Chiral Allylic and Allenic Stannanes as Reagents for Asymmetric Synthesis

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Contents

I. Introduction

In the synthesis of complex natural products one is frequently confronted with the task of creating intermediates possessing multiple contiguous stereogenic centers. Two important examples of particular interest to this review are polypropionates (polyketides) and carbohydrates.[1,2] The most efficient synthetic strategies for such compounds are those in which the joining of two subunits results in the simultaneous creation of adjacent stereocenters—as, for example, in the aldol condensation (eqs 1 and 3).[3] A related strategy entails the use of allylmetal reagents in place of enolates (eqs 2 and 4).[4]

In each of the foregoing strategies it is desirable to exert control over relative (*syn*/*anti*) as well as absolute (*R*/*S*) stereochemistry. This can be achieved in several ways:

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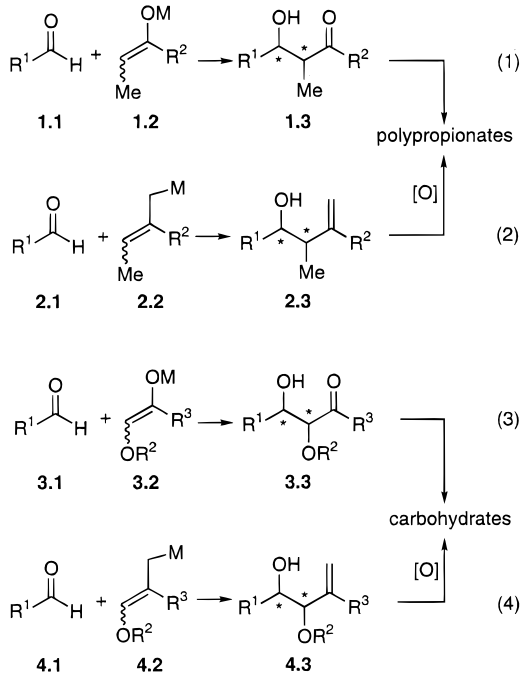
James A. Marshall received his B.S. degree from the University of Wisconsin and his Ph.D. degree from the University of Michigan, where he studied with Robert E. Ireland. He was an NIH postdoctoral fellow in William S. Johnson's laboratory at Stanford University after which, in 1962, he joined the faculty at Northwestern University. He was promoted to Professor in 1968 and subsequently moved, in 1980, to the University of South Carolina where he held the Guy Lipscomb Chair until 1995 when he accepted an appointment as Thomas Jefferson Professor of Chemistry at the University of Virginia. His professional interests lie in the area of natural products synthesis and stereocontrolled synthetic methodology. He currently resides in Charlottesville with his wife Liz, and their young son Andrew and infant daughter Samantha.



(1) *Substrate control*—addition of an achiral enolate or allylmetal reagent to a chiral (generally at the α-position) aldehyde. In this case, diastereoselectiv-

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ity is based on transition state preferences according to Cram−Felkin−Ahn considerations or by virtue of chelation.[5]

(2) *Reagent control*—addition of a chiral enolate or allylmetal reagent to an achiral aldehyde. Chiral enolates are most commonly accessed through incorporation of chiral auxiliaries in the form of esters, acyl amides (oxazolines), imides (oxazolidinones), or boron enolates.[3] Chiral allylmetal reagents typically incorporate chiral ligands.[4]

(3) *Double diastereodifferentiation*—addition of a chiral enolate or allylmetal reagent to a chiral aldehyde.[3] Enhanced stereoselection results when the aldehyde and reagent exhibit complementary facial preferences (matched case). Conversely, diminished stereoselection is observed when the aldehyde and reagent facial preferences are opposed (mismatched case).

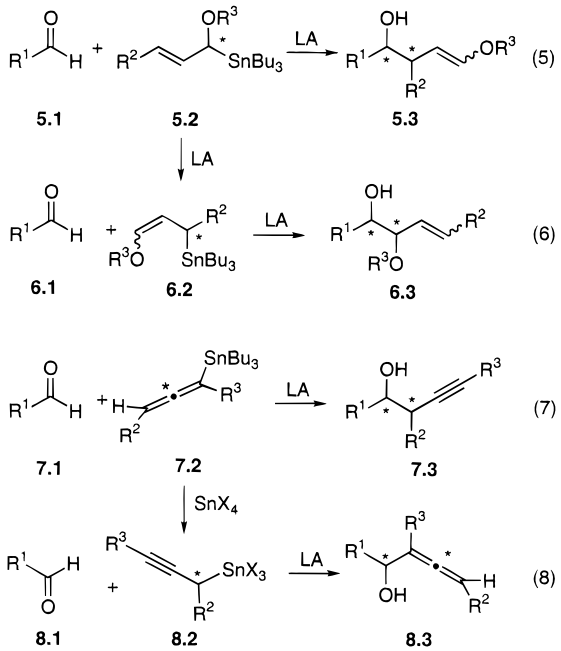
This review focuses on additions of chiral organotin compounds to chiral and achiral aldehydes leading to intermediates for polypropionate and carbohydrate synthesis. The approach differs from those mentioned above in that the stereogenicity is inherent to the reagent as opposed to a chiral ligand or auxiliary. Four types of reagents are discussed:

(1) α-Alkoxy allylic stannanes (cembrane and macrolide natural products, eq 5)

(2) γ-Alkoxy allylic stannanes (carbohydrates, eq 6)

(3) Allenic stannanes (polypropionate intermediates, eq 7); and

(4) Propargylic stannanes (2,5-dihydrofurans and polyethers, eq 8).



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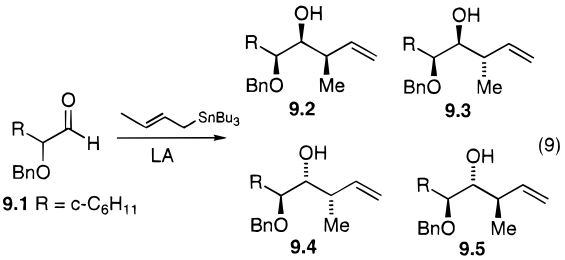
II. Background

A. Addition of Crotylstannanes to Aldehydes

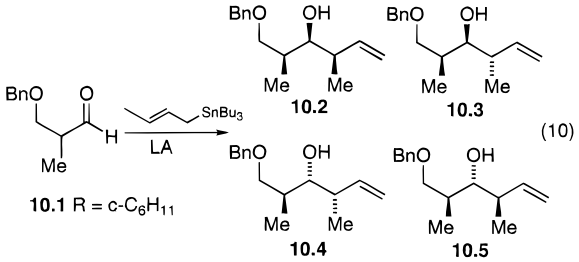
Although the origins of Lewis acid-promoted additions of allylic stannanes to aldehydes date back to 1979,[6] the studies of Keck and co-workers in the mid-1980's revealed the potential of these reactions for diastereoselective synthesis. In three early reports it was shown that the diastereoselectivity of the process is a function of the Lewis acid and the nature of the aldehyde.[7−9] Thus the addition of crotyl tri-*n*-butyltin to the α-benzyloxy aldehyde **9.1** is highly *syn* selective when $MgBr_2$ is employed as the promoter.[7] This reaction proceeds with chelation control. With $BF_3{\cdot}OEt_2$ the reaction is also *syn* selective but with diminished facial preference. This addition proceeds under Felkin−Ahn control.



(9)

LA	9.2	9.3	9.4	9.5
$BF_3{\bullet}OEt_2$	66	1	26	7
ZnI_2	49	49	1	1
$TiCl_4$	63	37	-	-
$MgBr_2$	92	8		

The *β*-benzyloxy aldehyde **10.1** also shows a distinct preference for *syn* addition with $MgBr_2$ as the Lewis acid.[8] In this case the *syn,anti* isomer **10.4** is the major adduct.



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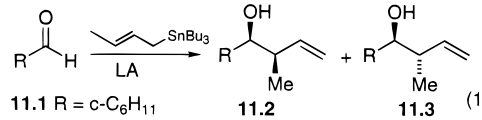
LA	10.2	10.3	10.4	10.5
$SnCl_4$	42	7	58	5
ZnI_2	48	-	40	-
$TiCl_4$	41	-	59	-
$MgBr_2$	7	10	81	2

An interesting crossover in *syn*/*anti* preference was noted when $TiCl_4$ was employed as the Lewis acid.[9] Thus addition of the crotylstannane to a 1:1 mixture of aldehyde **11.1** and $TiCl_4$ afforded the *syn* adduct **11.2** as the major product. However, when the aldehyde was added to premixed stannane and excess $TiCl_4$ the *anti* product **11.3** was strongly predominant. It was proposed that in the latter case, transmetalation occurs affording a transient allyltitanium species which then adds to the aldehyde by a cyclic *syn* process.



(11)

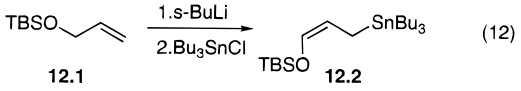
LA	11.2	11.3
$BF_3{\bullet}OEt_2$	96	4
$MgBr_2$	52	36[a]
$TiCl_4$ (1X)	90	7[a]
$TiCl_4$ (2X)	4	91[a]

[a] Plus minor amounts of other regioisomers

B. γ-Silyloxy and Alkoxy Allylic Stannanes

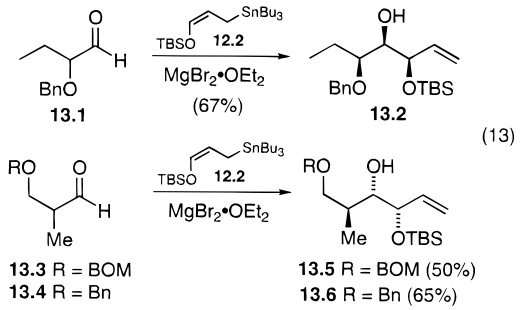
Similar trends were noted with the (γ-silyloxy)-allylstannane **12.2**.[10] This reagent was prepared by

lithiation of the allylic ether **12.1** and subsequent addition of Bu_3SnCl.



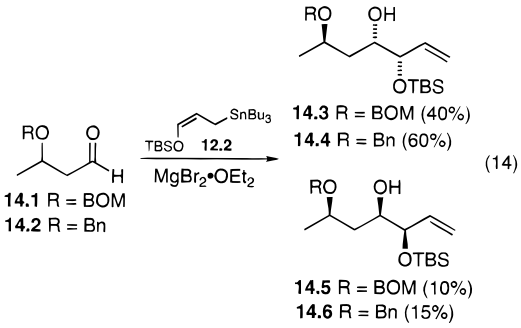
(12)

With $MgBr_2{\cdot}OEt_2$ as the Lewis acid promoter, stannane **12.2** afforded the *syn,syn* adduct **13.2** with aldehyde **13.1** and the *syn,anti* isomers **13.5** and **13.6** from aldehydes **13.3** and **13.4** respectively. In both cases the observed products arise by attack of the stannane on an internally chelated aldehyde.



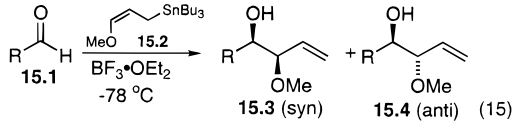
(13)

Selectivity is diminished in the case of aldehydes **14.1** and **14.2**.



(14)

In related studies, Koreeda found that the (γ-methoxy)allylstannane **15.2** gives mainly *syn* adducts **15.3** upon $BF_3{\cdot}OEt_2$-promoted addition to various aldehydes.[11]



(15)

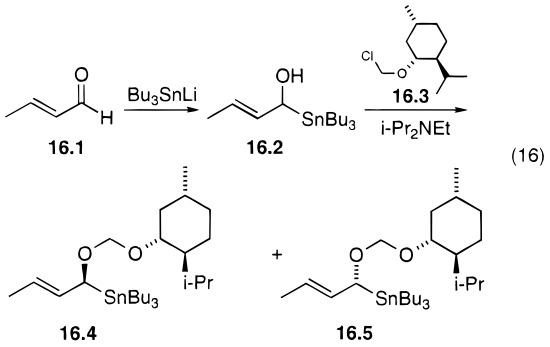
R	yield,%	syn:anti
Ph	86	10:1
i-Pr	60	25:1
c-C_6H_{11}	44	5:1

III. Enantioenriched α-Alkoxy Allylic Stannanes

A. Synthesis

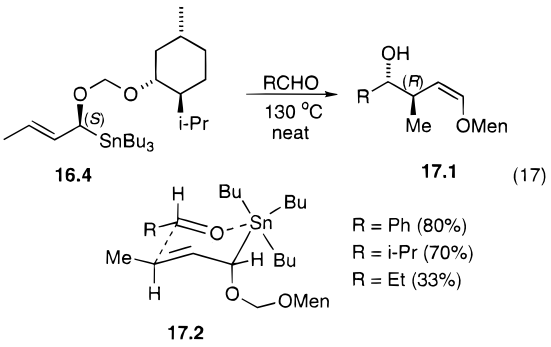
The prototype of these reagents was prepared by Thomas from the adduct **16.2** of crotonaldehyde and Bu_3SnLi, which affords upon treatment with (−)-(menthyloxymethyl)chloride and Hunig's base the labile diastereomeric (−)-(menthyloxy)methyl ethers **16.4** and **16.5** .[12] These diastereomers could be separated by column chromatography.

Thermolysis of, for example, **16.4** with aldehydes led to the adducts **17.1** stereospecifically (eq 17).



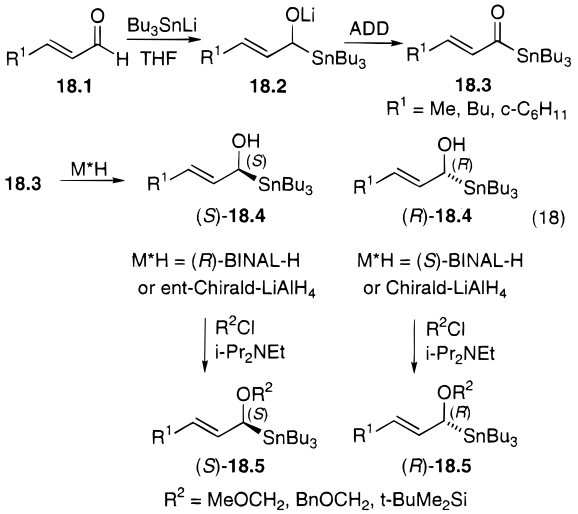
(16)

These results are consistent with the chair-like transition state **17.2**.



(17)

The first general approach to enantioenriched α-alkoxy stannanes was reported simultaneously by us and by Chong's group (eq 18).[13,14] In our approach, the lithio alkoxide **18.2**, derived from Bu_3SnLi and various enals, yielded the acylstannanes **18.3** upon treatment with azodicarbonyldipiperidine (ADD). Reduction with Noyori's BINAL-H reagents or with the Chirald or ent-Chirald-LAH reagent led to the α-hydroxystannanes (*S*) or (*R*)-**18.4**. The BINAL-H reductions afforded material of 95+% ee. The Chirald reagents, however, were less selective yielding alcohols of *ca.* 70% ee. These acid- and base-sensitive intermediates could be converted to stable alkoxymethyl or silyl ethers (*S*)- or (*R*)-**18.5**.

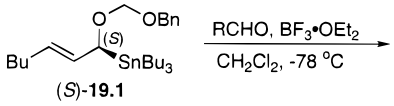


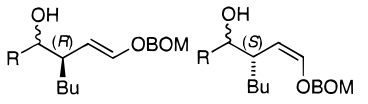
(18)

B. Additions to Achiral Aldehydes

The reaction of enantioenriched α-alkoxy allylic stannanes with achiral aldehydes proceeds with allylic inversion (S_E2' reaction). Typical results are

given in eq 19. Unlike the thermal reactions shown





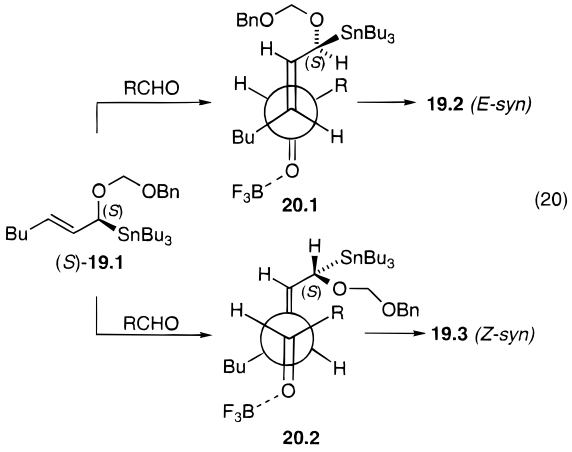
(19)

19.2 19.3

R	syn:anti	syn:anti	19.2/19.3
n-C_6H_{13}	>99:1	90:10	70:30
(E)-BuCH=CH	99:1	90:10	81:19
BuC≡C	88:12	60:40	58:42

in eq 17, Lewis acid-promoted additions afford mainly *syn* adducts. A molar equivalent of Lewis acid is generally required. It should be noted that there is a strong correlation (stereospecific) between the stannane configuration, the allylic center, and the double-bond stereochemistry of adducts **19.2** and **19.3**.

These results are consistent with an acyclic transition state, as first proposed by Yamamoto for crotylstannanes and illustrated in eq 20 for stannane (*S*)-**19.1**.[15] In this case the major (*syn*) adducts are



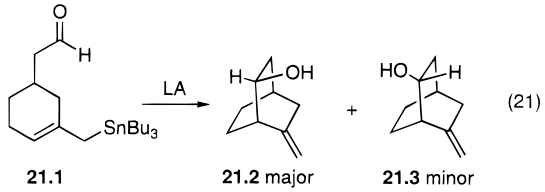
(20)

produced by way of the antiperiplanar orientation of the C−C double bond and the aldehyde CO as shown so as to minimize steric interactions between the stannane and aldehyde substituents Bu and R. The minor (*anti*) adducts most likely arise via transition states in which the C−C double bond of the stannane and the aldehyde CO adopt a synclinal arrangement with the sterically preferred *anti* arrangement of Bu and R substituents.

An essential feature of the Yamamoto transition state is the required *anti* relationship between the Bu_3Sn moiety and the forming C−C bond. It is this requirement that accounts for the stereospecificity of the additions.

In a study designed to probe the generality of the Yamamoto transition state proposal, Denmark examined the intramolecular addition of stannyl aldehyde **21.1** with a variety of Lewis acids.[16] In all cases the major adduct **21.2** was found to arise from a synclinal arrangement of the carbonyl and C−C double bond in discord with the Yamamoto proposal.

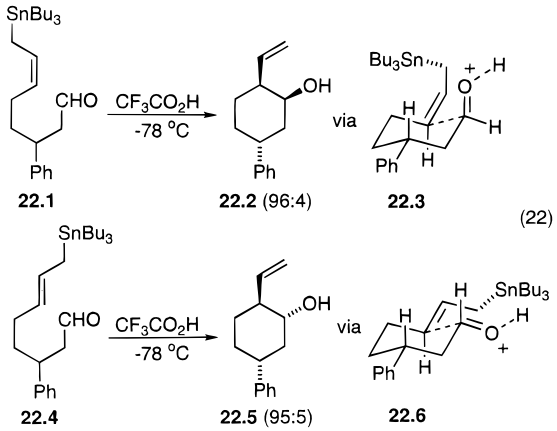
More recently, Keck and co-workers have reached a similar conclusion regarding cyclizations of the



21.1 21.2 major 21.3 minor

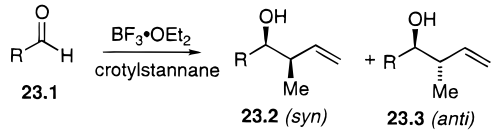
(21)

stannyl aldehydes **22.1** and **22.4**.[17] The major products from each reaction, **22.2** and **22.5**, are thought to arise via transition states **22.3** and **22.6**. It is suggested that orbital interactions between the allylstannane HOMO and the aldehyde−Lewis acid LUMO may lend stability to the depicted synclinal orientations.



(22)

In further studies along these lines, Keck *et al.* noted that the (*E*)-crotylstannane **23.4** was both more reactive and more *syn* selective than the (*Z*)-isomer **23.5** in additions to various aldehydes promoted by BF_3•OEt_2.[17] A detailed transition-state analysis indicated that synclinal and antiperiplanar arrangements may be comparable in energy and subtle steric and electronic effects may determine the ultimate product ratios.

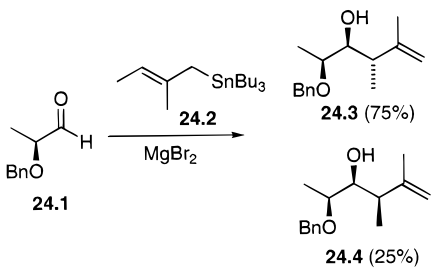


23.1 23.2 (*syn*) 23.3 (*anti*)

(23)

crotylstannane	*syn* product
SnBu3 (23.4)	highly favored
SnBu3 (23.5)	slightly favored

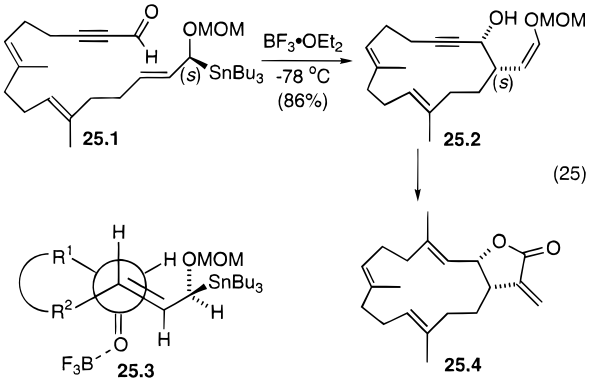
A synclinal transition state is also proposed to account for the preferred chelation controlled *anti* addition of stannane **24.2** to aldehyde **24.1**.[18]



(24)

In one of the earliest applications of this chemistry to natural product synthesis, we treated the enan-

tioenriched (*S*)-α-alkoxy allylic stannane ynol **25.1** with BF_3•OEt_2 at −78 °C to obtain the 14-membered cembranolide precursor **25.2** in 86% yield along with minor amounts of diastereomers (eq 25).[19]

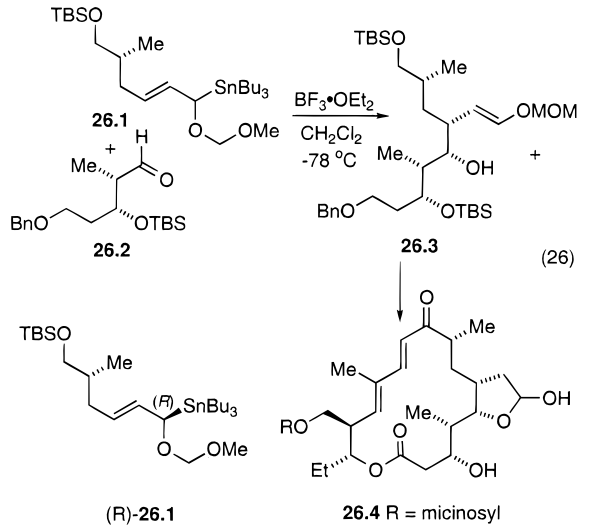


Interestingly, the (*Z*)-enol ether strongly predominates in this case, whereas the corresponding intermolecular additions shown in eq 19 favor the (*E*)-isomer. Because the aldehyde and stannane are connected by a carbon tether in **25.1**, the *anti* arrangement of C═O and C═C is disfavored relative to the *syn*. Hence cyclization likely proceeds via the synclinal arrangement as shown in **25.3**. In this regard the reaction is reminiscent of the intramolecular additions examined by Denmark[16] and Keck[17] depicted in eqs 21 and 22. Steric interactions between R^1 and R^2 tend to disfavor this orientation for intermolecular additions.

The cyclized alcohol **25.2** was converted to the natural cembranolide **25.4** by a series of routine steps.[19]

C. Additions to Chiral Aldehydes

A particularly interesting application is shown in eq 26. Here the α-alkoxy allylic stannane **26.1**, a 1:1 mixture of diastereoisomers at the allylic stereocenter, underwent BF_3-promoted reaction with the enantioenriched aldehyde **26.2** to yield the *syn* adduct **26.3** as a single isomer along with recovered and enantioenriched alkoxy stannane (*R*)-**26.1**.[20]

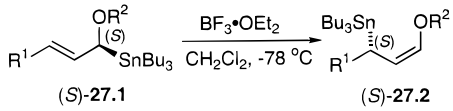


Accordingly, the (*S*)-diastereomer of stannane **26.1** preferentially adds to aldehyde **26.2** (matched pairing), to the near exclusion of (*R*)-**26.1** which is evidently mismatched with **26.2**. Adduct **26.3** was converted in two steps to an intermediate previously employed by Nicolaou in the total synthesis of micinosyl tylosin (**26.4**), a macrolide antibiotic.[21]

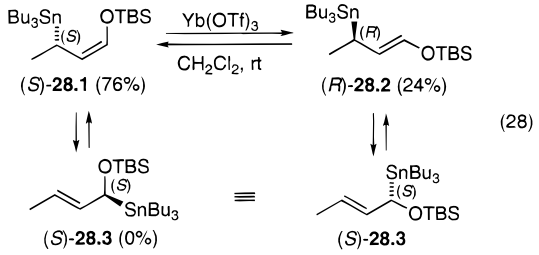
IV. Enantioenriched γ-Alkoxy and γ-Silyloxy Allylic Stannanes

A. Synthesis

In the absence of a reactive aldehyde, α-alkoxy and α-silyloxy allylic stannanes are isomerized by BF_3•-OEt_2 and other mild Lewis acids to (*Z*)-γ-alkoxy and (*Z*)-γ-silyloxy allylic stannanes (eq 27).[13,22] This isomerization proceeds by an intermolecular pathway with allylic and configurational inversion.[13] The isomerization can also be effected with TBSOTf, Bu_3-SnOTf, or $LiClO_4$ in Et_2O. In each case, the γ-(*Z*)-isomer is produced exclusively.



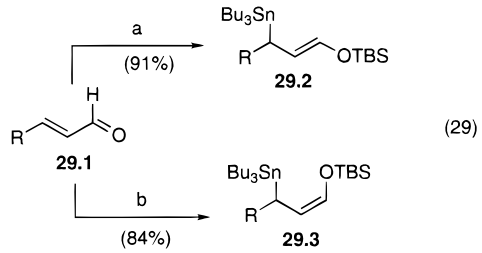
The use of stronger Lewis acids—$TiCl_4$, $SnCl_4$, $AlCl_3$, $ZnCl_2$—leads to decomposition of the stannanes. However, the lanthanide triflates $La(OTf)_3$, $Sc(OTf)_3$, and particularly $Yb(OTf)_3$ were found to catalyze interconversion of (*Z*)- and (*E*)-γ-silyloxy stannanes (*S*)-**28.1** and (*R*)-**28.2** (eq 28).[23] A roughly



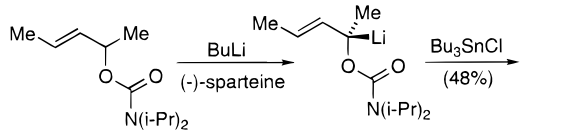
3:1 mixture of (*S*)-**28.1**/(*R*)-**28.2** was obtained starting from either (*S*)-**28.1**, (*R*)-**28.2**, or (*S*)-**28.3**, as expected for an equilibrium process. In each case, none of the α-isomer (*S*)-**28.3** was present at equilibrium. These results suggest that isomerizations of α- to γ-alkoxy and γ-silyloxy allylic stannanes catalyzed by BF_3, TBSOTf, and Bu_3SnOTf do not reach equilibrium as none of the (*E*)-isomers are formed in these reactions.

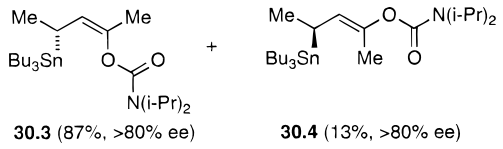
(*E*)-γ-Silyloxy allylic stannanes **29.2** can also be prepared directly from enals through 1,4-addition of the higher order cuprate $Bu(Bu_3Sn)Cu(CN)Li_2$, followed by trapping of the intermediate enolate with TBSCl.[24] Interestingly, 1,2-addition of Bu_3SnLi to such enals and subsequent reaction of the intermediate alcohol adduct with TBSOTf leads to the (*Z*)-γ-silyloxy allylic stannane **29.3** (eq 29).

Enantioenriched γ-acyloxy allylic stannanes have been prepared through lithiation of allylic carbamates such as **30.1** in the presence of the chiral coordinating amine base sparteine.[25] The intermediate lithio species **30.2** can be trapped with Bu_3SnCl

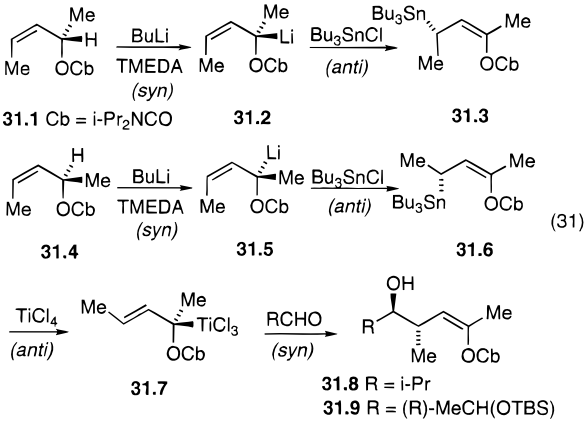


to afford the (*Z*)- and (*E*)-acyloxy stannanes **30.3** and **30.4** of greater than 80% ee.





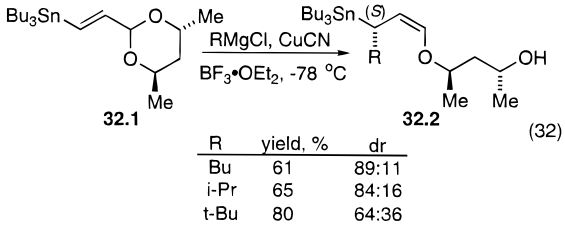
The nonracemic allylic carbamates **31.1** and **31.4** undergo lithiation with retention of configuration.[25] The transient organolithium intermediates react by an *anti* S_E2' pathway with Bu_3SnCl to afford the nonracemic tin reagents **31.3** and **31.6**. These intermediates can be converted to transient allyltitanium species such as **31.7** by *anti* S_E2' transmetalation with $TiCl_4$. Subsequent addition of aldehydes leads to the *anti* adducts **31.8** or **31.9** by a cyclic *syn* addition mechanism.



Recently, Quintard *et al.* showed that nonracemic *β*-stannyl acrolein acetals such as **32.1** undergo stereoselective S_N2' attack by organocopper reagents to yield *γ*-alkoxy allylic stannanes **32.2**.[26] This approach is complementary to the 1,3-isomerization route to chiral *γ*-alkoxy allylic stannanes (see eq 27).

B. Additions to Achiral Aldehydes

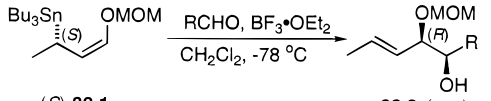
The foregoing *γ*-alkoxy and *γ*-silyloxy allylic stannanes react with aldehydes in the presence of certain Lewis acids, affording mainly *syn* monoprotected 1,2-diol adducts (eqs 33−35). Diastereoselectivity for a given aldehyde increases in the order (*Z*)-OMOM (**33.1**) < (*Z*)-OTBS (**28.1**) < (*E*)-OTBS (**28.2**).[24] The



R	yield, %	dr
Bu	61	89:11
i-Pr	65	84:16
t-Bu	80	64:36

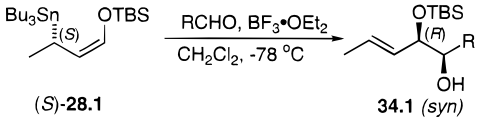
(32)

tendency for the (*E*)-stannane to show higher *syn* selectivity than the (*Z*)-isomer parallels the findings of Keck for the crotyl system (eq 23).[17]



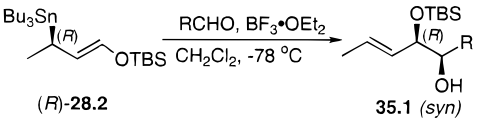
R	yield, %	*syn:anti*
n-C_6H_{13}	75	96:4
(E)-BuCH=CH	84	94:6
BuC≡C	70	90:10

(33)



R	yield, %	*syn:anti*
n-C_6H_{13}	86	97:3
(E)-BuCH=CH	81	>99:1
BuC≡C	84	93:7

(34)



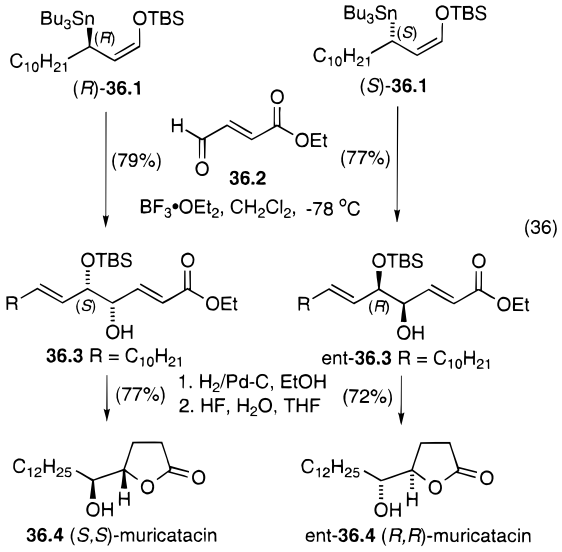
R	yield, %	*syn:anti*
c-C_6H_{11}	79	>99:1
(E)-BuCH=CH	83	>99:1
BuC≡C	87	97:3[a]

[a] 60:40 mixture of **35.1** and ent-**35.1**

(35)

In all cases save one, the foregoing reactions proceed stereospecifically by an *anti* S_E2' pathway, as proposed by Yamamoto (see eq 20). Thus, the ee of the stereogenic allylic center in the adduct is equal to that of the starting stannane. The one exception involves stannane (*R*)-**28.2** which affords nearly racemic adduct **35.1** with heptynal.[23] The recovered stannane (*R*)-**28.2** shows no loss of optical activity. Furthermore, the ee (>90%) of adducts **35.1** of (*E*)-2-heptenal and cyclohexanecarboxaldehyde is equivalent to that of stannane (*R*)-**28.2**. We therefore surmise that the addition to 2-heptynal must proceed by both an *anti* and a *syn* acyclic S_E2' pathway. This is the first instance of an acyclic *syn* addition to an aldehyde by an allylic stannane.

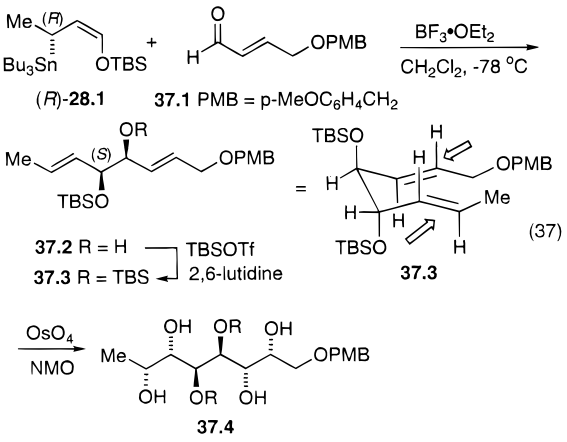
Our recent synthesis of (*S,S*)- and (*R,R*)-muricatacin (eq 36) illustrates the utility of enantioenriched *γ*-silyloxy allylic stannanes in this area.[27] The silyloxy stannanes (*R*)- and (*S*)-**36.1** of >90% ee were prepared from 2-tridecenal along the lines of eqs 18 and 27. Addition to enal **36.2**, obtained by ozonolysis of ethyl sorbate, afforded the (*S,S*)- and (*R,R*)-monosilylated diols **36.3** and *ent*-**36.3**, respectively, along with *ca.* 5% of the *anti* diastereomers. Hydrogenation followed by treatment with aqueous HF led



(36)

to the enantiomeric muricatacins **36.4** and *ent*-**36.4**. Both are found in Nature.

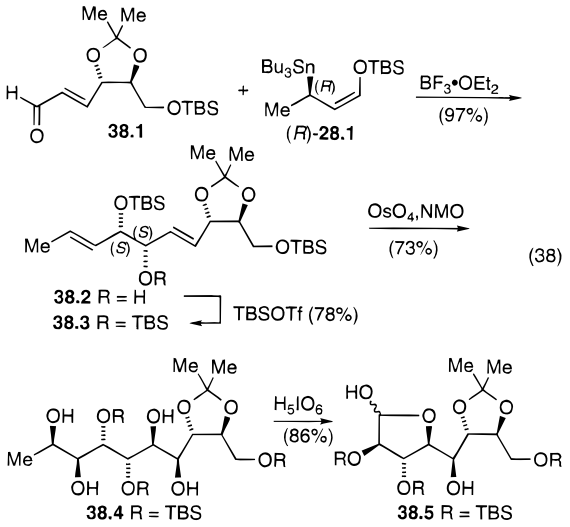
In a particularly intriguing application of the methodology, the adduct **37.2** of silyloxy stannane (*R*)-**28.1** and enal **37.1**, upon conversion to the bis-TBS ether **37.3**, afforded the tetrol **37.4** of >95% ee with >90% diastereoselectivity upon dihydroxylation with OsO_4−NMO.[28] The remarkable diastereoselectivity of this reaction is thought to arise from a strong preference for the chairlike conformation depicted as **37.3**.[29,30] In this conformation, the inside faces of the two double bonds are mutually shielded and attack is therefore directed to the outside faces, as indicated by the arrows. The sequence represents a particularly facile access to *syn,anti,syn,anti,syn* polyols.



(37)

In a further extension of this methodology, it was found that the bis-dihydroxylated products undergo selective oxidative cleavage to γ-lactols.[28] A typical case is illustrated in eq 38. Accordingly, enal **38.1** is converted to the bis-TBS ether **38.3** upon sequential treatment with the silyloxy stannane (*R*)-**28.1** and $BF_3{\cdot}OEt_2$ followed by silylation of the alcohol adduct with TBSOTf. Hydroxylation affords the tetrol **38.4** in 73% yield.

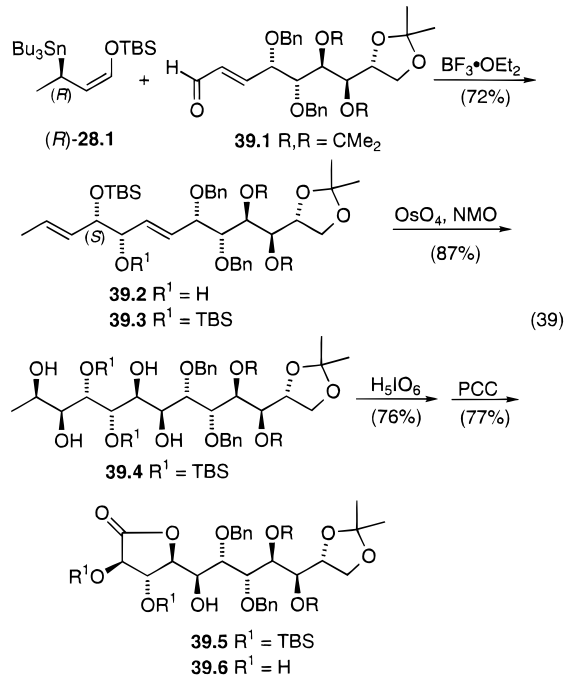
Treatment of **38.4** with H_5IO_6 results in selective cleavage of the less hindered diol. The success of this step is undoubtedly enhanced by the ready cyclization



(38)

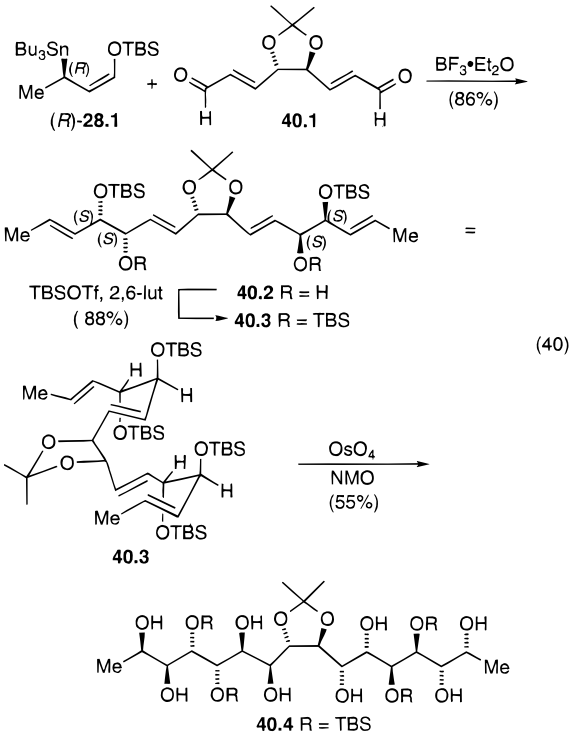
of the intermediate aldehyde to the lactol **38.5**, which is not affected by excess periodate. This conversion serves to internally protect the less reactive diol against cleavage.

The foregoing strategy is well suited to the synthesis of certain long-chain sugars. Thus enal **39.1**, prepared in several steps from D-mannitol, was converted to the bis-TBS ether **39.3** via the *syn* adduct **39.2**. Bis-hydroxylation yielded tetrol **39.4**, which was selectively cleaved and then oxidized with PCC to lactone **39.5**. Removal of the TBS ethers with TBAF gave lactone **39.6**, an intermediate in Schreiber's synthesis of (−)-hikizimycin.[31]



(39)

It was of interest to test the applicability of the foregoing hydroxylation strategy to bidirectional homologation. To that end, the dialdehyde **40.1** was prepared from the acetonide of (*R,R*)-diethyl tartrate. Bis-homologation with stannane (*R*)-**28.1** then TBS ether formation and hydroxylation afforded the polyol **40.4**, along with minor amounts of separable byproducts.



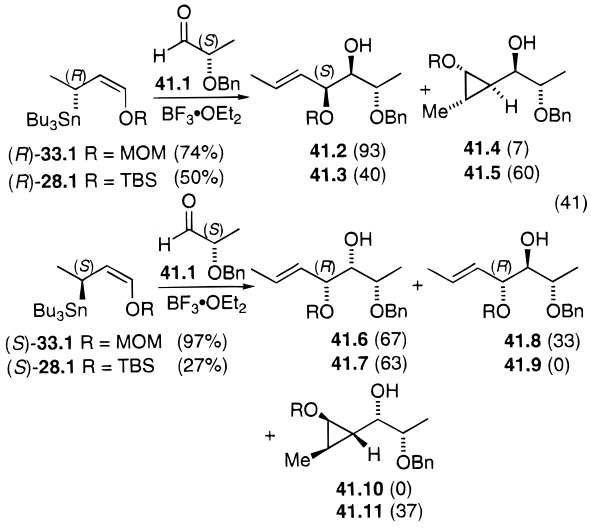
The stereochemistry of **40.4** derives from the depicted conformation of tetraene **40.3** in which the chairlike arrangement of each diene unit directs attack of OsO_4 to the outside faces of the double bonds. Presumably, the acetonide segment serves as a spacer to separate the two diene units from each other. Were this not the case, the two internal double bonds would experience mutual shielding of both faces, thereby diminishing their reactivity.

C. Additions to α-Alkoxy Aldehydes

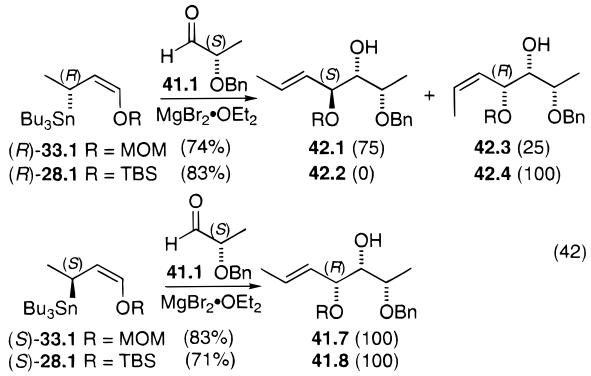
As a prelude to developing protocols for carbohydrate homologations, we examined additions of the γ-alkoxy and γ-silyloxy stannanes (*R*)-**33.1**/(*R*)-**28.1** and (*S*)-**33.1**/(*S*)-**28.1** to (*S*)-2-(benzyloxy)propanal (**41.1**) with the Lewis acids BF_3·OEt_2 and $MgBr_2$·OEt_2 as promoters in CH_2Cl_2.[20] In the BF_3 reaction, aldehyde **41.1** and the OMOM stannane (*R*)-**33.1** exhibited matched characteristics. The stannane enantiomer (*S*)-**33.1** was mismatched under these conditions. A small amount of the cyclopropane **41.4** (presumed stereochemistry) was also formed in the matched addition, but the mismatched pairing gave none of the analogous cyclopropane **41.10**. Interestingly, cyclopropane **41.5** was the major product in the BF_3-promoted reaction of the OTBS stannane (*R*)-**28.1** with aldehyde **41.1**.[32] The enantiomeric stannane (*S*)-**28.1** gave rise to the *syn,syn* adduct **41.7** as the major product with aldehyde **41.1**. None of the *anti* isomer **41.9** could be detected but a significant amount of the cyclopropane **41.11** was produced. Both OTBS stannane additions proceeded in relatively low yield.[30]

Cyclopropanes **41.5** and **41.11** must arise by oxygen-assisted attack of the double bond of (*R*)-**33.1**/**28.1**, and (*S*)-**28.1** on the aldehyde−BF_3 complex. Although rare, this mode of addition is not without precedent.[33]

As expected, matched/mismatched preferences were reversed in $MgBr_2$-promoted additions of the OMOM



stannanes (*R*)- and (*S*)-**33.1** with aldehyde **41.1** (eq 42). These reactions proceed through a chelated

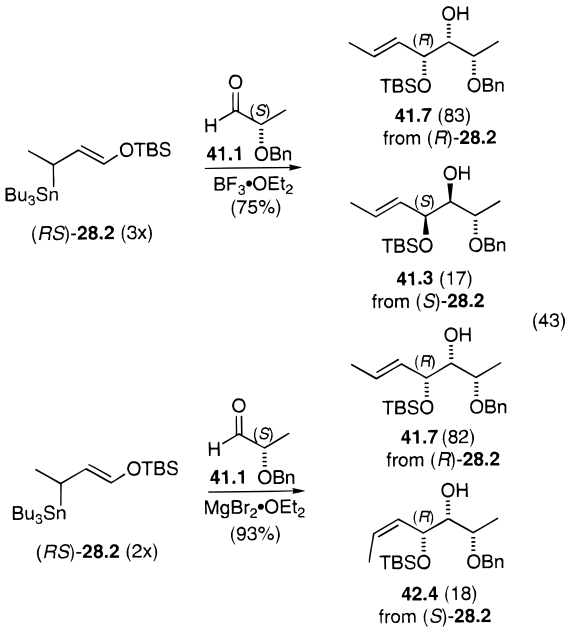


aldehyde which exerts a strong directing effect on the carbonyl addition. The BF_3 reactions, on the other hand, exhibit Felkin−Ahn transition state preferences and are largely reagent controlled.

Interestingly, the OTBS stannanes each gave a single adduct—**42.4** and **41.8**, respectively—with aldehyde **41.1** Thus, within the usual context of the terminology, neither pairing is mismatched. However, a competition experiment in which a 3-fold excess of racemic OTBS stannane was employed gave a 2.2:1 mixture of adducts **42.4** and **41.8** in 93% yield. By this criterion, the OTBS stannane (*R*)-**28.1** would appear to be matched and (*S*)-**28.1** mismatched with aldehyde **41.1**.[34]

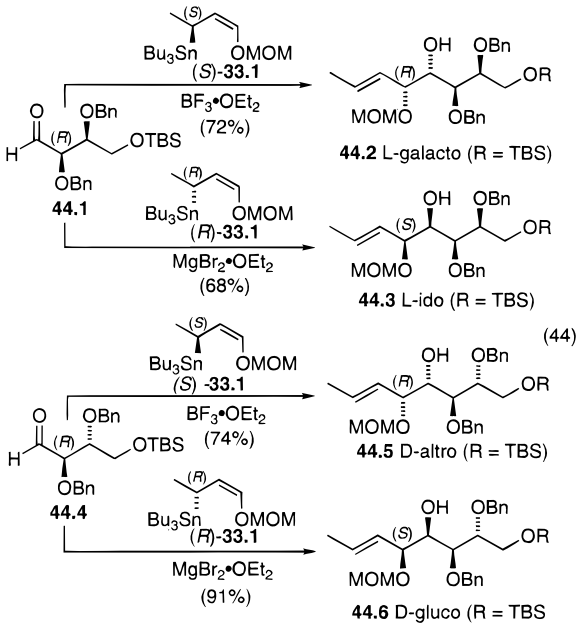
We also examined additions of racemic (*E*)-γ-silyloxy allylic stannane (*RS*)-**28.2** to aldehyde **41.1** under BF_3 and $MgBr_2$ promotion. In each case, only *syn* adducts were formed. Surprisingly, the (*R*)-enantiomer of stannane **28.2** appears to be matched with **41.1** in both reactions. The racemic (*E*)-γ-OMOM counterpart of stannane (*RS*)-**28.2** gave rise to mixtures of addition products unsuitable for synthetic applications.[32]

The four *syn* adducts **44.2**, **44.3**, **44.5**, and **44.6** of γ-OMOM stannanes (*S*)- and (*R*)-**33.1** and aldehydes **44.1** and **44.4** were secured as indicated in equation 44. These derive from matched pairings in Felkin−Ahn (BF_3) and chelation-controlled ($MgBr_2$) additions as established for aldehyde **41.1** (see eqs 41 and 42). As expected, the β-stereocenters of aldehydes **44.1**

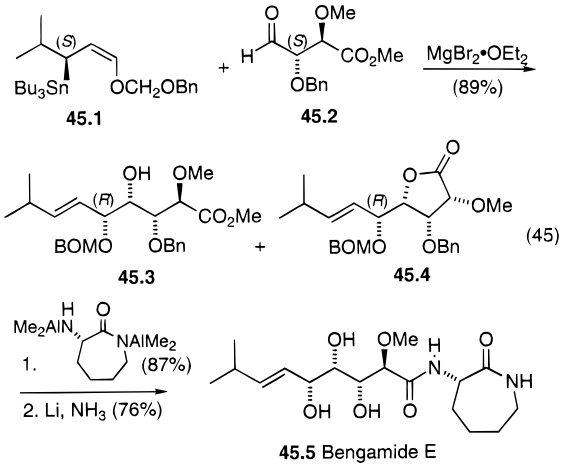


and **44.4** exert negligible influence on the direction of attack at the aldehyde carbonyl.

The appropriate pairings of stannanes (*S*)- and (*R*)-**33.1** with the enantiomers of aldehydes **44.1** and **44.4** would afford the enantiomeric adducts. It is therefore possible to prepare eight of the 16 hexose-related stereoisomers by this methodology, with complete control of stereochemistry. The synthesis of the remaining eight is described section V.B.



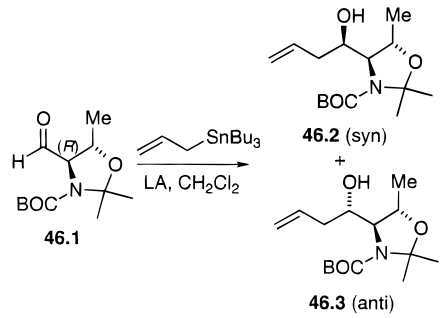
The (*S*)-γ-(benzyloxy)methoxy allylic stannane **45.1**, obtained by the route outlined in eqs 18 and 27, played a key role in our synthesis of bengamide E (**45.5**)—an unusual marine natural product with peptide, carbohydrate, and terpenic structural characteristics.[35,36] Accordingly, $MgBr_2$-promoted addition of the terpenic stannane **45.1** to the carbohydrate aldehyde **45.2**, derived from (*R*)-glyceraldehyde acetonide, afforded the (*E*)-*syn* adduct **45.3** and the related lactone **45.4** in a chelation-controlled reaction. Aminolysis of the mixture with (*S*)-2-aminocaprolactam followed by debenzylation with Li/NH_3 completed the synthesis.



D. Additions to α-Amino Aldehydes

The addition of organometallic reagents to *N*-protected α-amino aldehydes represents a straightforward route to biologically important β-amino alcohols.[37] Often, the requisite aldehydes can be prepared from available α-amino acids. However, the approach is limited by the ready epimerization of the aldehyde substrates and the general preference for *anti* additions through nonchelated transition states.

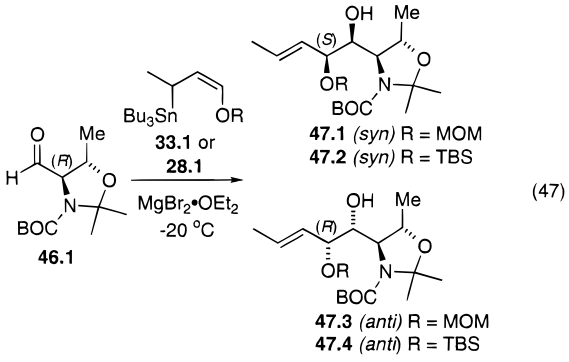
In some preliminary studies with the protected α-amino aldehyde **46.1** derived from threonine,[38] we found that BF_3-promoted addition of allyltri-*n*-butylstannane led mainly to the *anti* adduct **46.3** while the use of $MgBr_2$ afforded the *syn* adduct **46.2**.[39] The latter addition most likely involves a chelated aldehyde intermediate.



LA	T, °C	yield, %	syn:anti
$BF_3•OEt_2$	-78	84	12:88
$MgBr_2•OEt_2$	-20	87	83:17

The γ-oxygenated stannanes **33.1** and **28.1** were even more diastereoselective. With the racemic MOM derivative (*RS*)-**33.1** (2 equiv), an 87:13 mixture of *syn* and *anti* adducts **47.1** and **47.3** was secured in the $MgBr_2$ reaction. Stannane (*S*)-**33.1** of 85% ee was recovered in this experiment. Evidently, aldehyde **46.1** is strongly matched with (*R*)-**33.1** under these conditions. The OTBS stannane **28.1** was totally diastereoselective. In this case, none of the *anti* adduct **47.4** could be detected. When a 2.3-fold excess of (*R,S*)-**28.1** was employed, stannane(*S*)-**28** of 55% ee was recovered.

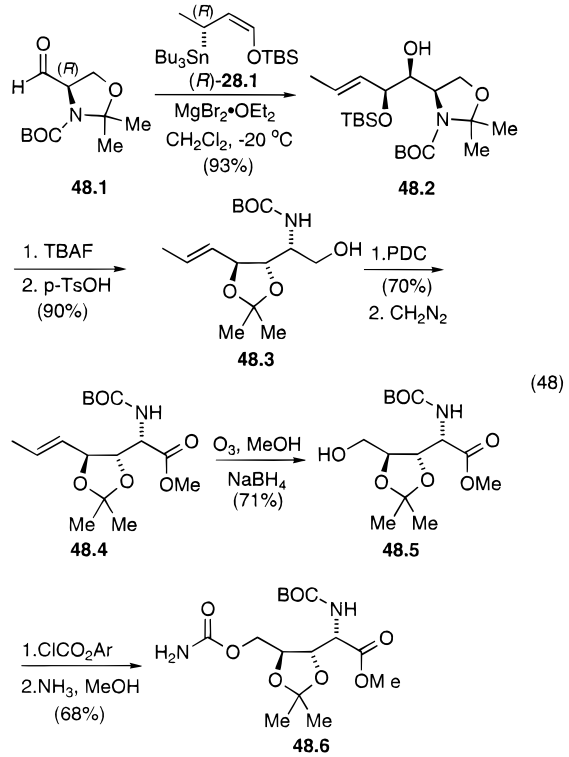
The serine-derived aldehyde **48.1** behaved comparably.[39] Addition of the (*R*)-OTBS stannane (*R*)-**28.1** gave the *syn* adduct **48.2** in over 90% yield. This



(47)

stannane	R	yield, %	*syn:anti*
(*RS*)-**33.1**	MOM	88	87:13
(*RS*)-**28.1**	TBS	70	>99:1
(*R*)-**28.1**	TBS	84	>99:1

product was converted to the protected α-amino ester **48.6**, an intermediate previously prepared by a nonselective sequence from L-tartaric acid.[40] The deprotected trihydroxy α-amino acid related to **48.6** is a common structural unit of the polyoxin antibiotics.[41]

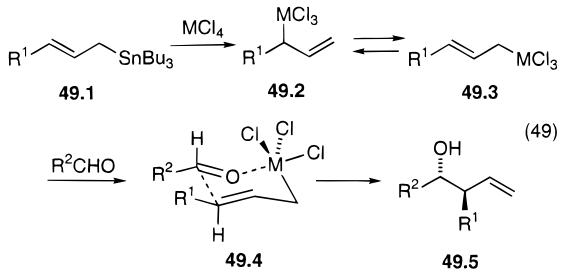


(48)

V. Transmetalations

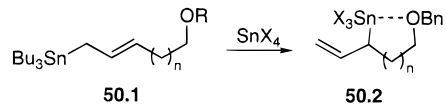
A. With $SnCl_4$

The Lewis acid-promoted reactions of allylic tributylstannanes with aldehydes discussed to this point lead to *syn* adducts by way of an acyclic *anti* S_E2' transition state, as illustrated in eq 20. The degree of diastereoselectivity and, in the case of chiral aldehyde substrates, the effective matching or mismatching characteristics depend upon substituents at the α and γ positions of the stannanes (see, *e.g.*, eqs 41−43). To access *anti* adducts, it is necessary to change the nature of the transition state. This can be achieved through transmetalation with, for example, $SnCl_4$ or $TiCl_4$ before addition of the aldehyde substrate.[9,42] Reaction then takes place by coordination of the aldehyde carbonyl with the Lewis acidic allylic trichlorotin or trichlorotitanium reagent through a six-center cyclic transition state (eq 49).

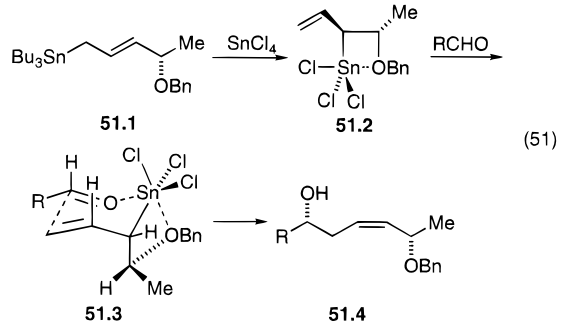


(49)

In the case of an unsymmetrical allylstannane such as **49.1**, the initial exchange occurs with allylic inversion to **49.2** but the products are those derived from **49.3**. Either the conversion of **49.2** to **49.3** is fast or the reaction of **49.3** with aldehydes is kinetically favored. Unfortunately, this approach to *anti* adducts fails with α- or γ-oxygenated allylic stannanes. These stannanes are destroyed by $SnCl_4$ or $TiCl_4$, or even by the milder alkoxy chloro titanium Lewis acids. However, Thomas has found that alkoxy substituents 1,4, 1,5, and to some extent 1,6 to a terminal Bu_3Sn grouping facilitate transmetalation with $SnCl_4$ and $SnBr_4$.[43] Evidently, chelation stabilizes the intermediate halo stannane (eq 50).

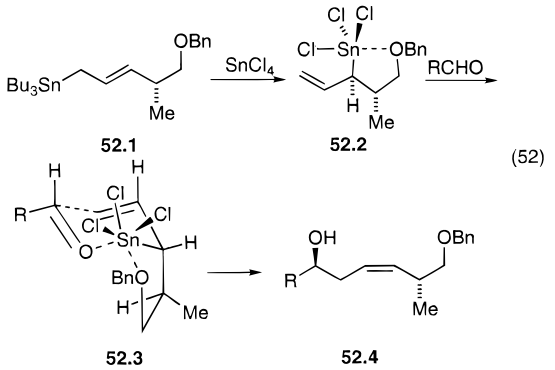


(50)



(51)

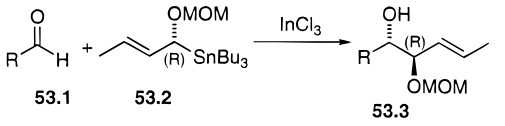
Certain enantioenriched representatives have been found to react stereoselectively with aldehydes to afford (*Z*)-homoallylic alcohols. Chelated bicyclic transition states are proposed for these additions, as illustrated in eqs 51 and 52.



(52)

B. With $InCl_3$

We have recently found that $InCl_3$ effects an apparent transmetalation of allylic stannanes yielding intermediates that react with aldehydes to afford *anti* adducts.[44] With α-OMOM allylic stannane **53.2**, monoprotected *anti*-1,2-diols **53.3** are produced (eq 53).

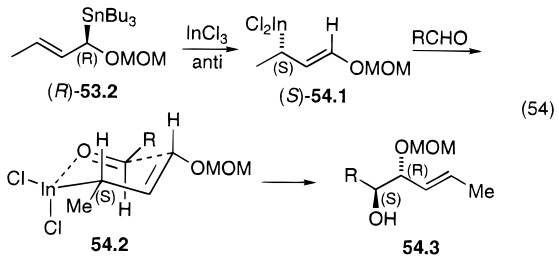


53.1 53.2 53.3

R	yield, %	anti:syn	ee, %
c-C_6H_{11}	88	96:4	>95%
(E)-BuCH=CH	87	83:17	>95%

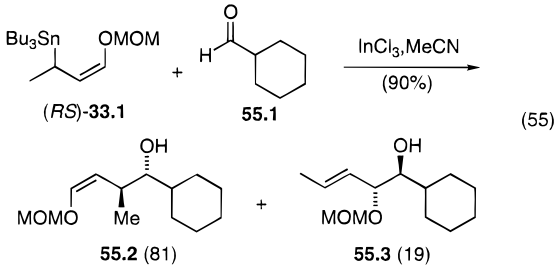
(53)

These additions can be carried out in acetonitrile, ethyl acetate, or acetone. In the latter case, a small amount of acetone adduct of the In reagent is formed. A possible pathway is depicted in eq 54. On the basis of product stereo- and regiochemistry, the transmetalation most likely proceeds by an *anti* S_E' process with subsequent addition through a cyclic six-center transition state shown in simplified form as **54.2**.



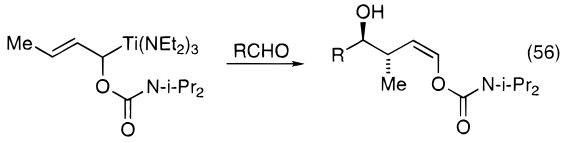
(*R*)-53.2 (*S*)-54.1 54.2 54.3 (54)

Additional support for this pathway was secured from reaction of the γ-OMOM allylic stannane (*RS*)-**33.1** with cyclohexanecarboxaldehyde (**55.1**). In this case, the *anti* enol ether **55.2** is the predominant product. This adduct would arise from the initial (kinetic) allylindium intermediate. The minor adduct **55.3** derives from partial isomerization of this indium species to the more stable γ-OMOM isomer and subsequent addition.



(*RS*)-33.1 55.1 55.2 (81) 55.3 (19) (55)

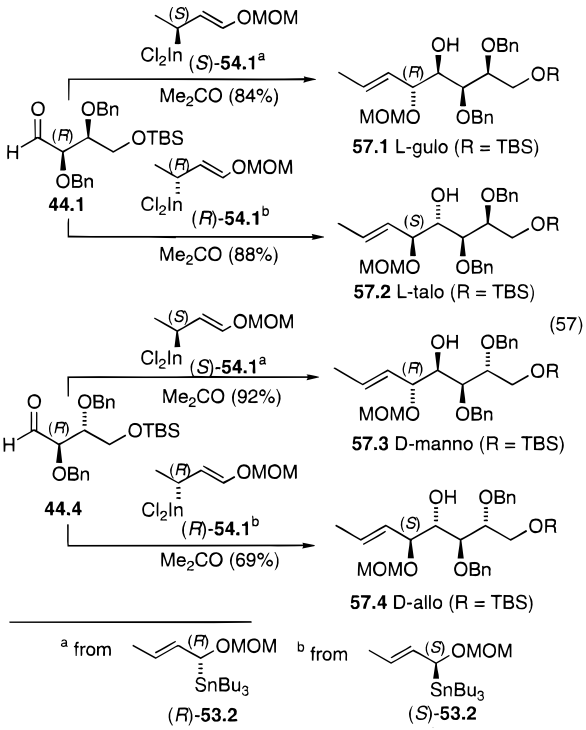
Interestingly, the (*Z*)-enol ether **55.2** is favored to the exclusion of the corresponding (*E*)-isomer. Similar findings were reported by Hoppe for additions of the titanium species **56.1** to aldehydes (eq 56).[25,45] Accordingly, it would appear that in these additions the OMOM and OCON(*i*-Pr)$_2$ substituents must prefer an axial-like orientation in a chair transition state such as **54.2** (see **17.2**).



56.1 56.2 (56)

In some preliminary experiments aimed at the synthesis of the four 2,3-*anti* hexose diastereomers (see eq 44 for the *syn* isomers), we examined additions of the putative allylindium species (*S*)- and (*R*)-**54.1** to the threose- and erythrose-related aldehydes **44.1** and **44.4**.[46] The racemic indium reagent (*RS*)-**54.1** afforded a *ca.* 2:1 mixture of *anti* adducts **57.1** and **57.2** in 90% yield. Accordingly, aldehyde **44.1** appears to be matched with indium reagent (*S*)-**54.1** (see eq 54 for the genesis of these indium species). The enantioenriched (*R*)-reagent afforded adduct **57.2** as the major product, with minor amounts (<20%) of diastereomers arising, in part, from enantiomers present in the enantioenriched reactants.

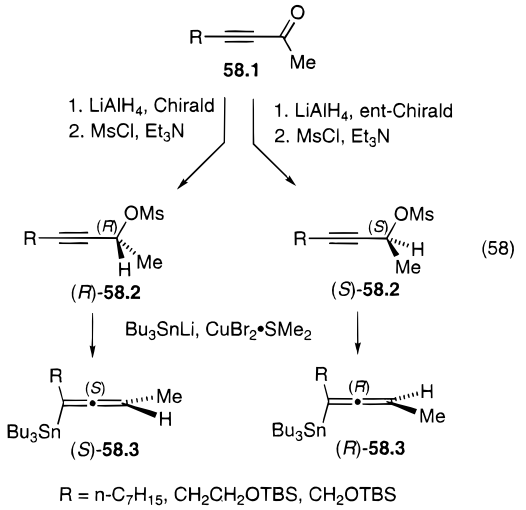
To complete the series, aldehyde **44.4** was converted to adduct **57.3** with reagent (*S*)-**54.1** and adduct **57.4** with the enantiomeric reagent under these conditions. In both mismatched cases, byproducts were formed in *ca.* 20% yield. As these byproducts are easily separable, it is possible to prepare the eight hexose-related adducts depicted in eqs 44 and 57 and their enantiomers in pure form, with good to excellent overall stereocontrol, from the enantiomeric α-OMOM stannanes **53.2** and the protected threose and erythrose aldehydes **44.1** and **44.4**, or the enantiomers.[46]



VI. Allenic Stannanes

A. Synthesis

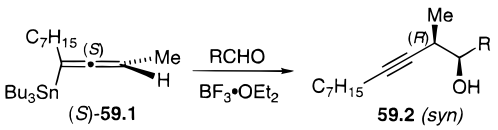
Enantioenriched propargylic mesylates such as (*R*)- and (*S*)-**58.2** (ee ~90%) can be readily prepared by reduction of the ketone **58.1** with the complex formed from $LiAlH_4$ and Chirald (Darvon alcohol), (2*S*,3*R*)-$PhCH_2C(Ph)(OH)CH(Me)CH_2NMe_2$, or its enantiomer, followed by treatment with MsCl and Et_3N.[47] These mesylates undergo efficient *anti* S_N2' displacement with the cuprate derived from equimolar quantities of Bu_3SnLi and $CuBr{\cdot}SMe_2$ to afford the (*S*)- and (*R*)-allenylstannanes **58.3**.[48]



(58)

B. Additions to Achiral Aldehydes

Allenic stannanes undergo S_E2' reactions with aldehydes in the presence of an equimolar quantity of $BF_3{\cdot}OEt_2$ or $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 to afford homopropargylic alcohol adducts. Typical results for stannane (*S*)-**59.1** are summarized in eq 59. With unbranched aldehydes such as heptanal, the *anti* adduct predominates. However, α-branching strongly favors the *syn* adducts **59.2**.[47,49]

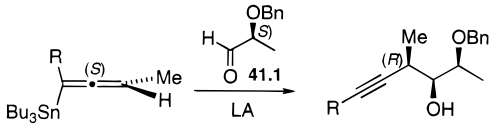


R	yield, %	*syn:anti*
C_6H_{13}	83	39:61
$(CH_3)_2CH$	80	99:1
$(CH_3)_3C$	92	99:1

(59)

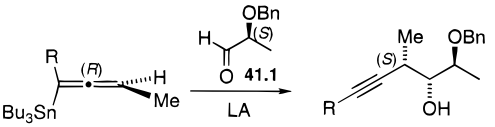
C. Additions to Chiral Aldehydes

The prototype (*S*)-α-alkoxy aldehyde **41.1** exhibits matching/mismatching characteristics in BF_3-promoted additions of allenic stannanes. Thus, stannanes (*S*)-**60.1** and (*S*)-**60.2** give rise to mixtures of *syn* adducts **60.3**/**60.4** and the alcohol epimers, whereas the enantiomeric stannanes afford the *syn* adducts **61.1** and **61.2** to the virtual exclusion of epimers.[47]



R	LA	yield, %	*syn:anti*
CH_2CH_3	$BF_3{\cdot}OEt_2$	92	87:13
CH_2OAc	$BF_3{\cdot}OEt_2$	95	68:32
CH_2CH_3	$MgBr_2{\cdot}OEt_2$	98	>99:1
CH_2OAc	$MgBr_2{\cdot}OEt_2$	97	>99:1

(60)



R	LA	yield, %	*syn:anti*
CH_2CH_3	$BF_3{\cdot}OEt_2$	89	>99:1
CH_2OAc	$BF_3{\cdot}OEt_2$	97	97:3
CH_2CH_3	$MgBr_2{\cdot}OEt_2$	95	1:99
CH_2OAc	$MgBr_2{\cdot}OEt_2$	97	1:99

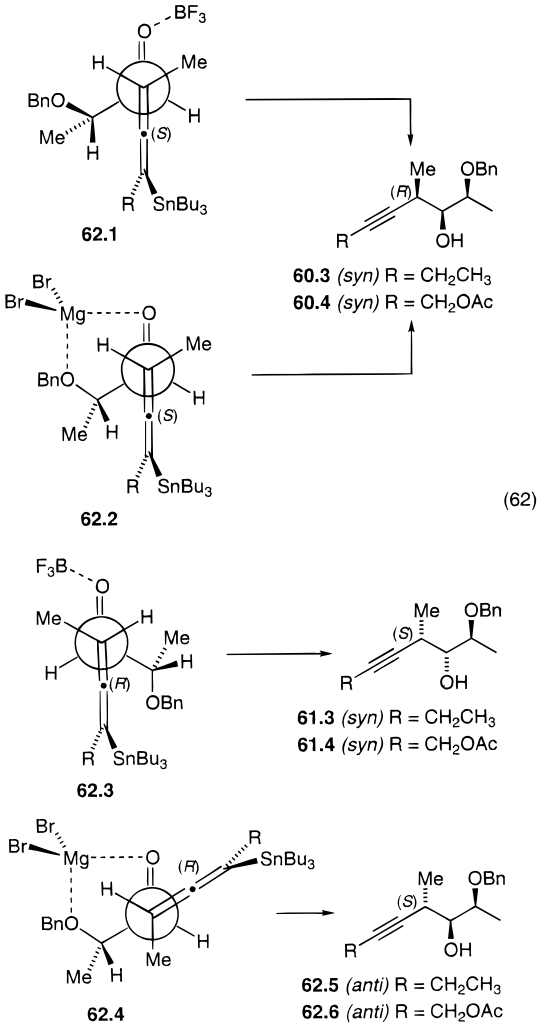
(61)

$MgBr_2$-promoted additions of these stannanes to aldehyde **41.1**, on the other hand, are strongly substrate controlled. Stannanes (*S*)-**60.1** and **60.2** afford the *syn* adducts **60.3** and **60.4** exclusively, whereas stannanes (*R*)-**60.1** and **60.2** are equally selective for the *anti* adducts **62.5** and **62.6**, respectively (eq 62).

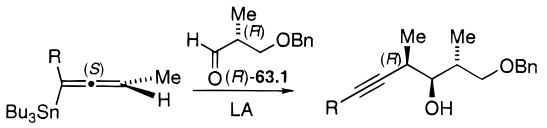
The BF_3 results can be reconciled by transition states **62.1** and **62.3**. In the former case, a Felkin−Ahn geometric arrangement would lead to the major adducts. The Cornforth transition state **62.3** accounts for the favored reaction pathway of stannanes (*R*) **60.1** and **60.2**, although a Felkin−Ahn orientation would serve equally well.

The $MgBr_2$ reactions most likely proceed through the chelated aldehyde, as shown in **62.2** and **62.4**. Approach to the aldehyde is strongly directed by the α-Me substituent, with the vinylic H of the stannane preferentially assuming a position over the most congested region of the chelate to minimize steric repulsions. For stereoelectronic reasons, the Bu_3Sn grouping is oriented *anti* to the forming C−C bond in all these additions. Interestingly, in order to satisfy the foregoing constraints, the allenylstannanes (*R*)-**60.1** and **60.2** must assume orientation **62.4** that leads to *anti* adducts **62.5** and **62.6**. *Anti* adducts are rarely formed in Lewis acid-promoted additions of allylic stannanes to aldehydes.[18]

Additions of allenylstannanes (*R*)- and (*S*)-**60.1**/**60.2** to (*R*)-2-methyl-3-(benzyloxy)propanal (**63.1**) were also examined.[50] In the BF_3 reactions, mismatching was observed with the former and matching with the latter. In both cases, the *syn* adducts **63.2**/**63.3** and **64.1**/**64.2** were predominant. These adducts were also favored in the $MgBr_2$ reactions, except for the ethyl system (*R*)-**60.1**. Here, an equal

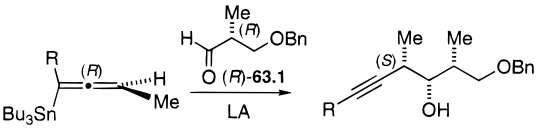


mixture of *syn* and *anti* products, **64.1** and the alcohol epimer, were formed.



(63)

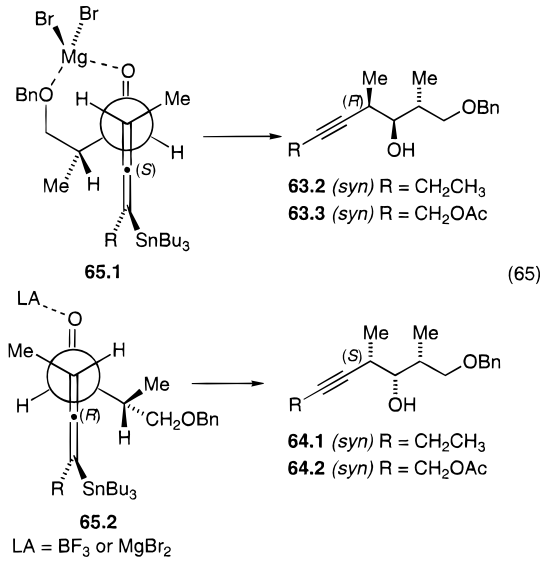
R	LA	yield, %	*syn:anti*
CH_2CH_3	BF_3•OEt_2	88	84:16
CH_2OAc	BF_3•OEt_2	98	83:17
CH_2CH_3	$MgBr_2$•OEt_2	93	>99:1
CH_2OAc	$MgBr_2$•OEt_2	95	>99:1



(64)

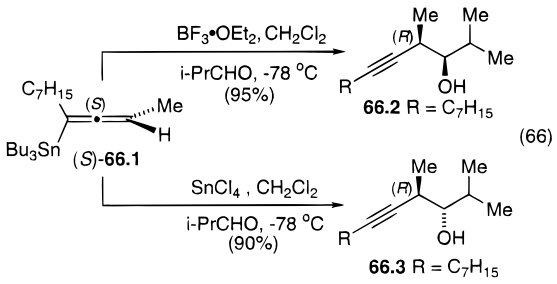
R	LA	yield, %	*syn:anti*
CH_2CH_3	BF_3•OEt_2	92	>99:1
CH_2OAc	BF_3•OEt_2	96	>99:1
CH_2CH_3	$MgBr_2$•OEt_2	95	50:50
CH_2OAc	$MgBr_2$•OEt_2	96	>99:1

Transition states **65.1** and **65.2** adequately account for the favored pathways. It is likely that in the $MgBr_2$ reaction the stannane (*R*)-**60.2** prefers the Felkin−Ahn transition state **65.2** to one resembling **62.4**, as none of the *anti* adduct is isolated from this reaction. The analogous reaction with stannane (*R*)-**60.1**, however, must proceed by both Felkin−Ahn and chelation pathways—for as yet unknown reasons.



D. Transmetalations with $SnCl_4$

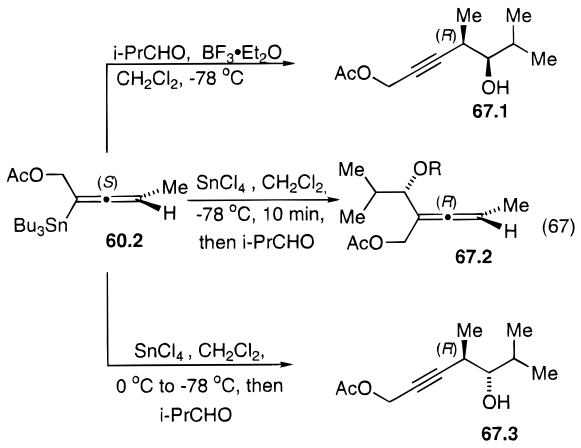
Adducts **63.2/63.3** and **64.1/64.2** represent two of the four "stereotriads" commonly found in natural products of the polypropionate family. To access the remaining two, it was necessary to modify the S_E2' addition in such a way that *anti* adducts would be favored. This was achieved through transmetalation of the allenylstannane with $SnCl_4$ followed by addition of the aldehyde.[51] The sequence was found to be stereospecific. Thus, whereas BF_3-promoted addition of allenylstannane (*S*)-**66.1** to isobutyraldehyde afforded the *syn* adduct **66.2**, brief treatment of stannane (*S*)-**66.1** with $SnCl_4$ followed by addition of the aldehyde gave the *anti* adduct **66.3**. In both cases, the ee of the adduct was equal to that of the stannane.



(66)

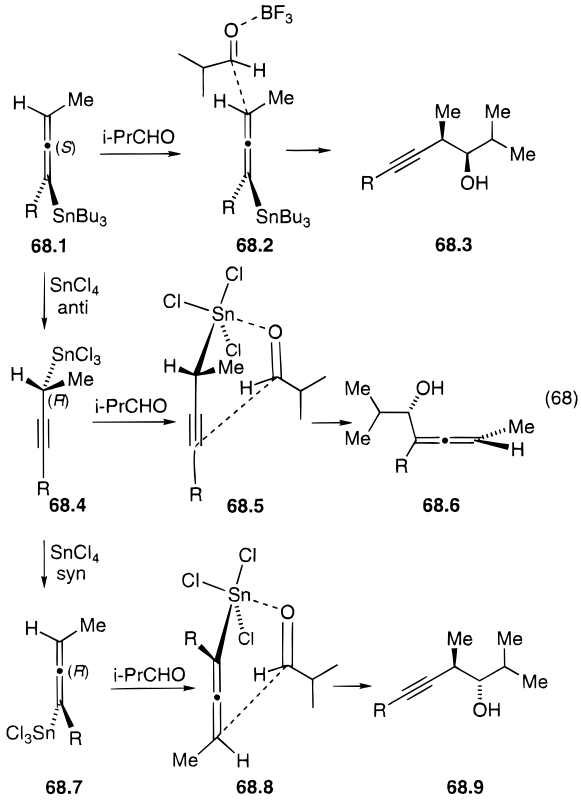
Reactions of allenylstannane (*S*)-**60.2** with isobutyraldehyde showed an interesting and revealing dichotomy. The BF_3-promoted addition proceeded as expected, affording the *syn* adduct **67.1**. The $SnCl_4$ reaction, however, gave rise to the allenylcarbinol **67.2** when the transmetalation step was conducted at −78 °C. In contrast, when the temperature was increased to 0 °C during the transmetalation phase of the reaction, and the aldehyde was added after cooling to −78 °C, then the *anti* propargylic adduct **67.3** was obtained as the sole product.[51]

As already noted, the BF_3 reaction proceeds by an acyclic transition state, as in **68.2**. Evidently, transmetalation with $SnCl_4$ follows an *anti* S_E2' pathway

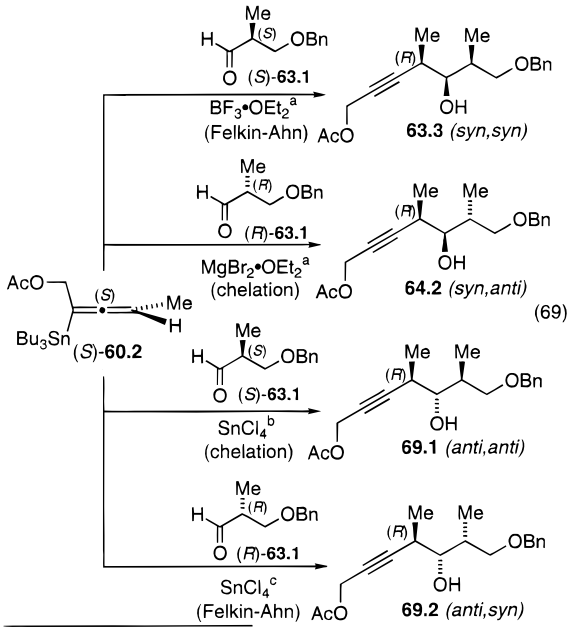


to give an intermediate propargyl chlorostannane **68.4** (eq 68). This intermediate, when intercepted by an aldehyde, affords the allenylcarbinol **68.6** by a six-center cyclic transition state **68.5**. The preference for **68.5** over the diastereomeric transition state is thought to arise from steric interactions between the propargylic Me and the ligands on tin (see section **VIII**).

In the absence of aldehyde, propargyl stannane **68.4** isomerizes to the allenyl stannane **68.7**. This process may be bimolecular and proceeds by a *syn* pathway. The rate of isomerization is considerably greater for R = C_7H_{15} or CH_3CH_2 than for R = CH_2-OAc. The allenyl chlorostannane **68.7** reacts with aldehydes by a cyclic six-center transition state **68.8** to yield the *anti* adduct **68.9**. The orientation depicted in **68.8** serves to minimize steric repulsion between the allenyl Me and the aldehyde *i*-Pr substituent.



Applying these concepts to allenylstannane (*S*)-**60.2** and the (*S*)- and (*R*)-2-methyl-3-(benzyloxy)-propanals **63.1**, we were able to synthesize each of the four stereotriad representatives—**63.3**, **64.2**, **69.1**, and **69.2**.[52] The former two arise through acyclic S_E2' transition states under Felkin–Ahn and chelation control, as previously detailed (eq 65). The *anti,anti* adduct **69.1** derives from the (*R*)-allenyl chlorostannane through a cyclic six-center transition state, as in **68.8**, involving a chelated (with $SnCl_4$) aldehyde (*S*)-**63.1**. The *anti,syn* adduct **69.2** is also derived from the (*R*)-allenylchlorostannane—attack occurring with Felkin–Ahn diastereocontrol.



[a] CH_2Cl_2 solvent, [b] CH_2Cl_2 or hexane solvent, [c] hexane solvent

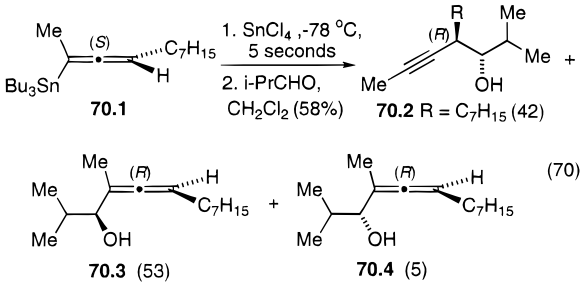
Interestingly, when this latter addition was conducted in CH_2Cl_2, the major product was the *anti, anti* adduct **69.1** arising from racemization of aldehyde (*S*)-**63.1** and preferential reaction of the stannane with the inverted aldehyde (*R*)-**63.1**. However, when hexane was employed as the solvent, racemization was significantly retarded and the *anti, syn* adduct **69.2** predominated 93:7.

VII. Propargylic Stannanes

A. Synthesis

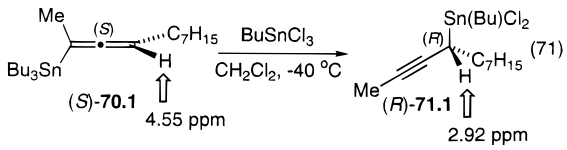
As noted in eq 68, the addition of $SnCl_4$ to allenylstannanes leads to the transient formation of propargylic chlorostannanes **68.4** by a presumed *anti* S_E' transmetalation. These rapidly isomerize to the more stable allenylstannanes **68.7**.[51] The overall process proceeds with inversion of allene configuration. When allenylstannane (*S*)-**70.1** is treated with a molar equivalent of $SnCl_4$ in CH_2Cl_2 at −78 °C, followed by immediate addition of isobutyraldehyde, a mixture of *anti* homopropargylic alcohol **70.2** and the *syn* and *anti* allenylcarbinols **70.3/70.4** is obtained in the ratio 42:53:5.[53] This ratio is critically dependent upon the timing of aldehyde addition and the stoichiometry.

Replacing $SnCl_4$ with $BuSnCl_3$ decreases the rate of both transmetalation and isomerization.[54] In the case of allenylstannane (*S*)-**70.1**, the transformation to propargylchlorostannane (*R*)-**71.1** can be observed in the ^1H NMR spectrum. Conversion to (*R*)-**71.1** at



(70)

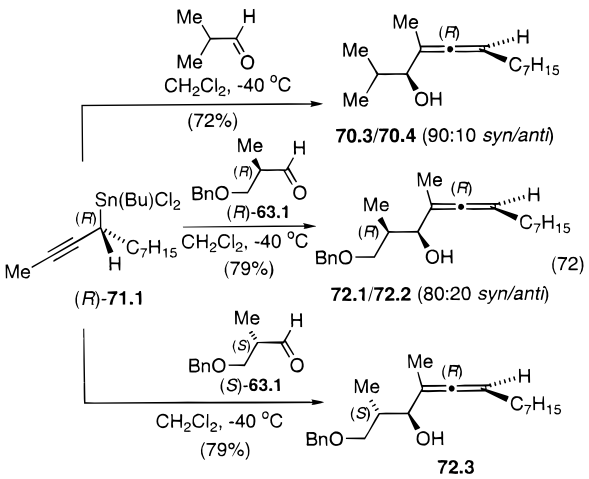
−40 °C is virtually instantaneous but the subsequent isomerization to allenylstannane requires several hours at room temperature.



(71)

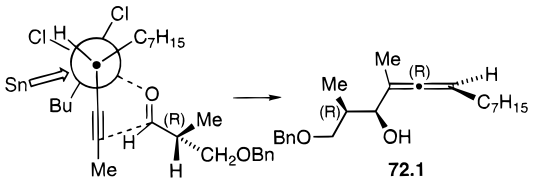
B. Additions to Aldehydes

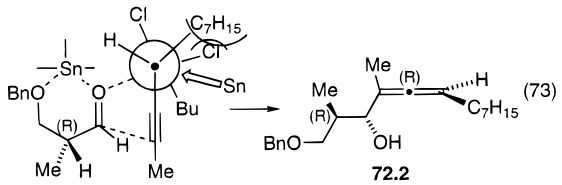
Propargylic stannane (*R*)-**71.1** adds to isobutyraldehyde, and aldehydes (*R*)- and (*S*)-**63.1**, to yield the allenylcarbinols **70.3/70.4**, **72.1/72.2**, and **72.3**. The high diastereoselectivity of these additions is somewhat surprising considering the arrangement of substituents on the forming C−C bond (see **68.5**, for example). Conceivably, differing steric interactions between the propargylic substituents (C_7H_{15} and H) with the Sn substituents (Cl and Bu) gives rise to energy differences in the diastereomeric transition states leading to *syn* and *anti* adducts [53]—favoring the former (see eq 73).



(72)

The matching/mismatching characteristics of stannane (*R*)-**71.1** with the (*S*)- and (*R*)-aldehydes **63.1** can be reconciled by this transition-state analysis and a consideration of aldehyde facial preferences under chelation or Felkin−Ahn control. In the matched pairing leading to adduct **72.3**, the diastereomerically favored stannane arrangement directs approach to the less hindered face of the chelated aldehyde (*S*)-**63.1** along the Dunitz−Bergi attack angle, as depicted in **73.3**. The major adduct **72.1** of the mismatched pairing arises from the diastereomerically favored stannane arrangement which approaches the aldehyde from the less hindered face according to Felkin−Ahn transition state preferences, as in **73.1**. In the arrangement **73.2** leading to the minor adduct **72.2**, the stannane adopts a sterically disfavored conformation and approaches the chelated aldehyde from the less hindered face.





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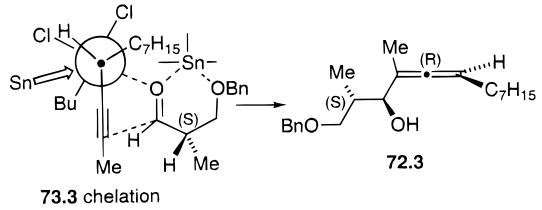
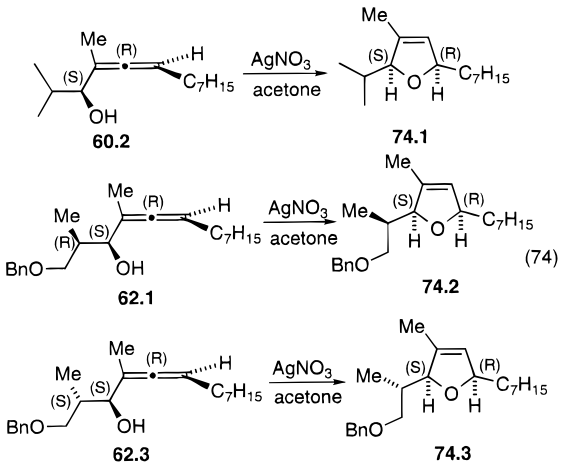


The aforementioned allenylcarbinols undergo stereospecific cyclization to 2,5-dihydrofurans **74.1**−**74.3** in the presence of catalytic $AgNO_3$. Such compounds are potential intermediates for the synthesis of polyether antibiotics.[55]

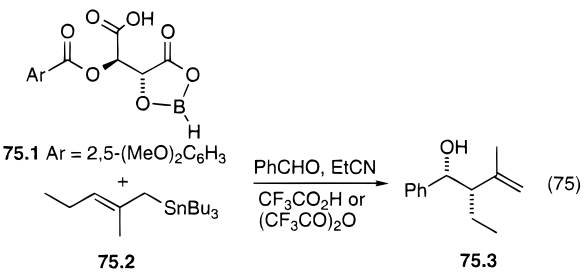


(74)

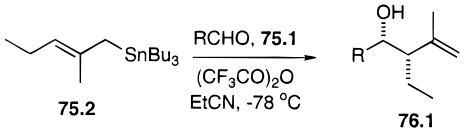
VIII. Future Directions

A. Chiral Catalysis

The use of chiral Lewis acids to promote or catalyze S_E' additions of achiral allylic stannanes to aldehydes has only recently been examined. We found that stannane **75.2** afforded adduct **75.3** of 70−80% ee with from 85:15 to 93:7 *syn*/*anti* diastereoselectivity upon treatment with benzaldehyde in the presence of 0.2−1.0 equivalents of Yamamoto's acyloxyborane catalyst **75.1**.[56,57] The reaction proceeded in near quantitative yield when $(CF_3CO_2)_2O$ was added to assist in regeneration of the catalyst. The addition was also accelerated by CF_3CO_2H.



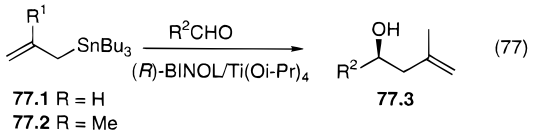
Significantly, this reaction could be extended to aliphatic aldehydes as illustrated in eq 76.



R	yield,%	syn:anti	ee, %(syn)
i-Pr	44	94:6	85
n-Pr	61	97:3	81
(*E*)-MeCH=CMe	70	94:6	86
(*E*)-MeCH=CH	85	92:8	95
Bu−C≡C	92	71:29	70

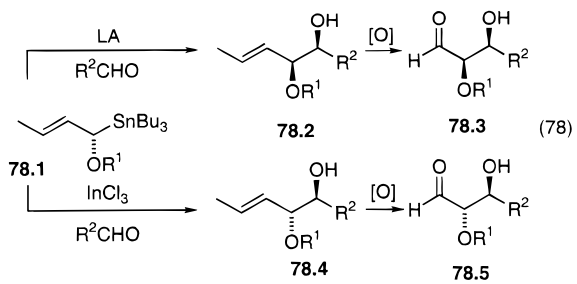
(76)

More recently Keck has found that additions of allyl tributyltin to various aldehydes can be effected by a catalyst prepared from 2,2′-binaphthol and Ti(O-*i*-Pr)$_4$.[58] Results to date have been quite promising with the allyl and methallyl reagents. At present it is not known if such catalysts can be employed with oxygenated or more highly substituted crotylstannanes. However, efforts in that direction are clearly warranted.

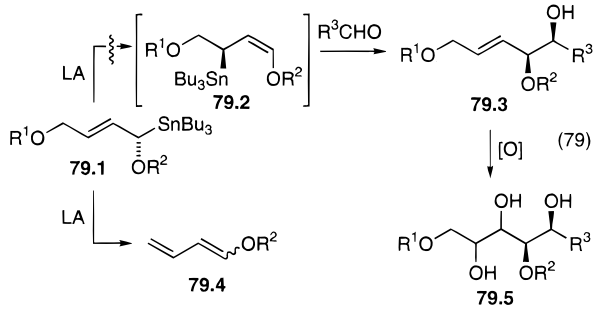


B. γ-Functionalized α-Alkoxy Allylic Stannanes

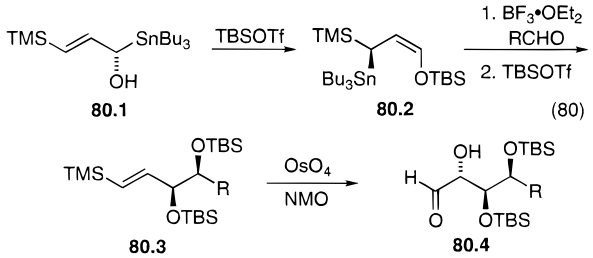
Our current strategy for carbohydrate homologation involves the *in situ* isomerization of a nonracemic α-alkoxy or silyloxy crotylstannane **78.1** to the γ-isomer followed by BF_3- or $MgBr_2$-promoted addition to an appropriate aldehyde. This sequence leads to the *syn* adducts **78.2**. The *anti* adducts **78.4** are prepared by *in situ* transmetalation of stannane **78.1** with $InCl_3$ in the presence of the aldehyde. Completion of the sequence involves oxidative cleavage of the double bond to the aldehydes **78.3** or **78.5**.



A potentially more efficient homologation sequence would start with a δ-oxygenated α-alkoxy or α-silyloxy crotylstannane **79.1** which by the aforementioned protocols would lead to the γ-alkoxy isomer **79.2**. Addition to an appropriate aldehyde followed by hydroxylation would afford the carbohydrate homologue **79.5**. This appealing variant of the chain-extension strategy has thus far proven elusive because all oxygenated stannanes of the type **79.1** which have been examined undergo competing elimination to the dienyl ethers **79.4** in the presence of Lewis acids such as $BF_3{\cdot}OEt_2$ that can promote additions to aldehydes.



We have recently found that the [γ-(trimethylsilyl)α-hydroxyallyl]stannane **80.1** can be converted to the γ-silyloxy isomer **80.2**.[59] Addition to aldehydes in the presence of $BF_3{\cdot}OEt_2$ proceeds efficiently to afford the *syn* adducts. The bis-TBS derivatives **80.3** can be hydroxylated with excellent diasterocontrol to yield the α-hydroxy aldehydes **80.4** directly. The scope of this efficient three-carbon homologation is currently under investigation.



IX. Conclusions

Enantioenriched allylic and allenic stannanes serve not only as versatile reagents for the synthesis of important classes of natural products, but also as useful probes of mechanistic details with regard to S_E' additions and transmetalations of organometallic compounds in general. The principles established with these stable and readily purifiable reagents should be generally applicable to other S_E' additions as well.

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