]

Based upon literature, it was proposed that non-racemic derivatives of α,α-disubstituted α-alkoxyorganostannanes may be accessed through one of two methods. In the first approach, the addition of tributyltinlithium to ketones containing a defined stereo-center would provide a mixture of diastereomers, which might be easily derivatized and separated by column chromatography. Selected protecting groups would allow tin-lithium exchange to occur and provide homochiral α,α-disubstituted carbanions (Scheme 78).

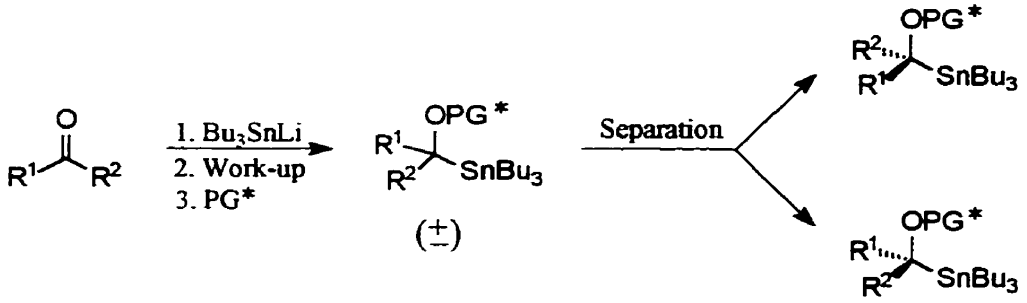
Scheme 78



Secondly, α,α-disubstituted α-hydroxystannanes would be prepared by the addition of tributyltinlithium to a prochiral ketone. The product would be protected with selected chiral

resolving agents to determine the feasibility of separating the resulting diastereomers by chromatographic methods (Scheme 79). Resolving agents which provide good separation must also either accommodate the transmetalation of these enriched stannanes, or be easily removed to allow reprotection with other groups that are compatible with transmetalation conditions.

Scheme 79



In both methods, the synthetic chemistry was optimized in order to obtain the best diastereomers for separation. This work was followed by the optimization of chromatographic conditions.

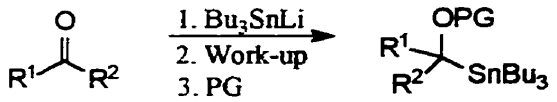
5.2 Results and Discussion

5.2.1 Preparation, Protection and Transmetalation of α,α-Dialkyl α-Alkoxyorganostannanes

In order to assess the feasibility of preparing enantiomerically enriched α,α-disubstituted α-alkoxyorganostannanes by either method shown in Scheme 78 and 79, a short study was undertaken to examine several aspects of this chemistry. Both Scheme 78 and 79 rely on the addition of tributyltinlithium to α-branched and non-branched ketones. Protection of these resulting α-hydroxystannanes and stabilization of the α,α-disubstituted α-alkoxyorganolithiums formed from tin-lithium exchange were expected to be exceedingly difficult due to the high degree of substitution and resulting steric environment. Therefore, the preparation of simple α-hydroxystannanes containing branched and non-branched side chains was performed to evaluate the protection of these species and their subsequent transmetalation and trapping, as well as to correlate these results to reported literature examples.[8,9] Shown in Table 18 are the yields of stannanes **201-207** prepared from tributyltinlithium (THF, -78°C) addition to various ketone substrates. The crude α-hydroxystannanes were immediately protected as the acetate [$(CH_3CO)_2O$, pyridine, DMAP], methoxymethyl ether (MOMCl, *i*-Pr_2NEt, CH_2Cl_2) or diethylcarbamate [*p*-NO_2-$C_6H_4OC(O)Cl$, pyridine; Et_2NH].[10] Stannane **201** was prepared to allow comparison to results obtained by McGarvey and co-workers.[8] Protection of α-hydroxystannanes with chloromethyl methyl ether highlighted the difficulty encountered as the steric bulk of the alcohols increased (compare entries 2, 4 and 7). The low yield of acetate **205** may possibly reflect the decomposition of the α,α-dialkyl α-hydroxystannane during the prolonged reaction time (24 hours) (entry 5). The preparation of carbamate **206** was also hampered by sluggish reactivity resulting in a low yield (entry 6). Despite the difficulties experienced in Chapter 4, carbamate **203** was obtained in comparatively good yield (68%) from the addition of MeMgBr to (1-tributylstannyl)propan-1-one (**180**) and subsequent protection of the hydroxyl group. The addition of organometallic reagents to acylstannanes remains

experimentally more convenient than the addition of tributyltinlithium to carbonyl compounds.

Table 18. Preparation of α,α-dialkyl α-alkoxyorganostannanes **201-207**.



201-207

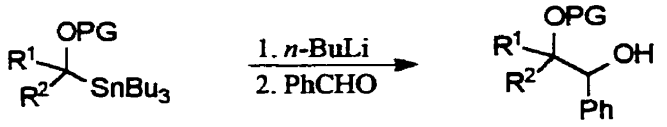
Entry	R^1	R^2	PG	% yield[a] (**201-207**)
1	-$(CH_2)_5$-		MOM	**201** (71)
2	Me	Et	MOM	**202** (57)
3[b]	Me	Et	Et_2NCO	**203** (68)
4	Me	*i*-Pr	MOM	**204** (33)
5	Me	*i*-Pr	CH_3CO	**205** (13)
6	Me	*i*-Pr	Et_2NCO	**206** (22)
7	Et	*i*-Pr	MOM	**207** (27)

[a] Isolated yields of chromatographically-pure products.
[b] Product obtained from MeMgBr addition to (1-tributylstannyl)propan-1-one (**180**) in Et_2O at 0°C.

From Table 18, it appears that α-alkoxystannanes which are branched on at least one of the side chains, to allow for enhanced chromatographic separation, result in lower yields (entries 4-7). Simple non-branched α,α-dialkyl α-alkoxystannanes are accessible in reasonable yields (entries 2 and 3).

The transmetalation of α,α-dialkyl α-alkoxystannanes obtained from the above study, with the exception of acetate **205**, were investigated to gain insight into the tin-lithium exchange process of these species and the effectiveness of the chosen protecting groups to stabilize the intermediate α-alkoxyorganolithiums (Table 19).

Table 19. Transmetalation and trapping of α,α-dialkyl α-alkoxyorganostannanes.[a]



201-206 **208-213**

Entry	R^1	R^2	PG	Solvent	Stannane **201-206**	Bu_4Sn (%)	SM (%)	(%) yield **208-213**
1[b]	-$(CH_2)_5$-		MOM	THF	**201**			**208** (0)
2	-$(CH_2)_5$-		MOM	THF	**201**	35	62	**209** (29)
3[b]	-$(CH_2)_5$-		MOM	DME	**201**			**208** (85)
4	-$(CH_2)_5$-		MOM	DME	**201**	91	2	**209** (80)
5	Me	Et	MOM	THF	**202**	32	63	**210** (28)
6	Me	Et	MOM	DME	**202**	87	6	**210** (80)
7[c]	Me	Et	MOM	DME	**202**	92	0	**210** (81)
8	Me	Et	Et_2NCO	THF	**203**	93	0	**211** (78)
9	Me	Et	Et_2NCO	DME	**203**	96	0	**211** (73)
10	Me	*i*-Pr	MOM	THF	**204**	8	89	**212** (0)
11	Me	*i*-Pr	MOM	DME	**204**	22	72	**212** (0)
12	Me	*i*-Pr	Et_2NCO	THF	**206**	30	63	**213** (0)
13	Me	*i*-Pr	Et_2NCO	DME	**206**	71	24	**213** (60)

[a] Transmetalations were performed with 2 equiv of *n*-BuLi at -78°C for 15 min unless otherwise noted.
[b] Reactions were performed with 1.1 equiv of *n*-BuLi at –78°C for 2 min followed by treatment with excess propionaldehyde: McGarvey, G.J. *et al. JACS.* **1988**, *110*, 842.
[c] Time of Sn-Li exchange was 120 minutes.

Results obtained from the transmetalation of stannane **201** in our laboratory correlate well with those shown previously by McGarvey *et al.*, with the exception of trials performed in THF (entries 1 and 2).[8] McGarvey had reported that tin-lithium exchange of **201** and trapping with excess propionaldehyde gave none of the expected product in THF.[8] However, we were able to obtain a 29% yield of **209** when trapping was performed with benzaldehyde. We had anticipated that the outcome of transmetalations performed with acyclic stannane **202** would be poorer in comparison to those obtained with the acetal **201** (compare entries 2 and 5 as well as 4 and 6). This hypothesis was the result of observations made from the

transmetalation of acyclic-[11] and cyclic-α-aminoorganostannanes.[12] Gawley and Zhang had demonstrated that 2-lithio-*N*-methylpiperidine and 2-lithio-*N*-methylpyrrolidine could be prepared from tin-lithium exchange.[12] These lithio-species showed chemical stability in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at temperatures up to –40°C. Work performed in our laboratory had shown that the acyclic 1-(*N,N*-dimethylamino)-1-tributylstannyl hexane would not undergo tin-lithium exchange at -78°C.[11] This exchange process was found to be favored at higher temperatures (0°C) but decomposition of the α-aminoorganolithium species was also observed under these conditions. However, near identical results were obtained for stannanes **201** and **202** under the same conditions. Tin-lithium exchange could be performed in THF but was favored in the more polar DME solvent (entries 5 and 6). The reaction noted in entry 6 returned a small quantity (6%) of starting material. By allowing the tin-lithium exchange of stannane **202** to proceed for a period of 120 minutes it was demonstrated that complete exchange takes place (entry 7). Although the yield of the product is not greatly increased (from 80 to 81%), it does demonstrate that the methoxymethyl-protected α-alkoxyorganolithium species formed is stable for long periods of time without showing significant decomposition. The tin-lithium exchange of carbamate **203** was expected to be superior to that observed for ether **202** based on the studies that were reported in Chapter 2. It was found that secondary α-alkoxyorgano-trimethylstannanes could undergo transmetalation and trapping in good yield when an *N,N*-diethylcarbamate is used as opposed to an acetal protecting group (i.e., MOM). Results shown in entries 5 and 8 confirm those expectations. Carbamate **203** undergoes almost quantitative exchange (93%) in THF as no starting material was isolated by silica gel column chromatography. Higher yields were anticipated by performing the reaction in DME as observed for ether **202** (entries 5 and 6). This was not the case for carbamate **203**; lower yields were obtained, which may be a reflection of difficulties associated with the isolation of the polar water-soluble product. Higher losses of product would be expected when aqueous work-ups are performed in the presence of trace amounts of the more polar DME solvent. Transmetalation of the branched stannane **204** gave the expected poor outcome reported in entry 10. Starting material was recovered in 89% with an observed 8% tin-lithium exchange. None of the desired product **212** was obtained. Similar results were observed for stannane **204** when the reaction was performed in DME (entry 11). The increased steric bulk

introduced by the branched isopropyl group of **204**, in comparison to the ethyl moiety of **202**, may cause a steric effect that negatively influences the formation of the α-alkoxy-organolithium intermediate. The level of tin-lithium exchange of carbamate **206** was much higher (30 and 71%) in THF and DME, respectively, when compared to ether **204**. However, the product **213** was obtained only when the tin-lithium exchange and trapping was performed in DME (entry 13). The 60% yield reported in entry 13 is based on the analysis of the product by GCMS and ^{1}H NMR spectroscopy. The crude reaction mixture exhibits a 1:1 distribution of isomers by GCMS analysis. However, only the low-R_f isomer of **213** can be cleanly obtained (31% yield) after column chromatography. The high-R_f isomer has the same polarity as the impurity 1-phenyl-1-pentanol, obtained from *n*-butyllithium addition to benzaldehyde, and can not be separated.

Results from this study indicate that there is a low probability of observing the successful transmetalation of diastereomeric stannanes, obtained as outlined in Scheme 78. Regardless of the protecting group chosen, sufficient stabilization of branched α,α-dialkyl α-alkoxyorganolithium species could not be obtained in this study. Pursuit of the route described in Scheme 79 (page 180), where acyclic α,α-dialkyl α-hydroxystannanes are protected with an optically pure reagent may be more successful. Acyclic, non-β-branched α,α-dialkyl α-alkoxystannanes containing a carbamate protecting group undergo successful transmetalation in THF. Acetal protecting groups (i.e., MOM) provide adequate stabilization to allow transmetalation to occur in DME solvent with slightly better yields of **209** and **210**. There appears to be no inherent difference between the transmetalation of acyclic and cyclic α,α-dialkyl α-alkoxystannanes The results obtained from this study suggest that the relative stabilities of α-alkoxyorganolithium and alkyllithium species are as shown in Figure 15. However, it must be noted that the results reflect kinetic and not thermodynamic stabilities.

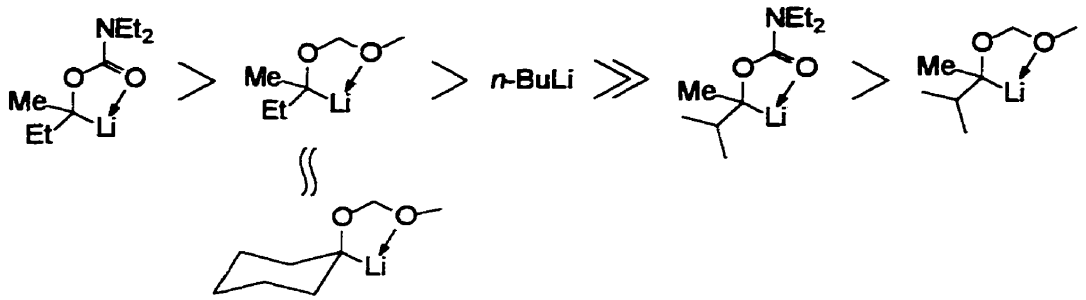
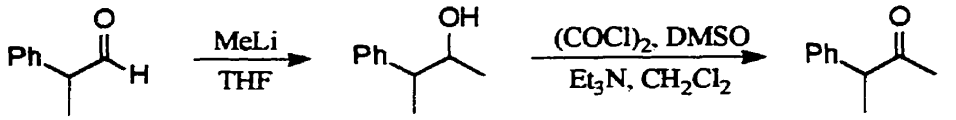


Figure 15. Relative stability of α,α-dialkyl α-alkoxyorganolithium and alkyllithium reagents generated by tin-lithium exchange.

5.2.2 Preparation of Diastereomeric α,α-Disubstituted α-Alkoxyorganostannanes

Results from Section 5.2.1 indicated that branching at the β-carbon of α,α-disubstituted α-alkoxystannanes disfavors tin-lithium exchange. We subsequently undertook a short study to examine whether the addition of tributyltinlithium could indeed be performed on carbonyl compounds to yield separable mixtures of diastereomers as outlined in Scheme 78. In adsorption chromatography, the separation of diastereomers is a function of the magnitudes of the binding between isomers and sorbent; in addition, the separation is also affected by repulsive interactions that are usually steric in nature.[1] It was assumed that optimal separation could be achieved by selecting carbonyl compounds whose adjacent carbon contained three very different groups. Still and Sreekumar had observed good results when additions of tributyltinlithium were performed to 2-benzylpropanal (Scheme 74).[3] The precursor aldehyde contained benzyl, methyl and hydrogen substituents. The resulting diastereomers **192a** and **192b** were cleanly separated by MPLC on silica gel. We chose to examine additions with 2-phenyl-1-propanal (**214**) and 3-phenyl-2-butanone (**215**). Ketone **215** was prepared from **214** by methylation, followed by Swern[13] oxidation in 50% overall yield (Scheme 80).

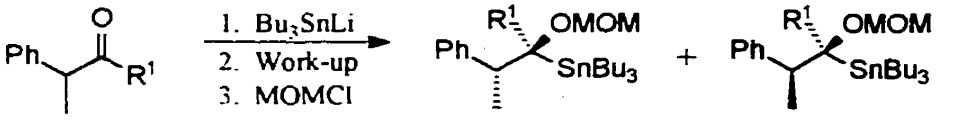
Scheme 80



214 **215**
50% yield

Both **214** and **215** contain an alkyl, aryl and hydrogen group. The difference in binding and sterics of these groups should aid in separation of diastereomers. α-Hydroxystannanes obtained from these additions were derivatized with chloromethyl methyl ether (*i*-Pr_2NEt, CH_2Cl_2). Results are shown in Table 20.

Table 20. Preparation of diastereomeric α-alkoxyorganostannanes **216** and **217**.



214 $R^1 = H$ **216a** **216b**
215 $R^1 = CH_3$ **217a** **217b**

Entry	R^1	Stannane	Solvent	% yield	dr[a]
1	H	**216**	Et_2O	42	10:90
2			THF	45	16:84
3[b]			THF	32	18:82
4	CH_3	**217**	Et_2O	25	0:100
5			THF	19	66:34
6[b]			THF	27	1:99

[a] Determined by GCMS analysis of crude reaction mixtures.
[b] Bu_3SnLi was added to a cooled (-78°C) slurry of $CeCl_3$ in THF and then warmed to -30°C for 45 min. The reaction was then cooled to -78°C before addition of the carbonyl substrate.

The observed yields of stannanes **216** and **217** are relatively consistent and appear to be independent of the choice of solvent. Additions to aldehyde **214** tended to give higher yields than additions to ketone **215**. This may in part be due to the increased steric crowding in the environment of the ketone versus the aldehyde. Felkin had originally studied the stereoselective reductions of ketone **215** (PhMeCHC(O)R^1, where R^1 = Me) with lithium aluminum hydride.[14] The selectivity of the reductions was shown to increase as the size of R^1 increased. The selectivity obtained in the formation of **217** (R^1 = Me) was found to be higher than that of **216** (R^1 = H), but only when the additions were carried out in diethyl ether (entries 1 and 4). Additions performed in THF, showed a decrease in selectivity when the size of R^1 increased (entries 2 and 5). Therefore, choice of solvent played a large role in the level of selectivity observed for these additions. The best selectivity was found to occur when the reaction was performed in diethyl ether. Of particular interest is the completely diastereoselective addition of tributyltinlithium to ketone **215** in diethyl ether (entry 4). Admittedly, a 2:98 diastereomeric ratio was obtained on a second trial of this reaction. This selectivity is still very impressive for these additions. This study did not attempt to determine the relative configuration of the diastereomers formed. Felkin[14]-Anh[15,16] models predict that the favored isomers would be (*RR,SS*)-**216**, -**217** with (*RS,SR*)-**216**, -**217** being disfavored due to gauche interactions (Figure 16).

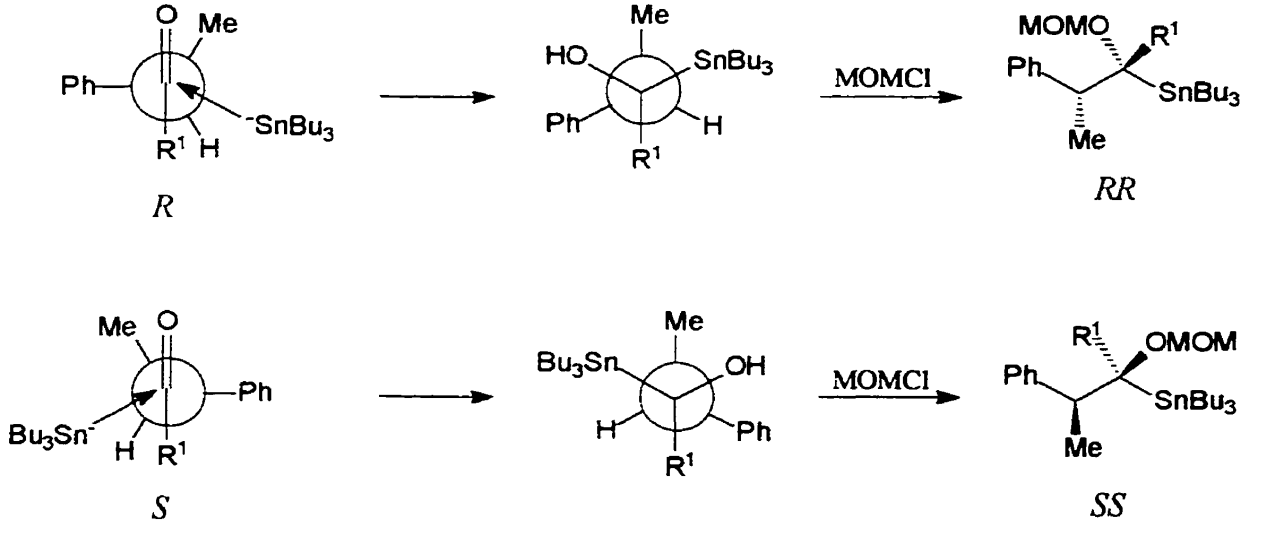


Figure 16. Favored Felkin-Anh type transition states for the addition of Bu_3SnLi to aldehyde **214** and ketone **215**.

Attempts were made to improve both the selectivity and the yield of trials performed in THF by employing cerium chloride as an additive. Cerium chloride has been used to suppress side-reactions such as enolization, reduction, condensation, conjugate addition, and pinacol coupling.[17] These side-reactions are commonly observed from the addition of organolithium and Grignard reagents with carbonyl compounds.[17] It was unclear whether these modes of reactivity were responsible for the low yields of **216** and **217** (Table 20). Addition of tributyltinlithium to **214** in the presence of cerium chloride gave no increase in selectivity (entry 3). A parallel experiment with **215** gave a dramatic increase and reversal in selectivity with no significant increase in the yield of stannane **217** (compare entries 5 and 6). The coordination of metals is known to activate carbonyls towards attack by nucleophiles.[18] This activation may occur by two different bonding schemes: σ or π (Figure 17).[19] Studies with Lewis acids such as boron[20] and tin[19] have shown that not only does σ-coordination predominate but these carbonyl-Lewis acid adducts are the more reactive species.[21] In general, σ-coordination is believed to occur with all main group, early transition, and lanthanide-based Lewis acids; however, examples of π-coordination are also known.[19]

σ-bonding π-bonding

Figure 17. Bonding modes for Lewis acid-carbonyl complexes.[19]

The Lewis acid may assume different positions during σ-coordination, e.g. in-plane-bent, in-plane linear, out-of-plane, etc. Therefore, its relative position may be represented by three variables: *r*, the Lewis acid-oxygen distance; two angles, ϕ (angle between Lewis acid and plane of aldehyde); and θ (C-O-M angle) (Figure 18).[19]

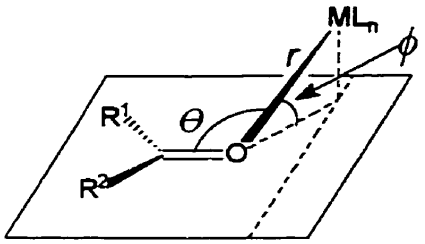


Figure 18. Geometrical descriptors for Lewis acid-carbonyl complexes.[19]

The geometry of Li^+ complexes with formaldehyde have been determined to be linear by ab initio MO calculations.[22] Azzaro found that complexation of Lewis acids with conformationally rigid α,β-unsaturated ketones takes place in a nonlinear fashion on the least sterically hindered side of the oxygen.[23,24] At this time we can only speculate that the cerium metal is involved in similar complexation, which gives rise to only one favorable diastereomeric transition state.

Isomers obtained from **216** and **217** did not resolve on TLC. Efforts to resolve them by column chromatography resulted in low levels of enrichment (< 20% de) as evidenced by GCMS analysis. No further attempts were made to effect complete resolution of either compound.

5.2.3 Resolution of Diastereomeric α,α-Disubstituted α-Alkoxyorganostannanes

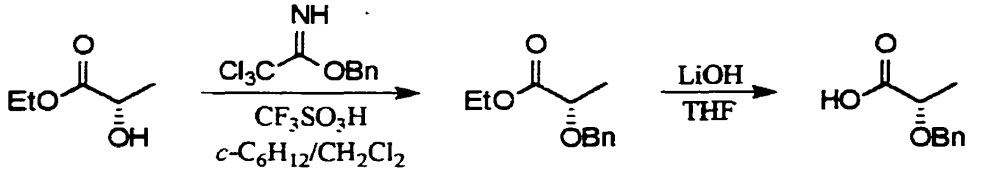
The resolution of α,α-disubstituted α-alkoxystannanes derivatized with a chiral protecting group was undertaken as proposed in Scheme 79 (page 180). α-Hydroxystannanes were derivatized as acetals, esters and carbamates. A brief discussion on each of these approaches is given in the following sections.

Resolution of Esters

α-Hydroxystannanes prepared from the condensation of tributyltinlithium with 3-methyl-2-butanone (**218**) were reacted with either (*S*)-α-methoxyphenylacetic acid (**219**) or

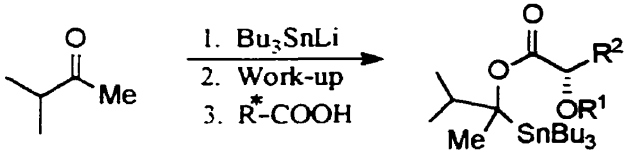
(*S*)-2-(benzyloxy)propanoic acid (**222**) under typical coupling conditions for the esterification of alcohols with carboxylic acids as shown in Table 21.[25,26] Acid **222** was prepared in two steps from (*S*)-ethyl lactate (Scheme 81). Benzylation followed by hydrolysis provided **222** in 75% yield from **220**.[27,28]

Scheme 81



220 **221** 51% yield **222** 100% yield

Table 21. Attempted coupling of α-hydroxystannanes with carboxylic acids **219** and **222**.



218 **223-224**

Entry	R^1	R^2	Acid	Reaction Conditions	Product
1	Me	Ph	**219**	DIPC, DMAP, CH_2Cl_2	**223**
2	Me	Ph	**219**	$(COCl)_2$, DMF, CH_3CN	**223**
3	Bn	Me	**222**	DIPC, HOBt, CH_2Cl_2	**224**
4	Bn	Me	**222**	DCBC, Pyridine, CH_2Cl_2	**224**

DIPC = 1,3-diisopropylcarbodiimide. DMAP = 4-(dimethylamino)pyridine.
HOBt = 1-hydroxybenzotriazole hydrate. DCBC = 2,6-dichlorobenzoyl chloride.

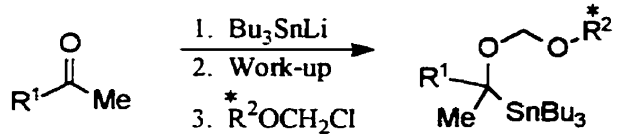
All entries in Table 21 rely on the nucleophilicity of the α,α-dialkyl α-hydroxystannane and the reaction with acid chlorides or activated carbonyl compounds. In each case examined, none of the desired product was formed. The α-hydroxystannanes were isolated underivatized. It was rationalized that the approach of the α-hydroxystannane to the

activated carbonyls may be impeded by the high degree of substitution of the chiral center on the carboxylic acid. Additional atom spacers between the coupling site and the chiral center may provide less steric interactions on the approach of the alcohol. This hypothesis was explored through the preparation of acetals as discussed in the following section.

Resolution of Acetals

The preparation of acetals from α-substituted α-alkoxystannanes and chloromethyl ether derivatives of chiral alcohols had been demonstrated by Thomas,[4,5] Gung[7] and Linderman[9] (Section 5.1). Chloromethyl ether reagents of selected chiral alcohols were prepared [$(CH_2O)_n$, HCl, CH_2Cl_2][9] and then reacted with α-hydroxystannanes (*i*-Pr_2NEt, DMAP, CH_2Cl_2) to yield diastereomeric acetals **225-230**. Derivatives are shown in Table 22.

Table 22. Stannyl acetals **225-230**.



225-230

Entry	R^1	$^*R^2$	% yield **225-230**
1	*i*-Pr	(1*R*,2*S*,5*R*)-menthyl	**225** (30)
2	*i*-Pr	(1*R*,2*S*,5*R*)-(8-phenyl)menthyl	**226** (57)
3	*n*-Bu	(1*R*,2*S*,5*R*)-(8-phenyl)menthyl	**227** (33)
4	*n*-Bu	(1*S*)-bornyl	**228** (37)
5	*n*-Hex	(1*R*,2*S*,5*R*)-(8-phenyl)menthyl	**229** (43)
6	*n*-Hex	(1*S*)-bornyl	**230** (33)

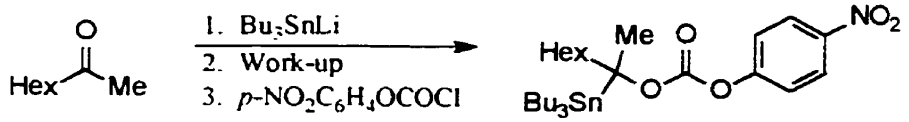
Diastereomers **225**, **227-230** showed no separation by TLC. Column chromatography on silica gel employing flash, gravity and radial techniques did not allow for the enrichment of these isomers. Isomers of stannane **226** showed minor levels of separation by TLC.

Unfortunately, attempts to achieve full separation by high performance liquid chromatography (HPLC) on a preparative silica gel column (hexanes/CH_2Cl_2) failed, because conditions could not be developed to allow adequate separation of the diastereomers. It appears that the additional alkyl substituent on the α,α-disubstituted α-hydroxystannane prevents differentiation of the isomers by the silica gel medium as has been observed for α-substituted α-hydroxystannanes.[4,5,6,7]

Resolution of Carbamates

It had been demonstrated that *N,N*-diethylcarbamates could be prepared from α,α-disubstituted α-hydroxystannanes (Table 18). The treatment of α,α-disubstituted α-hydroxystannanes with *p*-nitrophenyl chloroformate generates an intermediate *p*-nitrophenylcarbonate. The carbonates are then reacted with *N,N*-diethylamine to yield the desired dialkylcarbamates (Table 18, entry 3 and 6). The intermediate *p*-nitrophenylcarbonates could allow the preparation of diastereomeric carbamates by reaction with chiral primary and secondary amines. Still has also documented a similar approach with the exception that the α-substituted α-hydroxystannane employed was first derivatized to the corresponding chloroformate with phosgene and then reacted with a chiral primary amine *in situ* (Section 2.2.5, page 45).[3] Hence, 2-octanone (**231**) was reacted with tributyltinlithium (THF, -78°C) and then immediately protected after aqueous work-up with *p*-nitrophenyl chloroformate (pyridine) in hexanes/CH_3CN (1:1) to give carbonate **232** (Scheme 82).

Scheme 82

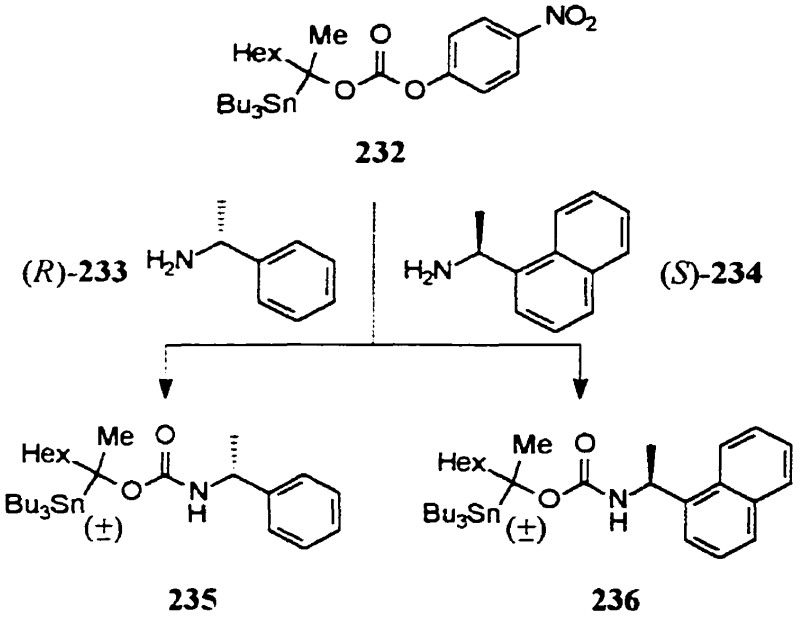


231 (±)-**232**

This use of hexanes/CH_3CN was found to be critical for the success of the reaction and greatly facilitates work-up and product isolation. The yields are almost quantitative by mass

balance. As discussed by Berge and Roberts, the mutual immiscibility of hexanes and acetonitrile allows for easy separation of reaction by-products.[29] The tributyltin species preferentialiy dissolve in the upper hexanes layer and the more polar components (*p*-nitrophenol, pyridinium hydrochloride, pyridine, and tributyltin chloride) dissolve in the lower acetonitrile layer. When this process is carried out in pyridine (with/without CH_2Cl_2) as solvent, the reaction is sluggish requiring longer periods of time for complete derivatization. Use of hexanes/acetonitrile allowed access to **232** essentially pure after work-up. This was particularly important since stannane **232** was found to decompose on silica gel during column chromatography resulting in the isolation of Bu_3SnH. Carbamates **235** and **236** were prepared from **232** by reaction with (*R*)-α-phenylethylamine (**233**) and (*S*)-α-naphthylethylamine (**234**) (Scheme 83).

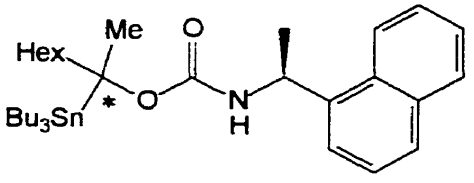
Scheme 83



Only stannane **236** separated into two defined spots by TLC. Stannane **236** was subsequently separated by flash chromatography using hexanes/ethyl acetate (60:1). Three to four passes were required to obtain quantities greater than one gram of each isomer. However, high-R_f-**236** was obtained in 81% yield (of a maximum 50% yield) with 91% de, and low-R_f-**236** was

obtained in 78% yield (of a maximum 50% yield) with 97% de, as determined by chiral HPLC (Figure 19).

Since tin-lithium exchange had been performed successfully on carbamate **203** (Table 19), it was deemed necessary to remove the 1-naphthylethylcarbamate protecting group and re-protect with the diethylcarbamate functionality. This procedure proved quite difficult as the carbamate functionality of **236** resisted removal by reduction (LAH, rt; DIBAL-H, 0°C) or hydrolysis (4 M NaOH; 5 M KOH). The only reagent that showed reduction as monitored by TLC, was alane at room temperature (~50% conversion after 12 hours). α-Hydroxy-stannanes are known to be thermally unstable. It was unclear whether warming a solution of **236** and alane in THF would promote both thermal decomposition and/or racemization. Fortunately, neither occurred as **236** was smoothly reduced in THF at 40°C in 6 hours (Scheme 84). The α-hydroxystannane thus obtained was derivatized to carbamate **237** in an overall yield of 75% from **236**. Carbamate **237** has been prepared by this method three times with an average yield of 78%.



236

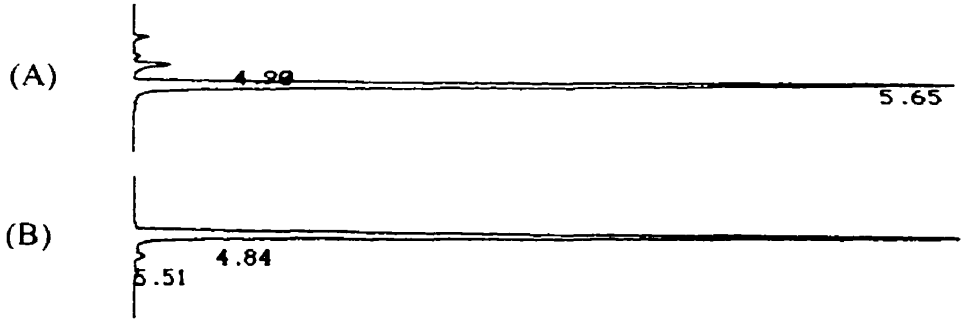
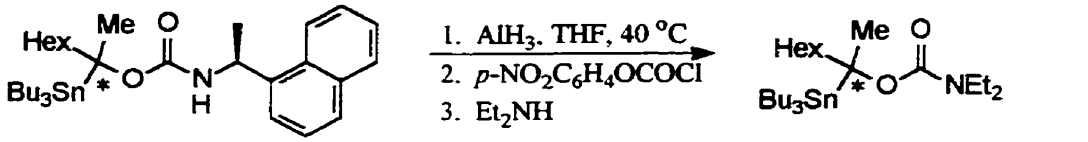


Figure 19. HPLC traces of resolved carbamate **236**: (A) high-R_f and (B) low-R_f. Conditions: Chiracel-OD column, hexanes-*i*-PrOH, 99:1 as eluent, flow rate of 1.0 mL/min, and detection at 254 nm. Numbers on traces represent the elution time in minutes.

Scheme 84. Preparation of diethylcarbamate **237**.

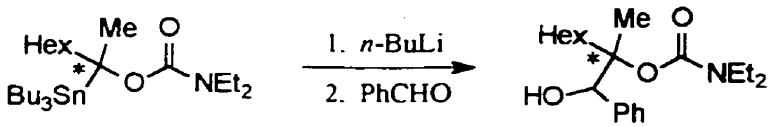


236
91% de
$[\alpha]_D^{25}$ –17.8° (*c*, 0.297, hexanes)

237
75% yield
91% ee
$[\alpha]_D^{25}$ –3.5° (*c*, 0.300, hexanes)

The configurational stability of the organolithium derived from carbamate **237** (91% ee) was assessed by performing tin-lithium exchanges for 15, 120 and 480 minutes at -78°C followed by trapping with benzaldehyde. Results from this study are shown in Table 23.

Table 23. Configurational stability of carbamate **237**.



237 **238**

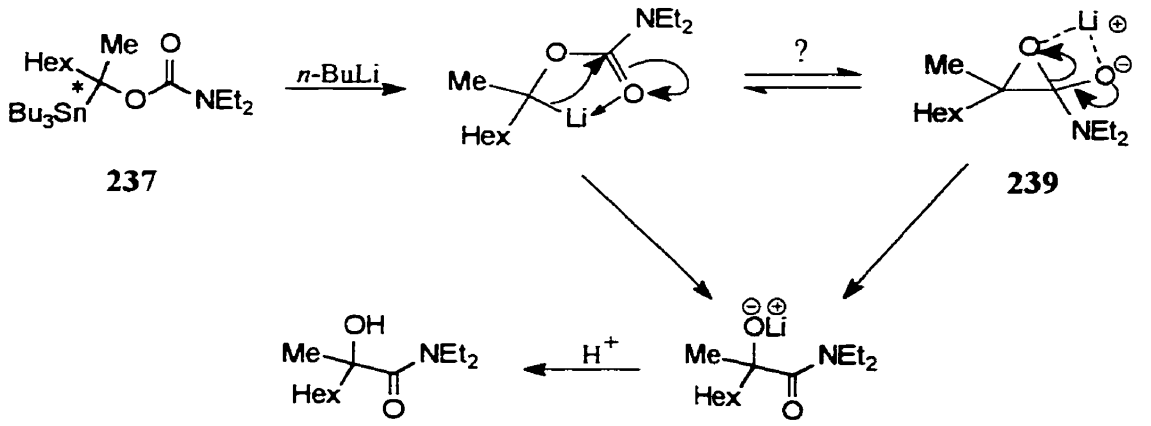
Entry	Time (min)	Bu_4Sn (%)	% SM **237**	% yield **238**	% ee[a] **238**	(%) migration **240**
1	15	42	54	44	91	0
2	120	75	21	38	91	0
3[b]	180	96	3	0	-:-	8
4	480	99	0	12	89	17

[a] Determined by HPLC on a Chiracel OD column.
[b] Reaction performed at –50°C.

Results from this study show that carbamate **237** can be transmetalated and trapped using benzaldehyde with essentially complete retention of stereochemistry (entries 1 and 2) (Table 23). After 480 minutes at –78°C the α-alkoxyorganolithium species exhibited only 2%

racemization. The tin-lithium exchange of **237** appears to be slower than that observed for carbamate **203** (93% after 15 min, Table 19, entry 8, page 183). However, trapping the carbanion of **237**, formed after 15 minutes, gives adduct **238** in quantitative yield based on recovery of starting material. After 120 minutes the carbanion generated from **237** is trapped to give a 38% yield of **238**, which is only 50% reacted based on the isolation of Bu_4Sn. Performing the tin-lithium exchange at higher temperatures (-50°C) leads to decomposition of the carbanion formed (entry 3). When the transmetalation is allowed to proceed for 480 minutes, complete tin-lithium exchange is observed, but only 12% of **238** is isolated. Also recovered is a 17% yield of the 1,2-migration product **240**, which had only been previously isolated when the reaction was performed at –50°C (Scheme 85). The rearrangement may pass through a tetrahedral intermediate **239**. Similar intermediates have been proposed for 1,2-carbamoyl migration of α-lithioalkyl carbamates (see Chapter 2, Scheme 44, page 53) and for the rearrangement of deprotonated (acyloxy)acetates to (acyl)hydroxyacetates[30] as well as for other reactions.[31,32]

Scheme 85



237 **239** **240**

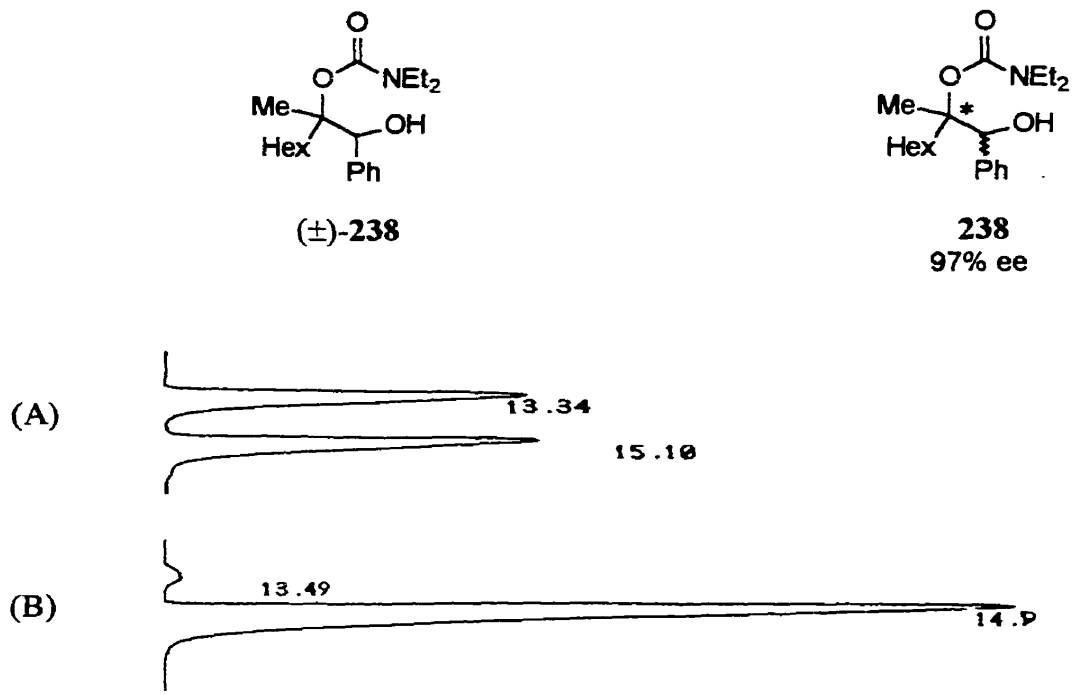


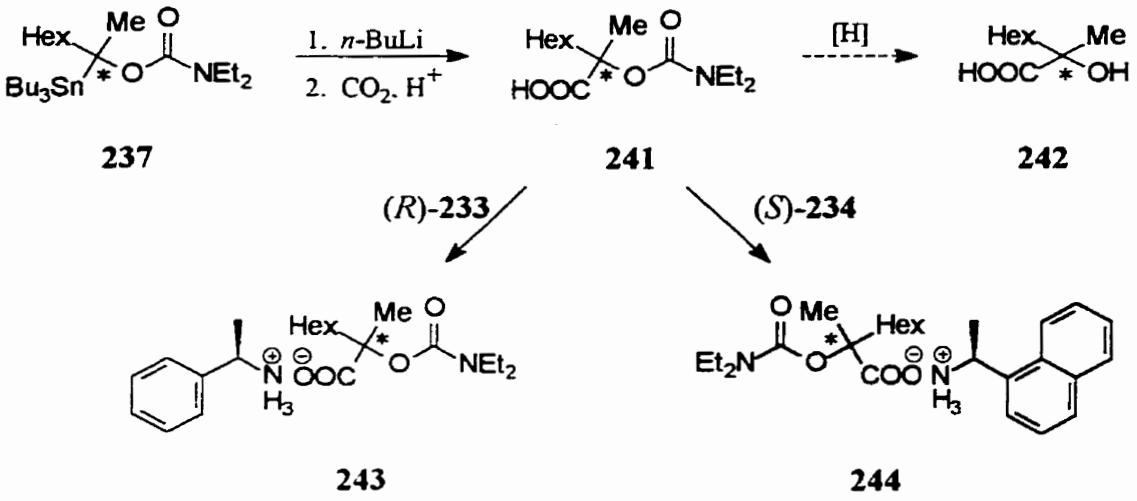
Figure 20. HPLC traces: (A) (±)-**238** and (B) enriched carbamate **238** of 97% ee. Conditions: Chiracel-OD column, hexanes-*i*-PrOH, 99:1 as eluent, flow rate of 1.0 mL/min, and detection at 254 nm. Numbers on traces represent the elution time in minutes.

5.2.4 Determination of Absolute Configuration for 1-(1-naphthylethyl)carbamates 236

Neither alcohol **238** nor the unprotected diol of **238** have been previously reported. 2-Hydroxy-2-methyloctanoic acid (**242**) is known but the absolute configuration has never been determined (Scheme 86).[33,34] Amine salts of **241** were prepared from (*R*)-phenylethylamine (**233**) and (*S*)-1-naphthylethylamine (**234**).[35] Compound **243** was a viscous oil that never crystallized on standing while **244** resulted in a white powder (Scheme 86). The ammonium salt **244** was recrystallized from hexanes/CH_2Cl_2 to provide crystals for X-ray analysis. The X-ray data were collected and analyzed by Dr. Nicholas J. Taylor, Department of Chemistry, University of Waterloo (see Appendix). The absolute configuration of the acid **241** was assigned *R* based on the known configuration of the (*S*)-1-(1-naphthylethyl)amine

(**234**). Since acid **241** was ultimately derived from the low-R_f isomer **236**, we can assign the configuration of the high-R_f isomer as (*S*)-**236.**

Scheme 86



5.2.5 Summary

α,α-Disubstituted α-alkoxystannanes were prepared from tributyltinlithium addition to ketones. The best yields (57-71%) were obtained from ketones which were either cyclic or contained no branching at the β-carbon (Table 18). Branched substituents resulted in much lower yields (13-33%). Cyclic α,α-dialkyl α-alkoxystannane **201** was found to undergo Sn-Li exchange in THF (Table 19). A better yield of the desired adduct **209** was obtained in DME. Acyclic α-alkoxystannanes **202** and **203** which contained no branched substituents were transmetalated in either THF or DME. The methoxymethyl ether **202** gave a better yield in DME while *N,N*-diethylcarbamate **203** gave comparable yields in either solvent. The methoxymethyl ether **204** showed 8% tin-lithium exchange in THF and 22% in DME but failed to provide the desired product. The *N,N*-diethylcarbamate **206** showed higher levels of tin-lithium exchange (30 and 71%) in THF and DME, respectively, but only provided product **213** (60% yield) in DME.

Addition of tributyltinlithium to carbonyl compounds **214** and **215** was found to be highly diastereoselective in diethyl ether (80 and 100% de) as determined by the analysis of methoxymethyl ethers by GCMS (Table 20). Moderate selectivities were observed in THF (68 and 32% de). The use of cerium chloride as an additive did not improve selectivity of additions performed with aldehyde **214**. However, the diastereoselectivity observed with methyl ketone **215** increased dramatically to 98% de with the use of cerium chloride. Felkin-Anh models predict that the favored isomers are (*RR*, *SS*)-**216**, -**217**. Efforts to separate diastereomers of **216** and **217** by silica gel chromatography were unsuccessful.

The α,α-dialkyl α-hydroxystannane prepared from 3-methyl-2-butanone (**218**) and tributyltinlithium could not be coupled with (*S*)-α-methoxyphenylacetic acid or (*S*)-2-(benzyloxy)propanoic acid (Table 21) The steric bulk of the α-hydroxystannane and branched acid chlorides may impede the coupling process.

Diastereomeric acetals **225-230** were prepared from selected α,α-dialkyl α-hydroxystannanes and chloromethyl ether reagents derived from menthol, (8-phenyl)menthol and borneol (Table 22). The (8-phenyl)menthyl derivative **226** showed the best separation by TLC. However, separation of **226** could not be attained by silica gel column chromatography or by HPLC.

Carbamate **236** prepared from (*S*)-(α)-naphthylethylamine (**234**) and carbonate **232** exhibited better separation, as monitored by TLC, than carbamate **235** prepared from (*R*)-(α)-phenylethylamine (**233**) and **232**. Separation of **236** was achieved by column chromatography to provide the high-R_f-isomer in 81% yield of 91% de and the low-R_f-isomer in 78% yield of 97% de. The (*S*)-1-naphthylethylcarbamate protecting group was easily cleaved with AlH_3. The liberated α-hydroxystannane was reprotected as the *N,N*-diethylcarbamate **237** in 75% overall yield. The α-alkoxyorganolithium formed from **237** after tin-lithium exchange was trapped with benzaldehyde, and the product was shown by chiral HPLC to be configurationally stable for up to 120 minutes at -78°C (Table 23). Decomposition of the carbanion is evident after 120 minutes at –78°C, as supported by a 38% yield of the adduct **238**. This carbanion is also susceptible to decomposition at higher temperatures as no product was isolated after 180 minutes at –50°C. Only 2% racemization was detected after 480 minutes at -78°C. However, the carbanion undergoes 1,2-migration to yield the α-hydroxy amide **240**. The absolute configuration of acid **241**, derived from carbamate **236** (low-R_f isomer), was determined to be *R* based on X-ray analysis of crystals obtained from the ammonium salt **244**.

In conclusion, a method of resolving α,α-disubstituted α-alkoxystannanes has been developed and demonstrated to allow access to these intermediates in high diastereomeric excess (up to 97% de). The resolving reagent can be removed by reduction with AlH_3 with no detectable racemization or decomposition of the α-hydroxystannane. Derivatization of this enantiomerically enriched α,α-disubstituted α-hydroxystannane as the *N,N*-diethyl-carbamate allows transmetalation and trapping to occur with complete retention of stereochemistry. This methodology should allow access to other homochiral α,α-disubstituted α-alkoxyorganolithium reagents, as generated through tin-lithium exchange.

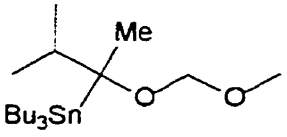
5.3 Experimental

5.3.1 General

The general procedures described in Section 2.3.1 are applicable here with the following additions. α-Alkoxystannane **201** has been reported previously and its preparation and spectral data were described.[8] The spectral data of α-alkoxystannane **202** were described earlier (Section 4.3.2); those for stannanes **204** and **207** are provided following this section. (8-Phenyl)menthol was prepared according to the procedure of Ort.[36] Borneol, menthol, 2-phenyl-1-propanal, (*S*)-(α)-methoxyphenylacetic acid, (*S*)-(α)-(1-naphthyl)ethylamine and (*R*)-(α)-phenylethylamine were purchased from Aldrich Chemical Company and used without further purification. Hexanes and acetonitrile were distilled from CaH_2 immediately prior to use.

High pressure liquid chromatography was performed on a Waters 600 using a Chiracel OD column, hexanes-*i*-PrOH, 99:1 as eluent, flow rate of 1.0 mL/min, and detection at 254 nm.

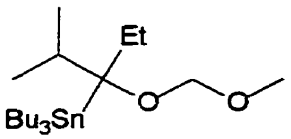
*5.3.2 2-Methoxymethoxy-2-tributystannyl-3-methyl butane (**204**)*



IR (neat) 2956, 2926, 1463, 1373, 1148, 1090, 1035, 917 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.65-1.10 [m, 21 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $(C\underline{H}_3)_2CH$], 1.15-1.70 (m 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 1.37 (s, 3 H, $C\underline{H}_3C$), 1.95 [septet, 1 H, J = 6.7 Hz, $(CH_3)_2C\underline{H}$], 3.34 (s, 3 H, $C\underline{H}_3O$), 4.63 (ABq, 2 H, J_{AB} = 6.8 Hz, Δν = 13.6 Hz, $OC\underline{H}_2O$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.76 (^1J = 306 Hz, $\underline{C}H_2Sn$), 13.69 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 18.25, 18.66 [$(\underline{C}H_3)_2CH$], 23.08 ($\underline{C}H_3C$), 27.73 ($^2J$ = 57 Hz, $\underline{C}H_2CH_2Sn$), 29.34 (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 37.47 [$(CH_3)_2\underline{C}H$], 55.74 ($O\underline{C}H_3$), 87.37 ($CH_3\underline{C}Sn$), 93.92 ($O\underline{C}H_2O$); MS

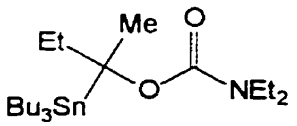
(EI) *m/z* 377 (1, M^+-C_4H_9), 291 (5), 235 (10), 179 (21), 121 (15), 45 (100); Anal. Calcd for $C_{19}H_{42}O_2Sn$: C, 54.17; H, 10.04. Found: C, 54.30; H, 10.22.

5.3.3 3-Methoxymethoxy-3-tributystannyl-2-methyl pentane (207)



IR (neat) 2920, 1459, 1378, 1146, 1037, 921, 868, 641 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.70-1.10 [m, 24 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$, $(C\underline{H}_3)_2CH$ and $C\underline{H}_3CH_2$], 1.20-2.00 (m 14 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_3C\underline{H}_2$), 2.10 [septet, 1 H, J = 6.7 Hz, $(CH_3)_2C\underline{H}$], 3.38 (s, 3 H, $C\underline{H}_3O$), 4.64 (ABq, 2 H, J_{AB} = 6.6 Hz, Δν = 11.4 Hz, $OC\underline{H}_2O$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.21 ($\underline{C}H_3CH_2$), 11.34 (^1J = 285, 270 Hz, $\underline{C}H_2Sn$), 13.53 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 17.49, 18.66 [$(\underline{C}H_3)_2CH$], 27.65 ($^2J$ = 57 Hz, $\underline{C}H_2CH_2Sn$), 27.75 ($CH_3\underline{C}H_2$), 29.29 (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 34.05 [$(CH_3)_2\underline{C}H$], 55.70 ($O\underline{C}H_3$), 93.73 ($O\underline{C}Sn$), 94.71 ($O\underline{C}H_2O$); MS (EI) *m/z* 391 (1, M^+-MOM), 291 (9), 235 (15), 179 (25), 145 (18), 121 (17), 45 (100); Anal. Calcd for $C_{20}H_{44}O_2Sn$: C, 55.19; H, 10.18. Found: C, 54.92; H, 9.92.

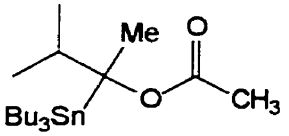
5.3.4 2-(N,N-Diethylcarbamoyloxy)-2-tributylstannyl butane (203)



To a cooled (0°C) solution of (1-tributylstannyl)propan-1-one (**179**) (448 mg, 1.29 mmol) in Et_2O (5 mL) was added MeMgBr (0.65 mL of a 3.0 M solution in Et_2O, 1.94 mmol). After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether (25 mL), washed with H_2O (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (water bath at room temperature).

Pyridine (5 mL) and *p*-$NO_2C_6H_4OCOCl$ (390.8 mg, 1.94 mmol) were added to a chilled (0°C) solution of the crude α-hydroxystannane. The ice bath was removed and the mixture stirred at room temperature until monitoring by TLC indicated the reaction was complete (5 h). The reaction was cooled (0°C) and Et_2NH (0.67 mL, 6.46 mmol) was added dropwise. The reaction stirred at room temperature until TLC indicated the complete consumption of carbonate (2 h). The solution was diluted with ether (50 mL), washed with 2 M HCl (2 × 25 mL), H_2O (25 mL), 3 M NaOH (3 × 25 mL), H_2O (25 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 827 mg of crude orange oil. Purification by flash chromatography on silica gel (25 g) using hexanes:ethyl acetate (initially 60:1 and then 40:1) provided 407 mg (68%) of the title compound as a colorless oil: IR (neat) 2958, 2928, 1664, 1475, 1458, 1426, 1378, 1286, 1188, 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.60-0.95 [m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2$], 1.07 (t, 6 H, J = 7.0 Hz, $C\underline{H}_3CH_2N$), 1.15-1.60 (m 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 1.39 (s, 3 H, $C\underline{H}_3C$), 1.65-1.85 (m, 2 H, $CH_3C\underline{H}_2$), 3.10-3.35 (bm, 4 H, $CH_3C\underline{H}_2N$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.76 ($C\underline{H}_3CH_2$), 11.29 (^1J = 309, 323 Hz, $\underline{C}H_2Sn$), 13.64 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.86 ($C\underline{H}_3CH_2N$), 25.83 ($C\underline{H}_3C$), 27.71 ($^2J$ = 59 Hz, $\underline{C}H_2CH_2Sn$), 29.30 (^3J = 18 Hz, $\underline{C}H_2CH_2CH_2Sn$), 34.27 ($CH_3C\underline{H}_2$), 41.31 ($CH_3C\underline{H}_2N$), 81.52 ($O\underline{C}Sn$), 156.59 ($\underline{C}O$); MS (EI) *m/z* 406 (29, M^+-C_4H_9), 350 (62), 236 (39), 177 (63), 121 (45), 100 (80), 72 (100); Anal. Calcd for $C_{21}H_{45}NO_2Sn$: C, 54.56; H, 9.81; N, 3.02. Found: C, 54.31; H, 9.64; N, 2.98.

5.3.5 2-Acetoxy-2-tributylstannyl-3-methyl butane (205)

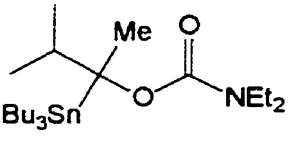


To a cold (0°C) solution of *i*-Pr_2NH (0.49 mL, 3.7 mmol) was added *n*-BuLi (3.48 mL of a 1.07 M solution in hexanes, 3.7 mmol). After the solution stirred for 15 min Bu_3SnH (1.0 mL, 3.7 mmol) was added and stirring was continued for a further 20 min. The

reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.40 mL, 3.7 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 2-tributylstannyl-3-methyl-2-butanol.

The crude 2-tributylstannyl-3-methyl-2-butanol was cooled (0°C) and then CH_2Cl_2 (2 mL), pyridine (0.22 mL, 2.7 mmol), acetic anhydride (0.21 mL, 2.2 mmol) and DMAP (21 mg, 0.18 mmol) were added. The ice bath was removed, and the mixture was stirred at room temperature for 24 hours. The crude mixture was diluted with ether (30 mL) and washed with 1 M HCl (3 × 10 mL), $NaHCO_3$ (20 mL), H_2O (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 576 mg of crude yellow oil. Column chromatography of this material on silica gel (17 g) using hexanes/ethyl acetate (40:1) afforded 100 mg (13%) of the title compound as a colorless oil: IR (neat) 2957, 2926 1714, 1673, 1463, 1370, 1271, 1017, 834, 664 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.60-1.05 [m, 21 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $(C\underline{H}_3)_2CH$], 1.20-1.65 (m 12 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$), 1.37 (s, 3 H, $C\underline{H}_3C$), 2.02 (s, 3 H, $C\underline{H}_3CO$), 2.16 [septet, 1 H, J = 6.7 Hz, $(CH_3)_2C\underline{H}$]; ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.52 (^1J = 309, 322 Hz, $\underline{C}H_2Sn$), 13.62 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 17.53 [$(\underline{C}H_3)_2CH$], 17.89 [$(\underline{C}H_3)_2CH$], 21.14, 21.24 ($\underline{C}H_3C$ and $\underline{C}H_3CO$), 27.65 (^2J = 60 Hz, $\underline{C}H_2CH_2Sn$), 29.19 (^3J = 17 Hz, $\underline{C}H_2CH_2CH_2Sn$), 34.88 [$(CH_3)_2\underline{C}H$], 85.60 ($O\underline{C}Sn$), 171.76 ($\underline{C}O$); MS (EI) *m/z* 363 (18, M^+-CH_3CO), 293 (63), 179 (100), 121 (38), 87 (23), 43 (42); Anal. Calcd for $C_{19}H_{40}O_2Sn$: C, 54.43; H, 9.61. Found: C, 54.20; H, 9.50.

5.3.6 2-(N,N-Diethylcarbamoyloxy)-2-tributylstannyl-3-methyl butane (206)



To a cold (0°C) solution of *i*-Pr_2NH (0.15 mL, 1.18 mmol) in THF (5 mL) was added *n*-BuLi (1.00 mL of a 1.18 M solution in hexanes, 1.18 mmol). After the solution stirred for

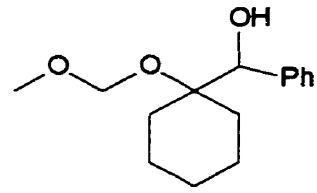
15 min, Bu_3SnH (0.32 mL, 1.18 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.12 mL, 1.18 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 2-tributylstannyl-2-butanol.

Pyridine (5 mL) and *p*-$NO_2C_6H_4OCOCl$ (357.1 mg, 1.77 mmol) were added to a chilled (0°C) solution of the crude α-hydroxystannane. The ice bath was removed and the mixture stirred at room temperature until TLC indicated the reaction was complete (5 h). The reaction was cooled (0°C) and Et_2NH (0.61 mL, 5.90 mmol) was added dropwise. The reaction stirred at room temperature until TLC indicated the complete consumption of carbonate (2 h). The solution was diluted with ether (40 mL), washed with 2 M HCl (2 × 20 mL), H_2O (20 mL), 3 M NaOH (3 × 20 mL), H_2O (20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 822 mg of crude orange oil. Purification by flash chromatography on silica gel (17 g) using hexanes:ethyl acetate (30:1) provided 116 mg (22%) of the title compound as a colorless oil: IR ($CHCl_3$) 2958, 2927, 1663, 1475, 1458, 1378, 1285, 1224, 1184, 1069, 1001 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.60-1.70 [m, 33 H, $C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2Sn$ and $(C\underline{H}_3)_2CH$], 1.08 (t, 6 H, J = 7.0 Hz, $C\underline{H}_3CH_2N$), 1.36 (s, 3 H, $C\underline{H}_3C$), 2.13 [septet, 1 H, J = 6.8 Hz, $(CH_3)_2C\underline{H}$], 3.22 (q, 4 H, J = 6.7 Hz, $CH_3C\underline{H}_2N$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.68 (^1J = 307, 321 Hz, $\underline{C}H_2Sn$), 13.71 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.7, 14.13 $\underline{C}H_3CH_2N$), 17.74, 18.18 [$(\underline{C}H_3)_2CH$], 21.77 ($\underline{C}H_3C$), 27.76 (^2J = 61 Hz, $\underline{C}H_2CH_2Sn$), 29.31 (^3J = 18 Hz, $\underline{C}H_2CH_2CH_2Sn$), 35.49 [$(CH_3)_2\underline{C}H$], 41.09, 41.44 ($CH_3\underline{C}H_2N$), 84 66 ($CH_3\underline{C}Sn$), 156.45 ($\underline{C}O$); MS (EI) *m/z* 420 (2, M^+-C_4H_9), 350 (7), 235 (4), 177 (7), 100 (11), 72 (13), 28 (100); Anal. Calcd for $C_{22}H_{47}NO_2Sn$: C, 55.47; H, 9.94, N, 2.94 Found: C, 55.34; H, 10.15; N, 2.89.

5.3.7 *Representative Procedure for the Transmetalation and Trapping of α,α-Dialkyl α-Alkoxyorganostannanes* ***201-204, 206***

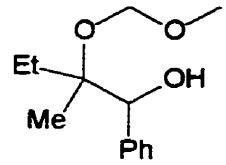
A representative procedure for the transmetalation of methoxymethyl ether **201** and trapping with PhCHO is given below, followed by spectral data of alcohols **209-211**, **213**. The yields of these alcohols can be found in Table 19.

(1R),(1S*)-1-(Hydroxybenzyl)-O-(methoxymethyl)cyclohexanol* ***(209)***



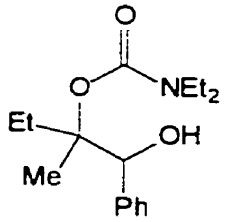
To a cold (-78°C) stirred solution of stannane **16** (182.2 mg, 0.42 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.82 mL of a 1.02 M solution in hexanes, 0.84 mmol). After 15 min, benzaldehyde (106.9 μL, 1.05 mmol) was added. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The resulting mixture was diluted with ether (25 mL), washed with H_2O (5 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography of the resulting oil (334.5 mg on 10 g of silica gel using 60:1 hexanes:ethyl acetate, initially, with gradual increase in solvent polarity) yielded 51 mg (35%) of Bu_4Sn and 31 mg (29% yield) of the expected product as a colorless oil: IR ($CHCl_3$) 3392, 3013, 2938, 1452, 1226, 1139, 1090, 1041, 1027, 926 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80-2.05 (m, 10 H, *c*-$C_6\underline{H}_{10}$), 3.51 (s, 3 H, $OC\underline{H}_3$), 4.03 (bs, 1 H, O<u>H</u>), 4.61 (s, 1 H, PhC<u>H</u>OH), 4.86 (ABq, 2 H, J_{AB} = 7.2 Hz, Δν = 8.7 Hz, $OC\underline{H}_2O$), 7.20-7.45 (m, 5 H, Ar<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.91, 21.33, 25.53, 27.63, 31.17 [-($\underline{C}H_2)_5$-], 55.69 ($O\underline{C}H_3$), 79.07 (Ph<u>C</u>HOH), 81.16 [PhCH(OH)<u>C</u>], 90.96 ($O\underline{C}H_2O$), 127.23, 127.52, 127.89 (Ar-<u>C</u>'s), 140.34 (*ipso*-Ar-<u>C</u>); MS (EI) *m/z* 205 (2, M^+-MOM), 143 (27), 120 (11), 107 (31), 99 (33), 45 (100); Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.85. Found: C, 71.96; H, 8.88.

(1R,2R*),(1R*,2S*)-2-(Methoxymethoxy)-2-methyl-1-phenyl-1-butanol (210)*



IR ($CHCl_3$) 3559, 3400, 3012, 1495, 1454, 1380, 1238, 1195, 1142, 1088, 1060, 1028, 913, 827 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (t, 1.5 H, J = 7.4 Hz, $C\underline{H}_3CH_2$), 0.88 (t, 1.5 H, J = 7.3 Hz, $C\underline{H}_3CH_2$), 1.10 (s, 1.5 H, $C\underline{H}_3C$), 1.16 (s, 1.5 H, $C\underline{H}_3C$), 1.20-1.44 (m, 1 H, $CH_3C\underline{H}_2$), 1.52-1.67 (m, 0.5 H, $CH_3C\underline{H}_2$), 1.79-1.94 (m, 0.5 H, $CH_3C\underline{H}_2$), 3.44 (s, 1.5 H, $OC\underline{H}_3$), 3.46 (s, 1.5 H, $OC\underline{H}_3$), 4.65 (d, 1 H, J = 2.0 Hz, PhC$\underline{H}$OH), 4.79 (ABq, 2 H, J_{AB} = 7.4 Hz, Δν = 9.7 Hz, $OC\underline{H}_2O$), 7.20-7.45 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.31, 7.54 ($\underline{C}H_3CH_2$), 16.55, 19.63 ($\underline{C}H_3C$), 26.12, 29.00 ($CH_3\underline{C}H_2$), 55.47, 55.60 ($O\underline{C}H_3$), 78.38, 79.14 (Ph$\underline{C}$HOH), 81.67, 82.55 [PhCH(OH)$\underline{C}$], 91.24, 91.26 ($O\underline{C}H_2O$), 127.30, 127.41, 127.56, 127.64, 127.80, 129.86 (Ar-$\underline{C}$'s), 140.30, 140.52 (*ipso*-Ar-$\underline{C}$'s); MS (EI) *m/z* 179 (4, M^+-MOM), 163 (7), 133 (11), 120 (20), 107 (74), 91 (25), 79 (23), 73 (23), 45 (100); Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.91; H, 8.98. Found: C, 69.86; H, 8.86.

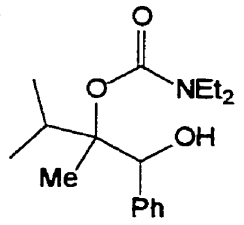
(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-2-methyl-1-phenyl-1-butanol (211)*



IR ($CHCl_3$) 3288, 2981, 1655, 1478, 1459, 1429, 1381, 1282, 1185 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80-1.25 (bm, 6 H, $C\underline{H}_3CH_2N$), 0.91 (t, 1.5 H, J = 7.4 Hz, $C\underline{H}_3CH_2$), 0.95 (t, 1.5 H, J = 7.4 Hz, $C\underline{H}_3CH_2$), 1.29 (s, 1.5 H, $C\underline{H}_3C$), 1.45 (s, 1.5 H, $C\underline{H}_3C$), 1.42-1.58 (m, 0.5 H, $CH_3C\underline{H}_2$), 1.65-1.80 (m, 0.5 H, $CH_3C\underline{H}_2$), 1.96-2.24 (m, 1 H, $CH_3C\underline{H}_2$), 3.00-3.50 (bm, 4 H, $CH_3C\underline{H}_2N$), 4.74 (d, 1 H, J = 1.5 Hz, PhC$\underline{H}$OH), 5.15-5.70 (bs, 1 H, O$\underline{H}$), 7.10-7.40 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.85, 8.02 ($\underline{C}H_3CH_2$), 13.37, 13.77 ($NCH_2\underline{C}H_3$), 20.42, 20.79 ($\underline{C}H_3C$), 28.55, 28.95 ($CH_3\underline{C}H_2$), 41.99 ($N\underline{C}H_2CH_3$), 79.04, 79.39 (Ph$\underline{C}$HOH),

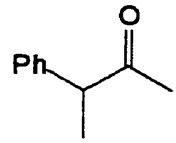
87.72, 87.97 [PhCH(OH)C], 127.23, 127.62, 127.63, 127.72, 127.77 (Ar-C's), 141.16, 141.19 (*ipso*-Ar-C's), 156.50, 156.54 (CO); MS (EI) *m/z* 207 (9, M^+-NEt_2), 148 (5), 116 (13), 100 (30), 91 (39), 28 (100); Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.01; N, 5.01. Found: C, 69.00; H, 8.87; N, 5.08.

(1R,2R*),(1R*,2S*)-2-(N,N-Diethylcarbamoyloxy)-2,3-dimethyl-1-phenyl-1-butanol (213)*



IR (neat) 3329, 2973, 1660, 1478, 1426, 1379, 1285, 1183, 1099, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, 3 H, *J* = 7.1 Hz, NCH_2CH_3), 0.92 [d, 3 H, *J* = 6.7 Hz, $(CH_3)_2CH$], 1.08 [d, 3 H, *J* = 6.9 Hz, $(CH_3)_2CH$], 1.18 (t, 3 H, *J* = 7.1 Hz, NCH_2CH_3), 1.61 (s, 3 H, CH_3C), 1.94 [septet, 1 H, *J* = 6.8 Hz, $(CH_3)_2CH$], 2.95-3.45 (m, 4 H, NCH_2CH_3), 4.83 (d, 1 H, *J* = 9.8 Hz, PhCHOH), 6.90 (d, 1 H, *J* = 9.9 Hz, OH), 7.20-7.40 (m, 5 H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.46, 13.68 (NCH_2CH_3), 14.19 (CH_3C), 17.53, 18.88 [$(CH_3)_2CH$], 33.61 [$(CH_3)_2CH$], 41.90, 42.28 (NCH_2CH_3), 77.05 (PhCHOH), 90.68 [PhCH(OH)C], 127.12, 127.46, 127.72, (Ar-C's), 141.48 (*ipso*-Ar-C), 156.94 (CO); MS (EI) *m/z* 250 [2, M^+-$(CH_3)_2CH$], 207 (34), 148 (22), 133 (21), 116 (45), 100 (74), 91 (100), 87 (11), 77 (12), 72 (25), 58 (11), 43 (23); Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.77. Found: C, 69.52; H, 9.07; N, 4.60.

5.3.8 Preparation of 3-Phenyl-2-butanone (215)



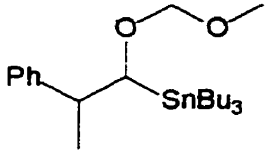
To a cold (-78°C) solution of 2-phenyl-1-propanal (4.95 mL, 37.3 mmol) in THF (20 mL) was added MeLi (31.05 mL of a 1.32 M solution in hexanes, 41.0 mmol). The reaction stirred at –78°C for 30 min and then was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was diluted with ether (100 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide crude orange oil, containing solid. The oil was filtered through a pad of silica (2 g) using hexanes:ethyl acetate (2:1) and then concentrated to yield 5.56 g of crude yellow oil.

To a cold (-60°C) solution of oxalyl chloride (3.58 mL, 41.0 mmol) in CH_2Cl_2 (90 mL) was added a solution of dimethyl sulfoxide (6.29 mL, 81.4 mmol) in CH_2Cl_2 (15 mL) dropwise, over a 10 min period. After 10 min of further stirring, a solution of crude 3-phenyl-2-butanol (5.56 g, 37.0 mmol) in CH_2Cl_2 (30 mL) was added over a 5 min period. The reaction stirred for a further 15 min and then Et_3N (25.79 mL, 185 mmol) was added over a period of 5 min at –60°C. The reaction was warmed to room temperature and then diluted with H_2O (30 mL). Stirring was continued for 10 min and then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phase was washed with 1 M HCl (2 × 100 mL), $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 178 g of crude orange oil. Purification by column chromatography on silica gel (195 g) using hexanes:ethyl acetate (initially 20:1, with gradual increase in solvent polarity to 5:1) yielded 2.75 g (50%) of the title compound as a colorless oil: MS (EI) *m/z* 148 (4, M^+), 133 (2), 105 (68), 103 (8), 91 (2), 79 (10), 77 (12), 63 (2), 51 (5), 43 (19), 32 (28), 28 (100).

5.3.9 *Representative Procedure for the Diastereoselective Addition of Tributyltinlithium to Carbonyl Substrates **214** and **215***

A representative procedure for the diastereoselective addition of tributyltinlithium to 2-phenyl-1-propanal (**214**) is given below, followed by spectral data of ethers **216** and **217**. The yield and diastereoselectivity of these ethers can be found in Table 20.

(1R,2R*),(1R*,2S*)-1-(Methoxymethoxy)-2-phenyl-1-tributylstannyl propane (**216**)*

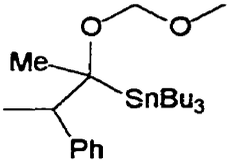


To a cold (0°C) solution of *i*-Pr_2NH (0.23 mL, 1.72 mmol) in Et_2O (5 mL) was added *n*-BuLi (1.22 mL of a 1.41 M solution in hexanes, 1.72 mmol). After the solution stirred for 15 min, Bu_3SnH (0.46 mL, 1.72 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 2-phenyl-1-propanal (0.27 mL, 2.06 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 2-phenyl-1-tributylstannyl-1-propanol.

Methylene chloride (2 mL), *i*-Pr_2NEt (0.90 mL, 5.15 mmol) and chloromethyl methyl ether (0.20 mL, 2.58 mmol) were added to a chilled (0°C) solution of the crude α-hydroxystannane. The ice bath was removed and the mixture stirred at room temperature until TLC indicated the reaction was complete (1 h). The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), and then diluted with ether (30 mL), washed with H_2O (15 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 848 mg of crude orange oil. Purification by flash chromatography on silica gel (17 g) using hexanes:ethyl acetate (40:1) provided 335 mg (42%) of the title compound as a colorless oil. Samples for GCMS were prepared in diethyl ether (Table 15, entry 1): IR ($CHCl_3$) 2961, 2928, 1733, 1683, 1645, 1586, 1457, 1262, 1078, 1026 cm^{-1}; ^1H

NMR (250 MHz, $CDCl_3$, asterisks denote major diastereomer) δ 0.55-1.00 (m, 15 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$), 1.10-1.75 (m, 12.48 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $C\underline{H}_3CHPh$), 1.39* (d, 2.52 H, J = 7.0 Hz, $C\underline{H}_3CHPh$), 3.11 (s, 0.48 H, $OC\underline{H}_3$), 3.23* (s, 2.52 H, $OC\underline{H}_3$), 3.05-3.30 (m, 1 H, $CH_3C\underline{H}Ph$), 4.17* (d, 0.84 H, J = 6.9 Hz, $C\underline{H}OMOM$), 4.22 (s, 0.16 H, $C\underline{H}OMOM$), 4.40-4.60 (m, 2 H, $OC\underline{H}_2O$), 7.10-7.35 (m, 5 H, Ar$\underline{H}$); MS (EI) *m/z* 413 (3, M^+-C_4H_9), 291 (11), 235 (18), 179 (37), 121 (25), 105 (14), 45 (100), 28 (46); Anal. Calcd for $C_{23}H_{42}O_2Sn$: C, 58.86; H, 9.02. Found: C, 59.02; H, 9.23.

(1R,2R*),(1R*,2S*)-2-(Methoxymethoxy)-3-phenyl-2-tributylstannyl butane (217)*



IR (neat) 2955, 2924, 1582, 1455, 1375, 1137, 1031, 915, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, asterisks denote major diastereomer) δ 0.70-1.05 (m, 15 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$), 1.15-1.70 (m, 14 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$, $C\underline{H}_3COMOM$ and $C\underline{H}_3CHPh$), 1.22* (s, 2 H, $C\underline{H}_3COMOM$), 1.30 (d, 2 H, J = 7.0 Hz, $C\underline{H}_3CHPh$), 2.90* (q, 0.67 H, J = 7.0 Hz, $CH_3C\underline{H}Ph$), 2.91 (q, 0.33 H, J = 7.1 Hz, $CH_3C\underline{H}Ph$), 3.30* (s, 2 H, $OC\underline{H}_3$), 3.32 (s, 1 H, $OC\underline{H}_3$), 4.62* (ABq, 1.34 H, J_{AB} = 7.0 Hz, Δν = 29.3 Hz, $OC\underline{H}_2O$), 4.65 (ABq, 0.66 H, J_{AB} = 6.9 Hz, Δν = 26.9 Hz, $OC\underline{H}_2O$), 7.10-7.40 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.79, 10.66* (^1J = 282, 295 Hz, $\underline{C}H_2Sn$), 13.61*, 13.64 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 15.59*, 19.08 ($\underline{C}H_3C$), 23.94*, 24.36 ($PhCH\underline{C}H_3$), 27.63, 27.58* ($^2J$ = 59 Hz, $\underline{C}H_2CH_2Sn$), 29.30, 29.22* (^3J = 19 Hz, $\underline{C}H_2CH_2CH_2Sn$), 49.85*, 50.15 ($Ph\underline{C}HCH_3$), 55.77, 55.85* ($O\underline{C}H_3$), 84.48*, 85.43 ($CH_3\underline{C}Sn$) 93.86*, 94.68 ($O\underline{C}H_2O$), 126.06, 126.26, 127.61, 127.93, 128.95, 129.48 (Ar-$\underline{C}$'s), 143.83, 146.04* (*ipso*-Ar-$\underline{C}$'s), MS (EI) *m/z* 439 (1, M^+-MOM), 291 (6), 235 (9), 179 (18), 161 (34), 121 (13), 45 (100), Anal. Calcd for $C_{24}H_{44}O_2Sn$: C, 59.64; H, 9.17. Found: C, 59.81; H, 8.98.

5.3.10 Reaction of Tributyltinlithium and $CeCl_3$ with 3-Phenyl-2-butanone (215)

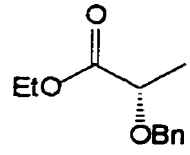
To a cold (0°C) solution of *i*-Pr_2NH (0.16 mL, 1.21 mmol) in THF (5 mL) was added *n*-BuLi (0.80 mL of a 1.50 M solution in hexanes, 1.21 mmol). After the solution stirred for 15 min, Bu_3SnH (0.32 mL, 1.21 mmol) was added and stirring was continued for a further 20 min. This solution was added via cannula to a previously prepared slurry of anhydrous $CeCl_3$ (539.8 mg, 1.45 mmol) in THF (5 mL) at -78°C. The reaction mixture was warmed to –30°C for 45 min, and then cooled to -78°C with stirring. To the reaction mixture was added 3-phenyl-2-butanone (180.1 mg, 1.21 mmol). The reaction was stirred at -78°C for 30 min, then warmed to -30°C over a 1 hour period and finally quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with 5% acetic acid solution (2 × 15 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude 3-phenyl-2-tributylstannyl-2-propanol.

Methylene chloride (2 mL), *i*-Pr_2NEt (0.63 mL, 3.62 mmol) and chloromethyl methyl ether (0.14 mL, 1.81 mmol) were added to a chilled (0°C) solution of the crude α-hydroxystannane. The ice bath was removed and the mixture stirred at room temperature until TLC indicated the reaction was complete (1 h). The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), and then diluted with ether (30 mL), washed with H_2O (15 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 532 mg of crude orange oil. Purification by flash chromatography on silica gel (16 g) using hexanes:ethyl acetate (40:1) provided 158 mg (27%) of ether **217**. Samples for GCMS were prepared in diethyl ether (Table 20, entry 6).

A similar experiment was performed using 2-phenyl-1-propanal (Table 20, entry 3).

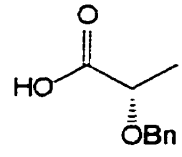
5.3.11 (S)-2-(Benzyloxy)propanoic acid (222)

(a) *Ethyl-(S)-2-(benzyloxy)propanoate (221)*



The procedure of Widmer was essentially followed.[27] To a cold (0°C) mixture of cyclohexane (2 mL) and CH_2Cl_2 (1 mL) was added (*S*)-ethyl lactate (1.00 mL, 8.8 mmol), benzyl-2,2,2-trichloroacetimidate (1.64 mL, 8.8 mmol), and triflic acid (78.1 μL, 0.8 mmol). The reaction was warmed to room temperature and allowed to stir for 1 hour. All solid was removed by filtration through a Celite® pad using cyclohexane:CH_2Cl_2 (2:1) as eluent. The filtrate was concentrated *in vacuo*. The remaining oil was dissolved in ether (40 mL) and washed with $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 2.2 g of yellow oil. Purification by column chromatography on silica gel (50 g) using hexanes:ethyl acetate (initially 20:1, with gradual increase in solvent polarity to 5:1) gave 930 mg (51%) of the title compound as a light yellow oil. The spectral data were identical to those previously reported.[27]

(b) *Preparation of the Title Compound (222)*



The hydrolysis of ester **221** was performed as outlined by Joullié *et al.*[28] To a cold (0°C) solution of ethyl-(*S*)-2-(benzyloxy)propanoate (466.8 mg, 2.24 mmol) in THF (22 mL) was added LiOH (22.4 mL of a 0.20 M aqueous solution, 4.48 mmol). The reaction was warmed to room temperature and stirred until monitoring by TLC indicated complete

hydrolysis of the ester (30 min). The solution was concentrated to half its volume and washed with ether (2 × 10 mL). The combined ether layers were re-extracted with $NaHCO_3$ (2 × 10 mL), and the aqueous layers were acidified to pH 4 with $KHSO_4$. The acidified layers were extracted with ether (3 × 15 mL). The combined ether layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide 409.3 mg (> 100%) of the title compound as an oil. The acid was used without further purification. The spectral data of **222** were identical to those previously reported.[37,38]

5.3.12 Attempted Esterification of (1-Hydroxy-1,2-dimethyl)propyl Tributylstannane with (S)-α-Methoxyphenylacetic Acid using DIPC and DMAP

The esterification was performed as outlined by Trost *et al.* (Method 1).[25] To a cold (0°C) solution of *i*-Pr_2NH (0.27 mL, 2.08 mmol) in THF (5 mL) was added *n*-BuLi (1.49 mL of a 1.40 M solution in hexanes, 2.08 mmol). After the solution stirred for 15 min, Bu_3SnH (0.56 mL, 2.08 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.22 mL, 2.08 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude (1-hydroxy-1,2-dimethyl)propyl tributylstannane.

Methylene chloride (19 mL), 1,3-diisopropylcarbodiimide (0.33 mL, 2.08 mmol), (*S*)-α-methoxyphenylacetic acid (316.4 mg, 2.08 mmol) and DMAP (25 mg, 0.20 mmol) were added to a chilled (0°C) solution of the crude α-hydroxystannane. The ice bath was removed and the mixture stirred at room temperature for 24 hours. TLC analysis of the reaction mixture revealed the absence of the desired ester **223**. Work-up and derivatization of this mixture was not performed (Table 21, entry 1).

5.3.13 Attempted Esterification of (1-Hydroxy-1,2-dimethyl)propyl Tributylstannane with (S)-α-Methoxyphenylacetyl Chloride

The esterification was performed as outlined by Trost *et al.* (Method 3).[25] To a cold (0°C) solution of *i*-Pr_2NH (0.22 mL, 1.71 mmol) in THF (5 mL) was added *n*-BuLi (1.22 mL of a 1.40 M solution in hexanes, 1.71 mmol). After the solution stirred for 15 min, Bu_3SnH (0.46 mL, 1.71 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.18 mL, 1.71 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude (1-hydroxy-1,2-dimethyl)propyl tributylstannane.

(S)-α-Methoxyphenylacetic acid (1.72 mL, 1.71 mmol) was added to a white suspension, which had been prepared by the slow addition of oxalyl chloride (1.72 mL of a 1 M solution in CH_2Cl_2, 1.72 mmol) to DMF (2.34 mL of a 1 M solution in CH_2Cl_2, 2.34 mmol) in acetonitrile (5 mL) at 0°C. After 5 min, a solution of the crude α-hydroxystannane (~ 1.71 mmol) in pyridine (2 mL) was added. The ice bath was removed and the mixture stirred at room temperature for 48 hours. The reaction mixture was diluted with ether (30 mL) and washed with 1 M $CuSO_4$ (2 × 15 mL), H_2O (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 645 mg of crude oil. TLC and ^1H NMR analysis of the crude mixture revealed the absence of the desired ester **223** (Table 21, entry 2).

5.3.14 Attempted Esterification of (1-Hydroxy-1,2-dimethyl)propyl Tributylstannane with (S)-2-(Benzyloxy)propanoic Acid using DIPC and HOBt

The esterification was performed as outlined by Trost *et al.* (Method 2).[25] To a cold (0°C) solution of *i*-Pr_2NH (0.45 mL, 3.40 mmol) in THF (5 mL) was added *n*-BuLi (2.91 mL of a 1.18 M solution in hexanes, 3.40 mmol). After the solution stirred for 15 min, Bu_3SnH (0.92 mL, 3.40 mmol) was added and stirring was continued for a further 20 min. The

reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.36 mL, 3.40 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude (1-hydroxy-1,2-dimethyl)propyl tributylstannane.

To a chilled (0°C) solution of the crude α-hydroxystannane in CH_2Cl_2 (10 mL) was added 1,3-diisopropylcarbodiimide (0.32 mL, 2.07 mmol), (*S*)-2-(benzyloxy)propanoic acid (409.3 mg, 2.27 mmol) and 1-hydroxybenzotriazole hydrate (306.9 mg, 2.27 mmol). The ice bath was removed and the mixture stirred at room temperature for 24 hours. TLC analysis of the reaction mixture revealed the absence of the desired ester **224**. Work-up and derivatization of this mixture was not performed (Table 21, entry 3).

5.3.15 Attempted Esterification of (1-Hydroxy-1,2-dimethyl)propyl Tributylstannane with (S)-2-(Benzyloxy)propanoic Acid using DCBC

The esterification was performed as reported by Sieber.[26] To a cold (0°C) solution of *i*-Pr_2NH (0.13 mL, 1.02 mmol) in THF (5 mL) was added *n*-BuLi (0.95 mL of a 1.07 M solution in hexanes, 1.02 mmol). After the solution stirred for 15 min, Bu_3SnH (0.27 mL, 1.02 mmol) was added and stirring was continued for a further 20 min. The reaction mixture was then cooled (-78°C), and 3-methyl-2-butanone (0.11 mL, 1.02 mmol) was added. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with ether (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* (room temperature bath) to provide crude (1-hydroxy-1,2-dimethyl)propyl tributylstannane.

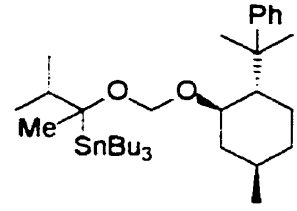
To a chilled (0°C) solution of the crude α-hydroxystannane in CH_2Cl_2 (2 mL) was added (*S*)-2-(benzyloxy)propanoic acid (183.2 mg, 1.02 mmol), pyridine (0.12 mL, 1.55 mmol), and 2,6-dichlorobenzoyl chloride (0.15 mL, 1.02 mmol. The ice bath was removed and the mixture stirred at room temperature for 24 hours. The reaction was quenched with $NaHCO_3$ (5 mL), diluted with ether (30 mL), and washed with H_2O (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. TLC and

^{1}H NMR analysis of the crude mixture revealed the absence of the desired ester **224** (Table 21, entry 4).

5.3.16 Representative Procedure for the Preparation of Acetal-Protected α,α-Dialkyl α-Hydroxystannanes 225-230

A representative procedure for the preparation of acetal **226** is given below, followed by ^{1}H NMR data of acetals **225-230**. The yield of these acetals can be found in Table 22.

(1R,1'R,2'S,5'R) and (1S,1'R,2'S,5'R)-1-[2-(1-Phenyl)isopropyl-5-methylcyclohexyloxy-methoxy]-1-methyl-1-(1-methylethyl)tributyl stannane (226)

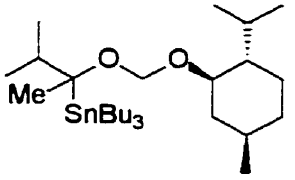


To a cold (0°C), stirred solution of diisopropylamine (0.17 mL, 1.3 mmol) in THF (10 mL) was added *n*-BuLi (1.12 mL of a 1.18 M solution in hexanes, 1.3 mmol). The reaction mixture was stirred at 0°C for 15 min Tributyltin hydride (0.36 mL, 1.3 mmol) was added and the mixture was stirred at 0°C for 15 min. The reaction was cooled to -78°C and 3-methyl-2-butanone (0.14 mL, 1.3 mmol) was added neat. After stirring at -78°C for 30 min, the reaction was quenched with saturated NH_4Cl solution and was allowed to warm to 0°C. The mixture was diluted with ether (40 mL) and the organic layer was washed with H_2O (10 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* (water bath at rt).

N,N-Diisopropylethylamine (0.50 mL, 6.6 mmol), DMAP (16.2 mg, 0.1 mmol) and chloromethyl 8-phenylmenthyl ether (1.12 g in CH_2Cl_2 (2 mL), 3.9 mmol) were added to a chilled (0°C) solution of the α-hydroxystannane in CH_2Cl_2 (2 mL). The reaction mixture

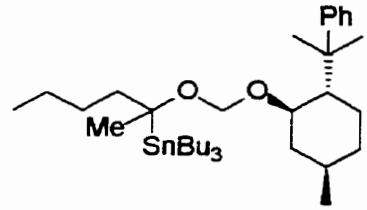
was allowed to warm to rt without removal of the cooling bath. After the reaction mixture was stirred at rt for 24 h, it was quenched with water and diluted with ether (30 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford 1.1 g of an orange oil. Purification of this material by chromatography (30 g of silica/g of substrate; 30:1 hexanes:ethyl acetate) afforded 0.46 g (57%) of **226** (1:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.60-1.10 [m, 30 H, $CH_3CH_2CH_2CH_2Sn$, $(CH_3)_2CHCSn$, $(CH_3)_2CH$, and CH_3CH], 1.15-1.70 (m, 19 H, $CH_3CH_2CH_2CH_2Sn$ and *c*-C_6H_7), 1.43 (s, 3 H, CH_3CSn), 1.87 [septet, 1 H, J = 6.7 Hz, $(CH_3)_2CHCSn$], 2.05-2.30 (m, 1 H, CH_3CH), 3.30-3.45 (m, 1 H, OCH_2OCH), 4.69 (ABq, 1 H, J_{AB} = 5.7 Hz, Δν = 30.0 Hz, OCH_2O), 4.57 (ABq, 1 H, J_{AB} = 5.6 Hz, Δν = 53.4 Hz, OCH_2O), 7.10-7.35 (m, 5 H, ArH).

(1R,1'R,2'S,5'R) and (1S,1'R,2'S,5'R)-1-[2-Isopropyl-5-methylcyclohexyloxymethoxy]-1-methyl-1-(1-methylethyl)tributyl stannane (225)



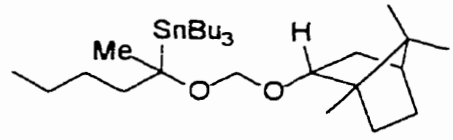
^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70-1.05 [m, 30 H, $CH_3CH_2CH_2CH_2Sn$, $(CH_3)_2CHCSn$, $(CH_3)_2CH$, and CH_3CH], 1.15-1.70 (m, 19 H, $CH_3CH_2CH_2CH_2Sn$ and *c*-C_6H_7), 1.40 (s, 3 H, CH_3CSn), 1.93 [septet, 1 H, J = 6.7 Hz, $(CH_3)_2CHC_6H_9$], 2.05-2.30 [m, 2 H, $(CH_3)_2CHCSn$ and CH_3CH], 3.20-3.36 (m, 1 H, OCH_2OCH), 4.69 (ABq, 1 H, J_{AB} = 5.7 Hz, Δν = 17.4 Hz, OCH_2O), 4.70 (ABq, 1 H, J_{AB} = 6.1 Hz, Δν = 55.3 Hz, OCH_2O).

(1R,1'R,2'S,5'R) and (1S,1'R,2'S,5'R)-1-[2-(1-Phenyl)isopropyl-5-methylcyclohexyloxy-methoxy]-1-butyl-1-methyl(tributyl) stannane (227)



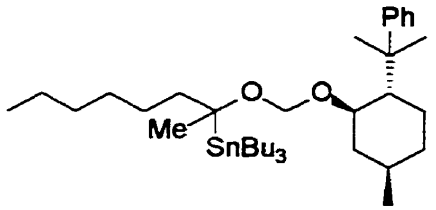
^{1}H NMR (200 MHz, $CDCl_3$) δ 0.60-1.10 [m, 27 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$, $C\underline{H}_3CH_2CH_2CH_2$, $(C\underline{H}_3)_2CH$, and $C\underline{H}_3CH$], 1.15-1.75 (m, 25 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and *c*-$C_6\underline{H}_7$), 1.42 (s, 3 H, $C\underline{H}_3CSn$), 2.05-2.30 (m, 2 H, $CH_3C\underline{H}$), 3.25-3.45 (m, 1 H, $OCH_2OC\underline{H}$), 4.54 (ABq, 1 H, J_{AB} = 6.2 Hz, Δν = 33.4 Hz, $OC\underline{H}_2O$), 4.55 (ABq, 1 H, J_{AB} = 6.2 Hz, Δν = 46.5 Hz, $OC\underline{H}_2O$), 7.00-7.40 (m, 5 H, Ar$\underline{H}$).

(1R,1'S) and (1S,1'S)-1-(Bornyloxy)-1-butyl-1-methyl(tributyl) stannane (228)



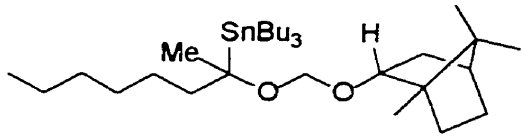
^{1}H NMR (250 MHz, $CDCl_3$) δ 0.60-1.80 [m, 49 H, $C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2Sn$, $C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $(C\underline{H}_3)_2C$, and $OCH_2OCHC(C\underline{H}_3)C\underline{H}_2C\underline{H}_2$-), 1.42 (s, 3 H, $C\underline{H}_3CSn$), 1.85-2.10 (m, 3 H, $OCH_2OCHC\underline{H}_2C\underline{H}$), 3.75-3.90 (m, 1 H, $OCH_2OC\underline{H}$), 4.62-4.75 (m, 2 H, $OC\underline{H}_2O$).

(1R,1'R,2'S,5'R) and (1S,1'R,2'S,5'R)-1-[2-(1-Phenyl)isopropyl-5-methylcyclohexyloxy-methoxy]-1-methyl-1-hexyl(tributyl) stannane (229)



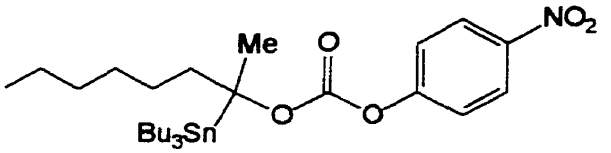
^{1}H NMR (250 MHz, $CDCl_3$) δ 0.60-1.05 [m, 27 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$, $C\underline{H}_3(CH_2)_4CH_2$, $(C\underline{H}_3)_2CH$, and $C\underline{H}_3CH$], 1.10-1.80 (m, 29 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$, $CH_3(C\underline{H}_2)_4C\underline{H}_2$ and *c*-$C_6\underline{H}_7$), 1.42 (s, 3 H, $C\underline{H}_3CSn$), 2.10-2.25 (m, 1 H, $CH_3C\underline{H}$), 3.25-3.45 (m, 1 H, $OCH_2OC\underline{H}$), 4.53 (ABq, 1 H, J_{AB} = 6.2 Hz, Δν = 41.1 Hz, $OC\underline{H}_2O$), 4.55 (ABq, 1 H, J_{AB} = 6.2 Hz, Δν = 58.4 Hz, $OC\underline{H}_2O$), 7.05-7.40 (m, 5 H, Ar$\underline{H}$).

(1R,1'S) and (1S,1'S)-1-(Bornyloxy)-1-hexyl-1-methyl(tributyl) stannane (230)



^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70-1.80 [m, 53 H, $C\underline{H}_3C\underline{H}_2C\underline{H}_2C\underline{H}_2Sn$, $C\underline{H}_3(C\underline{H}_2)_4C\underline{H}_2$, $(C\underline{H}_3)_2C$, and $OCH_2OCHC(C\underline{H}_3)C\underline{H}_2C\underline{H}_2$-), 1.41 (s, 3 H, $C\underline{H}_3CSn$), 1.85-2.20 (m, 3 H, $OCH_2OCHC\underline{H}_2C\underline{H}$), 3.75-3.90 (m, 1 H, $OCH_2OC\underline{H}$), 4.62-4.74 (m, 2 H, $OC\underline{H}_2O$).

5.3.17 2-p-Nitrophenylcarbonoyloxy-2-tributylstannyl octane (232)

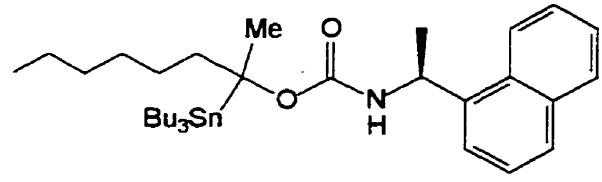


To a cold (0°C), stirred solution of diisopropylamine (0.49 mL, 3.70 mmol) in THF (10 mL) was added *n*-BuLi (2.27 mL of a 1.64 M solution in hexanes, 3.70 mmol). The reaction mixture was stirred at 0°C for 15 min. Tributyltin hydride (1.0 mL, 3.70 mmol) was added and the mixture was stirred at 0°C for 15 min. The reaction was cooled to -78°C and 2-octanone (0.58 mL, 3.70 mmol) was added neat. After stirring at -78°C for 30 min, the reaction was quenched with saturated NH_4Cl solution and was allowed to warm to 0°C. The mixture was diluted with ether (30 mL) and the organic layer was washed with H_2O (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* (water bath at room temperature).

p-Nitrophenyl chloroformate (1.12 g, 5.60 mmol) was added to a cold (0°C) solution of the α-hydroxystannane in pyridine (5 mL). The reaction was monitored by TLC for 1 h at room temperature, and was quenched with water (5 mL). The mixture was diluted with Et_2O (30 mL), washed with 1 M HCl (2 × 10 mL), $NaHCO_3$ (15 mL), H_2O (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 2.33 g of a colorless oil containing yellow solid. Purification of this material by chromatography (20 g of silica/g of substrate; using a gradient of 60:1 (100 mL), 40:1 (100 mL) and finally 20:1, hexanes:ethyl acetate) afforded 744.0 mg (34%) of **232** as a light yellow oil: IR ($CHCl_3$) 2958, 2828, 1747, 1527, 1349, 1278, 1226, 1207, 1163, 1121, 858 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ0.75-1.05 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2CH_2$), 1.15-2.10 (m, 22 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_3(C\underline{H}_2)_4C\underline{H}_2$), 1.57 (s, 3 H, $C\underline{H}_3C$), 7.26-7.32 (AA′ of AA′XX′, 2 H, Ar$\underline{H}$), 8.24-8.30 (XX′ of AA′XX′, 2 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.85 ($\underline{C}H_2Sn$), 13.65 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 14.04 ($\underline{C}H_3CH_2CH_2$), 22.58 ($\underline{C}H_3CSn$), 25.62 ($CH_3\underline{C}H_2CH_2$), 25.94 ($\underline{C}H_2CH_2C$), 27.56 ($\underline{C}H_2CH_2Sn$), 29.05 ($^3J$ = 18 Hz, $\underline{C}H_2CH_2CH_2Sn$), 29.57 ($\underline{C}H_2CH_2CH_2C$), 31.75 ($CH_3CH_2\underline{C}H_2$), 41.47 ($CH_2CH_2\underline{C}H_2C$), 89.22 ($CH_3\underline{C}Sn$),

121.81, 125.27, 145.22, 152.59 (Ar-C's), 155.75 (CO); MS (EI) *m/z* 528 (7, M^+-C_4H_9), 416 (3), 372 (11), 345 (100), 289 (32), 243 (34), 235 (38), 201 (46), 177 (27), 143 (61), 109 (47), 65 (32); Anal. Calcd for $C_{27}H_{47}NO_5Sn$: C, 55.49; H, 8.11; N, 2.40. Found: C, 55.68; H, 8.05; N, 2.33.

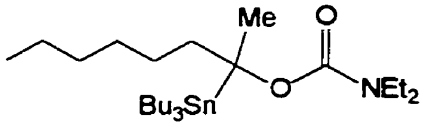
5.3.18 2-[(S)-1-(1-naphthyl)ethyl]carbamoyloxy-1-tributylstannyl octane (236)



To a cold (0°C) stirred solution of carbonate **232** (2.75 g, 4.70 mmol) in hexanes/acetonitrile (1:1, 2 mL) was added (*S*)-1-(1-naphthyl)ethylamine (1.90 mL, 11.75 mmol). After stirring for 2 h at room temperature, the reaction was diluted with hexanes (20 mL) and acetonitrile (20 mL). The layers were separated and the upper hexanes layer was washed with acetonitrile (2 × 10 mL), H_2O (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 3.24 g of a colorless oil. Resolution of this material (30 g of silica/g of substrate; 60:1 hexanes:ethyl acetate), required multiple elutions, but provided 1.17 g (81% yield) of the top isomer (91% de) and 1.14 g (78% yield) of the bottom isomer (97% de): colorless oil; high-R_f $[\alpha]_D^{25}$ −17.8 ° (*c*, 0.297, hexanes), low-R_f $[\alpha]_D^{25}$ −11.1 ° (*c*, 0.294, hexanes); IR (neat) 3445, 3333, 2956, 1715, 1601, 1523, 1442, 1376, 1312, 1229, 1048, 1028, 750, 691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.60-1.80 (m, 43 H, $CH_3CH_2CH_2CH_2Sn$, $CH_3(CH_2)_4CH_2$, CH_3CHN), 1.21 (s, 1.5 H, CH_3C), 1.36 (s, 1.5 H, CH_3C), 4.80-4.85 (m, 1 H, CH_3CHN), 5.45-5.70 (s, 1 H, NH), 7.35-7.60 (m, 4 H, ArH), 7.70-7.90 (m, 2 H, ArH), 8.00-8.20 (m, 1 H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, asterisks denotes high-R_f-isomer) δ 11.09*, 11.14 (^1J = 308, 323 Hz, CH_2Sn), 13.68*, 13.69 ($CH_3CH_2CH_2CH_2Sn$), 14.03, ($CH_3CH_2CH_2$), 21.59 (CH_3CHN), 22.57 (CH_3C), 25.50*, 25.66 (CH_3CH_2), 26.33, 26.35* (CH_2CH_2C), 27.64*, 27.66 (^2J = 60 Hz, CH_2CH_2Sn), 29.24*, 29.25 ($CH_2CH_2CH_2Sn$), 29.67*, 29,68 ($CH_2CH_2CH_2C$), 31.08, 31.78* ($CH_3CH_2CH_2$), 41.79*,

41.91 ($CH_2CH_2\underline{C}H_2C$), 46.15, 46.20* ($N\underline{C}HCH_3$), 81.31*, 81.43 ($CH_3\underline{C}Sn$), 122.18*, 122.24, 123.53*, 123.56, 125.17, 125.63*, 125.65, 126.21*, 126.25, 128.08*, 128.11, 128.70*, 128.72, 133.88*, 133.91, 138.82*, 138.83, 148.19*, 148.22 (Ar-$\underline{C}$'s), 156.36*, 156.37 ($\underline{C}O$); MS (FAB) *m/z* 617 (3, M^+), 560 (79), 448 (16), 404 (49), 345 (28), 290 (30), 235 (27), 177 (45), 155 (100), 69 (14); Anal. Calcd for $C_{33}H_{55}NO_2Sn$: C, 64.29; H, 8.99; N, 2.27. Found: C, 64.40; H, 9.14; N, 2.27.

5.3.19 2-N,N-Diethylcarbamoyloxy-1-tributylstannyl octane (237)

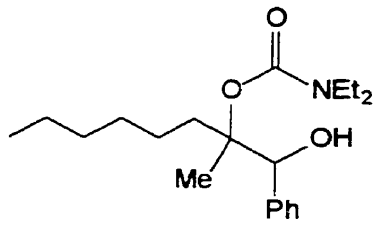


To a cold (0°C) stirred solution of carbamate **236** (576.2 mg, 0.93 mmol) was added AlH_3 (9.35 mL of a 0.5 M solution in THF, 4.67 mmol) in THF (7 mL). This mixture was then warmed to 40°C (warm water bath) and monitored by TLC for 12 h. The reaction was then cooled (0°C) and quenched with solid $Na_2SO_4 \bullet 10H_2O$. After the mixture stirred for 30 min at room temperature, all solids were removed by filtration through a Celite® pad using hexanes and then concentrated *in vacuo* (water bath at room temperature).

Pyridine (0.38 mL, 4.67 mmol) and *p*-$NO_2PhOCOCl$ (207.2 mg, 1.03 mmol) were added to a chilled (0°C) solution of the α-hydroxystannane in hexanes/acetonitrile (1:1, 10 mL). The reaction mixture stirred for 1 h at room temperature, and was then diluted with hexanes (20 mL) and acetonitrile (20 mL) After 5 min of stirring, the reaction was quenched with water (2 mL). The layers were separated and the hexane layer was washed with acetonitrile (20 mL). The combined acetonitrile washings were re-extracted with hexanes (3 × 10 mL). All hexane fractions were then concentrated *in vacuo*. The resulting crude carbonate was dissolved in hexanes/acetonitrile (1:1, 2 mL) and Et_2NH (0.48 mL, 4.67 mmol) was added. After stirring for 2 h at room temperature, the reaction was diluted with hexanes (20 mL) and acetonitrile (20 mL). The layers were separated and the upper hexanes layer was washed with acetonitrile (2 × 10 mL), H_2O (15 mL), brine (15 mL), dried

($MgSO_4$), filtered and concentrated *in vacuo* to afford 397.3 mg of colorless oil. Chromatography of this material (30 g of silica/g of substrate; 60:1 hexanes:ethyl acetate) afforded 390.5 mg (73%) of **237** as a colorless oil; IR ($CHCl_3$) 2957, 2928, 1663, 1475, 1458, 1426, 1378, 1285, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.65-1.00 (m, 18 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2Sn$ and $C\underline{H}_3CH_2CH_2$), 1.07 (t, 6H, J = 7.1 Hz, $(C\underline{H}_3CH_2)_2N$), 1.15-1.95 (m, 22 H, $CH_3C\underline{H}_2C\underline{H}_2CH_2Sn$ and $CH_3(C\underline{H}_2)_4C\underline{H}_2$), 1.40 (s, 3 H, $C\underline{H}_3C$), 3.10-3.35 (bm, 4 H, $(CH_3C\underline{H}_2)_2N$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.15 (^1J = 308, 322 Hz, $\underline{C}H_2Sn$), 13.6, 13.9 ($\underline{C}H_3CH_2N$), 13.64 ($\underline{C}H_3CH_2CH_2CH_2Sn$), 13.98 ($\underline{C}H_3CH_2CH_2$), 22.54 ($\underline{C}H_3C$), 25.67 ($CH_3\underline{C}H_2CH_2$), 26.36 ($\underline{C}H_2CH_2C$), 27.66 ($^2J$ = 60 Hz, $CH_3CH_2\underline{C}H_2CH_2Sn$), 29.23 ($^3J$ = 18 Hz, $CH_3\underline{C}H_2CH_2CH_2Sn$), 29.68 ($\underline{C}H_2CH_2CH_2C$), 31.80 ($CH_3CH_2\underline{C}H_2$), 41.04, 41.34 ($CH_3\underline{C}H_2N$), 41.91 ($CH_2CH_2\underline{C}H_2C$), 81.09 ($CH_3\underline{C}Sn$), 156.48 ($\underline{C}O$); MS (FAB) *m/z* 452 (92, M^+-C_4H_9), 342 (100), 231 (34), 173 (36), 116 (18), 98 (80), 87 (70), 72 (58); Anal. Calcd for $C_{25}H_{53}NO_2Sn$: C, 57.92; H, 10.30; N, 2.70. Found: C, 57.78; H, 10.06; N, 2.49.

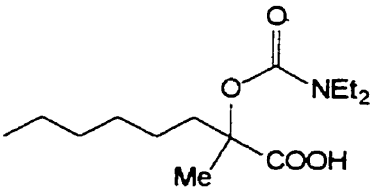
*5.3.20 2-(N,N-Diethylcarbamoyloxy)-2-methyl-1-phenyl-1-octanol (**238**)*



To a cold (-78°C) stirred solution of carbamate **237** (278.9 mg, 0.54 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.70 mL of a 1.54 M solution in hexanes, 1.08 mmol). After 15 min, benzaldehyde (136.7 μL, 1.35 mmol) was added. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The resulting mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography of the resulting oil (529.8 mg on 15 g of silica gel using 60:1 hexanes:ethyl acetate, initially, with gradual increase in solvent polarity) yielded 175 mg (94%) of Bu_4Sn and 82.1 mg (45% yield) of the expected product as a colorless oil; IR ($CHCl_3$) 3287, 2933, 1655, 1478, 1458, 1429, 1381, 1286, 1185, 1067, 980, 704 cm^{-1}; ^1H NMR (600 MHz,

$CDCl_3$) δ 0.80-0.90 (m, 3 H, $C\underline{H}_3CH_2CH_2$), 0.94 (t, 3 H, J = 6.8 Hz, $C\underline{H}_3CH_2N$), 1.14 (t, 3 H, J = 6.5 Hz, $C\underline{H}_3CH_2N$), 1.20-1.50 [m, 8 H, $CH_3(C\underline{H}_2)_4CH_2$], 1.26 (s, 1.5 H, $C\underline{H}_3C$), 1.42 (s, 1.5 H, $C\underline{H}_3C$), 1.68-1.80 (m, 1 H, $C\underline{H}_2C$), 1.96 (dt, 0.5 H, J = 3.2, 14.1 Hz, $C\underline{H}_2C$), 2.07 (dt, 0.5 H, J= 3.6, 14.1 Hz, $C\underline{H}_2C$), 3.00-3.35 (m, 4 H, $CH_3C\underline{H}_2N$), 4.70 (d, 0.5 H, J = 6.8 Hz, PhC$\underline{H}$OH), 4.72 (d, 0.5 H, J = 6.5 Hz, PhC$\underline{H}$OH), 6.23 (d, 0.5 H, J = 6.0 Hz, O$\underline{H}$), 6.32 (d, 0.5 H, J = 6.8 Hz, O$\underline{H}$), 7.20-7.35 (m, 5 H, Ar$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.37, 13.77, ($\underline{C}H_3CH_2N$), 13.95, 13.97, ($\underline{C}H_3CH_2CH_2$), 21.17, 21.69 ($\underline{C}H_3C$), 22.47, 22.49 ($CH_3\underline{C}H_2CH_2$), 23.45, 23.60 ($\underline{C}H_2CH_2C$), 29.54 ($\underline{C}H_2CH_2CH_2C$), 31.69, 31.70 ($CH_3CH_2\underline{C}H_2$), 35.66, 36.11 ($\underline{C}H_2C$), 42.00 ($CH_3\underline{C}H_2N$), 79.18, 79.54 (Ph$\underline{C}$HOH), 87.67, 87.77 [PhCH(OH)$\underline{C}$], 127.20, 127.22, 127.61, 127.63, 127.73, 127.78 (Ar-$\underline{C}$'s), 141.17, 141.21 (*ipso*-Ar-$\underline{C}$'s), 156.50, 156.53 ($\underline{C}$O); MS (EI) ***m/z*** 250 (2, M^+-C_6H_{13}), 207 (32, M^+-$C_8H_{16}O$), 148 (25), 116 (71), 105 (19), 100 (77), 91 (100), 72 (26), 43 (25); Anal. Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.18. Found: C, 71.74; H, 9.91; N, 3.94.

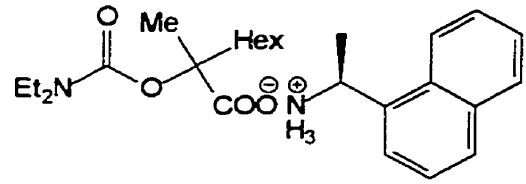
5.3.21 2-(N,N-Diethylcarbamoyloxy)-2-methyl-1-octanoic acid ***(241)***



To a cold (-78°C) stirred solution of carbamate **237** (214.2 mg, 0.41 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.30 mL of a 1.52 M solution in hexanes, 0.45 mmol). After 15 min. a slow stream of CO_2 was introduced for a period of 5 min. The reaction was quenched after 15 min with saturated aqueous NH_4Cl. The resulting mixture was diluted with ether (20 mL), and extracted with 1 M NaOH (3 × 10 mL). The combined basic extracts were washed with ether (15 mL), acidified with 2 M HCl and then re-extracted with ether (3 × 15 mL). The organic phase was washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 57 mg (51% yield) of the desired acid as a colorless oil. Concentration and chromatography of the initial ether layer (168.7 mg on 10 g of silica gel using 60:1

hexanes:ethyl acetate) yielded 110 mg (77%) of Bu_4Sn, 31 mg (14%) of starting material, and 12 mg (12%) of protonated product; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80-1.00 (m, 3 H, $C\underline{H}_3(CH_2)_4CH_2$), 1.05-1.45 (m, 8 H, $CH_3(C\underline{H}_2)_4CH_2$), 1.12 (t, 6 H, J = 7.0 Hz, $(C\underline{H}_3CH_2)_2N$), 1.59 (s, 3 H, $C\underline{H}_3C$), 1.75-2.05 (m, 2 H, $CH_3(CH_2)_4C\underline{H}_2$), 3.26 (bq, 4 H, J = 7.0 Hz, $(CH_3C\underline{H}_2)_2N$); MS (EI) *m/z* 250 (2, M^+-C_6H_{13}), 207 (32, M^+-$C_8H_{16}O$), 148 (25), 116 (71), 105 (19), 100 (77), 91 (100), 72 (26), 43 (25).

5.3.22 2-(N,N-Diethylcarbamoyloxy)-2-methyl-1-octanoic acid (S)-1-(1-naphthylethyl) ammonium salt (244)



The method of Nugier-Chauvin *et al.* was followed.[35] To a stirring solution of acid **241** (57.0 mg, 0.21 mmol) in Et_2O (2 mL) was added (*S*)-1-(1-naphthylethyl) amine (34 μL, 0.21 mmol). After stirring for 1 h at room temperature, the white solid formed in solution was collected on a Buchner funnel, washed with cold (0°C) hexanes and dried *in vacuo* to yield 62 mg of crude salt **244** as a white solid. The white powder was recrystallized from hexanes/CH_2Cl_2 (20:1).

5.4 References

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