in the formal valence state Cu^{3+} or even $Cu^{4+/3+}$ without the application of high oxygen pressure and/or the presence of a strongly electropositive ion like Ba^{2+}, it may be suspected that there is an important overlap of the Cu:$\sigma^*_{x^2-y^2}$ and O:2p bands. In such a case there is an alternative deformation, not previously considered, that can implement transfer of a disproportionation bipolaron from one copper center to another as a bipolaronic entity; it consists of Cu-O-Cu trimers that stabilize more O:2p hybridization in d-band bonding states (Cu-Cu bonding since these states are always antibonding with respect to the Cu-O interactions) and more Cu:3d character in the empty O:2p states. Thus formation of Cooper pairs instead of a charge-density wave may require that the Fermi energy intersect overlapping Cu:3d and O:2p bands.

Finally, the distinction between a Cooper pair as a large bipolaron and the small bipolaron originally identified[22] in Ti_4O_7 is worth pointing out. Ti_4O_7 consists of TiO_2 slabs between regularly spaced shear planes. Electrostatic repulsions between Ti^{4+} ions on either side of a shear plane introduce short Ti-O bonds at these ions; consequently the mobile electrons of this formally Ti^{4+}/Ti^{3+} mixed-valent system occupy titanium 3d-band states within the slabs. At lowest temperatures, these electrons condense out in an ordered array of Ti^{3+}-Ti^{3+} homopolar bonds across shared octahedral-site edges to form a standing charge-density wave. As the temperature is raised, there is a narrow temperature interval in which the dimers become disordered and mobile; at higher temperatures the electrons are not trapped but occupy normal narrow-band states. In this case, the mobile bipolarons move diffusively, so they have no meaningful **k** vector. These bipolarons do not condense out into a superconducting state. On the other hand, superconducting $Li[Ti_2]O_4$,[23] which has the spinel structure, undoubtedly has Cooper pairs in the superconducting state that are large bipolarons trapped in mobile Ti atom dimers or tetramers. Similarly, large disproportionation bipolarons must be distinguished from descrete formal valence states such as stationary Pb^{2+} ions condensed out, for example, of reduced PbO_2.

The analogy between the superconducting copper oxides and the superconducting $BaBi_xPb_{1-x}O_3$ perovskites[24] is close; but in the copper oxides the $\sigma^*_{x^2-y^2}$ band is not perturbed by substituting for copper whereas in $BaBi_xPb_{1-x}O_3$ the 6s band is strongly perturbed by substituting Bi for Pb.

The transition from mobile small bipolarons to Cooper pairs in mixed-valence systems as a function of bandwidth and band occupancy has never been adequately explored; it has been commonly assumed that either charge-density waves, which can be incommensurate, or diffusive small-bipolaron motion would always compete successfully with high-temperature superconductivity. It now appears that this assumption may not apply where the Fermi energy intersects two bands, one of which derives from an anion array and the other from a cation array.

Acknowledgment. We gratefully acknowledge the research support of the R. A. Welch Foundation of Houston, Texas. The first four authors also acknowledge support by the National Science Foundation under Grant DMR 8520028.

(22) Chakraverty, B. K. *J. Phys. Lett.* **1979**, *40*, L-99.

(23) Johnston, D. C. *J. Low-Temp. Phys.* **1976**, *25*, 145.

(24) Sleight, A. W.; Gillson, J. L.; Bielstedt, F. E. *Solid State Commun.* **1975**, *17*, 27.

Steric Effects, as well as σ^*-Orbital Energies, Are Important in Diastereoface Differentiation in Additions to Chiral Aldehydes[1]

Eric P. Lodge and Clayton H. Heathcock*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received November 20, 1986*

Abstract: Two series of chiral aldehydes (**5a-e** and **6a-d**) have been prepared and their aldol reactions with the lithium enolate of pinacolone examined. The observed diastereomer ratios (Table I) have been evaluated in terms of the Anh-Eisenstein interpretation of Felkin's model for 1,2-asymmetric induction. It is shown that the simple steric effects are at least as important as σ^*-orbital energies in determining which is the "large" group for the purpose of applying the Felkin model. In all but the simplest cases, it is necessary to evaluate a four-conformer equilibrium in order to confidently predict the sense and magnitude of 1,2-asymmetric induction in such reactions. For a purely qualitative approach to predicting the major isomer produced in the series studied, one may use the Felkin model for 1,2-asymmetric induction with the following order of ligand preferences for the anti position: MeO > *t*-Bu > Ph > *i*-Pr > Et > Me > H. The results of this study cannot be rationalized by either the Cieplak hypothesis or the Ruch-Ugi stereochemical analogy model.

Relative asymmetric induction[2] in additions to chiral aldehydes and ketones is a topic of great interest. In a pair of pioneering papers published in the early 1950s, Cram[3] and Prelog[4] set forth models for predicting the major diastereomer to be expected in nucleophilic additions to chiral carbonyl compounds.[5]

Of these seminal contributions, the most valuable from a practical point of view was Cram's rule for asymmetric induction in additions to carbonyl groups having an adjacent stereocenter, which proved to be exceedingly useful in correlating a large amount of experimental data.[6] The original formulation of Cram's rule was "...that diastereomer will predominate which would be formed by the approach of the entering group from the less hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least hindered bulky groups attached to the asymmetric center."[3] This statement implies a one-conformer model (**1a**) with major and minor diastereomers resulting from attack on the less and more hindered carbonyl faces. However, in a later paper on the subject, Cram and Kopecky presented a Newman projection of the con-

(1) Part 40 in the series "Acyclic Stereoselection". For part 39, see: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819.

(2) Bartlett, P. A. *Tetrahedron* **1980**, *45*, 2.

(3) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 3210.

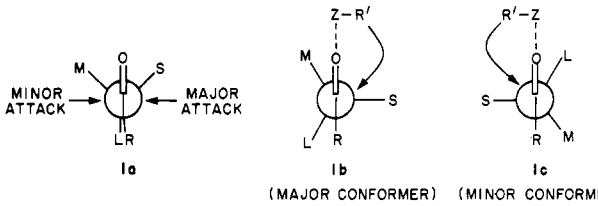
(4) Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308.

(5) An important insight into the problem of asymmetric induction in such reactions came in an earlier paper by Curtin and co-workers: Curtin, D. Y.; Harris, E. E.; Meislich, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 2901.

(6) See, inter alia: (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971; pp 84-132. (b) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 125-156.

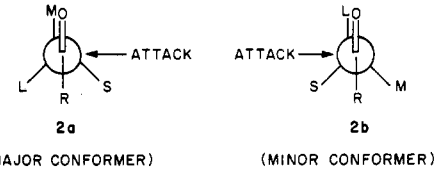
0002-7863/87/1509-3353$01.50/0

formation used that is assumed to lead to the major diastereomer, formula **1b**.[7] This formulation of Cram's rule implies a two-conformer model (**1b** and **1c**) in which the smallest ligand attached

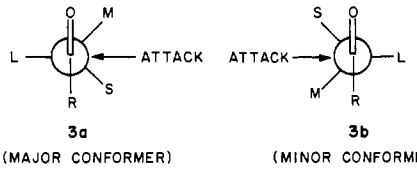


to the stereocenter is approximately perpendicular to the plane of the carbonyl group and attack of the nucleophile occurs from this face. Thus, stereodifferentiation would result from differential gauche interactions in **1b** and **1c**. It was assumed that the cation of the reagent (Li^+ or Mg^+) coordinates with the oxygen, which "therefore becomes effectively the bulkiest group in the molecule and tends to orient itself between the two least bulky groups attached to the adjacent asymmetric carbon atom".[3,8]

In 1967, Karabatsos pointed out certain limitations of Cram's model and proposed a model based on the known minimum energy conformations of aldehydes and ketones, wherein one ligand on the α-carbon is eclipsed with the carbonyl C–O bond.[9] In the Karabatsos formulation, the major and minor products would arise from attack on the less hindered face of conformers of the aldehyde or ketone in which the medium and large group are eclipsed with the C–O bond: **2a** and **2b**. The relative energies of these conformers are often known from other physical measurements.



Chêrest, Felkin, and Prudent noted that neither the Cram nor the Karabatsos models are particularly applicable to cyclohexanones and that neither model accounts for the effect of the carbonyl ligand R on the magnitude of stereoselectivity.[10] These workers proposed a third model which assumes that the dominant interaction is that between the incoming nucleophile and the largest group attached to the stereocenter; that is, that the nucleophile attacks antiperiplanar to the large group, as shown in **3a** and **3b**.



In the Felkin model, interaction of the carbonyl oxygen with the medium and small ligands is ignored and stereodifferentiation results from differences in the gauche interactions of R with these groups. The necessity of making this assumption, particularly for aldehydes, is an obvious weakness of the Felkin model. Nevertheless, it is assumed that the R:M interaction is greater than the R:S interaction and that conformation **3a** therefore leads to the major product.

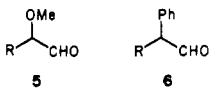
Anh and Eisenstein evaluated the Cram, Karabatsos, and Felkin models by ab initio calculation of hypothetical transition-state structures.[11] At the STO-3G level, the Felkin conformers **3a** and **3b** were found to be significantly lower in energy than the Cram conformers **1a–c**[12] or the Karabatsos conformers **2a** and **2b**. Anh and Eisenstein made two further intellectual contributions to the question. First, it was pointed out that incorporation of the Bürgi–Dunitz trajectory,[13] as shown in **4a** and **4b**, explains the

observed stereoselectivity without the necessity of assumptions relating to the relative magnitudes of O:M and R:M interactions. That is, it is implicitly assumed that conformations **4a** and **4b** are of comparable intrinsic energy and that stereodifferentiation arises from differential interactions of the attacking nucleophile with the small and medium ligands. Second, it was proposed on the basis of frontier molecular orbital arguments that the ligand with the lowest lying σ^* orbital, rather than the sterically most demanding group, is perpendicular to the carbonyl plane and anti to the attacking nucleophile.

The purpose of the current study was to evaluate the second Anh–Eisenstein postulate by examining the diastereofacial preferences of chiral aldehydes selected in such a manner that we might be able to separate steric and orbital energy effects.

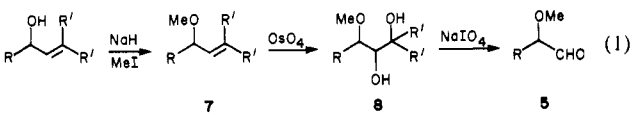
Preparation of Chiral Aldehydes

Two series of aldehydes, one set bearing an α-methoxy group (**5a–e**) and one possessing an α-phenyl group (**6a–d**), were employed in the study. As shown in eq 1, aldehydes **5a–d** resulted



a: R = Me; b: R = Et; c: R = *i*-Pr; d: R = *t*-Bu; e: R = Ph

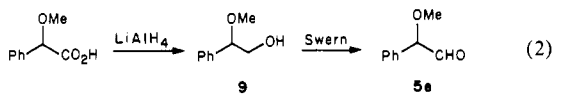
from sodium periodate cleavage of vicinal diols **8a–d** obtained by osmium tetraoxide oxidations of the allylic ethers **7a–d** prepared by O-methylation of known allylic alcohols. Aldehyde **5e** was



(1)

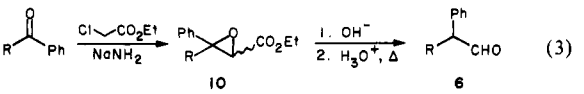
a: R = R′ = Me; b: R = Et, R′ = H; c: R = *i*-Pr, R′ = H; d: R = *t*-Bu, R′ = H

prepared from *O*-methylmandelic acid, via methoxy alcohol **9**, as shown in eq 2. Aldehydes **6b** and **6c** were prepared from the



(2)

appropriate ketones by the Darzens glycidic ester condensation,[14] followed by saponification and decarboxylation (eq 3). Aldehyde



(3)

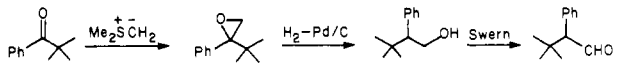
b: R = Et; c: R = *i*-Pr

(7) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(8) Subsequent discussions of Cram's rule have not been consistent in treating it as either a one-conformer or two-conformer model. For example, whereas Morrison and Mosher[6a] and Eliel[6b] have used the two-conformer models **1b** and **1c** in their reviews, Karabatsos[9] and Anh[11] have criticized the rule on the basis of the one-conformer model **1a**. In his important paper on the subject,[10] Felkin illustrated both the one-conformer and two-conformer models.
(9) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.
(10) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(11) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.
(12) Although the Anh–Eisenstein paper discusses Cram's model in terms of the one-conformer model **1a**, it may be seen from Figure 2 in that paper that conformers **1b** and **1c** are both calculated to be of higher energy than that of **1a**.
(13) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.
(14) Newman, M. S. *Org. React.* (*N.Y.*) **1949**, *5*, 413.

Table I. Diastereomer Ratios in Aldol Reactions of Pinacolone with Aldehydes **5a–e** and **6a–d**

aldehyde	R	ratio **11**:**12** or **13**:**14**
5a	Me	58:42 (1.41:1)
5b	Et	76:24 (3.05:1)
5c	*i*-Pr	92:8 (12.4:1)
5d	*t*-Bu	93:7 (13.8:1)
5e	Ph	83:17 (4.84:1)
6a	Me	78:22 (3.64:1)
6b	Et	86:14 (6.05:1)
6c	*i*-Pr	70:30 (2.25:1)
6d	*t*-Bu	37:63 (1:1.7)

6d could not be obtained by this method, as phenyl *tert*-butyl ketone does not undergo the Darzens condensation. This aldehyde was accessible, however, as shown in eq 4. Phenyl *tert*-butyl

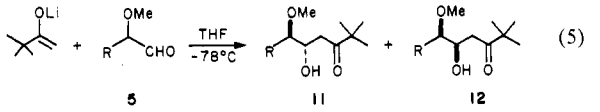


11 12 6d (4)

ketone does react with dimethylsulfonium methylide.[15] The resulting epoxide **11** is hydrogenolyzed to alcohol **12**, which is oxidized to obtain **6d**.[16] The final aldehyde in this series, 2-phenylpropanal (**6a**), was available from commercial sources.

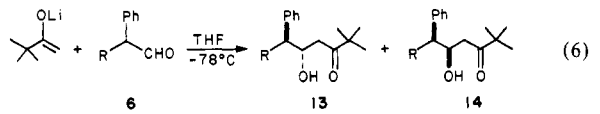
Results

Each of the aldehydes was allowed to react with the lithium enolate of pinacolone in THF at −78 °C under identical conditions. Each reaction was performed three times, and the results were averaged. The reactions of the two series of aldehydes are shown in eq 5 and 6, and the resulting diastereomer ratios are compiled in Table I.



5 11 12 (5)

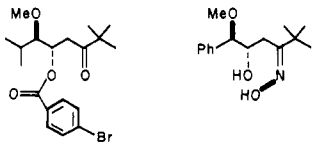
a: R = Me; b: R = Et; c: R = *i*-Pr; d: R = *t*-Bu; e: R = Ph



6 13 14 (6)

a: R = Me; b: R = Et; c: R = *i*-Pr; d: R = *t*-Bu

Structures of aldols **11–14** were determined by a combination of single-crystal X-ray analysis, NMR correlations, and reasonable analogy. In the α-methoxy series, the structures of compounds **11c** and **11e** were determined by X-ray analysis of *p*-bromobenzoate ester **15** and oxime **16**. The stereostructures of the remaining compounds arising from type **5** aldehydes were assigned by analogy.



15 16

For the aldol products stemming from type **6** aldehydes, the ^{1}H NMR chemical shifts for the *tert*-butyl resonances were examined. Acyclic compounds having vicinal stereocenters, each bearing one hydrogen, normally exist in the conformation in which the hydrogens are anti, in order to minimize gauche interactions. In the case of **13a–d** and **14a–d**, the pertinent conformers are as follows:

Table II. ^{1}H NMR Chemical Shifts of the *tert*-Butyl Resonances in Aldols **13a–d** and **14a–d**

aldehyde	R	$\delta_{t\text{-Bu}}$ (major)	$\delta_{t\text{-Bu}}$ (minor)
6a	Me	1.01	1.09
6b	Et	0.99	1.08
6c	*i*-Pr	0.99	1.04
6d	*t*-Bu	1.03, 1.02	1.01, 0.93

13 14

In such compounds, a substituent gauche to a phenyl group usually experiences an upfield shift, due to the shielding effect of the aromatic ring.[17] Therefore, the *tert*-butyl chemical shifts for compounds **13a–d** are expected to be upfield of the corresponding resonances in compounds **14a–d**.[18] The *tert*-butyl chemical shifts for the major and minor aldol products are listed in Table II. In entries **a–c**, the *tert*-butyl resonances for the major diastereomers are upfield of the corresponding resonances for the minor diastereomers. The major and minor diastereomers are therefore compounds **13a–c** and **14a–c**, respectively.

The *tert*-butyl resonances for entry **d** suggest that the major diastereomer in this case is **14d** rather than **13d**. This supposition was verified by single-crystal X-ray analysis of the major diastereomer, which indeed showed it to be isomer **14d**.

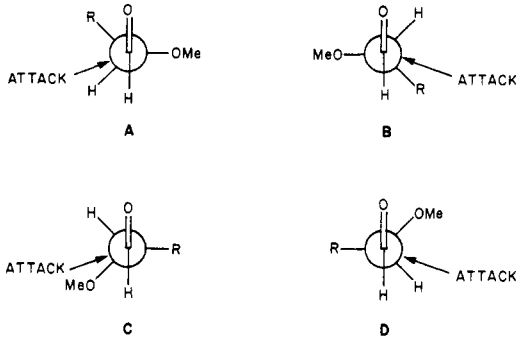
Discussion

The major diastereomer for each reaction in the α-methoxy aldehyde series is that product predicted by the Felkin model if one assumes that the methoxy group is the anti group. This is to be expected on the basis of the Anh–Eisenstein hypothesis, as carbon–heteroatom bonds have significantly lower σ*-orbital energies than carbon-carbon bonds. Furthermore, as the size of R increases in the series Me, Et, *i*-Pr, *t*-Bu, diastereofacial selection increases, as expected from a comparison of the interactions between the attacking nucleophile and either H or R (see **4a** and **4b**). Note, however, that the ratio seen in the reaction of aldehyde **5d** (R = *t*-Bu) relative to aldehyde **5c** (R = *i*-Pr) is much smaller than expected considering the relative sizes of isopropyl and *tert*-butyl groups.[19] The comparatively low diastereoselectivity observed for addition to aldehyde **5e** is also somewhat surprising. A phenyl group is commonly considered to be larger than isopropyl,[19] but application of the Felkin–Anh model with the observed diastereomer ratio would lead to the conclusion that phenyl is only slightly larger than ethyl. In order to clarify these points, it is necessary to examine the results of the aldol reactions of type **6** aldehydes.

At first inspection, the diastereoselection results using type **6** aldehydes assume no apparent pattern. In this series, the Anh–Eisenstein hypothesis leads us to place phenyl anti to the attacking nucleophile, since bonds to sp^2 carbons should have lower σ*-orbital energies than bonds to sp^3 carbons.[20,21] Thus, by this model, the

(15) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(16) Mancuso, A. J.; Huong, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(17) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330.
(18) Diastereomers **11e** and **12e**, whose stereostructures are firmly established by the X-ray structure of **16**, provide additional precedent for this generalization: the *tert*-butyl signals in these two isomers have chemical shifts of δ 1.11 and 1.07, respectively.
(19) Hirsh, J. A. *Top. Stereochem.* **1967**, *1*, 199.
(20) MNDO calculations on methane give a lowest σ*-orbital energy of 4.38 eV. For benzene, the lowest σ* orbital, which is principally associated with C–H bonds, has an energy of 3.93 eV.

Chart I



major diastereomer should be **13** in each case. Furthermore, as in the reactions of the series **5** aldehydes, the diastereofacial selectivity should increase as the size of R increases. As shown in Table I, aldehydes **6a** and **6b** follow the predicted pattern. However, with **6c** the magnitude of the stereoselectivity observed is not as great as expected, and with **6d** the Anh–Eisenstein hypothesis actually predicts the wrong product.[22]

The data presented in Table I can be rationalized by Felkin transition states, if one evaluates a four-conformer equilibrium (Chart I). Quite simply, we believe our data show that the Anh–Eisenstein hypothesis is only partly correct. For purposes of applying the Felkin model for 1,2-asymmetric induction, the choice of "large" ligand should consider *both* the natures of the bonds from the stereocenter to the three ligands and the steric bulk of the three ligands. In additions to aldehydes **5a–e**, the methoxy seems to take the role of "large" group when it is pitted against methyl, ethyl, or isopropyl. As a result of preferred reaction through conformer A, the major products are aldols **11a–c**; the minor products **12a–c** presumably result from addition to conformer B. However, with aldehyde **5d**, the bulk of *tert*-butyl becomes important enough to partially compensate for the Anh–Eisenstein effect. In this case, we think that conformers C and D, in which the *tert*-butyl plays the role of "large" group, are also important. Reaction through these conformers alone would presumably give rise to a **11d**:**12d** ratio of less than unity. Thus, the observed **11d**:**12d** ratio of 13.8:1 may reflect an exceedingly high ratio from the fraction of the reaction proceeding through the methoxy anti conformers A and B, tempered by a **11d**:**12d** ratio of less than one from the fraction of the reaction proceeding through the *tert*-butyl anti conformers C and D.

A similar argument may be advanced to explain the lower than expected **11e**:**12e** ratio in the reaction of aldehyde **5e**. Although phenyl is not nearly as large as *tert*-butyl, it is larger than isopropyl. In addition, the σ^* orbital of a C_{sp^2}–C_{sp^3} bond, while certainly not as low in energy as that of a C–O bond, is lower than that of a C_{sp^3}–C_{sp^3} bond.[20] With this aldehyde, we think that approximately three-fourths of the reaction occurs through the methoxy anti conformer A, leading to product **11e**, and that the other fourth occurs through the phenyl anti conformers C and D.

The same behavior is seen in the reactions of aldehydes **6a–d**. The low diastereoselection observed for **6c** and the reversed diastereoselection observed for **6d** are readily understood if one

Chart II

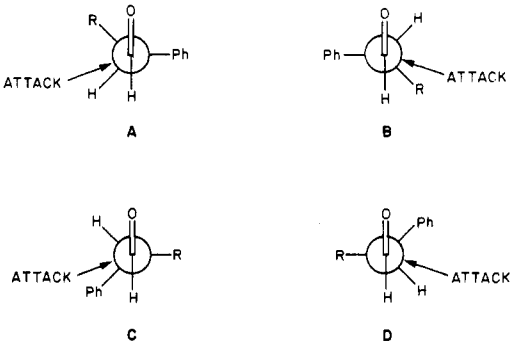


Chart III

evaluates a four-conformer equilibrium. For small R groups (methyl and ethyl), both the greater steric bulk of phenyl and the lower σ^*-orbital energy of the C_{sp^2}–C_{sp^3} bond favor conformers A and B. Accordingly, as predicted from the Anh–Eisenstein hypothesis, the **13b**:**14b** ratio is greater than the **13a**:**14a** ratio. When R = *i*-Pr, however, isopropyl anti conformers (C and D) come into play. The more these conformers are involved, the more of diastereomer **14c** will be produced, since reaction through D should be more important than reaction through C. To a first approximation, the results suggest that **6c** reacts about two-thirds through conformer A and one-third through conformer D. With aldehyde **6d**, the importance of the *tert*-butyl anti conformer D is even greater; in this case, reaction appears to proceed about two-thirds through D and one-third through A.

The contributions of the non-Anh conformations[23] are more pronounced in type **6** aldehydes because in these compounds both non-hydrogen substituents are carbon groups, differing only in bulk and in the hybridization of the attached carbon . As there is less difference between the σ^*-orbital energies of C_{sp^3}–C_{sp^3} and C_{sp^3}–C_{sp^2} bonds than between carbon–carbon and carbon–heteroatom bonds, non-Anh conformers are more accessible in this series.

Our results are in qualitative agreement with a force field model for diastereoface differentiation recently devised by Wu and Houk.[24,25]

Our discussion would not be complete without a consideration of the hypothesis of Cieplak regarding the stereochemistry of nucleophilic additions to cyclohexanones.[26] Briefly, Cieplak proposes that the forming bond is characterized by a low-lying σ^* orbital and that electron donation into this orbital stabilizes the transition structure, lowers the activation energy, and enhances reaction. He further proposes that C–H bonds are better electron donors than C–C bonds and uses this assumption to rationalize the well-known proclivity of rigid cyclohexanones to undergo reduction from the axial direction, affording mainly the equatorial alcohols. Rozeboom and Houk have pointed out that there is considerable experimental evidence that C–C bonds are actually better donors than C–H bonds.[27] Nevertheless, the Cieplak theory

(21) A reviewer has debated this argument, citing polarographic studies on dialkyl peroxides, which suggest that an increase in alkyl substitution lowers the σ^*-orbital energy of a bond [Fukui, K.; Morokuma, K.; Kato, H.; Yonezawa, T. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 217], and on alkyl(triphenyl)-phosphonium salts, wherein the fraction of (alkane + triphenylphosphine) produced in the reduction of $Ph_3RP^+X^-$ is 5.5%, 35%, 52%, and 85% for R = Me, Et, *i*-Pr, and *t*-Bu, respectively [Horner, L.; Röttger, R.; Fuchs, H. *Chem. Ber.* **1963**, *96*, 3141] We appreciate having these interesting data called to our attention and grant the possibility that an increase in alkyl substitution on a bond may lower the σ^*-orbital energy. However, we believe the effect would be quite small (Fukui and co-workers suggest that the difference in LUMO energies for methyl hydroperoxide and *tert*-butyl hydroperoxide is only 0.0058 eV. The Horner data are interesting but probably reflect radical stability more than they do the σ^*-orbital energy.

(22) It has previously been noted that diastereoface differentiation is lower in aldehyde **6c** than in **6a** or **6b**: (a) Reference 9. (b) Jones, P. R.; Goller, E. J.; Kauffman, W. J. *J. Org. Chem.* **1971**, *36*, 3311. (c) Fleming. I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149.

(23) For the purpose of this discussion, we refer to the "Anh conformation" as that proposed by the Anh–Eisenstein hypothesis to be of lower energy; e.g., the conformation with the ligand on the stereogenic α-carbon having the lower energy σ^* orbital perpendicular to the carbonyl group and anti to the incoming nucleophile. "Non-Anh" conformations are conformations having one of the other two ligands in this position.

(24) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 0000. We thank Professor Houk for providing us with a preprint of his paper.

(25) Houk, K. N., personal communication.

(26) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(27) Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189. See also ref 24.

has been adopted by several other workers.[28]

Application of Cieplak's hypothesis to the series of aldehydes **5a–e** leads to the two structures shown in Chart III. The model would predict the preference for attack as shown in A should *decrease* as the size of R increases, which is exactly contrary to the results shown in Table I.[29]

Finally, the data presented in Table I allow one to test the applicability of the Ruch–Ugi "stereochemical analogy model"[30] to such nucleophilic additions. In brief, no good fit to this quantitative model is observed.

Conclusions

In summary, we have studied the reactions of two sets of α-chiral aldehydes with the lithium enolate of pinacolone. Our results can be accommodated within the general framework of Felkin's model for 1,2-asymmetric induction. They are in general agreement with the Anh–Eisenstein rationale for the Felkin model. However, we believe that the latter rationale is incomplete and that σ^*-orbital energies can be counterbalanced by steric effects. There is an electronic effect (σ^*-orbital energies) that causes the preference for anti to be MeO > Ph > H > R and a steric effect that leads to the order of preference *t*-Bu > Ph > *i*-Pr > Et > Me > H. In general, a four-conformer equilibrium should be considered. For a purely qualitative approach to predicting the major isomer produced in the series studied, one may use the Felkin model with the following order of ligand preferences for the anti position: MeO > *t*-Bu > Ph > *i*-Pr > Et > Me > H. The results are decidedly not in agreement with the Cieplak hypothesis and cannot be accommodated within the framework of the Ruch–Ugi stereochemical analogy model.

Experimental Section

General Data. Unless otherwise indicated, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under a nitrogen atmosphere immediately prior to use. Diisopropylamine was distilled from CaH_2 under a nitrogen atmosphere immediately before use. Pinacolone was distilled from CaH_2 and stored over 3-Å molecular sieves. A commercial sample of 2-phenylpropanal (Aldrich Co., contains ca. 15% acetophenone) was conveniently purified via its bisulfite addition product.[31] All reactions involving organometallic reagents were conducted under a dry nitrogen or dry argon atmosphere. Upon workup, solvents were evaporated at reduced pressure by using a rotary evaporator, unless otherwise indicated. Melting points were measured in Pyrex capillaries by using a Büchi apparatus. Boiling points and melting points are uncorrected. Infrared spectra (IR) were measured as neat thin films between NaCl plates or as solutions in NaCl cells with the indicated solvent. Unless otherwise specified, the solvent for NMR spectra was $CDCl_3$. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Gas chromatography (GC) was performed either on a Hewlett-Packard 5890A capillary gas chromatograph, using helium as carrier gas, a 25-m cross-linked 5% Ph Me silicone column, and fitted with a flame ionization detector (fid), or on a Varian Aerograph series 1400 gas chromatograph, using helium as carrier gas, a 3-m 10% OV-101 on Chromosorb G column, and fitted with a thermal conductivity detector (tcd). Data were quantified by a Hewlett-Packard 3390A integrator. Column chromatography was performed by using F. Merck 60 70–230 mesh silica gel. Flash chromatography refers to the procedure of Still, Kahn, and Mitra[32] and was performed by using 230–400 mesh silica gel. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley. X-ray crystallography was performed at the Chexray facility at the University of California, Berkeley. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. All lithium aluminum hydride reductions were worked up by the procedure described by Fieser and Fieser (*n*, *n*, 3*n*).[33]

4-Methoxy-2-methyl-2-pentene (7a). A solution of 20.00 g (0.20 mol) of 4-methyl-3-penten-2-ol in 25 mL of dry ether was added dropwise to a mechanically stirring suspension of 12.45 g (0.26 mol) of 50% sodium hydride (rendered oil-free) in 100 mL of dry ether under N_2. The mixture was refluxed for 1 h and cooled to room temperature, and 20 mL (0.32 mol) of freshly distilled methyl iodide was added dropwise. The mixture was refluxed for 8 h, after which time no starting material was visible by TLC. The reaction was cooled in ice, quenched with 15 mL of water, and diluted with 250 mL of pentane. The mixture was separated, and the organics were washed with brine (4 × 100 mL), dried over K_2CO_3, and distilled. The fraction boiling at 98–110 °C was collected to yield 16.25 g (71%) of the desired allylic ether as a colorless liquid: IR ($CHCl_3$) 3015, 2985, 2940, 2835, 1454, 1382, 1109, 1077 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, 3 J = 6.3), 1.68 (d, 3, J = 1.3), 1.74 (d, 3, J = 1.2), 3.24 (s, 3), 4.02 (m, 1), 5.05 (ddd, 1, J = 8.9, 1.4, 1.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.065, 21.175, 25.736, 55.439, 73.187, 127.190, 134.924. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.38; H, 12.60.

4-Methoxy-2-methylpentane-2,3-diol (8a). To a solution of 10.00 g (87.6 mmol) of 4-methoxy-2-methyl-2-pentene, 13.24 g (119.1 mmol) of trimethylamine *N*-oxide dihydrate, and 7.08 mL (87.6 mmol) of pyridine in 30 mL of water and 100 mL of *tert*-butyl alcohol was added 1.5 mL of 0.1 M osmium tetraoxide in *tert*-butyl alcohol. The mixture was refluxed for 60 h and quenched with 70 mL of 20% aqueous $NaHSO_3$. The mixture was concentrated to remove *tert*-butyl alcohol and saturated with solid NaCl. The mixture was extracted with ether (3 × 125 mL), and the combined organics were dried over $MgSO_4$ and concentrated. The crude diol was purified by Kuegelrohr distillation (50 °C (25 μm)) to yield 8.63 g (66%) of the desired diol as a colorless liquid: IR ($CHCl_3$) 3570, 3460, 2985, 2940, 2900, 1469, 1380, 1088 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 3), 1.26 (s, 3), 1.27 (d, 3, J = 6.0), 2.22 (d, 1, J = 4.5), 3.20 (s, 1), 3.36 (s, 3), 3.35–3.46 (m, 2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.418, 25.825, 25.849, 55.887, 72.450, 78.324, 78.811. Anal. Calcd for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.36; H, 11.06.

2-Methoxypropanal (5a). To a stirring solution of 8.00 g (54.0 mmol) of 4-methoxy-2-methylpentane-2,3-diol in 35 mL of ether was added 12.7 g (59.4 mmol) of sodium periodate. To this stirring suspension was added 10.0 mL of water dropwise so that a gentle reflux was maintained. The mixture was stirred at room temperature for 2 h, and the organic layer was decanted from the white aqueous slurry. The aqueous layer was stirred with ether (3 × 5 mL), and the combined organics were dried over $MgSO_4$ and distilled through an efficient column. The fraction boiling at 80–88 °C was collected to yield 0.24 g (5%) of the desired aldehyde as a colorless liquid: IR (neat) 2995, 2945, 2840, 1742, 1455, 1380, 1206, 1154, 1096 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.29 (d, 3, J = 6.9), 3.45 (s, 3), 3.71 (dq, 1, J = 7.0, 1.7), 9.66 (d, 1, J = 1.7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.799, 57.591, 81.515, 203.437; HRMS calcd for C_4H_8O 88.0524, found 88.0524.

3-Methoxy-1-pentene (7b). A solution of 17.23 g (0.20 mol) of 1-penten-3-ol in 25 mL of dry ether was added dropwise to an ice-cold, mechanically stirring suspension of 14.40 g (0.30 mol) of 50% sodium hydride (rendered oil free) in 90 mL of dry ether and 10 mL of dry Me_2SO under N_2. The mixture was refluxed for 24 h and cooled in ice, and 62.3 mL (1.00 mol) of methyl iodide was added dropwise. The mixture was refluxed for 24 h, cooled in ice, and quenched with 18 mL of water. The mixture was separated, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organics were dried over $MgSO_4$ and distilled. The fraction boiling at 73–85 °C was collected to yield 12.93 g (65%) of the desired allylic ether as a colorless liquid: IR ($CHCl_3$) 3025, 2985, 2950, 1472, 1428, 1095, 1003 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 3, J = 7.5), 1.46–1.66 (m, 2), 3.28 (s, 3), 3.39–3.47 (m, 1), 5.15–5.23 (m, 2), 5.57–5.71 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.574, 28.074, 56.100, 84.412, 117.106, 138.653. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.69; H, 12.22.

3-Methoxypentane-1,2-diol (8b). To a stirring solution of 11.00 g (0.11 mol) of 3-methoxy-1-pentene, 16.60 g (0.15 mol) of trimethylamine *N*-oxide dihydrate, and 8.9 mL (0.11 mol) of pyridine in 25 mL of water and 100 mL of *tert*-butyl alcohol was added 1.00 g (3.9 mmol) of osmium tetraoxide. The mixture was refluxed for 48 h, cooled to room temperature, and quenched with 60 mL of 20% aqueous $NaHSO_3$. The mixture was concentrated to remove *tert*-butyl alcohol and saturated with solid NaCl. The mixture was extracted with ether (4 × 150 mL), and the combined organics were dried over $MgSO_4$ and concentrated. The crude diol was purified by Kuegelrohr distillation (75 °C (200 μm)) to yield 9.45 g (64%) of the desired diol as a colorless liquid: IR ($CHCl_3$) 3580,

(28) (a) Danishefsky, S.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3674. (b) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(29) It is noted, however, that the Cieplak model is not inconsistent with the results observed with aldehydes **6a–d**.

(30) Ruch, E.; Ugi, I. *Top. Stereochem.* **1969**, *4*, 99.

(31) Heathcock, C. H.; Kiyooka, S.-I.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(33) Fieser, L.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 582.

3490, 3025, 2985, 2955, 2900, 1472, 1103, 1064 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 3, J = 7.5), 1.45–1.58 (m, 1), 1.58–1.72 (m, 1), 2.32 (br, 2), 3.28 (m, 1), 3.43 (s, 3), 3.61–3.78 (m, 2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.425, 22.529, 58.206, 63.361, 71.948, 84.202. Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.82; H, 10.33.

2-Methoxybutanal (5b). In a 100-mL three-necked flask fitted with two reflux condensers and a serum septum, 21.92 g (102.5 mmol) of sodium periodate was added in one portion to a stirring solution of 11.00 g (82.0 mmol) of 3-methoxypentane-1,2-diol in 40 mL of ether. To this mixture was added 1.0 mL of water dropwise, initiating a strongly exothermic reaction. When the reflux subsided, 19 mL of water was slowly added, and the reaction was monitored by TLC. The reaction was stirred periodically with a glass rod for 2 h. The organics were decanted from the mixture, and the white aqueous slurry was stirred with ether (4 × 8 mL). The combined organics were dried over $MgSO_4$ and distilled through an efficient column. The fraction boiling at 106–108 °C was collected to yield 5.40 g (64%) of the desired aldehyde as a colorless liquid: IR ($CDCl_3$) 3002, 2970, 2916, 2860, 2290, 1749, 1476, 1391, 1227, 1159, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 3, J = 7.5), 1.63–1.75 (m, 2), 3.43 (s, 3), 3.49 (m, 1), 9.63 (d, 1, J = 2.0); ^{13}C NMR (126 MHz, $CDCl_3$) δ 8.952, 22.885, 58.087, 86.737, 203.928; HRMS calcd for $C_5H_{10}O_2$ 102.0682, found 102.0682.

3-Methoxy-4-methyl-1-pentene (7c). A solution of 40.00 g (0.40 mol) of 4-methyl-1-penten-3-ol[34] in 50 mL of dry ether was added dropwise to a suspension of 24.00 g (0.50 mol) of 50% sodium hydride (rendered oil free) in 200 mL of dry ether under N_2. The mixture was refluxed for 18 h and cooled to room temperature, and 36.0 mL (0.58 mol) of freshly distilled methyl iodide was added dropwise. The mixture was refluxed for 24 h, cooled in ice, and quenched with 18 mL of brine. The organics were decanted, and the aqueous sludge was rinsed with ether (4 × 25 mL). The combined organics were washed with brine (4 × 75 mL), dried over $MgSO_4$, and distilled. The fraction boiling at 91–99 °C was collected to yield 32.62 g (72%) of the desired allylic ether as a colorless liquid: IR ($CHCl_3$) 3035, 2986, 2960, 2848, 1482, 1096 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (d, 3, J = 6.8), 0.92 (d, 3, J = 6.8), 1.75 (m, 1), 3.20 (dd, 1, J = 7.2, 6.9), 3.27 (s, 3), 5.13–5.26 (m, 2), 5.57–5.67 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.104, 18.539, 32.408, 56.423, 88.554, 117.933, 136.995. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.50; H, 12.54.

3-Methoxy-4-methylpentane-1,2-diol (8c). To a solution of 15.00 g (131.4 mmol) of 3-methoxy-4-methyl-1-pentene, 20.37 g (183.3 mmol) of trimethylamine *N*-oxide dihydrate, and 10.6 mL (131.4 mmol) of pyridine in 108 mL of *tert*-butyl alcohol and 27 mL of water was added 1.09 (3.9 mmol) of osmium tetraoxide with stirring. The mixture was refluxed for 24 h, cooled, and quenched with 60 mL of 20% aqueous $NaHSO_3$, and the mixture was concentrated to remove *tert*-butyl alcohol. The residue was saturated with solid NaCl and extracted with ether (4 × 150 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude diol was purified by Kuegelrohr distillation (75 °C (45 μm)) to yield 15.36 g (79%) of the desired diol as a slightly yellow liquid: IR ($CHCl_3$) 3590, 2980, 3035, 2990, 2960, 2900, 1480, 1398, 1377, 1106, 1067 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, 3, J = 6.9), 0.99 (d, 3, J = 6.7), 1.87 (m, 1, J = 6.7), 2.40 (m, 1), 2.51 (d, 1, J = 6.7), 3.06 (dd, 1, J = 5.3, 4.8), 3.51 (s, 3), 3.75 (m, 3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.405, 19.530, 29.623, 61.086, 63.560, 71.845, 87.981. Anal. Calcd for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.43; H, 11.01.

2-Methoxy-3-methylbutanal (5c). In a 100-mL three-necked flask fitted with two reflux condensers and a serum septum, 21.39 g (100.0 mmol) of sodium periodate was added in one portion to a stirring solution of 11.86 g (80.0 mmol) of 3-methoxy-4-methylpentane-1,2-diol in 40 mL of ether. To this mixture was added 1.0 mL of water dropwise, initiating a strongly exothermic reaction. When the reflux subsided, 19 mL of water was slowly added, and the reaction was monitored by TLC. The reaction was stirred periodically with a spatula for $2^1/_2$ h. The organics were decanted from the mixture, and the white aqueous slurry was stirred with ether (3 × 10 mL). The combined organics were dried over $MgSO_4$ and distilled. The fraction boiling at 119–121 °C was collected to yield 6.56 g (71%) of the desired aldehyde as a colorless liquid: IR (neat) 2975, 2890, 2845, 1743, 1474, 1397, 1138, 1116, 1083, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, 3, J = 6.8), 0.97 (d, 3, J = 6.9), 2.05 (m, 1, J = 5.8), 3.26 (dd, 1, J = 5.6, 2.6), 9.64 (d, 1, J = 2.6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.418, 18.283, 29.792, 58.773, 90.510, 204.650; HRMS calcd for $C_6H_{12}O_2$ 116.0837, found 117.0919 ($C_6H_{13}O_2$; M + 1), 87.0819 ($C_5H_{11}O$; M − CHO).

3-Methoxy-4,4-dimethyl-1-pentene (7d). A solution of 15.80 g (0.13 mol) of 4,4-dimethyl-1-penten-3-ol[35] in 25 mL of dry ether was added dropwise to a suspension of 16.80 g (0.35 mol) of 50% sodium hydride (rendered oil-free) in 75 mL of dry ether and 10 mL of dry Me_2SO under N_2. The mixture was refluxed for 24 h and cooled to room temperature, and 40.50 mL (0.65 mol) of freshly distilled methyl iodide was added dropwise. The mixture was refluxed for 24 h, cooled in ice, and quenched with 18 mL of water. The mixture was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organics were dried over $MgSO_4$ and distilled. The fraction boiling at 107–112 °C was collected to yield 11.71 g (70%) of the desired allylic ether as a colorless liquid: IR (neat) 3010, 2990, 2938, 2900, 2850, 1387, 1196, 1138, 1113 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 9), 3.07 (d, 1, J = 8.1), 3.25 (s, 3), 5.12–5.28 (m, 2), 5.61–5.72 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.983 (3 C), 34.387, 56.864, 91.473, 118.385, 135.825. Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.61; H, 12.60.

3-Methoxy-4,4-dimethylpentene-1,2-diol (8d). To a solution of 10.00 g (78.0 mmol) of 3-methoxy-4,4-dimethyl-1-pentene, 11.79 g (106.1 mmol) of trimethylamine *N*-oxide dihydrate, and 6.31 mL (78.0 mmol) of pyridine in 16 mL of water and 64 mL of *tert*-butyl alcohol was added 0.51 g (1.9 mmol) of osmium tetraoxide. The mixture was refluxed for 18 h, cooled to room temperature, and quenched with 40 mL of 20% aqueous $NaHSO_3$. The mixture was concentrated to remove *tert*-butyl alcohol. The residue was saturated with solid NaCl and extracted with ether (3 × 150 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude diol was purified by Kuegelrohr distillation (64 °C (60 μm)) to yield 8.52 g (67%) of the desired diol as a colorless liquid: IR (neat) 3430, 2991, 2940, 2907, 2860, 1497, 1482, 1410, 1376, 1197, 1124, 1058 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (s, 9), 2.34 (d, 1, J = 4.8), 2.44 (d, 1, J = 4.0), 3.01 (d, 1, J = 2.2), 3.54 (s, 3), 3.81 (m, 3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.609 (3 C), 35.284, 62.176, 64.436, 72.330, 92.419. Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.06; H, 11.34.

2-Methoxy-3,3-dimethylbutanal (5d). In a 100-mL three-necked flask fitted with two reflux condensers and a serum septum, 13.19 g (61.6 mmol) of sodium periodate was added in one portion to a stirring solution of 8.00 g (49.3 mmol) of 3-methoxy-4,4-dimethylpentane-1,2-diol in 30 mL of ether. To this mixture was added 1.0 mL of water, initiating a strongly exothermic reaction. When the reflux subsided, 14.0 mL of water was slowly added, and the reaction was monitored by TLC. The reaction was stirred periodically with a spatula for $3^1/_2$ h. The organics were decanted from the mixture, and the white aqueous slurry was stirred with ether (3 × 10 mL). The combined organics were dried over $MgSO_4$ and distilled through an efficient column. The fraction boiling at 124–130 °C was collected to yield 5.24 g (82%) of the desired aldehyde as a colorless liquid: IR (neat) 2975, 2882, 2837, 1738, 1472, 1367, 1187, 1108 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 9), 3.08 (d, 1, J = 3.3), 3.40 (s, 3), 9.73 (d, 1, J = 3.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.934 (3 C), 35.175, 58.955, 93.025, 205.473. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.37; H, 10.76.

2-Methoxy-2-phenylethanol (9). A solution of 4.00 g (24.1 mmol) of *O*-methylmandelic acid[36] in 5 mL of dry ether was added dropwise to a stirring suspension of 2.28 g (60.2 mmol) of lithium aluminum hydride in 20 mL of dry ether under N_2. The reaction was stirred at room temperature for $1^1/_2$ h and worked up in the usual *n*, *n*, 3*n* manner. The mixture was filtered, and the solids were briefly refluxed in 10 mL of ether. The combined organics were dried over $MgSO_4$ and concentrated to yield 3.51 g (88%) of the pure desired alcohol as a colorless liquid: IR ($CHCl_3$) 3600, 3020, 2945, 2880, 2846, 1608, 1496, 1460, 1401, 1360, 1117 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.33 (dd, 1, J = 8.7, 4.1), 3.31 (s, 3), 3.64 (m, 2), 4.31 (dd, 1, J = 8.0, 4.2), 7.29–7.38 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.719, 67.122, 84.679, 126.734 (2 C), 127.959, 128.374 (2 C), 138.199. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.77; H, 7.95.

2-Methoxy-2-phenylethanal (5e). A solution of 2.05 mL (28.9 mmol) of dry Me_2SO in 10 mL of CH_2Cl_2 was added dropwise to a cooled solution of 1.26 mL (14.5 mmol) of freshly distilled oxalyl chloride in 60 mL of dry CH_2Cl_2 at such a rate that the reaction temperature remained at −61 to −59 °C. After 20 min at −65 to −61 °C, a solution of 2.00 g (13.1 mmol) of 2-methoxy-2-phenylethanol in 7 mL of CH_2Cl_2 was added dropwise at such a rate that the temperature remained at −61 to −58 °C. After 5 min, 9.16 mL (65.7 mmol) of distilled triethylamine was added dropwise to maintain the reaction temperature at −60 to −57 °C. The mixture was warmed to 0 °C, and 20 mL of water was added. The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was diluted with 40 mL of ether and washed with cold 1% HCl (3 × 20 mL) and brine (20 mL). The

(34) Vig, O. P.; Aggarwal, R. C.; Sharma, M. C.; Sharma, S. D. *Indian J. Chem., Sect. B* **1979**, *17B*, 558.

(35) Vittorelli, P.; Peter-Katalinie, J.; Mukherjee-Müller, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1379.

(36) Nielson, D. G.; Peters, D. A. V. *J. Chem. Soc.* **1962**, 1519.

organics were dried over $MgSO_4$ and concentrated to leave 1.80 g of a slightly yellow liquid. The crude product was flash chromatographed on 50 g of silica gel eluted with 5:1 hexanes/EtOAc. From this was isolated 0.86 g (44%) of the desired aldehyde: IR ($CHCl_3$) 3030, 2945, 2840, 1742, 1605, 1493, 1455, 1113 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.45 (s, 1), 4.65 (d, 1, J = 1.6), 7.35–7.43 (m, 5), 9.60 (d, 1, J = 1.6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.108, 88.059, 127.337 (2 C), 127.483, 128.880 (2 C), 129.402, 198,105; HRMS calcd for $C_9H_{10}O_2$ 150.0678, found 150.0678.

2-Phenylbutanal (6b). To a solution of 1.55 g (67.4 mmol) of sodium in absolute ethanol was slowly added 14.10 g (64.0 mmol) of 3-carbethoxy-2-ethyl-2-phenyloxirane (**10b**)[37] under N_2. The solution was cooled in ice, and 1.5 mL of water was slowly added. The mixture was evaporated to leave a glass which was powdered to yield 14.53 g of the crude sodium salt. The salt was dissolved in 35 mL of 6% HCl and warmed to 75 °C as CO_2 evolved. The mixture was heated at 75–80 °C for 2 h, and an oil separated. The mixture was separated, and the aqueous layer was extracted with benzene (30 mL). The combined organics were dried over Na_2SO_4 overnight and concentrated. The crude product was distilled at reduced pressure through an efficient column. The fraction boiling at 103–106 °C (15 mm) was collected to yield 6.49 g (68%) of the desired aldehyde as a colorless liquid: IR ($CHCl_3$) 3050, 3005, 2430, 1730, 1532, 1430, 1063 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3, J = 7.4), 1.79 (m, 1, J = 6.1), 2.12 (m, 1, J = 6.7), 3.41 (ddd, 1, J = 7.0, 7.0, 2.0), 7.18–7.41 (m, 5), 9.68 (d, 1, J = 2.0); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.635, 22.867, 60.785, 127.447, 128.759 (2 C), 128.936 (2 C), 136.239, 200.925. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.87; H, 8.10.

3-Methyl-2-phenylbutanal (6c). To a solution of 1.41 g (61.5 mmol) of sodium in 24 mL of absolute ethanol was slowly added 12.00 g (51.2 mmol) of 3-carbethoxy-2-(1-methylethyl)-2-phenyloxirane (**10c**)[38] under N_2. The solution was cooled in ice, and 1.2 mL of water was slowly added. The mixture was evaporated to leave a glass which was powdered. The crude sodium salt was dissolved in 30 mL of 6% HCl and warmed to 80 °C for 8 h to evolve CO_2. An oil separated that was collected, and the aqueous layer was extracted with benzene (30 mL). The combined organics were dried over Na_2SO_4 overnight and concentrated. The crude product was distilled at reduced pressure through an efficient column. The fraction boiling at 107–112 °C (15 mm) was collected to yield 6.06 g (73%) of the desired aldehyde as a colorless liquid: IR ($CHCl_3$) 3030, 2980, 2410, 1730, 1522, 1426, 1051 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, 3, J = 6.7), 1.05 (d, 3, J = 6.4), 2.40 (m, 1), 3.18 (dd, 1, J = 9.5, 3.3), 7.17–7.40 (m, 5), 9.70 (d, 1, J = 3.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.930, 21.065, 28.672, 66.732, 127.362, 128.795 (2 C), 129.217 (2 C), 135.399, 200.980. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.31; H, 8.62.

2-(1,1-Dimethylethyl)-2-phenyloxirane (11). A mixture of 3.00 g (62.9 mmol) of 50% sodium hydride (rendered oil-free) in 35 mL of dry Me_2SO was heated at 70 °C for 1 h. The mixture was cooled to room temperature, diluted with 40 mL of dry THF, and cooled in a NaCl–ice bath. A solution of 12.83 g (62.9 mmol) of trimethylsulfonium iodide in 50 mL of dry Me_2SO was added at such a rate that the reaction temperature did not exceed 5 °C. The mixture was stirred for 2 min, and 8.50 g (52.4 mmol) of phenyl *tert*-butyl ketone[39] was added at such a rate that the reaction temperature did not exceed 6 °C. The mixture was stirred at −4 °C for 15 min and at room temperature for 1 h, and it was then poured into 450 mL of water and extracted with ether (4 × 200 mL). The combined organics were dried over $MgSO_4$ and concentrated to leave 8.96 g of the crude product. The crude epoxide was distilled at reduced pressure through an efficient column. The fraction boiling at 109–112 °C (12 mm) was collected to yield 6.51 g (60%) of the desired epoxide as a colorless liquid: IR (neat) 3067, 2978, 2881, 1484, 1450, 1396, 1367, 1342, 1208 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (s, 9), 2.65 (d, 1, J = 5.0), 3.11 (d, 1, J = 5.1), 7.25–7.43 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.298 (3 C), 28.174, 33.720, 50.800, 127.251 (2 C), 128.289, 128.785 (2 C), 130.346. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.15.

3,3-Dimethyl-2-phenylbutanol (12). To a solution of 2.00 g (11.3 mmol) of oxirane **11** and 1.5 mL of acetic acid in 30 mL of EtOAc was added 0.40 g (0.38 mmol) of 10% palladium on charcoal. The mixture was stirred under hydrogen atmosphere for 6 days. The reaction mixture was filtered through Celite and concentrated to yield 1.86 g of a solid. The crude product was chromatographed on 80 g of silica gel eluted with 2:1 hexanes/ether to yield 1.27 g (95% based on recovered epoxide) of the desired alcohol as a white solid: mp 74–75 °C; IR ($CHCl_3$) 3595, 3016, 2980, 2910, 1496, 1483, 1458, 1404, 1371, 1042 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (s, 9), 1.10 (br, 1), 2.68 (dd, 1, J = 8.1, 7.3), 4.02 (d, 2, J = 8.4), 7.20–7.35 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.411 (3 C), 33.024, 58.971, 62.597, 126.768 (2 C), 128.159 (2 C), 129.768, 140.013. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.62; H, 10.23.

3,3-Dimethyl-2-phenylbutanal (6d). A solution of 0.88 mL (12.3 mmol) of dry Me_2SO in 6 mL of dry CH_2Cl_2 was added dropwise to a −78 °C solution of 0.54 mL (6.2 mmol) of freshly distilled oxalyl chloride in 25 mL of dry CH_2Cl_2 at a rate such that the temperature remained at −78 to −65 °C. The mixture was stirred at −78 °C for 20 min, and a solution of 1.00 g (5.6 mmol) of alcohol **12** in 6 mL of dry CH_2Cl_2 was added dropwise at a rate such that the reaction temperature remained at −78 to −65 °C. The mixture was stirred at −78 °C for 5 min, and 3.91 mL (28.0 mmol) of triethylamine was added dropwise, again maintaining the reaction temperature at −78 to −65 °C. The reaction mixture was warmed to 0 °C, and 17 mL of water was added. After being warmed to room temperature, the mixture was diluted with 30 mL of ether and separated and the aqueous layer was extracted with ether (25 mL). The combined organics were washed with cold 1% HCl (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated to leave 0.96 g of a colorless liquid. The crude aldehyde was chromatographed on 60 g of silica gel eluted with 2:1 hexanes/ether. Aldehyde **6d** (0.91 g, 92%) was isolated as a colorless liquid: IR (neat) 2977, 2922, 2885, 2734, 1727, 1496, 1484, 1460, 1401, 1383, 1226 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (s, 9), 3.29 (d, 1, J = 3.5), 7.21–7.36 (m, 5), 10.01 (d, 1, J = 3.5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.188 (3 C), 34.547, 68.357, 127.261, 128.295 (2 C), 130.359 (2 C), 135.231, 202.218. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.64; H, 9.06.

General Procedure for Aldol Reactions. All glassware was oven- or flame-dried and stored in a dessicator until immediately prior to use. All additions were made by syringe using a Sage Instruments Model 341 syringe pump. All reactions were performed under a dry argon atmosphere. The solutions of pinacolone in THF and aldehyde in THF were mixed in 1-dram vials fitted with septa. Each reaction was performed three times. Analyses of the diastereomer ratios were performed by capillary gas chromatography, and the response factors for the two diastereomers of each reaction were assumed to be identical. The ratios recorded are the averages of several capillary GC runs for all three of the reactions for each aldehyde.

To a stirring, 0 °C solution of 154 μL (1.10 mmol) of diisopropylamine in 1.00 mL of THF was added 0.64 mL (1.64 M, 1.05 mmol) of *n*-butyllithium in hexanes over 8 min. The solution was stirred for 5 min at 0 °C, then plunged into a dry ice/acetone bath, and stirred for 5 min. A solution of 125 μL (1.00 mmol) of pinacolone in 0.25 mL of THF was added over a 12-min period. The mixing vial was rinsed with 0.25 mL of THF and the rinse was added to the reaction mixture over a 1-min period. The mixture was stirred at −78 °C for 10 min, and a solution of 1.15 mmol of the aldehyde in 0.25 mL THF was added over a 13–16-min period. The mixing vial was rinsed with 0.25 mL of THF, and the rinse was added to the reaction mixture over a 1-min period. The reaction was stirred for 15 min at −78 °C, quenched by rapid addition of 1.0 mL of saturated aqueous $NaHCO_3$, and warmed to room temperature. The mixture was diluted with 20 mL of ether and separated, and the organic phase was washed with 5-mL portions of saturated $NaHCO_3$, water, and brine. The organics were dried over $MgSO_4$ and concentrated to yield the crude product mixture. The crude product was eluted through 2.5 g of flash silica gel to remove base-line impurities and the diastereomer ratio determined by capillary GC. In each experimental, the major diastereomer is listed first. In some cases, full analytical data was unobtainable, owing to small quantities of one diastereomer or to difficulties in diastereomer separation.

(5*SR*,6*RS*)- and (5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2-dimethylheptan-3-one (11a and 12a). A solution of 101 mg (1.15 mmol) of 2-methoxypropanal (**5a**) in 0.25 mL of THF was used. The reaction yielded 112 mg (57%) of the diastereomer mixture, in a ratio of 1.41:1. The diastereomers could not be separated; HRMS (mixture of diastereomers) calcd for $C_{10}H_{20}O_3$ 118.1420, found 118.1420.

Major: IR (neat) 3480, 2990, 2955, 2890, 1711, 1487, 1472, 1375, 1146, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 9), 1.16 (d, 3, J = 6.1), 2.70 (m, 2), 3.19 (d, 1, J = 4.1), 3.33 (m, 1), 3.37 (s, 3), 3.95 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.677, 26.168 (3 C), 38.432, 44.382, 56.588, 70.475, 78.971, 217.133.

Minor: IR (neat) 3480, 2990, 2955, 2890, 1711, 1487, 1472, 1375, 1146, 1100 cm^{-1}; ^1H NMR 250 MHz, $CDCl_3$) δ 1.16 (s, 9), 1.16 (d, 3, J = 6.1), 2.72 (m, 2), 3.02 (d, 1, J = 4.0), 3.30 (m, 1), 3.36 (s, 3), 4.03 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.263, 26.124 (3 C), 38.813, 44.354, 56.635, 70.034, 78.478, 216.354.

(5*SR*,6*RS*)- and (5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2-dimethyloctan-3-one (11b and 12b). A solution of 118 mg (1.15 mmol) of 2-

(37) Kulkarni, B. D.; Rao, A. S. *Synthesis* **1976**, 454.
(38) Cram, D. J.; Abd Elhafez, F. A.; Nyquist, H. L. *J. Am. Chem. Soc.* **1954**, *76*, 22.
(39) Jorgensen, M. J. *Org. React. (N.Y.)* **1970**, *18*, 59.

methoxylbutanal (**5b**) in 0.25 mL of THF was used. The reaction yielded 160 mg (69%) of the diastereomeric mixture, in a ratio of 3.05:1. The diastereomers were separated by flash chromatography on 3.0 g of silica gel eluted with 20% ether/hexanes.

Major: IR ($CDCl_3$): 3585, 2995, 2960, 2900, 1703, 1491, 1477, 1378, 1107 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3 J = 7.4), 1.16 (s, 9), 1.52–1.62 (m, 2), 2.73 (m, 2), 3.15 (q, 1, J = 6.4), 3.23 (d, 1, J = 4.0), 3.42 (s, 3), 4.04 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.304, 22.426, 26.275 (3 C), 38.350, 44.489, 58.111, 68.879, 84.408, 217.818. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.08; H, 10.96.

Minor: IR ($CDCl_3$) 3585, 3000, 2965, 2910, 1701, 1466, 1370, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (t, 3, J = 7.4), 1.16 (s, 9), 1.41–1.66 (m, 2), 2.70 (d, 2, J = 6.1), 2.92 (d, 1, J = 4.5), 3.06 (m, 1), 3.41 (s, 3), 4.14 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$, partial) δ 9.974, 22.093, 26.239 (3 C), 39.195, 58.135, 67.884, 84.262.

(5*SR*,6*RS*)- and (5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2,7-trimethyloctan-3-one (11c and 12c). A solution of 134 mg (1.15 mmol) of 2-methoxy-3-methylbutanal (**5c**) in 0.25 mL of THF was used. The reaction yielded 198 mg (80%) of the diastereomer mixture, in a ratio of 12.43:1. The diastereomers were separated by flash chromatography on 5 g of silica gel eluted with 6:1 hexanes/EtOAc.

Major: IR ($CHCl_3$) 3550, 2985, 2950, 2922, 2880, 1695, 1483, 1470, 1374, 1106 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 6, J = 7.0), 1.16 (s, 9), 1.84 (m, 1, J = 6.0), 2.74 (m, 2), 2.95 (t, 1, J = 5.5), 3.36 (d, 1, J = 4.0), 3.50 (s, 3), 4.08 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.747, 19.639, 26.271 (3 C), 29.695, 38.258, 44.451, 60.985, 68.921, 88.813, 218.272. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.65; H, 10.98.

Minor (partial): ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (d, 3, J = 6.8), 0.99 (d, 3, J = 6.8), 1.16 (s, 9), 1.96 (m, 1, J = 6.8), 2.63 (dd, 1, J = 7.5, 4.3), 2.79 (m, 2), 3.49 (s, 3), 4.18 (m, 1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.23, 19.21, 26.10 (3 C), 40.54, 60.38, 67.77, 88.11.

(5*SR*,6*RS*)- and (5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2,7,7-tetramethyloctan-3-one (11d and 12d). A solution of 132 mg (1.15 mmol) of 2-methoxy-3,3-dimethylbutanal (**5d**) in 0.25 mL of THF was used. The reaction yielded 202 mg (76%) of the diastereomer mixture, in a ratio of 13.80:1. The diastereomers were separated by flash chromatography on 3 g of silica gel eluted with 20% ether/hexanes.

Major: IR (neat) 3510, 2970, 2925, 2885, 1709, 1487, 1405, 1371, 1118 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (s, 9), 1.16 (s, 9), 2.70 (dd, 1, J = 18.3, 9.2), 2.88 (d, 1, J = 17.7), 2.88 (d, 1, J = 12.1), 3.50 (s, 3), 3.53 (d, 1, J = 3.6), 4.17 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) 26.306 (3 C), 26.654 (3 C), 35.203, 39.137, 44.433, 61.639, 69.349, 92.343, 218.890. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.68; H, 11.24.

Minor (partial): ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (s, 9), 1.16 (s, 9), 1.59 (b s, 1), 2.71 (m, 3), 2.90 (m, 1), 3.56 (s, 3), 4.24 (m, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.283 (3 C), 26.807 (3 C), 43.562, 66.573, 90.186, 215.134.

(5*SR*,6*RS*)- and (5*RS*,6*RS*)-5-Hydroxy-6-methoxy-2,2-dimethyl-6-phenylhexan-3-one (11e and 12e). A solution of 173 mg (1.15 mmol) of 2-methoxy-2-phenylethanal (**5e**) in 0.25 mL of THF was used. The reaction yielded 195 mg (68%) of the diastereomer mixture, in a ratio of 4.84:1. The diastereomers were separated by flash chromatography on 6 g of silica gel eluted with 6:1 hexanes/EtOAc.

Major: IR ($CHCl_3$) 3590, 3015, 2975, 2940, 2913, 1693, 1603, 1481, 1457, 1370, 1124 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 9), 2.75 (m, 2), 3.08 (d, 1, J = 4.2), 3.28 (s, 3), 4.20 (m, 2), 7.28–7.42 (m, 5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.21 (3 C), 38.41, 44.40, 57.11, 71.35, 85.79, 127.39 (2 C), 127.96, 128.36 (2 C), 129.00, 216.92. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.77; H, 8.67.

Minor: IR ($CHCl_3$) 3585, 2990, 2955, 2925, 1711, 1483, 1459, 1400, 1373, 1121 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 9), 2.44 (dd, 1, J = 16.1, 3.3), 2.59 (dd, 1, J = 16.1, 8.2), 3.08 (m, 1), 3.26 (s, 3), 4.20 (m, 2), 7.30–7.38 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.083 (3 C), 39.017, 44.312, 57.001, 71.352, 86.352, 127.600 (2 C), 128.234, 128.488 (2 C), 138.088, 215.141. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 8.77.

(5*SR*,6*SR*)- and (5*RS*,6*SR*)-5-Hydroxy-2,2-dimethyl-6-phenylheptan-3-one (13a and 14a). A solution of 154 mg (1.15 mmol) of 2-phenylpropanal (**6a**) in 0.25 mL of THF was used. The reaction yielded 243 mg (90%) of the diastereomer mixture, in a ratio of 3.64:1. The two diastereomers were identified by comparison with the spectra of authentic samples.[40]

(5*SR*,6*SR*)- and (5*RS*,6*SR*)-5-Hydroxy-2,2-dimethyl-6-phenyloctan-3-one (13b and 14b). A solution of 171 mg (1.15 mmol) of 2-phenylbutanal (**6b**) in 0.25 mL of THF was used. The reaction yielded 240 mg (84%) of the diastereomer mixture, in a ratio of 6.05:1. The diastereomers were separated by flash chromatography on 6 g of silica gel eluted with 15% ether/hexanes.

Major: mp 73–74 °C; IR ($CHCl_3$) 3540, 3015, 2980, 2943, 2885, 1694, 1497, 1482, 1467, 1457, 1369, 1075 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.73 (t, 3, J = 7.4), 1.00 (s, 9), 1.61 (m, 1), 2.18 (m, 1), 2.41 (m, 2), 2.51 (m, 1), 3.44 (d, 1, J = 4.1), 4.08 (m, 1), 7.11–7.33 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.915, 24.863, 26.117 (3 C), 41.167, 44.361, 53.571, 71.783, 126.563, 128.353 (2 C), 128.474 (2 C), 142.091, 218.168. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.22; H, 9.86.

Minor (partial): ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (t, 3, J = 7.4), 1.08 (s, 9), 1.81 (m, 1), 2.17 (m, 1), 2.82 (m, 1), 2.50 (m, 1), 2.63 (dd, 1), 2.93 (d, 1), 4.25 (m, 1), 7.10–7.34 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.193, 24.664, 26.176 (3 C), 44.333, 52.969, 128.168 (2 C), 128.523, 129.008 (2 C), 141.199, 217.233.

(5*SR*,6*SR*)- and (5*RS*,6*SR*)-5-Hydroxy-2,2,7-trimethyl-6-phenyloctan-3-one (13c and 14c). A solution of 188 mg (1.15 mmol) of 3-methyl-2-phenylbutanal (**6c**) in 0.25 mL of THF was used. The reaction yielded 217 mg (72%) of the diastereomer mixture, in a ratio of 2.25:1. The diastereomers were separated by flash chromatography usig 6.0 g of silica gel eluted with 20% ether/hexanes.

Major: mp 44–45 °C; IR ($CHCl_3$) 3540, 2985, 2950, 2895, 1704, 1487, 1473, 1374, 1082 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, 3, J = 7.0), 0.84 (d, 3, J = 6.9), 0.99 (s, 9), 2.36 (dd, 1, J = 17.9, 8.5), 2.45 (m, 1), 2.48 (dd, 1, J = 17.9, 2.4), 2.60 (dd, 1, J = 9.9, 4.9), 3.48 (d, 1, J = 4.3), 4.42 (m, 1), 7.04–7.32 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.411, 21.637, 26.043 (3 C), 27.392, 41.371, 44.362, 56.867, 68.436, 126.489, 127.930 (2 C), 129.611 (2 C), 139.280, 218.457. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 78.04; H, 10.07.

Minor: mp 69–70 °C; IR ($CHCl_3$) 3560, 3000, 2960, 2900, 1696, 1478, 1454, 1387, 1364, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.68 (d, 3, J = 6.6), 1.04 (s, 9), 1.11 (d, 3, J = 6.4), 2.12 (m, 1), 2.13 (dd, 1, J = 17.8, 9.5), 2.23 (m, 1), 2.49 (dd, 1, J = 17.9, 2.7), 3.00 (d, 1, J = 3.0), 4.51 (m, 1), 7.22–7.32 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.159, 21.576, 26.220 (3 C), 29.359, 42.303, 44.305, 58.225, 67.212, 126.358, 127.932 (2 C), 129.761 (2 C), 140.916, 217.861. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.85; H, 10.17.

(5*RS*,6*SR*)- and (5*SR*,6*SR*)-5-Hydroxy-2,2,7,7-tetramethyl-6-phenyloctan-3-one (13d and 14d). A solution of 203 mg (1.15 mmol) of 3,3-dimethyl-2-phenylbutanal (**6d**) in 0.25 mL of THF was used. The reaction yielded 291 mg (92%) of the diastereomer mixture, in a ratio of 1.70:1. The diastereomers were separated by flash chromatography on 6 g of silica gel eluted with 7:1 hexanes/ether.

Major: mp 114–115 °C;[41] IR ($CDCl_3$) 3570, 2985, 2925, 2890, 1696, 1484, 1400, 1371, 1233, 1104 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (s, 9), 1.03 (s, 9), 2.17 (m, 2), 2.41 (dd, 1, J = 17.9, 2.6), 3.09 (d, 1, J = 2.8), 4.70 (m, 1), 7.25–7.29 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.189 (3 C), 29.357 (3 C), 34.448, 43.248, 44.295, 60.482, 67.995, 126.217, 127.360 (2 C), 128.093 (2 C), 139.717, 218.226. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.14; H, 10.03.

Minor: mp 38–39 °C; IR ($CDCl_3$) 3545, 2980, 2925, 2887, 1696, 1484, 1400, 1370, 1232, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (s, 9), 1.01 (s, 9), 2.36 (m, 2), 2.56 (d, 1, J = 10.4), 3.51 (d, 1, J = 4.7), 4.49 (m, 1), 7.05–7.29 (m, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.074 (3 C), 29.865 (3 C), 34.090, 42.746, 44.290, 60.204, 70.198, 126.344, 128.068 (4 C), 142.555, 218.747. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.05; H, 10.29.

(5*SR*,6*RS*)-6-Methoxy-2,2,7-trimethyl-3-oxoheptan-5-yl 4-Bromobenzoate (15). To an ice-cold solution of 20 mg (0.09 mmol) of aldol **11c** in 0.5 mL of CH_2Cl_2 was added 20 mg (0.10 mmol) of 4-bromobenzoic acid, 0.5 mg (0.05 mmol) of DMAP, and 21 mg (0.10 mmol) of DCC. The mixture was warmed to room temperature and stirred for 18 h, whereupon an additional 21 mg (0.10 mmol) of DCC was added. After 8 h, the mixture was diluted with 5 mL of CH_2Cl_2, dried over $MgSO_4$, and evaporated to leave 57 mg of a white solid. The crude product was flash chromatographed on 2.5 g of silica gel eluted with 7:1 hexanes/EtOAc, and 26 mg (72%) of the desired ester was isolated. The pure ester was recrystallized from pentane to yield crystals of X-ray quality: mp 75–76 °C;[41] IR ($CHCl_3$) 2990, 2960, 2145, 1722, 1600, 1488, 1409, 1377, 1284, 1124, 1112 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (d, 3, J = 6.6), 1.03 (d, 3, J = 6.8), 1.15 (s, 9), 1.66 (m, 1), 3.21 (m, 2), 3.47 (s, 3), 5.79 (m, 1), 7.56 (d, 2 J = 8.6), 7.85 (d, 2 J = 8.6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.081, 19.158, 26.055 (3 C), 30.837,

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

(41) Experimental details for the X-ray structure of this compound, along with its atomic coordinates, are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Any request should be accompanied by the full literature citation for this article.

35.162, 44.378, 60.983, 72.923, 87.785, 128.021, 129.137, 131.013 (2 C), 131.708 (2 C), 164.825, 212.395.

(5*SR*,6*RS*)-5-Hydroxy-6-methoxy-2,2-dimethyl-6-phenylhexan-3-one Oxime (16). A solution of 25 mg (0.10 mmol) of aldol **11e**, 100 mg (1.50 mmol) of hydroxylamine hydrochloride, and 50 mg (0.50 mmol) of sodium hydroxide in 1 mL of 95% ethanol was refluxed for 3 days. The mixture was poured into 10 mL of 1 *N* aqueous HCl and extracted with ether (3 × 15 mL). The combined organics were washed with 5-mL portions of saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The mixture was concentrated, and the crude product was flash chromatographed on 1.3 g of silica gel eluted with 20% ether/hexanes to yield 16 mg (60%) of the desired oxime: mp 97-98 °C;[4] IR ($CDCl_3$) 3490, 3270, 2361, 1469, 1458, 1369, 1198, 1131 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (s, 9), 2.52 (dd, 1, J = 13.8, 2.3), 2.78 (dd, 1, J = 13.8, 10.0), 3.32 (s, 3), 3.85 (d, 1, J = 4.3), 3.97 (m, 1), 4.21 (d, 1, J = 5.2), 7.29-7.37 (m, 5), 9.35 (s, 1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.663 (3 C), 28.184, 37.868, 57.358, 74.152, 87.234, 127.340 (2 C), 127.810, 128.324 (2 C), 138.730, 166.444.

Acknowledgment. This research was supported by a research grant from the United States Public Health Service (AI-15027). We thank Professor K. N. Houk for helpful discussion.

Far Ultraviolet Circular Dichroism Observations on the Substituted Benzene Chromophore[1]

W. Curtis Johnson, Jr.,[2a] Luca P. Fontana,[2b] and Howard E. Smith*[2b]

Contribution from the Department of Biochemistry and Biophysics, Oregon State University, Corvallis, Oregon 97331, and the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235. *Received November 24, 1986*

Abstract: The electronic absorption (EA) and circular dichroism (CD) of two chiral α-phenylalkylamines and five chiral α-phenylalkylamine hydrochlorides were measured far into the vacuum ultraviolet region. The EA for all seven compounds is similar to that of benzene, showing transitions assigned to the B_{2u}, the B_{1u}, and the E_{1u} states. In addition to the Cotton effects (CEs) associated with the B_{2u} transition at 245-270 nm, there are two or more CEs associated with electronic transitions at shorter wavelengths. When only two of these shorter wavelength CEs are observed, they are easily assigned to the corresponding electronic transitions. As the alkyl group on the chiral substituent becomes bulkier, the CD spectrum becomes more complex, and there is increased intensity. These changes explain the earlier observation of a negative background optical rotatory dispersion (ORD) from 240-225 nm for (*S*)-α-phenylethylamine but a positive background curve for (*S*)-α-phenylneopentylamine. In contrast to the B_{2u} CEs which for a particular configuration may change sign on para substitution of the benzene ring, the CD associated with the strongly allowed E_{1u} transition is independent of para substitution and therefore is valuable for determining absolute configuration when an α-phenylalkylamine has a para substituent. However, when the CD spectrum is complex, it becomes difficult to recognize which CE is associated with this transition.

The benzene chromophore shows three well-defined electronic absorption (EA) bands above 175 nm (Table I).[3] Each is the result of a $\pi \rightarrow \pi^*$ transition, but only the B_{2u} band shows in solution a well-defined vibrational fine structure. The E_{1u} transition centered near 180 nm is doubly degenerate and, as shown by its high molar absorptivity (ϵ), is strongly allowed. Both the B_{1u} and B_{2u} transitions are dipole forbidden for the static molecule. Their intensities are lower than that of the E_{1u} transition and are due to molecular vibration.

If the benzene ring is substituted with a chiral group, the position of the absorption bands may be somewhat shifted and their intensities slightly altered, but the spectrum is essentially unchanged.[3] More importantly, the transitions are now optically active, and Cotton effects (CEs) are associated with the absorption bands.[7] This optical activity is determined by the configuration and conformation of the molecule and can be observed as the dispersive spectroscopic property, optical rotatory dispersion (ORD), and as the absorptive spectroscopic property, circular dichroism (CD). For laboratories interested in the synthesis of asymmetric, organic molecules, optical activity in either its dispersive or absorptive form is the obvious method for determining absolute configuration.

Table I. Benzene Spectral Data

designation[a]	absorption band maximum	
	λ,[b] nm	ϵ[c]
B_{2u} (^1L_b)	254[d]	204
B_{1u} (^1L_a)	203.5[d]	7400
E_{1u} ($^1B_{ab}$)	183.5[e]	46000

[a] Reference 4. [b] Wavelength. [c] Molar absorptivity. [d] Reference 5, water as solvent. [e] Reference 6, *n*-heptane as solvent.

Attempts to relate the configuration of chiral benzene compounds to their CD have focused almost exclusively on utilization of the sign and magnitude of the easily observed CEs associated with the B_{2u} transition.[8] In terms of the *S* enantiomers, ORD measurements[9] in methanol reveal a number of positive CEs associated with this transition for α-phenylalkylamines (*S*)-**1**-**3** and their hydrochlorides (*S*)-**1**-**3**·HCl.

These CEs are superimposed on a strong background curve which is the sum of the long wavelength wings of CEs below 240 nm.[9] The contributions from the short wavelengths far override

(1) This is part 32 in the Vanderbilt University series Optically Active Amines. Part 31 is ref 11.
(2) (a) Oregon State University. (b) Vanderbilt University.
(3) Robin, M. B. *Higher Excited States of Polyatomic Molecules*; Academic Press: New York, 1975; Vol II, pp 209-257.
(4) Klevens, H. B.; Platt, J. R. *J. Chem. Phys.* **1949**, *17*, 470-481.
(5) Doub, L.; Vandenbelt, J. M. *J. Am. Chem. Soc.* **1947**, *69*, 2714-2723.
(6) Platt, J. R.; Klevens, H. B. *Chem. Rev.* **1947**, *41*, 301-310.
(7) Johnson, W. C., Jr. *Ann. Rev. Phys. Chem.* **1978**, *29*, 93-114.
(8) Legrand, M.; Rougier, M. J. In *Stereochemistry*; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 2, pp 33-183.
(9) Smith, H. E.; Warren, M. E., Jr.; Katzin, L. I. *Tetrahedron* **1968**, *24*, 1327-1335.

0002-7863/87/1509-3361$01.50/0