Acyclic Diastereoselectivity in the Lewis Acid Promoted Additions of Chiral, β-Methyl-Substituted (*E*)-Crotylsilanes with Achiral Aldehydes

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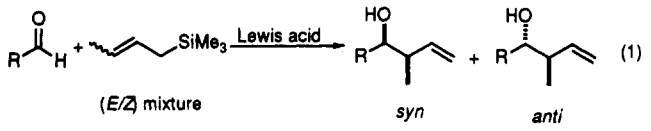
Received September 14, 1992

Summary: The diastereoselection in the Lewis acid promoted addition of chiral, β-methyl-substituted (*E*)-crotylsilanes (*S*)-**1a** and (*R*)-**1b** with α-(benzyloxy)acetaldehyde (**2**) is reversed from syn to anti by changing the Lewis acid from $BF_3{\cdot}OEt_2$ (non-chelation-controlled conditions) to $MgBr_2{\cdot}OEt_2$, a Lewis acid that is capable of forming a strong chelate with the α-(benzyloxy) group of the aldehyde. The reactions result in the formation of the syn homoallylic alcohols **3** or the complementary anti products **4**.

Many laboratories have focused on the development of chiral allyl- and crotylmetal reagents as propionate enolate equivalents for enantioselective carbon–carbon bond formation in the aldol-like construction of homoallylic alcohols.[1] The allylsilane–aldehyde addition has proven to be a synthetically useful method for such a carbon–carbon bond construction, its utility emerged as a consequence of the high yields and the excellent regio- and stereoselectivity that is reached, as well as the mild reaction conditions under which it can be performed. When the allylsilane is substituted at the γ-position, two enantiomeric pairs of syn/anti diastereomers are produced favoring the formation of the syn stereoisomer (eq 1).[2] The syn/anti selectivity is determined by the arrangement of participating π-bonds in the transition states.



(1)

Despite the many advances in this field, only a few reports have addressed the issue of acyclic diastereoface selectivity (enantioselection) in addition reactions to C=X π bonds.[1,3] Therefore, research efforts that provide new methods for the production of such reagents and make possible the development of new asymmetric transformations would be an important contribution to the field of acyclic diastereoselection.[4]

In recent reports from our laboratory we have described the use of functionalized (*E*)-crotylsilanes as carbon nucleophiles in highly diastereo- and enantioselective addition reactions to acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of syn-disposed homoallylic ethers,[5] tetrahydrofurans,[6] and γ-alkoxy-α-amino acid synthons.[7] Elucidation of reaction conditions and mechanism by which the illustrated (*E*)-crotylsilanes undergo additions to C=X π bonds, followed by either elimination of silicon (acyclic chain formation) or 1,2-silyl migration and cyclization (furan construction), would be useful both for gaining a fundamental understanding of these bond forming processes and for the design of more advanced reagents that utilize these intrinsic properties for facial bias. Recently, Mikami and co-workers have shown that the reaction of achiral, (*E*) and (*Z*) β-methyl-substituted crotylstannanes and silanes with 2-(benzyloxy)propanal afforded homoallylic alcohols favoring the anti or syn diastereomers depending on chelation- and non-chelation-controlled conditions, respectively.[8]

The results of our experiments concerning the diastereoselectivity in the Lewis acid promoted addition reactions of (*E*)-(3*S*)-methyl 4-methyl-3-(trimethylsilyl)hex-4-enoate ((*S*)-**1a**) and (*E*)-(3*R*)-methyl 4-methyl-3-(trimethylsilyl)hex-4-enoate ((*R*)-**1b**) with α-(benzyloxy)-acetaldehyde (**2**) are described here. The present method for the asymmetric construction of anti-disposed homoallylic alcohols is an extension of those earlier studies from our laboratory and is based on our developing chiral allylsilane-based bond construction methodology.

Preparation of β-Methyl (*E*)-Crotylsilanes (*S*)-1a and (*R*)-1b. The success of this study was predicated on our ability to produce enantiomerically enriched β-methyl (*E*)-crotylsilanes in useful quantities. The synthesis of these materials is summarized in Scheme I and begins with a "reverse Brook" rearrangement on the trimethylsilyl ether of tiglic alcohol **5** to produce the α-hydroxy allylsilane **6**.[9] The racemic (*E*)-vinylsilane **7** was produced through a boron trifluoride etherate ($BF_3{\cdot}OEt_2$) catalyzed allylic acetate isomerization on the derived acetate of **6**.[10] An enzymic resolution employing *Pseudomonas* AK in pentane catalyzed the transesterification of **7**, affording highly

(1) Reviews on allylmetal chemistry: (a) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555–566. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles*, **1982**, *18*, 357. (c) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.

(2) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557–558.

(3) For recent reviews on the chemistry of allylsilanes see: (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575. (b) Majetich, G. *Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp 173–240. (c) Birkofer, L.; Stuhl, O. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley and Sons: New York, 1989; Chapter 10. (d) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1–22. For discussion concerning the mechanisms and stereochemistry of S_E'-type reactions see: (e) Matassa, V. G.; Jenkins, P. R.; Kumin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, *29*, 321–343 and references cited therein. (f) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053–1065.

(4) (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963–4965. (c) Wetter, H.; Scherer, P., Schweizer, W. B. *Helv. Chim. Acta* **1979**, *62*, 1985–1989. (d) Wetter, H.; Scherer, P. *Helv. Chim. Acta* **1983**, *66*, 118–122.

(5) (a) Aryl acetals: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (b) Hetero-substituted acetals: Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755–5758.

(6) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870.

(7) Panek, J. S., Yang, M., Muler, I. *J. Org. Chem.* **1992**, *57*, 4063–4064.

(8) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161–1163.

(9) (a) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Essay 9, Molecular Rearrangements of Organosilicon Compounds. (b) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-H.; Szczepanski, S. W. *Org. Synth.* **1987**, *66*, 14–21. (c) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-H.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393–5396.

(10) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1990**, *55*, 5564–5567.

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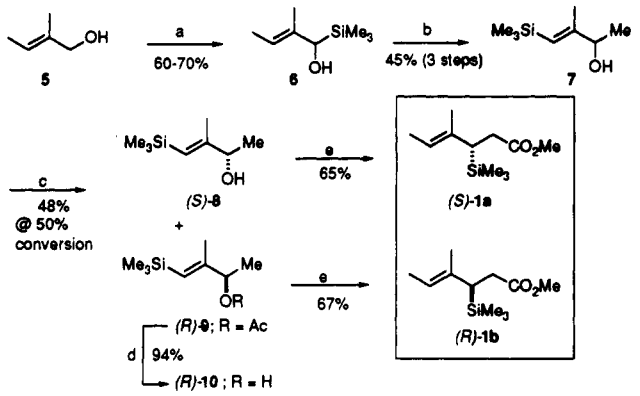
Scheme I[a]

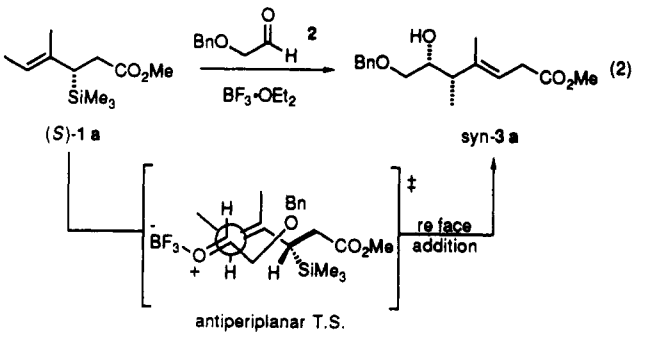


[a] Legend: (a) (i) ^{n}BuLi (1.1 equiv), THF, −78 °C, (ii) Me_3SiCl (1.1 equiv), (iii) ^{t}BuLi (3.0 equiv), −78 °C → −35 °C, 8 h, then NH_4Cl; (b) (i) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, (ii) $BF_3{\cdot}OEt_2$ (0.3 equiv), 0 °C → rt, 1 h, (iii) $LiAlH_4$, THF; (c) Lipase Amano-AK (0.5 wt. equiv), vinyl acetate (5.0 equiv), pentane, 10 h, rt; (d) $LiAlH_4$, THF; (e) $(MeO)_3CMe$ (4.0 equiv), cat. propionic acid, toluene, reflux.

enantiomerically enriched (*S*)-(*E*)-1-(trimethylsilyl)-2-methyl-1-buten-3-ol ((*S*)-**8**) ($[\alpha]^{24}_D = -9.0°$, $c = 1.00$) and (*R*)-(*E*)-1-(trimethylsilyl)-2-methyl-1-buten-3-yl acetate ((*R*)-**9**) ($[\alpha]^{24}_D = +51.3°$, $c = 2.03$).[11] A lithium aluminum hydride reduction of (*R*)-acetate **9** provided nearly enantiomerically pure alcohol (*R*)-**10** ($[\alpha]^{24}_D = +10.1°$, $c = 2.35$).[12] Finally, the β-methyl (*E*)-crotylsilanes (*S*)-**1a** ($[\alpha]^{24}_D = -20.6°$, $c = 2.33$) and (*R*)-**1b** ($[\alpha]^{24}_D = +22.8°$, $c = 2.79$) were produced in good yield by an ortho ester Claisen rearrangement with trimethylortho acetate.[13,14]

The results of the asymmetric addition reactions of β-methyl substituted (*E*)-crotylsilanes (*S*)-**1a** and (*R*)-**1b** are summarized in Table I. The data in Table I show that good levels of selectivity are reached, but with an opposite stereochemical sense, in reactions catalyzed by $BF_3{\cdot}OEt_2$ (nonchelation) and magnesium bromide etherate ($MgBr_2{\cdot}OEt_2$) (chelation control).[15] The $BF_3{\cdot}OEt_2$-catalyzed reaction of (*S*)-**1a** with aldehyde **2** at −78 °C afforded the homoallylic alcohols **3a** and **4a** as a 6.5:1 mixture of diastereomers (entry 1). Warming the reaction mixture to −30 °C resulted in the loss of diastereoselection. In this case, the formation of a small amount of the tetrahydrofuran **11** derived from an anti S_E' addition and subsequent 1,2-silyl migration and heterocyclization was also detected (entry 2).[6] The same tetrahydrofuran was obtained in substantial amounts by the use of tin(IV) chloride ($SnCl_4$) at −78 °C (entry 6). Interestingly, warming the $SnCl_4$-catalyzed reaction mixture to −35 °C resulted in the loss of this furan (entry 5). To determine the origin of this tetrahydrofuran, **11** was treated with $SnCl_4$ (1.0 equiv) at −35 °C, promoting an elimination process which afforded cleanly and in high yield (83%) the anti-homoallylic alcohol **4a** as a single diastereomer. This allowed us to assign unambiguously the relative stereochemistry of this furan and to conclude that its formation takes place via a similar reaction transition state as the one that affords the anti-homoallylic alcohol **4a**. The use of $MgBr_2{\cdot}OEt_2$ afforded the anti-homoallylic alcohols **3a** and **4a** as a 1:12.2 mixture of diastereomers, respectively (entry 8), the reaction taking place only after warming to −25 °C. To illustrate that the enantiomeric homoallylic alcohols **3b** and **4b** could be obtained, addition reactions with the *R* enantiomer (**1b**) catalyzed by $BF_3{\cdot}OEt_2$ and $MgBr_2{\cdot}OEt_2$ were performed, and as anticipated similar levels of diastereoface selection were obtained (entries 9 and 10).

Not surprisingly, the β-methyl substituted (*E*)-crotylsilanes exhibited greater reactivity than the parent (*E*)-crotylsilanes.[16] That the $BF_3{\cdot}OEt_2$-catalyzed reaction of (*S*)-**1a** with **2** afforded the syn homoallylic alcohol **3a** as the major diastereomer is consistent with literature precedence and our earlier reports concerning the asymmetric additions of chiral (*E*)-crotylsilanes to acetals (eq 2). The formation of the syn-homoallylic alcohol may be



interpreted to occur via a transition state (TS) where the reacting π-bonds are positioned at 180° to each other (antiperiplanar).

In contrast, the use of $MgBr_2{\cdot}OEt_2$ in a chelation-controlled addition afforded the complementary anti-homoallylic alcohol *anti*-**4a** as the major diastereomer (eq 3).[17] In this case, the silane adds to the *si* face of the chelated aldehyde complex and thus the stereochemical outcome is perhaps best rationalized with a synclinal TS.[8] In this transition state the reacting π-bonds are arranged at approximately 30° with each other and the vinyl hydrogen (smallest group) is placed in the sterically most

(11) Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *32*, 4085–4088.

(12) The enantiomeric purity of compounds **8** and **10** was determined to be >96% ee by ^{1}H-NMR on the mandelate esters obtained by a DCC coupling to (*R*)-*O*-acetylmandelic acid (cf. Whitesell, J. K.; Reynolds, D. J. *J. Org. Chem.* **1983**, *48*, 3548–3551). The absolute stereochemistry of the resolved alcohol was assigned by analogy with prior published reports involving similar structural types (see: (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129–6139. (b) Panek, J. S.; Sparks, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 801–816).

(13) (a) Murphy, P. J.; Spencer, J. L.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1051–1054. (b) Johnson, W. S.; Werthemann, L.; Barlett, W. R.; Brocksom, T. J.; Li, T-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

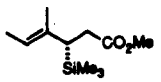
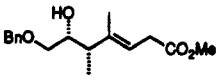
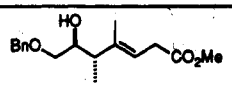
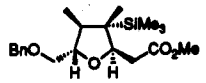
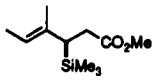
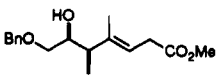
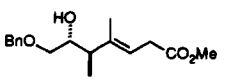
(14) The ee of the Claisen products **1a** and **1b** was determined to be >96%, and was accomplished by a Mosher analysis using the method of Trost et al. [cf. Trost, B. M.; Belletire, J. M.; Godleski, S.; McDougal, P. G.; Balkovek, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374] on the (*R*)-*O*-acetyl mandelate esters of the primary alcohols derived from the reduction of the methyl ester of the β-methyl crotylsilanes. Methyl ester reduction of **1a** and **1b** with DIBAL-H (2.5 equiv, THF, −78 °C), followed by esterification of the primary alcohol with (*R*)-*O*-acetylmandelic acid [1.3 equiv, DCC (1.2 equiv), CH_2Cl_2, cat. DMAP] [cf. ref 12 above] afforded the new mandelate esters in 93 and 91% yields, respectively (two steps).

(15) The stereochemistry of the reaction products was assigned as syn or anti based on the analysis of ^{1}H-NMR coupling constants ($^3J_{H2,H3}$) of the derived acetonides. These acetonides were obtained by (a) oxidative cleavage of the double bond [cat. OsO_4, TMANO and then $NaIO_4$, acetone: H_2O = 1:1, rt], stereoselective reduction of the resultant β-hydroxy ketone with cathecolborane (CB, THF, −10 °C), and transketalization (2,2-dimethoxypropane, cat. *p*-TsOH). See supplementary material for details.

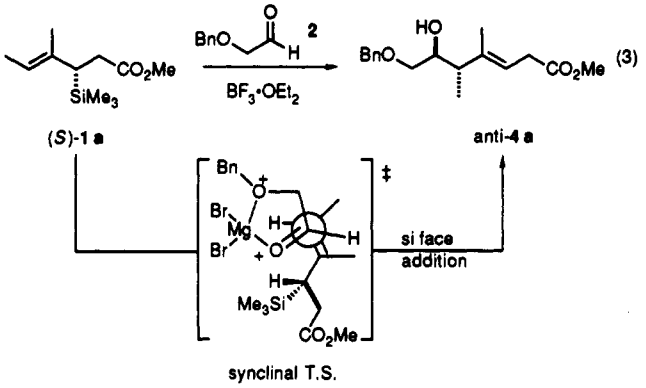
(16) This evidence supports the already well-established notion that allylsilane additions take place via the participation of an intermediate carbocation β-to the silicon atom. The methyl substituent at this position provides enhanced stability to this intermediate. For a discussion see Fleming, I. et al. in ref 3a.

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

Table I. Diastereoselective Additions of Chiral, β-Substituted-(*E*)-Crotylsilanes to α-Benzyloxy Acetaldehyde

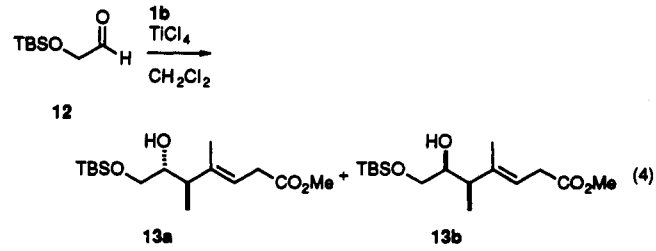
entry	silane	Lewis acid[a] (temp, °C)	relative ratios of products[b]			overall yield[c] (%)
						
	(*S*)-1a		(5*S*, 6*R*)-3a	(5*S*, 6*S*)-4a	11	
1		$BF_3{\cdot}OEt_2$ (−78)	6.5	1.0	0.0	68
2		$BF_3{\cdot}OEt_2$ (−78 → −30)	5.3	1.0	0.33	60
3		$ZnCl_2$ (−78 → 0)	2.0	1.0	0.0	58
4		$AlCl_3$ (−78)	1.2	1.0	0.0	54
5		$SnCl_4$ (−78 → −35)	1.0	2.2	0.0	48
6		$SnCl_4$ (−78)	1.0	2.0	2.0	60
7		$TiCl_4$ (−78)	1.0	4.2	0.0	57
8		$MgBr_2{\cdot}OEt_2$ (−25)[d]	1.0	12.2	0.0	59
						
	(*R*)-1b		(5*R*, 6*S*)-3b	(5*R*, 6*R*)-4b		
9		$BF_3{\cdot}OEt_2$ (−78)	5.0	1.0		65
10		$MgBr_2{\cdot}OEt_2$(−25)[d]	1.0[e]	14.7[e]		48

[a] Unless otherwise noted all reactions were performed at 0.25 M in substrate in CH_2Cl_2, the Lewis acid introduced at −78 °C to a solution of the aldehyde and silane reagent under N_2. [b] Unless otherwise stated, determined by ^{1}H-NMR analysis (270 or 400 MHz) of the crude reaction mixture. [c] Isolated yield after chromatography on SiO_2. [d] Precomplexation of the aldehyde with the Lewis acid at rt for 0.5 h and then cooling to −78 °C and addition of the silane reagent 1a or 1b in a solution of CH_2Cl_2. [e] Weight ratio isolated after column chromatography on SiO_2.



demanding position. Further, the destabilizing interactions are decreased because the Lewis acid is no longer on the carbonyl group anti to the aldehyde substituent, but is instead syn to the chelated aldehyde. Other strong chelating Lewis acids such as $SnCl_4$ and $TiCl_4$ also display a preference for the formation of the anti diastereomer, that is, a reaction on the *si* face of the aldehyde via a synclinal transition state. This preference is expressed, in the $SnCl_4$ case, in the formation of the trans 2,5-disubstituted tetrahydrofuran 11. It is unclear at this point why no furan with the opposite relative stereochemistry at the 5-position, which would result from the same transition state as for the formation of the syn diastereomer **3a** (*re* face addition), has been detected. Also unclear at this moment is why the aluminum and zinc catalysts still display a slight preference for the formation of the syn diastereomer.

In order to ascertain whether both β-substitution on the silane reagent and chelation are needed to effect reversal of diastereoselection the following experiment was performed; addition of (*S*)-**1b** to α-[(*tert*-butyldimethylsilyl)oxy]acetaldehyde (**12**). This aldehyde should be prevented from undergoing a chelation-controlled addition, irrespective of the nature of the Lewis acid used, because of the lower basicity of the oxygen lone pairs compared to the α-(benzyloxy)acetaldehyde (**2**).[18] Under $TiCl_4$ activation (1.5 equiv, −78 °C, 8 h), this aldehyde produced a 1.5:1 ratio of anti and syn diastereomers **13a** and **b** in a combined yield of 35% (no furan was detected, eq 4).[19] This represents a substantial increase of syn selectivity when compared with the 4.2:1 anti/syn ratio obtained in entry 7 (Table I).[20]

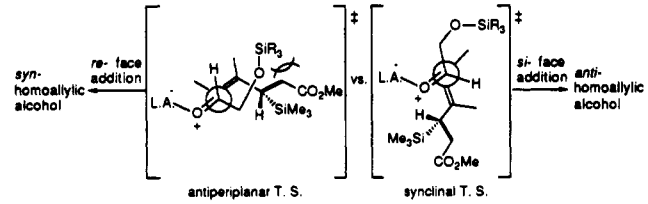


In conclusion, although achiral β-methyl-substituted allylstannanes have been employed as carbon nucleophiles in chelation-controlled additions to aldehydes, the present study considerably extends those original observations, as it documents the participation of chiral β-methyl-

(18) (a) For a recent example see: Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1990**, *55*, 6071–6073. (b) For a recent discussion, see: Chen, X.; Hortelano, E. R.; Eliel, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 6130–6131. (c) For leading references citing the older literature thoroughly, see: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697–703. (d) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 2953–2964.

(19) The stereochemistry of these addition products **13a** and **13b** was assigned by comparison to the products obtained from reaction of α-[(*tert*-butyldimethylsilyl)oxy] acetaldehyde **12** and **1b** under $BF_3{\cdot}OEt_2$ activation (48% syn, 18% furan) and $MgBr_2{\cdot}OEt_2$ activation (18%, only anti); the detail of these experiments will be reported in due course.

(20) The product distribution still favoring the anti product may be due to the propensity for this system to prefer a synclinal transition state due to nonbonding, destabilizing interactions between the large silicon protecting group and the incoming crotylsilane reagent. This repulsion seems more pronounced when the transition state is drawn depicting the aldehyde in the correct Cornforth conformation [cf. (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112–117. (b) Panek, J. S.; Beresis, R. *J. Org. Chem.*, in press] as shown below for the addition of the (*S*)-**1a** enantiomer. Experiments are underway to shed light on this hypothesis [cf. also ref 18b above].



substituted (*E*)-crotylsilanes in the asymmetric addition with an achiral aldehyde, producing syn or anti homoallylic alcohols with useful levels of selectivity. Further exploration of these chiral silane reagents is currently 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).

Supplementary Material Available: Experimental procedures for the reaction of the crotylsilane reagents **1a** and **1b** with aldehyde **2** and spectral data for all reaction products as well as the assignment of the relative stereochemistry of the syn and anti homoallylic alcohols **3** and **4** (6 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.