Effects of Olefin Geometry on the Stereochemistry of Lewis Acid Mediated Additions of Crotylstannanes to Aldehydes

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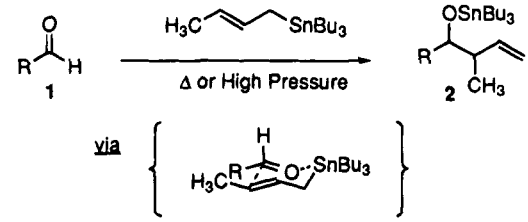
The role of the double bond geometry (*E*/*Z* stereochemistry) in reactions of crotylstannanes with aldehydes has been examined for representative "simple", α-alkoxy, and β-alkoxy aldehydes. For the reaction of crotylstannane with simple achiral aliphatic, aromatic, or α,β unsaturated aldehydes mediated by $BF_3{\cdot}Et_2O$, use of the *E* crotylstannane gives much enhanced syn selectivity over that obtained with *Z* (e.g., 43:1 vs 4:1 with benzaldehyde). A synclinal transition state in which the CH_2SnBu_3 group is *gauche* to oxygen is proposed to explain these results. For α-alkoxy aldehydes, use of the *E* stannane with $MgBr_2$ gives the highest *syn* selectivity, while the *Z* stannane gives slightly better stereoselectivity with β-alkoxy substrates. In contrast, the use of $TiCl_4$ gives *anti* products preferentially from the *E* stannane and either α or β-alkoxy substrates.

Introduction

Since the initial studies of the reactions of allylstannanes with aldehydes more than a decade ago,[1] this methodology has emerged as an important reaction type and has seen extensive development and applications in synthesis.[2] Such reactions have in common with those of other allylmetals[3] the possibility of proceeding through "closed" Zimmerman–Traxler-type transition states, in which the tin atom is transferred to oxygen concomitant with C–C bond formation (eq 1), or *via* "open" transition states not involving a cyclic array comprised by the two reactants (eq 2). For allylstannanes, reactions *via* closed transition states are implicated for purely thermal reactions,[4] at high pressure[5] and under conditions which lead to transmetalation of trialkylallylstannanes with Lewis acidic metals.[6] However, the most commonly used reaction conditions, involving the Lewis acid promoted[7] reaction of trialkylallylstannanes with aldehydes, are believed to occur *via* open transition states[8] in the absence of transmetalation processes which lead to a new allylmetal of enhanced Lewis acidity. Such is the case, for example, in the now familiar reaction of allyltri-*n*-butylstannane or crotyltri-*n*-butylstannane with aldehydes promoted by $BF_3{\cdot}Et_2O$.[1,9]



(1)

In the original report of the reaction of crotyltri-*n*-butylstannane with aldehydes,[9a] Yamamoto proposed that such reactions occur *via* an open transition state, and suggested that an antiperiplanar arrangement (180° dihedral angle) of the reacting π systems was preferred.

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(5) (a) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 489. (b) Isaacs, N. S.; Marshall, R. L.; Young, D. J. *Tetrahedron Lett.* **1992**, *33*, 3023.

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(7) Although many of these reactions have been referred to a "Lewis acid catalyzed" they are more accurately described as Lewis acid promoted reactions.[3]

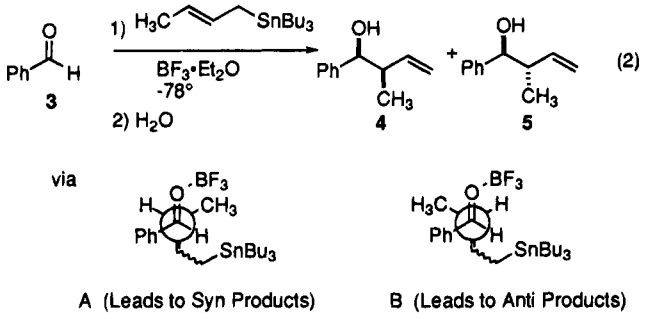
(8) Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45. Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

(9) (a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. (b) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239.

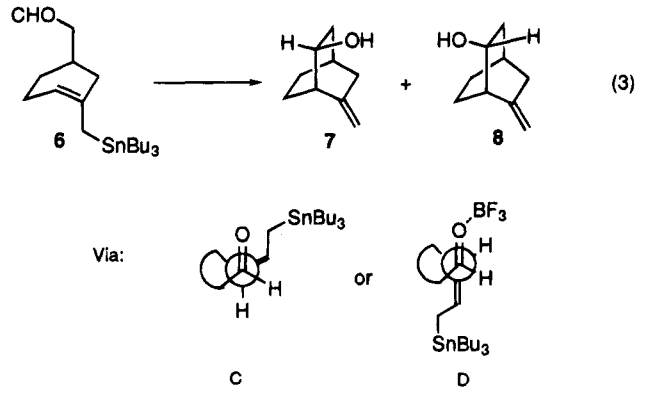
0022-3263/94/1959-7889$04.50/0

Specifically, the antiperiplanar arrangement shown as A below was suggested as preferred over the alternative antiperiplanar arrangement B to account for the observed *syn* stereoselectivity of the reaction. It was further stated that the *E/Z* olefin stereochemistry in the stannane was inconsequential since both the *E and* Z isomers led to the *syn* product preferentially. The preference for transition state A over B was attributed to steric interactions between the aldehyde R group and the methyl group of the crotylstannane, which are *anti* in A but *gauche* in B.

Denmark has investigated the intramolecular reactions of a substrate designed to have available only two transition state arrangements.[10] Thus, cyclization of **6** can lead to only two products, **7** and **8**, *via* transition states (depicted as Newman projections) C and D, respectively. Transition state D can be recognized as similar to the Yamamoto transition state B (eq 2) while C involves a synclinal arrangement (60° dihedral angle) of the reacting π systems.

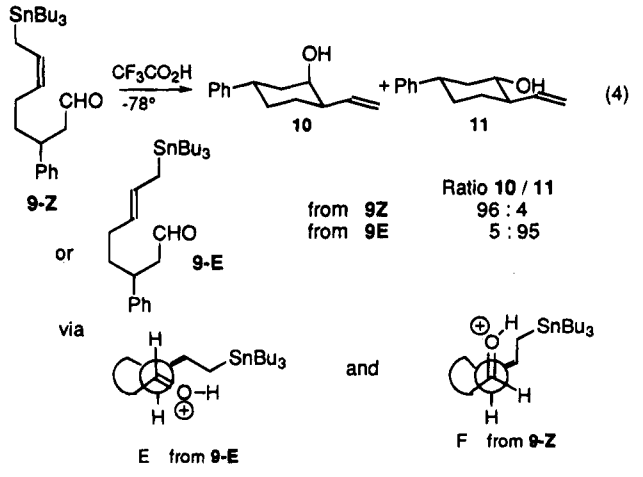


The results showed that the synclinal transition state C was, in general, strongly preferred over the antiperiplanar alternative D. Thus, **7** was produced with 92:8 diastereoselectivity using BF_3•Et_2O and 99:1 diastereoselectivity using trifluoroacetic acid. Stereoselectivity was diminished using more bulky Lewis acids such as diethylaluminum chloride.



Despite the significance and potential implications of the Denmark study, most rationalizations for the observed stereochemistry of bimolecular allylstannane aldehyde condensations have proposed antiperiplanar transition states to account for the observed reaction stereoselectivity, and most analyses dismiss any role for stannane stereochemistry in controlling reaction diastereoselectivity.[3] Thus the Yamamoto statement that both *Z* and *E* crotyltri-*n*-butylstannanes afford predominately *syn* products upon reaction with benzaldehyde in the presence of BF_3•Et_2O has been tacitly extended. Many of our own studies in this area, conducted primarily in the context of potential synthetic applications, clearly show that this is not the case. We record herein the results of studies which indicate that the diastereoselectivity observed in such reactions is a sensitive function of aldehyde structure, stannane stereochemistry, and Lewis acid utilized. Results are presented for three aldehyde structural classes of synthetic importance: "simple" aliphatic and aromatic aldehydes, α-alkoxy aliphatic aldehydes, and β-alkoxy aliphatic aldehydes. For the latter two cases, previous studies[11] have shown that high levels of diastereofacial selectivity can be realized in such additions *via* "chelation control".[12,13]

We have previously reported evidence which implies a role for stannane olefinic geometry in determining the stereoselectivity of such reactions.[6e] Since a consideration of all *possible* transition state geometries for allylstannane-aldehyde condensations (even when limited to staggered arrangements), coupled with sorting through large amounts of experimental data, can be a confusing and difficult task, it will prove useful for the present discussion to briefly consider another result which may be used to guide such considerations. We have also studied *intramolecular* versions of these reaction processes but in cyclic, structurally unencumbered systems such as **9** which permit the allylstannane *E/Z* olefin stereochemistry to be varied.[14] Although it is certainly not our intention to detail the results here, a description of just one result (the case of CF_3CO_2H as Lewis acid) is especially relevant, since it clearly reveals a very significant role for allylstannane olefin geometry which is both nonobvious and contrathermodynamic. Moreover, a consideration of this result can provide some focus for an analysis of the myriad of possibilities for the bimolecular process (eq 4).



Cyclization of **9**-*E* or **9**-*Z* using CF_3CO_2H at −78 °C leads to products **10** and **11** along with small amounts of two other diastereomers (not depicted). As shown in eq 4, the results with the *E* and *Z* stannanes are dramatically different and essentially reversed. The *E*

(10) (a) Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984. (b) Denmark, S. E.; Weber, E. J.; Wilson, T.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053. (c) In another intramolecular case, Yamamoto has suggested that reactions using Bronstead acids and conventional Lewis acids (BF_3, $TiCl_4$) proceed *via* different mechanisms: Gevargyan,V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 1313.

(11) (a) Keck. G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck. G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (c) Keck. G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

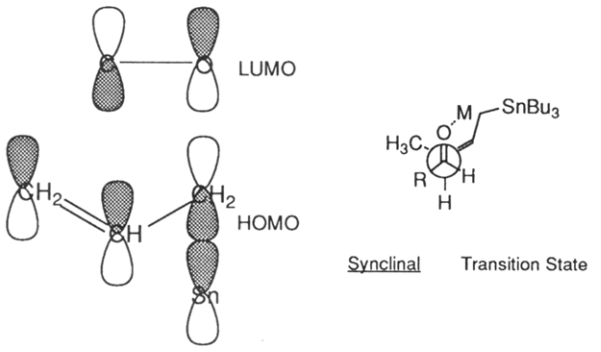
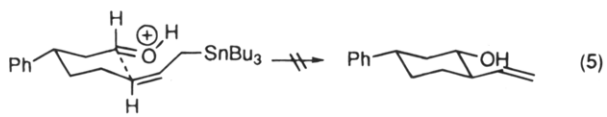


Figure 1. Proposed frontier molecular orbital interaction in the synclinal transition state.

stannane must therefore cyclize through a transition state array shown as Newman projection E, while the *Z* stannane must react as depicted in F. Notice that both E and F correspond to the same type of synclinal arrangement previously depicted as C (eq 3), in which the stannyl substituted methylene group is *syn* to the carbonyl oxygen. For convenience, we shall henceforth refer to this particular topology as *syn*-synclinal. That the stereoselectivity is not controlled either by thermodynamics (product stability) or conventional steric arguments is immediately apparent in that the *Z* stannane preferentially cyclizes to the axial hydroxy compound **10**; steric reasoning would suggest that product **11** should be preferred as the forming vinyl and hydroxyl moieties would both be oriented equatorially on the developing six-membered ring.

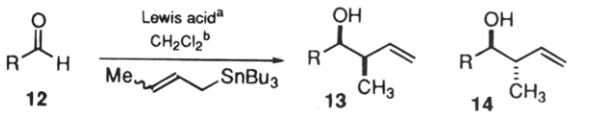


(5)

A possible explanation for these results can be advanced based upon FMO theory.[10b] The dominant molecular orbital interaction leading to bonding will of course be that between the LUMO of the aldehyde and the HOMO of the allylstannane nucleophile. In the *syn*-synclinal arrangements depicted above, there is the possibility for a secondary, stabilizing interaction which is unique to this transition state geometry, and not possible in antiperiplanar or *other synclinal* transition states.

It is important to note that non-bonded interactions between reactants may exist, and be of considerable importance, in the bimolecular reactions described herein which are not present in intramolecular substrates such as **6** and **9**. Nonetheless, the results with **6** and **9** point to an important stereoelectronic control element which should be considered in any analysis of stereoselectivity for the bimolecular reaction process.[15] With this in mind, we now consider the results for the bimolecular reactions of crotyltri-*n*-butylstannane, beginning with the results for the reaction with "simple" aliphatic and aromatic aldehydes.

Table 1. Stereoselectivity in Reactions of *E*/*Z* Crotylstannanes with Simple Aldehydes



entry	substrate	*E*:*Z* Stannane	13	14	ratio of 13:14[c]	yield[d] (%)
1	**12a**, R = *c*-C_6H_{11}	90:10	94	6	14.9:1	88
2		74:26	86	14	5.98:1	80
3		12:88	58	42	1.41:1	82
4	**12b**, R = C_6H_5	90:10	98	2	42.8:1	85
5		74:26	95	5	19.3:1	86
6		12:88	81	19	4.2:1	80
7	**12c**, R = $C_6H_5CH{=}CH$	90:10	98	2	49:1	81
8		74:26	92.4	7.6	12.2:1	86
9		12:88	81.5	18.5	4.41:1	82

[a] 1.0 equiv of $BF_3{\cdot}OEt_2$ at −78 °C. [b] Aldehydes 0.10 M in CH_2Cl_2. [c] Ratios determined by GC (response factors assumed to be equal). These values were verified by NMR. [d] These values refer to isolated yields.

Results

Diastereoselectivity of Reactions of Simple Aldehydes with *E* and *Z* Crotyltri-*n*-butylstannane. Three aldehydes—cyclohexanecarboxaldehyde, benzaldehyde, and cinnamaldehyde—were chosen as representative aliphatic, aromatic, and α,β unsaturated substrates. Crotylstannanes enriched in either the *E* or *Z* isomer were prepared by reaction of the corresponding crotyl chlorides[16] with lithiotri-*n*-butylstannane generated by deprotonation of tri-*n*-butylstannane with LDA.[17] Since in no case were the *E*/*Z* stannanes obtained completely free of their geometric isomer, and since the composition of the mixtures obtained varied somewhat from run to run, the isomeric composition of each lot of stannanes was measured by NMR and VPC analysis. Also employed were *E*/*Z* mixtures of more equal composition prepared by addition of a mixture of commercially available crotyl chloride and tri-*n*-butyltin chloride to magnesium turnings in THF.[18]

The results of these studies, shown in Table 1, clearly reveal a very significant correlation between the *E*/*Z* stereochemistry of the crotylstannane and the *level* of diastereoselectivity realized in the addition reactions. In all cases, the major diastereomer of product is *syn*; however, the observed level of diastereoselectivity is seen to be much higher for the *E* stannane than for the *Z*. Thus, in the reaction with cyclohexanecarboxaldehyde *syn* selectivity drops from *ca.* 15:1 with the *E* stannane

(12) (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org Chem.* **1986**, *51*, 5478.

(13) (a) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881. (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327. (d) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(14) Keck, G. E.; Dougherty, S. M.; Savin, K. A., submitted for publication.

(15) The preference for *syn*-synclinal transition state topologies with **6** and **9** can be ascribed to factors other than secondary orbital overlap as suggested herein. Denmark has suggested[10b] that minimization of charge separation may be important. *Syn*-synclinal arrays would also be required if transfer of tin to oxygen (as in the thermal process) were involved. A pathway involving silicon transfer has recently been described: Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077.

(16) (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359. (b) Babler, J. H. *J. Org. Chem.* **1976**, *41*, 1262.

(17) (a) Matarasso-Tchiroukhine, E.; Cadiot, P. J. *Organometallic Chem.* **1976**, *121*, 155. (b) Matarasso-Tchiroukhine, E.; Cadiot, P. *J. Organometallic Chem.* **1976**, *121*, 169.

(18) Weiner, M.; Seyferth, D. *J. Org. Chem.* **1961**, *26*, 4797.

to only 1.4:1 with the *Z*. The same effects are observed with benzaldehyde and cinnamaldehyde, but these reactions show higher diastereoselectivity. Thus, with cinnamaldehyde and the *E* stannane, a 49:1 ratio of *syn*/*anti* products is obtained, which is eroded to 4.4:1 when the *Z* stannane is used. Again, although both reactions are *syn* selective, a much higher *syn* selectivity is seen with the *E* stannane.

Discussion

Stereoselectivity of Reactions with Aldehydes 12a-c. We begin with the reasonable assumption, for which considerable evidence is available,[19] that complexation of the aldehyde with the monodentate Lewis acid BF_3 occurs preferentially *anti* to the R group of the aldehyde. Secondly, only staggered transition state arrays will be considered, although it is recognized that distortions away from ideal staggered representations may well occur. Each pair of reactants then has available six potential transition state arrays—two *syn*-synclinal (stannyl methylene *gauche* to oxygen), two antiperiplanar arrays, and two other synclinal arrays in which the stannyl methylene is oriented away from the oxygen. These pairs are shown as Z_1–Z_6 and E_1–E_6 in Figure 2, along with an A/S descriptor for the *anti* or *syn* product formed *via* that transition state. The 3,4 pair in each case corresponds to the antiperiplanar transition states suggested by Yamamoto to account for the *syn*-selectivity observed. An implicit assumption of this hypothesis, revealed by inspecting each of the 3,4 pairs, is that steric interference between R and CH_3 is expected to be more important than that between CH_3 of the stannane and BF_3 attached to the carbonyl oxygen. It is not clear why, if this is the case, that *syn*-selectivity should be higher when R is sp^2 hybridized (benzaldehyde, cinnamaldehyde) than when R is sp^3 hybridized (cyclohexanecarboxaldehyde). The *syn*-synclinal transition states (1,2 pairs) which could benefit from favorable secondary orbital overlap are distinguished in each case by potential steric interactions between BF_3 and the stannyl methylene carbon or the methyl group of the crotylstannane. It can be seen that in both possible *syn*-synclinal transition states (Z_1, Z_2) with the *Z* stannane, such a potential steric interaction between either the CH_2 or CH_3 of the stannane and BF_3 is present; in contrast, transition state E_2 for the *E* stannane suffers no such steric difficulties. With respect to the final pairs, there would seem to be little to distinguish Z_5 and Z_6, while for E_5 and E_6, E_6, leading to the *syn* product, would seem sterically less crowded than E_5, which has a BF_3–CH_3 interaction. It is extremely difficult to evaluate non-bonded interactions for the various possibilities in even a semiquantitative manner, particularly since hybridization is changing at several atoms in going from reactants to products.

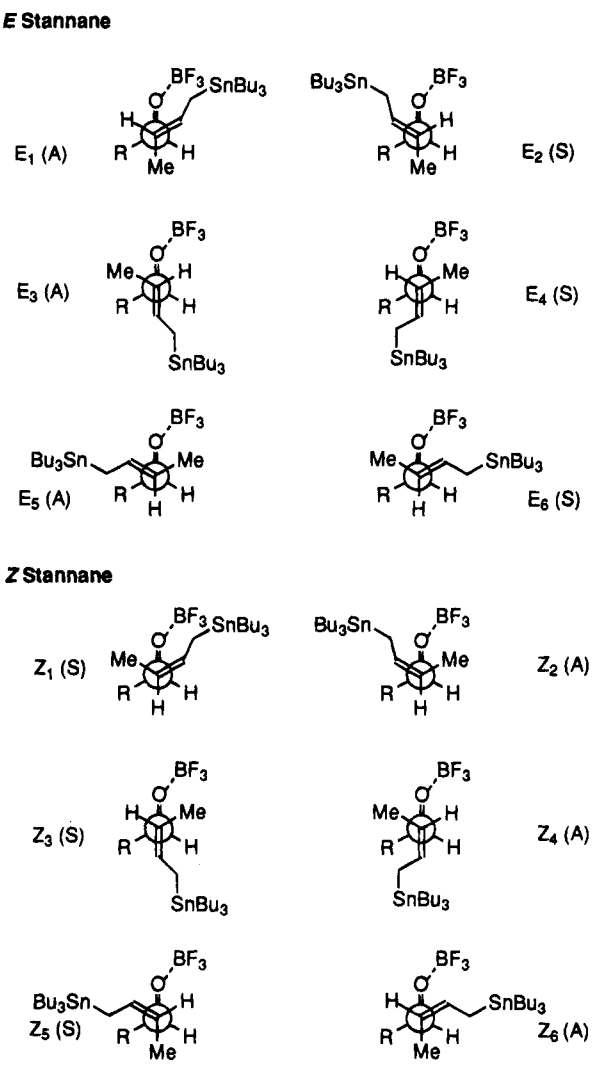


Figure 2. Staggered transition states for reaction of *E*/*Z* crotylstannanes with simple aldehydes.

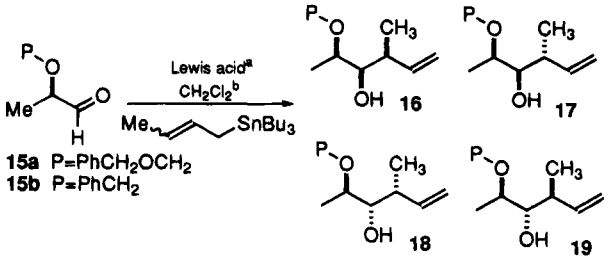
Overall, however, the S/A pairs Z_1–Z_2, Z_3–Z_4, and Z_5–Z_6 would appear to be fairly similar with respect to steric interactions, with no clear cut preference for any particular arrangement evident. Likewise, the Z_1–Z_2 pair which could potentially benefit from secondary orbital overlap are each compromised by a steric interaction which would appear similar in magnitude. Taken together, the implication is that no particular transition state of Z_1–Z_6 should be especially favored, and this is precisely what is observed. Stereoselectivity with the *Z* stannane varies from modest (4:1) to almost negligible (1.4:1) with the substrates examined.

On the other hand, for the *E* stannane, one array does stand out as particularly favorable. Representation E_2 would appear to have no serious steric problems, and also can potentially benefit from secondary orbital overlap. On this basis, high *syn* selectivity might be expected with the *E* stannane, as is observed. Of the remaining transition states, E_6, also leading to a *syn* product would appear quite unemcumbered, as does E_3, which would lead to *anti* product. Indeed, if for some reasons antiperiplanar arrangements were intrinsically preferred, one might expect this reaction to be *anti* selective, since E_2 and E_3 are virtually identical with respect to steric interactions. Taken together with the results of the intramolecular experiments with substrates **6** and **9**, the high *syn* selectivity observed with the *E* stannane is most

(19) (a) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133. (c) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370.

(20) (a) Gung has suggested, based upon stereochemical results with α-(alkoxy)allylstannanes, that aromatic aldehydes react with these reagents *via* a BF_3 complex of *E* configuration, while aliphatic aldehydes react preferentially *via* a higher energy *Z* complex. The cases studied by Jung are somewhat more complex than those described herein due to the presence of the allylic oxygen substituent α to tin and the resulting conformational effects on the nucleophilicity of the olefinic π bond in the S_E2' reaction with a BF_3-aldehyde complex. (b) Gung, B. W.; Peat, A. J.; Snook, B. M.; Smith, D. T. *Tetrahedron Lett.* **1991**, 32, 453. (c) Gung, B. W. *Tetrahedron Lett.* **1991**, *32*, 2867. (d) Gung, B. W.; Smtih, D. T.; Wolf, M. A. *Tetrahedron* **1992**, *48*, 5455.

Table 2. Stereochemical Results with α-Alkoxy Aldehydes



entry	substrate	*E*:*Z* stannane	16	17	ratio of 16:17[c]	yield[d] (%)
1	**15a**	90:10	91	9	9.55:1	88
2		76:24	88	12	7.42:1	85
3		12:88	85	15	5.71:1	80
4	**15b**	90:10	92.5	7.5	12.3:1	84
5[e]		90:10	93	7	13.6:1	89
6		76:24	91.2	8.8	10.4:1	79
7		12:88	78.6	21.4	3.7:1	82

[a] 2.0 equiv of $MgBr_2{\cdot}OEt_2$ at −23 °C. [b] Aldehydes 0.10 M in CH_2Cl_2. [c] Ratios determined by GC (response factors assumed to be equal). These results were verified by NMR. [d] These values refer to isolated yields. [e] This reaction was run on 80 times the scale of the other reactions in this table.

reasonably attributed to a preference for the sterically unencumbered *syn*-synclinal arrangement E_2 over other synclinal or antiperiplanar alternatives.

One final point related to the above should be mentioned. If non-bonded steric repulsions were the sole source of the *syn/anti* selectivity observed, the *syn/anti* ratio would be expected to decrease when the R group of the aldehyde is planar and less sterically demanding. On the other hand, if transition state stabilization due to secondary orbital overlap is in fact responsible for a preference for the *syn*-synclinal array E_2 with the *E* stannane, then this effect should depend not only upon the overlap (transition state geometry) but also in an inverse way upon the HOMO-LUMO energy gap. Thus the higher *syn*−*anti* selectivity observed with substrates **1b** and **1c** may also result, at least in part, from the lower LUMO energies in these conjugated substrates.

Diastereoselectivity in Reactions of Crotylstannanes with α-Alkoxy Aldehydes. Certain α-alkoxy aldehydes are known to undergo highly diastereoselective additions with allyl or crotyl (mixture of *Z* and *E*) stannanes when Lewis acids capable of chelate formation are utilized. Magnesium bromide was found to be particularly effective in this regard.[13a] Additions to **15a** and **15b** were carried out with the enriched *Z* and *E* crotylstannanes, and the results are summarized in Table 2.

The simple diastereoselectivity of the bond construction (*syn*−*anti* ratio) is revealed in these cases as the ratio of products **16**:**17**, since **18** and **19** were not formed in detectable amounts. With both the benzyl substrate **15b** and in the benzyloxymethyl compound **15a**, *syn* selectivity is again observed with both the *E* and *Z* stannanes. However, the differences observed here are considerably smaller than for the previous reactions with simple aldehydes. Thus, *syn* selectivity ranges from 5.7:1 to 9.6:1 with **15a**, and from 3.7:1 to 12.3:1 with **15b**; the highest *syn* selectivity is again observed with the *E* stannane.

Potential transition state topologies for these reactions are shown in Figure 3. Of these, only E_1, E_4 and Z_3, Z_6

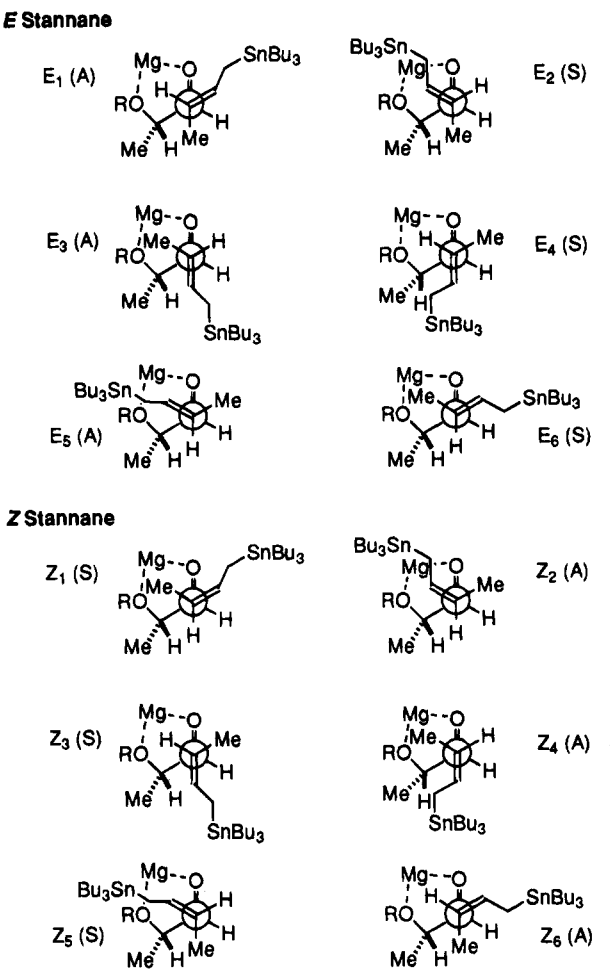


Figure 3. Staggered transition states for reaction of crotylstannane with chelated α-alkoxy aldehydes.

appear viable, as all other transition states position a non-hydrogen substituent over the interior of the five-membered chelate ring. The stereochemical results can then be interpreted to suggest that antiperiplanar transition states are preferred over their synclinal counterparts in these cases (E_4 over E_1, Z_3 over Z_6).

Although transition states such as E_2 or E_3 would appear high in energy due to simple steric considerations, additional evidence was sought to confirm that such transition states could be excluded from consideration. Thus, measurements of relative rates of reaction were made for competition experiments with allyl stannane, *E* crotylstannane, *Z* crotylstannane, and prenylstannane for reaction with the magnesium bromide complex of **15b**. Results from Mayr[21] suggest that crotylstannane as well as crotyl silane should be a priori an order of magnitude more nucleophilic than the corresponding allyl compounds, and by similar reasoning prenyl compounds even more so. One can expect that the relative rate for prenyl stannane with its gem dimethyl allyl terminus provides a rough estimate of the energetic cost of placing a methyl group endo, or inside the chelate ring in the transition state. The results are given in Table 3 and show that relative to allylstannane, both the *Z* and *E* crotylstannanes react more slowly, but the effect is not large. In

(21) (a) Hagen, G.; Mayr, H. *J. Am. Chem.* **1991**, *113*, 4954. (b) Bartl, J.; Steenken, S.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 7710. (c) Fleming, I. *Chemtracts* **1992**, *5*, 8. (d) Quintard, J.-P.; Dumartin, G.; Elissondo, B.; Rahm, A.; Pereyre, M. *Tetrahedron* **1989**, *45*, 1017. (e) Mayr, H.; Hagen, G. *J. Chem. Soc. Chem. Commun.* **1989**, 91.

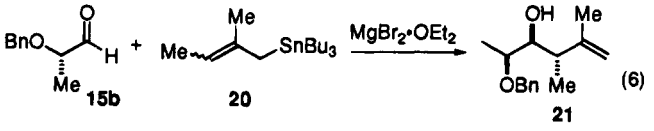
Table 3. Relative Rate Study between Allylstannanes

entry	competitor[a]	relative rate[b]
1	allylstannane	1
2	*E* crotylstannane	0.77[c]
3	*Z* crotylstannane	0.29[c]
4	prenylstannane	0.03

[a] Reactions were performed by addition of the Lewis acid ($MgBr_2$·OEt_2, 1.1 equiv) to a solution of the aldehyde (compound **7**) in CH_2Cl_2 at −23 °C. Reactions were quenched by addition of saturated aqueous $NaHCO_3$ after 6 h. [b] Ratios were determined by GC analysis of an aliquot that was taken with aqueous workup, drying over Na_2SO_4, and filtration through a short plug of silica gel. Response factors were assumed to be equal for diastereomers. [c] Relative rates are consistent with previously published results.[20]

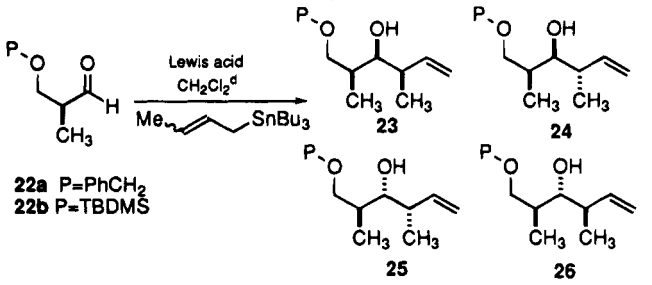
contrast, prenylstannane, which can react only by placing a non-hydrogen substituent over the interior of the chelate, reacts at only 3% of the rate for allylstannane. Hence, restricting the discussion of available transition state geometries to "hydrogen inside" arrays appears valid. It is of interest to note, however, that the *E* stannane reacts faster than the *Z* and yet displays higher *syn* stereoselectivity.

It is not at all clear why antiperiplanar transition states should be so strongly preferred over synclinal alternatives in these reactions. Modeling *via* 3-D graphics reveals no serious steric interactions in transition state E_1, for example, which would lead to the *anti* product. Indeed, evidence for the involvement of this transition state arrangement has been presented earlier. It would appear that the factors responsible may be primarily electronic in origin and are very poorly understood. Very relevant to this interpretation is the Nakai report that reaction of stannane **20**, possessing a β-methyl substituent, with aldehyde **15b** and $MgBr_2$ gives predominantly the *anti* product **21** (3:1 *anti/syn* stereoselectivity).[22a] Quite clearly, transition state E_4 is now disfavored relative to E_1, even though sterically these should be virtually identical with stannane **20**. For synthetic purposes, however, it is clear that use of *E* crotylstannane maximizes *syn/anti* selectivity in reactions with chelated α-alkoxyaldehydes.



Diastereoselectivity in Reactions with β-Alkoxyaldehydes. Similar experiments were conducted with the β-alkoxy aldehyde **22a** and the β-siloxy substrate **22b**. Once again, a significant effect of stannane geometry upon product stereochemistry was observed. For the β-siloxy aldehyde **22b** with BF_3 as the Lewis acid, the effect was essentially identical to that observed with simply aldehydes and BF_3: *syn* selectivity increased dramatically (from 3:1 to 99:1) upon changing from *Z* to *E* stannane. As previously reported,[11e,13b] facial selectivity in accord with Felkin-Anh control is very high in this system, and only products **23** and **24** were formed in detectable amounts. See Table 4.

Table 4. Stereochemical Results with β-Alkoxy Aldehydes



entry	ald	tin *E*:*Z* mix	L.A.	23	24	25	26	yield[f] (%)
1	**22a**	90:10	$TiCl_4$[a]			41	59	82
2		76:24	$TiCl_4$			57	43	76
3		12:88	$TiCl_4$			80	20	80
4	**22b**	93:7	BF_3[b]	99	1			86
5		55:45	BF_3	95	5			83
6		8:92	BF_3	75	25			88
8	**22a**	93:7	$MgBr_2$[c]	9	5	73	13	
9		56:44	$MgBr_2$	6	5	75	14	
10		2:98	$MgBr_2$	5	0	87	8	

[a] 0.95 equiv of $TiCl_4$ at −23 °C, under conditions which preclude transmetalation. [b] 2.0 equiv of BF_3·OEt_2 at −85 °C. [c] 1.0 equiv of $MgBr_2$·Et_2O at −85 °C. [d] Aldehydes 0.10 M in CH_2Cl_2. [e] Ratios determined by GC (response factors assumed to be equal). [f] These values refer to isolated yields.

With the β-benzyloxy substrate **22a**, facial selectivity can be controlled by chelation with $MgBr_2$ and $TiCl_4$ as Lewis acids.[11e] Using $MgBr_2$, best results were obtained with the *Z* stannane, but the differences in product ratios were not large. With $TiCl_4$ only the products (**25** and **26**) of chelation controlled addition were observed. Once again, however, best results were obtained with the *Z* stannane, which yielded 80% of the *syn*/chelation product **25** relative to 20% of the *anti*. With the *E* stannane, modest (1.5:1) *anti* selectivity was observed, again in a chelation controlled sense. Hence it was of interest to investigate the α-benzyloxy substrate **15b** with $TiCl_4$ as well. Again, complete "chelation control" was observed, and this reaction was also modestly (2.5:1) *anti* selective with the *E* stannane, but *syn* selective (3.2:1) with the *Z*. Thus, in both the α-alkoxy and β-alkoxy cases, use of the *E* stannane with $TiCl_4$ favors the *anti* product, while $MgBr_2$ gives the expected *syn* selectivity.

With **22b** and BF_3, the results parallel those obtained with simple aldehydes and BF_3, and require little additional comment. The β-siloxy substituent serves as a superb "Felkin–Anh directing group" in this substrate, and a dramatic improvement in *syn* stereoselectivity can be realized by using *E* crotylstannane rather than the more commonly employed *E*-*Z* mixture.

With both **22a** and **15b**, use of $TiCl_4$ results in an *anti* selective reaction. In these cases, transition state structures involving chelated intermediates similar to that shown as E_1 in Figure 3 must be involved, the only differences being the replacement of $MgBr_2$ with $TiCl_4$ and the involvement of a six-ring (rather than five) chelate with substrate **22a**. Evidently the "*syn*-synclinal" array E_1 is now slightly preferred over the antiperiplanar alternative. This result is consistent with increased Lewis acid strength (in terms of carbonyl activation) lowering the energy of the carbonyl LUMO (π*) and making secondary orbital overlap more important, but

(22) (a) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc. Chem. Commun.* **1990**, 1161. (b) Interestingly, Gung and coworkers find that for the related pair of α-alkoxy stannanes **27** and **28**, the β-methyl compound **27** gives much higher *syn* selectivity than does **28** in reaction with aldehydes promoted by BF_3·Et_2O:

Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron Lett.* **1991**, *32*, 13.

it certainly does not establish such a hypothesis as correct. At any rate, from a purely synthetic perspective, the best procedure for obtaining the *syn* product with chelation control employs $MgBr_2$ and the *Z* stannane; however, the differences in product distributions observed with the *E* and *Z* stannanes are simply too small to provide meaningful mechanistic information.

Summary and Conclusions

The results of this investigation clearly show that, contrary to popular opinion, stannane geometry can play a very significant role in determining the stereoselectivity of reactions of crotylstannanes with a variety of common aldehyde structural types. "*Syn*-synclinal" transition states appear to best explain the results for BF_3 promoted reactions. For reactions involving chelated structures, the energies of synclinal arrays and antiperiplanar arrays must be quite close, as the preference for one over the other can be changed by subtle changes in stannane substitution or changes in the Lewis acid employed. Stronger Lewis acids (e.g., $TiCl_4$ vs $MgBr_2$) seem to prefer *syn*-synclinal arrays, while weaker ones prefer antiperiplanar arrays. β substituents retard reaction and are probably never "endo" in reactions involving chelates. *E* stannanes give much higher *syn* selectivity than *Z* in BF_3 promoted reactions. Much diminished effects in terms of stereoselectivity are observed in reactions involving chelates, but $MgBr_2$ and *E* crotyl stannane prove optimal for α-alkoxy aldehydes, while for β-alkoxy aldehydes, $MgBr_2$ and the *Z* stannane give slightly better results.

Professor Fleming, in his Chemtracts analysis of the paper by Mikami, Kanamato, Loh, and Nakai,[22a] has already provided an insightful conclusion to the results obtained in this study:[23]

> We are still far from understanding the reasons for the high diastereoselectivity often shown in reactions of this type, in spite of their fundamental nature. It is likely that synclinal and antiperiplanar transition structures are inherently close in energy, and that it is indeed subtle balances among the substituents that determine which pathway is followed.

The union of two sp^2 centers to form two new sp^3 centers with attendant stereochemistry is indeed one of the most fundamental and important organic transformations. Our own view is that experiment will probably not take us much further in terms of predictive power, and we hope that this problem might attract the attention of a brave group of theoretically inclined chemists who may be able to provide a more rigorous fundamental platform for rationalization of an ever increasing body of experimental results.

Experimental Section

General Methods. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon Press. Ltd.: Oxford, 1966). Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone ketyl prior to use. Methylene chloride was distilled from CaH_2 prior to use. Titanium tetrachloride and boron trifloride etherate were purchased and distilled prior to use. (*R*)-(+)-lactic acid isobutyl ester was purchased and used without further purification. Crotylstannane was obtained as a 55:45 *E*:*Z* mixture by the method of Wiemer and Seyferth.[18] *E*-crotyl stannane (93:7, *E*:*Z*) and (90:10, *E*:*Z*) and *Z*-crotylstannane (92:8, *Z*:*E* and 88:12, *Z*:*E*) as well as the 74:26, *E*:*Z* mixture were obtained by tin anion displacement[17] of the respective crotyl chlorides.[16] Thin layer chromatography was performed on Merk Kiesegel 60 F_{254} plates eluting with the indicated solvents, visualized by a 254 nm UV lamp, and stained with an ethanolic 12-molybdophosphoric acid solution. Flash and gravity column chromatography were performed using Davisil 62 silica gel dry packed in glass columns eluting with freshly distilled EtOAc and hexane mixtures as described by Still.[24] Preparative chromatography was also carried out using a Chromatotron and glass plates coated with silica gel (P.F. 254 60) of 2 and 4 mm thickness. Gas capillary chromatography was performed with J and W 15 or 30 m capillary columns DB-5 (1 mm) and DX-4 (0.25 mm) using He as the carrier gas (80 psi) and flame ionization by hydrogen (40 psi) and air (60 psi). Proton nuclear magnetic resonance (^1H NMR) spectra were acquired at 300 MHz with chemical shifts reported in parts per million downfield from TMS (internal reference) for ^1H. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were acquired at 75 MHz with chemical shifts reported in parts per million downfield relative to the center line of the triplet of $CDCl_3$ at 77.0 ppm. NMR spectra reported are for the major diastereomers. IR spectra were obtained from a Perkin-Elmer 298 spectrophotometer and are approximate (± 5 cm^{-1}). Mass spectra were acquired on a VG Micromass 7070 double focusing high resolution mass spectrometer under the conditions listed. Exact mass were calculated with an internal standard whose mass was within $\pm 10\%$ of the sample. Analytical C and H combustion analysis were performed by Desert Analytics, Tucson, AZ, or by Atlantic Microlab, Inc., Norcross, GA. All reactions were performed in flame or oven dried flasks under a positive pressure of nitrogen unless otherwise indicated. Liquid reagents and solvents were introduced by oven dried syringes through septa sealed flasks.

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to Simple Aldehydes: Preparation of 13a,b,c.[25] Preparation of 4-Hydroxy-3-methyl-5-cyclohexylbutene (13a). To a stirring solution of cyclohexanecarboxaldehyde (**12a**, 30 mg, 29 μL, 0.283 mmol) in CH_2Cl_2 (2.9 mL) at -78 °C was added $BF_3{\cdot}OEt_2$ (44 mg, 38 μL, 0.311 mmol) dropwise. The reaction became slightly yellow and remained clear and was allowed to stir for 15 min at which time the crotylstannane (197 mg, 0.566 mmol) was added down the side of the flask to provide for ample cooling. The mixture faded slightly to afford a clear and faintly yellow solution. The reaction was judged complete after 1 h and was quenched cold with saturated aqueous $NaHCO_3$ (3 mL) as the bath was removed. After warming to room temperature the mixture was extracted with methylene chloride (3×10 mL), dried over Na_2SO_4 and filtered through a plug of Celite (0.5 cm) and silica gel (2 cm) and the solvent was evaporated under reduced pressure to give the crude product as a clear colorless liquid. The material was then analyzed by GC on a GC DX-4 15 m column 100–180 °C at 3.5 °C/min: major 13.93 min, minor 13.43 min.

1-Phenyl-3-hydroxy-4-methyl-1,5-hexadiene (13c): 300 MHz ^1H NMR ($CDCl_3$) δ 7.38–7.22 (m, 5 H), 6.56 (d, $J = 15.9$ Hz, 1 H), 6.21 (dd, $J = 15.8$, 6.60 Hz, 1 H), 5.83 (ddd, $J = 16.4$, 11.6, 7.48 Hz, 1 H), 5.16 (d, $J = 16.4$ Hz, 1 H), 5.11 (d, $J = 11.6$ Hz, 1 H), 4.18 (dd, $J = 6.30$, 5.40 Hz, 1 H), 2.45 (dq, $J = 6.0$, 0.9 Hz, 1 H), 2.02 (bs, 1 H), 1.07 (d, $J = 7.0$ Hz, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 139.8, 136.7, 131.1, 129.9, 128.5, 127.5, 126.4, 115.9, 75.7, 43.8, 14.8; IR (neat) 3065, 3015, 2974, 2932, 1721, 1599, 1495, 1453, 1219, 968, 911, 745, 698, 486, 457. HRMS calcd for ($C_{13}H_{16}O$) 188.1200, found 188.1184; GC column DX-4 15 m, 110–180 °C at 3.0 °C/min, minor 21.18 min, major 21.47 min.

(23) Fleming, I. *Chemtracts* **1991**, *4*, 21.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(25) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to α-Alkoxy Aldehydes 15a,b[26] with Magnesium Bromide Etherate: Preparation of 16 and 17.[27] Preparation of (2*R*,3*R*,4*S*)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (17). Into an oven dried 100 mL round bottom flask with stir bar was weighed aldehyde **15b** (0.450 g, 2.74 mmol) which was diluted with 30 mL of methylene chloride. After cooling to −23 °C for 10 min magnesium bromide etherate (1.141 g, 5.48 mmol) was added in one portion as a white powder. The mixture became cloudy, and then over the next 10 min the solid material partially dissolved and the solution became slightly yellow. After 15 min tributylcrotylstannane (1.42 g, 4.11 mmol) was added dropwise *via* syringe down the side of the flask to allow for ample cooling. The mixture was stirred for an additional 2 h at −23 °C before the bath was allowed to expire. After stirring for 12 h at room temperature saturated aqueous $NaHCO_3$ (30 mL) was added, and stirring was continued for 25 min. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), dried over Na_2SO_4 and filtered through a plug of Celite (1 cm) and silica gel (2 cm). The solvent was removed in vacuo and the crude product was purified *via* radial plate liquid chromatography. The material was loaded onto a 4 mm plate with hexanes (3 mL) and eluted with 150 mL of hexanes, 100 mL of 5% EtOAc/heaxanes, 100 mL of 10% EtOAc/hexanes and 150 mL of 15% EtOAc/hexanes to give the product **17** as a clear colorless liquid (0.509 g, 85%).

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to α-Alkoxy Aldehydes 15a,b with Titanium Tetrachloride. Preparation of (2*R*,3*R*,4*S*)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (16 and 17). To a stirring solution of the aldehyde **15b** (20.4 mg, 0.100 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added titanium tetrachloride (18.3 mg, 0.095 mmol) dropwise *via* syringe. The solution became yellow but remained clear and was mixed for 10 min after which time crotyl tri-*n*-butylstannane (76.5 mg, 0.220 mmol) was added dropwise *via* syringe down the side of the flask to allow for ample cooling and was washed in with CH_2Cl_2 (200 mL). The solution was stirred for 2 h at −78 °C and then quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was allowed to stir for 25 min and then extracted with CH_2Cl_2 (4 × 5 mL portions), dried over Na_2SO_4, filtered through a plug of Celite (1 cm) and silica gel (2 cm) and then the solvent was removed in vacuo to yield a crude product which was analyzed by GC on a GC DX-4 15 m column 120−180 °C at 3.5 °C/min, minor, 13.72 min, major 14.00 min.

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to α-Methyl-β-siloxy Aldehyde 22b[28,29] with Boron Trifluoride Etherate: Preparation of 23[29] and 24. To a −85 °C stirring solution of 3-[(tert-butyldimethylsilyl)oxy]-2-methylpropanal **22b** (1.08 g, 5.37 mmol) in methylene chloride (10 mL) was added boron trifluoride etherate (1.69 g, 11.20 mmol) dropwise *via* syringe. After 10 min crotyltri-*n*-butylstannane (cis:trans, 50:50, 2.03 g, 5.92 mmol) was added dropwise (neat) *via* syringe. The mixture was stirred for 30 min and then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) at −85 °C and was then allowed to warm to room temperature. The mixture was then diluted with ether (30 mL), the organic phase was washed with water and brine, dried over Na_2SO_4, and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel eluting with 200 mL of hexanes, 200 mL of 10% EtOAc/hexanes to afford a mixture of **23** and **24** (1.28 g, 92%) as a clear colorless liquid. Major diastereomer **23**: 300 MHz ^1H NMR ($CDCl_3$) δ 5.61 (ddd, J = 17.2, 10.2, 8.5 Hz, 1H), 5.08−4.94 (m, 2H), 3.77 (dd, J = 9.8, 3.5 Hz, 1H), 3.66 (dd, J = 9.8, 4.2 Hz, 1H), 3.56 (dd, J = 9.1, 2.1 Hz, 1H), 3.24 (bs, 1H), 2.30−2.27 (m, 1H), 1.79−1.75 (m, 1H), 1.10(d, J = 6.6 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 141.8, 114.7, 78.1,69.4, 42.4, 36.6, 25.9, 18.2, 17.3, 9.3, −5.5, −5.6; IR (neat) 3481, 3079, 2958, 2930, 2861, 1643, 1472, 1363, 1092, 1017; high resolution mass spectrum, m/z (relative intensity) observed 201.1304 ($M - C_4H_9^+$, 22, $C_{10}H_{21}O_2Si$), calcd 201.1304, 145 (22), 109 (87), 75 (100); GC column DX-4 30 m, 130−230 °C at 3.5 °C/min, 3.36 min.

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to α-Methyl-β-(benzyloxy) Aldehyde 22a[28,29] with Titanium Tetrachloride: Preparation of 23−26.[29] To a −85 °C stirring solution of 3-(benzyloxy)-2-methyl-propanal **22a** (32.2 mg, 0.180 mmol) in methylene chloride (5 mL) was added titanium tetrachloride (33.3 mg, 0.176 mmol, 19.3 μL) dropwise *via* syringe (a bright yellow color persisted). After 10 min, crotyltri-*n*-butylstannane (cis:trans, 50:50, 62.0 mg, 0.180 mmol, 52 μL) was added dropwise (neat) *via* syringe down the side of the flask to allow for ample cooling (the reaction became colorless). After 5 min the mixture was quenched cold by the addition of saturated aqueous $NaHCO_3$ (2 mL) at −90 °C and then allowed to warm to room temperature. The mixture was then diluted with ether (20 mL), the organic phase was washed with water and brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was chromatographed on silica gel eluting with 50 mL of hexanes, 100 mL of 5% EtOAc/hexanes, and 100 mL of 10% EtOAc/hexanes to afford 37.1 mg (88%) of a clear colorless liquid.

General Procedure for the Lewis Acid Promoted Addition of Crotylstannane to α-Methyl-β-(benzyloxy) Aldehyde 22a with Magnesium Bromide Etherate: Preparation of 23−26.[29] To a −23 °C stirring solution of 3-(benzyloxy)-2-methylpropanal **22a** (39 mg, 0.217 mmol) in methylene chloride (3 mL) was added magnesium bromide etherate (62 mg, 0.238 mmol) as a solid in one portion (the mixture became cloudy white and slightly yellow). After 10 min, crotyltri-*n*-butylstannane (cis:trans, 44:56, 82 mg, 68 μL, 0.283 mmol) was added dropwise (neat) *via* syringe down the side of the flask to allow for ample cooling. After 1 h at −23 °C the solution was allowed to warm to room temperature (ca. 2 h). After 1 h at room temperature the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and diluted with ether (15 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed on silica gel eluting with 50 mL of hexanes, 100 mL of 5% EtOAc/hexanes, 100 mL of 10% EtOAc/hexanes to afford 44.3 mg (87%) of a clear colorless liquid.

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