

Double Stereodifferentiation in the Lewis Acid Promoted Addition of Chiral (*E*)-Crotylsilanes with (*S*)-2-(Benzyloxy)propanal. Effect of Lewis Acid on Reaction Diastereoselection

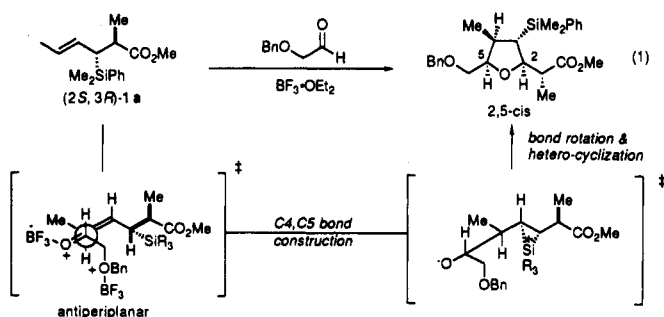
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Received October 29, 1992 (Revised Manuscript Received December 11, 1992)

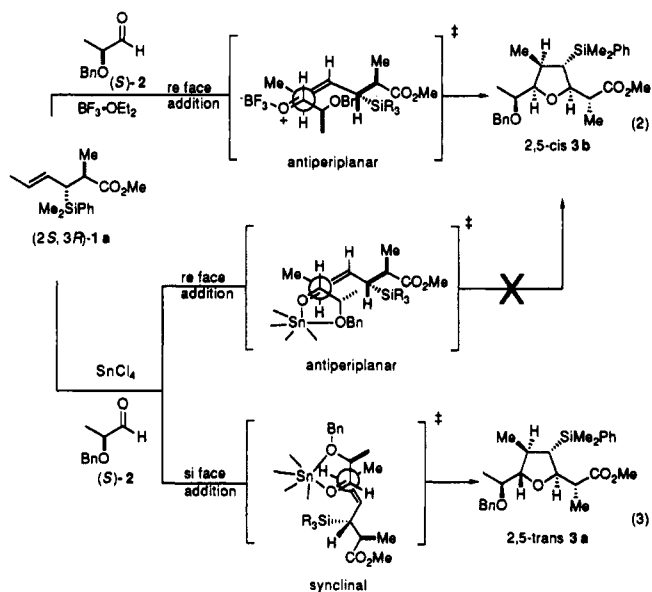
Summary: Methyl α -methyl- β -(dimethylphenylsilyl)-(*E*)-hex-4-enoates (*2S,3R*)-**1a** undergo $\text{BF}_3\cdot\text{OEt}_2$ -promoted additions with (*S*)-2-(benzyloxy)propanal (**2**) producing nearly enantiomerically pure *cis*-2,5-substituted tetrahydrofurans **3** whereas the reactions run under chelation controlled conditions employing SnCl_4 resulted in the formation of the complementary *trans*-2,5-disubstituted tetrahydrofuran. Additions to the enantiomeric silane (*2R,3S*)-**1b** utilizing $\text{BF}_3\cdot\text{OEt}_2$ or SnCl_4 afforded the *cis*-2,5-disubstituted furan stereochemistry in both cases.

The Lewis acid promoted condensation reaction of allylsilanes with aldehydes is a widely used method for the stereoselective formation of homoallylic alcohols.^{1,2} In a recent report from our laboratory we have described a highly enantioselective tetrahydrofuran synthesis based on a boron trifluoride etherate promoted addition reaction of chiral (*E*)-crotylsilanes to achiral aldehydes. That study resulted in the development of a useful strategy for the asymmetric construction of *cis*-2,5-disubstituted tetrahydrofurans and documented the participation of chiral (*E*)-crotylsilanes in a highly diastereoselective addition to heterosubstituted aldehydes initiating a silicon migration and subsequent heterocyclization.³ The reaction process is illustrated in eq 1.



In a study designed to determine the extent of double stereodifferentiation in our developing asymmetric allylsilane based bond construction methodology we examined the Lewis acid promoted reactions of the chiral (*E*)-crotylsilanes (*2S,3R*)-**1a** and (*2R,3S*)-**1b**⁴ with (*S*)-2-

(benzyloxy)propanal (**2**).⁵ The reactions result in the construction of nearly diastereomerically pure tetrahydrofurans **3** with the corresponding homoallylic alcohols **4** produced as the minor product in most cases. The formation of the *cis*-2,5- or *trans*-2,5-disubstituted tetrahydrofuran products was shown to be dependent on the type of Lewis acid and absolute stereochemistry of the silane reagent. Under $\text{BF}_3\cdot\text{OEt}_2$ catalysis (non-chelation-controlled conditions) a *cis*-2,5-disubstituted tetrahydrofuran **3b** is produced with **1a**. This stereochemical outcome is consistent with an anti- S_E pathway through an anti-periplanar arrangement of the participating π bonds. Rotation about the C1–C2 bond of the aldehyde will minimize destabilizing steric interactions between the silane and the methyl group of the aldehyde, positioning these groups in the least sterically demanding positions. The conformation of the aldehyde is consistent with stereoelectronic preferences as well, where the aldehyde is shown in a Cornforth conformation with the electronegative benzyloxy group positioned antiperiplanar to the aldehyde carbonyl (eq 2).⁶ Thus, a combination of steric and stereoelectronic factors are responsible for the acyclic diastereoselection. In contrast, the use of SnCl_4 , a Lewis acid that is capable of forming a chelate with the α -benzyloxy group of the aldehyde, results in the formation of the diastereomeric *trans*-2,5-disubstituted tetrahydrofuran **3a**, eq 3.



The results of this study concerning the double asymmetric induction in the Lewis Acid catalyzed reactions with **2** are summarized in Table I. A trend of diastere-

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Table I. Double Asymmetric Induction in Additions of Chiral (*E*)-Crotylsilanes to (*S*)-2-(Benzyloxy)propanal

entry	aldehyde ^a	<i>(E)</i> -crotylsilane ^b	reaction condn ^c LA/temp/time	reaction products, ^d (% yield) ^e		ratio anti/syn C4/C5 (furan)/ ^f
				tetrahydrofuran	homoallylic alcohol	
1.			SnCl ₄ -35 °C/12h			>40:1
2.	2	1a	BF ₃ ·OEt ₂ -25 °C/12h			40:1
3.	2		BF ₃ ·OEt ₂ -25 °C/12h			>40:1
4.	2	1b	SnCl ₄ -35 °C/12h			>40:1
5.	2	1b	AlCl ₃ -30 °C/12h			>40:1
6.	2	1a	AlCl ₃ -30 °C/12h			>40:1
7.	2	1a	TiCl ₄ -65 °C/12h			g
8.	2	1b	TiCl ₄ -65 °C/12h			g

^a (*S*)-2-(Benzyloxy)propanal (98% ee) was prepared according to the procedure of Mislow (see ref 5). ^b The (*E*)-crotylsilanes were prepared by electrophilic addition to chiral β -(dimethylphenylsilyl) ester enolates (see ref 4). ^c All reactions were carried out in CH₂Cl₂ (0.5 M) and were started at -78 °C before warming to the indicated temperature. 1.5 equiv of Lewis acid and 1.3 equiv of aldehyde were used except for cases employing BF₃·OEt₂ (2.5 equiv) and AlCl₃ (2.0 equiv). ^d The absolute stereochemistry is assigned based on an anti S_E addition and the relative stereochemistry assigned using 2D NOE experiments and coupling constant analysis of six-membered acetonides (see supplementary material). ^e All yields are based on pure materials isolated by chromatography (SiO₂). ^f Ratios of products were determined by ¹H NMR (400 MHz) operating at S/N of >200:1 and capillary GLC. ^g Only product isolated after chromatography on SiO₂.

oselectivity with allylsilanes has emerged which is consistent with a stereospecific anti S_E pathway as originally documented by Fleming^{7a,b} and Kumada^{7c,d} and which has been confirmed in recent reports by Nakai⁸ and

Marshall⁹ as well as from our laboratory.¹⁰ Entries 1 and 2 illustrate the effect of Lewis acid on reaction diastereoselection. For instance, the SnCl₄-catalyzed reaction with silane 1a afforded the trans-2,5-disubstituted tetrahydrofuran 3a in good yield.¹¹ In contrast, the BF₃·OEt₂-promoted reaction produced the complementary cis-2,5-disubstituted tetrahydrofurans 3b.¹² The corresponding homoallylic alcohols 4a and 4b were also produced in small

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(11) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ¹H NMR, ¹³C NMR, IR, MS, and HRMS spectral data.

(12) The stereochemistry of the derived tetrahydrofuran products was assigned as cis or trans based on 2D NOE experiments and multiple difference NOE experiments.

amounts (less than 5%) presumably through an anti S_E pathway. After confirming the reversal of diastereoselection in the formation of the trans-substituted furan, we surveyed a limited number of Lewis acids likely to chelate with the aldehyde to examine the scope of this asymmetric carbon-carbon bond-forming process.

In general, the cases where Lewis acids that chelate were used, the formation of cis- or trans-2,5-substituted tetrahydrofurans were shown to be dependent on the pairing of the absolute stereochemistry of the crotylsilane and the aldehyde. The SnCl_4 -promoted addition of (2*S*,3*R*)-1a with 2 leading to furan 3b can be rationalized as proceeding through an antiperiplanar transition state (DMPS group is on the opposite face and perpendicular to the developing β -silyl carbocation) that encounters a destabilizing steric interaction generated by the methyl substituent of the aldehyde penetrating the plane occupied by the crotylsilane. This destabilizing interaction may be avoided if the condensation proceeds through a synclinal transition state, with addition to the *si*-face of the aldehyde producing the complementary trans-2,5-disubstituted furan (eq 3). To underscore the subtle nature of these double asymmetric additions, the aldehyde π -face selection with the enantiomeric silane reagent (2*R*,3*S*)-1b is independent of the type of Lewis acid employed, as both $\text{BF}_3\cdot\text{OEt}_2$ and SnCl_4 produce the cis-2,5-disubstituted tetrahydrofuran 3c. This too is best explained by an antiperiplanar attack which minimizes any developing nonbonded steric interactions. It is rationalized in the nonchelating case by C1-C2 aldehyde bond rotation and in the chelation case by the position of the C2 methyl of the aldehyde away from the approaching silyl group providing no steric penalty for antiperiplanar attack. The SnCl_4 -promoted additions with silane 1b produced a 1:1 mixture of the cis-2,5-disubstituted tetrahydrofuran 3c and syn-homoallylic alcohol 4e (entry 4). When AlCl_3 was used to catalyze the reaction a similar stereochemical pattern was observed producing the homoallylic alcohol 4c as a single diastereomer, indicating that the asymmetric C-C bond construction may occur through an antiperiplanar transition state (entry 5). In contrast, entry 6 shows that the trans-2,5-disubstituted tetrahydrofuran 3a was produced as a single diastereomer from silane 1a. This result runs against conventional wisdom as AlCl_3 is normally thought of as a monodentate Lewis acid, and

reaction products attributed to a chelation-controlled addition have not been recognized or reported. In the presence of 2.0 equiv of AlCl_3 , the reaction diastereoselectivity is high, affording the trans tetrahydrofuran product presumably through a chelated aldehyde.¹³ The resultant AlCl_2 -aldehyde complex might be expected to be produced through metathesis of AlCl_3 to a AlCl_2 - AlCl_4 complex prior to chelation with the aldehyde.¹⁴ Interestingly, TiCl_4 yields exclusively syn and anti homoallylic alcohols 4a and 4c, respectively, which is in accordance with diastereoface selectivity of similar Lewis Acids capable of chelation. The low yields associated with these cases (entries 7 and 8) are the result of competing protodesilylation pathways of the silane reagents.¹⁵ A pattern has emerged in the data presented in Table I which indicates an increased propensity of homoallylic alcohol formation of allylsilane-aldehyde condensations catalyzed by AlCl_3 and SnCl_4 proceeding via an antiperiplanar transition state (*re*-face addition), while the synclinal transition state (*si* face addition) leads predominantly to tetrahydrofuran construction. A possible explanation for these tendencies would be the proximity of the derived alkoxide to the emerging carbocation on the crotylsilane in the synclinal arrangement, facilitating 1,2-silyl migration and subsequent cyclization.

In conclusion, the diastereoface selection in the Lewis acid promoted additions of (*S*)-2-(benzyloxy)propanal with chiral (*E*)-crotylsilanes may be reversed depending on the nature of the Lewis acid and the pairing of the two chiral reaction components. It appears that the double stereodifferentiating process is manifested in the fractionation between the anti addition pathway followed by 1,2-silyl migration and cyclization (tetrahydrofuran construction) and the corresponding homoallylic alcohols 4 (anti- S_E addition). The levels of diastereoselectivity do not appear to be altered to any appreciable extent between the enantiomeric silanes 1a and 1b. The present study extends the synthetic utility of our developing allylsilane bond construction methodology as applied to the construction of functionalized tetrahydrofurans with complementary trans-2,5 stereochemistry and the corresponding homoallylic alcohols. Further development and application of these chiral silane reagents in the synthesis of polypropionate natural products is underway in our laboratory and will be reported in due course.

Acknowledgment. This work has been financially supported by the National Institutes of Health (CA47249), and we also acknowledge the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research (ACS-PRF No. 25590-AC1). We are grateful to Mr. Michael Creech for performing mass spectral measurements.

Supplementary Material Available: General experimental procedures for the Lewis acid promoted addition reactions, relative stereochemical assignments, as well as spectral data for all reaction products (4 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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(15) The intervening protodesilylation pathway is evidenced by the formation of (2*R*)- and (2*S*)-methyl 2-methylhex-3-enoate in the crude reaction mixture.

(13) A similar argument has been used to explain enhanced dienophile reactivity and reaction diastereoselection in asymmetric Diels-Alder reactions of chiral α,β -unsaturated *N*-acyloxazolidinones catalyzed by diethylaluminum chloride (cf. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* 1988, 110, 1238-1256). A plausible transition state involving the methathesized AlCl_2 - AlCl_4 complex is illustrated with the chelated aldehyde in the equation below.

