Stereochemical Studies on the Addition of Allylsilanes to Aldehydes. The S_E' Component

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Summary: Compounds (*l*)-**1** and (*u*)-**1** have revealed both the position of the silicon electrofuge and the relative orientation of the double bonds in the allylmetal–aldehyde addition. Cyclization was found to proceed with high selectivity via an anti S_E' pathway regardless of the proximal/distal ratio.

The allylmetal–aldehyde addition has proven to be one of the most synthetically useful methods of carbon–carbon bond formation.[1] The utility of this reaction derives from the high yield, excellent regio- and stereoselectivity, and mild conditions under which the reaction can be performed. When the allylmetal is substituted at the γ-terminus, four isomers (two enantiomeric pairs of syn and anti diastereomers) can be formed. The syn/anti selection process is determined by the preferred orientation of the reactive double bonds in the transition structure. The enantioselection process is determined by the diastereoface discrimination with chiral allylmetals.[2-4] Several hypotheses have been advanced to explain the high degree of stereocontrol observed in the allylsilane–aldehyde condensation.[1,4a-c,5,6] The two limiting hypotheses identify the torsional angle between the double bonds (synclinal (60°) and antiperiplanar (180°)) and minimization of nonbonded interactions as key features for internal diastereoselection. The external induction process is governed primarily by the relative disposition of the metal electrofuge and the aldehyde (syn or anti S_E') in the transition structure (Scheme 1). Thus, the orientation of the double bonds and the location of the metal in the transition structure uniquely define the stereochemical outcome of the reaction. In previous stereochemical studies of the allylation reaction these two features have been treated independently.[4a-c] *We describe herein results from a model which unambiguously establishes* ***both*** *the position of the silicon electrofuge* ***and*** *the relative disposition of the double bonds in the transition structure of the allylsilane aldehyde addition.*

The model system previously described by us[6] for the determination of double bond orientation was modified for this study ((*l*)-**1**, Scheme 2).[7] Inspection of molecular models reveals that the silyl aldehyde is constrained to four limiting transition structures generated either by rotation about the C(1)–C(2) bond or by rotation about the C(3′)–C(7′) bond. Reaction through the different conformations leads to the diastereomeric alcohols (*E* or *Z*)-**2a** and **2b**. The use of the deuterium label in **1** assures that there is no extraneous steric bias toward either the syn or the anti S_E' pathways.[8]

The synthesis of model system **1** is shown in Scheme 3.[9] Starting from the bicyclic ketone[10] **3**, the deuterium-labeled keto acid **5** was prepared by treatment with d_2-triethyl phosphonoacetate in an Emmons–Wadsworth reaction[11] followed by saponification of the ester **4**. Transformation of acid **5** into lactone **7** involved a decarboxylative bromination[12] followed by Baeyer–Villiger oxidation of the bromoketone **6**. The lactones (*E*)- and (*Z*)-**7** were separated by chromatography. The carbonyl group in lactone **7** was then protected as its enolate (Ph_3CLi), and the vinyl hydrogen was introduced by lithium–halogen exchange to give **8**. The position of the deuterium atom in lactone **8** was established by 1D-NOE.[13] The lactone **8** was then opened in an anti S_N2' fashion[14] with phenyldimethylsilyl cuprate[8a] to give **10** after esterification of the acid **9**. Ester **10** was finally

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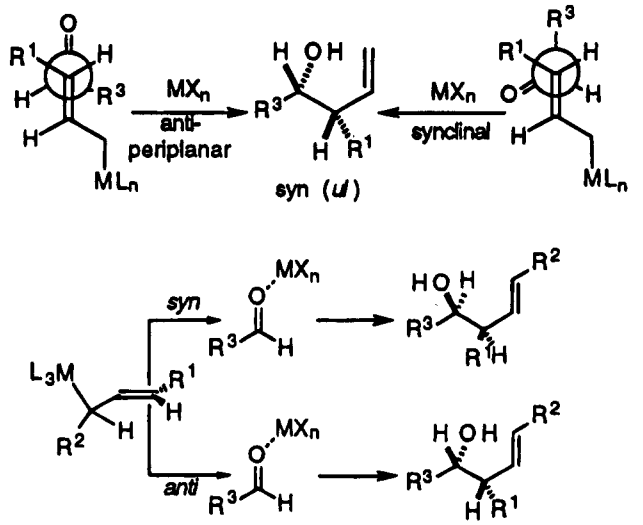
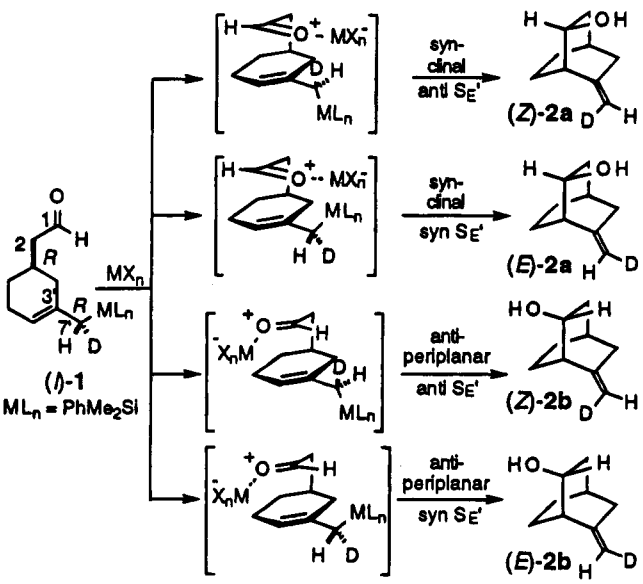
Scheme 1



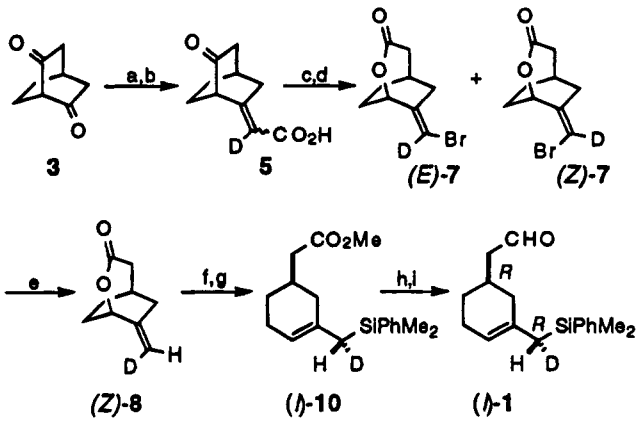
Scheme 2



transformed into aldehyde **1** by $LiAlH_4$ reduction and Collins oxidation of the alcohol **11**. Both diastereomeric silyl aldehydes (*l*)-**1** and (*u*)-**1** were synthesized with >95% deuterium incorporation from the corresponding lactones (*E*)-**5** and (*Z*)-**5**.[15]

The results from the cyclization of **1** with various Lewis acids are shown in Table 1.[16a-c] As was seen previously for the *trimethylsilyl* model,[6] the ratio of proximal to distal diastereomers displayed a Lewis acid dependence.

Scheme 3[a]



[a] Key: (a) $(EtO)_2P(O)CD_2CO_2Et$, NaH, PhH, 80 °C, 2 h, 70%; (b) KOH, EtOH, H_2O, 0 °C, 8 h, 86%; (c) NaH, Br_2, DMF, rt, 30 min, 60%; (d) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 0 °C, 90 min, 48% (*E*)-**7** and 42% (*Z*)-**7**, separate (silica gel); (e) Ph_3CH, *n*-BuLi (1 equiv), THF, −78 °C, (*E*)-**7**, 5 min then *t*-BuLi (3 equiv) 5 min, −78 °C; 70%; (f) CuI, $PhMe_2SiLi$, 0 °C, 2 h, 75%; (g) CH_2N_2, 100%; (h) $LiAlH_4$, Et_2O, 0 °C, 2 h, 79%; (i) pyridine, CrO_3, CH_2Cl_2, rt, 2 h, 75%.

The reactions strongly favor the anti S_E' pathway (selectivities >95%) regardless of the Lewis acid employed and regardless of the internal stereochemical outcome. As expected, reaction with either diastereomer ((*l*)- or (*u*)-**1**) gave identical results. The only divergence from this behavior was seen when fluoride ion was used to initiate the reaction. With fluoride, the distal product was dominant as before[6] but was formed by a combination of *both* syn and anti S_E' pathways.[16d]

On the basis of these results it is clear that *the silicon electrofuge is located away from the approaching electrophile regardless of Lewis acid or double bond orientation in the allylsilane–aldehyde addition.* The Lewis acid only influences the synclinal vs antiperiplanar orientation of double bonds, most likely due to differences in effective bulk of the various Lewis acids employed.[6]

The most intriguing results are those from the reaction promoted by fluoride. These reactions are not rigorously electrophilic substitutions but rather nucleophilic additions. Indeed, there is much speculation in the literature as to the exact nature of the reactive intermediate, i.e., a fluorosiliconate or an allyl anion.[17] Our results unambiguously rule out the intermediacy of a free allyl anion since the **2a/2b** ratio is different for the syn compared to the anti S_E' pathways.[18] That a significant fraction of the product arose from a syn S_E' process indicates little stereoelectronic preference in the anionic mode. The larger distal/proximal ratio for the syn compared to the anti mode suggests a steric contribution to the internal stereoselection and also rules out the intervention of closed transition structures.[19] We had previously suggested a Coulombic repulsion to explain the distal preference in fluoride-induced reactions.[6]

Both Fleming[8] and Kitching[20] have studied the S_E' reaction of allylic silanes with electrophiles and have

(13) At 500 MHz all of the methylidene protons were clearly resolved. 1D-NOE studies of the protio compound **8** confirmed the location of the individual methylidene protons. Irradiation of the bridgehead proton HC(1) in the protiolactone **8** resulted in a 6% NOE enhancement to the more downfield methylidene proton (this proton assigned as *Z*).

(14) The stereochemical course of this opening was established by reconversion of ester (*l*)-**10** to deuteriolactone (*Z*)-**8**. For a review of organocopper S_N2' opening of vinyl oxiranes see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

(15) The deuterium content in the model system was analyzed by mass spectroscopy of the final product **1** as well as by ^1H NMR analysis of the precursor lactone, **8**.

(16) (a) All cyclizations were proven to be under kinetic control. (b) The stereostructure of the products (*E* or *Z*)-**2a** and (*E* or *Z*)-**2b** was assigned by ^1H-NMR analysis. (c) For all reagents studied, the reactions went to completion as judged by GC analysis with an internal standard. (d) Control experiments clearly excluded the possibility that **1** was undergoing isomerization prior to closure.

(17) For a discussion of the fluoride-induced reactions of allylsilanes see: Majetich, G. In *Organic Synthesis, Theory and Applications*; Hudlicky, T., Ed.; JAI Press, Inc.: Greenwich, CT, 1989; pp 173–240.

(18) For (*l*)-**1** (**2a/2b**): anti S_E', 25/75; syn S_E', 11/89. For (*u*)-**1** (**2a/2b**): anti S_E', 20/80; syn S_E', 7/93.

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Table 1. Cyclization of Model (*l*)-1 and (*u*)-1[a]

entry	model	reagent	proximal/distal (**2a**/**2b**)[b]	(**2a**) *Z*/*E*[c]	(**2b**) *Z*/*E*[c]	proximal % anti S_E'[d]	distal % anti S_E'[d]
1	(*l*)-**1**	BF_3·OEt_2	75/25	94/6	94/6	100	100
2	(*l*)-**1**	$SnCl_4$	60/40	91/9	94/6	97	100
3	(*l*)-**1**	CF_3SO_3H[e]	95/5	93/7	94/6	99	100
4	(*l*)-**1**	$SiCl_4$	98/2	95/5		100	
5	(*l*)-**1**	*n*-$Bu_4N^+F^-$[f]	20/80	80/20	60/40	85	65
6	(*u*)-**1**	BF_3·OEt_2	73/27	7/93	6/94	97	100
7	(*u*)-**1**	$SnCl_4$	62/38	8/92	6/94	96	100
8	(*u*)-**1**	CF_3SO_3H[e]	94/6	7/93		98	
9	(*u*)-**1**	$SiCl_4$	98/2	5/95		100	
10	(*u*)-**1**	*n*-$Bu_4N^+F^-$[f]	16/84	15/85	35/65	90	70

[a] All cyclizations (in duplicate) were performed with 1.05 equiv of Lewis acid at −78 °C except where noted. [b] Ratios determined by GC analysis using cyclododecane as internal standard. Complete conversion was observed in each case. [c] Ratios were determined by ^{1}H-NMR analysis. [d] % Anti S_E' based on 94.5% d_1-content in (*l*)-**1** and (*u*)-**1**. [e] 0.95 equiv of triflic acid used. [f] Cyclization with *n*-$Bu_4N^+F^-$ performed at 70 °C.

found that the selection process can be attributed to a stereoelectronic preference for anti attack[21,22] but that stereochemical constraints imposed by substitution around silicon[8g] or by ring systems[20d] also play a role. Further, Hayashi[4a-c,23] and Wetter[24] have both studied the reactions of optically active *acyclic* allylsilanes. In the model studied by Hayashi, products from only an anti S_E' process were observed (with aldehydes as well), while Wetter saw products from both syn and anti pathways depending upon the electrophile. In these cases steric shielding and Coulombic attraction effects were invoked as modifiers of the intrinsic anti preference. We have also demonstrated a strong anti preference in the silicon-directed Nazarov cyclization.[25] Our results clearly demonstrate that the silicon group is stereoresponsive to the approach of the electrophile, independent of Lewis acid and double bond orientation. Extension of this study to the stereochemical course of allylstannane aldehyde addition is described in the following paper.[26]

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Supplementary Material Available: Full characterization of (*u*)-**1**, (*l*)-**1**, and **4**−**11** as well as the general procedure for reaction of **1** with Lewis acids (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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