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Stereochemistry of the Allylation and Crotylation Reactions of α-Methyl-*β*-hydroxy Aldehydes with Allyl- and Crotyltrifluorosilanes. Synthesis of *anti,anti*-Dipropionate Stereotriads and Stereodivergent Pathways for the Reactions with 2,3-*anti*- and 2,3-*syn*-α-Methyl-*β*-hydroxy Aldehydes

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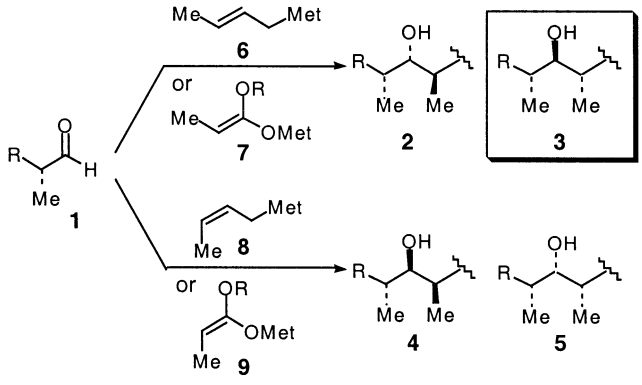
A new method for the stereoselective synthesis of the *anti,anti*-dipropionate stereotriad via the reaction of α-methyl-*β*-hydroxy aldehydes with (*Z*)-crotyltrifluorosilane (**24**) is described. These reactions were designed to occur through bicyclic transition states (e.g., **31**) in which the silane reagent is covalently bound to the *β*-hydroxyl group of the aldehyde and the crotyl group is transferred intramolecularly. This methodology was used to synthesize the C(7)−C(16) segment (**58**) of zincophorin, which contains a synthetically challenging *all-anti* stereopentad unit. Surprisingly, 2,3-*anti*- and 2,3-*syn*-α-methyl-*β*-hydroxy aldehydes react in a stereodivergent manner with **24**: 2,3-*anti*-*β*-hydroxy aldehydes give the targeted *anti,anti*-dipropionate adducts with high selectivity, but the reactions of 2,3-*syn*-*β*-hydroxy aldehydes are poorly selective. The stereodivergent behavior of 2,3-*syn*- vs 2,3-*anti*-α-methyl-*β*-hydroxy aldehydes is also exhibited in their reactions with the allyl- (**68**) and (*E*)-crotyltrifluorosilanes (**27**). Competition experiments performed with *β*-hydroxy aldehydes **37a** (anti) and the corresponding *p*-methoxybenzyl (PMB) ether **48**, and between aldehyde **39** (syn) and the PMB ether **90**, established that the 2,3-*anti*-*β*-hydroxy aldehydes react predominantly through bicyclic transition states while the 2,3-*syn* aldehydes react predominantly through conventional Zimmerman−Traxler transition states. NMR studies established that both the 2,3-*syn* and the 2,3-*anti* aldehydes form stable, pentavalent silicate intermediates (**98** and **100**) with $PhSiF_3$, but chelated structures **99** and **101** could not be detected. The activation energies for the competing bicyclic and conventional Zimmerman−Traxler transition states were calculated by using semiemperical methods (MNDO/d). These calculations indicate that the stereodivergent behavior of the 2,3-*syn*-*β*-hydroxy aldehydes and the 2,3-*anti*-*β*-hydroxy aldehydes is due to differences in nonbonded interactions in the bicyclic transition states. Specifically, nonbonded interactions in the bicyclic transition states for the allylation/crotylation reactions of the 2,3-*syn*-*β*-hydroxy aldehydes permits the traditional Zimmerman−Traxler transition states to be preferentially utilized.

Introduction

Much effort in the area of acyclic stereocontrol has been focused on the development of highly stereoselective methods for synthesis of the four "dipropionate" stereotriads **2**, **3**, **4**, and **5**, which are commonly found subunits in polyketide natural products.[2] Of these stereotriads, the *anti,anti*-isomer **3** has historically been the most challenging to synthesize.[2,3] In many cases, indirect methods involving multistep sequences have been employed for the synthesis of stereotriad **3**.[3]

The stereoselective synthesis of the *anti,anti*-dipropionate **3** via the reaction of **1** with an (*E*)-crotylmetal reagent **6** or an (*E*)-(O)-enolate **7** is inherently problematic as it must arise from a disfavored transition state **12** where the reagent adds to the chiral aldehyde in an anti-Felkin manner.[4−8] This is illustrated below for the reaction of **1** with (*E*)-crotylmetal reagent **6**.[9] The 3,4-*anti*-4,5-*syn* homoallylic alcohol **11**, which arises through



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(2) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.
(3) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629.

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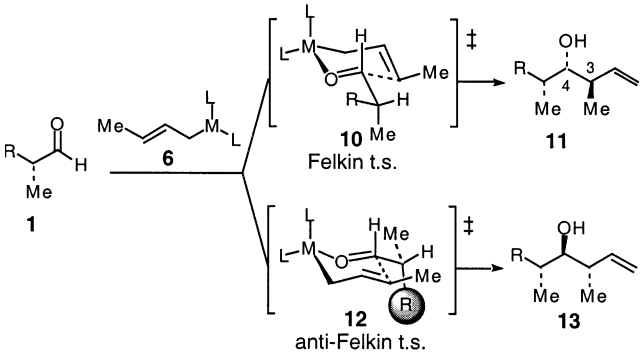
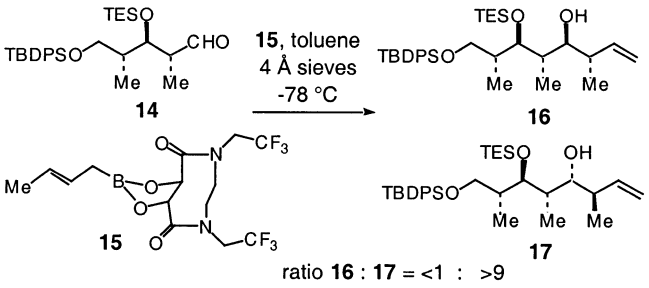
the Felkin−Anh transition state **10**,[10−12] is favored in these reactions, and as the size of R increases relative to Me, the selectivity for **11** increases proportionately since the competing anti-Felkin transition state, **12**, becomes increasingly destabilized by the gauche interactions between the reagent γ-methyl and the aldehyde R group.[4−7]



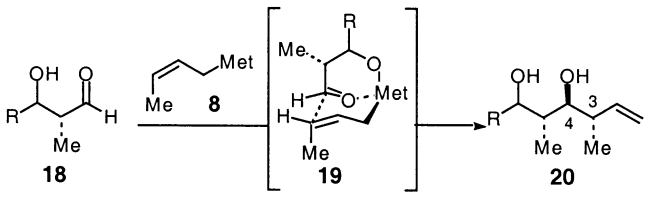
In principle, *anti*,*anti*-dipropionate synthons **3** or **13** can be prepared directly from **1** by using chiral crotylmetal reagents or chiral enolates. However, the intrinsic diastereofacial bias of **1** requires that **3** be produced via mismatched double asymmetric reactions.[13] For example, the often used, easily synthesized tartrate ester-derived (*E*)-crotylboronate reagent developed in our laboratory[6,14] and the (*E*)-crotyldiisopinocampheylborane developed by Brown[15,16] have demonstrated proficiency in overcoming the diastereofacial bias of chiral aldehydes in cases when the aldehyde R group is relatively nonsterically demanding.[4,7] In more challenging cases involving aldehyde substrates in which the R substituent (see **1**) is quite sterically demanding, however, these reagents fail to give synthetically useful levels of selectivity for the *anti*,*anti*-dipropionate.[6,17,18] For example, attempts to achieve a reagent-controlled mismatched crotylboration of **14** with use of (*E*)-crotylboronate **15**[19] containing our most highly enantioselective tartramide auxiliary gave a disappointing ca. 9:1 mixture favoring the undesired diastereomer **17**.[20]



The highly enantioselective enol borane and crotylboronate reagents developed by Masamune[21,22] and Hoffmann[3,23,24] have been used successfully in challenging examples of mismatched double asymmetric reactions leading to the *anti*,*anti*-dipropionate stereotriad. However, the complex, multistep sequences required for synthesis of these reagents have restricted their widespread use in organic synthesis.

Marshall[25] and Panek[26,27] have demonstrated that chelation-controlled addition of chiral Type II[9] allenylstannane and crotylsilane reagents to α-methyl-β-benzyloxy substituted aldehydes provide *anti*,*anti*-dipropionate adducts selectively.[7,28] However, the Marshall and Panek reagents also require multistep preparations, and this method for the synthesis of the *anti*,*anti* stereotriad is limited to chiral aldehydes that possess β-alkoxy ether protecting groups that are capable of participating in chelate-controlled carbonyl addition reactions.[29−31]

Our inability to achieve selective access to **16** by using the highly enantioselective chiral (*E*)-crotyboronate **15**[19,20] led us to explore a conceptually different strategy that uses the intrinsic diastereofacial selectivity preference of the chiral aldehyde to direct the formation of the subsequent stereocenters. We envisiaged that this could be accomplished via the reaction of a α-methyl-β-hydroxy aldehyde with a (*Z*)-crotylmetal reagent **8** that proceeds by way of the bicyclic transition state **19** in which the β-hydroxyl group of **18** is engaged in a chelate with the (*Z*)-crotylmetal reagent. Bond formation should then occur anti to the aldehyde α-methyl group, thus favoring the 3,4-*anti*-4,5-*anti*-dipropionate **20** without recourse to expensive chiral reagents. Several examples of stereoselective intramolecular allylation reactions occurring through α- or β-hydroxyl chelation had been reported prior to the initiation of our work.[32−38]



Initial attempts to obtain the *anti*,*anti*-dipropionate adduct via the reaction of β-hydroxy aldehyde **21** with

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(9) For the definition of Type I−Type III allylorganometallic reagents, see: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655−1660.
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(15) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 3701.
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(20) Grover, P. T. Ph.D. Thesis, Indiana University, 1994.
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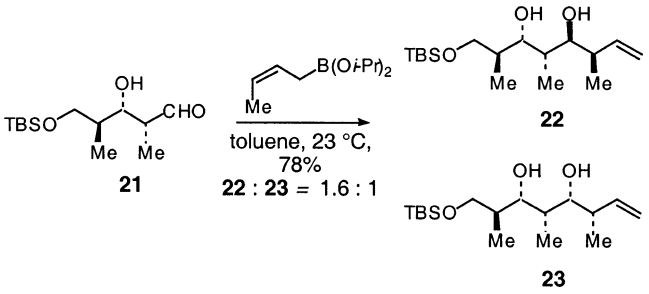
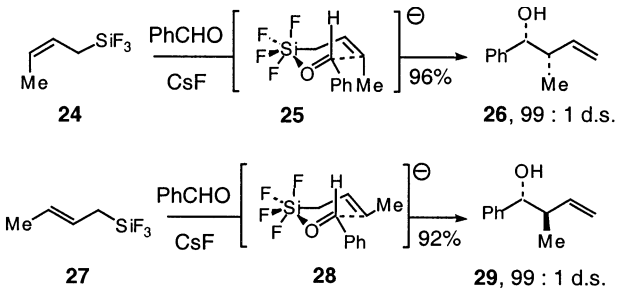
(22) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673. See, in particular, the conversion of **13** to **15** therein.

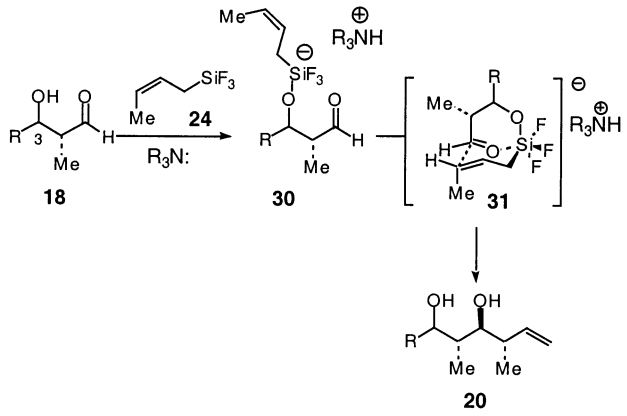
(*Z*)-crotyldiisopropylboronate[36−38] were unsuccessful.[39] This reaction provided a mixture of **22** and **23**, the products of normal Zimmerman−Traxler transition pathways.[4] Assuming that our lack of success with this experiment arose from the reluctance of the diisopropyl (*Z*)-crotylboronate to esterify with the *β*-hydroxyl group of **21**, as crotylboronates do not require nucleophilic activation for normal, nonchelated carbonyl addition to occur, we turned our attention toward the use of a (*Z*)-crotylmetal reagent that requires nucleophilic activation for reaction with carbonyl electrophiles.



Allyl- and crotylsilanes that contain electronegative substituents (e.g., −OMe, −Cl, or −F) at silicon are known to undergo nucleophile-promoted addition reactions with carbonyl compounds via the usual Type I allylation pathway.[40−46] For example, the reaction of benzaldehyde with (*Z*)-crotyltrifluorosilane (**24**) in the presence of CsF gives the syn homoallylic alcohol **26** with 99:1 selectivity, while the (*E*)-crotylsilane reagent **27** gives the anti homoallylic alcohol **29**, also with 99:1 selectivity.[42] Formation of a pentavalent silicate species by addition of a nucleophile to the silicon center of **24** and **27** serves to increase the nucleophilicity of the *γ*-carbon of the crotyl unit without substantially decreasing the Lewis acidity of the silicon center,[47,48] which then engages with carbonyl substrates via Zimmerman−Traxler allylation transition states **25** and **28** to give the homoallylic alcohol products with excellent stereoselectivity. Several reports of enantioselective allylation and crotylation reactions of achiral aldehydes and trichloroallylsilanes catalyzed by chiral nucleophiles have appeared.[49−60] In addition, several applications of allyltrifluorosilanes for allylation reactions of α-hydroxy ketones, α-diketones, and salicaldehyde derivatives have also been reported, where the reagent is activated by chelation to the substrate.[33−35]



Accordingly, we envisioned that the *β*-hydroxyl group of aldehyde **18** would add to the silicon center of (*Z*)-crotyltrifluorosilane **24** to generate the pentacoordinate crotylsilicate intermediate **30**, which would then undergo crotyl transfer via the bicyclic transition state **31**, thereby affording the *anti*,*anti*-dipropionate **20**. We report here the full details of our development of this reaction, including our observation that the success of this process is highly dependent on the stereochemistry of the C(3) stereocenter of **18**. Preliminary accounts of this work have appeared previously.[61,62]



Results and Discussion

Development of the Chelate-Controlled (Z)-Crotylsilylation Reaction. (*Z*)-Crotyltrifluorosilane **24** with

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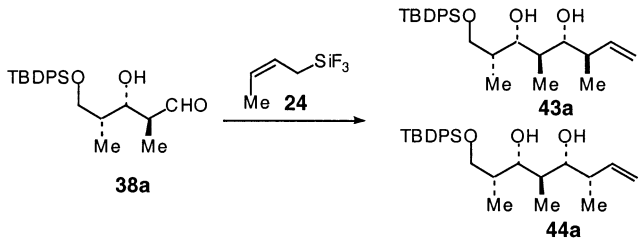
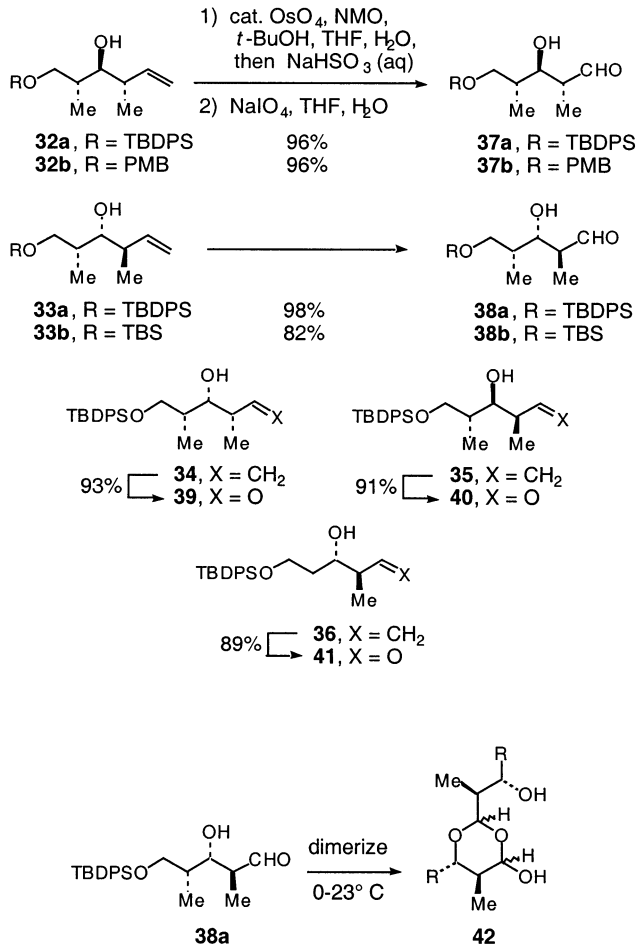
TABLE 1. Crotylation of β-Hydroxyaldehyde 38a and (*Z*)-Crotyltrifluorosilane (24): Optimization of Reaction Conditions



entry	conditions[a]	yield (%)	**43a**:**44a**
1[b]	1−7 equiv of **24,** 1−5 equiv of *i*-Pr_2NEt or Et_3N, CH_2Cl_2, 0 °C, 24−36 h	40−75	75:25 to 95:5[d]
2	1.5 equiv of **24**, 1.5 equiv of *i*-Pr_2NEt or 2 equiv of H_2O, CH_2Cl_2, 0 °C, 24−36 h	24	10:90
3	5 equiv of **24**, 5 equiv of *i*-Pr_2NEt, 4 Å molecular sieves, CH_2Cl_2, −10 °C, 36 h	36	95:5
4	3 equiv of **24**, 3 equiv of *i*-Pr_2NEt, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 36 h	75	95:5
5	3 equiv of **24**, 3 equiv of *i*-Pr_2NEt, 4 Å molecular sieves, toluene, 0 °C, 36 h	n.d.	84:16[c]
6	3 equiv of **24**, 3 equiv of *i*-Pr_2NEt, 4 Å molecular sieves, THF, 0 °C, 36 h	n.d.	76:24[c]

[a] All reactions were run at 0.08 M concentration with respect to **38a**. [b] Reactions run at several different concentrations. [c] Sum of two minor diastereomers. [d] Variable from run to run.

an isomeric purity of 98:2 was prepared in two steps from 1,3-butadiene by using the procedure reported by Kira (82% overall yield).[42] α-Methyl-β-hydroxy aldehydes **37**−**41** were prepared from the homoallylic alcohol precursors **32**−**36**[6] by a two-step procedure involving olefin dihydroxylation[63] (OsO_4) and oxidative diol cleavage ($NaIO_4$). The crude β-hydroxy aldehydes so prepared were very clean by ^1H NMR analysis and were used directly in the crotylation reactions without purification. In some cases, the aldehydes were prepared by ozonolysis of the homoallylic alcohol precursors with pyridine as an additive to decompose the ozonide.[64] The β-hydroxy aldehydes were unstable to chromatographic purification, which invariably provided dehydration products and/or epimers at the α-center. The β-hydroxy aldehydes were also unstable with respect to dimerization (cf., **38a** to **42**) when stored neat at 0 or 23 °C.[65] Therefore, **37**−**41** were used immediately after preparation in the subsequent crotylation reactions.



Initial studies of the (*Z*)-crotylation reaction of aldehyde **38a** and (Z)-crotyltrifluorosilane (**24**) in the presence of a tertiary amine base revealed that the desired *anti*,*anti*-adduct **43a** was formed as the major product. However, product yields at the outset of these investigations were low (ca. 40%) and the stereoselectivity was variable, with the ratio of **43a**:**44a** ranging from 75:25 to 95:5 (Table 1, entry 1). Adventitious water was identified as being responsible for the variable stereoselectivity in these initial reactions. Indeed, when the reaction of **38a** and **24** was performed in the presence of added water (2 equiv), the 3,4-*syn*-4,5-*anti* dipropionate **44a** was produced as the major product (d.s. 90:10), with only minor amounts of the 3,4-*anti*-4,5-*anti* dipropionate **43a** formed (Table 1, entry 2). It is known that water can act as a nucleophile to catalyze the reactions of aldehydes with allyl- and crotyltrifluorosilanes.[66] The 3,4-*syn*-4,5-*anti* stereochemistry of **44a** indicates that the

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(55) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977.
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(57) Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951.
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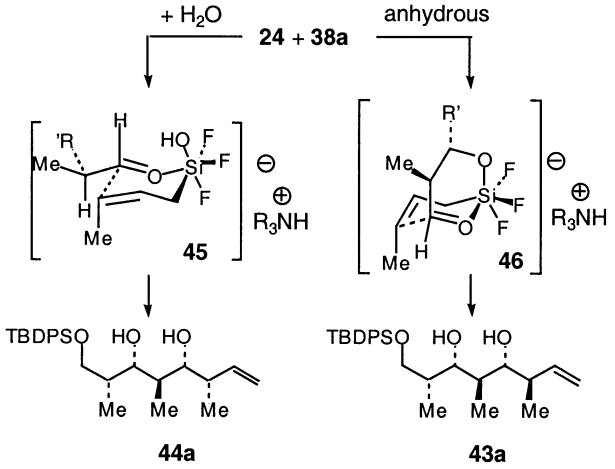
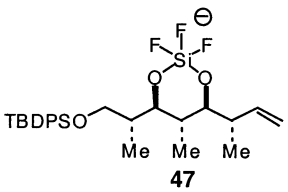
water-facilitated reaction occurs predominantly through the normal chairlike Zimmerman−Traxler transition state **45**,[4,5] and not the internally chelated, bicyclic transition state **46**. Fortunately, the deleterious effect of water on the reaction stereoselectivity can be minimized by rigorously drying the aldehyde substrate in vacuo (ca. 0.1 atm) for 1 h prior to use and by treating a solution of the aldehyde in CH_2Cl_2 with 4 Å molecular sieves prior to the addition of the crotylsilane reagent and the amine base. Typically, we have used an amount of sieves equivalent (by weight) to the amount of β-hydroxy aldehyde employed in the reaction. Under these conditions, a 95:5 mixture of diastereomers **43a** and **44a** was obtained consistently for reactions performed in CH_2Cl_2 (entries 3 and 4). Use of 4 Å molecular sieves also had a beneficial effect on the yield of homoallylic alcohol, possibly by decreasing competitive aldehyde dimer (e.g., **42**) formation if the reaction mixture is wet.

The reaction concentration also proved be an important factor in obtaining the crotylation products in good yield. A concentration of 0.08 M with respect to the aldehyde was optimal. Poor yields were obtained at concentrations greater than 0.1 M, an observation likely due to competitive formation of aldehyde dimer, e.g. **42**, at higher reaction concentrations.

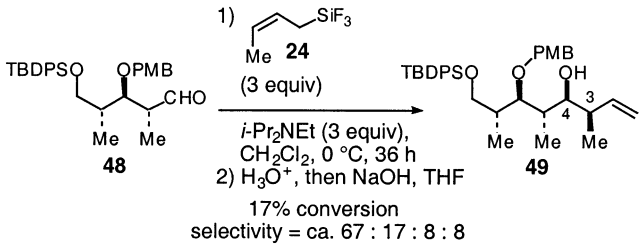


The stoichiometry of the (*Z*)-crotyltrifluorosilane relative to the β-hydroxyaldehyde affected the reaction efficiency, but not the stereoselectivity. In general, 3 equiv of **24** was necessary to obtain optimal yields (Table 1, entry 4). The reaction temperature also influenced the efficiency, as a considerably lower yield of homoallylic alcohols was obtained at −10 °C compared to reactions performed at 0 °C (Table 1, entries 3 and 4). Of the three solvents examined, the reaction stereoselectvity was much better in CH_2Cl_2 (selectivity = 95:5, Table 1 entry 4) than in toluene (84:16, entry 5) or THF (76:24, entry 6).

A sequential acidic (1 N HCl, 15 min) and then basic (3:1 THF:1 N NaOH, 1 h) workup was required to hydrolyze the intermediate silylene ketals (e.g., **47**) which are observed in these reactions.



In cases where the β-hydroxyl group is protected, the reaction proceeds very slowly and preferentially provides the 3,4-*syn* homoallylic alcohol product. For example, the reaction of (*Z*)-crotylsilane **24** and aldehyde **48** with the β-hydroxyl group protected as a *p*-methoxybenzyl (PMB) ether proceeded to only 17% conversion after 36 h and gave a 67:17:8:8 mixture of products, among which the 3,4-*syn*-4,5-*anti* adduct **49** predominated. The stereochemistry of **49** is consistent with its formation through a conventional anti-Felkin Zimmerman−Traxler transition state analogous to **45**.



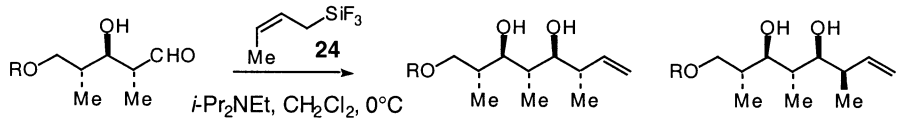
Results of reactions of (*Z*)-crotyltrifluorosilane **24** and α-methyl-β-hydroxy aldehydes **37**−**41** are summarized in Table 2. The crotylation reactions of the 2,3-*anti* aldehydes **37**, **38**, and **41** were generally quite selective for the 3,4-*anti*-4,5-*anti* dipropionate products **43**, **50**, and **52** (entries 1−5). The reaction diastereoselectivity and yield were affected only slightly with changes in the aldehyde δ-alkoxy protecting group (entries 2−4) and γ-carbon stereochemistry (entries 1 and 3). When the γ-carbon of the aldehyde substrate is unsubstituted, as with **41**, the diastereoselectivity is somewhat diminished (e.g., compare entries 3 and 5).

Surprisingly, a different pattern of stereoselectivity emerged in the reactions of the 2,3-syn-α-methyl-β-hydroxy aldehydes **39** and **40**. In these cases, the reactions were much less selective and the major products **54** and **56** possess 3,4-*syn*-4,5-*anti* stereochemistry (Table 2, entries 6 and 7). All attempts to obtain the desired *anti,anti*-dipropionate products **55** and **57** from **39** and **40** by changing reaction conditions were unsuccessful. The stereochemistry of the two major products (entries 6 and 7) in these cases is consistent with reactions proceeding by way of the usual Zimmerman−Traxler transition state analogous to **45**,[4,5] and not the bicyclic transition states (like **46**) that we had targeted in these experiments. Additional studies designed to probe the surprising divergence of stereoselectivity of the (*Z*)-crotylation reactions of the 2,3-*anti* and 2,3-*syn* aldehydes are presented subsequently.

Synthesis of the C(7)−C(16) Fragment of Zincophorin. The *anti,anti,anti,anti*-stereopentad unit spanning the C(8)−C(12) fragment of zincophorin[67,68] provided an ideal target for demonstrating the utility of our new methodology for the synthesis of *anti,anti*-dipropionates. We targeted **58**, which had been previously synthesized by Danishefsky and co-workers en route to their total

(67) Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501.
(68) Schade, W.; Grafe, U.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836.

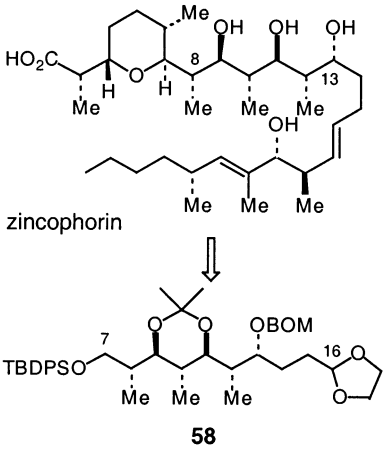
TABLE 2. Reactions of Chiral *β*-Hydroxy-α-methyl Aldehydes 37−41 and (*Z*)-Crotyltrifluorosilane



Entry					Selectivity [c,d,e]
1	**37a**, R = TBDPS	75%	**50a**, R = TBDPS	**51a**, R = TBDPS	93 : 6 : 1
2	**37b**, R = PMB	75%	**50b**, R = PMB	**51b**, R = PMB	85 : 15 : 0
3	**38a**, R = TBDPS	75%	**43a**, R = TBDPS	**44a**, R = TBDPS	95 : 5 : 0
4[f]	**38b**, R = TBS	63%	**43b**, R = TBS	**44b**, R = TBS	96 : 4 : 0
5	**41**, R = TBDPS	76%	**52**, R = TBDPS	**53**, R = TBDPS	82 : 12 : 6
6[f,g]	**39**, R = TBDPS	44%	**54**, R = TBDPS	**55**, R = TBDPS	50 : 24 : 26
7[f,g]	**40**, R = TBDPS	48%	**56**, R = TBDPS	**57**, R = TBDPS	50 : 33 : 17

[a] All reactions were conducted with 3 equiv of **24** and 3 equiv of *i*-Pr_2NEt in CH_2Cl_2 at 0 °C in the presence of 4 Å molecular sieves for 36 h, unless noted otherwise. [b] Yields are reported for the mixture of homoallylic alchol products. [c] Product ratios were determined by ^1H NMR analysis (400 or 500 MHz) of the crude reaction mixture. In all cases, products were separable by chromatographic methods. [d] Product ratio refers to the two major products whose structures are shown; the third figure is the sum of the other two product diastereomers from each reaction. [e] Stereochemical assignments for all homoallylic alcohol products are summarized in the Supporting Information.[f] 7 equiv of **24** and 5 equiv of *i*-Pr_2NEt were used. [g] The reaction time was 72 h in this case.

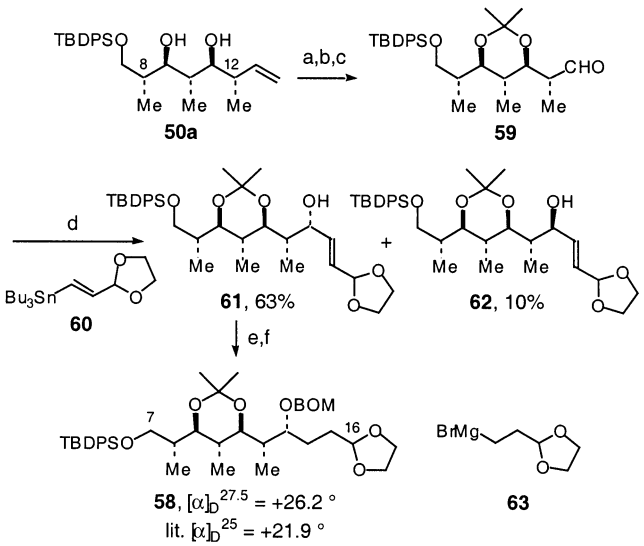
synthesis of the natural product.[69] After our work on this problem was completed, the same intermediate was synthesized by Marshall via double asymmetric reactions of chiral allenyltin reagents.[70]



Diol **50a**, which we had already prepared with 93:6:1 selectivity via the (*Z*)-crotylation of **37a** (Table 2), served as the starting material for the synthesis of **58**. Protection of the 1,3-diol unit as an acetonide followed by olefin dihydroxylation afforded an inconsequential mixture of diastereomeric diols (94% yield, selectivity = 87:13) that was subsequently treated with $NaIO_4$, thereby providing the sensitive aldehyde **59** in 90% yield. We had hoped originally that the synthesis of **58** would be easily accomplished by treatment of **59** with Grignard reagent **63**.[71] However, in our hands this reaction proceeded in very poor yield with 1−3 equiv of **63**. For example, treatment of **59** with 3 equiv of **63** and 3 equiv of $CeCl_3$ in THF from −78 to 23 °C provided the targeted carbonyl addition product in only 4% yield. After our work, Marshall accomplished this conversion by using a very large excess of the Grignard reagent.[70] Interestingly, the reaction of **59** with allyltributylstannane and $BF_3{\cdot}Et_2O$ in toluene at −78 °C provided an 83:17 mixture of products (94% yield) among which the anti-Felkin diastereomer predominated! At this juncture, we used the

(69) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.
(70) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701.
(71) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

vinyllithium reagent derived from vinylstannane **60**. Thus, treatment of **60** with n-BuLi in THF at −90 °C followed by addition of **59** afforded an 86:14 mixture of **61** (Felkin) and **62** in a combined yield of 73%. The sensitive allylic alcohol **61** was hydrogenated over Pd/C in benzene. Protection of the hydroxyl group as a benzyloxymethoxy (BOM) ether then completed our synthesis of the C(7)−C(16) segment **58** of zincophorin. The stereochemistry of our sample was assigned by comparison of the spectroscopic data for **58** kindly provided by Prof. Danishefsky. This synthesis provides unequivocal confirmation of the stereochemistry of **50a**.

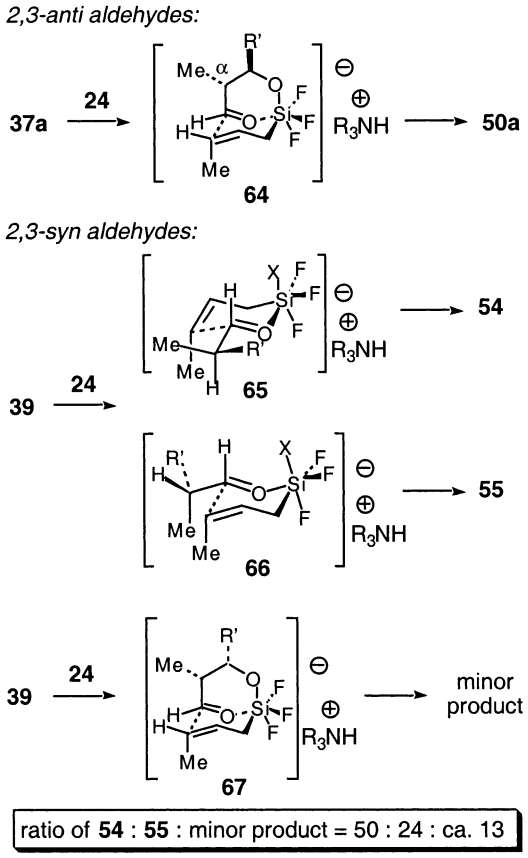


(a) 2-methoxypropene, cat. PPTS, CH_2Cl_2; (b) OsO_4, NMO (94%); (c) $NaIO_4$, THF, H_2O (90%); (d) **60**, *n*-BuLi, THF, -90 °C→ -78 °C; (e) H_2, Pd/C, benzene (84%); (f) BOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, reflux (86%).

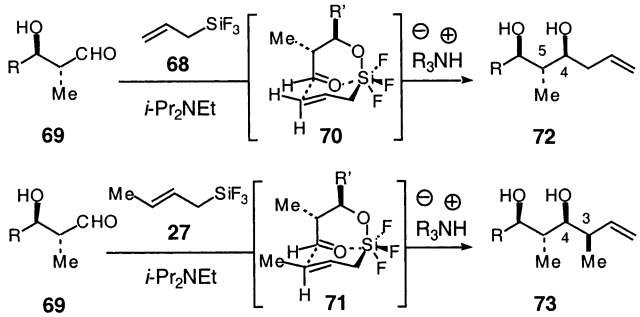
Stereodivergent Behavior of 2,3-*anti* and 2,3-*syn*-α-Methyl-*β*-hydroxy Aldehydes in Reactions with Allyl- and (*E*)-Crotyltrifluorosilanes. The (*Z*)-crotylation reactions of the 2,3-*anti*-α-methyl-*β*-hydroxy aldehydes **37a** with (*Z*)-crotyltrifluorosilane **24** provides the *anti*,*anti*-dipropionate stereotriad **50a** with high selectivity (Table 2). The formation of the 3,4-*anti*-4,5-*anti* stereochemistry of adduct **50a** can be rationalized by invoking the bicyclic transition state **64** where C−C bond formation occurs anti to the aldehyde α-methyl group.

However, the (*Z*)-crotylation reactions of 2,3-*syn*-α-methyl-*β*-hydroxy aldehyde **39** under comparable conditions gave much more complex product mixtures. The major products (**54** and **55**) of this reaction possess 3,4-*syn* stereochemistry, suggesting that the crotylation of **39** (and of other 2,3-*syn*-*β*-hydroxy aldehydes such as **40**) proceeds via the normal Zimmerman−Traxler transition states **65** and **66**,[4,5] rather than the anticipated bicyclic transition state **67**. Undefined at present is the identity of the nucleophilic promotor, X, of the reactions of the 2,3-*syn* aldehydes that proceed by way of **65** and **66**, but as will be shown subsequently the free alcohol unit of **39** is a potential candidate, as is adventitious water or fluoride ion deriving from the reagent or a reaction intermediate.

To probe the generality of this allylation process and also to gain additional insight into the striking stereo-



divergent behavior of the 2,3-*anti*- vs 2,3-*syn*-*β*-hydroxy aldehydes, we examined the reactions of α-methyl-*β*-hydroxy aldehydes **37a**, **38a**, **39**, and **40** with the allyl- and (*E*)-crotyltrifluorosilane reagents **68** and **27**. On the basis of the results of the reactions of 2,3-*anti* aldehydes with (*Z*)-crotyltrifluorosilane **24** (vide supra), we predicted that the 4,5-*anti*-adducts **72** and the 3,4-*syn*-4,5-*anti* adducts **73** would emerge as the major products of allylation of 2,3-*anti* aldehydes of type **69**.

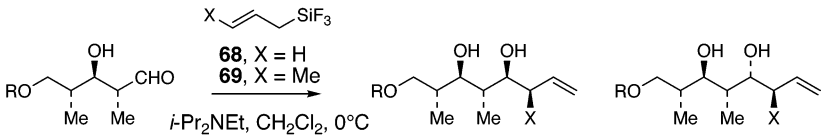


Allyl- and (*E*)-crotyltrifluorosilanes **68** and **27** are readily available from allyltrichlorosilane precursors by silyl chloride to silyl fluoride exchange, using antimony trifluoride.[42,72] Allyltrichlorosilane is commercially available (Aldrich), while isomerically pure (*E*)-crotyltrichlorosilane was prepared from (*E*)-crotyl chloride following Kira's procedure.[42]

Reactions of *β*-hydroxy aldehydes **37a**, **38a**, **39**, and **40** with the allyl- and (*E*)-crotyltrifluorosilanes **68** and **27**

(72) Mironov, V. F. *Bull. Acad. Sci. USSR (Engl. Trans.)* **1962**, 1797.

TABLE 3. Reactions of Chiral β-Hydroxy-α-Methyl Aldehydes with Allyltrifluorosilane (68) and (*E*)-Crotyltrifluorosilane (27)[a,b]

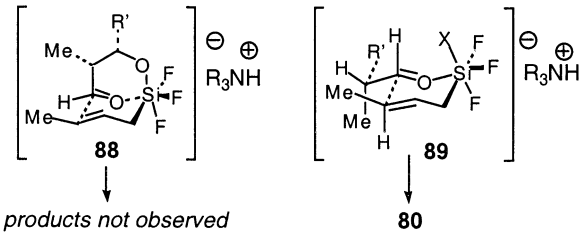


Entry (reagent)					Selectivity[c,d,e]
1 (**68**)	**37a**, R = TBDPS	73%	**74**, X = H	**75**, X = H	90 : 10
2 (**27**)	**37a**, R = TBDPS	75%	**51a**, X = Me	**76**, X = Me	95 : 5
3 (**68**)	**38a**, R = TBDPS	74%	**77**, X = H	**78**, X = H	90 : 10
4 (**27**)	**38a**, R = TBDPS	66%	**44a**, X = Me	**79**, X = Me	93 : 5 : 2
5 (**68**)	**39**, R = TBDPS	71%	**80**, X = H	**81**, X = H	52 : 48
6 (**27**)	**39**, R = TBDPS	80%	**82**, X = Me	**83**, X = Me	89 : 9 : 2
7 (**68**)	**40**, R = TBDPS	71%	**84**, X = H	**85**, X = H	58 : 42
8 (**27**)	**40**, R = TBDPS	42%	**86**, X = Me	**87**, X = Me	72 : 14 : 14

[a] All reactions were conducted with 3 equiv of **68** or **27** and 3 equiv of *i*-Pr_2NEt in CH_2Cl_2 at 0 °C in the presence of 4 Å molecular sieves for 36 h, unless noted otherwise. [b] Yields are reported for the mixture of homoallylic alchol products. [c] Product ratios were determined by ^1H NMR analysis (400 or 500 MHz) of the crude reaction mixture. In most cases, products were separable by chromatographic methods. [d] Product ratio refers to the two major products whose structures are shown; the third figure is the sum of the other two product diastereomers from each reaction. [e] Stereochemical assignments for all homoallylic alcohol products are summarized in the Supporting Information. [f] The reaction time in this case was 48 h. [g] This reaction was performed for 7 equiv of **27** and 5 equiv of *i*-Pr_2NEt for 72 h.

were performed with the conditions determined to be optimal for the (*Z*)-crotylation reactions of these substrates (Table 3). The reactions of 2,3-*anti* aldehydes **37a** and **38a** with reagents **68** and **27** were quite selective (90:10 to 95:5 d.s.) for the 4,5-*anti* adducts **74** and **51a** from **37a** (entries 1 and 2), and **77** and **44a** from **38a** (entries 3 and 4). The stereochemistry of the major products of these reactions is consistent with pathways involving bicyclic transition states **70** and **71**.

In contrast to the excellent results in the allylation reaction of aldehydes **37a** and **38a**, allylation reactions of 2,3-*syn* aldehydes **39** and **40** with allyltrifluorosilane **68** were virtually nonselective (Table 3, entries 5 and 7). The (*E*)-crotylations of **39** and **40** were reasonably selective for **82** and **86** (entries 6 and 8). However, the 3,4-*anti* stereochemistry of **82** and **86** suggests that they arise via Felkin-selective Zimmerman−Traxler transition state **89**,[4−6] and not by way of the bicyclic transition structure **88**.



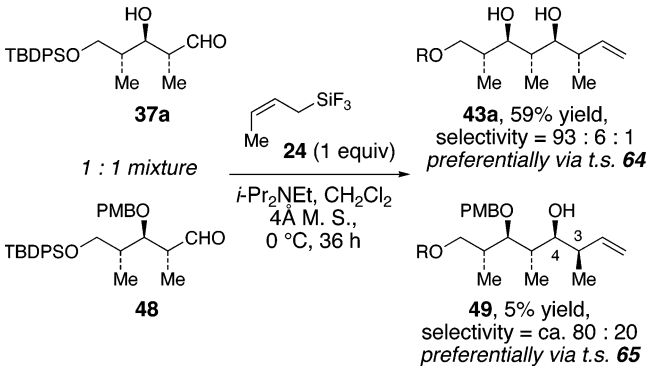
Because we had previously observed that adventitious water could easily divert the (*Z*)-crotylation reaction of the 2,3-*anti* aldehyde **38a** with **24** to produce the 3,4-*syn*-4,5-*anti* diastereomer **44a** in preference to the desired 3,4-*anti*-4,5-*anti* **43a** (Table 1), we suspected that the 2,3-*syn* aldehydes might be more sensitive to the presence of an added nucleophile, much more so than the reactions of the 2,3-*anti* aldehydes. However, attempts to improve the stereoselectivity of the (*Z*)- or (*E*)-crotylation reactions of the 2,3-*syn* aldehydes by using scrupulously purified reagents and solvents were unproductive.

These observations led us to consider the possibility that the aberrant behavior of the 2,3-*syn* aldehydes **39** and **40** in these allylation reactions could be explained by assuming that the hydroxyl group of one molecule of **39** and **40** activates the reagent, and that the resulting pentacoordinate allylsilicate intermediate then reacts with a second molecule of **39** and **40** via an intermolecular transition state (e.g., **65**, **66**, or **89**, where −X in these structures is a second molecule of the β-hydroxy aldehyde substrate).

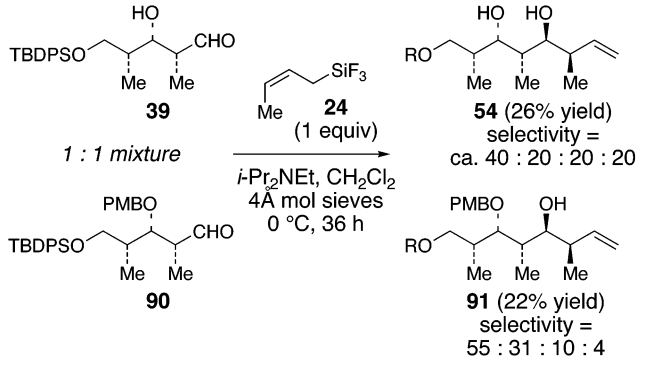
This hypothesis was probed by performing a series of competition experiments.[73,74] In one experiment, a 1:1 mixture of the 2,3-*anti*-β-hydroxy aldehyde **37a** and PMB ether **48** (1 equiv of each) was treated with 1 equiv of

(73) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862.
(74) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

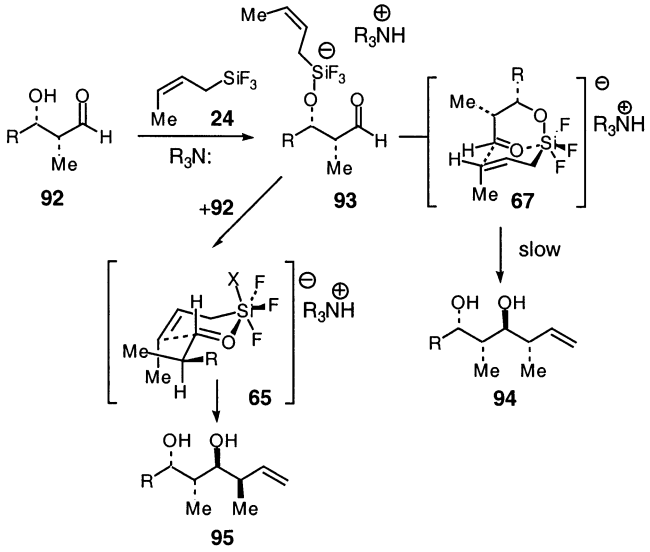
(*Z*)-crotyltrifluorosilane **24** under standard conditions. This provided a 94:6 mixture of **50a** and **51a** in 59% yield. Only a 5% yield of products was obtained from the crotylation of the PMB ether-protected aldehyde **48**, of which **49** possessing 3,4-*syn*-4,5-*anti* stereochemistry predominated (9:1 d.s.). It is striking that the selectivity of the products deriving from **37a** was the same under the conditions of this competition experiment as in the experiments summarized in Table 2, again implicating the involvement of t.s. **64** in the major pathway leading to **50a**. Moreover, the ratio of the two major products deriving from **48** is comparable to that obtained in experiments performed with **48** alone (vide supra). The 3,4-*syn*-4,5-*anti* stereochemistry of **49** again implicates the involvement of the conventional anti-Felkin Zimmerman−Traxler transiton state **65**. Importantly, this experiment reveals that **37a** reacts considerably faster than **48**, and that the presence of the other component in the reaction mixture had little, if any, effect on the product distribution.



Strikingly different results were obtained when a 1:1 mixture of the 2,3-*syn*-*β*-hydroxy aldehyde **39** and the corresponding PMB ether **90** was treated with 1 equiv of (*Z*)-crotyltrifluorosilane **24**. This reaction provided a ca. 50:20:20:10 mixture of the four diastereomers deriving from **39** in 26% yield, among which **54** predominated. In addition, four products (ratio = 55:31:10:4, of which **91** predominated) deriving from **90** were obtained in combined 22% yield. The 3,4-*syn*-4,5-*anti* stereochemistry of the major adducts **54** and **91** indicates that both aldehydes react substantially through the anti-Felkin Zimmerman−Traxler transition state **65**.



That both aldehydes, **39** and **90**, react at comparable rates under these conditions is consistent with the thesis that **39** promotes the reactions of **39** and **24**, as well as of **90** with **24**. This is illustrated in the following diagram, using the generalized *β*-hydroxy aldehyde **92** as the substrate. Complexation of **92** to the crotyltrifluorosilane **24** provides intermediate **93**. The data suggest that reaction by way of t.s. **67** with internal chelation of the aldehyde carbonyl and intramolecular crotyl transfer is quite slow, since **94** is a minor product of these experiments. Alternatively, if the silicon center of **93** preferentially coordinates with a second equivalent of the aldehyde substrate, the opportunity then exists for a conventional crotylation to proceed by way of **65**. We would expect that aldehydes **39** and **90** would be comparably reactive with **93**, as is borne out by the experimental results. This hypothesis is also consistent with knowledge that external nucleophiles such as CsF, ROH, phosphonamides, etc., are viable nucleophilic catalysts for aldehyde allylation reactions with allyltrifluorosilanes.[33,34,40,42,45,49,50,52−56,66]



On the Origin of the Stereodivergent Behavior of 2,3-*anti*- and 2,3-*syn*-α-Methyl-*β*-hydroxy Adehydes in Their Allylation Reactions with Allyl- and Crotyltrifluorosilanes. The data summarized in the preceding sections of this paper are consistent with the proposal that the 2,3-*syn* aldehydes **39** and **40** react with

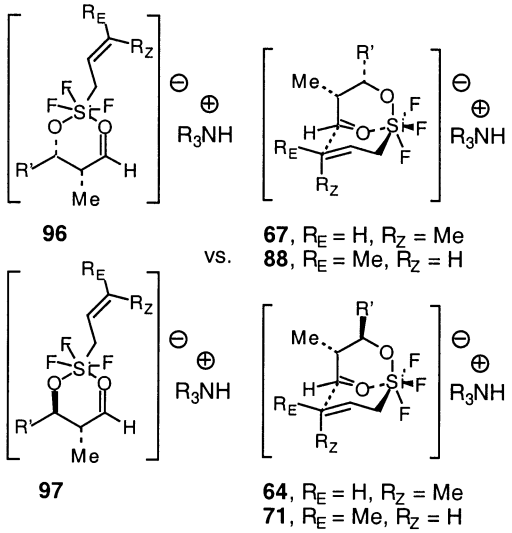
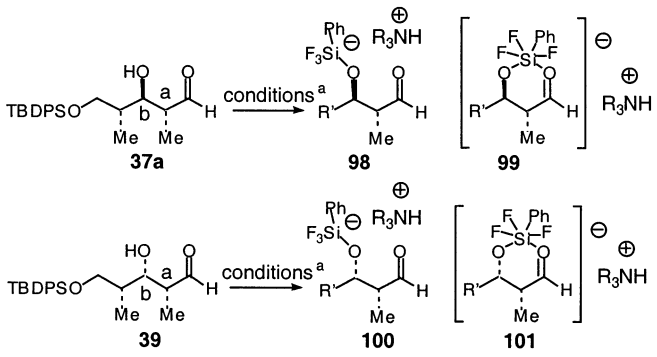


TABLE 4. NMR Data for Aldehyde−$PhSiF_3$ Complexes



sample	^{1}H NMR, δ formyl H	Ha	Hb	J_{Ha-Hb}, Hz	^{13}C NMR, δ carbonyl	^{19}F NMR[b]
2,3-*anti* **37a**	9.80	2.59	3.76	5.1	205.5	
complex **98**[a]	9.73	2.82	4.42	5.9	203.4	−117.7[c]
2,3-*syn* **39**	9.64	2.58	4.11	5.3	204.4	
complex **100**[a]	9.65	2.65	4.78	4.5	202.9	−117.6[c]

[a] Generated by treatment of **37a** or **39** with $PhSiF_3$ (1 equiv), i-Pr2NEt (1 equiv), 4 Å molecular sieves in CD_2Cl_2, 23 °C. [b] The ^{19}F resonance of $PhSiF_3$ in CD_2Cl_2 appears at −141.0 ppm. [c] Fluorine chemical shift (δ) relative to $CFCl_3$.

(*Z*)-**24** and (*E*)-**27** preferentially by way of the conventional Zimmerman−Traxler transition structures **65** and **89**, respectively, whereas the 2,3-*anti*-*β*-hydroxy aldehydes **37a** and **38a** react with (*Z*)-**24** and (*E*)-**27** by way of the bicyclic transition states **64** and **71**. However, it is not obvious a priori why the bicyclic transition states **67** and **88** for the crotylation reactions of the 2,3-*syn*-*β*-hydroxy aldehydes are so much less favorable than **64** and **71** for the 2,3-*anti*-*β*-hydroxy aldeyhydes. It is conceivable that the stereodivergent behavior of the 2,3-*anti* and 2,3-*syn*-*β*-hydroxy aldehydes is due to the inability of the 2,3-*syn*-*β*-hydroxy aldehydes to form the required six-centered chelate, **96**, owing to the requirement that one alkyl substituent (Me or R′) must be axial in the chelate. However, it is also possible that the problem resides with nonbonded interactions that develop in the bicyclic transition states **67** or **88**.[75] We considered the latter to be most probable, since it is likely that the C−C bond forming event is rate determining. Nevertheless, we decided to probe these possibilities by performing NMR studies of model aldehyde−fluorosilane complexes, and by molecular modeling studies of the reaction transition states.

NMR Studies. Reports by Keck[76−78] and Denmark[79,80] suggested that it might be possible to determine if chelates **99** or **101** are stable, observable intermediates. We examined the ^{1}H, ^{13}C, and ^{19}F NMR spectra of the complexes formed between the 2,3-*anti* and 2,3-*syn* aldehydes **37a** and **39** with phenyltrifluorosilane ($PhSiF_3$)[81] in the presence of *i*-Pr_2NEt. Phenyltrifluorosilane was used in this study since its Lewis acidity should be comparable to that of the allyl- and crotyltrifluorosilanes **24**, **27**, and **68**, but will not react with the aldehydes.

Key NMR data for aldehydes **37a** and **39** and their complexes with $PhSiF_3$ are summarized in Table 4. On the basis of these data, we conclude that the aldehyde−$PhSiF_3$ chelates **99** and **101** are not observable by NMR spectroscopy. Significantly, the ^{13}C chemical shifts of the carbonyl carbons of the complexed species appear within 2 ppm of those of the starting aldehydes, indicating that the aldehyde is not complexed to the silane reagent (one would expect a significant downfield shift of the aldehyde carbonyl carbon if complexation occurred).[76−80] Moreover, the $J_{a,b}$ coupling constants of the complexed species are inconsistent with cyclic structures. This is especially apparent for the complex formed between $PhSiF_3$ and the 2,3-*anti* aldehyde **37a**, where a large coupling constant (9−12 Hz) would be expected for a structure such as **99**; $J_{a,b} = 5.9$ Hz was observed instead. The ^{1}H and ^{13}C NMR spectra of these complexes showed little temperature dependence over a 23 to −60 °C range.

The ^{19}F chemical shifts of the aldehyde−$PhSiF_3$ complexes appear as broad singlets at −117.7 and −117.6 ppm for the 2,3-*anti* and 2,3-*syn* aldehyde−$PhSiF_3$ complexes, respectively. This is a substantial change relative to the ^{19}F resonance for $PhSiF_3$, which is a sharp singlet at −141.0 ppm, and appears as a broad singlet at −140.8 ppm in the presence of *i*-Pr_2NEt (^{19}F δ relative to $CFCl_3$). The ^{19}F signals at ca. −117 ppm are consistent with the formation of hypervalent silicate species. For example, the ^{19}F resonance of the pentacoordinate silicate $[(C_3H_7)][SiF_4C_4H_9]$ appears at −116.6 ppm in CH_2Cl_2.[82] We could not ascertain from these spectra if the observed species (**98** and **100**) are pentacoordinate or hexacoordiante silicates as the ^{19}F signals of hexacoordinate silicates are also reported to appear in this region at 23 °C.[83,84] Additionally, we were unable to observe F−F coupling

(75) We thank a referee of our inital communication for suggesting that we attempt to differentiate between these possibilities.
(76) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.
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(82) Klanberg, F.; Muetterties, E. L. *Inorg. Chem.* **1968**, *7*, 155.
(83) Marat, R. K.; Janzen, A. F. *Can. J. Chem.* **1977**, *55*, 1167.
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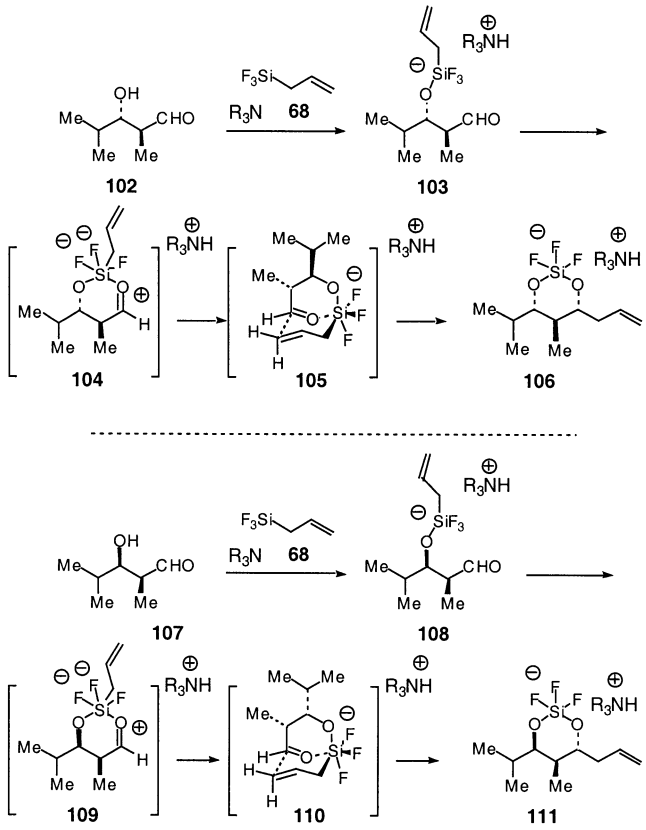
at temperatures ranging from 23 to −60 °C, which could have been a useful indicator of the geometry at the silicon center; presumably inter- or intramolecular fluoride exchange processes are rapid under the observation conditions.[83,84]

Molecular Modeling Studies. We employed semiempirical molecular modeling calculations to aid in our analysis. The calculations were performed to compare the relative energies required for formation of the 2,3-*syn*- and 2,3-*anti*-*β*-hydroxy aldehyde chelates, should they be discrete reaction intermediates, and to investigate the relative contributions that nonbonded interactions at the transition states make to the stereodivergent behavior of the 2,3-*syn* and 2,3-*anti* aldehydes in the crotylsilylation reactions.

The MNDO/d semiempirical basis set[85,86] in the Spartan[87] molecular modeling software package was used for these calculations because it contains parameters for hypervalent silicon atoms that take into account the participation of d orbitals. Although the absolute activation energies calculated by semiempirical methods are not expected to be meaningful, comparisons of the calculated activation energies of several related processes (i.e., determination of relative activation energies) should be more reliable due to cancellation of systematic errors.

The lengths of the six bonds involved in each of the transition state cores were fixed (according to Houk's "fixed core method"),[88] using bond lengths obtained by Kira et al.,[48] who performed ab initio molecular orbital calculations with the Gaussian 82[89] and HONDO[90] programs using the MIDI-4(*)[91,92] basis set to locate the transition state for the reaction of tetrafluoroallylsilicate with formaldehyde. Kira et al. did not include the counterion in their calculated transition structure, and likewise, we also ignored the counterion (*i*-Pr_2NEtH^+) in our calculations, with the assumption that the counterion would affect each transition state in a similar manner, and thus would be canceled out when we compared relative transition state activation energies.

The transition states were approximated with the Linear Synchronous Transit method, which interpolates geometry between that of the reactant and that of the product. The transition states were then minimized by fixing the core, using the bond lengths derived from Kira's transition state calculation[48] and minimizing the geometry about the core. The bond angles in the transition state core were allowed to vary in the calculations. The lowest energy transition state for each case was located by calculating the energies of a family of transition states containing different aldehyde side-chain rotamers. In the following transition state structures, H−H distances less than 2.3 Å are highlighted to point out destabilizing van der Waals interactions, and eclipsed ethane conformations are also pointed out when observed, as these interactions generally cost a molecular conformation ca. 3 kcal/mol.



The allylation reactions of 2,3-*anti* and 2,3-*syn*-*β*-hydroxy aldehydes were modeled for the formation of the desired 4,5-*anti* adducts, **106** and **111**, using the structurally simplified aldehydes **102** and **107**. The silicate intermediates **103** and **108** served as the ground states for these reactions (as supported by our NMR studies, which show that these species are stable intermediates).

The activation energies were calculated from the differences in energy between the pentacoordinate silicate intermediates **103** and **108** and the intramolecular, bicyclic transition states **105** and **110** (vide infra). Additionally, the difference in energy between the pentacoordinate silicates **103** and **108** and the chelate intermediates **104** and **109** gave us the energies required for chelate formation.

The lowest energy conformations for the 2,3-*anti* and 2,3-*syn* aldehyde ground states **103** and **108** are shown in Figure 1. In these structures, axial placement of the aldehyde fragment (coordinated to silicon via the hydroxyl group) and equatorial placement of the allyl group about the trigonal bipyramidal silicate center provided the lowest energy arrangement. The calculated energies for the ground state conformations of **103** and **108** are within 0.2 kcal/mol of each another.

Results of calculations of the chelated intermediates and transition states involved in the allylation reactions of the 2,3-*anti* aldehyde **102** and the 2,3-*syn* aldehyde **107** are shown in Figure 2.

In transition state **105** for the 2,3-*anti* aldehyde, which leads directly to adduct **106**, the only potentially desta-

(85) Thiel, W.; Voityuk, A. A. *Theor. Chim. Acta* **1992**, *81*, 391.
(86) Thiel, W.; Voityuk, A. A. *Int. J. Quantum Chem.* **1992**, *44*, 807.
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(88) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.
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(90) Dupuis, M.; Watts, J. D.; Villar, H. O.; Hurst, G. J. B. *HONDO*, 7.0 ed.; IBM Corporation, Scientific Engineering Computations: Kingston, NY 12401; QCPE No. 544, Indiana University: Bloomington, IN.

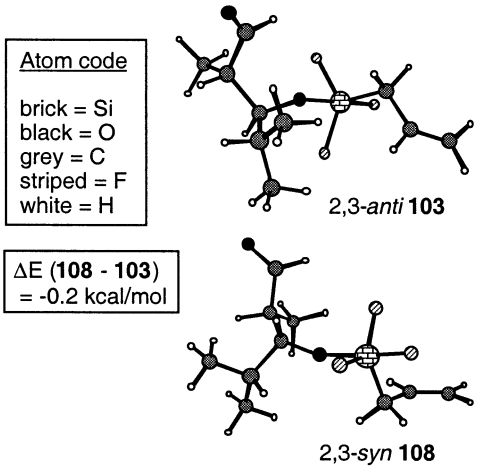

FIGURE 1. Minimized structures of **103** and **108.**

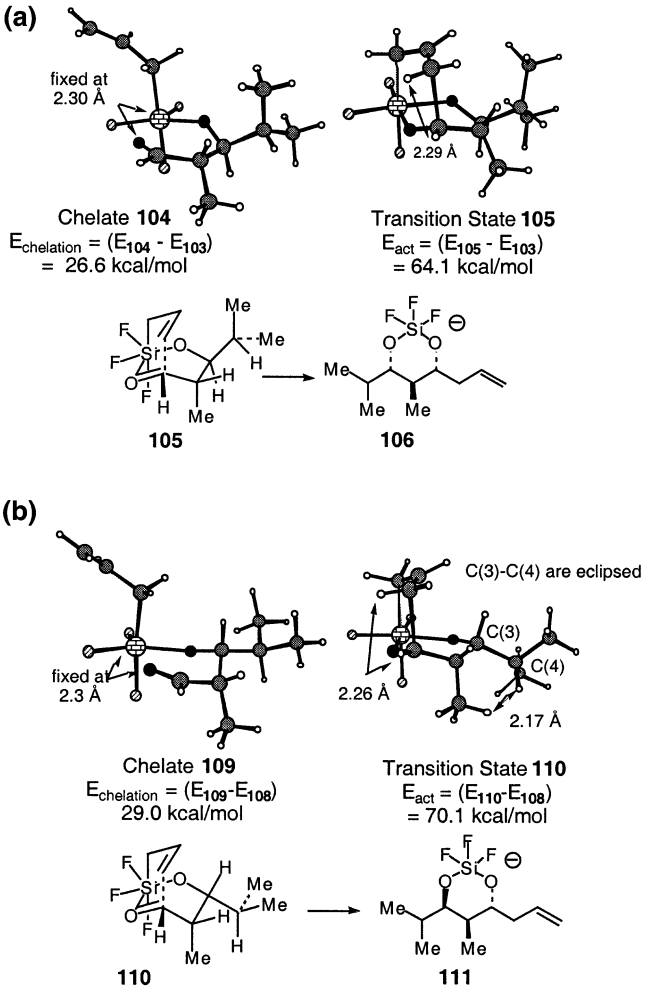

FIGURE 2. (a) Intramolecular reaction of allyltrifluorosilane **68** with a 2,3-*anti*-*β*-hydroxy aldehyde **102**. (b) Intramolecular reaction of allyltrifluorosilane **68** with 2,3-*syn*-*β*-hydroxy aldehyde **107**.

bilizing interaction observed is between the aldehyde formyl hydrogen and one of the allylsilane C*γ*-hydrogens (2.29 Å separation in this structure). The energy of activation in this reaction was calculated to be 64.1 kcal/mol ($E_{act} = E_{105} - E_{103}$). The atoms involved in bond formation and bond breaking adopt a chairlike orientation. The corresponding boatlike transition state, which is higher in energy for most aldol and allylation reactions,[88,93,94] was calculated to be 3.0 kcal/mol higher in energy than **105**. However, the chelate ring bends away from the allyl group in this transition state, and adopts an overall boatlike conformation. This trend is consistent for all of the bicyclic allylation transition states that we calculated.

The energy required for chelate formation with the 2,3-*anti* aldehyde was calculated as 26.6 kcal/mol by taking the difference in energy between chelate **104** and ground state **103**. In chelate **104** (and in all other of the chelate models that we calculated) the silicon−carbonyl oxygen distance was fixed at 2.3 Å to simulate a loose association (for reference, the Si−O silyl ether bond length in **104** is 1.88 Å). The Si−O distance had to be fixed because the modeling program did not accept direct bonding between these atoms.[48]

In the bicyclic transition state **110** for the reaction of the 2,3-*syn*-*β*-hydroxy aldehyde **107** with allyltrifluorosilane, which led to the 4,5-*anti* adduct **111**, the chelate ring must bend away from the allyl group to avoid steric interactions with the allyl group of the allylsilane, thus bringing the C(2) methyl and the C(3) isopropyl groups closer together. To relieve steric interactions, the C(3) isopropyl group rotates, causing the C(3)−C(4) bond to become eclipsed. The C(4) hydrogen is within 2.17 Å of one of the hydrogens of the C(2) methyl group. Additionally, the allyl group bends away from the chelate ring, bringing the formyl hydrogen and one of the hydrogens on the allylsilane *γ*-C within 2.26 Å of one another. The activation energy for this reaction was calculated to be 70.1 kcal/mol. The energy required for the 2,3-*syn* aldehyde to adopt the chelate structure **109** was calculated as 29.0 kcal/mol.

A comparison of the calculated activation energies for the allylation reactions proceeding by way of bicyclic transition structures **105** and **110** reveals that the activation energy for the allylation reaction of the 2,3-*syn* aldehyde is 6.0 kcal/mol greater than that of the 2,3-*anti* aldehyde. In comparing the calculated energies of chelation of the two aldehydes, we find that the chelate formation with the 2,3-*syn* aldehyde **107** requires 2.1 kcal/mol more energy than does chelate formation for the 2,3-*anti* aldehyde **102**.

In an analogous manner, the chelation and the activation energies for the reactions of aldehydes **102** and **107** with the (*E*)- and (*Z*)-crotyltrifluorosilane reagents were calculated. The results of these calculations closely parallel the reactions of these aldehydes with the allyltrifluorosilane reagent (see Table 5). A more complete discussion of the calculations of the transition states involving the (*E*)- and (*Z*)-crotyltrifluorosilane reagents is provided in the Supporting Information.

These calculations are consistent with the conclusion that the stereodivergent behavior of the two aldehyde classes is the result of the different levels of destabilizing nonbonded interactions experienced in the bicyclic transition states. However, because the stereochemical out-

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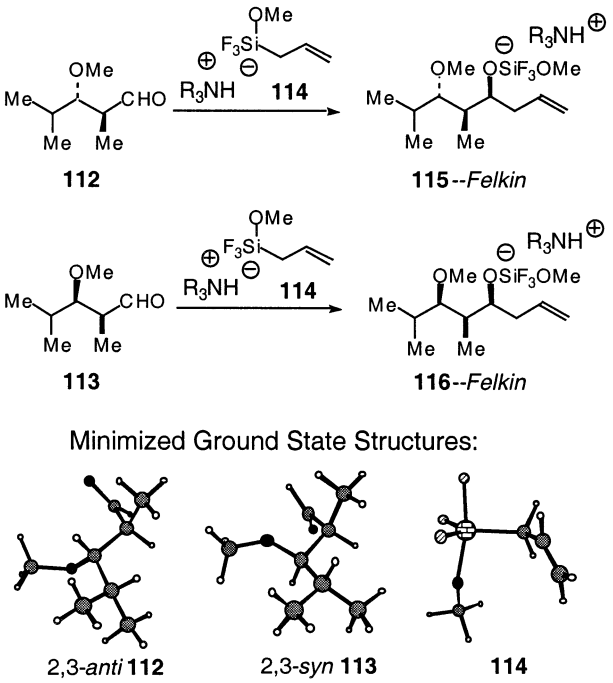
TABLE 5. Comparison of the Calculated Chelation and Activation Energies (kcal/mol) for the Allylation and Crotylation Reactions of β-Hydroxy Aldehydes via Chelated Bicyclic Transition States

reagent	$\Delta E_{chelate}$(anti − syn)	ΔE_{act}(anti − syn)
68, allyl	−2.1	−6.0
27, (*E*)-crotyl	−1.9	−3.7
24, (*Z*)-crotyl	−1.9	−6.4

come of the allylation/crotylation reactions is determined by competition between the bicyclic and conventional Zimmerman−Traxler pathways, we also used semi-emperical calculations to estimate the activation energies for the latter processes for both aldehyde classes. Again, it must be noted that these calculations are qualitative in nature, as they are based on the fixed core of Kira's allylation transiton state.[48] These calculations only account for differences in enthalpy. The loss of entropy in a bimolecular reaction would be another factor that could disfavor the conventional Zimmerman−Traxler pathways.

The Zimmerman−Traxler allylation reactions of 2,3-*anti* and 2,3-*syn* aldehydes with allyltrifluorosilane were modeled by the reactions of the β-methoxy aldehydes **112** and **113** with the methoxyallyltrifluorosilicate **114**. In reality, these reactions probably take place between two equivalents of the silicate−aldehyde complex, e.g. **103**, one to serve as the aldehyde, the other to serve as the allylating reagent. For ease of molecular modeling of the transition states, however, the simplified β-methoxy aldehydes **112** and **113** and the simplified methoxy allylsilane **114** were used. The transition states leading to the Felkin adducts **115** (derived from **112**) and **116** (derived from **113**) were calculated. The activation energies were calculated from the difference between the Zimmerman−Traxler transition states and the sum of the ground states for the two reactants (e.g., $E_{g.s.} = E_{114} + E_{112}$). The ground-state energy for the 2,3-*anti*-β-methoxy aldehyde **112** was calculated to be 1.6 kcal/mol lower than that calculated for the 2,3-*syn* aldehyde **113**.



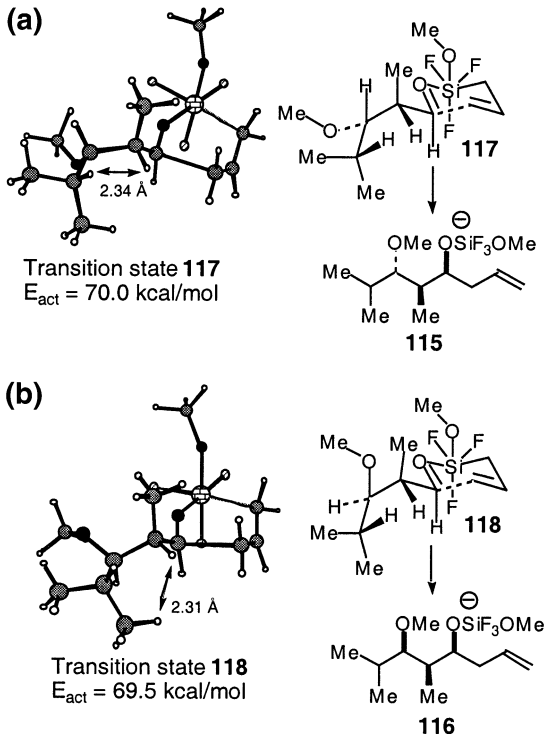


FIGURE 3. (a) Reaction of allyltrifluorosilane with 2,3-*anti*-β-methoxy aldehyde **112**. (b) Reaction of allyltrifluorosilane with 2,3-*syn*-β-methoxy aldehyde **113.**

Results from the modeling of the Zimmerman−Traxler transition states are shown in Figure 3. No destabilizing van der Waals or eclipsed interactions were observed in the Felkin transition state **117** for the 2,3-*anti* aldehyde **112**, and the activation energy for this reaction was calculated to be 70.0 kcal/mol [$E_{act} = E_{117} - (E_{112} + E_{114})$].

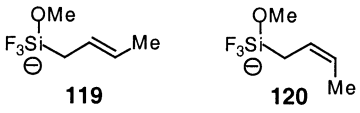
Also, no destabilizing interactions were observed in the Felkin transition state **118** for the 2,3-*syn*-β-methoxy aldehyde **113**. The activation energy for this reaction was calculated to be 69.5 kcal/mol [$E_{act} = E_{118} - (E_{113} + E_{118})$], which is only 0.5 kcal/mol lower than the activation energy calculated for the analogous reaction for the 2,3-*anti*-β-methoxy aldehyde **112**.

In an analogous manner, the activation energies for the reactions of the 2,3-*anti*- and 2,3-*syn*-β-methoxy aldehydes **112** and **113** with the (*E*)- and (*Z*)-methoxytrifluorocrotylsilicates **119** and **120** were calculated (for additional discussion complete with figures, see Supporting Information). A summary of the activation energies for the traditional allylation reactions of the 2,3-*anti* and 2,3-*syn* aldehydes with allyl- and (*E*)- and (*Z*)-methoxytrifluorosilicates is provided in Table 6.

These computational results indicate that the small energetic difference in the Zimmerman−Traxler mediated allylation reactions of the two aldehydes **112** and **113** is not a significant contributor toward their stereodivergent behavior that was observed.

Several general trends have appeared in these calculations. By comparing the activation energies of the bicyclic, internally chelated allylation/crotylation reactions of the 2,3-*anti*- and 2,3-*syn*-β-hydroxy aldehydes, we find that in each case the 2,3-*anti* aldehydes have lower activation energies than do the 2,3-*syn* aldehydes with energetic differences ranging from 3.7 to 6.4 kcal/mol (Table 5). On

TABLE 6. Comparison of the Activation Energies (kcal/mol) for the Zimmerman−Traxler Mediated Allylation Reactions



119 **120**

silicate	ΔE_{act}(anti − syn)
114, allyl	0.5
119, (*E*)-crotyl	1.6
212, (*Z*)-crotyl	3.0

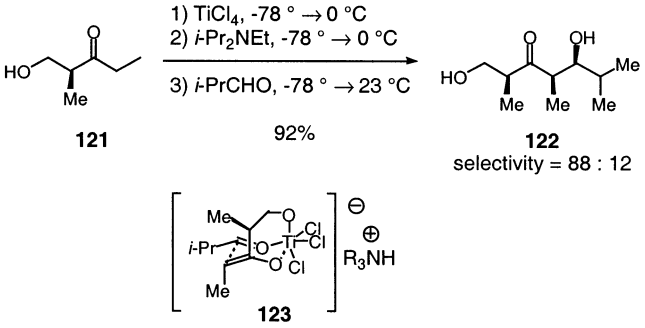
the other hand, comparison of the calculated activation energies of the Zimmerman−Traxler mediated reactions of the 2,3-*anti* and 2,3-*syn* aldehydes with the allyl-(crotyl)trifluorosilane reagents shows that the reactions of the 2,3-*syn* aldehydes have lower activation energies than the 2,3-*anti* aldehydes, but with a smaller energetic preference of 0.5−3.0 kcal/mol (Table 6). Additionally, we have found that the 2,3-*anti* aldehydes more easily adopt chelate structures, e.g. **104**, than do the 2,3-*syn* aldehydes (e.g., **109**), with chelate formation being 1.9−2.1 kcal/mol less endothermic in the latter cases. However, comparison of the energies required for formation of the chelates (e.g., 26.6 kcal/mol to form chelate **104** from ground state **103**) vs the energies of activation for the overall reaction (e.g., 64.1 kcal/mol to transition state **105** from ground state **103**) reveals that, according to these calculations, chelation is not the rate determining step, and therefore differences in the rates of chelate formation of the 2,3-*syn* vs 2,3-*anti* aldehydes cannot account for the stereodivergent behavior of the two aldehyde classes. *It thus appears that the most significant factor in the stereodivergent behavior of 2,3-anti vs 2,3-syn aldehydes in their reactions with allyl- and crotyltrifluorosilanes arises from the different degrees of strain or nonbonded interactions experienced by the two aldehydes in the bicyclic allylation transition states.*

These models indicate that in a 6,6-bicyclic transition state (e.g. **105** and **110**, Figure 2), one ring will prefer to adopt a chairlike orientation while the other ring will adopt a boatlike conformation to avoid transannular nonbonded interactions between them. The boatlike conformation of the chelate ring brings the C(2) and C(3) aldehyde substituents closer together, a situation that is more easily accommodated by the 2,3-*anti* aldehydes than by the 2,3-*syn* aldehydes. These models may be predictive of other designed 6,6-bicyclic transition states, e.g. other chelate-controlled allylation or aldol reactions.[95]

Conclusion

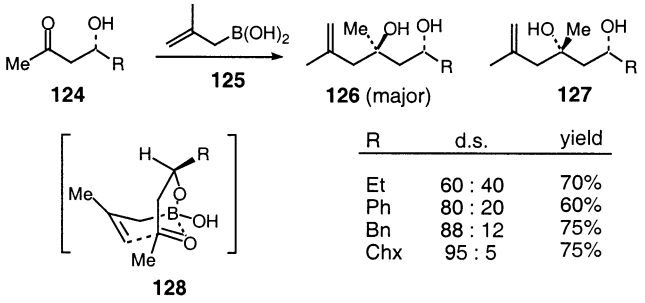
The initial objectives of this study focused on the development of a concise, efficient solution to the problem posed by the *anti*,*anti*-dipropionate stereotriad (cf., **16**). As the science progressed, we were led to examine in detail the fundamental properties of the proposed bicyclic transition state **64**. The general rule we have gleaned from this exercise is that the 2,3-*anti*-*β*-hydroxy aldehydes are excellent substrates for this reaction, but that the 2,3-*syn*-*β*-hydroxy aldehydes are not. Our computational analysis suggests that in the productive bicyclic transition state, one ring will prefer to adopt a chairlike orientation while the other ring will adopt a boatlike conformation to avoid transannular nonbonded interactions between them. The boatlike conformation of the chelate ring brings the C(2) and C(3) aldehyde substituents closer together, a situation that is more easily accommodated by the 2,3-*anti* aldehydes than by the 2,3-*syn*-*β*-hydroxy aldehydes. The latter interaction destabilizes the chelated bicyclic transition state for the allylation/crotylation reactions of the 2,3-*syn*-*β*-hydroxy aldehydes, thereby allowing the traditional Zimmerman−Traxler-type transition states to be competitive in such cases.

Ideally, a study that would separate the intrinsic selectivity of the α- and *β*-stereocenters of the aldehyde could assist in an analysis of the influence of each stereocenter on these bicyclic transition states. Although we did not study substrates with a single stereocenter at these positions, analogous examples are available in the literature. For example, the effect of the α-methyl stereocenter on the course of the reaction is demonstrated in an analogous reaction where an α-chiral titanium (*Z*)-(O)-enolate reacts with isobutyraldehyde to generate the aldol adduct **122** as the predominant isomer. The stereochemistry of **122** is best rationalized as having been created through the bicyclic transition state **123**.[96]



121 **122** **123**

The intrinsic preference of the *β*-stereocenter of our aldehydes may be interpolated from the analogous reactions of *β*-hydroxy ketones with allyl- and crotylboronic acids.[38] As illustrated in the equation below, the major product of these reactions contains the 1,3-*anti* diol relationship, which is consistent with having emerged from the bicyclic transition state **128**.



124 **125** **126** (major) **127**

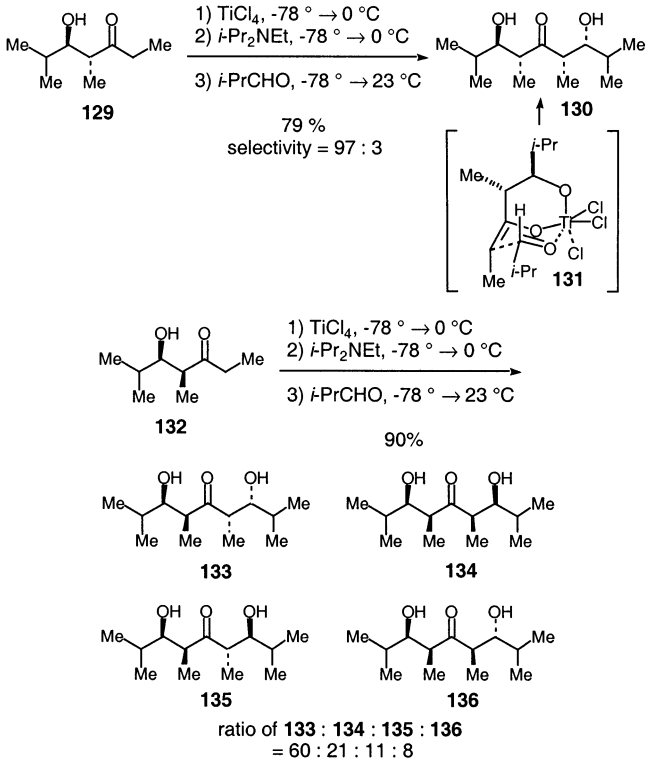
R	d.s.	yield
Et	60 : 40	70%
Ph	80 : 20	60%
Bn	88 : 12	75%
Chx	95 : 5	75%

128

(95) The transition states are likely to be very sensitive to the aldehyde substitution pattern. Most of the reactions reported herein and all of the calculations were performed with *β*-branched aldehydes. It is possible that unbranched aldehydes will experience fewer nonbonded interactions in the transition states, with different selectivities than the examples discussed here.

(96) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

Taken together, these examples indicate that from a simple, linear analysis (if one were to add the effects of the α- and *β*-stereocenters on the product outcome), the 2,3-*syn* aldehydes should be more amenable to the bicyclic transition state than the 2,3-*anti* aldehydes. But this is not the case. This phenomena has also been observed in a recent example involving *syn*- and *anti*-α-methyl-*β*-hydroxy titanium enolates.[96] Although the authors were unable to offer a mechanistic explanation for their results, they observed a stereodivergence between these two enolate classes: the enolate generated from the 2,3-*anti* ethyl ketone **129** selectively reacted with isobutyraldehyde to provide the aldol adduct **130**, while the enolate derived from the 2,3-*syn* ketone **132** gave a mixture of the four aldol adducts **133**−**136**.[96] We can analyze these results in light of our data if we assume that the key steric interactions felt in these bicyclic transition states are valid within a small range of bond lengths and bond angles as these factors will vary depending upon the type of atoms invoved in the transition state core. Transition state **131** for the 2,3-*anti* enolate derived from **129** should be favored for the creation of aldol adduct **130**, whereas an analogous transition state for the 2,3-*syn* enolate, which would lead to adduct **134**, is unfavorable due to the nonbonded interactions that would exist between the α- and *β*-substitutents of the enolate in the bicyclic transition state.



Finally, the analysis presented herein is also relevant to the results of tandem aldol−allylation reactions, using strained silacycles recently reported by Leighton.[97]

Acknowledgment. Financial support provided by the National Institute of General Medical Sciences (GM 38436) is gratefully acknowledged. We thank Dr. Marty Pagel (Indiana University) for assisting with the MOPAC calculations, Prof. Ted Widlanski (Indiana University) for helpful discussions, and Prof. Mark Banaszak-Holl (University of Michigan) for use of his Spartan program. We also thank Roxanne Kunz and Dustin Mergot for assistance with the preparation of this manuscript.

Supporting Information Available: Complete experimental details, stereostructure proofs for allylation products, details of MOPAC calculations, and copies of ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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