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1,3-Asymmetric Induction in Hydride Addition Reactions to β-Substituted Ketones. A Model for Chirality Transfer

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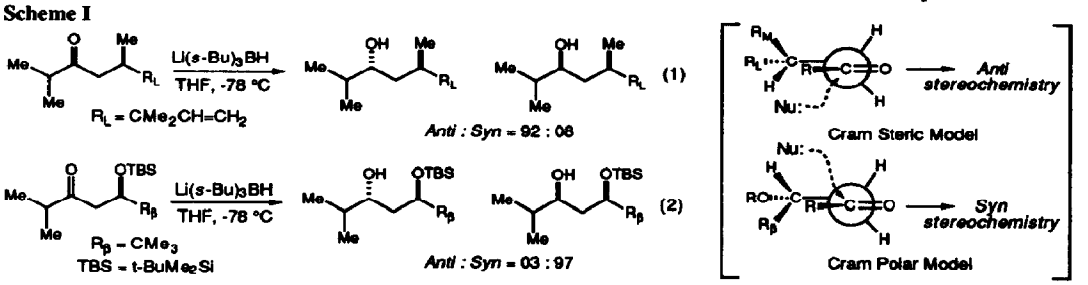
Abstract: We report the 1,3-asymmetric induction observed in the additions of various hydride reagents to β-substituted ketones. Both the nature of the β-substituents and the size of the achiral alkyl group attached to the carbonyl moiety have a significant effect on the direction and degree of carbonyl diastereofacial selectivity. A revision of Cram's polar model for 1,3-asymmetric induction is proposed to account for these results.

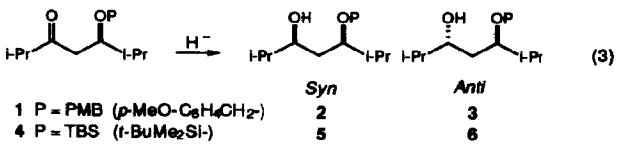
The purpose of this Letter is to highlight the turnover in stereoselectivity that is dependent upon the nature of the β-substituent (alkyl vs. alkoxy) in the reductions of acyclic β-substituted ketones. Two representative reductions that illustrate this observation are provided below (Scheme I).[1,2] We propose that electrostatic effects[3] due to the presence of the β-heteroatom substituent are responsible for the observed reversal in π-facial selectivity, rather than internal chelation.[4] The sterically demanding borohydride reagent, lithium tri-*sec*-butylborohydride, has been compared with other common nucleophilic and electrophilic reducing agents, and is generally the most stereoselective of the metal hydrides evaluated. Revision in the Cram polar and steric transition state models for 1,3-asymmetric induction[1a] is presented to rationalize the trends observed for these and related processes.

Scheme I



β-Alkoxyketones. Representative metal hydrides, including the sterically demanding reagents Li(*s*-Bu)$_3$BH (L-Selectride) and Li(*t*-BuO)$_3$AlH and the electrophilic reducing agents diisobutylaluminum hydride (DIBAL-H) and 9-borabicyclo[3.3.1]nonane (9-BBN), were evaluated against a series of β-alkoxyketones.[5] Permutations in the steric requirements of the β-alkyl substituent (R_β), the alkyl group appended to the carbonyl moiety (R), and the hydroxyl protecting group (P) were made.

Ketones **1** and **4** (eq 3) were selected to gauge the influence of the hydroxyl protecting group on the course of the reaction. Reduction of these substrates with the illustrated hydride reagents (Table I) revealed that formation of the 1,3-*syn* products **2** and **5** was preferred irrespective of the nature of the hydroxyl protecting group. While internal chelation[4] of the substrate followed by external hydride delivery accounts for formation of the 1,3-*syn* diastereomer,[6] we believe that reaction through such a chelated intermediate, particularly in the strong donor solvent THF, is not responsible for the observed stereoinduction in these cases. This assertion is supported by the fact that the highest *syn* selectivity shown in Table I (94:6) was achieved in the reduction of the silyl protected hydroxy ketone **4**.[7] It is also significant that the highest levels 1,3-*syn* stereoselection in these reactions were achieved with Li(*s*-Bu)$_3$BH, a reagent which is generally not disposed toward chelation-controlled reduction.[8]



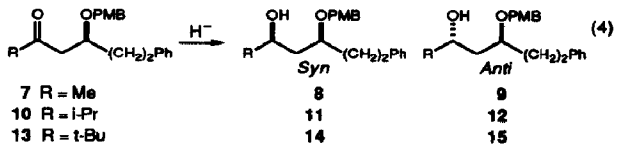
	Syn	Anti
1 P = PMB (*p*-MeO-$C_6H_4CH_2$-)	2	3
4 P = TBS (*t*-BuMe$_2$Si-)	5	6

(3)

Table I. Reductions of β-Substituted Ketones (eq 3)[a]

hydride	2 : 3 (P = PMB)	5 : 6 (P = TBS)
Li(*s*-Bu)$_3$BH	81 : 19	94 : 06
Li(*t*-BuO)$_3$AlH	77 : 23	87 : 13
DIBAL-H	78 : 22	73 : 27
9-BBN	58 : 42	50 : 50

[a] Determined by GLC analysis of the unpurified reaction mixtures.



	Syn	Anti
7 R = Me	8	9
10 R = i-Pr	11	12
13 R = t-Bu	14	15

(4)

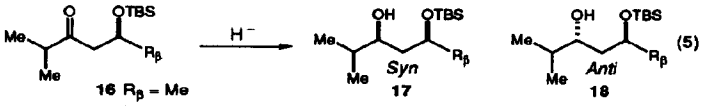
Table II. Influence of Alkyl Group (R) on Reduction (eq 4)[a]

hydride	8 : 9 R = Me	11 : 12 R = i-Pr	14 : 15 R = t-Bu
Li(*s*-Bu)$_3$BH	51 : 49	79 : 21	73 : 27
Li(*t*-BuO)$_3$AlH	56 : 44	69 : 31	75 : 25
DIBAL-H	54 : 46	59 : 41	76 : 24
9-BBN	51 : 49	55 : 45	86 : 14

[a] Determined by GLC analysis of the unpurified reaction mixtures.

In order to probe the influence of the alkyl substituent (R) appended to the carbonyl moiety, substrates **7**, **10**, and **13** were subjected to the standard set of reduction conditions (eq 4, Table II). These substrates were also designed to evaluate the impact of the polar alkoxy substituent in a setting where the steric requirements of both β-substituents (CH_2CH_2Ar and OCH_2Ar) are comparable. The data in Table II document that enhanced selectivity is observed as the size of the carbonyl substituent (R) is increased with the *tert*-Bu ketone **13** generally exhibiting the highest levels of *syn* diastereoselection. In contrast, methyl ketone **7** exhibits poor carbonyl face selectivity irrespective of the hydride source.

The influence of the size of the β-alkyl group (R_β) on reaction diastereoselectivity was examined in the reduction of β-OTBS ketones **16**, **19**, **4**, and **22**[5b] (eq 5, Table III). For both of the nucleophilic hydride reagents, Li(*s*-Bu)$_3$BH and Li(*t*-BuO)$_3$AlH, a strong correlation between *syn* diastereoselection and the steric demands of R_β is evident from the data.



	Syn	Anti
16 R_β = Me	17	18
19 R_β = CH_2CH_2Ph	20	21
4 R_β = i-Pr	5	6
22 R_β = t-Bu	23	24

(5)

Table III. Influence of Substitutent (R_β) in the Illustrated Hydride Reductions (eq 5)[a]

hydride	17 : 18 R_β = Me	20 : 21 R_β = CH_2CH_2Ph	5 : 6 R_β = i-Pr	23 : 24 R_β = t-Bu
Li(*s*-Bu)$_3$BH	74 : 26	92 : 08	94 : 06	97 : 03
Li(*t*-BuO)$_3$AlH	78 : 22	83 : 17	87 : 13	91 : 09
DIBAL-H	69 : 31	69 : 31	73 : 27	76 : 24
9-BBN	72 : 28	67 : 33	50 : 50	79 : 21

[a] Diastereoselectivity was determined by GLC analysis of the unpurified reaction mixtures.

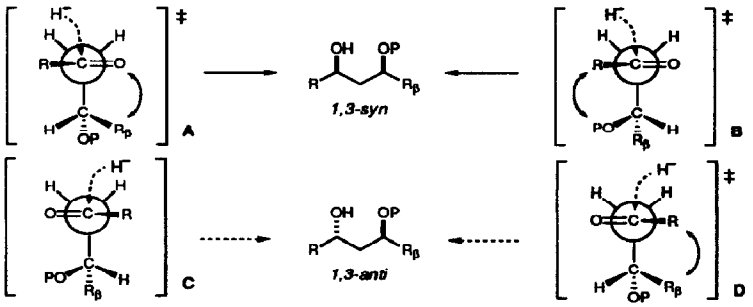
Based on the above observations, the following generalizations may be made: A) a turnover in carbonyl π-facial selectivity is observed upon changing the β-substituent (alkyl→OP); B) enhanced 1,3-*syn* stereoselectivity in the reduction of β-alkoxy ketones is observed with an increase in either the size of the β-alkyl moiety (R_β), the acyl substituent (R), or the hydroxyl protecting group (P). A transition state model that accounts for this reversal in diastereofacial selectivity as well as the other trends outlined above is currently lacking.

A revision of the Cram polar model for 1,3-stereoinduction[1a] has been suggested in the preceding Letter.[9] The specific objection to this model hinges on the utilization of eclipsed rather than staggered transition structures (see Scheme I). As for predictive capacity, the Cram polar model does not correlate the influence of the carbonyl substituent (R) on reaction diastereoselectivity (Table II). On the other hand, electrostatic effects are clearly

playing an important role in governing the sense of asymmetric induction as highlighted in the cases cited in eq 1 and 2. The following revision of Cram's original polar model for 1,3-asymmetric induction is proposed below.

Revised Polar Model. It is proposed that those transition structures wherein the β-carbon (C_β) is oriented perpendicular to the σ framework of the carbonyl moiety be considered in recognition of the Felkin postulate, supported by subsequent computational studies, that the staggered conformation between C_α and the trigonal carbon undergoing reaction is preferred in such addition processes.[10] Staggered transition structures **A** and **B** account for the data reported in this study. In both of these structures, the dipoles associated with C_β–OR and the transforming carbonyl moiety are stabilizing. In distinguishing between these two alternatives, structure **A** accounts for the dependence of 1,3-induction on the size of the carbonyl substituent (R) that is not handled by Cram's original proposal. The principal destabilizing element in **B** is the nonbonding PO↔(R)C=O interaction. However, transition structure **B** might well be favored in addition reactions to those substrates having sterically demanding R_β substituents (e.g. eq 2). For purposes of comparison, from the preceding Letter we have concluded that the preferred transition structure in the Mukaiyama aldol addition to β-alkoxyaldehydes is that corresponding to **B** (R = H), where the indicated nonbonding interaction PO↔(H)C=O has been substantially diminished. Examination of potential transition states leading to the *anti* product diastereomer[11] lead us to conclude that **D** is disfavored on the basis of steric considerations (R_β↔(R)C=O), while destabilizing electrostatic interactions are present in **C**. We also suggest that it is the electrostatic destabilization of **C** which differentiates the present polar model from the steric model **E** provided in Scheme III (OR = R_M).

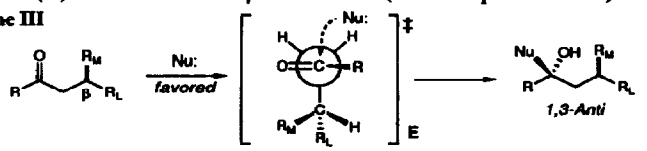
Scheme II



Finally, why is reaction diastereoselectivity generally elevated with an increase in steric requirements of the hydride reagent? We speculate that the illustrated *anti*, rather than *gauche*,[10] relationship between nucleophile and C_β is enforced with sterically demanding nucleophiles.

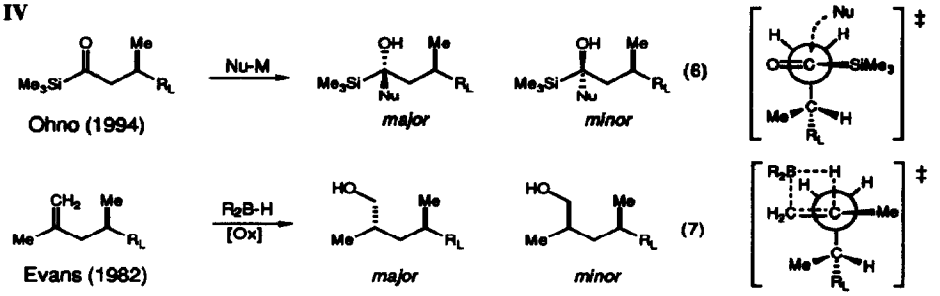
Steric Models for 1,3-Asymmetric Induction. The Cram steric model (1968) for 1,3-induction in carbonyl addition has been widely recognized (Scheme I).[1a] A less highly cited, but nonetheless significant study by Jacques and co-workers[1b] in the same year rationalized the stereochemical course of the hydride reductions of β-alkyl substituted ketones (eq 1) through transition structures which may be closer to the consensus view of the preferred geometries for these processes.[10] In view of the relevance of the Jacques proposal to the present investigation, it is reinterpreted here: A) Staggered rather than eclipsed transition structures are preferred having *anti* orientation between C_β and the forming bond (Felkin). B) The dominant destabilizing interactions are between the acyl carbon substituent (R) and the β-substituents. These interactions are minimized in **E** where the illustrated relationship between (R) and the smallest β-substituent (H in the present case) is established.

Scheme III



A restatement of this model has recently been reported by Ohno[1d] to account for the stereochemical course of nucleophilic additions to β-substituted acylsilanes (eq 6). Some years ago we also employed an analysis related to that described by Jacques to rationalize the stereochemical course of the illustrated hydroboration reaction (eq 7).[12]

Scheme IV



The models for 1,3-asymmetric induction presented above and in the previous Letter rationalize the π-facial selectivity that is observed in the absence of internal chelation in the nucleophilic additions to β-substituted aldehydes and ketones. Ongoing theoretical and experimental studies to further investigate the nature of 1,3-induction will be reported in due course.

References and Footnotes

1) For examples of nucleophilic additions to β-alkyl substituted ketones see: (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011-4018, and 4019-4026. (b) Brienne, M-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, 1036-1047. (c) Fleming I.; Lawrence, N. *J. Chem. Soc. Perkin Trans. 1* **1992**, 3309-3318. (d) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1994**, *35*, 741-744.

2) For examples of the nucleophilic additions to protected β-alkoxy ketones see: (a) Ukaji, Y; Kanda, K.; Yamamoto, K; Fujisawa, T. *Chem. Lett.* **1990**, 597-600. (b) Arco, M. J; Trammel, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075-2083. (c) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967-2980. For reductions of β-amino ketones see: (d) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1213-1214. (e) Tramontini, M. *Synthesis* **1982**, 605-644.

3) For an example of the influence of remote electrostatic effects on carbonyl π-facial selectivity see; Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018-5027.

4) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748-2755. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462-468 and references cited therein. (c) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48* 2803-2894.

5) (a) The reductions were carried out at the following temperatures in THF: Li(s-Bu)$_3$BH and DIBAL-H at -78 °C; Li(t-BuO)$_3$AlH and 9-BBN dimer at 0 °C to room temperature. Stereochemical assignments involved conversion of the 1,3-diols into the corresponding acetonides or benzylidene acetals, and analysis by NMR spectroscopy (see ref. 9). (b) The DIBAL-H reduction of substrate **22** was carried out in a variety of solvents to give the following ratios (1,3-*syn* : 1,3-*anti*): THF (76 : 24), Et$_2$O (63 : 27), CH_2Cl_2 (62 : 38), and toluene (64 : 36).

6) (a) For a review of hydride additions to carbonyl compounds see: Greeves, N. in *Comprehensive Organic Synthesis*,; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol 1, Chapter 1. (b) For examples of diastereoselective hydride additions to ketones see: Nogradi, M. in *Stereoselective Synthesis*; VCH, New York, 1986; Chapter 3.2.

7) (a) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021-1024. (b) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136-8141. However, for recent evidence in support of chelation by a vicinal OTBS group see: (c) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778-1784.

8) For examples illustrating the lack of chelation in the reductions of protected hydroxy-ketones with Li(s-Bu)$_3$BH see: (a) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139-5142. (b) Larcheveque, M.; Lalande, J. *J. Chem. Soc., Chem. Commun.* **1985**, 83-84.

9) Evans, D. A.; Duffy, J. L; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, this issue.

10) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199-2204. For computational evidence supporting the importance of noneclipsed geometries in carbonyl addition see: (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61-70. (c) Padden-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162-7166. (d) 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.

11) It is not suggested that C and D 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.

12) (a) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577-4580. (b) For a related example see ref. 1c. (c) Computational support for the model proposed by us has been reported by Houk, ref. 10d.

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