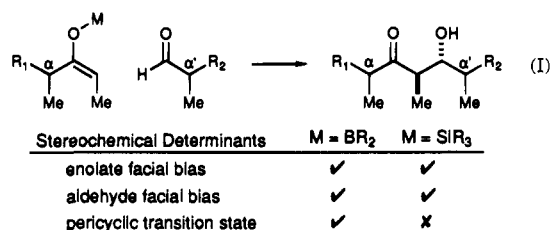## Double Stereodifferentiating Lewis Acid-Promoted (Mukaiyama) Aldol Bond Constructions

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The development of predictable strategies for the execution of double stereodifferentiating aldol reactions is an important objective.[1] For substituted enolate- and enolsilane-based processes, there are at least three identifiable stereochemical determinants that influence reaction diastereoselectivity (eq I).

| Stereochemical Determinants	M = BR₂	M = SiR₃
enolate facial bias	✔	✔
aldehyde facial bias	✔	✔
pericyclic transition state	✔	✗

Two of these determinants are associated with the local chirality of the individual reaction partners. For example, enolate (enolsilane) chirality influences the *absolute* stereochemistry of the forming methyl-bearing stereocenter, and in a similar fashion, aldehyde chirality controls the *absolute* stereochemical outcome of the incipient hydroxyl-bearing stereocenter. The third determinant, the pericyclic transition state, imposes a *relative* stereochemical relationship between the developing stereocenters.[2] This important control element is present in the aldol reactions of metal enolates (M = BR₂, TiX₃, Li, etc.) but is absent in the Lewis acid-catalyzed (Mukaiyama) enolsilane aldol variants that proceed *via* open transition states.[3]

The purpose of this Communication is to summarize our results from a general investigation of the synthetic utility of double stereodifferentiating Mukaiyama aldol reactions. All chiral reactants employed in this study possess the absolute stereochemical relationships denoted in the accompanying graphics.

Aldehyde Component. The absolute configuration of the newly formed hydroxyl stereocenter in Mukaiyama aldol reactions is dominated by the diastereofacial bias of the chiral aldehyde. Aldehydes 2a,b exhibit excellent levels of Felkin[4] face selectivity in their BF₃·OEt₂-promoted reactions[5] with achiral (E)- and (Z)-enolsilane derivatives 1a,b (Scheme 1).[6] In fact, anti-Felkin aldol adducts are detected in only one of the four reactions (eq 4).[7] The other important trend in this set of reactions is the consistent predisposition for the formation of the *syn* aldol product diastereomer irrespective of enolsilane geometry.[8]

Scheme 1. Aldehyde Face Selectivity[a]
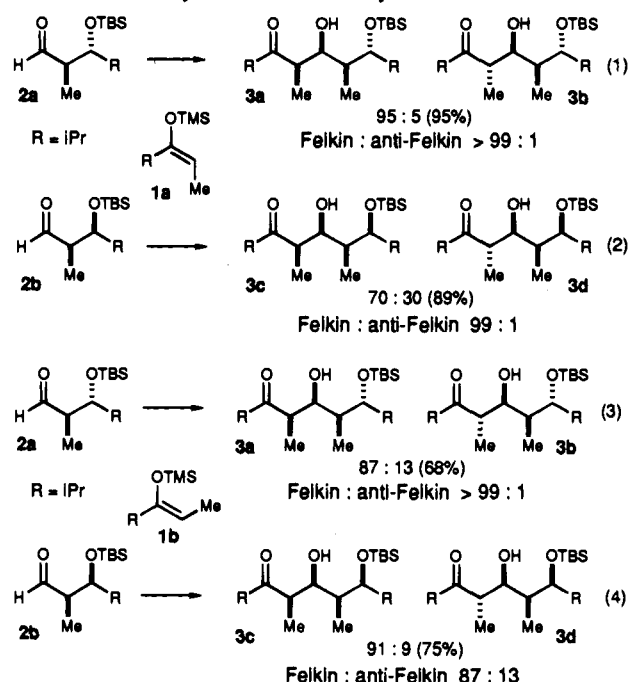
[a] See ref 6 for reaction conditions and protocol for product analysis.

Scheme 2. (E)- and (Z)-Enolsilane Face Selectivity[a]
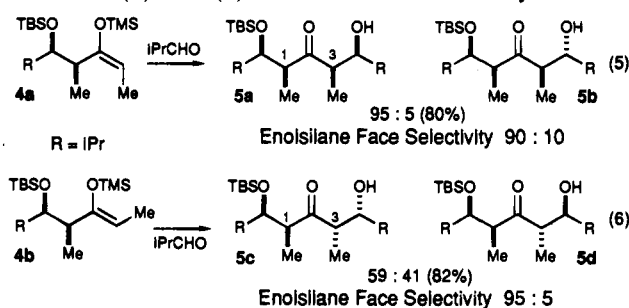
[a] See ref 6 for reaction conditions and protocol for product analysis.

Enolsilane Component. Chiral enolsilanes 4a,b were prepared in ≥40:1 geometric purity according to literature precedent.[9] The important stereochemical determinant evaluated in Scheme 2 is enolsilane face selectivity, which controls the direction and degree of asymmetric induction at the incipient methyl-bearing stereocenter. From the data presented, it is evident that both (E)- and (Z)-enolsilane substrates 4a,b display excellent levels of asymmetric induction and complementary face selectivities in their BF₃·OEt₂-promoted reactions with

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

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

(6) General experimental procedure: A stirred solution of enolsilane (1 equiv) and aldehyde (1 equiv) in anhydrous CH₂Cl₂ (0.05 M) at −78 °C was treated with BF₃·OEt₂ (1.3 equiv). The reaction mixture was stirred at −78 °C for 1−2 h (for double stereodifferentiating reactions, the reaction was gradually warmed to −30 °C and stirred for an additional 8 h). After an extractive isolation, the product mixture was flash-chromatographed on silica gel (5−10% EtOAc/hexane eluant) to afford the individual aldol adducts. The characterization of all new compounds is described in the supporting information. Product ratios were determined by GLC analysis after silylation of the unpurified reaction mixtures.

(7) The *anti* stereochemical relationship between α and β stereocenters of aldehyde 2a mutually reinforce addition to the Felkin diastereoface: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619—6620.

(8) Danishefsky has reported many potentially related reactions between achiral siloxydienes and chiral aldehydes: Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59—68 and references cited therein.

(9) For preparation of (E)-enolsilanes, see: (a) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571—9574. For preparation of (Z)-enolsilanes, see: (b) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526—5528.

Scheme 3. Double Stereodifferentiating *Syn* Aldol Reactions with Enolsilanes[a]
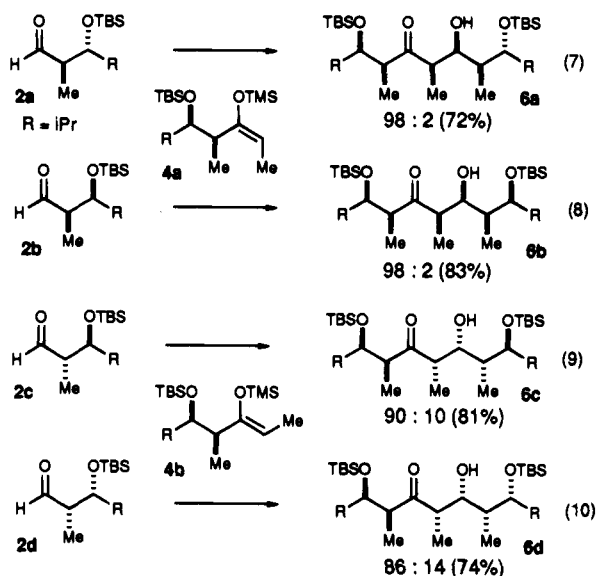
a See ref 6 for reaction conditions and protocol for product analysis.

isobutyraldehyde (eqs 5 and 6).[6] While the (*E*)-enolsilane provides the 1,3-*syn*-dimethyl relationship (eq 5), the corresponding (*Z*)-enol derivative affords the less accessible 1,3-*anti*-dimethyl relationship (eq 6) in their respective aldol reactions. This reversal in enolsilane face selectivity is significant in that the related (*Z*)- and (*E*)-enolate-based aldol reactions (boron and titanium) proceed with 1,3-*syn*-dimethyl selectivity across the developing carbonyl moiety.[10,11]

Reaction Diastereoselectivity (*Syn* vs *Anti*). Due to the intermediacy of open transition states,[12] there is no direct correlation between product stereochemistry and enolsilane geometry in these reactions.[13] Nevertheless, the BF₃·OEt₂-mediated reactions illustrated in Schemes 1 and 2 exhibit a persistent level of *syn* reaction diastereoselectivity. This uniform tendency for *syn* aldol product formation that is independent of enolsilane geometry is reminiscent of the stereoconvergency observed in crotylstannane[12b,14] and crotylsilane additions.[15]

Double Stereodifferentiating Aldol Reactions. In principle, either *syn* or *anti* aldol reactions may be designed from the individual face selectivities exhibited by the enolsilane and aldehyde reaction partners (cf. Schemes 1 and 2). However, one must also consider the intrinsic bias for *syn* aldol diastereoselection that is associated with the above processes. Accordingly, those reaction partners that might reinforce the stereochemical predisposition for *syn* aldol product formation were investigated first (Scheme 3). The resulting double stereodifferentiating reactions all proved to be highly diastereoselective. For example, the reactions between (*E*)-enolsilane **4a** and aldehydes **2a,b** afford single *syn* aldol product diastereomers in excellent yields (Scheme 3, eqs 7 and 8).[6] The

Mukaiyama aldol reactions of (*Z*)-enolsilane **4b** (Scheme 3, eqs 9 and 10) are equally exciting since the normally observed face selectivity for boron and titanium enolates (1,3-*syn*-dimethyl) has been reversed (1,3-*anti*-dimethyl) in these enolsilane variants. It is also important to note that each of these Lewis acid-promoted *syn* aldol reactions provides the Felkin diastereomer with high selectivity. At the present time, this type of aldol bond construction is generally difficult to perform in high selectivity utilizing metal enolate technology.[16]
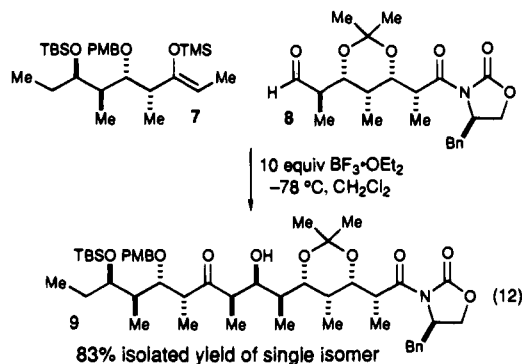
The *syn*-selective reactions illustrated in Scheme 3 represent four of the eight possible reactant pair permutations. The other four reactions (**4b** with aldehydes **2a,b**; **4a** with aldehydes **2c,d**) are potentially useful *anti*-selective aldol bond constructions which must confront the intrinsic bias for *syn* aldol diastereoselection. The aldol coupling between (*E*)-enolsilane **4a** and aldehyde **2d** (eq 11) is representative of this family of reactions, which are not as selective as the previously described processes.
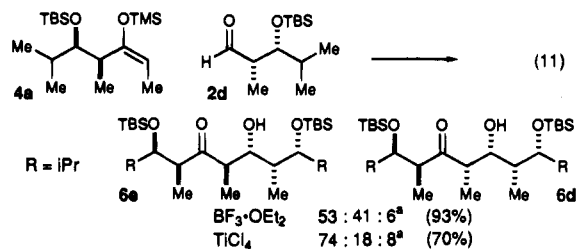
(a) The third unpictured diastereomer is the *syn* aldol *anti*-Felkin diastereomer.

It is interesting that the TiCl₄-mediated reaction exhibits enhanced induction relative to the standard BF₃·OEt₂ variant. It is our intention to evaluate the impact of other Lewis acids on these reactions as a vehicle for improving the utility of this family of bond constructions.

The methodology described above has been successfully incorporated into a recently completed synthesis of 6-deoxyerythronolide B. In the relevant aldol bond construction, the coupling of (*Z*)-enolsilane **7** with chiral aldehyde **8** proceeds with high diastereoselectivity to give the illustrated *syn* aldol adduct **9** in 83% isolated yield (eq 12). The complexity of this bond construction clearly demonstrates the synthetic utility of these double stereodifferentiating aldol reactions.

Supporting Information Available: Experimental procedures for all reactions, product stereochemical proofs, and characterization of all new compounds (24 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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(13) For example, see: Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037 and references cited therein.

(14) Keck, G. E.; Savin, K. E.; Cressman, E. N. K.; Abbott, D. *J. Org. Chem.* **1994**, *59*, 7889−7896.

(15) Hayashi, H.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963−4965.

(16) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.