CHIRAL STANNANES FOR ASYMMETRIC SYNTHESIS

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Abstract Nonracemic α - and γ -alkoxy and silyloxy allylic stannanes are easily prepared through reduction of acyl stannanes with chiral hydrides such as BINAL-H or ChiralD followed by etherification of the hydroxy stannane products. The α -isomers add to aldehydes to afford mainly syn adducts which can be converted to γ -lactones upon hydrolysis and oxidation. This reaction can be used to prepare cyclic adducts which serve as useful intermediates for the synthesis of cembrane natural products. With α -chiral aldehydes, matched/mismatched pairing is observed. The stereochemical outcome is consistent with an acyclic Felkin-Ahn transition state. γ -Alkoxy stannanes show analogous reactivity. Additions to aldehydes lead to syn 1,2-diol derivatives. Matched/mismatched pairings are observed with α -chiral aldehydes. The reaction is particularly useful as a method for carbohydrate chain extension.

Introduction

Allylmetal reagents have assumed an important role in modern organic synthesis.¹ Of particular interest are α,γ -disubstituted reagents which add to carbonyl components to afford homoallylic alcohols (eq 1). Such reactions can lead to mainly syn or anti products depending

upon reaction conditions and the nature of M. Reagents in which M = SnBu_3 or SnMe_3 , in contrast to those where M = e.g. MgBr , TiCl_3 , CrX_3 , SnX_3 and the like, are relatively stable and can be isolated, purified, and stored.² One potential complication is the facile 1,3-isomerization of the foregoing reagents under reaction conditions conducive to addition.³ Thus, both stereoisomers and regioisomers can be formed as products. In the case of R_3Sn reagents, additions promoted by Lewis acids favor the syn adducts, regardless of double bond geometry, in

keeping with an acyclic transition state as first proposed by Yamamoto (eq 2).⁴ An additional complicating factor is the possible formation of (E) and (Z) double bond isomers.

Allylic stannanes in which one of the substituents (R^1 , R^2) is alkoxy are of special interest. The α -alkoxy isomers are readily prepared by addition of Bu_3SnLi (or Me_3SnLi) to an enal followed by treatment with a reactive alkylating agent (eq 3).^{5,6} Attempts to alkylate the

hydroxy stannane with less reactive alkylating agents (CH_3I , CH_3OTf , $\text{CH}_2=\text{CHCH}_2\text{I}$) requiring strong base (NaH , KHMDs , BuLi) leads to recovered enal through retrostannation. The intermediate lithio alkoxide adduct can be converted *in situ* to an α,β -unsaturated acylstannane upon treatment with ADD or DIAD.⁶ Reduction with a chiral reducing agent, then alcohol protection, affords nonracemic α -alkoxy allylic stannanes (eq 4). The use of Noyori's (*R*)-BINAL-

a) (*R*)-BINAL-H; $i\text{-Pr}_2\text{NEt}$, R^2X ; b) Chirald-LAH ($\rightarrow \sim 70\%$ ee) or (*S*)-BINAL-H ($\rightarrow \sim 95\%$ ee); $i\text{-Pr}_2\text{NEt}$, R^2X .

H reagent leads to (*S*) alkoxy stannanes of $>95\%$ ee.⁷ The less expensive Chirald-LAH reagent of Mosher⁸ affords the (*R*)-enantiomers of *ca* 70% ee whereas (*S*)-BINAL-H, as expected, gives products of $>95\%$ ee.

Additions of the nonracemic α -alkoxy allylic stannanes to aldehydes is stereospecific and generally quite stereoselective as illustrated in Table 1.⁶ Accordingly, the (*S*)-stannanes afford

Table 1. Addition of α -Alkoxy Allylstannanes to Representative Achiral Aldehydes

$\text{Bu-CH=CH-CH(OR}^2\text{)(S)SnBu}_3$				
$\text{RCHO, CH}_2\text{Cl}_2, \text{BF}_3\text{OEt}_2, -78^\circ\text{C}$				
$\text{R-CH(OH)-CH(Bu)-CH=CH-OBOM}$	$\text{R-CH(OH)-CH(S)-CH=CH-OBOM}$	$\text{R-CH(OH)-CH(R)-CH=CH-OBOM}$	$\text{R-CH(OH)-CH(S)-CH=CH-OBOM}$	
syn E	syn Z	anti E	anti Z	
R	yield, %	syn E	syn Z	syn:anti
$n\text{-C}_6\text{H}_{13}$	80	70	27	97:3
(<i>E</i>)- $\text{C}_4\text{H}_9\text{CH=CH}$	72	80	17	97:3
$\text{C}_4\text{H}_9\text{C}\equiv\text{C}$	88	51	25	76:24

products in which the allylic center is (*R*) in the (*E*) and (*S*) in the (*Z*) product. The syn diastereomers are highly favored, though less so with alkynyl aldehydes, presumably for steric reasons. The major products of these additions are derived from transition states in which the alkyl groups (*R*¹ and *R*²) assume a preferred anti arrangement and the breaking C-Sn bond aligns anti periplanar to the forming C-C bond (Figure 1).

Figure 1. Transition states for S_E' additions of α -alkoxy allylic stannanes

The reaction can be employed intramolecularly for the formation of macrocyclic alcohols. This methodology is well suited to the synthesis of cembrane lactones (eq 5).⁹

Macrocyclizations are also efficiently achieved with allenylstannanes as illustrated in eq 6.¹⁰ The homopropargylic alcohol products are readily converted to 2,5-furanocycles upon oxidation and isomerization.¹¹

In the absence of a reactive aldehyde, α -alkoxy allylic stannanes undergo stereospecific anti 1,3-isomerization with Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ (eq 7).⁶ The reaction affords (*Z*)- γ -

Table 2. Addition of (E)- and (Z)- γ -Alkoxy Allylstannanes to Aldehydes

R	yield, %	syn:anti from (E)-stannane (Z)-stannane	
n-C ₆ H ₁₃	89	>99:1	97:3
(E)-C ₄ H ₉ CH=CH	84	>99:1	>99:1
C ₄ H ₉ C≡C	84	>99:1	93:7
c-C ₆ H ₁₁	79	>99:1	94:6

As a measure of relative reactivity, pairs of allylic stannanes were allowed to react with limited cyclohexenecarbaldehyde in the presence of BF₃·OEt₂ under controlled conditions (stannane 1: stannane 2: aldehyde: BF₃·OEt₂ = 1:1:1:1). Product ratios and, where possible, recovered stannane, were measured by GC analysis and/or ¹H NMR integration. The following order was found (Fig 3):

Figure 3. Relative reactivity of allylic stannanes toward c-C₆H₁₁CHO

Thus, alkoxy and, to a lesser extent, alkyl substitution tends to lower the reactivity of the allylic stannane. However, the effect is modest, at best.

Results and Discussion

α -Alkoxy allylic stannanes show double diastereoselection in additions to α -chiral aldehydes as exemplified in eq 10.^{14,15} The observed selectivity is understandable from the Felkin-Ahn and Yamamoto transition state models for the addition. In mismatched additions, adducts resulting from the isomerized γ -alkoxy allylic stannanes are often isolated, in keeping with the lesser reactivity of the aldehydes towards the α -isomers. An extreme case in point is shown in eq 11 wherein the mono protected 1,2-diol is the exclusive product from an attempted intramolecular α -alkoxy allylic stannane cyclization (eq 11).¹⁶

The intermolecular addition has been used to synthesize macrolide precursors, as illustrated in eq 12.¹⁵ In this case, a single adduct was isolated, indicative of highly favorable matching of stannane and aldehyde.

The addition of γ -alkoxy allylic stannanes to α -alkoxy aldehydes leads to monoprotected syn 1,2-diols with high stereoselectivity.¹⁴ The absolute configuration of these products is reagent dependent. The acetogenins (-) and (+)-muricatacin proved suitable targets for this methodology (eq 13).¹⁷

The diene diol derivatives obtained from additions of γ -silyloxy allylic stannanes to enals can be further transformed through hydroxylation of the double bonds to ω -deoxy sugar derivatives. The *bis*-TBS derivatives show high anti selectivity in these conversions (eq 14).

Addition to suitably protected carbohydrates and other α -alkoxy aldehydes provides an alternative method for carbohydrate elaboration as illustrated in eq 15.¹⁴ With these systems, MgBr_2 can be used as the Lewis acid. The additions take place through a chelated

aldehyde and provide for pairing of aldehyde and stannane component complementary to that of $\text{BF}_3 \cdot \text{OEt}_2$ (eq 16).

It is also possible to access higher carbohydrates through chain extension of readily available lower homologues, as illustrated in eq 17.

The MgBr_2 promoted addition has been used in an efficient synthesis of bengamide E (eq 18).¹⁸

Conclusions: The foregoing examples illustrate the potential of nonracemic α and γ -alkoxy allylic stannanes in synthesis. These reagents are particularly effective in macrocyclizations and acyclic chain elongation. Product stereochemistry can be predicted with a high degree of certainty when the stannane configuration is known. With α -alkoxy aldehyde substrates, complementary stereochemical results can be realized through proper choice of Lewis acid. MgBr_2 leads to syn, syn adducts through a chelation controlled transition state whereas BF_3 affords syn, anti products by way of a Felkin-Ahn transition state. The use of γ -alkoxy allylic stannanes in these additions provides a convenient method for carbohydrate synthesis and chain elongation.

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