Diastereoselective Aldol and Allylstannane Addition Reactions. The Merged Stereochemical Impact of α and β Aldehyde Substituents

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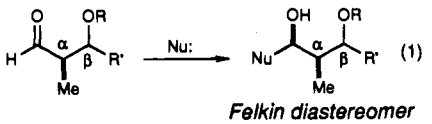
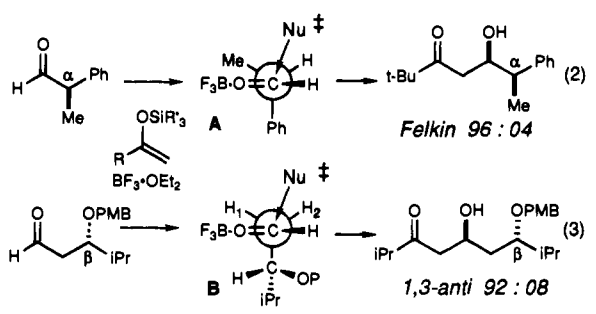
Conventional wisdom states that the stereogenic center proximal to the carbonyl exerts the dominant influence on π-facial selectivity in the addition of nucleophiles to α,β-disubstituted aldehydes (eq 1). In this Communication, we



(1)

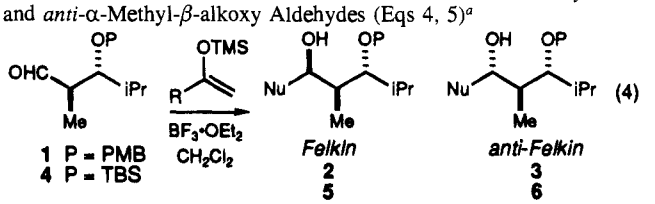
document cases in which the more remote β-heteroatom-substituted stereocenter can become the dominant control element in the carbonyl addition process under conditions where chelate organization is precluded. We have also identified the diastereomeric relationships between α-alkyl and β-alkoxy substituents that are either mutually reinforcing or nonreinforcing with regard to carbonyl π-facial selectivity in these reactions.

The cumulative impact of α and β substituents on π-facial selectivity is introduced in the context of the Mukaiyama aldol reaction.[1] It has been well documented that the additions of enolsilanes to both α- and β-substituted aldehydes proceed with excellent diastereoselection (eqs 2, 3).[2,3] The selectivity of the



former reaction is readily accommodated by the Felkin–Anh transition state model **A**,[4] while the 1,3-asymmetric induction model **B** accounts for the stereochemical outcome of the latter process.[3a] These results raise the prospect that there might exist intrinsic stereochemical relationships between α and β substituents that are either mutually reinforcing or opposing. The merged stereoinduction model for *anti*-disubstituted aldehydes, created by replacement of H_1 in model **B** with a methyl group, predicts preferential formation of the Felkin/1,3-*anti* diastereomer in the additions to aldehydes **1** and **4** (Table 1, eq 4). Since those factors that control α and β stereoinduction appear to be mutually reinforcing in these substrates, one might

Table 1. Lewis Acid-Promoted Addition of Enolsilanes to *syn*- and *anti*-α-Methyl-β-alkoxy Aldehydes (Eqs 4, 5)[a]



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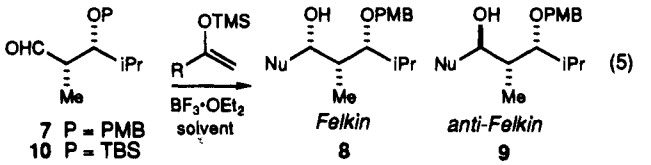
entry	R	2 : 3 (P = PMB)	(%)	5 : 6 (P = TBS)	(%)
A	t-Bu	99 : 01	(94)	99 : 01	(93)
B	i-Pr	98 : 02	(98)	95 : 05	(88)
C	Me	97 : 03	(86)	71 : 29	(92)



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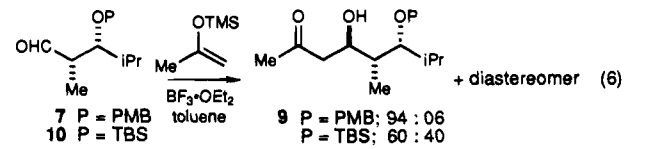
entry	R	8 : 9 (CH_2Cl_2)	(%)	8 : 9 (toluene)	(%)
A	t-Bu	96 : 04	(89)	88 : 12	(75)
B	i-Pr	56 : 44	(98)	32 : 68	(86)
C	Me	17 : 83	(82)	06 : 94	(92)

[a] All reactions were carried out with 1 equiv of BF_3•OEt_2 in CH_2Cl_2 or toluene at −78 °C. Ratios were determined by GLC analysis after silylation (TMS-imidazole) of the unpurified reaction mixtures. Yields are reported for the diastereomeric mixture of adducts. Complete characterization of the product diastereomers is available in the supplementary material.

anticipate the process to be highly diastereoselective. Indeed, we have found that excellent diastereoselection is achieved in the BF_3•OEt_2-promoted reactions with *anti*-substituted aldehydes **1** and **4** (Table 1, eq 4).[5]

The analysis becomes more complex for *syn*-substituted aldehydes such as **7** and **10**, since the diastereofacial bias imposed on the carbonyl moiety from α and β substituents is now nonreinforcing (Table 1, eq 5). From an examination of the data, two trends are evident. First, a turnover in carbonyl face selectivity (Felkin → anti-Felkin) is observed upon decreasing the size of the enolsilane substituent R (*t*-Bu → Me). This nonintuitive reversal of carbonyl face selectivity implies that the β stereocenter has become the dominant control element in the reactions with the less sterically demanding enolsilanes. Second, a decrease in the solvent polarity (CH_2Cl_2 → toluene) consistently provides more of the anti-Felkin product diastereomer, implying that 1,3-induction is enhanced relative to 1,2-induction in nonpolar media. We have postulated that the electrostatic effect imparted by the β heteroatom is the significant stereochemical determinant in these and related addition reactions.[3a] To our knowledge, these are the first examples of anti-Felkin selective Mukaiyama aldol reactions under conditions known to preclude chelate organization. These same trends were also observed in the corresponding reactions with β-OTBS (*tert*-butyldimethylsilyl)-substituted aldehyde **10**, although the anti-Felkin bias is attenuated, presumably due to the increased steric requirements of the silicon protecting group (eq 6).[6]



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(1) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (b) 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, pp 629–660.

(2) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668.

(3) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537–8540 and references cited therein. (b) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729–732.

(4) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61–70. (c) 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*, 1108–1117.

(5) For a related example, see: Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441–444.

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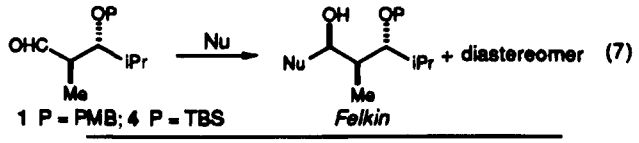
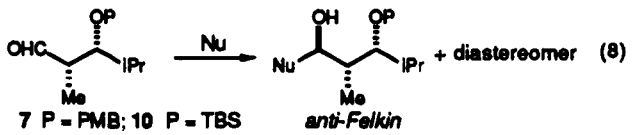
Table 2. Addition of Selected Nucleophiles to *syn*- and *anti*-α-Methyl-β-alkoxy Aldehydes (Eqs 7, 8)[a]



Nu	RCHO	Felkin : anti-Felkin
Bu_3Sn	1[b]	>99 : 1
Bu_3Sn, Me	1[b]	>99 : 1
Me_2CH, OBR_2	1[c]	69 : 31
Me_3C, OBR_2	1[c]	73 : 27
Me_2CH, OLi	1[d]	72 : 28
	4	65 : 35
Me_3C, OLi	1[d]	67 : 33
	4	58 : 42
BrMg	1[e]	61 : 39
BrMg, Me	1[e]	85 : 15



Nu	RCHO	Felkin : anti-Felkin
Bu_3Sn	7[b]	13 : 87
Bu_3Sn, Me	7[b]	20 : 80
Me_2CH, OBR_2	7[c]	23 : 77
Me_3C, OBR_2	7[c]	20 : 80
Me_2CH, OLi	7[d]	18 : 82
	10	13 : 87
Me_3C, OLi	7[d]	11 : 89
	10	08 : 92
BrMg	1[e]	74 : 26
BrMg, Me	1[e]	70 : 30

[a] Ratios were determined by GLC analysis after silylation (TMS-imidazole) of the unpurified reaction mixtures. Complete characterization of the product diastereomers is available in the supplementary material. [b] Allylstannane conditions, toluene, −78 °C, 1 equiv of $BF_3{\cdot}OEt_2$. [c] P_eB = 9-borabicyclo[3.3.1]nonyl(9-BBN). 9-BBN enolate conditions, CH_2Cl_2, −78 °C. [d] Lithium enolate conditions, THF, −78 °C. [e] Grignard reaction conditions, THF, −78 °C.

We have observed that other reactions also follow the stereochemical precedent established by the preceding aldol additions. For example, the $BF_3{\cdot}OEt_2$-promoted additions of allyl- and β-methallylstannanes[7] to aldehydes **1** and **7** also follow opposite stereochemical paths (Table 2), in direct analogy to the aldol reactions of unhindered enolsilanes. While exclusive formation of the anticipated Felkin product diastereomer was obtained in the reaction with *anti*-substituted aldehyde **1** (Table 2, eq 7), β-heteroatom-dominated facial control in the reaction with *syn*-substituted aldehyde **7** provided principally the anti-Felkin product diastereomer (Table 2, eq 8). Finally, the illustrated 9-BBN boron and lithium enolates derived from methyl isopropyl ketone and pinacolone further reinforce the stereochemical trends established in the preceding examples.[8,9] As a counterpoint to these observations, Grignard reagents undergo moderate levels of Felkin-controlled addition with both families of diastereomeric aldehydes. Furthermore, allylboronate[10] additions to related aldehyde diastereomers exhibit low levels of Felkin control in both instances.[11] One might project that the transition states of these reactions exhibit less charge separation and are accordingly less subject to the electrostatic influence of β heteroatom substituents.

Although the prospect for chelate-controlled addition[12,13] may be raised in the aldol reactions of the illustrated lithium enolates, neither kinetic nor stereochemical evidence for chelation in the reactions of lithium enolates in THF with α-alkoxy aldehydes has been found.[14] The comparable levels of induction with the PMB- and TBS-protected aldehydes further argue against the importance of chelation in the reactions of lithium enolates in THF.

We thus conclude that carbonyl addition reactions of unhindered trigonal nucleophiles that proceed through polar transition states may be influenced by β heteroatom substituents. The addition reactions of these nucleophiles to aldehydes bearing α-alkyl as well as β-alkoxy substituents are highly stereoregular when the indicated substituents are in the *anti* (mutually reinforcing) diastereomeric relationship, as in aldehydes **1** and **4**. In contrast, when these same substituents are in the *syn* diastereomeric (nonreinforcing) relationship, this family of nucleophiles will add to *syn* aldehydes such as **7** and **10** through the anti-Felkin mode with dominant stereocontrol emanating from the more remote β heteroatom substituent. The magnitude of the β heteroatom stereochemical determinant seems to be coupled to the polarity of the transition state of the addition process and to the type of nucleophile employed. Accordingly, both nucleophile structure and reaction type appear to be important reaction attributes for dominant control from β heteroatom substituents. The importance of this stereochemical control element in the analysis of complex aldol reactions will be reported in due course.

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Supplementary Material Available: Experimental procedures for all reactions, product stereochemical proofs, and characterization of all new compounds (36 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfiche version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(6) The diastereoselection is also attenuated in the analogous additions to β-silyloxy, α-unsubstituted ahdehydes, see ref 3a.

(7) For a review of allylmetal addition reactions, see: Yamamoto, Y.; Asoa, N. *Chem. Rev.* **1993**, *93*, 2207−2293.

(8) For related addition reactions to *syn*-substituted aldehydes see: Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *33*, 6129−6132.

(9) For a recent systematic investigation of methyl ketone aldol reactions with complex aldehyde substrates, see: Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443−3446.

(10) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966−3979.

(11) These same nucleophiles also fail to exhibit significant levels of 1,3-stereoinduction in additions to β-alkoxy aldehydes lacking an α-methyl substituent: (a) Reetz M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31−42.

(12) For a review of chelation, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(13) Masamune, S.; Ellingboe, J. W.; Choy, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 5526−5528.

(14) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846−3856. (b) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302−1312.