Transition-State Models

Resurrecting the Cornforth Model for Carbonyl Addition: Studies on the Origin of 1,2-Asymmetric Induction in Enolate Additions to Heteroatom-Substituted Aldehydes**

David A. Evans, Sarah J. Siska, and Victor J. Cee*

Transition-state models that reliably predict the stereochemical outcome of pivotal organic reactions are essential to synthesis design. This statement is true even if the proposed model is purely empirical. Historically, such has been the case for models that predict the stereochemical course of nucleophilic additions to chiral α-substituted aldehydes and

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[*] Prof. D. A. Evans, S. J. Siska, V. J. Cee
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

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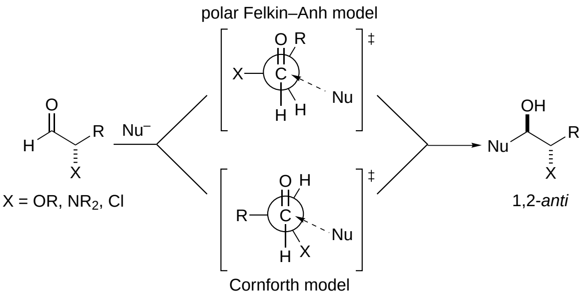
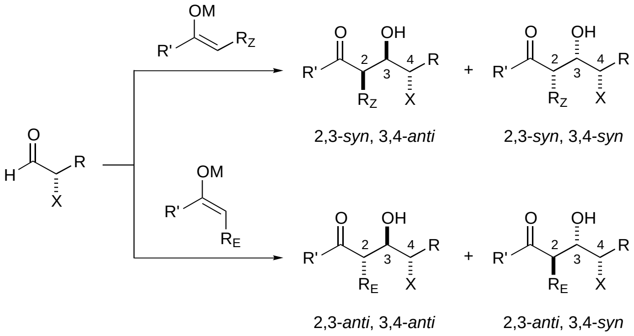
ketones.[1] The first stereoinduction model for this process was introduced by Cram and Elhafez in 1952.[2] More realistic models have subsequently evolved over the last five decades on the basis of new insights into stabilizing transition-state geometries and interactions.[3]

The present study is concerned with the design of experiments that might differentiate between the polar Felkin–Anh (PFA)[3d,4,5] and modified[6] Cornforth[3a,7] models for α-heteroatom-substituted aldehydes (Scheme 1). In the absence of chelate organization, both models predict the observed 1,2-*anti* product stereochemistry through different rotamers of the α-stereocenter. The PFA model[3d,4,5] is based on transition-state stabilization through hyperconjugative interaction of the forming bond (HOMO) with the best vicinal acceptor, the C–X bond (LUMO); in contrast, the Cornforth model[3a,6,7] is based on dipole minimization between the C–X bond and the adjacent carbonyl group. Since Anh and Eisenstein's pioneering theoretical investigation,[4] however, the PFA model has been commonly accepted as the preferred explanation for 1,2-asymmetric induction in α-heteroatom-substituted aldehydes. Subsequent theoretical studies have generally supported the PFA model,[5] although there are some exceptions.[7] Experimentally, these two transition-state models can be distinguished for carbonyl addition reactions in which the nucleophile imposes a transition-state conformational constraint on the orientation of the α-stereocenter of the electrophile. Substituted enolate nucleophiles meet this criterion (see below). Accordingly, we report a systematic study of aldol reactions between methyl-substituted *Z* and *E* enolates and α-oxygen-substituted aldehydes. In this study, the observed dependence of diastereofacial selectivity on enolate configuration is more consistent with the Cornforth model. This conclusion has also been drawn by both Hoffmann et al. and Roush et al. in their comparable studies on aldehyde crotylboration.[8]



Scheme 1. Stereochemical models for 1,2-induction in α-heteroatom-substituted aldehydes.

Boron-mediated aldol reactions[9] between *Z*- and *E*-substituted enolates and a chiral aldehyde provide two principal diastereomers for each reaction (Scheme 2) since boron enolate configuration strongly correlates with the product stereochemistry (2,3-relationship).[9a] The enolate configuration can also greatly affect the aldehyde diastereofacial selectivity (3,4-relationship) as a result of potential destabilizing *syn*-pentane interactions between the enolate substituent and the α stereocenter of the aldehyde in the transition state.[10] In this study, we have included the data for the analogous lithium enolates for reference purposes and acknowledge the fact that these nucleophiles are inherently less diastereoselective (2,3-relationship). Mechanistic projections from lithium enolates, while less reliable, are nonetheless important for the purpose of generalization.



Scheme 2. Aldol reactions of an α-heteroatom-substituted aldehyde with substituted enolates.

The cyclic transition states for the aldol reaction between substituted enolates and an α-heteroatom-substituted aldehyde are shown in Figure 1. Structures **I** and **II** incorporate the rotamer of the α stereocenter advanced by the PFA model, while structures **III** and **IV** incorporate the rotamer of the Cornforth model. The enolate substituent imposes an additional conformational constraint on the aldehyde rotamer due to the possibility of destabilizing *syn*-pentane interactions. It is through analysis of these interactions that the following predictions can be made regarding the relationship between enolate configuration and aldehyde diastereofacial selectivity.

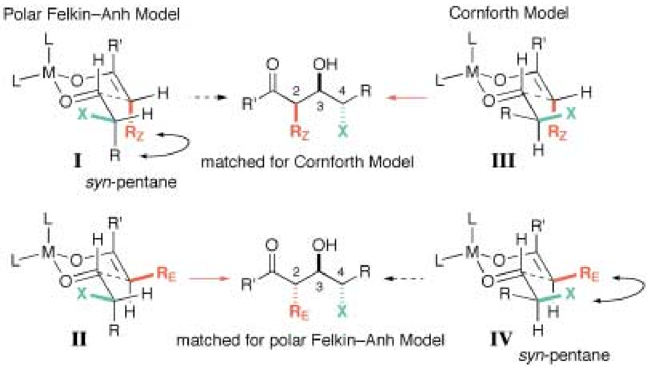


Figure 1. Comparative transition state analysis using the polar Felkin–Anh and Cornforth models.

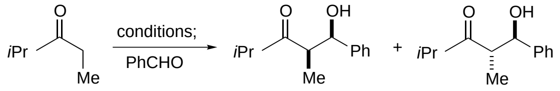
PFA model prediction: The *Z* enolate substituent causes a destabilizing *syn*-pentane interaction (**I**), while the *E* enolate substituent experiences no such interaction (**II**). *Therefore,* E *enolates are predicted to give superior 3,4-*anti *selectivity relative to* Z *enolates.*

Cornforth model prediction: The *E* enolate substituent causes a destabilizing *syn*-pentane interaction (**IV**), while the

Z enolate substituent experiences no such interaction (**III**). *Therefore,* Z *enolates are predicted to give superior 3,4-*anti *selectivity relative to* E *enolates.* As a consequence of this dichotomy, the experimentally determined relationship between enolate configuration and aldehyde diastereofacial selectivity should validate a single model for asymmetric induction.

Boron and lithium enolates of both *Z* and *E* configurations are readily available from 2-methyl-3-pentanone (Table 1).[11] The configurational purity of *Z* and *E* boron enolates correlates well with the *syn*/*anti* ratio of the aldol adducts. While *Z* and *E* lithium enolates are also formed with good configurational purity, the characteristic decline in *syn*/*anti* selectivity is observed, particularly with the *E* enolate.[9]

Table 1: Enolization and aldol addition of 2-methyl-3-pentanone.



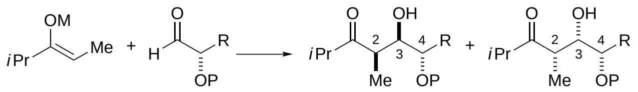
1 **2**

Conditions[a]	Solvent	Configuration (Z:E)[d]	**1**:**2**[d]	Yield [%][e]
9-BBNOTf, DIPEA	Et$_2$O	95:05[b]	94:06	82
(*c*-Hex)$_2$BCl, TEA	Et$_2$O	07:93[b]	04:96	79
LiHMDS	THF	95:05[c]	90:10	66
LiNTMS(*t*Bu)	THF	09:91[c]	48:52	86

[a] For reaction conditions, see Experimental Section. [b] Boron enolates were treated with *n*BuLi, then silylated with trimethylsilyl chloride. [c] Lithium enolates were silylated directly with trimethylsilyl chloride. [d] Ratios were determined by integration of the ^{1}H NMR spectrum of the unpurified reaction mixture. [e] Yields are reported for the mixture of diastereomeric adducts.

The *Z* boron and *Z* lithium enolates of 2-methyl-3-pentanone were allowed to react with a representative set of α-oxygen-substituted aldehydes (Table 2). As anticipated for *Z* enolates, the 2,3-*syn* aldol adducts **3** and **4** predominate.[9] The diastereofacial selectivity is uniformly high, with the 3,4-*anti* diastereomer **3** being greatly favored. This observation alone is inconsistent with the PFA model, which predicts a destabilizing *syn*-pentane interaction in the transition state (Figure 1, **I**) leading to the observed products.

Table 2: Aldol reactions of *Z* enolates.[a]



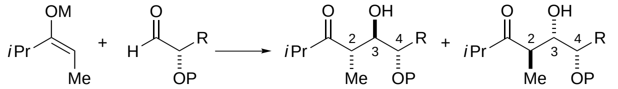
3 **4**

M	P	R	2,3-*syn*:2,3-*anti*	**3**:**4**	Yield [%][c]
9-BBN	Bn	Me	95:05[b]	89:11[b]	95
9-BBN	Bn	*i*Pr	95:05	98:02	73
9-BBN	TBS	Me	93:07	98:02	77
9-BBN	TBS	*i*Pr	94:06	98:02	72
Li	Bn	Me	93:07[b]	89:11[b]	67
Li	Bn	*i*Pr	98:02	98:02	77
Li	TBS	Me	96:04	95:05	65
Li	TBS	*i*Pr	98:02	99:01	71

[a] For reaction conditions, see Experimental Section. All products were unambiguously characterized. Ratios were determined by GC analysis after silylation (TMS-imidazole) or acetylation (Ac$_2$O/pyr) of the unpurified reaction mixtures, unless noted. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixtures. [c] Yields are reported for the mixture of diastereomeric adducts.

The analogous reactions of the *E* boron enolate provide predominantly 2,3-*anti* aldol adducts **5** and **6** (Table 3). In striking contrast to the reactions of *Z* boron enolates, the diastereofacial selectivity is uniformly poor and often favors the 3,4-*syn* diastereomer **6**. As anticipated, the *E* lithium enolate affords poor 2,3-*anti*/2,3-*syn* selectivity, but exhibits moderate diastereofacial selectivity within the 3,4-*anti* diastereomer manifold. Overall, relative to *Z* enolates, the *E* enolates result in greatly diminished levels of 3,4-*anti* diastereoselection.[12] This finding is inconsistent with the PFA model, which contains reinforcing steric and stereoelectronic effects for *E* enolates (Figure 1, **II**). In the Cornforth model for *E* enolates, the *syn*-pentane and C–X dipole control elements are not reinforcing (Figure 1, **IV**), a circumstance that would be expected to lead to diminished aldehyde face selectivity.

Table 3: Aldol reactions of *E* enolates.[a]

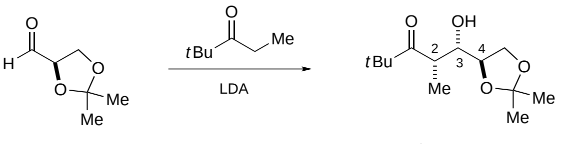


5 **6**

M	P	R	2,3-*anti*:2,3-*syn*	**5**:**6**	Yield [%]
(*c*-Hex)$_2$B	Bn	Me	>99:01[b]	33:67[b]	59
(*c*-Hex)$_2$B	Bn	*i*Pr	>99:01	67:33	77
(*c*-Hex)$_2$B	TBS	Me	>99:01	21:79	77
(*c*-Hex)$_2$B	TBS	*i*Pr	>99:01	43:57	85
Li	Bn	Me	45:55[b]	93:07[b]	92
Li	Bn	*i*Pr	46:54	80:20	78
Li	TBS	Me	62:38	85:15	78
Li	TBS	*i*Pr	67:33	88:12	80

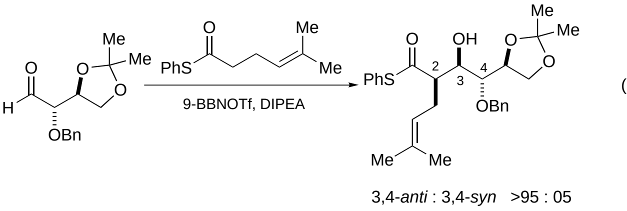
[a] For reaction conditions, see Experimental Section. All products were unambiguously characterized. Ratios were determined by GC analysis after silylation (TMS-imidazole) or acetylation (Ac$_2$O/pyr) of the unpurified reaction mixtures, unless noted. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixtures. [c] Yields are reported for the mixture of diastereomeric adducts.

Other reactions between achiral, substituted sp^2 nucleophiles and α-oxygen-substituted aldehydes have been reported.[8,13,14] Lithium, boron, and titanium enolates have been shown to provide *syn* aldol adducts with high levels of selectivity for the 3,4-*anti* diastereomer [Eqs. (1)–(3)].[13a,c,e] While Urpí and co-workers have noted the inconsistency of

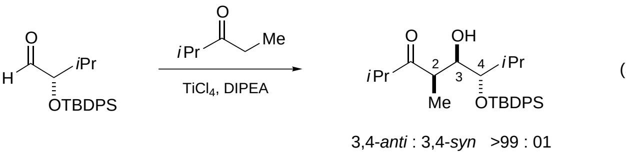


(1)

3,4-*anti* : 3,4-*syn* 85 : 15



(2)



(3)

these results [Eq. (3)] with the PFA model,[13e] a satisfactory explanation was not presented. In light of the preceding analysis, the high 2,3-*syn*, 3,4-*anti* diastereoselectivity in these cases is consistent with a *Z* enolate reacting via a Cornforth transition state (Figure 1, **III**). The mechanistically related crotylboration of chiral oxygen-substituted aldehydes has provided further corroboration of the Cornforth model.[8,14,15]

The modified[6] Cornforth model[3a] (Scheme 1) is receiving increasing support from the growing body of experimental data on nucleophilic additions to α-heteroatom-substituted aldehydes. The success of this model might be because of a concurrence of optimal positions for the aldehyde heteroatom and alkyl substituents in the transition state of nucleophilic addition reactions. The experimental evidence applies directly only to differentially substituted sp^2 nucleophiles reacting with aldehydes via pericyclic chair transition states. However, it is plausible that the factors stabilizing the Cornforth transition states in these specific cases are operating in all nucleophilic additions to α-heteroatom-substituted carbonyl groups. Further experimental and theoretical work will be necessary to substantiate this hypothesis.[16]

Experimental Section

General procedure for the aldol reactions of 9-borabicyclo[3.3.1]-nonyl (9-BBN) enolates: To a 0.2 M solution of ketone (1.0 equiv) in Et_2O at 0 °C was added 1.2 equivalents of diisopropylethylamine and 1.1 equivalents of 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate. The resulting light yellow suspension was warmed to ambient temperature and stirred for 1 h, then cooled to −78 °C. A solution of aldehyde (1.0 equiv) in Et_2O was added. The mixture was stirred at −78 °C for 2 h, then warmed to 0 °C and stirred for 10 min. The reaction was quenched at 0 °C by the sequential addition of equal quantities of 0.05 M pH 7 buffer, MeOH, and 30 % aqueous H_2O_2. The mixture was stirred vigorously at ambient temperature for 30 min, and was then diluted with pH 7 buffer and CH_2Cl_2, and extracted twice with CH_2Cl_2. The combined organic layers were washed with 1:1 saturated aqueous $NaHCO_3$:0.1 N aqueous $Na_2S_2O_3$, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel chromatography.

General procedure for the aldol reactions of dicyclohexylboryl enolates: To a 0.2 M solution of ketone (1.0 equiv) in Et_2O at 0 °C was added 1.05 equivalents of dicyclohexylboron chloride and 1.1 equivalents of triethylamine. The resulting white suspension was stirred at 0 °C for 1 h, then cooled to −78 °C. A solution of aldehyde (1.0 equiv) in Et_2O was added. The reaction mixture was stirred at −78 °C for 2 h, then warmed to 0 °C and stirred for 10 min. The reaction was quenched and isolated as described for 9-BBN enolates.

General procedure for the aldol reactions of Z lithium enolates: To a 0.1 M solution of hexamethyldisilazane (1.1 equiv) in THF at 0 °C was added 1.1 equivalents of *n*-butyllithium (2.95 M in hexanes). The solution was stirred for 10 min at 0 °C, then cooled to −78 °C. Ketone (1.0 equiv) was added slowly, and the resulting solution was stirred at −78 °C for 1 h. A solution of aldehyde (1.0 equiv) in THF was added. The reaction mixture was stirred at −78 °C for 10 min, then the reaction was quenched by adding 1:1 (v:v) saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature with vigorous stirring, then diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl and brine. The aqueous washings were extracted with an additional portion of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel chromatography.

General procedure for the aldol reactions of *E* lithium enolates**:** To a 0.1 M solution of *tert*-butyl(trimethylsilyl)amine (1.2 equiv) in THF at 0 °C was added 1.1 equivalents of *n*-butyllithium (2.95 M in hexanes) rapidly dropwise. The solution was warmed to ambient temperature and stirred for 15 min. Ketone (1.0 equiv) was added rapidly dropwise, and the solution was stirred for 30 s at ambient temperature, then cooled to −78 °C. A solution of aldehyde (1.0 equiv) in THF was added. The reaction mixture was stirred at −78 °C for 10 min, then the reaction was quenched and isolated as described for the *Z* lithium enolate reaction.

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Keywords: aldol reaction · reaction mechanisms · stereoselectivity · transition states

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[16] Abbreviations: PFA = polar Felkin–Anh; DIPEA = diisopropylethylamine; 9-BBNOTf = 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate; TEA = triethylamine; LiHMDS = lithium hexamethyldisilazide; TMS = trimethylsilyl; THF = tetrahydrofuran; Bn = benzyl; TBS = *tert*-butyldimethylsilyl; pyr = pyridine; LDA = lithium diisopropylamide; TBDPS = *tert*-butyldiphenylsilyl.