The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of α- and β-Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles

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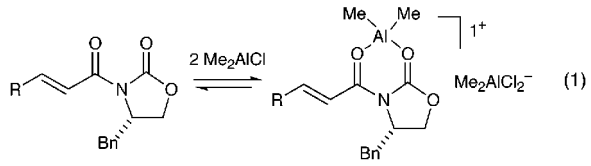
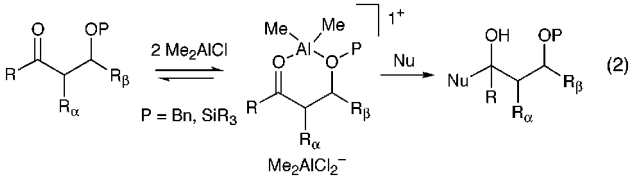
Abstract: A systematic investigation of the stereoselectivity in Lewis acid-promoted (Mukaiyama) aldol reactions of achiral unsubstituted enolsilanes and chiral β-hydroxy aldehydes proceeding under conditions favoring chelation control is presented. Good stereocontrol can be realized for enolsilane aldol reactions of β-alkoxy and β-silyloxy aldehydes bearing only an α- or a β-stereogenic center. Examination of the chelated intermediates for α,β-disubstituted aldehydes concludes that the syn aldehyde diastereomer possesses the arrangement of stereocenters wherein the α- and β-substituents impart a reinforcing facial bias upon the aldehyde carbonyl. Aldol reactions of syn aldehydes were thus observed to proceed with uniformly excellent diastereofacial selectivity. Aldol reactions of the corresponding anti aldehydes containing opposing stereocontrol elements at the α- and β-positions exhibit variable and unpredictable selectivity.

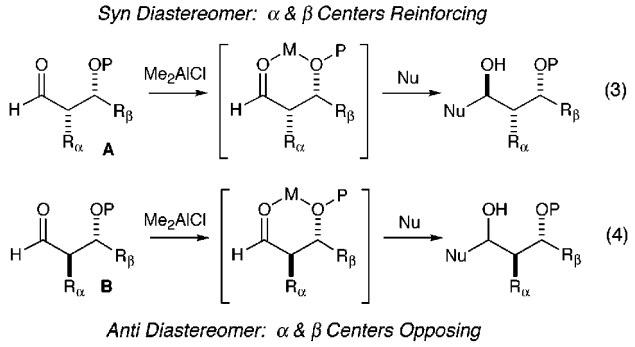
Objectives

The integration of chelate organization into the design of stereoselective processes is widespread. Numerous examples incorporate this stereochemical control element into diastereoselective and enantioselective carbonyl addition,[1,2] chiral enolate−electrophile reactions,[3] and cycloadditions.[4] During the development of the oxazolidinone-based Diels−Alder reactions some years ago,[4a] a number of Lewis acids, including both $SnCl_4$ and $TiCl_4$, were surveyed by us for their ability to activate the dienophilic component through chelate organization; however, none of these Lewis acids delivered either the reactivity or the diastereoselectivity displayed by dimethylaluminum chloride (Me_2AlCl), which was proposed to chelate the substrate through the illustrated cationic complex (eq 1).[4a,5] The present study has extended the exceptional chelating potential of Me_2AlCl, and its companion Lewis acid $MeAlCl_2$, to chelate-organized carbonyl addition reactions where the chelating heteroatom may include alkyl ethers as well as hindered silyloxy substituents (eq 2).[5]





The objectives of this investigation are two-fold: (A) to document the scope and limitations of Me_2AlCl and $MeAlCl_2$ as chelating Lewis acids in enolsilane addition reactions with β-alkoxycarbonyl substrates and (B) to document that the chelate-promoted enolsilane addition reactions of diastereomeric aldehydes **A** and **B** reveal either enhanced carbonyl face selectivities for the syn aldehyde diastereomer (eq 3) or eroded face selectivities for the corresponding anti diastereomer (eq 4). Such predictions follow from an analysis of the metal



(1) (a) For an excellent review of Cram's rule, including a review of chelation controlled reactions, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468 and references therein.

(2) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. Evans, D. A.; Burgey, C. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 686−699 and references therein.

(3) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23.

(4) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (c) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Engl.* **1998**, *24*, 3372−3375.

(5) For a preliminary communication of aspects of this study see: (a) Evans, D. A.; Allison, B. A.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457−4460. (b) Evans, D. A.; Halstead, D. P.; Allison, B. A. *Tetrahedron Lett.* **1999**, *40*, 4461−4462.

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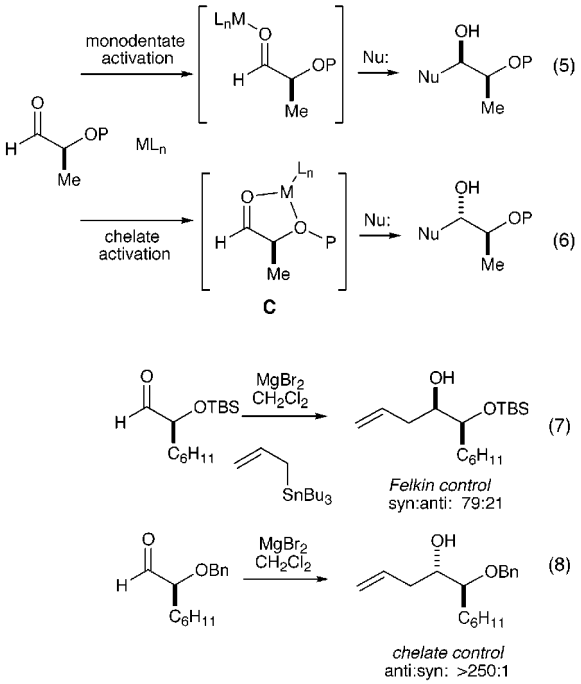
chelates derived from syn and anti aldehyde diastereomers, respectively. This stereochemical issue has not been systematically explored particularly in comparison with the corresponding reactions under nonchelating conditions.[6] This investigation is intended as a companion to our earlier study in this area where it was documented that the two stereocenters in syn aldehyde **A** are *nonreinforcing* in carbonyl additions promoted by nonchelating Lewis acids while the two stereocenters in anti aldehyde **B** are *reinforcing*.[7]

Background

The analysis of carbonyl π-facial selectivity has attracted immense interest since Cram's pioneering studies on the stereoselective addition of organometallic reagents to chiral acyclic carbonyl substrates bearing vicinal alkyl and heteroatom substituents.[8] In his series of investigations, "open-chain" and "chelation" transition state models were proposed to account for stereoselective nucleophilic carbonyl addition reactions to these families of substrates, respectively. While Cram's models for stereoinduction followed from the results of organometallic addition reactions, these transition state models through their modern refinements (Felkin-Anh)[9] have been applied to the broader field of Lewis acid-mediated carbonyl addition processes.[10] Carbonyl substrates such as **A** and **B** (eqs 3and 4) that exhibit the potential for chelation-controlled addition[1,11] are of particular interest in this investigation. However, such substrates, while exhibiting the potential for chelate control, may react through either "open-chain" (Felkin) or "chelated" transition states. In substrates such as α-alkoxy carbonyl derivatives, the consequence of either Felkin monodentate (eq 5) or chelate carbonyl activation (eq 6) has a direct bearing on the stereochemical outcome of the reaction. In fact, the stereochemical outcome of this reaction provides strong circumstantial evidence of the mode of carbonyl activation.[12]

A number of factors are responsible for determining which mode of Lewis acid-substrate activation might be anticipated. Such factors include the nature of the coordinating Lewis acid ($BF_3{\cdot}OEt_2$ vs $TiCl_4$) and the nature of the oxygen protecting group, P (Bn vs t-$BuMe_2Si$),[13,14] and the reaction solvent (CH_2Cl_2 vs THF).[15] The impact of many of these variables has been highlighted by Keck in his study of the catalyzed addition of allylstannanes to α-alkoxy aldehydes (eqs 7 and 8).[14] In the cited examples, the impact of the oxygen protecting group on the mode of substrate activation is illustrated. This and related cases provide additional evidence that hindered silyl ethers do not generally participate in chelate organization.



***β*-Chelation: 1,2-Induction.** The currently embraced Felkin-Anh model[8d,e] and the chelate-controlled addition model are illustrated in Scheme 1 for α-methyl β-alkoxy aldehydes **1** and **2** (eqs 9 and 10). As with α-alkoxy aldehydes, the two control elements lead to different product diastereomers. It has been well precedented that metal ion chelation between the carbonyl and β-oxygen substituent provides a conformationally constrained six-membered ring having sterically differentiated diastereofaces (eq 10). Observation of Lewis acid−substrate complexation by NMR spectroscopy suggests that the favored chelate conformation positions the α-alkyl substituent in the pseudoequatorial position of the chair conformer.[16] Addition of the nucleophile to the anti-Felkin[17] diastereoface opposite the α-alkyl group affords the 1,2-anti OH-Me relationship in the adduct.[18] The NMR study not withstanding, both half-chair and boat transition state chelate geometries rationalize the sense of asymmetric induction (eq 10).

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(7) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(8) (a) Cram D. J.; Abd Elhafez, F. A *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748−2755. (c) Cram, D. J.; Leitereg, T. H. *J. Am. Chem. Soc.* **1968**, *90*, 4019−4026.

(9) Several "open chain" models have been presented since Cram: (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112−127. (b) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367−1371. (c) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61−70. (e) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (f) For an excellent review of Cram's rule see ref 1a.

(10) For reviews of Lewis acid-promoted reactions, see: (a) Enolsilanes: Gennari, C. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds Part 2*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York 1991; Chapter 2.4. (b) Allylsilanes and allylstannanes: Fleming, I. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds Part 2*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York 1991; Chapter 2.2.

(11) (a) Eliel E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 5, pp 125−155. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. (c) Reference 1. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214−4223.

(12) For the first direct evidence for chelate control see: Reetz, M.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477−479.

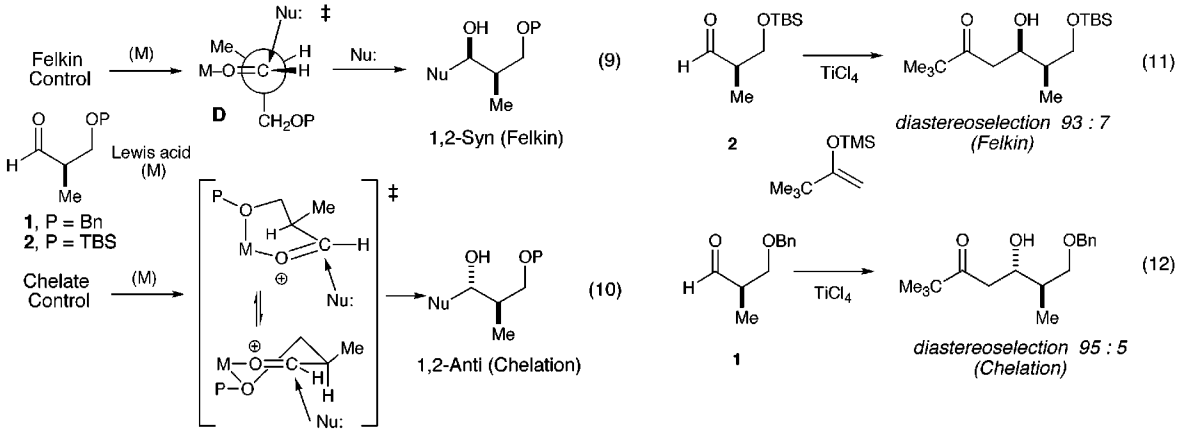
(13) (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355−2358. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478−5480. (c) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136−8141. (d) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600−1602. (e) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021−1024. (f) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113−3122. (g) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649−5652. (h) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *28*, 3223−3226. (i) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484−489. (j) Ukaji, Y.; Kanda, H.; Yamamoto, K.; Fujisawa, T. *Chem. Lett.* **1990**, 597−600. For evidence supporting chelation of an OTBS group, see: (k) Chen, X.; Hortelano, R. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784. (l) Williard, M. J.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539−5541.

(14) (a) Sujishi, S.; Witz, S. *J. Am. Chem. Soc.* **1954**, *76*, 4631−4636. (b) Shea, K. J.; Gobeille, R.; Bramblett, J.; Thompson, E. *J. Am. Chem. Soc.* **1978**, *100*, 1611−1613. (c) West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5−9. (d) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279−280. (e) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697−703.

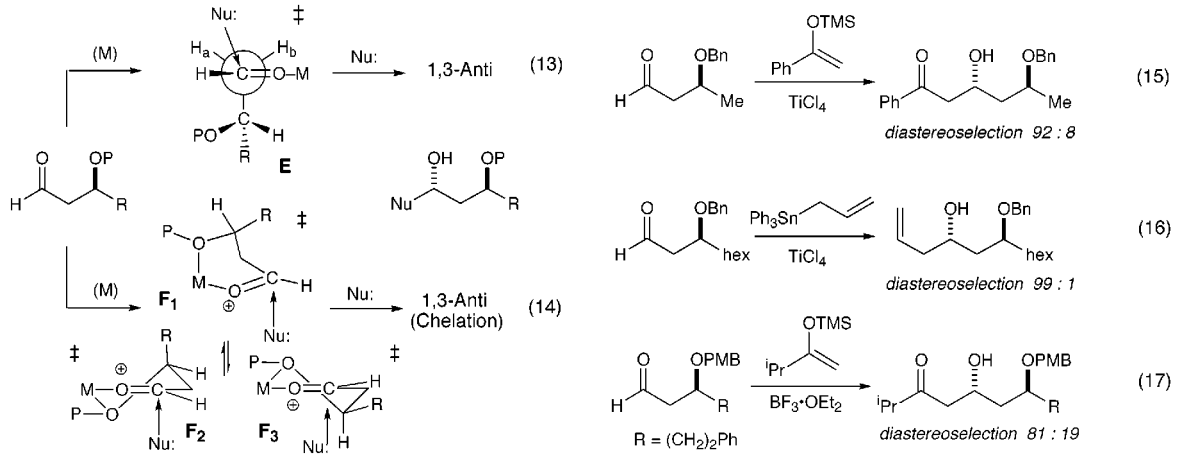
(15) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268.

(16) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849.

Scheme 1



Scheme 2



Under traditionally favorable chelating reaction conditions ($TiCl_4$, benzyl protecting group), good levels of chelation control can be obtained from the α-stereocenter of a β-alkoxy aldehyde (eq 12). If chelate organization is to be suppressed, *tert*-butyldimethylsilyl (TBS) or related protecting groups are employed (cf. eq 7). With such substrates, a return to Felkin control occurs despite use of potentially chelating Lewis acids (eq 11).[19] Accordingly, a stereochemical analysis of these reactions (eqs 11 and 12) provides circumstantial evidence for the operational stereochemical control element for the addition process. From these data, one may reasonably conclude that the TBS-protected aldehyde **2** is not chelate-activated by $TiCl_4$. Spectroscopic support for the lack of chelation for this substrate with $SnCl_4$ and $MgBr_2$ has also been provided by Keck, substantiating that hindered silicon protecting groups thwart chelate control in Lewis acid-mediated reactions.[20]

***β*-Chelation: 1,3-Induction.** Our open-chain 1,3-induction model **E**[21] and the corresponding chelate-controlled model **F** are illustrated in Scheme 2 for β-alkoxy aldehydes substituted in the β-position (eqs 13 and 14).[22] In contrast to the previous case (Scheme 1), the open-chain and chelation addition modes cannot be distinguished by the stereochemical outcome of the reaction as both control elements lead to the 1,3-anti-diol product diastereomer. It seems reasonable that nucleophile addition through either the boat conformation $\mathbf{F_1}$ or either of the half-chair conformations $\mathbf{F_2}$ or $\mathbf{F_3}$ might be considered for the chelated transition state (eq 14). Excellent anti diastereoselectivity in these systems can be achieved under standard chelating conditions (eqs 15[21] and 16[13b]). Keck has provided spectroscopic evidence that $\mathbf{F_3}$ is the preferred conformation for the $TiCl_4$-chelate when protecting group P is sterically more demanding than a methyl group due to the destabilizing gauche P ↔ R interaction.[13b] The authors conclude that high reaction diastereoselection requires reaction via this conformation. The critical evidence upon which this conclusion rests is the direct correlation of the size of the ether substituent with chelate-controlled addition diastereoselection. In this study, stereoelectronic issues were not raised (vide infra). Finally, it is evident that good 1,3-anti induction is also possible where chelation is precluded by the choice of Lewis acid (eq 17).[20] Accordingly, a stereochem-

(17) The term "anti-Felkin" refers to the carbonyl diastereoface that is disfavored according to the Felkin-Anh model for carbonyl π-facial selectivity.[8c−e] The anti-Felkin adduct resulting from addition to the anti-Felkin diastereoface can be recognized for all α-substituted aldehydes in this study as that adduct diastereomer in which the aldehyde α-methyl group and the new hydroxyl group are anti to one another when the product is drawn with the carbon backbone extended. The anti-Felkin product is the product of chelation control for all substrates in this study. The "Felkin" adduct is the product with the 1,2-syn Me ↔ OH relationship.

(18) (a) Kiyooka, S.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4765. (b) Reetz, M. T.; Kessler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (c) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411−1415. (d) Burke, S. D.; Piscopio, A. D.; Marron, B. E.; Matulenko, M. A.; Pan, G. *Tetrahedron Lett.* **1991**, *32*, 857−858.

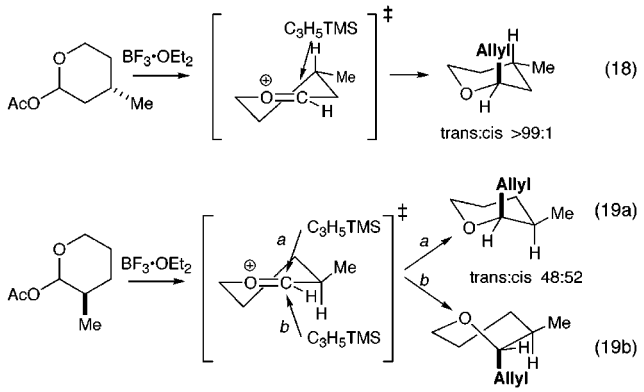
(19) This study, Table 1.

(20) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284.

(21) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540.

(22) For an early study on the addition of silcon nucleophiles to β-alkoxyaldehydes see: Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835.

Scheme 3



ical analysis of these reactions provides no evidence of the operational stereochemical control element.

Stereoelectronic Considerations. The high diastereoselection observed for the chelate-controlled addition might be attributed solely to steric factors; however, stereoelectronic control elements cannot be ignored. While stereoelectronic factors for these addition reactions have not been systematically addressed, these electronic effects may be extrapolated from the addition of nucleophiles to six-membered cyclic oxo-carbenium ions (Scheme 3), which exhibit a conformational bias for nucleophilic attack from the pseudoaxial carbonyl diastereoface (eqs 18 and 19).[23] Recent examples provided by Woerpel document the strong bias for axial attack by allyltrimethylsilane on 4-alkyl-substituted oxocarbenium ions (eq 18). The analysis of the stereochemical outcome for the allylsilane addition to the 3-methyl analogue is more complicated (eqs 19a,b). Woerpel suggests that axial nucleophile addition syn to the methyl substituent, while favored stereoelectronically, is disfavored sterically (eq 19a, Path a). Nucleophilic addition to the oxo-carbenium diastereoface anti to the methyl substituent, while favored sterically, is forced to proceed via a twist-boat transition state (eq 19b, Path b). In the present instance, the poorly diastereoselective outcome suggests that steric and electronic factors are closely balanced. While these cases implicate a stereoelectronic component in chelate-controlled additions, the longer metal−oxygen bond lengths in the Lewis acid-chelated transition structures afford greater conformational flexibility, including the possible intervention of lower energy boat geometries (vide infra). Such geometry changes will therefore necessarily modify the stereochemical trends documented by the oxo-carbenium ion analogies.

Results and Discussion

The objectives in this study are to develop a consistent set of data that might reveal diastereoselectivity trends in the chelate-controlled addition reactions of nucleophiles to syn and anti aldehyde chelates **I** and **J** (Scheme 4). In this analysis, the individual contributions from the α and *β* stereocenters will be documented from the diastereoselectivity trends observed for the chelate-controlled additions of the monosubstituted chelates **G** and **H**. In support of model predictions, the syn relationship in chelate **I** is predicted to be reinforcing while the anti chelate diastereomer **J** is predicted to be opposing. A parallel theme in this study has been the documentation of the "super-chelating" capabilities of Me_2AlCl and $MeAlCl_2$, Lewis acids that will chelate with virtually any alkoxy substituent. Our results are detailed in the following discussion.

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Scheme 4

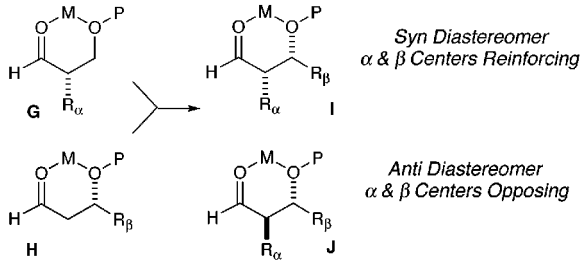


Chart 1

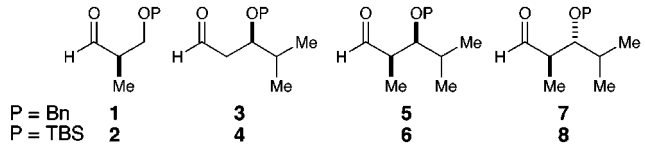
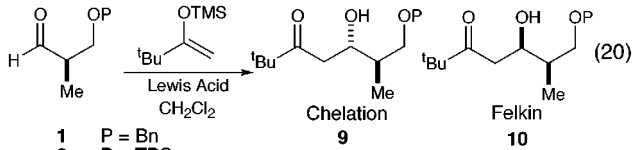


Table 1.[a] Lewis Acid-Promoted Aldol Reactions of α-Substituted Aldehydes **1** and **2** (Eq 20)



1 P = Bn **9** **10**
2 P = TBS **11** **12**

entry	Lewis acid[b]	**1** P = Bn **9 : 10** (%)	**2** P = TBS **11 : 12** (%)
A	$BF_3{\cdot}OEt_2$	26 : 74 (76)	09 : 91 (55)
B	$SnCl_4$	50 : 50 (87)	07 : 93 (41)
C	$TiCl_4$	**97 : 03** (74)	07 : 93 (55)
D	Me_2AlCl	90 : 10 (45)	**97 : 03** (62)[c]
E	$MeAlCl_2$	78 : 22 (70)	77 : 23 (55)

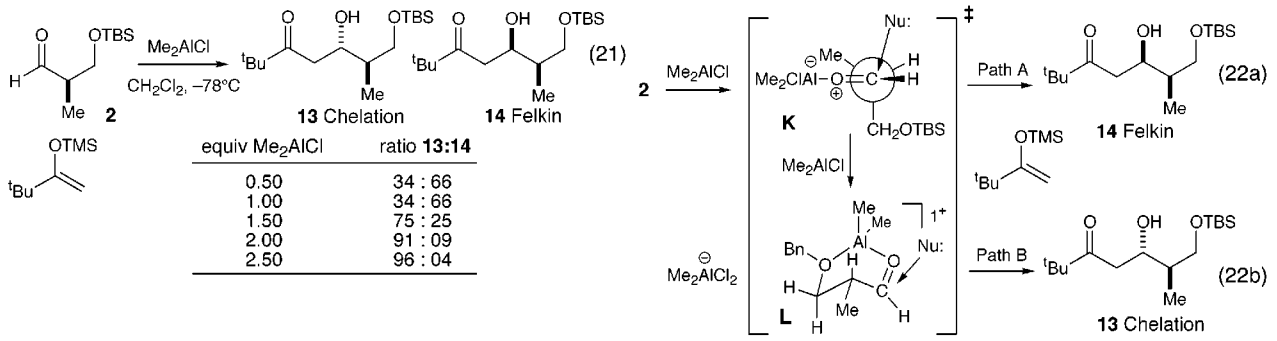
[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 20 min. Ratios were determined by GLC analysis after silylation (TMS-imidazole) or acylation (Ac_2O) of the unpurified reaction mixtures. Yields are reported for the mixture of diastereomers. [b] Reactions were run with 1.0 equiv of $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ and 2.5 equiv of Me_2AlCl and $MeAlCl_2$. Use of 2.5 equiv of $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ had no effect on diastereoselectivity. [c] This reaction was run at −90 °C. At −78 °C, 96:04 (32).

Model Reactions. The reliability of the data reflecting chelation control in this study hinges upon establishing appropriate model aldol reactions. We selected the set of simple *β*-alkoxy aldehydes **1**−**8** (Chart 1) as substrates for study. The benzyl (Bn) and *tert*-butyldimethylsilyl (TBS) protected *β*-oxygen substituents were chosen as representative alkyl and silyl protecting groups, and the isopropyl *β*-carbon substituent was selected to model the steric environment of polypropionate aldehydes. Addition reactions to substrates **1**−**4** were defined to assay the facial bias afforded by the aldehyde α and *β* stereocenters independently under chelating conditions. The merged impact of both stereocenters on the addition process will then be evaluated with aldehydes **5**−**8**. Chelation-controlled reactions were carried out with $TiCl_4$, $SnCl_4$, Me_2AlCl, and $MeAlCl_2$ as chelating Lewis acids. In addition, each reaction was run with $BF_3{\cdot}OEt_2$ to allow for direct comparison with an unambiguously Felkin-controlled reaction.[1a]

1,2-Induction. Studies began with an examination of 1,2-induction in aldol addition reactions of α-methyl-substituted aldehydes **1** and **2** (Table 1, eq 20).[24] The analysis of a Lewis acid-catalyzed nucleophilic addition to aldehydes **1** and **2** may be readily achieved since Felkin control leads to the syn product diastereomer while chelation control affords the analogous anti

(24) Unambiguous stereochemical proofs for all product diastereomers are detailed in the Supporting Information.

Scheme 5



equiv Me_2AlCl	ratio **13:14**
0.50	34 : 66
1.00	34 : 66
1.50	75 : 25
2.00	91 : 09
2.50	96 : 04

[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 20 min. Ratios were determined by GLC analysis after silylation (TMS-imidazole) of the unpurified reaction mixtures.

product diastereomer (cf. Scheme 1). Felkin-controlled addition to either aldehyde (BF_3·OEt_2, entry A) afforded the 1,2-syn adduct with good to high stereoselectivity. For reactions of **1**, the chelating Lewis acids all showed the expected increased proportion of chelation-product **9** with the $TiCl_4$-promoted addition exhibiting the highest level of chelation control (97:3 entry C) followed by Me_2AlCl (90:10 entry D). Surprisingly, $SnCl_4$ showed the lowest propensity for chelate control with aldehyde **1** (50:50 entry B). The unique chelating ability of Me_2-AlCl and $MeAlCl_2$ becomes apparent when aldol additions to the TBS-protected aldehyde **2** were carried out. While $TiCl_4$ and $SnCl_4$ exhibited good Felkin control (93:7), both of the aluminum halide based Lewis acids retained the capacity for chelation even with the OTBS moiety. The high chelate selectivity afforded by Me_2AlCl (97:3, entry D) identifies the unique role that this Lewis acid can play in this and related addition reactions.

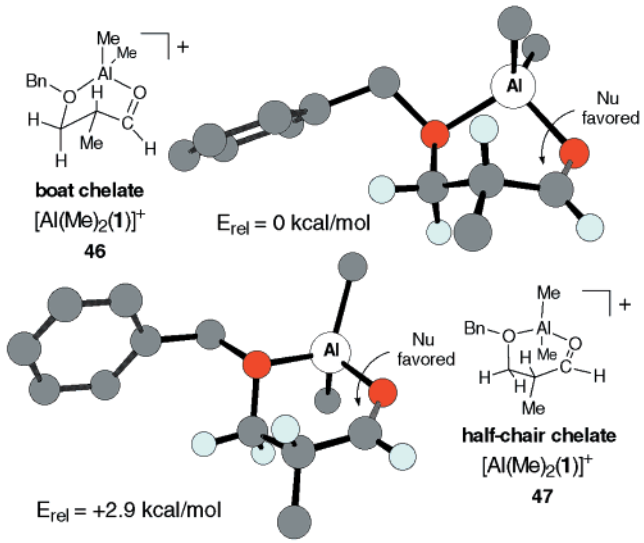
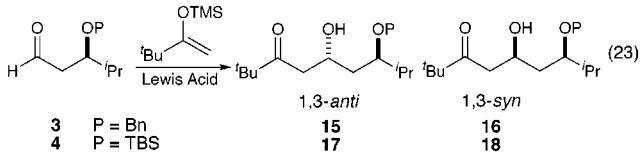


Figure 1. PM3 minimized cationic aluminum chelates of aldehyde **1** in boat and half-chair conformations.

The chelating ability of Me_2AlCl is dependent on the Lewis acid:substrate stoichiometry (Scheme 5). At low ratios of Lewis acid, the addition process exhibits dominant Felkin selectivity (eq 22a). As the relative amount of Me_2AlCl is increased, the carbonyl face selectivity reverses and the process becomes highly chelate selective (eq 22b). The reversal in aldehyde face selectivity is consistent with the Me_2AlCl induced conversion of complex **K** to the chelated cationic boat complex **L** or its less stable half-chair conformer (vide infra, cf. Figure 1). While

Table 2.[a] Lewis Acid-Promoted Aldol Reactions of β-Alkoxy Aldehydes **3** and **4** (Eq 23)



3 P = Bn
4 P = TBS
15 **17** **16** **18**

		3 P = Bn		**4** P = TBS	
entry	Lewis acid[b]	**15** : **16**	(%)	**17** : **18**	(%)
A	BF_3·OEt_2	87 : 13	(75)	88 : 12	(84)
B	$SnCl_4$	47 : 53	(83)	79 : 21	(86)
C	$TiCl_4$	89 : 11	(87)	81 : 19	(64)
D	Me_2AlCl	81 : 19	(73)	88 : 12	(62)
E	$MeAlCl_2$	79 : 21	(88)	94 : 06	(92)

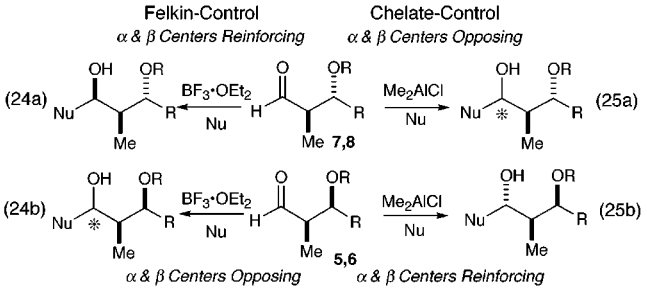
[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

this type of ligand metathesis is precedented for aluminum halide complexes,[25] it has not been a widely recognized strategy for generating highly Lewis acidic metal complexes.[26] We first encountered the highly chelating nature of Me_2AlCl in our imide-based Diels−Alder investigations some years ago (eq 1).[4b] In this study a dramatic change in dienophilic reactivity and selectivity accompanied an increase in the Lewis acid:dienophile stoichiometry. Castellino has reported spectroscopic studies supporting the proposed dienophile−Lewis acid complex illustrated in eq 1.[27] The trends associated with Me_2AlCl are also observed with $MeAlCl_2$ in the enolsilane aldol reactions investigated here.

1,3-Induction. The stereochemical outcome of the Lewis acid-catalyzed nucleophilic addition to aldehydes **3** and **4** may not be readily interpreted since both open-chain and chelation control lead to the same product diastereomer (cf. Scheme 2, eqs 13 and 14). In accord with expectation, reactions of both benzyl- and TBS-protected aldehydes **3** and **4** selectively afforded the anti product diastereomer for all the chelating Lewis acids, with the lone exception of $SnCl_4$, which afforded minimal selectivity (Table 2). We and others have amply documented that the 1,3-anti product stereochemistry results from nonchelate controlled addition to β-alkoxy aldehydes (entry A).[28] While the origin of the stereochemical control element cannot be

(25) (a) Lehmkuhl, H.; Kobs, H.-D. *Liebigs Ann. Chem.* **1968**, *719*, 11−19. (b) Reference 4a.
(26) (a) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840−7850. (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158−1161.
(27) (a) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987. (b) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197−5200.
(28) (a) Reference 20. (b) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732. (c) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31−42.

Scheme 6



assigned for the chelating Lewis acids on the basis of the product stereochemical analysis, it is reasonable to conclude that the BF_3·OEt_2-mediated addition is representative of the stereochemical control afforded by a nonchelate-controlled addition. It is noteworthy that the diastereoselectivity for nearly all of the ostensibly chelation-controlled reactions is surprisingly similar to the nonchelate-controlled additions. The most diastereoselective addition was that observed for the $MeAlCl_2$-promoted addition to the TBS-protected aldehyde **4**.

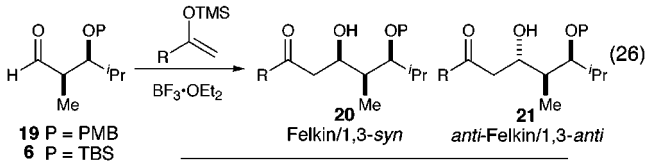
Merged 1,2- and 1,3-Asymmetric Induction. In our previous work on this topic, we carried out a detailed study of the BF_3·OEt_2-promoted additions to diastereomeric aldehyde pairs **5**,**6** and **7**,**8** to determine whether any trends might be established with regard to the relative contributions of the individual α and *β* stereocenters on the stereochemical outcome of the Felkin-controlled reactions.[29] From the independent analysis of α and *β* aldehyde stereocenters in Lewis acid-induced enolsilane addition under chelating and nonchelating conditions, the following trends are noted: For the aldehyde α-stereocenter, it is evident from our data that the 1,2-syn (OH ↔ Me) relationship is favored under nonchelating conditions while the 1,2-anti (OH ↔ Me) relationship is favored under chelating conditions (Table 1). For the *β*-stereocenter, nucleophilic addition favors the formation of the 1,3-anti (OH ↔ OR) relationship under both chelating and nonchelating conditions (Table 2).

Nonchelating Lewis Acids. In our integrated model for Felkin-controlled additions with this family of substrates, the data lead to the conclusion that the resident stereocenters in anti aldehydes **7** and **8** both support addition to the same activated aldehyde diastereoface to afford the 1,2-syn/1,3-anti adduct diastereomer (Scheme 6, eq 24a). Accordingly, the anti aldehyde diastereomeric relationship was identified as stereoreinforcing under nonchelating conditions. This addition process is stereoregular for all enolsilane structures. Conversely, the resident stereocenters in syn aldehyde diastereomers **5** and **6** were identified as nonreinforcing under nonchelating conditions (Scheme 6, eq 24b). With sterically demanding enolsilanes, the α stereocenter and its associated steric effects are the dominant stereocontrol element where the preference for the 1,2-syn (OH ↔ Me) relationship overrides the 1,3-anti (OH ↔ OR) electronic bias imposed by the *β*-OR substituent. As the enolsilane steric requirements diminish, t-Bu → Me (Table 3), the electrostatic contributions of the *β*-OR substituent in **5** and **6** become dominant and a reversal in face selectivity is noted.[29]

Chelating Lewis acids. In the present investigation, we have evaluated the complementary chelate-controlled addition reactions of syn aldehydes **5** and **6** and the anti diastereomers **7** and **8** to formally establish the trends in face selectivity for enolsilane nucleophiles. By inspection, it was predicted that the

(29) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. J.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619−6620. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

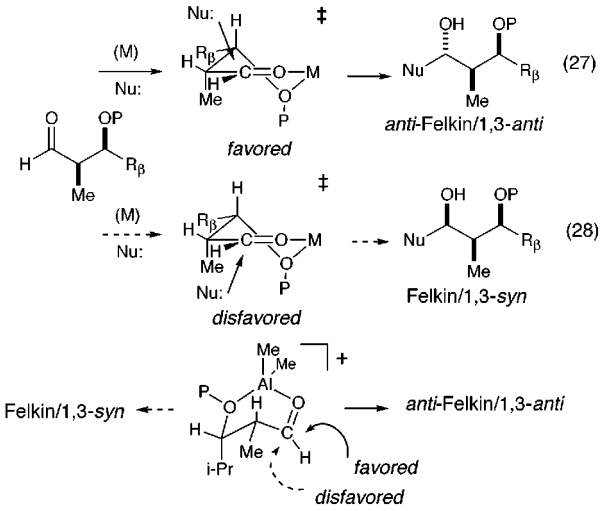
Table 3. Dependence of the Selectivity of Felkin-Controlled Reactions on Nucleophile Size (Eq 26)



entry	R	P = PMB **20** : **21**	P = TBS **20** : **21**[a]
A	t-Bu	96 : 04	94 : 06
B	i-Pr	56 : 44	75 : 25
C	Me	17 : 83	40 : 60

[a] Reactions were run in toluene at −78 °C.

resident stereocenters in syn aldehydes **5** and **6** should be reinforcing (eq 25b) under chelating conditions. As eqs 27 and 28 imply, the α and *β* stereocenters in the syn aldehyde diastereomer family mutually reinforce the chelate-mediated addition process thus favoring the anti-Felkin/1,3-anti adduct (eq 27). Conversely, the resident stereocenters in anti aldehydes **7** and **8** should be nonreinforcing (eq 25a) under chelating conditions. The chelate geometries depicted below are illustrated for a generic metal in one of the half-chair conformations. Semiempirical calculations (PM3) carried out on the cationic dimethylaluminum chelates suggest that the boat chelates are lower in energy than their chair counterparts (vide infra, cf. Figure 3).



To properly assay for the mode of activation in the Lewis acid-activated additions to the syn aldehydes **5** and **6**, we have carefully chosen pinacolone enolsilane as the participating nucleophile. With this enolsilane, Felkin- and chelation-controlled additions lead to opposite product diastereomers (compare Table 3, entry A with eq 27). In contrast, less sterically demanding enolsilanes afford the same product diastereomer independent of the mode of activation (compare Table 3, entry C with eq 27). The reaction of syn aldehyde **5** and the pinacolone-derived enolsilane with BF_3·OEt_2 (nonchelation) afforded the expected Felkin/1,3-syn aldol adduct **23** with high (95:5) selectivity (Table 4, entry A) while the same reaction promoted by Me_2AlCl (chelation) afforded chelate-mediated adduct **22** in 99:1 selectivity (Table 4, entry D). These data demonstrate the dramatic reversal of stereochemistry in comparing the two modes of activation. The cationic aluminum Lewis acid affords exceptional chelation control as contributed by the reinforcing stereocontrol elements in **5**. The same trend is also observed for the Me_2AlCl- and $MeAlCl_2$-catalyzed additions with the silyl-protected syn aldehyde **6** (entries D and E, Table

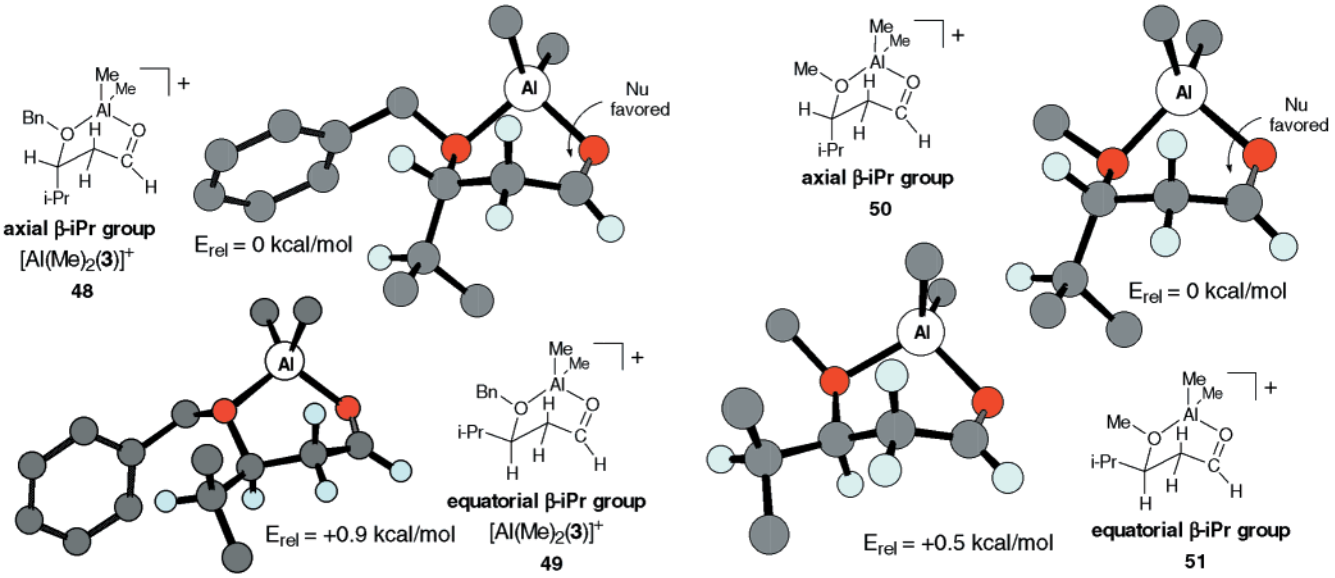


Figure 2. PM3 minimized cationic aluminum chelates of aldehyde **3** and the corresponding β-OMe aldehyde analogue.

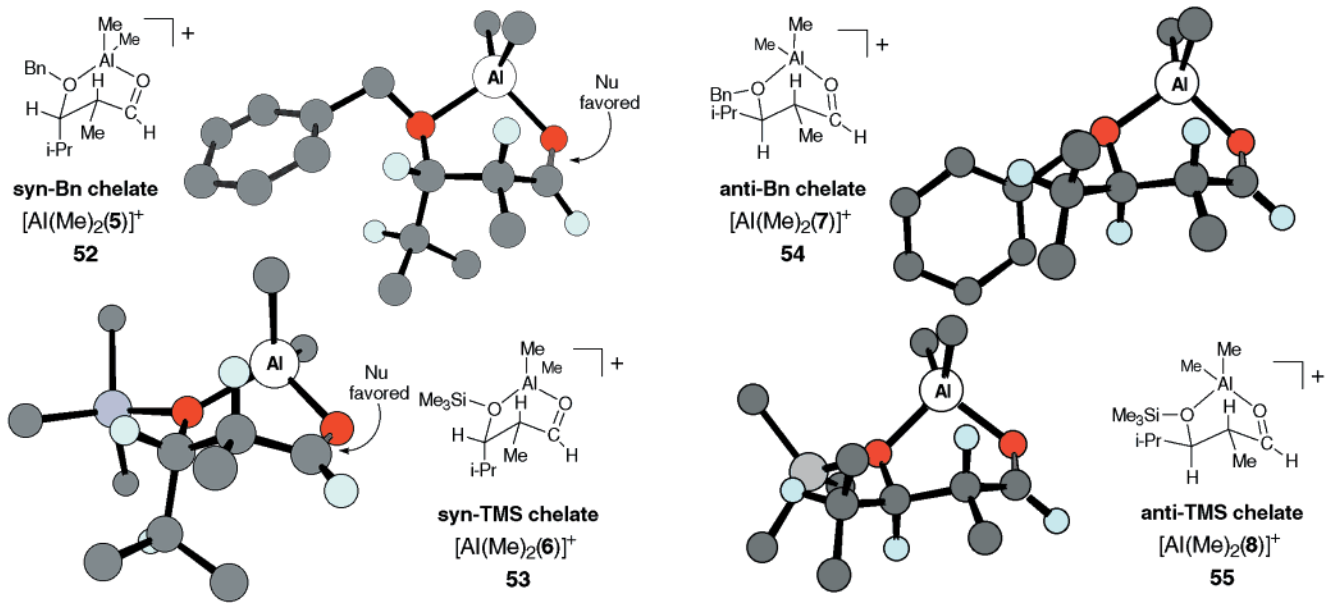
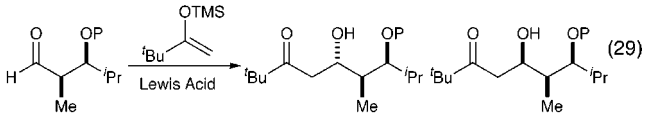


Figure 3. PM3 minimized cationic aluminum chelates of syn-substituted aldehydes **5** and **6** and anti-substituted aldehydes **7** and **8**. The *tert*-butyldimethylsilyl (TBS) protecting group in **6** and **8** has been substituted by a trimethylsilyl (TMS) group to simplify the calculations.

4). In each case a dramatic turnover in stereochemistry is seen, ~5:95 Felkin → >96:4 chelation, upon going from single-point activation (BF_3·OEt_2) to chelate activation. It is noteworthy that the degree of selectivity in chelation-controlled reactions of **5** and **6** is enhanced relative to that in reactions of aldehydes **1**−**4**, which bear only one stereocenter (cf. Tables 1 and 2). The trends established in Table 4 for the Me_2AlCl-mediated addition reactions also hold for less hindered enolsilanes (Table 5, eq 30).[30]

When the catalyzed pinacolone enolsilane additions with aldehydes **5** and **6** (eq 29) were employed to assay the chelating ability of other common chelating Lewis acids, it was found that both $TiCl_4$ and $SnCl_4$ exhibit little to no chelating capability. While $TiCl_4$ does effect excellent levels of chelate organization

Table 4.[a] Lewis Acid-Promoted Aldol Reactions of Syn-Substituted α-Methyl-β-alkoxy Aldehydes **5** and **6** (Eq 29)



5 P = Bn **22** **23**
6 P = TBS **24** **25**

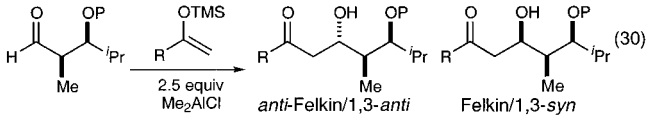
entry	Lewis acid[b]	**5** P = Bn **22**:**23** (%)	**6** P = TBS **24**:**25** (%)
A	BF_3·OEt_2	05:95 (78)	04:96 (91)
B	$SnCl_4$	05:95 (32)	01:99 (41)
C	$TiCl_4$	38:62 (22)	02:98 (71)
D	Me_2AlCl	99:01 (73)	97:03 (51)
E	$MeAlCl_2$	99:01 (81)	96:04 (71)

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

in additions to less hindered substrates (no β-substituent, Table 1), we suggest that the more pronounced steric congestion in

(30) The reaction of acetone enolsilane and **6** (Table 5, entry A) appears to proceed by addition to the nonchelated 1:1 complex of **6** with Me_2AlCl. If only 1 equiv of Me_2AlCl is used, nearly identical results are observed. Additionally, these results are consistent with the same reaction mediated by BF_3·OEt_2, which afforded a 42:58 anti-Felkin/Felkin ratio of aldol adducts.

Table 5.[a] Lewis Acid-Promoted Aldol Reactions of Syn-Substituted α-Methyl-β-alkoxy Aldehydes **19** and **6** with Various Enolsilanes (Eq 30)

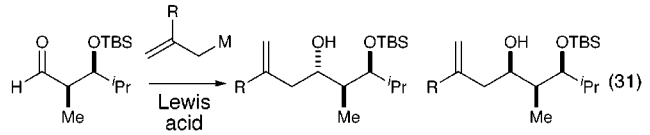


19 P = PMB **26** **27**
6 P = TBS **28** **29**

entry	R	**19** P = PMB **26** : **27** (%)	**6** P = TBS **28** : **29** (%)
A	Me	94 : 06 (69)	49 : 51 (80)
B	*i*-Pr	98 : 02 (63)	96 : 04 (53)
C	*t*-Bu	98 : 02 (59)	97 : 03 (51)

[a] See Table 1, footnote *a*.

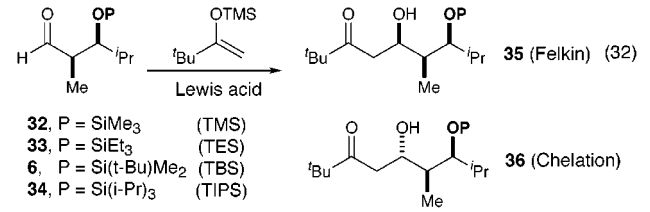
Table 6. Addition of Allylsilanes to Aldehyde **6** (Eq 31)[a]



entry	nucleophile	Lewis acid[b]	**30** : **31** (%)
A	Me_3Si	Me_2AlCl	99 : 01 (84)
B		$MeAlCl_2$	95 : 05 (84)
C	Bu_3Sn	Me_2AlCl	93 : 07 (75)
D		$MeAlCl_2$	86 : 14 (74)
E	Me_3Si	Me_2AlCl	90 : 10 (63)
F	Me	$MeAlCl_2$	88 : 12 (81)

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

Table 7. Evaluation of Silicon Protecting Groups with Aldehydes **32**−**34** and **6** (Eq 32)[a]



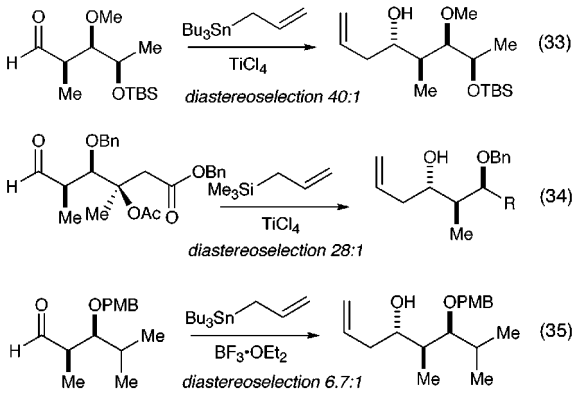
32, P = $SiMe_3$ (TMS)
33, P = $SiEt_3$ (TES)
6, P = Si(t-Bu)Me_2 (TBS)
34, P = Si(i-Pr)$_3$ (TIPS)

entry	Lewis acid[b]	**32** P = TMS **35**:**36**	**33** P = TES **35**:**36**	**6** P = TBS **35**:**36**	**34** P = TIPS **35**:**36**
A	$BF_3{\cdot}OEt_2$	95:05	98:02	96:04	97:03
D	Me_2AlCl	02:98	02:98	03:97	35:65
E	$MeAlCl_2$	02:98	10:90	04:96	38:62

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

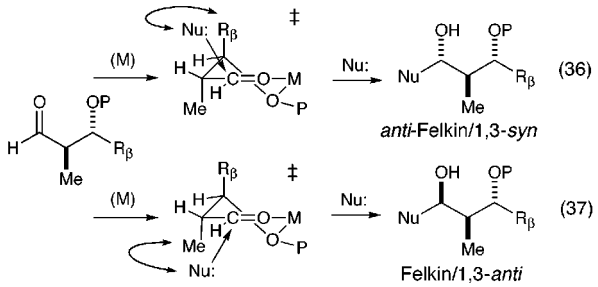
the chelates of aldehydes **5** and **6** thwart chelate organization in these more hindered aldehyde substrates.

Other nucleophiles such as allylsilanes and allylstannanes are also accommodated by the aluminum Lewis acids (Table 6, eq 31). Good to excellent chelation control is observed for all reactions of silyl-protected aldehyde **6**. While these studies have emphasized the stereochemical elements of the addition process, these reactions perform successfully at preparative scale with no degradation of yield or stereoselectivity demonstrating the synthetic utility of these transformations. The generality of silyloxy group chelation with Me_2AlCl and $MeAlCl_2$ was also evaluated with aldehydes **32**−**34** (Table 7, eq 32). Excellent levels of chelation control are maintained with silyl groups sterically smaller than TBS; however, the chelating ability of the aluminum Lewis acids is partially curtailed in the limit by the sterically demanding triisopropylsilyl (TIPS) group in **34**.



It is instructive to revisit some of the catalyzed addition reactions of 1,2-syn disubstituted aldehydes reported in the literature. For example, diastereoselective allylstannane and allylsilane additions (eqs 33 and 34) have been reported during the course of studies by Keck (rhizoxin)[31] and Panek (mycotrienin I).[32] Both authors have suggested that these addition reactions are chelate-controlled processes based on the Lewis acid employed ($TiCl_4$) and the stereochemical outcome of the addition; however, the analysis, based on stereochemical outcome alone, is deceptive for syn aldehydes. We have just established that Felkin and chelate-controlled additions with sterically nondemanding nucleophiles afford the same product diastereomer. For example, the analogous $BF_3{\cdot}OEt_2$ catalyzed allylstannane addition also affords the "chelate" product (eq 35).[20] Accordingly, our studies call into question the intervention of chelation control in eqs 33 and 34. Furthermore, from the data presented in the preceding discussion, it has been demonstrated (Table 4) that $TiCl_4$ is not a good chelating Lewis acid for this family of aldehyde substrates. Hence we conclude that the additions illustrated in eqs 33 and 34, in contrast to the authors' suggestions, are likely not to be chelate-controlled processes.

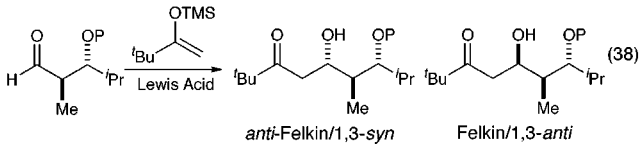
Inspection of the chelate of the anti-substituted aldehyde reveals the nonreinforcing nature of this stereochemical array. The chelated intermediate disposes the α and β substituents on opposite sides of the coordinated carbonyl. Nucleophile approach from the anti-Felkin face of the carbonyl encounters steric encumbrance from the β-alkyl substituent (eq 36) while the α-methyl group hinders nucleophilic addition to the Felkin carbonyl diastereoface (eq 37). Ultimately, addition to the anti-substituted aldehyde should result in diminished stereoselectivity under chelate control. Semiempirical calculations (PM3) carried out on the cationic dimethylaluminum chelates suggest that the boat chelates are lower in energy than their chair counterparts (vide infra, cf. Figure 3).



(31) Keck, G. E.; Savin, K. A.; Weglartz, M. A.; Cressman, E. N. K. *Tetrahedron Lett.* **1996**, *37*, 3291−3294.

(32) Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S. *Am. Chem. Soc.* **1998**, *120*, 4123−4134.

Table 8.[a] Aldol Reactions of Anti-Substituted Aldehydes **7** and **8** (Eq 38)



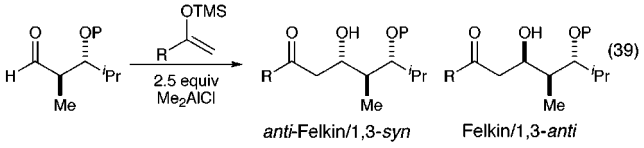
7 P = Bn **8** P = TBS

37 **39** **38** **40**

entry	Lewis acid[b]	**7** P = Bn **37** : **38** (%)	**8** P = TBS **39** : **40** (%)
A	$BF_3{\cdot}OEt_2$	01 : 99 (79)	01 : 99 (91)
B	Me_2AlCl	54 : 46 (41)	23 : 77 (56)
C	$MeAlCl_2$	20 : 80 (71)	08 : 92 (54)

[a] See Table 1, footnote *a*. [b] See Table 1, footnote *b*.

Table 9.[a] Aldol Reactions of Anti-Substituted Aldehydes **41** and **8** with Representative Enolsilanes (Eq 39)



41 P = PMB **8** P = TBS

42 **44** **43** **45**

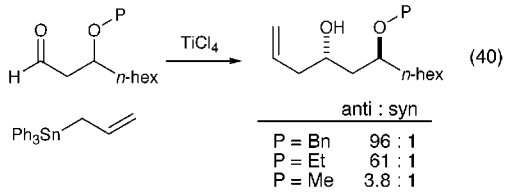
entry	R	**41** P = PMB **42** : **43** (%)	**8** P = TBS **44** : **45** (%)
A	Me	34 : 66 (58)	38 : 62 (67)
B	*i*-Pr	69 : 31 (67)	19 : 81 (53)
C	*t*-Bu	52 : 48 (55)	23 : 77 (56)

[a] See Table 1, footnote *a*.

This prediction is borne out experimentally with Me_2AlCl and $MeAlCl_2$ as chelating Lewis acids (Table 8, eq 38). Reaction of the anti aldehydes **7** and **8** under chelating conditions provides low to moderate stereoselection (entries B and C). These data substantiate that modest reaction diastereoselection is to be anticipated for the nonreinforcing anti aldehyde diastereomer under chelate-controlled substrate activation. In contrast, the anti diastereomeric relationship is reinforcing under single point Lewis acid activation. Again, this point is confirmed by the exceptional Felkin selectivity observed with $BF_3{\cdot}OEt_2$ (99:1). Modest stereoselectivity is also observed across the range of substituted enolsilanes with Me_2AlCl (Table 9, eq 39). Based on the weight of evidence, it is presumed that chelate control is operating in all of these addition processes.

Chelate Models. A series of semiempirical calculations (PM3) were carried out to probe the conformations of the putative cationic aluminum chelates involved in the above reactions.[33] While one cannot make any definitive statements about transition state geometries from these ground-state calculations, some inferences may be made on probable reacting geometries. Geometry optimization of the $Me_2Al(+)$ chelate of α-methyl substituted aldehyde **1** from different starting geometries located the two low-energy boat and half-chair conformations (Figure 1). These calculations signal that the boat conformer **46** is more stable than the half-chair conformer **47** by approximately 3 kcal/mol.[34] By inspection, the observed sense of asymmetric induction may be rationalized from either chelate conformer, but the implication is that boat geometries may be the preferred conformation of dimethylaluminum chelates of β-alkoxy aldehydes.

Calculations on the dimethylaluminum chelates of β-substituted β-alkoxy aldehyde **3** also signal that boat conformations are preferred over their chair counterparts.[35] Within the boat conformation manifold, the disposition of the β-isopropyl substituent (pseudoaxial vs pseudoequatorial) is examined through structures **48**−**51** (Figure 2). There is a modest preference, 0.9 kcal/mol, for the pseudoaxial β-substituent in the chelate of **3** (**48** vs **49**). Presumably the vicinal gauche interaction between the oxygen protecting group and the isopropyl substituent (Bn ↔ $CHMe_2$) in chelate **49** is destabilizing thus forcing the isopropyl substituent into a pseudoaxial orientation. The size of the oxygen protecting group influences the relative energies of the boat conformers. For example, the pseudoaxial isopropyl boat conformer **50**, in which the β-benzyloxy substituent has been replaced with a β-methoxy substituent, is now only 0.5 kcal/mol more stable than the pseudoequatorial isopropyl boat conformer **51**.[36] This trend supports the premise that the gauche interaction between the oxygen protecting group and the isopropyl substituent (Bn ↔ $CHMe_2$) in chelate **49** is more strongly destabilizing than the analogous interaction (Me ↔ $CHMe_2$) in chelate **51**. Diastereoselection trends in the chelate-mediated allylstannane addition to β-alkoxy aldehydes document that the steric requirements of the β-alkoxy substituent directly correlate with reaction diastereoselection, with the larger alkoxy residues being more diastereoselective (eq 40).[13b] The suggestion, supported by the calculations of Figure 3, is that the pseudoaxial isopropyl group is responsible for good chelation control with these type of substrates.



Computationally generated structures for the $Me_2Al(+)$ chelates of syn and anti aldehydes **5**−**8** are shown in Figure 3. The syn-substituted chelates **52** and **53** incorporate the best features of the above models for 1,2 and 1,3 induction, and mutually reinforcing stereocenters are evident. The lowest energy conformations are the illustrated boat geometries with a pseudoaxial β-isopropyl group and a pseudoequatorial α-methyl group, which both direct nucleophilic approach to the anti-Felkin aldehyde diastereoface. While our original stereochemical predictions were based upon consideration of chair-like models, these boat structures do not alter those predictions. For the anti chelates the more energetically favorable boat conformations are the illustrated ones in which both the α and β substituents reside equatorially.[37] These structures closely

(33) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220. Calculations were performed within the SPARTAN computational platform on SGI Indigo workstations: SPARTAN Version 5.0, Wavefunction, Inc.; Irvine, CA.

(34) PM3 calculations on the corresponding TMS-protected aldehyde show the same trend. The boat conformer is 2.7 kcal/mol lower in energy than the half-chair.

(35) PM3 optimizations lead to the following relative energies: boat-$[Al(Me)_2(\mathbf{3})]^+$, E_{rel} = 0 kcal/mol; half-chair-$[Al(Me)_2(\mathbf{3})]^+$, E_{rel} = +1.9 kcal/mol.

(36) Calculations on the TMS-protected aldehyde chelates corresponding to **48** and **49** showed only a small (0.3 kcal/mol) energy difference. The very bulky silyl group equalizes the energy differences between the two boat conformers, which are due to steric interactions between the protecting group and the pseudoaxial or pseudoequatorial isopropyl group.

(37) The trans-diaxial boat conformations were also examined. These conformation were higher in energy than the illustrated diequatorial ones apparently as a result of the severe 1,4-diaxial repulsion between the α-methyl group and the axial methyl group on aluminum. E_{rel}(diaxial anti-Bn chelate) = +7.7 kcal/mol. E_{rel}(diaxial anti-TMS chelate) = +9.6 kcal/mol.

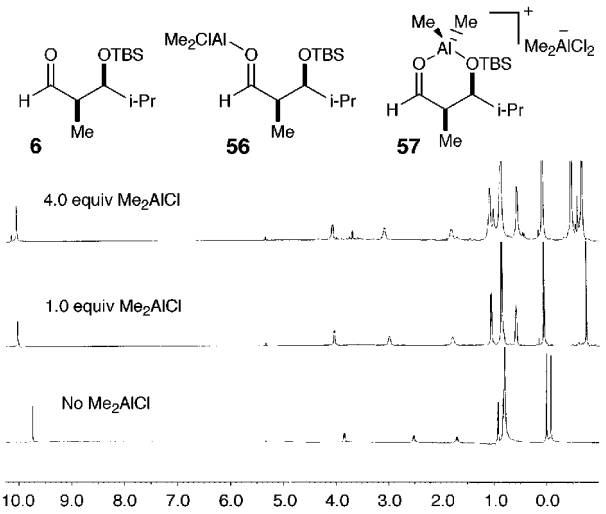


Figure 4. ^{1}H NMR spectra of aldehyde **6** with 0.0, 1.0, and 4.0 equiv of Me_2AlCl recorded at −70 °C.

resemble those found for the α-methyl chelates (Figure 1) suggesting that at best, chelate-controlled additions to these aldehydes may behave similarly to reactions of the α-methyl aldehydes. However, the stereochemical results indicate that the *β*-alkyl group is not a passive substituent as these boat chelates may suggest. In fact, the *β*-substituent is the dominant control element in several reactions of the anti-substituted aldehydes in which the Felkin/1,3-anti product diastereomer is seen to predominate (cf. Tables 8 and 9). From this analysis no clear trends are present for prediction of stereocontrol for chelate-controlled reactions in the nonreinforcing scenario. For the most part, diminished stereoselectivity is to be expected in these reactions.

NMR Studies and Mechanism of OTBS Chelation. Although the evidence in support of chelation of OTBS groups in aldehydes **2**, **4**, and **6** with Me_2AlCl or $MeAlCl_2$ as Lewis acids is strong (Tables 1, 2, and 4), this stereochemical evidence is indirect at best. For lack of further evidence, the results may be attributed to anomalous cases of anti-Felkin selective nonchelation-mediated addition reactions. Since Lewis acid coordination of silyl-bearing oxygen groups has been a contentious issue for some time,[12,13] it was appropriate to seek more direct evidence for the proposed chelation. Earlier NMR studies have shown the lack of chelation of *β*-OTBS-substituted aldehydes with $SnCl_4$ and $MgBr_2$ as Lewis acids.[20] Our stereochemical results with $TiCl_4$ and $SnCl_4$ continue to support this trend, while the behavior of Me_2AlCl and $MeAlCl_2$ was markedly different for identical reactions of OTBS-substituted aldehydes. The following results from low-temperature NMR complexation studies indicate that the proposed cationic aluminum chelates can be observed for certain *β*-alkoxy carbonyl substrates and implicate true chelates in the highly selective aluminum-mediated reactions of *β*-OTBS aldehydes presented above.

Attempts were first made to observe the chelate of syn aldehyde **6**; however, even in the presence of up to 4.0 equiv of Me_2AlCl, the cationic 2:1 (Me_2AlCl·aldehyde) complex **57** could not be unambiguously discerned in the ^{1}H NMR spectrum (Figure 4). The bottom spectrum represents the free aldehyde at −70 °C with no added Lewis acid. When 0.5 equiv of Me_2AlCl is added, two species are observed in a 1:1 ratio, the uncomplexed aldehyde and a new species whose NMR is the middle spectrum. At exactly 1 equiv of Me_2AlCl, all of the aldehyde is converted to the middle spectrum, which is assigned to the single-point activated **6**·Me_2AlCl complex **56**. There is a clear, significant downfield shift of the aldehyde proton indicating carbonyl complexation. There are downfield shifts of the aliphatic protons in the 1.5−4 ppm region as well, with the degree of shift commensurate with the distance of the protons from the coordinated aldehyde. A new upfield 6-proton singlet at −0.9 ppm due to the methyl groups on aluminum has appeared. At any number of equivalents of Me_2AlCl above 1.0, however, no change in the ^{1}H spectrum is observed with the exception of the growth of the resonance due to uncomplexed excess Me_2AlCl at −0.5 ppm (top spectrum, Figure 4). Although **57** was not observed, the existence of the cationic chelate is not entirely ruled out as one may still postulate that the chelate is an equilibrium intermediate present in a low concentration below the sensitivity threshold of the NMR spectrometer.

It was thought that a surrogate for the aldehyde carbonyl possessing slightly greater Lewis basicity may allow generation of the cationic chelate in observable quantities. Toward this end, methyl ketone **58** was prepared. Salient portions of the ^{1}H and ^{13}C NMR spectra of methyl ketone **58** with Me_2AlCl are reproduced in Figure 5. Again, the bottom spectra are those of the uncomplexed substrate prior to addition of Lewis acid at −70 °C. At 1.0 equiv of Me_2AlCl, complete conversion to a single new species is again observed (middle spectra). This is assigned as the 1:1 complex **59**. The most significant downfield shifts in the ^{1}H spectrum of **59** are those of the methyl group and the methine proton which flank the ketone. The proton neighboring the OTBS group (3.6 ppm) is nearly unaffected. The ^{13}C spectrum also clearly indicates single-point binding to the ketone. A 23 ppm downfield shift of the ketone carbon is observed with no change in the chemical shift of the carbon bearing the OTBS substituent (77 ppm). Unlike for the aldehyde **6**, a new species is produced as greater than 1 equiv of Me_2AlCl is titrated into the NMR sample. Intermediate spectra between 1.0 and 4.0 equiv show increasing ratios of the new complex, indicating an equilibrium that is driven toward the new complex by mass action with excess Lewis acid. The final spectra recorded at 4.0 equiv of Me_2AlCl show near complete conversion to the new species, which is assigned as the cationic complex **60** based upon downfield shifts in both the ^{1}H and ^{13}C spectra. Particularly striking are the shifts of the carbon bearing the OTBS group, which now lies 11 ppm downfield from the 1:1 complex, and the proton on this carbon, which has moved 0.5 ppm farther downfield. In the ^{1}H spectrum the methyl ketone singlet undergoes an additional downfield shift, and the diastereotopic methyl groups bound to silicon in the TBS group undergo a 0.5 ppm downfield shift. The two new methyl singlets located upfield at −0.5 ppm are assigned to the methyl groups on the cationic aluminum center of **60**. These methyl groups have become diastereotopic from the 1:1 complex as a result of the generation of the rigid six-membered chelate ring. In identical complexation studies with $TiCl_4$ and $SnCl_4$, unambiguous coordination to the carbonyl was observed, but no significant chemical shift changes were seen for any protons or carbons associated with the *β*-OTBS group.

Chelate-Controlled Reductions. In an effort to expand the scope of the Al-mediated chelate-controlled addition reactions, the reductions of *β*-alkoxy and *β*-silyloxy ketones were explored. These reductions were expected to follow the same trends in facial selectivity as has been observed with the enolsilane nucleophiles in the preceding parts of this paper. Stereoselective reductions of this type would provide access to valuable 1,3-polyol synthons.[38] The use of Me_2AlCl as the chelating Lewis

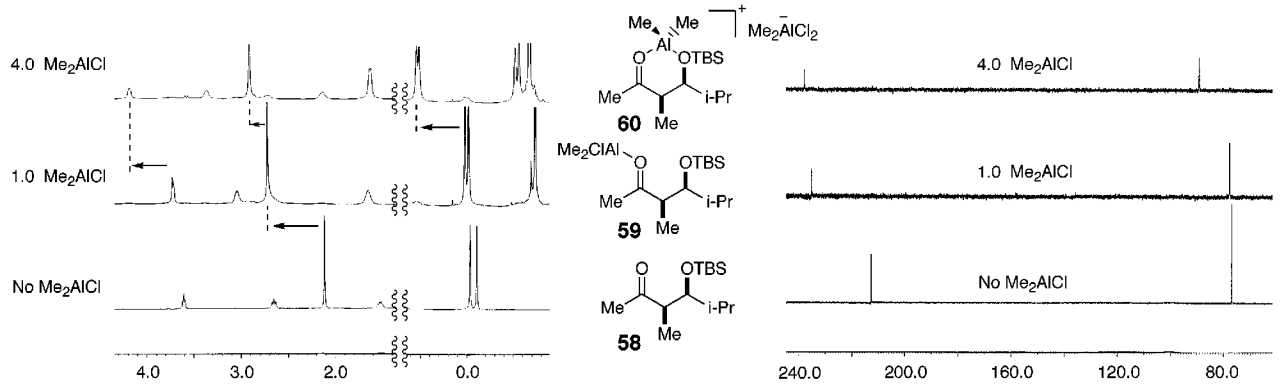
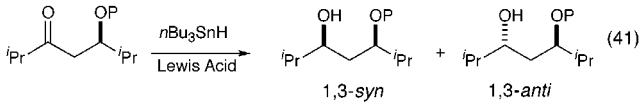


Figure 5. ^{1}H and ^{13}C NMR spectra of methyl ketone **58** with 0.0, 1.0, and 4.0 equiv of Me_2AlCl recorded at −70 °C. Significant downfield chemical shift changes in the ^{1}H NMR spectra are indicated by arrows.

Table 10.[a] Lewis Acid-Promoted Reductions of β-Alkoxy Ketones **61** and **62** (Eq 41)

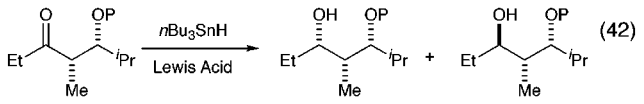


61 P = Bn
62 P = TBS
63 **65**
64 **66**

		61 P = Bn	**62** P = TBS
entry	Lewis acid[b]	**63** : **64** (%)	**65** : **66** (%)
A	Me_2AlCl	92 : 08 (75)	90 : 10 (88)
B	$MeAlCl_2$	92 : 08 (77)	89 : 11 (85)
C	$BF_3{\cdot}OEt_2$	70 : 30 (75)	60 : 40 (80)

[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 1 h. Ratios were determined by ^{1}H NMR analysis (500 MHz) of the unpurified reaction mixtures. Yields are reported for the mixture of diastereomers. [b] Reactions were run with 1.0 equiv of $BF_3{\cdot}OEt_2$ and 2.5 equiv of Me_2AlCl and $MeAlCl_2$. Use of 2.5 equiv of $BF_3{\cdot}OEt_2$ had no effect on diastereoselectivity.

Table 11.[a] Lewis Acid-Promoted Reductions of Syn-Substituted α-Methyl-β-alkoxy Ketones **67** and **68** (Eq 42)



67 P = Bn
68 P = TBS
69 **71**
70 **72**

		67 P = Bn	**68** P = TBS
entry	Lewis acid[b]	**69** : **70** (%)	**71** : **72** (%)
A	Me_2AlCl	90 : 10 (78)	95 : 05 (92)
B	$MeAlCl_2$	89 : 11 (75)	95 : 05 (89)
C	$BF_3{\cdot}OEt_2$	40 : 60 (80)	33 : 67 (83)

[a] See Table 10, footnote *a*. [b] See Table 10, footnote *b*.

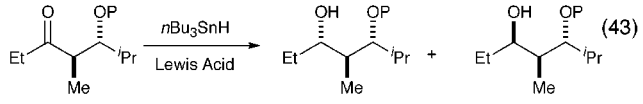
acid in these reductions should allow for the incorporation of both β-alkoxy and β-silyloxy substituents into the stereoselecive reduction. We have selected a set of simple β-alkoxy ketones as substrates for this study (**61**/**62**, Table 10; **67**/**68**, Table 11; **73**/**74**, Table 12).

Our initial investigation into these chelate-controlled reductions centered around the choice of a mild hydride source. A number of trialkylsilanes were surveyed[39] as hydride donors in the reductions of ketones **61** and **62** (Table 10). However, all of the trialkylsilanes proved to be ineffective at temperatures ranging from −78 °C to room temperature. As such, we

(38) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645.

(39) Silanes surveyed included Et_3SiH, Me_2PhSiH, Ph_3SiH, and $(TMS)_3SiH$.

Table 12.[a] Lewis Acid-Promoted Reductions of Anti-Substituted α-Methyl-β-alkoxy Ketones **73** and **74** (Eq 43)



73 P = Bn
74 P = TBS
75 **77**
76 **78**

		73 P = Bn	**74** P = TBS
Entry	Lewis acid[b]	**75** : **76** (%)	**77** : **78** (%)
A	Me_2AlCl	85 : 15 (80)	50 : 50 (93)
B	$MeAlCl_2$	88 : 12 (78)	55 : 45 (90)
C	$BF_3{\cdot}OEt_2$	55 : 45 (83)	50 : 50 (85)

[a] See Table 10, footnote *a*. [b] See Table 10, footnote *b*.

explored the use of nBu$_3$SnH as a more nucleophilic hydride source. The use of nBu$_3$SnH at −78 °C in methylene chloride proved to be optimal for the reduction of the selected ketone substrates.[40]

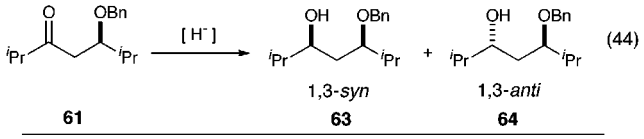
***β*-Chelation: 1,3-Asymmetric Induction.** The stereochemical outcome of the Lewis acid mediated reductions of ketones **61** and **62** was consistent with the Felkin and chelate transition state models (cf. Scheme 2, eqs 13 and 14). In these cases, the Felkin and chelate models lead to the same major product diastereomer; however, the chelating Lewis acids proved far more selective for the 1,3-syn product diastereomer than $BF_3{\cdot}OEt_2$ (Table 10). It is presumed that the selectivity of the $BF_3{\cdot}OEt_2$-mediated reduction is representative of the stereochemical control that can be achieved by a purely Felkin-controlled addition. The most diastereoselective reaction was that observed for the Me_2AlCl- or $MeAlCl_2$-promoted reduction of the benzyl-protected ketone **61**.

Merged 1,2- and 1,3-Asymmetric Induction. We have evaluated the chelate-controlled reductions of syn ketones **67** and **68** (Table 11) and the anti diastereomers **73** and **74** (Table 12) to verify trends in facial selectivity in the case of a hydride nucleophile. The transition state models for the syn ketones **67** and **68** (eqs 27 and 28) predict that the resident stereocenters should be mutually reinforcing under chelate-controlled conditions. As a result, reductions of the syn-disubstituted ketones should strongly favor the 1,3-syn adduct (Table 11, eq 42).

Indeed, the reductions of syn ketones **67** and **68** promoted by Me_2AlCl (chelation) afforded the anti-Felkin/1,3-syn products **69** and **71** with high levels of selectivity (Table 11, entries A and B). The data in Table 11 clearly illustrate the reversal of

(40) For further information on the optimal reaction conditions see the Supporting Information.

Table 13. [a] Survey of Hydride Reductions with β-Benzyloxy Ketone **61** (Eq 44)



(44)

61 **63** **64**

Entry	Reducing Agent	**63** : **64** (%)
A	Me_2AlCl / nBu_3SnH[a]	92 : 08 (75)
B	$Zn(BH_4)_2$[b]	50 : 50 (72)
C	Dibal-H[a]	55 : 45 (78)
D	L-Selectride[b]	84 : 16 (76)

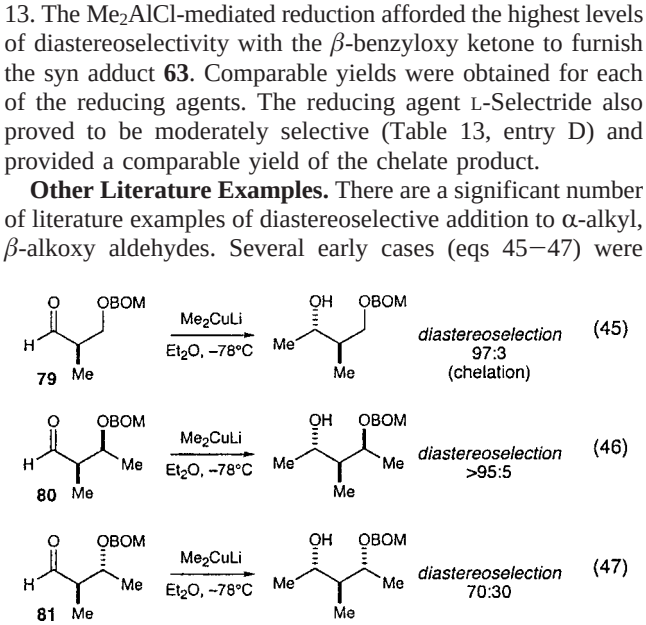
[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 1 h. Ratios were determined by ^1H NMR analysis (500 MHz) of the unpurified reaction mixtures. Yields are reported for the mixture of diastereomers. [b] Reactions were carried out in THF at −78 °C for 1 h.

stereochemistry for the monodentate ($BF_3{\cdot}OEt_2$) and bidentate (Me_2AlCl, $MeAlCl_2$) modes of activation. The cationic aluminum Lewis acids provide exceptional chelation control for the silyl-protected syn ketone **68** due to the reinforcing stereochemical elements. The diastereoselectivity in the chelate-controlled reductions of **68** is enhanced relative to silyloxy ketone **62** which bears only one stereocenter (cf. Table 10).

The transition state models outlined in eqs 36 and 37 are relevant to the chelate-controlled reductions of the anti-disubstituted ketones (**73** and **74**). In these cases, the α- and β-substituents are nonreinforcing as the nucleophile will encounter steric encumbrance upon approach to either carbonyl diastereoface. Therefore, the reductions of the anti-disubstituted ketones are predicted to show diminished stereoselectivity under chelation control. This prediction is confirmed experimentally with both Me_2AlCl and $MeAlCl_2$ as the chelating Lewis acids (Table 12, eq 43). The reduction of ketones **73** and **74** under chelate conditions affords low levels of diastereoselection (Table 12, entries A and B). These data are consistent with the diastereoselectivities observed for the addition of enolsilanes to anti-substituted aldehydes (cf. Table 8). Reductions under nonchelating conditions also afford equally poor levels of stereoinduction (Table 12, entry C).

Synthetic Utility of the Al-Mediated Reductions. A comparison of the utility of these chelate-controlled reductions versus other commonly employed reducing agents is provided in Table 13. The Me_2AlCl-mediated reduction afforded the highest levels of diastereoselectivity with the β-benzyloxy ketone to furnish the syn adduct **63**. Comparable yields were obtained for each of the reducing agents. The reducing agent L-Selectride also proved to be moderately selective (Table 13, entry D) and provided a comparable yield of the chelate product.

Other Literature Examples. There are a significant number of literature examples of diastereoselective addition to α-alkyl, β-alkoxy aldehydes. Several early cases (eqs 45−47) were reported by Still and Schneider.[6] This study revealed that lithium dimethylcuprate adds to aldehyde **79** in a highly diastereoselective fashion (eq 45). The anti stereochemical outcome (cf. Scheme 1, Table 1) provides compelling circumstantial evidence that $LiCuMe_2$ (in diethyl ether) is participating in a chelate-controlled addition. In contrast, MeMgBr exhibits no diastereoselectivity. While the stereochemical outcome of this addition is not general for all organocuprates,[6,41] this case is relevant to the following two examples (eqs 46 and 47). We now know that in syn aldehyde **80** the two stereocenters are mutually reinforcing for a chelate-controlled addition while in the anti aldehyde diastereomer **81** the two stereocenters are nonreinforcing (cf. eqs 3 and 4, Scheme 6). The observed trends in diastereoselection support the premise that chelation control is operating in all three cases.



The four titanium tetrachloride-catalyzed additions illustrated below (eqs 48−51) deserve comment. The highly diastereoselective allylsilane addition to aldehyde **82** has been reported by Roush (eq 48)[42] while the related addition has been carried out by Panek (eq 49).[43] On the surface, both of these reactions appear to be chelate controlled on the basis of the stereochemical outcome (eq 3, Table 6); however, syn aldehydes such as **82** and **83** afford the indicated stereochemical outcome even with a nonchelating Lewis acid such as $BF_3{\cdot}OEt_2$ in allylmetal additions (eq 35). As we have previously demonstrated, syn aldehyde diastereomers such as **82** and **83** also deliver the same observed stereochemical outcome from open-chain Felkin-like additions with sterically "small" nucleophiles. In these additions, the two stereocenters are nonreinforcing and the dominant control element is the β-alkoxy substituent.[29b] If chelate control were not operating in these additions, sterically more demanding nucleophiles would exhibit a *reversal* in aldehyde face selectivity as documented in Table 3 (eq 26). On the other hand, if chelate organization was involved, sterically demanding nucleophiles would *maintain* the same carbonyl face selectivity. Such a case has been recently reported by Panek (eq 50).[44] If chelate control were not operational, the indicated hindered enolsilane should afford the Felkin alcohol diastereomer. Since the anti-Felkin (chelation) product is observed in this case, we conclude that all three reactions appear to be chelate controlled. Our own studies provide some indication that the maintenance of chelation control in titanium tetrachloride-catalyzed additions is not universal and is subject to subtle steric effects (see Table 4, eq 29). For example, the aldol addition to aldehyde **5** affords principally the Felkin adduct (62:38, eq 51). By inspection, aldehyde **5** carries the branched isopropyl substituent at the β oxygen-bearing carbon while aldehydes **82**−**84** carry unbranched substituents at this position. Further studies with homogeneous families of nucleophiles might be useful in pinning down the origin of these rather subtle steric effects.

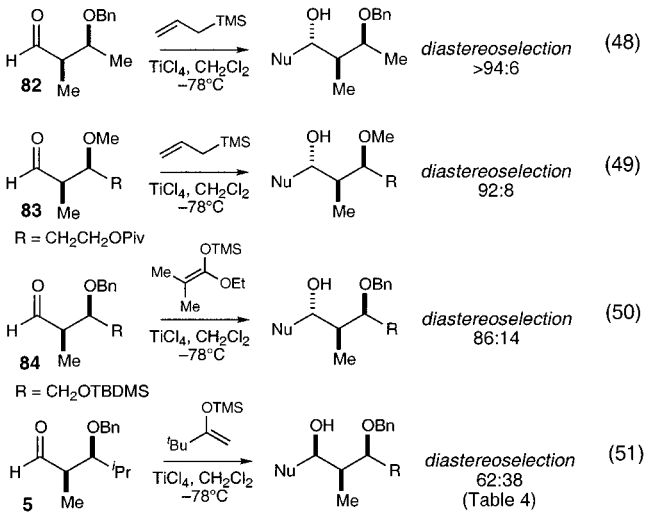
Chelate Control in Synthetic Planning. There are several conclusions that may be drawn with regard to the prediction of reliably stereoselective addition reactions to α-alkyl-β-alkoxy aldehydes from the data contained in this and our previous paper[29] on this topic. (A) The illustrated syn aldehyde diastereomer, activated by a chelating Lewis acid, will undergo predictable, stereoregular additions to afford the anti-Felkin/1,3-anti product diastereomer (eq 52). (B) The illustrated anti

(41) For additional cases see: Burke, S. D.; Piscopio, A. D.; Marron, B. E.; Matulenko, M. A.; Pan, G. *Tetrehedron Lett.* **1991**, *32*, 857−858 and references therein.

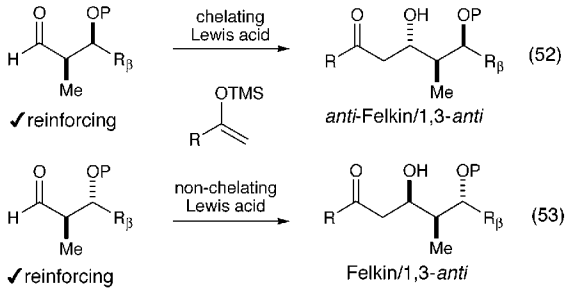
(42) Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474−478.

(43) Panek, J. S.; Berseis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494−6495.

(44) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575−5578.

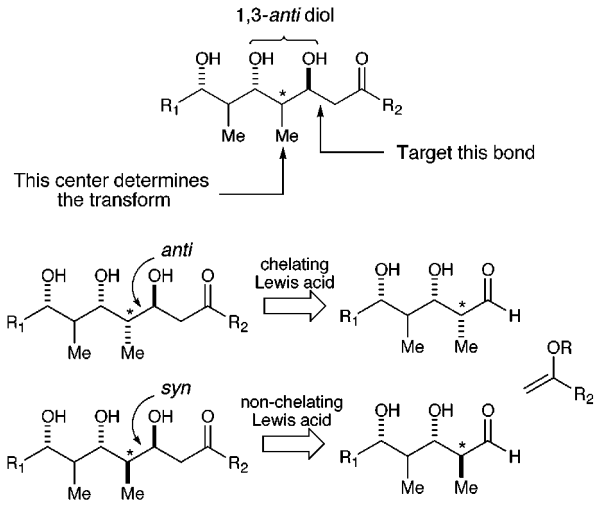


aldehyde diastereomer, activated by a nonchelating Lewis acid, will undergo stereoselective additions to afford the Felkin/1,3-anti product diastereomer (eq 53). In both instances, the stereochemical relationships are reinforcing under the stated type of Lewis acid activation. In contrast, the anti aldehyde diastereomer, reacting under the influence of chelate control, will exhibit lower diastereoselection as will the syn aldehyde diastereomer, reacting with nonchelating Lewis acids.



Taken together, these stereochemical relationships outline a basis for first-order analysis of stereocontrol in polypropionate synthesis (Scheme 7). In the retrosynthetic analysis of a 1,3-polyol chain, one key stereochemical element is the anti 1,3-diol array because the reinforcing stereochemical conditions for both chelation and nonchelation control favor generation of the adduct bearing the anti 1,3-diol (eqs 52 and 53). Carbon−carbon bond disconnections targeted around this stereochemical feature should be stereoregular. In principle, the carbon−carbon bond at either terminus of the anti 1,3-diol could be disconnected separating the target molecule into an α-alkyl-β-alkoxy aldehyde and an enolate derivative. Once an appropriate bond disconnection is chosen, the relative stereochemistry of the central methyl-bearing carbon will determine the type of reaction

Scheme 7



conditions necessary to favor the desired stereochemical outcome. The 1,2-anti Me ↔ OH relationship signals a transform for chelation control while the analogous syn relationship calls for nonchelation control.

This analysis is, of course, dependent upon dominant stereocontrol emanating from the chirality resident in the aldehyde fragment and considers only the prochirality of the trigonal aldehyde carbon. An additional control element is introduced if the enolate derivative is also prochiral, and furthermore, if the enolate bears chirality, then a deeper level of analysis will be necessary for the double stereodifferentiating aldol coupling process.[45] In the higher order analysis, the above inherent stereochemical preferences of the aldehyde chirality remain the same, but stereocontrol elements in the aldehyde may be subjugated by stereochemical influences from the enolate component.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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