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1,3-Asymmetric Induction in the Aldol Addition Reactions of Methyl Ketone Enolates and Enolsilanes to β-Substituted Aldehydes. A Model for Chirality Transfer

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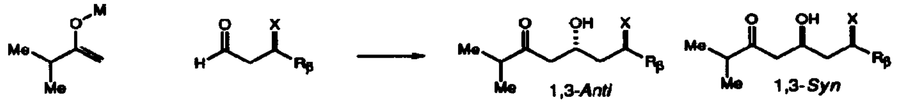
Abstract: The direction and degree of 1,3-asymmetric induction have been evaluated in the addition of metal enolates and enolsilanes to aldehydes substituted at the β position with both polar (OR, OAc, Cl) and nonpolar (Me) substituents. A model for 1,3-asymmetric induction for polar addition processes such as the Mukaiyama aldol reaction is proposed to account for the documented trends in reaction diastereoselection for polar β-substituents.

Nucleophilic carbonyl addition reactions continue to be ranked among the premier chemical transformations in organic synthesis. With regard to the stereochemical aspects of this process, significant effort has been expended in the development of transition state models that account for the impact of proximal substituents on carbonyl π-facial selectivity. Heteroatom substituents positioned either α or β to the reacting carbonyl moiety raise the potential for transition state chelate organization, and Cram's chelation models have been both well recognized and heavily exploited in the prediction of reaction diastereoselection.[1] In those substrates lacking the potential for chelate organization, the interplay of steric and electronic effects are accounted for by the Felkin-Anh paradigm which generally provides a useful stereoinduction model for substrates bearing stereogenic centers α to the carbonyl moiety.[2] In contrast, comparable models acknowledging the influence of β-substituents on reaction diastereoselectivity have been less well developed.[3]

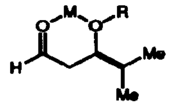
The purpose of this Letter is to address the issue of 1,3-asymmetric induction in the addition of metal enolate and enolsilane nucleophiles to β-substituted aldehydes (eq 1) with the objective of identifying the relative importance of polar, steric, and chelate substituent effects in dictating reaction diastereoselection. In this study, enolate structure, with the exception of the metal ion (M), has been held constant.



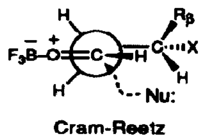
(1)

M = Li, TiCl$_n$, BR$_2$, SiMe$_3$ X = OPMB, OTBS, OAc, Cl

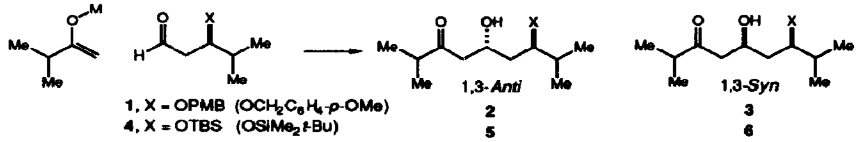
The addition of 3-methyl-2-butanone-derived enolates to β-oxygen substituted aldehydes **1** and **4** was carried out under a variety of conditions (eq 2, Table I). It is assumed that the Li, Ti, and B enolates react through closed transition states, but that only the Li and Ti enolate nucleophiles might exhibit the potential for chelate organization.[4] In contrast, the $BF_3{\bullet}OEt_2$-promoted enolsilane aldol reaction ($M = SiMe_3$)[5] is presumed to proceed through an open transition state where chelate organization is again precluded due to the limitations of four-coordinacy at boron.[6] The data in Table I indicate that the formation of the 1,3-*anti* products **2** and **5** is generally preferred irrespective of the nature of the oxygen protecting group.[7] The formation of the 1,3-*anti* product diastereomer is consistent with the intervention of the illustrated internal chelate, and this may be one possible explanation for the results of the lithium and titanium mediated aldol reactions of aldehyde **1** (entries A, B). However, for aldehyde **4** internal chelation is strongly disfavored by the *tert*-butyldimethylsilyl (TBS) protecting group.[8] In addition, it is highly improbable that the *anti* stereochemical outcome of the $BF_3{\bullet}OEt_2$-promoted aldol reaction[9] (entry D) is also chelate controlled. Reetz has



postulated that *anti* stereoinduction for this process probably arises from transition state polar effects[3f] and has invoked the illustrated Cram polar model[3d,e] to account for the results. From these and related Lewis acid promoted addition reactions,[10] it is evident that remote electrostatic effects can play a significant role in influencing the stereochemical outcome of these processes and that this stereocontrol element will assume greater importance for those reactions proceeding through more polar transition states.



Cram-Reetz



(2)

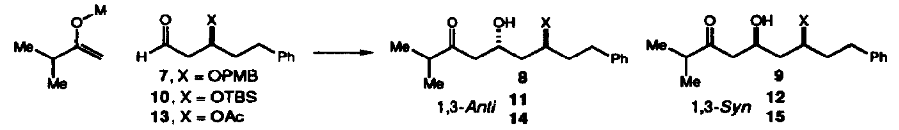
Table I. Aldol Reactions of 3-Methyl-2-butanone Enolates with β-Substituted Aldehydes (eq 2)[a]

entry	conditions	metal (M)	2 : 3 (X = PMB)	(%)	5 : 6 (X = TBS)	(%)
A	LDA	M = Li	71 : 29	(100)	76 : 24	(91)
B	$TiCl_4$ / iPr_2NEt	M = $TiCl_n$	60 : 40	(98)	58 : 42	(88)
C	9-BBNOTf / iPr_2NEt	M = BR_2	42 : 58	(82)	52 : 48	(79)
D	BF_3·OEt_2	M = $SiMe_3$	92 : 8	(91)	80 : 20	(84)

[a] The above footnote corresponds to Table II, footnote a

In order to further evaluate the interplay of steric and electrostatic effects on the addition process, aldehyde **7** was synthesized with β-substituents (OCH_2Ar vs. CH_2CH_2Ar) of similar size but different electronic properties (eq 3). The aldol reactions employing the Li, Ti, and B enolates generally exhibited low diastereofacial selectivity with this substrate (Table II). These results are consistent with the generalization that electrostatic effects alone do not provide a strong diastereofacial bias for these aldol processes. In contrast, synthetically useful levels of *anti* diastereoselection were obtained in the more polar Lewis acid promoted enolsilane aldol variant (entry D) with aldehydes **7**, **10**, and **16** containing β-OPMB, -OTBS, and -Cl substituents, respectively. As a control experiment, the $SnCl_4$-promoted enolsilane aldol reaction was also carried out under conditions where chelate organization, if intervening, should be expected to afford good levels of *anti* diastereoselection. From the data presented, we conclude that with $SnCl_4$, only the -OPMB and -OAc substituents might be involved in chelation in the reactions with aldehydes **7** and **13**. On the other hand, the poor diastereoselection observed with aldehyde **10** again provides qualitative support for the conclusion that the -OTBS substituent does not participate in chelate organization even under favorable circumstances.[8]

To assess steric contributions to 1,3-asymmetric induction in the absence of any electrostatic effects, aldehyde **19** was subjected to the representative set of aldol reactions (eq 4, Table III). From the data in Table III, it is



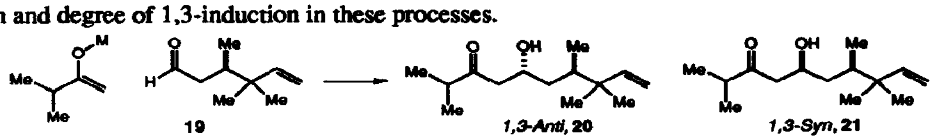
(3)

Table II. Influence of the β Aldehyde Substituent in the Illustrated Aldol Addition Reaction (eq 3)[a]

entry	Conditions	metal (M)	8 : 9 (X = OPMB)	11 : 12 (X = OTBS)	14 : 15 (X = OAc)	17 : 18 (X = Cl)[b]
A	LDA	M = Li	53 : 47 (94)	61 : 39 (96)	59 : 41 (82)	80 : 20 (65)
B	$TiCl_4$ / iPr_2NEt	M = $TiCl_n$	58 : 42 (84)	62 : 38 (93)	31 : 69 (79)	63 : 37 (75)
C	9-BBNOTf / iPr_2NEt	M = BR_2	44 : 56 (77)	52 : 48 (82)	27 : 73 (77)	23 : 77 (68)
D	BF_3·OEt_2	M = $SiMe_3$	81 : 19 (87)	73 : 27 (90)	43 : 57 (79)	83 : 17 (84)
E	$SnCl_4$[c]	M = $SiMe_3$	95 : 5 (79)	48 : 52 (83)	89 : 11 (85)	–

[a] All reactions were carried out at -78 °C in either THF (entry A) or CH_2Cl_2 (entries B-E). Product ratios were determined by GLC analysis of the silylated reaction mixtures. Yields are reported for the mixtures of product diastereomers. [b] Stereochemical assignments were secured through independent synthesis. [c] Lewis acid was precomplexed with the aldehyde prior to enolsilane addition.

evident that the β-steric component of 1,3-induction provides low diastereoselectivity of variable direction.[11] The observations outlined above imply that cooperative steric and electrostatic effects combine to influence the direction and degree of 1,3-induction in these processes.



19 1,3-*Anti*, **20** 1,3-*Syn*, **21** (4)

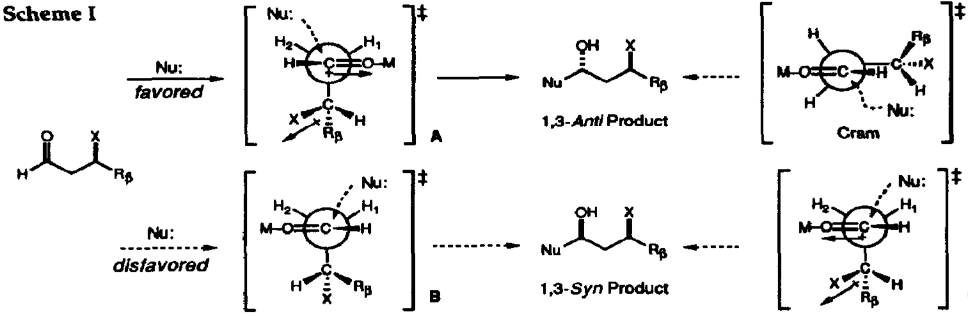
Table III. Aldol Reactions with Sterically Differentiated β-Substituents (eq 4)[a]

entry	Conditions	metal (M)	20 : 21	(%)
A	LDA	M = Li	64 : 36	(80)
B	$TiCl_4$ / iPr_2NEt	M = $TiCl_n$	36 : 64	(100)
C	9-BBNOTf / iPr_2NEt	M = BR_2	34 : 66	(92)
D	$BF_3{\cdot}OEt_2$	M = $SiMe_3$	58 : 42	(88)
E	$SnCl_4$[c]	M = $SiMe_3$	58 : 42	(79)

The above footnotes correspond to those found in Table II, footnotes a,b.

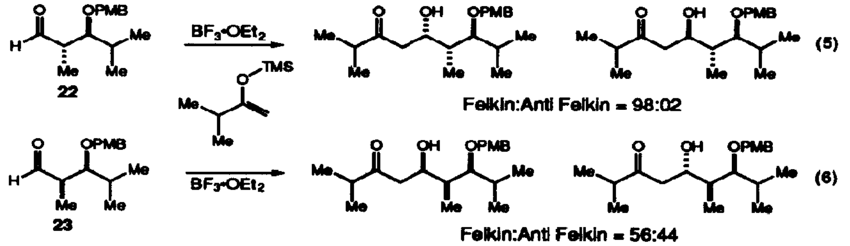
The Model. We propose a revised model for 1,3-asymmetric induction for nucleophilic additions to aldehydes bearing polar substituents in the β-position (Scheme I). In the illustrated transition structures, the descriptor R_β denotes the β-carbon alkyl substituent, while X denotes the "polar" heteroatom substituent (OR, Cl, etc.). For transition structures **A**, **B**, and **C**, the β-carbon (C_β) is oriented perpendicular to the σ framework of the carbonyl moiety. This is in accord with the Felkin assertion that the staggered conformation between C_α and the trigonal carbon undergoing reaction is preferred in such addition processes.[12] Complementary minimization of interacting dipoles and nonbonded interactions favors reaction through transition state **A**. Structure **B** suffers from a destabilizing *gauche* interaction ($R_\beta \leftrightarrow C{=}O$), which should be amplified with larger R_β substituents. Transition state **C** is disfavored due to electrostatic interactions between the C=O and polar β-substituent.[13] It follows that 1,3-*anti* diastereoselection should be enhanced with an increase in the steric requirement of R_β, and this trend is evident in the data presented in Tables I-II, particularly for the Mukaiyama aldol reaction. This model modifies the Cram polar model by replacement of the destabilizing gauche ($R_\beta \leftrightarrow C{=}O$) and ($C_\beta \leftrightarrow Nu$) and eclipsing ($C_\beta \leftrightarrow (H)C{=}O$) interactions with the illustrated staggered geometry.

Scheme I



Of the reaction variants examined, the Lewis acid-promoted Mukaiyama aldol process generally exhibits the most synthetically useful levels (3-12:1) of 1,3-asymmetric induction (Tables I-III), even with those substrates wherein the size difference between the X and R_β is minimal (Table II). It is presumed that electrostatic effects more strongly influence this family of polar transition states than the less polar enolate based processes. A more complex dipole at the β-position, as in β-OAc aldehyde **13**, may complicate the electrostatic influence of the polar substituent X and thereby provide less predictable results.[14]

Complex Aldehydes. For aldehydes such as **22** and **23** bearing stereocenters at both the α and β positions, the Felkin and 1,3-asymmetric induction models may be integrated. Analysis of the respective transition structures for the two Mukaiyama aldol reactions correctly predicts that **22** should exhibit a more pronounced facial bias (eq 5), since both stereocenters mutually reinforce addition from the same carbonyl diastereoface (replace H_1 for Me in **A**). In contrast, the two stereogenic centers in aldehyde **23**, which are not reinforcing (replace H_2 for Me in **A**), should lead to diminished reaction diastereoselection (eq 6). The results summarized below provide a gratifying illustration of this projection.



Complementary studies on the diastereoselective reduction of β-alkoxyketones and a related model rationalizing the stereochemical control elements in these reactions may be found in the accompanying Letter.[15]

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13) It is not suggested that **B** and **C** are the only transition states which might give rise to the minor product diastereomer. It is reasonable that transition structures possessing a *gauche* relationship between C_β and nucleophile should also be considered.

14) Low or variable diastereoselectivity in $BF_3•OEt_2$ mediated Mukaiyama aldol reactions has been observed elsewhere for substrates with complex dipole protecting groups at the β-oxygen. For β-O-methoxymethyl (MOM), see: (a) Roy, R.; Rey, A. W. *Synlett* **1990**, 448-450. No 1,3-induction was observed in the $BF_3•OEt_2$ promoted Mukaiyama aldol addition to a β-O-*p*-methoxybenzyloxymethyl (BOM) substituted aldehyde: (b) Evans, D. A.; Carter, P. H. unpublished results.

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