Reversal of π-Facial Diastereoselection upon Electronegative Substitution of the Substrate and the Reagent

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Abstract: Electronegative substitution at C-3 of cyclohexanone and methylenecyclohexane is found to increase the relative proportion of axial attack in a number of reactions widely differing from the points of view of the transition-state polarization, geometry, and electron deficiency. Reactions examined included alkyllithium additions, oxymercurations, osmylations, and peracid epoxidations. Plots of log k_{ax}/k_{eq} vs σ_I (r^2 values of 0.952, 0.940, and 0.977 in three different methyllithium additions for eight data sets ($P < 0.1\%$) in each case) reveal that the sensitivity of the k_{ax}/k_{eq} ratio to the change in electronegativity of the C-3 substituents does not depend on the transition-state polarization, i.e., on the reaction mechanism. An increase in proportion of axial attack is also observed when the electronegativity of a substituent on a carbon nucleophile is increased. Moreover, the slopes ($b_I = \Delta\rho$) of the log k_{ax}/k_{eq} vs σ_I plots decrease as the electronegativity of the nucleophile substituents increases in the series $^-CH_2SC_6H_5$, $^-CH_2SO(=NCH_3)C_6H_5$, $^-CH_2{}^+S(CH_3)_2$ ($\Delta\rho$ = 1.869, 1.086, and 0.794, respectively). The combination of the two substitution effects can result in a complete reversal of the stereochemistry of carbanion additions to cyclohexanone. Addition of $PhSCH_2Li$ (THF, −78 °C) to 3-(trimethylsilyl)cyclohexanone occurs with a strong preference for the less hindered equatorial approach (90/10). Addition of $PhSO(=NCH_3)CH_2Li$ (where two electron-withdrawing groups are attached to the sulfur atom, so that both lone pairs of electrons are bonded) to 3-(trimethylsilyl)cyclohexanone is not selective (45/55), and addition of the same reagent to 3-(trifluoromethyl)cyclohexanone occurs with a strong preference for the more hindered axial approach (17/83). These findings appear inconsistent with the predictions of the Felkin, Klein, and Ashby or Nguyen Trong Anh models of stereochemistry of reactions in cyclohexane-based systems, but are consistent with the Cieplak model based on the concept of transition-state stabilization by electron donation into the vacant orbital σ_s^* associated with the incipient bond.

Changes in electronic properties of a stereogenic center without accompanying changes in steric interactions at that site offer an important method to probe stereoelectronic effects. Introduced as a concept in pioneering studies of nucleophilic additions to cyclohexanones,[1] such modifications continue to attract interest as tools of mechanistic investigations of π-facial diastereoselection.[2] The interest in practical applications of these modifications may also grow in the wake of observations such as the discovery of a dramatic reversal of the normal L-Selectride preference for the less hindered equatorial approach in the reductions of 4-pyranones.[3] Recently, the first systematic and comprehensive study of the impact of electronic modifications of the inducing center of stereoselectivity of nucleophile capture by either a carbonyl group or a carbonium ion was reported.[4] Using the sterically nonbiased system of 5-substituted 2-adamantanones, le Noble and co-workers addressed the fundamental problem of the nature and importance of hyperconjugative σ assistance in such reactions. The surprisingly large effects of remote substitution observed in these studies are consistent with earlier propositions of Cieplak.[5] le Noble's study has established a firm foundation for evaluation of the theories of π-facial diastereoselection and has shown that electronic modifications (without concommitant steric perturbations) of a given diastereoselection system dramatically influence diastereoface selectivity.

We have been interested in exploitation of the same approach to probing stereoelectronic effects in an attempt to address basic questions raised by theories of π-facial stereoselection. We were particularly intrigued by the generality of stereoelectronic control in reactions of diverse mechanisms and the importance of σ assistance in sterically biased systems. For this purpose, we have carried out an investigation of various reactions of cyclohexanones and methylenecyclohexanes substituted at C-3 by groups of varying electronegativity and of large steric bulk. Among the reactions studied, organolithium, organocuprate, and sulfur ylide additions to cyclohexanones represented polar additions to a carbonyl group where the CC bond formation is the rate-limiting step.[6] The structure of these reagents conveniently permits varying substitution of the incipient bond, i.e., electron affinity of the transition state, and allows avoidance of the unfortunate controversy concerning "product development control".[7] Oxymercuration of methylenecyclohexanes represents polar additions to alkenes, where the CO bond formation is the rate-limiting step, since it was carried out under conditions ensuring reversible formation of the mercurinium ion.[8] Finally, peracid epoxidation and osmylation of

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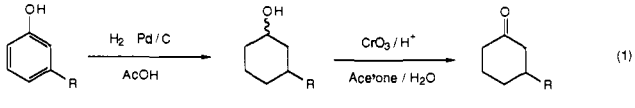
methylenecyclohexanes represented reactions that appear to depend on the nucleophilicity of the olefin.[9,10] Thus, two types of reactions, where the direction of the transition-state polarization with respect to the inducing centers is expected to be reversed, have been investigated: (i) C or O nucleophile capture by a carbonyl group or a carbonium ion like intermediate, and (ii) electrophile capture by an alkene. These reactions also significantly differ in regard to the transition-state electron affinity and the transition-state geometry. While all are believed to proceed through "early" reactant-like transition states (with the incipient center retaining to a large extent the sp^2 character),[11] they represent a wide spectrum as far as the angle formed by the incipient bond and the double bond axis is concerned.[12]

From the experimental point of view, it was important that these reactions were known to be, in general, suitable for stereoselectivity investigations, i.e., to be irreversible and high-yielding. The major advantage, however, offered by the selected set was the standardization of structural assignments and determination of product ratios; all the products could be readily converted into mixtures of 3-substituted 1-methylcyclohexanols, thus simplifying stereochemical assignments and quantitation of the diastereomeric mixtures.

In this article, we describe the synthesis of C(3)-substituted cyclohexanones and methylenecyclohexanes, the investigation of stereoselectivity of the aforementioned reactions, and the evaluation of several currently discussed models of stereoelectronic effects in π-facial diastereoselection in the light of the results obtained.[13]

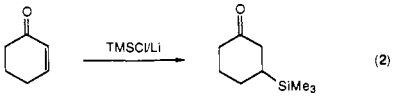
Results

A. Synthesis of 3-Substituted Cyclohexanones. Hydrogenation of the appropriate phenol followed by Jones oxidation of the mixture of epimeric alcohols gave 3-(trifluoromethyl)cyclohexanone and 3-*tert*-butylcyclohexanone (eq 1).[14]



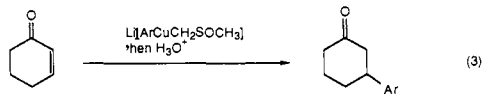
(1)

Attempts to prepare 3-(trimethylsilyl)cyclohexanone by the method of Still involving conjugate addition of (trimethylsilyl)-lithium in HMPA to 2-cyclohexen-1-one were not successful.[15] The preparation of the desired silylcyclohexanone was accomplished in modest yield by using the TMSCl/Li procedure of Kitching (eq 2).[16] Aryl cuprate additions to 2-cyclohexen-1-one



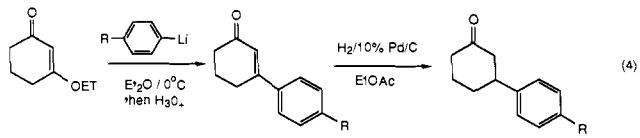
(2)

using a mixed cuprate procedure developed in these laboratories gave moderate yields of 3-phenylcyclohexanone and 3-(*p*-tolyl)-cyclohexanone (eq 3).[17]



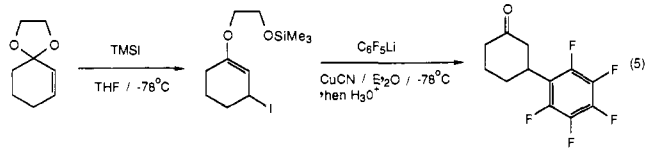
(3)

Cuprate-mediated addition of (4-methoxyphenyl)lithium and [4-(trifluoromethyl)phenyl]lithium to 2-cyclohexen-1-one as above gave the desired products in modest yields. As purification of the products proved to be difficult, a two-step procedure was used. The appropriate aryllithium was added to 3-ethoxy-2-cyclohexen-1-one, resulting in the expected 1,2 addition. The reaction mixture was worked up under acidic conditions to produce the 3-aryl-2-cyclohexen-1-ones. The purified products were hydrogenated to afford the desired 3-arylcyclohexanones (eq 4).



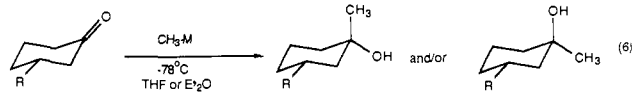
(4)

Attempted preparation of 3-(pentafluorophenyl)cyclohexanone using the cuprate methodology (eq 3) did not produce substantial quantities of the desired product. Starting 2-cyclohexen-1-one was recovered along with a trace of 1,4-addition product. Addition of (pentafluorophenyl)lithium to 3-ethoxy-2-cyclohexen-1-one followed by acidification gave 3-(pentafluorophenyl)-2-cyclohexen-1-one in good yield. Hydrogenation under a variety of conditions was uniformly unsuccessful. Other methods of reduction (Bu_3SnH/AIBN, Red Al/CuBr, $NaBH_4$/pyridine, K/liquid NH_3) also did not produce the desired product in acceptable yields. These approaches were abandoned in favor of a procedure developed in our laboratory.[18] The ethylene ketal of 2-cyclohexen-1-one was treated with trimethylsilyl iodide to afford the allylic iodide. Addition of the preformed cuprate from (pentafluorophenyl)lithium to the allylic iodide effected displacement of the iodide. Without further purification, the enol ether was subjected to acid hydrolysis, affording 3-(pentafluorophenyl)-cyclohexanone in good yields (eq 5).



(5)

B. Nucleophilic Additions to 3-Substituted Cyclohexanones. Methyllithium (low halide content) in hexane was added to the cyclohexanones at −78 °C in anhydrous ether or THF to produce the 1-methylcyclohexanols (eq 6). Additions of 3 equiv of MeLi (as above) and 1 equiv of CuI in dry diethyl ether at −78 °C (conditions known to favor equatorial addition of methyl) were also examined.[19]



(6)

Thiomethyl anions or related sulfur-stabilized carbanions add to ketones readily and irreversibly giving 2-hydroxysulfide derivatives, which can be converted to methyl alcohols by Raney nickel hydrogenolysis. Conversion of *N,S*-dimethyl-*S*-phenylsulfoximine[20] and thioanisole[21] to lithium reagents by BuLi in dry

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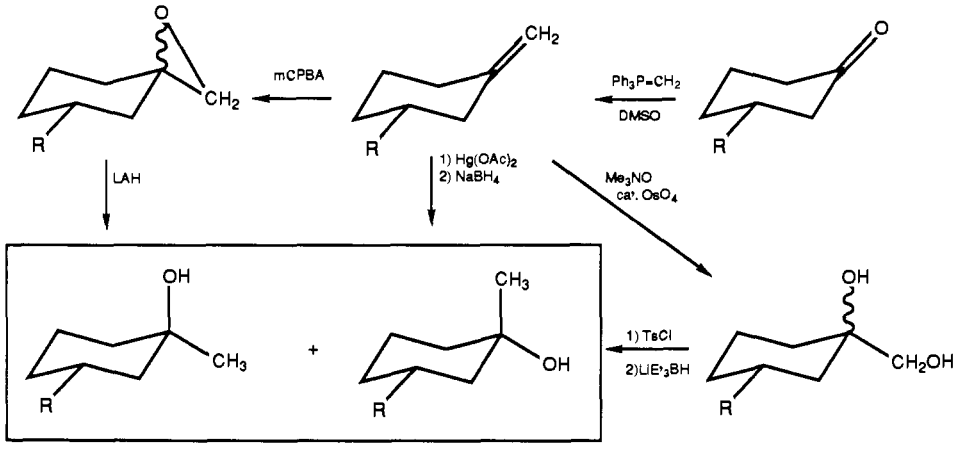
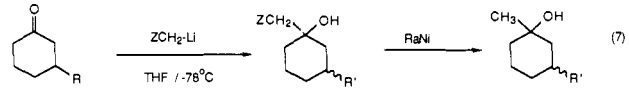
Scheme I

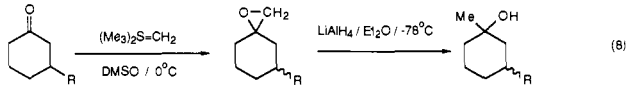


THF followed by addition of the ketone at −78 °C gave 2-hydroxysulfoximines and 2-hydroxy sulfides, respectively. The 2-hydroxysulfoximine adducts could not be readily analyzed directly due to the presence of four diastereomers. The 2-hydroxy sulfides were analyzed by HPLC. Both series of adducts were converted to methylcyclohexanols by Raney nickel (W-2) desulfurization (eq 7). The resulting methylcarbinols were analyzed by HPLC or GC.



(7)

Conversion of the cyclohexanones to epoxides was achieved by using Corey's dimethylsulfonium methylide in DMSO at 0 °C (eq 8).[22] The oxiranes were analyzed by HPLC or GC. Conversion of the oxiranes to methyl carbinols was effected by opening of the epoxide with $LiAlH_4$ in dry diethyl ether at −78 °C. Once again the tertiary alcohols were analyzed by HPLC or GC; the results were consistent with those obtained by direct analysis of the oxiranes.



(8)

C. Stereochemical Assignments. The methylcarbinols (eq 6–8) were separated by radial chromatography using hexane/ethyl acetate as eluant. The separated and purified diastereomers were individually characterized. Assignment of the stereochemistry of the methylcarbinols was effected by a number of methods. The diastereomers that eluted slower on silica gel were assigned to be the ones with the equatorial hydroxyls.[23] The opposite diastereomers with the axial hydroxyls showed increased propensities toward loss of water from the parent ion in mass spectrometry.[24] In ^{13}C NMR spectra the compounds assigned as axial hydroxyl diastereomers exhibited the quaternary carbinol carbon signal at higher fields compared to the equatorial hydroxyl diastereomer.[25] The results of these studies are summarized in Table I.

D. Preparation and Reactions of 3-Substituted Methylenecyclohexanes. Our series of cyclohexanones were converted to the methylenecyclohexanes by using Corey's procedure[26] for the Wittig reaction. The reagents chosen for study were those which gave products readily transformable to methylcarbonols (Scheme I) allowing facile comparison with the nucleophilic results and unambiguous structure assignments.

Reaction of the exocyclic methylenes with mercuric acetate in water effected oxymercuration of the alkene.[27] Sodium borohydride in 3 N NaOH effected reductive demercuration, giving the methylcarbinols. Oxymercuration occurs by attack of a nucleophile on an activated electrophilic complex. The electrophilic species is formed by a reversible complexation of the electrophile with the alkene. The complex is attacked by a solvent anti to the "onium" group and at the center more capable of stabilizing a carbonium ion. This final step occurs irreversibly. Oxidation of the methylenecyclohexanes with *m*-chloroperoxybenzoic acid (mCPBA) afforded the epoxides. The epoxides, per se, were

Table I. Percentage of Axial Attack in Reactions of C(3)-Substituted Cyclohexanones and Methylenecyclohexanes

Entry	R=	1 CH_3Li Ether -78°C	2 $Li_2(CH_3)_3Cu$ Ether -78°C	3 CH_3Li THF -78°C	4 $PhSCH_2Li$ THF -78°C	5 $PhS(O)(NMe)CH_2Li$ THF -78°C	6 $(CH_3)_2S{=}CH_2$ DMSO 0°C
a	$Si(CH_3)_3$	>5	2	22	>0	55	44
b	*t*-Bu	>9	3	27	>>	56	48
c	H[e]	2>[b]	6[b]		>7[c]; 20[d]		80[e]; 55[f]
d	C_6H_4-OMe-*p*	24	8	30	>6	66	44
e	C_6H_4-Me-*p*	23	8	30	19	65	48
f	C_6H_5	25	7	30	>5	65	45
g	C_6H_4-CF_3-*p*	26	>0	36	24	72	46
h	C_6F_5	34	2>	50	28	70	58
i	CF_3	50	42	58	53	83	69

Entry	R=	7 $Hg(OAc)_2$ H_2O 0°C	8 mCPBA CH_2Cl_2 0°C	9 OsO_4/Me_3NO THF/H_2O 25°C
j	$Si(CH_3)_3$	40	52	7
k	*t*-Bu	56[g]; 58[h]	60[i]	
l	H[a]	69[g]; 70[i]	69[k]	14[j]
m	C_6H_5	67	70	15
n	C_6H_4-CF_3-*p*	70	75	>4
o	CF_3	92		

[a] The ratios shown are those of diastereomeric products from 4-*tert*-butylcyclohexanone and 4-*tert*-butylmethylenecyclohexane. [b] Reference 19. [c] Reference 94c. [d] Reference 6. [e] Reference 22. [f] Davies, R.; Kluge, A. F.; Maddox, M. L.; Sparacino, M. L. *J. Org. Chem.* **1983**, *48*, 255. [g] Reference 27c. [h] Jasserand, D.; Granger, R.; Girard, J.-P.; Chapat, J.-P. *C. R. Acad. Sci. Ser. C* **1971**, *272C*, 1693. [i] Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron* **1976**, *32*, 1535. [j] Reference 99b. [k] Reference 99a. [l] Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628.

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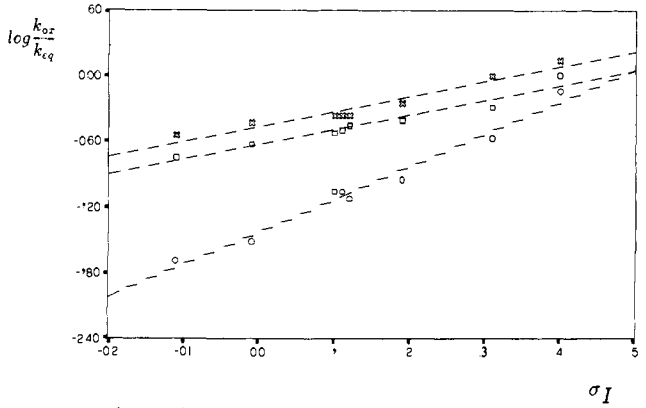


Figure 1. Plots of log k_{ax}/k_{eq} vs σ_I for methyllithium additions to C-(3)-substituted cyclohexanones (eq 6) and least-squares linear regression analysis: (□) CH_3Li/Et_2O **1ab**, **1d–i**, $r^2 = 0.952$, $P = 0.000$, $\hat{Y} = -0.634 + 1.359X$, SE $b_0 = 0.026$, SE $b_1 = 0.124$; (○) $LiCu(CH_3)_2/LiCH_3/Et_2O$ **2ab**, **2d–i**, $r^2 = 0.977$, $P = 0.000$, $\hat{Y} = -1.425 + 2.962X$, SE $b_0 = 0.038$, SE $b_1 = 0.186$; (×) CH_3Li/THF **3ab**, **3d–i**, $r^2 = 0.940$, $P = 0.000$, $\hat{Y} = -0.465 + 1.373X$, SE $b_0 = 0.029$, SE $b_1 = 0.142$.

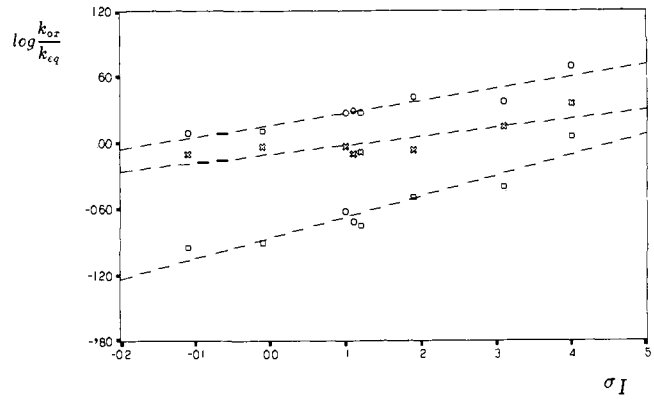


Figure 2. Plots of log k_{ax}/k_{eq} vs σ_I for additions of sulfur-stabilized carbanions to C(3)-substituted cyclohexanones (eq 7 and 8) and least-squares linear regression analysis: (○) $PhSCH_2Li$/THF **4ab**, **4d–i**, $r^2 = 0.894$, $P = 0.000$, $Y = -0.862 + 1.869X$, SE $b_0 = 0.054$, SE $b_1 = 0.262$; (□) $PhS(O)(NMe)CH_2Li$/THF **5ab**, **5d–i**, $r^2 = 0.873$, $P = 0.001$, $\hat{Y} = 0.160 + 1.086X$, SE $b_0 = 0.035$, SE $b_1 = 0.169$; (×) $(CH_3)_2S{=}CH_2$/DMSO **6ab**, **6d–i**, $r^2 = 0.667$, $P = 0.013$, $\hat{Y} = -0.104 + 0.794X$, SE, $b_0 = 0.047$, SE $b_1 = 0.229$.

analyzed by HPLC or GC when a clean separation was obtained. The mixtures of epoxides were converted into the methylcarbinols by reduction with lithium aluminum hydride. During the epoxidation reactions an interesting observation was made. Epoxidation of 3-(trimethylsilyl)methylenecyclohexane occurred readily with mCPBA in diethyl ether at −78 °C. When 3-phenylmethylenecyclohexane was treated under the same conditions, the reaction did not proceed and starting material was recovered. The rate enhancement by the trimethylsilyl group is indicative of increased alkene nucleophilicity. Along with rate enhancement, increased equatorial attack was observed.

Catalytic osmylation of the methylenecyclohexanes afforded mixtures of diastereomeric *vic*-diols.[28] Direct analyses of the mixtures by GC or HPLC were difficult due to the high polarity of the diols. The ratio of diastereomers could be determined by integration of the OCH_2 ^1H NMR signals. The diols were quantitatively converted into acetonides by treatment with 2,2-dimethoxypropane. GC or HPLC analysis of the reaction mixtures gave ratios consistent (within experimental error) with the ^1H NMR integration results. The assignments of the stereoisomers were assured by conversion of the diols to the known methylcarbinols. This was accomplished by a two-step procedure. The primary alcohol was selectively tosylated. The tosylate was removed by reduction with lithium triethylborohydride.

Discussion

A. Analysis of the Stereoselectivity Results. It has been pointed out earlier that at −78 °C a methyl group is almost as good a conformation biasing group as a *tert*-butyl substituent.[29] The two "smaller" substituents used in our investigation, $Si(CH_3)_3$ and CF_3, have significantly higher conformational energies than a methyl group.[30] In the presence of a β-carbonyl group or a methylene group, these values might slightly decrease; replacement of the β sp^3 carbon by sp^2 carbon atom was reported to lower conformational energies of a number of substituents.[31,32] However, the effect is actually rather small for a methyl group and possibly negligible for an isopropyl group;[31d] the same seems to be true for chlorine, bromine, and a methylthio group.[32d] Therefore, we assume for the purpose of interpretation of our data that all the cyclohexanones and methylenecyclohexanes investigated are conformationally homogeneous at −78 °C and, most likely, at room temperature as well.

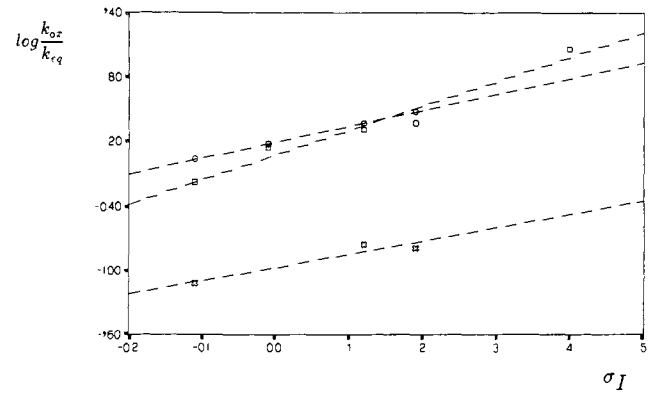


Figure 3. Plots of log k_{ax}/k_{eq} vs σ_I for the oxidation reactions of C-(3)-substituted methylenecyclohexanes (Scheme I) and least-squares linear regression analysis: (○) $Hg(OAc)_2/H_2O$/THF **7jk**, **7m–o**, $r^2 = 0.958$, $P = 0.004$, $\hat{Y} = 0.071 + 2.276X$, SE $b_0 = 0.058$, SE $b_1 = 0.274$; (□) mCPBA/CH_2Cl_2 **8jk**, **8mn**, $r^2 = 1.000$, $P = 0.000$, $\hat{Y} = 0.194 + 1.473X$, SE, $b_0 = 0.002$, SE $b_1 = 0.018$; (×) OsO_4–Me_3NO/THF–H_2O **9j**, **9mn**, $r^2 = 0.906$, $P = 0.198$, $\hat{Y} = -0.971 + 1.239X$, SE $b_0 = 0.058$, SE $b_1 = 0.398$.

The results are presented in Table I, where the C-3 groups are listed according to Charton's preferred σ_I values.[33] The ratios of diastereomeric products for 4-*tert*-butylcyclohexanone and 4-*tert*-butylmethylcyclohexane are used as the surrogate reference points for the hypothetical 3-H substituted compounds.

It can be seen that, in general, these literature data very closely overlap the data for the 3-phenyl entries **1f–6f** and **7m–9m**, Table I. In every case, further examination reveals a consistent pattern of the C-3 substituent effect. As compared to 3-H and 3-phenyl groups, the electron-releasing 3-*tert*-butyl and 3-trimethylsilyl groups decrease the percentage of the axial attack. The electron-withdrawing $C_6H_4CF_3$, C_6F_5, and CF_3 groups always increase the yield of the axial attack.

(28) Van Rheenan, V.; Kelly, R. C.; Chi, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(29) Hutchins, R. O. *J. Org. Chem.* **1977**, *42*, 920.
(30) Della, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 5221. Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153.
(31) (a) Klyne, W. *Experientia* **1956**, *12*, 119. (b) Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 2201. (c) Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414. (d) Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 777.
(32) (a) Lambert, J. B.; Clikeman, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 4203. (b) Lambert, J. B.; Taba, K. M. *J. Am. Chem. Soc.* **1981**, *103*, 5828. (c) Bergesen, K.; Carden, B. M.; Cook, M. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1001. (d) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173. (e) Bowen, J. P.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 1830.
(33) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119. σ_I for 4-$F_3CC_6H_4$ was 0.19 calculated from eq 21 of Table 45 in this reference: M. Charton, private communication. The available range of the σ_I constants is ~1.2, for instance: CO_2^-, −0.19; and Me_3N^+, 1.07. Entries **4–6** are ordered according to the increasing electronegativity of the sulfur substituent at the methyl carbanion: PhS, 0.31, −0.24; $MeSO_2$, 0.59, 0.11; Me_2S^+, 0.90, 0.24; σ_I and σ_R, respectively.

Plots of the log k_{ax}/k_{eq} vs σ_1 constants (see Figures 1–3) reveal excellent or highly significant ($P < 0.1\%$) linear corelations for entries **1–5**, **7**, and **8**, Table I; for the entry **9** the number of points is too low to produce a significant correlation. The intercept values (b_0 in the linear regression equations $\hat{Y} = b_0 + b_1X$ in Figures 1–3) must depend both on the steric and stereoelectronic contributions. The slopes of the least-squares regression lines (b_1, Figures 1–3) reflect sensitivity of the k_{ax}/k_{eq} ratio in a given reaction to electronegativity of C-3 substitution.

The most striking observation is that the b_1 values do not seem to be related to the mechanism of addition to the double bond, that is to the polarization of the transition state. When the electronegativity of the C-3 group increases, relative yield of the axial approach increased in both nucleophile capture reactions (entries **1–7**), and electrophile capture reactions (entries **8** and **9**). In spite of the variation in the slope magnitudes, b_1 coefficients are actually very similar in reactions of nonstabilized and stabilized carbanions, as well as neutral reagents, cf. entries **1**, **3**, **5**, and **8** (Table I).

How does this effect arise? The slope cofficient b_1 corresponds to the difference $\Delta\rho$ of the ρ coefficients (for C-3 substitution) of the axial and equatorial reactions.

$$\Delta\rho = \rho_{(ax)} - \rho_{(eq)} > 0$$

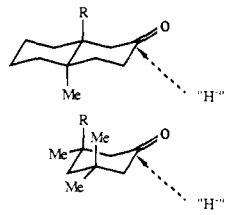
In the case of *nucleophilic* additions to cyclohexanones, $\rho_{(ax)}$ must be greater than $\rho_{(eq)}$

$$\rho_{(ax)} > \rho_{(eq)}$$

because electron-withdrawing substitution, as expected and experimentally observed,[34] accelerates such reactions, that is ρ is in general positive. Thus, either there is an extra acceleration of the axial attack or the inductive acceleration of the equatorial attack is not as effective. One of the most obvious answers is that the axial attack is extra accelerated by electrostatic (dipole–dipole) stabilization of the transition state. However, we would expect in such a case that the slopes of regression lines be very different for nucleophile and electrophilic additions. In other words, this proposition does not explain the fact that the same effect is observed in reactions of methylenecyclohexanes. Another reason for an extra acceleration of the axial attack could perhaps be a conformational effect of the C-3 substituents leading to a "flattening" of the ring and a concomitant decrease in steric hindrance. To the best of our knowledge, this possibility has never been raised in the discussions of conformational effects in cyclohexyl derivatives, and it does not seem that the distortion could be significant. In any event, however, we would then expect *all the slopes to be quite similar*. This is not the case. Thus, the phenomenon does not seem to be readily explicable on the theory that the axial attack is facilitated by the C-3 substitution above the level of the inductive acceleration. In contrast, the counterintuitive proposition that the inductive acceleration is diminished or even obliterated in the case of the equatorial attack receives, surprisingly, a considerable support in the scattered literature data. The selected examples from four independent studies[1a,7a,35] are presented in Figure 4.

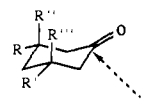
Figure 4a shows a decrease of the absolute rate constants for equatorial delivery of $LiAlH(O\text{-}t\text{-}Bu)_3$ reduction when the axial C-3 hydrogen atom is replaced by fluorine in two different ketons.[1a,35a] The change of steric hindrance to the axial attack does not allow here comparison of the axial rate constants. Figure 4b shows a unique anomaly in regard to the effect of the alkyl substitution on the rates of cyclohexanone reductions. Atachment of the successive C-3 and C-5 methyl groups increases the relative

(a) Rates of equatorial attack by $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF at 25 °C.[1a,37a]



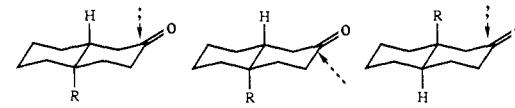
	$k_{eq} \times 10^3$ mol^{-1}sec^{-1}
R = H	140.0
R = F	24.0
R = Cl	4.5
R = H	11.5 ± 1
R = F	5.3 ± 0.4

(b) Relative rates of attack by $LiAlH_4$ in Et_2O at 25 °C.[7a]



	k_{rel}
R = R' = R'' = R''' = H	(1.0)
R = R' = Me; R'' = R''' = H	1.8
R = R' = R'' = Me; R''' = H	4.0
R = R' = R'' = R''' = Me	3.7

(c) Relative rates of addition of various nucleophiles to *trans*-2-decalones.[37b]



R =	H	Me	$COOEt$	H	Me	$COOEt$	$COOEt$
$MeMgI/Et_2O$	(1.0)	0.9	1.8	2.3	1.5	1.8	3.4
MeMgI/benzene	(1.0)	0.8	2.0	2.5	1.6	2.0	8.7
Me_3Al (1:1)/benzene	(1.0)	0.4	0.7	3.7	1.3	2.0	2.1
MeLi, -78 °C/Et_2O	(1.0)	1.2	3.2	3.3	3.1	1.3	3.6
Me_2CuLi/Et_2O	(1.0)	0.9	2.5	8.3	5.4	3.7	5.4

Figure 4. Kinetic data on nucleophilic additions to various cyclohexanones and *trans*-2-decalones.

rate constant for the equatorial attack.[7a] The examples presented in Figure 4c enable us to examine the effect of an electron-withdrawing group (C-4 carboxylate) on the axial and equatorial rate constants of organometallic additions.[35b] The comparison of the data in the first and third columns (along the lines and not down the columns, i.e., for each reagent separately) shows that such a group does indeed accelerate the axial addition (except perhaps in the case of trimethylaluminum). However, the data on the fourth and the sixth columns reveal that the same group *slows down* the equatorial addition in every case. The effect of the C-3 carboxylate on the rate of equatorial addition (compare the fourth and seventh columns) is erratic. Thus, these four studies show that $\rho_{(eq)}$ (for C-3 or C-4 substitution) can be *negative*, i.e., electron-withdrawing groups that invariably accelerate axial attack can sometimes *decelerate* equatorial attack!

In the case of *electrophilic* additions, where $\rho < 0$, that is

$$|\rho_{(eq)}| > |\rho_{(ax)}|$$

the effect can also arise due to an extra deceleration of the equatorial attack. There is not sufficient kinetic data to evaluate this possibility.[36]

From the practical point of view, it is important to notice that given the range of available σ_1 values[33] and the range of observed slope values expressed in kilocalories per mole (up to 4.2 kcal·mol^{-1}, entry **2**), our examples suggest that the remote substitution might change the diastereomer ratio in reactions of cyclohexane-based systems by up to 4 orders of magnitude. The actual increments of the $\Delta G_{(eq)}^{\ddagger} - \Delta G_{(ax)}^{\ddagger}$ difference (between the Me_3Si and CF_3 groups, i.e., half of the σ_1 scale is covered) range from ~2.2 kcal·mol^{-1} (entry **2**) to ~0.6–0.8 kcal·mol^{-1} (entries **5** and **6**). It is worthwhile to remember that the fundamental distinction between the axial and equatorial positions with regard to chemical reactivity was inferred from the results of the reactions such as

(34) Smith, G. G.; Bayer, R. P. *Tetrahedron* **1962**, *18*, 323. Perry, J. A.; Warren, K. D. *J. Chem. Soc.* **1965**, 4049. Bowden, K.; Hardy, M. *Tetrahedron* **1966**, *22*, 1169. Ayres, D. C.; Sawdaye, R.; Kirk, D. N. *J. Chem. Soc. B* **1970**, 1133. Wiegers, K. E.; Smith, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 1480. The effect of alkyl substitution is opposite: e.g., ref 7cd; Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

(35) (a) Agami, C.; Kazakos, A.; Levisalles, J.; Sevin, A. *Tetrahedron* **1980**, *36*, 2977. (b) Di Maio, G.; Li, W.; Migneco, L.; Vecchi, E. *Tetrahedron* **1986**, *42*, 4837.

(36) To the best of our knowledge, the only available kinetic study of epoxidation of methylenecyclohexanes deals with C(2)-substituted compounds: Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549.

sodium reduction of steroidal ketones in alcoholic solvents, bromine additions to steroidal olefins, oxidation and esterification of cyclohexanols, and hydrolysis of esters and from the results of alcohol and dibromide equilibrations.[37] The differences in the corresponding rate constants or equilibrium constants are very rarely greater than 10-fold.[37b] Thus, in this context, the observed effects are indeed remarkable.

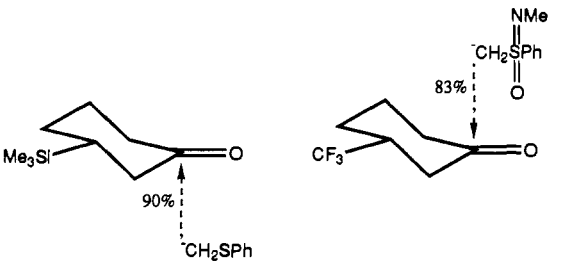
The observed effects of C-3 substitution can be compared with the effect of electronegative substitution of the nucleophile. Entries **4–6** (Table I) represent a series of nucleophilic additions where the carbanion is substituted by an increasingly electronegative group (see Figure 2).[33] There seems to be two consequences of the increase in electronegativity of this substitution. The relative yield of the axial attack increases; the intercepts (b_0) shift from -0.862 ± 0.054 for **4** to 0.160 ± 0.035 for **5** and -0.104 ± 0.047 for **6** (Figures 1 and 2). Thus, regardless of the method of increasing electronegativity of the sulfur substituent, the ratio of diastereoisomers changes in the same direction; a difference in steric demand of the two reagents might be responsible for the lack of a strict correlation. The second effect of electron-withdrawing substitution of the nucleophile is a decrease of the sensitivity of the k_{ax}/k_{eq} ratio to C-3 substitution; the slope values (b_1) are lowered, $\Delta\rho = 1.869 \pm 0.262$ for **4**, 1.086 ± 0.169 for **5**, and 0.794 ± 0.229 for **6**, that is in the sequence of increasing electronegativity of the sulfur substituent (Figure 2)!

The effect of the reagent structure on stereochemistry of nucleophilic additions to cyclohexanones is often interpreted in terms of the change in the steric demand. Obviously, attachment of an additional group should increase the bulk of a nucleophile. At the same time, stabilization of the anion might reduce solvation and self-association of the reagent and thereby effectively decreases its steric demand.[38] In addition, a change in the transition-state geometry ("tightness", angle of attack, manner of metal ion participation) might simply change the sensitivity of the reagent to steric hindrance. It does not seem, however, that any purely steric effect can explain the observed phenomenon because the increase in the intercept value b_0 is clearly coupled with the decrease in the slope magnitude b_1. The decrease in $\Delta\rho$ upon the electronegative substitution of the reagent means that the effect of C-3 substitution that depresses $\rho_{(eq)}$ became relatively less important, i.e., electronegative substitution of the reagent must have increased the absolute magnitude of the stereoelectronic effect that is being modified by C-3 substitution. In other words, stereoelectronic control apparently increases if the transition state becomes more electron deficient; this would also explain the increase in the intercept values.

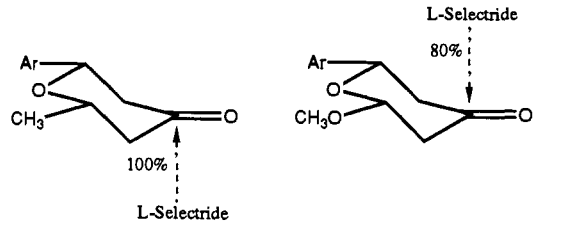
The obvious importance of the observation of the decrease in $\Delta\rho$ raises the question of significance and reproducibility of the b_1 values. It is then somewhat reassuring to compare the results of the two MeLi additions, in Et_2O and THF, entries **1** and **3**, which show that our methodology seems to be quite reliable in this respect.

It is interesting to note that the combination of the two substitution effects (C-3 and the nucleophile) results in a complete reversal of the stereochemical preferences in carbanion additions to cyclohexanones, cf. entries **4a**, **5a**, and **5i**. $PhSCH_2Li$ adds to 3-(trimethylsilyl)cyclohexanone from the less hindered equatorial side in ratio 90/10, cf. **4a**. The reagent $PhS(O)(NMe)CH_2Li$, wherein two electron-withdrawing groups are attached to the sulfur atom of the nucleophile so that both lone pairs of electrons are bonded, attacks the same ketone with a slight preference for the axial side, 45/55 (entry **5a**). Finally, when in addition, the $SiMe_3$ group is exchanged for the CF_3 group, a strong preference (17/83) for the more hindered axial approach results (entry **5i**) (Table I and Scheme II).

Scheme II



Scheme III



It is also worthwhile to notice the importance of our observations from the heuristic point of view. For example, examination of the sensitivity of stereoselection to remote substitution seems to open a fascinating way to study solvent and solute effects on nucleophilic additions to cyclohexanones. It can be seen that a change of solvent, cf. entries **1a–i** and **3a–i** (Table I), does not significantly affect stereoelectronic control in methyllithium addition since the principal result is a small shift of the intercept, possibly due to an increase in steric demand. In contrast, methyllithiumcuprate addition (entries **2a–i**) seems to proceed through an entirely different transition state, from the point of view of electronic demand. The high equatorial selectivity of this reagent would usually be interpreted in terms of the increase in steric bulk. The results for the entries **4–6** suggest that the transition state for the methyllithiumcuprate addition is also significantly less electron-deficient!

Prior to the initiation of this study, very few data on the effects of electron-releasing or -withdrawing C-3 and C-4 substitution of cyclohexanones on stereoselectivity of their reactions were available (and almost none in the case of methylenecyclohexane reactions).[39] The three most systematic studies of the effects of such substitution which pioneered this approach are, unfortunately, flawed for different reasons.[40] Recently, however, this situation has changed with the appearance of several already mentioned reports concerning the effects of electron-withdrawing groups. First, Danishefsky and Langer observed a complete reversal of the usual preference of L- and K-Selectrides for the less hindered equatorial approach to the six-membered cyclic ketones,[3] apparently as a result of the replacement of a methyl group by a methoxy group (Scheme III). Second, le Noble et al. have shown

(37) (a) Barton, D. H. R. *Experientia* **1950**, *6*, 316. (b) For instance, the axial cyclohexanols are oxidized 3–6 times faster and esterified with anhydrides 2.5–3.8 times slower than the equatorial cyclohexanols; the axial esters are hydrolyzed 2.5 (*p*-nitrobenzoates) and 6.7 (acetates) times slower than the equatorial ones; the axial tosylates are displaced by nucleophiles 2.3–4.0 times faster, and the formation of diaxial dihalogenides with cholest-2-ene is 2.6 (Cl_2) and 8.9 (Br_2) times faster than the formation of diequatorial adducts. Data from: Eliel, E. L. et al. *Conformational Analysis*; J. Wiley & Sons: New York, London, Sydney, 1965; pp 73ff.

(38) However, studies of selectivity of $LiAl(OR)_3H$ (Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890) and methylmagnesium additions (Jones, P. R.; Goller, E. J.; Kaufmann, W. J. *J. Org. Chem.* **1969**, *34*, 3566) as a function of concentration demonstrated that self-association of the reagent does not decrease, as one would expect, the yield of the axial attack.

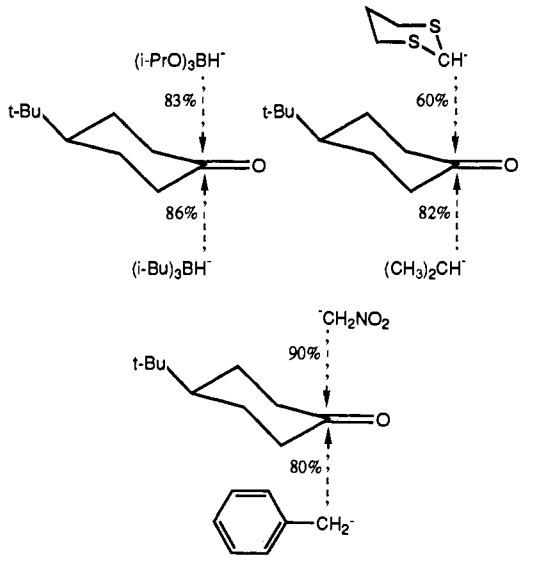
(39) Agami, C.; Fadlallah, M.; Kazakos, A.; Levisalles, J. *Tetrahedron* **1979**, *35*, 969. Akhrem, A. A.; Kamernitskii, A. V.; Prokhoda, A. M. *Zh. Org. Khim.* **1967**, *3*, 50, 57. Monson, R. S.; Przybycien, D.; Baraze, A. *J. Org. Chem.* **1970**, *35*, 1700. Richer, J.-P.; Perelman, D.; Baskevitch, N. *Tetrahedron Lett.* **1975**, 2627. Aycard, J.-P.; Lafrance, R.; Boyer, B. *Can. J. Chem.* **1979**, *57*, 2823. Wickham, G.; Olszowy, H. A.; Kitching, W. *J. Org. Chem.* **1982**, *47*, 3788. Ochiai, M.; Ukita, T.; Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 637; **1984**, 1007. Rothberg, I.; Sundoro, B.; Balanikas, G.; Kirsch, S. *J. Org. Chem.* **1983**, *48*, 4345. Katvalyan, G. T.; Semenova, N. A.; Mistryukov, E. A. *Izv. Akad. Nauk. SSSR* **1976**, *129*. Katvalyan, G. T.; Mistryukov, E. A. *Ibid.* **1976**, 220; *Ibid.* **1976**, 1335. Lantvoev, V. I. *Zh. Org. Khim.* **1976**, *12*, 2361; *Ibid.* **1977**, *13*, 88; *Ibid.* **1980**, *16*, 1659.

(40) Reference lab: C-3 substituents are axial. Reference 1c: the use of 2-*tert*-butyl group to lock cyclohexanone conformation has been questioned, cf. references in ref 32. Reference 1d: wrong assignment of the diastereomer structures. Reference 1e: substrates are conformationally flexible.

that stereoselectivity of $NaBH_4$ reductions of para-substituted 5-phenyl-2-adamantanones correlates with Hammett constants of the para substituents and found very large such effects in reactions of nucleophile capture by 2-adamantyl cations.[4a] Subsequently, le Noble's group reported the same effects of 5-fluoro substitution on stereoselectivity of 2-methyleneadamantane reactions,[4b] thermal and photocycloadditions of thioadamantanone,[4d] and extended their examination of C-5 substituents to electropositive tin and silicon groups.[4f] Thus, our results consolidate the recently emerging picture of the effects of electron-withdrawing and -releasing groups of the inducing center on the course of the π-facial diastereoselection.

As far as the effects of electronic modifications of the reagents are concerned, the situation is somewhat different. Numerous data on the stereochemistry of hydride,[7fg,41] ylide,[6,42] enolate,[43] alkyl metal,[44] and allyl metal[45] additions to cyclohexanones, as well as on the stereochemistry of catalytic hydrogenations of methylenecyclohexanes,[46] oxidation of thianes,[47] and alkylation of piperidines by methylating and benzylating agents[48] are available. In each case, a full spectrum of stereoselectivities has been found, which suggests that it would be difficult to rationalize the results without invoking stereoselectronic control in determination of stereochemistry of these reactions. However, the diversity of the reagents and reaction conditions, and in some cases, the lack of even rudimentary knowledge of the rate-limiting step and the transition-state structure, make it difficult to interpret the wealth of data. As a result, even though a number of examples suggested a relationship between the stereoselectivity and the electronegativity of the substitution of the incipient bond, no such link was generally recognized. It has been pointed out that the yield of axial attack of substituted carbanions appears to qualitatively correlate with the Hammett constants of the substituents (Table V in ref 5). A few particularly interesting examples of the effect of electronegative substitution of the nucleophile on stereoselection are shown in Scheme IV.[49] To the extent that one agrees on a discernible trend in these data,[5,49] the results for the entries **4–6** are consistent with the literature. It should be noted, however, that there is no significant effect of para substituents on stereoselectivity of phenylmagnesium reagent additions to 5-fluoro-2-adamantanone.[4e] No evidence is available on the effect of electronegative substitution of the electrophile reagents on the k_{ax}/k_{eq} ratios in reactions of methylenecyclohexanes.[50]

Scheme IV



Thus, the following major points can be made on the basis of the data reported here:

First, the effect of remote substitution of the ring bonds on stereoselectivity is the same in nucleophilic and electrophilic additions to trigonal carbon atoms.

Second, dependence of stereoselectivity (log k_{ax}/k_{eq}) on electronegativity of C-3 substitution is linear and $\Delta\rho > 0$; that is, such a substitution increases the yield of the axial approach. The

(41) For the selected examples, see the following. (a) Alkoxy and alkyl aluminum hydrides and borohydrides: References 7a and 38. Heinsohn, G. E.; Ashby, E. C. *J. Org. Chem.* **1973**, *38*, 4232. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. Brown, H. C.; Cha, J. S.; Nazer, B. *Inorg. Chem.* **1984**, *23*, 2929. Brown, H. C.; Cha, J. S.; Nazer, B.; Kim, S. C.; Krishnamurthy, S.; Brown, C. A. *J. Org. Chem.* **1984**, *49*, 885. Kim, S.; Moon, Y. C.; Ahn, K. H. *J. Org. Chem.* **1982**, *47*, 3311. Capka, M.; Chvalovsky, V.; Kochloeff, K.; Kraus, K. *Collect. Czech. Chem. Commun.* **1969**, *34*, 118. (b) Alkoxy and alkylamino magnesium hydrides: Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1560, 1564. Ashby, E. C.; Noding, S. A.; Goel, A. B. *J. Org. Chem.* **1980**, *45*, 1028. (c) Silanes: Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3821. Doyle, M. P.; McOsker, C. C.; Ball, N.; West, C. T. *J. Org. Chem.* **1977**, *42*, 1922. (d) Tin hydrides: Kuivila, H. G.; Beumel, O. F., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1246. (e) Boranes: Klein, J.; Dunkelblum, E. *Isr. J. Chem.* **1967**, *5*, 181.

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(50) However, electronegative substitution of an alkene appears to increase the k_{ax}/k_{eq} ratio in reactions of addition with the 4-*tert*-butylcyclohexyl radical: Giese, B. *Angew. Chem.*, in press, cf. Table IV.

variation in b_1 values appears difficult to explain on the basis of theories invoking extra facilitation of the axial attack by dipole–dipole interactions or steric and conformational effects. It suggests that the phenomenon arises dur to a stereoelectronic effect which, according to some literature data, might result in depressing of the inductive acceleration of the equatorial attack.

Third, electronegative substitution of the reagent also increases the yield of the axial approach in nucleophilic additions to cyclohexanones (raising the intercept b_0) and at the same time decreases the sensitivity of the product ratio to the change in electronegativity of the remote substitution (lowering the slope b_1). This leads to the conclusion that stereoelectronic control is enhanced in the electron-deficient transition states. Any purely steric effect related to the changes in solvation, association, metal ion participation, or transition-state geometry would be expected to affect only the intercepts of the regression lines.

The implicit assumption here, common to all the attempts at rationalization of the stereochemistry of reactions in cyclohexane-based systems, is that the change in the diastereoisomer ratio reflects the change in the enthalpy of activation. In spite of the very large negative entropies of activation for different nucleophilic additions to carbonyl groups, this assumption is probably correct.[7f] The similarity of the effect of C-3 substitution on stereochemistry of organometallic additions in THF and of peracid epoxidation in methylene chloride offers an additional reassurance that the change in the entropy of solvation of the transition state cannot be the major factor responsible for the shift of stereoselectivity.

B. Models of Stereoelectronic Effects in π-Facial Diastereoselection. The results described here constitute a challenging test of the theories of stereoselectronic effects in π-facial diastereoselection. Over the last two decades, several approaches to the problem of the nature of nonsteric factors in asymmetric introduction evolved within the framework of the PMO approximation.

The first approach, focusing on the analysis of the ground-state properties of the substrates of π-facial diastereoselection, was advanced by Fukui. Developing his FMO treatment of stereoselection,[51] Fukui et al. have shown that the 2p electron density is not distributed symmetrically about the sp^2 plane of a trigonal atom that is placed in an asymmetric environment; such nonequivalent orbital extension has been found in the 2-norbornyl radical,[51b] norbornene,[51c] 5-substituted cyclopentadienes,[51d] and cyclobutenes,[51d] while Anh et al. found nonequivalent distribution of π-electron density of the carbonyl group in chiral aldehydes and ketones.[52] It has been proposed that reactions such as electrophilic additions to alkenes or cycloadditions of electron-poor dienophiles, that is, reactions controlled by the interaction of the electrophile's LUMO with the chiral substrate's HOMO, will preferentially occur on the sp^2 face where the HOMO is more extended. Conversely, the preference to attack this face in reactions assumed to be controlled by the interaction with the chiral substrate's LUMO, such as nucleophilic additions to alkenes, would be reduced or even reversed; as a corollary, a reversal of electron demand of cycloaddition educts could be expected to result in a reversal of the sense of induction.[51d]

Subsequently, similar analyses were employed in the interpretation of stereochemistry of reactions in cyclohexane-based systems (cyclohexanones, methylenecyclohexanes, thianes) with one trigonal atom in the ring,[53a] 4-substituted cyclohexenones and 3-substituted cyclohexenone enolates,[54a] of stereoselection in reactions of vinylogous displacement and elimination[54b] and in reactions of cyclohexenes,[53b] of the effects of remote substituents on stereochemistry of hydride reduction of adamantanones[1d] and of the stereochemistry of cycloadditions to dienes grafted onto the bicyclo[2.2.1]heptane skeleton.[55-58] In the attempt to demonstrate nonequivalent distribution of π-electron density in asymmetric environment by experimental methods, Paquette et al. undertook a systematic examination of the spectroscopic evidence and face-selective complexation of Lewis acids.[59]

In spite of the different views on the question of the origin of nonequivalent orbital extension, all the above enumerated studies accepted the basic premise that it is possible to predict the sense of stereoselection by extrapolation of the ground-state distortion of the symmetry of the π-orbital system imposed by its dissymetric environment.

More recently, however, other aspects of the ground-state perturbation of the π system gained attention. Beside the symmetry with respect to the nodal planes, the energy of the HOMO and LUMO orbitals was pointed out to vary depending on the asymmetric environment. A wealth of experimental evidence, going back to Corey's early observations on conformational equilibria and spectra of α-halo ketones,[60] indicates that an electron acceptor bond aligned with the π system lowers the energy of the HOMO and LUMO orbitals, thus enhancing electrophilicity and decreasing nucleophilicity of the π system. This effect was invoked by Eschenmoser to explain relatively high reactivity of *N*-furanosyl nitrones toward nonactivated alkenes,[61] and by Anh et al. to explain stereoselection in nucleophilic additions to carbonyl compounds.[62] Subsequently, this effect was suggested to be the basis of stereoselection in reactions of allyl alcohols and ethers with osmium tetroxide,[63] nitrile oxides,[64] peroxides (Sharpless epoxidation),[65] and dienes.[66] In a similar vein, interaction with an anti acceptor bond was also invoked to explain stereoelectronic control in cuprate additions to allylic or activated double bonds[67,68] and in dipolar addition to 3,4-disubstituted cyclobutenes.[69] The opposite effect due to the presence of an electron donor bond was proposed to explain selection of reactive conformations in alkylations of chiral β-stannyl and β-silyl ester enolates.[2b-d]

In the meantime, development of the computational methods was taken advantage of to step beyond the FMO approximation and probe the differences in the total electrostatic interaction energy on the diastereofaces of a perturbed π system. Thus, reactivity of two faces of a nonplanar enamine toward electrophiles was modeled by using the proton as a probe,[70] in studies related

(51) (a) Fukui, K. *Theory of Orientation and Stereoselection*; Springer Verlag: Heidelberg, 1979. (b) Fujimoto, H.; Fukui, K. *Tetrahedron Lett.* **1966**, 5551. (c) Fukui, K.; Inagaki, S. *Chem. Lett.* **1974**, 509. (d) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054.

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(61) Cf. footnote 9, p 1280, in: Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273.

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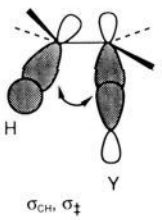
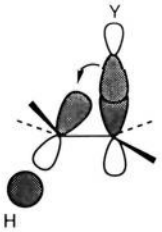
Chart I



σ_{CH}, $\sigma_{\ddagger}$

Chart II



$\sigma_{\ddagger}$, σ^*_{CH}

Chart III

σ_{CH}, $\sigma^*_{\ddagger}$

to Eschenmoser's and Dunitz's investigation of the mechanism of aldol catalysis by chiral amines.[71] The hydride probe was used in calculations of the electrostatic potential on the two faces of cyclohexanone complexed by a lithium cation,[72] both hydride and proton probes were used on bicyclo[2.2.1]heptene,[73] and most recently, Hehre and co-workers reported use of this method in an extensive effort to model stereoselection in electrophilic and nucleophilic additions to chiral alkenes using proton and hydride probes,[74] while Smith and co-workers interpreted, on this basis, stereoselectivity of cuprate additions to cyclopentenones.[68]

Finally, nonequivalent orbital extension, induced by an asymmetric environment of the sp^2 atom, was shown by Fukui and co-workers to be accompanied by an out-of-plane distortion (partial pyramidalization) of this atom.[51b] Such distortions were considered by several authors to be an important factor, aiding or at least paralleling stereoselection. Examples include the discussion of stereochemistry of nucleophilic additions to cyclohexanones,[75] a general treatment of alkene chemistry,[76a] discussions of the mechanism of amide proteolysis[76b] and of the exo attack preference in reactions of bicyclo[2.2.1]heptene derivatives,[77] the explanation of stereoselectivity of cycloadditions to cyclobutene derivatives[78] and, most recently, an interpretation of stereoselection of cuprate additions to chiral 2,6-disubstituted 1,3-dioxin-4-ones.[79] In the last case the concept of out-of-plane distortions of the substrate ring has been extended into a general principle relating partial pyramidalization of the incipient center and the sense of π-facial diastereoselection.

The second approach developed over the last two decades abandons altogether the basic premise of all the propositions enumerated above and focuses instead on the differences in relative stabilities of the diastereomeric transition states resulting from interactions of the incipient bond with the environment of the two nonequivalent faces of a trigonal center. The principal electronic factor differentiating two faces of an sp^2 atom placed in an asymmetric environment is assumed to be the nature of the σ bonds interacting with the incipient bond. The problem is thus reduced to the problem of torsional interactions, that is, interactions of the single bonds that give rise to torsional barriers. There are, in the framework of the one-electron MO theory, three kinds of such interactions for a given set of two vicinal σ bonds, σ_1 and σ_2: (1) four-electron interaction (σ_1, σ_2), which is destabilizing (repulsive interaction of two occupied orbitals, torsional strain); (2) two-electron interaction (σ_1, σ_2^*), which is stabilizing (charge-transfer interaction of an occupied σ_1 and a vacant σ_2^* orbital); (3) the alternative two-electron stabilizing interaction (σ_1^*, σ_2).[80]

Given that $\sigma_1 = \sigma_{\ddagger}$, i.e., the incipient bond, and $\sigma_2 = \sigma_{CH}$, each of these interactions was invoked in successive attempts to formulate models of stereoelectronic effects in π-facial diastereoselection (see Charts I–III). The first to introduce the concept of the incipient bond and its torsional interactions were Schleyer[81] and Felkin et al.[82] (Chart I).

It was proposed that in spite of only partial bonding, the incipient bond suffers torsional repulsion in case of eclipsing vicinal σ bonds almost as severe as a fully formed bond, in particular in reactions where transition-state geometry or molecular geometry enforce such elipsing.[82] The proposition has acquired widely accepted status as the textbook explanation of the stereochemistry of nucleophilic additions to cyclohexanones.[83] It was corroborated by structural studies of cyclohexanones and heterocyclohexanones[84] and by the successes of force field models of stereoselection in nucleophilic additions to alicyclic and acyclic carbonyl compounds.[85,86] More recently, the effect of torsional strain was postulated to be a major effect determining stereoselection in acyclic systems in general, as well as in cycloadditions in the isodicyclopentadienyl systems.[87]

Anh et al.[62] introduced the concept of stabilizing interactions of the incipient bond with the vicinal σ bonds, proposing that the

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high-lying σ orbital of the incipient bond delocalizes in a hyperconjugative interaction into their vacant σ^* orbitals (Chart II).

This proposition was supported by ab initio calculations, which showed that the approach of a hydride ion to a carbonyl group is increasingly stabilized by an antiperiplanar σ bond in the order CH < CC < CCl, that is, in the order of lowering σ^*-orbital energy.[88] In the view of many authors, this proposition supplemented the Felkin model and one often encounters references to the Felkin–Anh model, i.e., the model of 1,2 asymmetric induction in nucleophilic additions to acyclic chiral aldehydes and ketones, where the polar ligand of lowest σ orbital, and not the ligand of greatest steric bulk, is considered as the "large" ligand.[89] Recently, the effect of replacement of the quasi-axial CH bonds by CC bonds on the rate of ^{18}O exchange was interpreted as evidence that the interaction of this transition state with one σ_{CC}^* is worth 1.9 kcal mol^{-1} more than the one with a single σ_{CH}^*.[90]

The alternative stabilizing interaction of the incipient bond with neighboring *occupied* orbitals was postulated as an overriding stereoelectronic factor in π-facial diastereoselection by Cieplak[5] (Chart III).

Such an interaction might dominate transition-state interactions with the vicinal bonds, it is argued, even in the case of nucleophilic additions to carbonyl, because the incipient bond, as an elongated and polarized σ bond, is inherently electron deficient. This proposition attempts to generalize the concepts of the kinetic anomeric effect[91] and the kinetic α effect[92,93] and, as pointed out by le Noble, extends the concept of σ assistance in formation of carbonium ions to the reverse process of nucleophile capture.

As we have mentioned before, a number of recently reported stereoselectivity phenomena in both nucleophilic additions to carbonyls and electrophilic additions to olefins were interpreted on the basis of this proposition.[3,4,13,94] The underlying concept of transition-state stabilization by two-electron interactions of the σ^* orbital of the newly formed bond (σ_+^*) is supported by ab initio calculations.[93]

C. Evaluation of the Currently Discussed Models. How do all these hypotheses and models fare in the light of our and other recently published results concerning stereochemistry of cyclohexanone and methylenecyclohexane reactions?

The classical attempt to apply Fukui's hypothesis to interpret stereochemistry of nucleophilic additions to cyclohexanones as well as electrophilic additions to methylenecyclohexanes, thianes, etc., was described by Klein[53a] and subsequently reinterpreted by Ashby and Boone.[7b,95] Klein proposed that hyperconjugation of the ring CC bonds with the π system, believed at the time to be the major interaction between polarizable bonds and the carbonyl group,[60] forces nonequivalent distribution of π-electron density; as a result, the HOMO orbital should be more extended on the equatorial face of the trigonal center. Therefore, electrophilic reagents should prefer the equatorial attack for both steric and stereoelectronic reasons: there is no effect foreseen that would promote the axial attack of an electrophile. Nucleophilic reagents would prefer the axial approach, since the LUMO orbital is more extended on the axial face of the trigonal center, except for the ones that are very bulky. Thus, the model predicts opposite preferences for nucleophilic and electrophilic reagents in reactions of cyclohexane-based systems.

The second prediction one can make[96] is that electron-withdrawing substitution of the CC bonds should lower dissymetry of π-electron density (due to a decrease in hyperconjugation) and therefore lower the expected preferences, e.g., for the axial attck by a nucleophile.

The accumulated evidence clearly contradicts both of Klein's predictions. The preference for axial attack is observed not only in nucleophilic additions to ketones, olefins,[97] and carbonium ions.[98] In addition to peracid epoxidations,[38,99] this preference is observed in additions of iodine(I) azide and I_2–$(SCN)_2$,[100] diimide reductions,[101] radical substitutions and additions,[50,102] and [2 + 2] cycloadditions of electron-deficient enophiles,[103] i.e., in reactions that should occur on the equatorial face of methylenecyclohexanes. As for the substitution of the CC bonds, it produces a result exactly opposite to the one predicted by Klein's model.[4] Finally, there is a difficulty, as in the case of other models extrapolating ground-state distortions,[55] in accommodating the effects of the reagent structure; an attempt to supplement Klein's model with the concept of hard and soft nucleophiles has not been elaborated.[104]

It should be noted that the model of Hehre et al., while using an entirely different technique, also concludes that a nucleophilic attack occurs from the face of smaller and electrophilic attack from the face of larger negative charge density: "product stereochemistry is dictated early along the reaction coordinate on the basis of electrostatic consideration".[74] No attempt was made to apply a molecular reactivity modeling approach to cyclohexane-based systems, but one cannot expect this approach to succeed any better than the Klein model in explaining the described results.

The torsional strain model[82] proposes that the axial preference is a result of destabilization of the equatorial transition state by repulsive interactions of the incipient bond with the C(2)–H and C(6)–H bonds. The model does not attribute any role to the interactions with the ring CC bonds, because it is believed that due to flattening of the ring no eclipsing (or much less severe) occurs in the axial transition state. This model predicts that

(88) This result was obtained with the minimal basis set STO-3G. The more recent calculations with the 3-21G and 6-31G* basis sets established *the reversed order* of stabilization C–CH_3 < C–H.[86a]

(89) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484.

(90) Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580. It is found that the introduction of one axial CH_3 group in 5,7-dihydro-1,11-dimethyl-5*H*-dibenzo[*a*,*c*]cyclohepten-6-one produces a large decrease of the ^{18}O exchange rate, but the second axial group has a small retarding effect. The fact that retardation is not doubled is taken as the evidence for the presence of a transition-state stabilizing effect of the second axial CH_3 group. The first axial CH_3 group is proposed to introduce a large steric hindrance, while the stabilization by the second axial CH_3 group is attributed to the fact that the antiperiplanar (app) C–CH_3 bond is a better *acceptor* than the app C–H bond. *It should be stressed, however, that these observations can be equally well rationalized by the Cieplak model.* The large decrease in the exchange rate would be explained as a result of the replacement of the axial, app C–H bond by a *poorer donor*, the C–CH_3 bond, and the second decrease as a result of a modest steric hindrance. According to this interpretation, Fraser and Stanciulescu results show that the stabilizing interaction between the incipient bond and an app C–H bond in H_2O addition to a ketone is ~1.4 kcal mol^{-1} greater than that involving an app C–CH_3 bond.

(91) Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950. Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463.

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(94) (a) Meyers, A. I.; Romina, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245. (b) Matsumura, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1929. (c) Hannaby, M.; Warren, S. *Tetrahedron Lett.* **1985**, *26*, 3133.

(95) Predictions of both models are identical.

(96) Agami et al. were first to suggest that the effect of ring substitution on the stereochemistry of hydride reduction of cyclohexanones refutes the Klein model.[1b]

(97) Kruger, D.; Sopchik, A. E.; Kingsbury, C. A. *J. Org. Chem.* **1983**, *49*, 778.

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(99) (a) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1987**, *32*, 1363. (b) Sevin, A.; Cense, J. M. *Bull. Soc. Chim. Fr.* **1974**, 963.

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stereoelectronic control should be maximized in electron-rich transition states since the effect depends on the repulsion of occupied orbitals.

Two arguments can be raised against these propositions. First, it has been shown here that the nature of stereoelectronic control is probably the same in reactions of very different degree of elipsing in the transition states. Regardless of the degree of steric bias, that is, both in the reactions of cyclohexane- and adamantane-based systems, similar stereoselectivities were found in additions of nucleophiles to carbonyl group, presumably attacking the double bond at an obtuse angle, and in epoxidations or carbene additions of corresponding methylene derivatives,[4b] where the reagent attacks the double bond at an acute angle and no eclipsing occurs. In other words, the differences in the angle of reagent attack (obtuse or acute angle) and, consequently, the degree of elipsing, do not seem to be relevant.

Recently, the results obtained in modeling stereoselection by MM2 force field were interpreted as the evidence supporting the Felkin model.[86] Using parameterization supplied by the authors, we found that indeed the difference in final steric energy of the two transition states for the hydride addition to cyclohexanone is mostly accounted for by the difference in torsional contribution.[105] However, we found no basis for the claim that this result supports the Felkin hypothesis of torsional strain.

According to Felkin, the major contribution to the energy difference between the axial and equatorial transition states would be a destabilizing interaction in the latter due to eclipsing of the incipient bond and the axial CH bonds. *In fact, this contribution is negligible in Houk's model.* The torsional parameters selected for the CH–incipient bond interactions are not very different from the standard CH–CH torsional potentials in the MM2 field: [0.000, 0.000, 0.300] vs [0.000, 0.000, 0.237]. Moreover, both transition states as calculated by Houk's model are "late", at least halfway advanced. Torsional angles formed by the incipient bond with the C(2)–H and C(6)–H bonds during the equatorial attack are ~45°, instead of ~0° envisioned by Felkin. In other words, there is very little, if any, eclipsing of the incipient bond with the CH or the ring CC bonds in either transition state produced by Houk's model.

Further examination of Houk's result reveals that nearly the entire energy difference in favor of the axial transition state is produced by two unprecedented torsional interactions, which are introduced by unusual parameterization for the CC bond–incipient bond torsional potential [−0.200, −0.200, 0.400], and for the CC bond–CO bond torsional potential [−0.400, 0.500, −0.200].

The first potential results in the gauche stabilization of the axial transition state! Stabilization of that kind, although of different origin, has been postulated by Cieplak,[5] vide infra, and not by Felkin. The second potential produces a sizable destabilization of the equatorial transition state when the CO bond and the ring CC bonds form a dihedral angle of 90°. Destabilizing interaction between these groups, although again of different origin, has of course been postulated by the model of product development control, not by Felkin. Therefore, even accepting the premise that MM2 results provide any clues as to what is the physical nature of the effect in question, we cannot see how the Houk and Wu results can be interpreted as supportive of the torsional strain hypothesis.

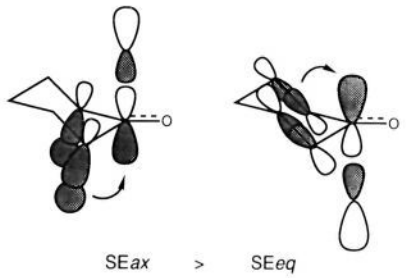
Our second argument is that the Felkin model fails to predict the effect of electronegative substitution of the nucleophilic reagents on stereochemistry of addition to cyclohexanones.

The torsional strain hypothesis invokes interactions of two doubly occupied molecular orbitals, which lead to net four-electron destabilization, DE, which increases as the overlap integral of the two molecular orbitals, and the *mean of their energies*, ϵ_0, increase (eq 9). Therefore, stabilized carbanions would be expected to

$$DE = \frac{4S_{ij}^2(\epsilon_0 - k)}{1 - S_{ij}^2} \qquad (9)$$

(105) Froimowitz, M.; Cieplak, A. S., unpublished.

Chart IV



SE*ax* > SE*eq*

be less axially selective than alkyl metals. Electronegative substitution of the carbanion should lower the σ_+ orbital energy of the incipient bond and, consequently, DE in the equatorial transition state. In other words, an electron-depleted incident bond should suffer less severe repulsive interactions with the C(2)–H and C(6)–H bonds.

This prediction is clearly contradicted by our data. *Stereoelectronic control in additions to cyclohexanones seems to be greater, in general, in the electron-deficient transition states, not in the electron-rich ones.*

Anh et al. did not attribute any role in stereoselection to the ring CC bonds for the same reasons as Felkin.[75] The axial preference in nucleophilic attack on cyclohexanone arises, it is proposed, through delocalization of the incipient bond into σ^* orbitals of the C(2)–H and C(6)–H bonds, which are in a better antiperiplanar alignment than the ring CC bonds due to the flattening of the ring. Thus, the effect should also be maximized in the electron-rich transition states; that is, stabilized carbanions should display smaller preference for the axial attack. In other words, this model also fails to predict the effect of electron-withdrawing substitution of the nucleophiles. Moreover, if one assumes that there is even a minor stabilizing interaction between the incipient bond and the σ_{CC}^* orbitals, electron-withdrawing substitution of these bonds should promote equatorial attack of nucleophiles due to improved stabilization of the equatorial transition state. *In the case of 5-substituted adamantanones, Anh's model predicts the preference for an attack anti to an electron-withdrawing substituent.* These predictions are clearly contradicted by the results presented by us and others.[3,4]

The explanation of stereoselection in reactions of the cyclohexane-related systems based on the Cieplak proposition is as follows. During the axial attack of a reagent, the vacant orbital σ_+^* that develops along with the formation of the incipient bond interacts with the filled orbitals of the C(2)–H and C(6)–H bonds. During the equatorial attack, the σ_+^* orbital interacts with the filled orbitals of the ring bonds C(2)–C(3) and C(5)–C(6). The effect of steric hindrance favors, obviously, the equatorial attack. The effect of hyperconjugative σ assistance, however, favors the axial attack, because the CH bonds are better donors than the CC bonds,[90,106,107] and consequently σ_{CH}, σ_+^* stabilization energy

(106) This assumption is consistent with the wealth of data on the properties of the axial and equatorial bonds and on conformational equilibria of cyclohexane derivatives.[5] For a recent appraisal of the Baker–Nathan order problem, see also: Brown, H. C.; Periasamy, M.; Perumal, P. T. *J. Org. Chem.* **1984**, *49*, 2754. Edlund, U. *Org. Magn. Reson.* **1978**, *11*, 516. Coney, B. T.; Happer, D. A. R. *Aust. J. Chem.* **1987**, *40*, 1537; for a demonstration of the CC and CH hyperconjugation and the Baker–Nathan order in the ground state. The study of hyperconjugative involvement of the CC and CH bonds in the cyclohexyl carbonium ion system (Kirchen, R. P.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811) promises to provide a direct, clear-cut evidence of greater donor ability of the CH bonds. For a recent comment on CC and CH hyperconjugation in aldehydes, see: Laube, T.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 5511. For a comparison of the C_{sp^3}–C_{sp^2} and C_{sp^3}–H donor capabilities, see: Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876. Finally, as far as the ab initio calculations of the transition-state stabilities are concerned, the recent results obtained with the extended basis sets are consistent with the Cieplak model.[86a,88]

is greater than the σ_{CC}, $\sigma_{\ddagger}$* stabilization energy (Chart IV).

The interactions invoked here, of a doubly occupied molecular orbital with a vacant molecular orbital, lead to two-electron stabilization, SE, which is inversely proportional to the energy separation of the two orbitals and directly proportional to the square of their overlap (eq 10).

$$SE = \frac{2k^2S_{ij}^2}{\epsilon(\sigma_i) - \epsilon(\sigma_j)} \quad (10)$$

Assuming that the difference between the two-electron stabilization in the axial and equatorial transition states determines the extent of stereoelectronic control in these reactions, we can formulate predictions concerning the effects of the substrate and the reagent substitution on the ratio of diastereomeric products of a nucleophile addition to cyclohexanone (eq 11). If the overlap

$$\log k_{ax}/k_{eq} \propto SE_{ax} - SE_{eq} \quad (11)$$

is assumed to be constant, independent of substitution and changes in the transition-state geometry, then

$$SE_{ax} - SE_{eq} \propto \frac{1}{\epsilon(\sigma_{\ddagger}^*) - (\epsilon(\sigma_{CH})} - \frac{1}{\epsilon(\sigma_I^*) - \epsilon(\sigma_{CC})} \quad (12)$$

and

$$SE_{ax} - SE_{eq} \propto \frac{\epsilon(\sigma_{CH}) - \epsilon(\sigma_{CC})}{(\epsilon(\sigma_{\ddagger}^*) - \epsilon(\sigma_{CH}))(\epsilon(\sigma_{\ddagger}^*) - \epsilon(\sigma_{CC}))} \quad (13)$$

If the $\sigma_{\ddagger}$* orbital energy is high compared to the σ_{CC} and σ_{CH} bond energies, then

$$\epsilon(\sigma_{\ddagger}^*) - \epsilon(\sigma_{CH}) \approx \epsilon(\sigma_{\ddagger}^*) - \epsilon(\sigma_{CC}) = \Delta\epsilon \quad (14)$$

and

$$\log \frac{k_{ax}}{k_{eq}} \propto \frac{\epsilon(\sigma_{CH}) - \epsilon(\sigma_{CC})}{(\Delta\epsilon)^2} \quad (15)$$

If $\Delta\epsilon$ = const, the ratio of the axial and equatorial attack products should be linearly dependent on the energy level of the ring σ_{CC} bonds (eq 16). Hence, the relative yield of the axial approach

$$\log k_{ax}/k_{eq} \propto \epsilon(\sigma_{CH}) - \epsilon(\sigma_{CC}) \quad (16)$$

of a given nucleophile should increase upon sterically remote, electronegative substitution of the cyclohexanone ring (C-3 and C-4), if we assume that such a substitution will primarily affect the σ_{CC} energy. On the other hand, if $\epsilon(\sigma_{CC})$ = const, then

$$\log k_{ax}/k_{eq} \propto 1/(\Delta\epsilon)^2 \quad (17)$$

Equation 17 infers that electronegative substitution of the nucleophile, which lowers the $\sigma_{\ddagger}$* energy level, i.e., decreases the energy gap $\Delta\epsilon$, should also increase the relative yield of the axial attack.[108]

A further implication of the model is that the effect of electronegative substitution of the ring bonds should depend on the energy level of the $\sigma_{\ddagger}$* orbital. Namely, the lower this level (the higher electron affinity of the transition state), the less sensitive the k_{ax}/k_{eq} ratio is expected to be to the remote C-3 or C-4 substitution (the lower the log k_{ax}/k_{eq} vs σ_I slope). This follows from the examination of the derivatives of $SE_{ax} - SE_{eq}$ as a function of the σ_{CC} energy level. If $\sigma_{\ddagger}$* is high, the log k_{ax}/k_{eq} vs σ_I plot is approximately linear (eq 16) and the slope is

$$\frac{d(SE_{ax} - SE_{eq})}{d(\epsilon(\sigma_{CC}))} \propto -1 \quad (18)$$

If $\sigma_{\ddagger}$* is low (eq 12), then

$$\frac{d(SE_{ax} - SE_{eq})}{d(\epsilon(\sigma_{CC}))} \propto -\frac{1}{(\epsilon(\sigma_{\ddagger}^*) - \epsilon(\sigma_{CC}))^2} \quad (19)$$

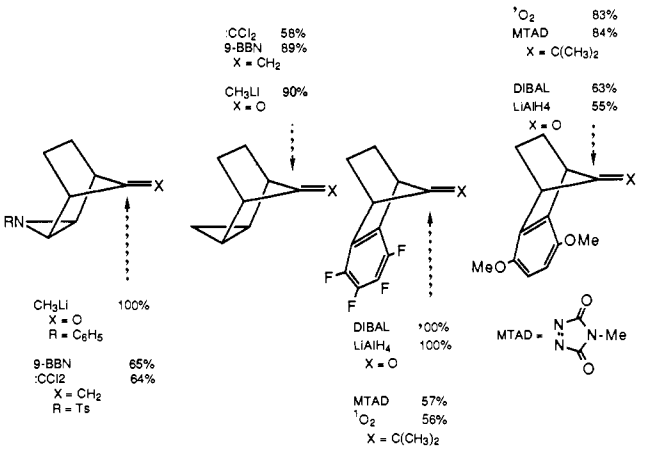
and the derivative goes to zero when $\epsilon(\sigma_{CC})$ is lowered by electronegative substitution (σ_I increases).

It should be stressed that since we consider only the energy level of the incipient bond $\sigma_{\ddagger}$* orbital, the basic outcome should be independent of the reaction mechanism, i.e., of the polarization of the incipient bond. In particular, the nature of the stereoelectronic control in the reactions of cyclohexane-based systems should be the same for polar additions (nucleophilic or *electrophilic*), radical additions, or recombinations and cycloadditions.

Finally, it is interesting to consider kinetic implications of the eq 11–16. Lowering of the $\epsilon(\sigma_{CC})$ due to electron-withdrawing substitution increases log k_{ax}/k_{eq} (eq 16) because it diminishes stabilization of the equatorial transition state SE_{eq}. In the case of nucleophilic additions to cyclohexanones, it means that the accelerating inductive effect of electronegative C-3 substitution fully operates only during the axial attack, while it is partly offset during the equatorial attack. This is equivalent to saying that $\rho_{(eq)}$ is always smaller than $\rho_{(ax)}$. If the decrease of SE_{eq} completely offsets the inductive effect, the equatorial rate constant k_{eq} would decrease in absolute terms, that is $\rho_{(eq)}$ would be less than zero. In other words, contrary to the common intuitive assumption, it is implied that remote electron-withdrawing substitution of the cyclohexanone ring might actually *slow down* nucleophilic addition on the equatorial face, and conversely, electron-releasing alkyl substitution might accelerate these additions.

The results summarized in Table I and in Figures 1–4 support this model on all five accounts.

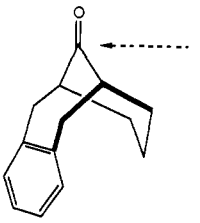
Scheme V



(107) This tenet was recently disputed on the basis of the fact that ionization potentials in the series of piperidine and 2-methyl-, *cis*-2,6-dimethyl- and 2,2,6,6-tetramethylpiperidine decrease in a nonlinear fashion; 8.70, 8.63, 8.53, 8.04 eV: Roseboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189. *The phenomenon is taken as the evidence that CC bonds are better donors than CH bonds*, because the authors attribute the extra decrease in the last case to the hyperconjugative stabilization of the N radical cation by the axial CC bonds C(2)–CH_3 and C(6)–CH_3 that replaced the axial C(2)–H and C(6)–H bonds. There is, however, another possible explanation of this extra decrease, which has not been considered by Roseboom and Houk. Conformational energy of the methyl group in 2-methylpiperidine is very high (A = 2.5 kcal mol^{-1}: Eliel, E. L.; Kandasamy, D.; Yen, C.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698). The 1,3 syn-diaxial interaction of the C(2)–CH_3 and C(6)–CH_3 methyl groups in 2,2,6,6-tetramethylpiperidine produces therefore a significant ring distortion (examination of the Cambridge Structural Database 1986 Version I reveals that the tetrahedral valency angle on the nitrogen found in piperidines is increased to the trigonal value in 2,2,6,6-tetramethylpiperidines, 122°, SD 4.6°, 62 entries). Since ionization potentials of amines and ethers are known to decrease when the ring size and the endocyclic valency angle increase (Yoshikawa, K.; Hashimoto, M.; Morishima, I. *J. Am. Chem. Soc.* **1974**, *96*, 288. Levy, G.; De Loth, P. *C. R. Acad. Sci. Ser. C* **1974**, *279C*, 331), this distortion seems to be the most likely reason for the extra decrease in the 2,2,6,6-tetramethylpiperidine case.

(108) As pointed out earlier,[5] incorporation of an electron acceptor or donor into the transition state should also lead to change of $\Delta\epsilon$, e.g., Lewis acid complexation of the carbonyl group would be expected to increase the relative yield of the axial approach product in nucleophilic addition. Such effects have been reported. For instance, Doyle et al.[41c] emphasized Lewis acid promotion of the more hindered approach in these reactions; see also: Quintard, J.-P.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1972**, 1950. For the most dramatic examples of the Lewis acid effect, see: Marouka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588. Ashby, E. C.; Yu, S.; Roling, P. V. *J. Org. Chem.* **1972**, *37*, 1918. Laemmle, J. T.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526. For a recent review of enantioselective carbonyl additions that involve Lewis acid incorporation into the transition state, see: Evans, D. A. *Science* **1988**, *240*, 420.

Chart V



It seems that this model can also be applied to a number of other systems. As shown in Scheme V, changes in electron-donor abilities of the σ or π orbitals on the less hindered side in the bicyclo[2.2.1]heptane skeleton result in the characteristic reversals of stereochemical preferences of different reagents regardless of the mechanism of the reaction on the double bond.[109,110]

It must be emphasized that the model should predict *the change* in stereoselectivity upon sterically neutral substitution of the substrates or the reagents; it cannot, however, predict the outcome of a single reaction in a new sterically biased or π donor containing system, because it is difficult to assess a priori the relative importance of steric and stereoelectronic factors.[111] For instance, the recently extended criticism of our hypothesis is based on the assumption of full similarity between the carbonyl environments in cyclohexanone and benzocyclohepten-4-one.[112] From the point of view of hyperconjugative assistance, however, the presence of the benzene ring not only introduces a π donor, but can be expected to affect σ donation as well (the α,β and α′,β′ CC bonds become benzylic bonds). As the results for 3-phenylcyclohexanone (entries **1f–3f**, Table I) indicate, the phenyl ring does not act as a more electronegative substituent than the hydrogen atom (cf. **1c–3c**, Table I); within the framework of our model, this might be explained as a result of mesomeric assistance to σ_{CC} hyperconjugation. In addition, the axial face of benzocyclohepten-4-one appears to be significantly more hindered to reagents reacting via "early" transition states, because of the boat conformation-like rotation of the β,β′ methylene groups in the seven-membered ring, which brings the axial hydrogens into flagpole positions to form a "canopy" over the carbonyl group. Thus, the assumption of full similarity of the environments of the carbonyl groups in cyclohexanone and 4-benzoheptenone might not be justified. In fact, highly stereoselective hydride and organometallic additions to 12-oxo-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanobenzocyclononene (Chart V) and other ketones closely related to 4-benzoheptenone have been reported.[113] The configuration of the products and the reactive conformation of the benzobicyclic skeleton have not been rigorously established, but in all likelihood these results provide evidence that the axial faces in cyclohexanone and in 4-benzocycloheptenone are very different.

Conclusions

The preference for the axial approach in reactions of cyclohexanones and related systems is now generally believed to be a result of a stereoelectronic effect.[114] We can now say that this effect is enhanced when the transition state for a nucleophilic addition and the ring bonds become more electron deficient. It has been shown that electron-withdrawing modifications both at C-3 position and at the reagent increase the percentage of the axial attack and that their impact can be of sufficient importance to obliterate the effect of steric hindrance; in fact, the combination of the two substitution effects can result in a complete reversal of the stereochemistry of carbanion additions. In the case of nucleophilic additions, sensitivity of the product ratio to C-3 substitution was shown to decrease with increasing electron deficiency of the transition state. Nevertheless, C-3 substitution was shown to affect, in the same way, stereoselection in reactions as different as alkyllithium additions to cyclohexanones and oxymercuration or peracid epoxidation of methylenecyclohexanes. Therefore, it appears that the nature of stereoelectronic control in these cyclic systems is essentially the same in all those reactions and that the extent of this control depends mostly on the electron affinity of the transition state, while the polarization and geometry of the transition state seem less important.

The impact of electron-withdrawing and releasing substitution on π-facial diastereoselection is now sufficiently well documented to consider its accommodation by the theories of stereoelectronic control the sine qua non of validation. The models that invoke the effects of ground-state distortions or repulsive torsional interactions appear to fail this test. In contrast, the data reported here are consistent with the predictions of the Cieplak model, which attributes stereoelecronic control in cyclohexane-based systems to electron donation into the $\sigma_{\ddagger}^*$ orbital, the vacant orbital associated with the incipient bond.

Experimental Section

Published procedures were used for the preparation of 3-(trifluoromethyl)cyclohexanone,[14] 3-*tert*-butylcyclohexanone,[14] and 3-(trimethylsilyl)cyclohexanone.[16]

3-Phenylcyclohexanone. To a 500-mL three-necked flask equipped with a mechanical stirrer and containing argon were added bromobenzene (17.27 g, 0.11 mol) and dry diethyl ether (200 mL). After cooling in a salt–ice bath for 15 min, *n*-BuLi (71 mL, 0.11 mol) in hexane was added and the mixture was stirred 1 h at 0 °C. To a 100-mL reaction flask containing argon were added anhydrous ether (75 mL) and dry dimethyl sulfoxide (7.81 mL, 0.11 mol). The reaction mixture was cooled to 0 °C, and *n*-BuLi (71 mL, 0.11 mol) in hexane was added. Copper(I) iodide (20.9 g, 0.11 mol) was added to the phenyllithium solution, and the resultant mixture was stirred for 15 min. After cooling to −78 °C, the dimsyl anion was added via transfer needle. After 10 min, 2-cyclohexen-1-one (9.61 g, 0.1 mol) in anhydrous ether (10 mL) was added.

(109) Gassman, P. G.; Schaffhausen, J. G.; Reynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6408. Gassman, P. G.; Schaffhausen, J. G.; Starkey, F. D.; Raynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6411. Hoffman, R. W.; Hauel, N. Landman, B. *Chem. Ber.* **1983**, *116*, 389. Paquette, L. A.; Klinger, F.; Hertel, L. W. *J. Org. Chem.* **1981**, *46*, 4403. Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Bohm, M. C.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1981**, *103*, 7106. Okada, K.; Tomita, S.; Oda, M. *Tetrahedron Lett.* **1986**, *27*, 2645.

(110) In order to apply the model to the systems with the heteroatom-carrying stereogenic centers, one needs to gauge relative σ-donor capabilities of the single bonds other than C–C and C–H bonds and to determine to what extent factors such as conformation of the heteroatom ligand, substitution of the heteroatom bond, and mechanism of the reaction affect hyperconjugation of the π and n electrons. If the latter does not take place, the bonds to first-row atoms C–N, C–O, C–F are expected to be progressively poorer donors than the C–C and C–H bonds, while the bonds to second-row atoms C–Si, C–P, C–S are expected to be better donors, but less and less so going to the right in the row and in the absence of electronegative substitution. The last in the row C–Cl bond should always be a poorer donor. For an example of a computational result indicating that σ_{CCl} is a significantly poorer donor than σ_{CS}, see: Bernardi, F.; Bottoni, A.; Fossey, J.; Sorba, J. *Tetrahedron* **1986**, *42*, 5567. It is interesting to note that under these assumptions, the Cieplak model provides a simple rationalization of the increasing number of data on stereochemistry of cycloadditions to 5-substituted cyclopentadienes: Woodward, R. B.; Katz, T. J. *Tetrahedron* **1969**, *5*, 70. Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183. Jones, D. W. *J. Chem. Soc., Chem.* commun. **1980**, 739. Macaulay, J. B.; Fallis, A. *J. Am. Chem. Soc.* **1988**, *110*, 4074. Breslow, R.; Hoffman, J. M. H., Jr.; Perchonock, C. *Tetrahedron Lett.* **1973**, 3723. As expected, electronegative substitution of the reagent reverses the preference for the less hindered approach in favor of the more hindered approach that is anti to the better σ donor: Williamson, K. L.; Hsu, L. Y.; Lacko, R.; Youn, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129. Williamson, K. L.; Li Hsu, Y. F. *J. Am. Chem. Soc.* **1970**, *92*, 7385. The latter phenomenon was also observed in the case of cycloadditions of nitrile oxides to 3,4-dichlorocyclobutene (Bianchi, G.; De Micheli, C.; Gamba, A.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 137, compare entries *d* and *g–j* in Table I, p 138) but the replacement of Cl by S does not reverse the syn preference observed in cycloadditions of diazomethanes in this system and the reason for the discrepancy is not apparent: Landen, H.; Margraf, B.; Martin, H.-D.; Steigel, A. *Tetrahedron Lett.* **1988**, *29*, 6597. For another example of the anti approach to a better σ donor in cycloaddition reactions, see: Dolbier, W. R., Jr.; Wicks, G. E.; Burkholder, C. R. *J. Org. Chem.* **1987**, *52*, 2196. Dolbier, W. R., Jr.; Burkholder, C. R.; Wicks, G. E.; Palenik, G. J.; Gawron, M. *J. Am. Chem. Soc.* **1985**, *107*, 7183.

(111) "Qualitative MO theory asserts its power in the predictions of trends rather than isolated events".[80a]

(112) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328.

(113) Hahn, W. E.; Jatczak, M. *Pol. J. Chem.* **1979**, *53*, 1221. Woo, E. P.; Mak, K. T. *Tetrahedron Lett.* **1974**, 4095.

(114) To the best of our knowledge, this conclusion was formulated for the first time in 1962: Kamernitskii, A. V.; Akhrem, A. A. *Tetrahedron* **1962**, *18*, 705.

The reaction mixture was allowed to stir for 3 h at −78 °C, then was quenched by addition to aqueous NH_4Cl/NH_4OH (100 mL), and extracted with ether (3 × 200 mL). The ether extracts were washed with brine (25 mL) and dried over $MgSO_4$. Distillation [110 °C (0.5 mmHg)] yielded 17.4 g (75%) of 3-phenylcyclohexanone[115] as an oil: IR (neat) 2940, 1714, 1454, 1227, 753, 698 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.2 (s, 5 H), 1.50–3.50 (m, 9 H).

3-(*p*-Tolyl)cyclohexan-1-one. Utilizing a similar procedure as described above for 3-phenylcyclohexanone the addition of the *p*-tolyl cuprate yielded 41.5% of 3-(*p*-tolyl)cyclohexan-1-one: bp 110 °C (0.5 mmHg); IR (CCl_4) 2936, 1714, 1546, 1246 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.2 (s, 4 H), 2.30 (s, 3 H), 3.30–1.00 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 210.52, 141.58, 136.25, 129.36, 126.50, 49.05, 44.38, 41.13, 32.94, 25.53, 20.92. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.63. Found: C, 82.73; H, 8.63.

3-[*p*-(Trifluoromethyl)phenyl]-2-cyclohexen-1-one. To an oven-dried 1-L three-necked flask containing argon and equipped with a mechanical stirrer were added 4-bromobenzotrifluoride (26.72 g, 0.119 mol) and dry diethyl ether (900 mL). The mixture was cooled to 0 °C and *n*-BuLi (74.2 mL, 0.115 mol) in hexane added slowly with stirring over 10 min, during which time the solution turned red. After stirring for 30 min at 0 °C, 3-ethoxy-2-cyclohexen-1-one (15.42 g, 0.110 mol) in anhydrous ether (20 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C then quenched with 3 N HCl at 0 °C with vigorous stirring. The mixture was extracted with diethyl ether (3 × 250 mL). The combined extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$, and concentrated. The crude product was distilled under high vacuum, flash chromatographed on silica gel (5:1 hexane/EtOAc), and recrystallized from diethyl ether to afford 17.65 g (67%) of the title compound as a solid: mp 62.5–63 °C; ^1H NMR (CCl_4, 60 MHz) δ 7.66 (s, 4 H), 6.32 (t, J = 2 Hz, 1 H), 1.00–3.02 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 199.34, 158.08, 142.74, 127.09, 126.57, 125.92, 125.72, 37.29, 28.26, 22.81.

3-[4-(Trifluoromethyl)phenyl]cyclohexanone. A solution of 3-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one (17.38 g, 0.072 mol) in ethyl acetate (75 mL) containing 10% Pd/C (0.75 g) was shaken under a 30 psi hydrogen atmosphere for 8 h. The catalyst was filtered off and the filtrate concentrated. Flash chromatography (silica gel, 10:1 hexane/EtOAc) gave three fractions: *cis* and *trans*-3-[*p*-(trifluoromethyl)-phenyl]cyclohexanol, (4.33 g), starting material (5.22 g), and 3-[4-(trifluoromethyl)phenyl]cyclohexanone (8.43 g). The cyclohexanols were oxidized by Jones procedure (72%). The product [11.55 g (66%) after recrystallization from hexane]: mp 58–60 °C; IR (CCl_4) 2937, 1720, 1320, 1163, 1125, 1063 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.57 (d, J = 8 Hz, 2 H), 7.26 (d, J = 8 Hz, 2 H), 1.52–3.54 (m, 9 H). Anal. Calcd for $C_{13}H_{13}F_3O$: C, 64.46; H, 5.41. Found: C, 64.35; H, 5.41.

3-(4-Methoxyphenyl)cyclohexanone. The same procedure as in the above two cases was used. The addition of (*p*-methoxyphenyl)lithium (0.13 mol), prepared from *n*-BuLi (84 mL, 0.13 mol) and *p*-bromoanisole (25 g, 0.13 mol), to 3-ethoxy-2-cyclohexen-1-one (18.7 g, 0.133 mol) produced 3-(4-methoxyphenyl)-2-cyclohexen-1-one (14.36 g, 51%) as a white crystalline solid: mp 83–84 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.41 (d, J = 9 Hz, 2 H), 6.80 (d, J = 9 Hz, 2 H), 6.23 (t, J = 0.5 Hz, 1 H), 3.81 (s, 3 H), 1.81–3.02 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 199.53, 161.40, 158.93, 130.99, 127.67, 123.84, 114.29, 55.36, 37.23, 27.94, 22.87.

The product (11.91 g, 0.055 mol) from above was hydrogenated as previously described, 3-(4-methoxyphenyl)-2-cyclohexen-1-one, 10% Pd/C (0.8 g), and ethyl acetate (200 mL) at 32 psi, to afford 3-(4-methoxyphenyl)cyclohexanone (3.11 g) and *cis* and *trans*-3-(4-methoxyphenyl)cyclohexanol (4.54 g). The cyclohexanols were oxidized by using Jones reagent to give 6.51 g (58%) of 3-(4-methoxyphenyl)cyclohexanone as a white crystalline solid: mp 34–35 °C; IR (CCl_4) 3000, 2988, 1716, 1513, 1250, 1178, 1039, 859 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 7.00 (d, J = 9 Hz, 2 H), 6.63 (d, J = 9 Hz, 2 H), 3.70 (s, 3 H), 1.22–3.00 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 210.84, 158.34, 136.64, 127.48, 114.09, 55.29, 49.25, 43.99, 41.19, 33.07, 25.47. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.69; 7.64.

3-(2,3,4,5,6-Pentafluorophenyl)cyclohexanone. Bromopentafluorobenzene (4.91 g, 20 mmol) in dry diethyl ether (15 mL) was cooled to −78 °C. *n*-BuLi (12.34 mL, 20 mmol) was added dropwise with stirring. After 1 h at −78 °C, the solution was added to CuCN (0.895 g, 10 mmol) in dry diethyl ether (10 mL) at −78 °C. The reaction mixture was stirred 15 min at −78 °C and 15 min at −30 °C and then allowed to warm to room temperature. The solution was recooled to −30 °C.

To a 100-mL oven-dried reaction flask containing argon was added 2-cyclohexen-1-one ethylene ketal (1.40 g, 10 mmol) and dry THF (10 mL). After the above mixture was cooled to −78 °C, iodotrimethylsilane (1.42 mL, 10 mmol) was added and the reaction mixture was stirred for 5 min. The above cuprate solution at −30 °C was added by cannula. The reaction mixture was stirred at −78 °C for 30 min, quenched by addition to water (50 mL), and extracted with diethyl ether (3 × 100 mL). The combined ether extracts were washed with brine and dried over $MgSO_4$. Concentration, followed by flash chromatography (40:1 hexane/EtOAc) gave 3.76 g (99%) of crude 3-(pentafluorophenyl)-2-cyclohexen-1-one: ^1H NMR (CCl_4, 60 MHz) δ 4.21–4.85 (m, 1 H), 3.50–4.20 (m, 4 H), 1.00–3.02 (m, 7 H), 0.15 (s, 9 H).

The above product (3.76 g) was added to a solution of 6 N HCl (5 mL), THF (20 mL), and acetone (20 mL). The mixture was refluxed overnight. After being cooled to room temperature, the reaction mixture was carefully poured into 10% $NaHCO_3$ (20 mL). Diethyl ether (3 × 200 mL) extraction followed by washing the extracts with 10% $NaHCO_3$ (50 mL) and then saturated aqueous brine (50) mL) and rotary evaporation afforded crude 3-(pentafluorophenyl)cyclohexanone. Purification by flash chromatography (silica gel, 50:1 hexane/EtOAc) produced 1.67 g (64%) of pure 3-(2,3,4,5,6-pentafluorophenyl)cyclohexanone as a white crystalline solid: mp 50.5–51.5 °C; IR ($CDCl_3$) 2947, 1718, 1501, 1001, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.00–4.00 (m); ^{13}C NMR ($CDCl_3$) δ 208.30, 45.42, 40.93, 34.70, 29.69, 25.40. Anal. Calcd for $C_{12}H_9F_5O$: C, 54.56; H, 3.43. Found: C, 54.64; H, 3.33.

General Procedure for Methylenecyclohexanes. The appropriate cyclohexanone was methylenated with triphenylphosphonium methylide in DMSO as described by Corey.[26] The workup was varied according to the volatility of the methylenecyclohexane produced.

3-Phenylmethylenecyclohexane. The reaction mixture was quenched with water (25 mL) and extracted with (3 × 100 mL) pentane, and the crude product was flash chromatographed on silica gel (50:1 hexane/EtOAc). 3-Phenylcyclohexanone (3.48 g, 0.02 mmol) gave 2.86 g (83%) of the title compound as a colorless oil: IR (neat) 3072, 3036, 2933, 1651, 1607, 1448, 750, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.20 (s, 5 H), 4.65 (s, 2 H), 1.00–3.00 (m, 9 H).

3-[4-(Trifluoromethyl)phenyl]methylenecyclohexane. The reaction mixture was quenched with water (25 mL), extracted with pentane (3 × 100 mL), and flash chromatographed on silica gel (50:1 hexane/EtOAc). The product (85%) was obtained as a colorless oil: IR (neat) 3070, 2950, 1650, 1614, 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.45 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 4.70 (s, 2 H), 3.00–1.00 (m, 9 H).

3-(Trimethylsilyl)methylenecyclohexane. The product was distilled directly from the reaction mixture under vacuum [35 °C (10 mmHg)]. Flash chromatography on silica gel (pentane) afforded the title compound (70%) as a oil: IR (CCl_4) 3075, 2920, 1652, 1448, 1249, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 4.64 (ns, 2 H), 2.70–0.50 (m, 9 H), 0.00 (s, 9 H).

3-(Trifluoromethyl)methylenecyclohexane. The product was distilled directly from the reaction flask under vacuum [35 °C (10 mmHg)]. The product was redistilled. (To ensure pure product, the starting Wittig salt must be free of residual benzene.) From the ketone (1.81 g, 11 mmol) was obtained 1.62 g (90%) of the desired product as a clear oil: IR ($CDCl_3$) 3075, 2916, 1654, 1270, 1249, 1150, 1119 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 4.73 (s, 2 H), 3.00–1.00 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 145.44, 132.99, 129.29, 125.60, 121.90, 109.51, 43.75, 43.40, 43.05, 42.70, 34.14, 33.58, 25.87, 24.70.

General Procedures for Addition of Methyllithium. To an oven-dried 25-mL reaction vessel containing argon was added dry diethyl ether or THF (5 mL). The solvent was cooled to −78 °C and methyllithium (0.71 mL, 1.1 mmol) in pentane (low halide content) was added. After stirring for 2 min at −78 °C, the ketone (1.0 mmol) in anhydrous ether or THF (1.0 mL) was added dropwise. After stirring at −78 °C for 2 h the reaction was quenched by addition to saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ether (3 × 75 mL), and the combined extracts were washed with water (10 mL). The ether extracts were dried over $MgSO_4$ and concentrated. The products were subjected to GC or HPLC analysis.

Analysis of Diastereomers. The above reaction mixtures were not purified due to potential preferential recovery of one of the diastereomers. In the two-step procedure, the intermediates were carried on without purification after GC or HPLC analysis.

The reaction mixtures were analyzed by HPLC equipped with a ultraviolet detector (when UV active) or by GC equipped with a thermal conductivity detector (when not UV active). In each case the sample was injected three times to check for reproducibility. The average of the relative areas of the peaks from the three injections was used as the ratio.

To ensure that the two diastereomers were being detected with equal sensitivity, a known mixture prepared from two separated diastereomers was analyzed by the normal methods, the deviation of the GC of HPLC areas was <±2%. Analytical high-performance liquid chromatography (HPLC) was performed on a Varian Associates Model 5000 liquid chromatograph equipped with a Du Pont Zorbax TM Sil (5–6-μm) steel

(115) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133.

column (4.6 mm × 25 cm) and a UV detector.

Gas chromatography (GC) was performed on a Hewlett-Packard 5750 equipped with a thermal conductivity detector. Glass columns were prepared with one of the following packings being used: (a) 10% Carbowax 20M on Chromasorb W 40/60 mesh, $^1/_4$ × 9 in.; (b) 20% EGS on Chromasorb W 40/60 mesh, $^1/_4$ × 12 in.; (c) 3% OV-275 on Chromasorb W-AW 100/120 mesh, $^1/_4$ × 12 in.

General Procedure for the Addition of $(CH_3)_3CuLi_2$.[19] To an oven-dried 25-mL reaction flask containing argon were added Cu(I)I (0.19 g, 1.0 mmol) and anhydrous diethyl ether (5 mL). The reaction mixture was stirred for 0 °C for 15 min and then CH_3Li (2.0 mL, 3.1 mmol) in pentane was added. The cuprate was stirred for 15 min at 0 °C and then cooled to −78 °C for 10 min. The ketone (1.0 mmol) in dry ether (1.0 mL) was added dropwise. After being stirred for 2 h at −78 °C, the reaction was quenched into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with diethyl ether (3 × 75 mL), and the combined extracts were washed with water (10 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The products were subjected to GC or HPLC analysis.

Procedure for the Addition of *N,S*-Dimethyl-*S*-phenylsulfoximine. A solution of *n*-BuLi in hexane (1.55M) was added to a solution of *N,S*-dimethyl-*S*-phenylsulfoximine[6,20] (0.355 g, 2.1 mmol) and triphenylmethane (3 mg) in anhydrous THF (21 mL) maintained at 0 °C until an orange color persisted. The solution was stirred for 15 min at 0 °C. After cooling to −78 °C, the ketone (2.0 mmol) in dry THF (1 mL) was added dropwise and the reaction mixture stirred for 2 h at −78 °C. The reaction mixture was poured into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with diethyl ether (3 × 150 mL) and the combined extracts were washed with water (20 mL). The extracts were dried ($MgSO_4$) and concentrated.

Addition of Thioanisole.[21] *n*-BuLi (1.42 mL, 2.2 mmol, 1.55 M) in hexane was added to a solution of thioanisole (0.273 g, 2.2 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.258 g, 2.3 mmol), and dry THF (21 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then cooled to −78 °C. The ketone (2.0 mmol) in dry THF (1.0 mL) was added dropwise and the reaction mixture stirred for 2 h at −78 °C. Workup was effected by pouring the reaction mixture into saturated and aqueous NH_4Cl (50 mL). Extraction with diethyl ether (3 × 150 mL), washing the combined extracts with 2 N HCl (50 mL) and then water (25 mL), drying ($MgSO_4$), and concentration afforded the 1-[(phenylthio)methyl]cyclohexanols. The adducts were analyzed by HPLC and the ratios compared with the results after Raney nickel W-2 (RaNi) desulfurization.

Raney Nickel (W-2) Desulfurization of Sulfoximines and Sulfides. The adducts (2 mmol) were dissolved in absolute ethanol (20 mL). RaNi was added until TLC indicated the reaction was complete. When TLC analysis indicated the absence of starting material, the reaction was filtered through Celite and the filter cake washed with CH_2Cl_2. The filtrate was dried ($MgSO_4$) and concentrated.

Addition of Dimethylsulfonium Methylide.[22] To an oven-dried 25-mL reaction flask containing argon was added 50% NaH oil dispersion (0.101 g, 2.1 mmol). The oil was removed by washing with dry hexane (3 × 15 mL) and the residual hexane removed under aspirator vacuum. The reaction mixture was placed into inert atmosphere and anhydrous DMSO (2 mL) added dropwise with stirring. After heating for 45 min at 60 °C the flask was cooled to room temperature and dry THF (3 mL) added. A solution of trimethylsulfonium iodide (0.429 g, 2.1 mmol) in dry DMSO (2 mL) was added to the reaction mixture at −10 °C. The ketone (2.0 mmol) in dry DMSO/THF (0.5 mL/0.5 mL) was quickly added after 1 min. The reaction mixture was allowed to stir for 2 h at −10 °C. Workup was effected by decanting the reaction mixture into water (50 mL) and extracting with diethyl ether (3 × 150 mL). The combined extracts were washed with water (50 mL), dried ($MgSO_4$), and concentrated. The resulting oxiranes were analyzed by GC or HPLC and the ratios compared with the product ratios after reduction with $LiAlH_4$.

$LiAlH_4$ Reduction of the Oxiranes. The oxirane mixture (2.0 mmol) in 5 mL of dry diethyl ether was added dropwise to a stirred suspension of $LiAlH_4$ (0.076 g, 2.0 mL) in 5 mL of anhydrous diethyl ether. The reaction was followed by TLF until all the oxirane was consumed. The reaction mixture was carefully poured into water (50 mL), dried ($MgSO_4$), and concentrated under vacuum. The concentrate was dissolved in 6 mL of ether and analyzed by GC or HPLC.

***cis*-3-*tert*-Butyl-1-methylcyclohexanol**: mp 84.5–86 °C; IR (CCl_4) 3620, 3020, 2960, 1368, 1214, 860 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 2.00–0.80 (m, 10 H), 1.20 (s, 3 H), 0.83 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 70.17, 42.88, 39.96, 38.59, 32.10, 27.42, 26.51, 22.09; MS calcd for $C_{11}H_{22}O$ 170.1670, found 170.1666.

***trans*-3-*tert*-Butyl-1-methylcyclohexanol**: colorless oil: IR (CCl_4) 3620, 2960, 1550, 1368, 1250, 860, 800 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 2.00–0.80 (m, 10 H), 1.12 (s, 3 H), 0.86 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 71.67, 45.62, 41.85, 40.29, 31.97, 27.23, 26.58, 25.58, 23.78.

***cis*-1-Methyl-3-(trimethylsilyl)cyclohexanol**: mp 61–61 °C; IR (CCl_4) 3620, 2922, 1248, 1215, 863 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 2.00–0.50 (m, 10 H), 1.10 (s, 3 H), −0.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 68.68, 39.51, 38.73, 31.58, 26.12, 23.00, 20.41, −3.63. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.21; H, 12.04.

***trans*-1-Methyl-3-(trimethylsilyl)cyclohexanol**: clear liquid; IR (CCl_4) 3615, 2925, 1246, 1213, 861, 830 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 2.20–0.50 (m, 10 H), 1.16 (s, 3 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 71.28, 41.46, 40.87, 26.45, 25.73, 25.41, 23.59, −3.63; MS calcd for $C_{10}H_{22}OSi$ 186.1441, found 171 (M − 15).

***cis*-1-Methyl-3-(*p*-methoxyphenyl)cyclohexanol**: clear oil; IR (CCl_4) 3618, 2927, 1509, 1237 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 6.98, 6.61 (dd, *J* = 8 Hz, 4 H), 3.70 (s, 3 H), 3.30–0.65 (m, 13 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.89, 139.30, 127.74, 113.83, 70.11, 55.23, 46.85, 38.59, 38.33, 33.59, 31.97, 22.09; MS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1469.

***trans*-1-Methyl-3-(*p*-methoxyphenyl)cyclohexanol**: mp 58–60 °C; IR (CCl_4) 3617, 2935, 1609, 1500, 1437, 1174, 1035 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 7.20–6.40 (q, *J* = 8 Hz, 4 H), 3.70 (s, 3 H), 3.00–0.65 (m, 13 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.02, 138.65, 127.61, 113.83, 71.47, 55.23, 48.34, 41.19, 40.15, 34.18, 25.99, 24.11; MS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1469.

***cis*-1-Methyl-3-(*p*-tolyl)cyclohexanol**: clear liquid; IR (CCl_4) 3621, 2920, 1514, 1447, 1372, 1140, 950, 928 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 6.93 (s, 4 H), 3.40–0.80 (m, 10 H), 2.30 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.98, 135.15, 128.98, 126.70, 69.92, 46.59, 38.79, 38.21, 33.34, 31.78, 21.90, 20.80; MS calcd for $C_{14}H_{20}O$ 204.1514, found 204.1509.

***trans*-1-Methyl-3-(*p*-tolyl)cyclohexanol**: bp 120–130 °C (0.09 mmHg); IR (CCl_4) 3621, 2925, 1550, 1518, 1250, 1110 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 7.00 (s, 4 H), 3.00–0.80 (m, 10 H), 2.30 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.37, 135.38, 128.95, 126.55, 71.29, 48.11, 41.56, 40.00, 34.02, 25.91, 24.02, 20.91; MS calcd for $C_{14}H_{20}O$ 204.1514, found 204.1518.

***cis*-1-Methyl-3-phenylcyclohexanol**: clear oil; IR (CCl_4) 3620, 2925, 1603, 1493, 1450, 1374, 1141, 950, 693 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 7.07 (s, 5 H), 3.40–0.80 (m, 10 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.97, 128.20, 126.77, 125.79, 69.85, 46.46, 39.25, 38.14, 33.21, 31.78, 21.90; MS calcd for $C_{13}H_{18}O$ 190.1357, found 190.1363.

***trans*-1-Methyl-3-phenylcyclohexanol**: clear liquid; bp 130 °C (0.75 mmHg); IR (CCl_4) 3605, 2930, 1604, 1494, 1450, 1369, 1120, 914 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz), δ 7.07 (s, 5 H), 3.15–0.80 (m, 10 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.45, 128.45, 126.83, 126.11, 71.41, 48.14, 42.10, 40.15, 33.98, 25.99, 24.17; MS calcd for $C_{13}H_{18}O$ 190.1357, found 190.1360.

***cis*-3-[4-(Trifluoromethyl)phenyl]-1-methylcyclohexanol**: viscous clear liquid; IR (CCl_4) 3620, 2929, 1619, 1323, 1193, 1120, 1065 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 7.44, (d, *J* = 8 Hz, 2 H), 7.20 (d, *J* = 8 Hz, 2 H), 3.40–0.80 (m, 10 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.00, 127.22, 125.40, 69.78, 46.26, 39.31, 38.27, 33.07, 31.97, 21.83; MS calcd for $C_{14}H_{17}F_3O$ 258.1231, 240.11256 (M−H_2O); found 240.1132.

***trans*-3-[4-(Trifluoromethyl)phenyl]-1-methylcyclohexanol**: viscous clear liquid; IR (CCl_4) 3616, 2915, 1619, 1323, 1163, 1126, 1066 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 7.44 (d, *J* = 8 Hz, 2 H), 7.20 (d, *J* = 8 Hz, 2 H), 3.00–0.80 (m, 10 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.35, 127.28, 125.53, 125.27, 71.28, 47.75, 41.97, 40.02, 33.66, 25.99, 23.97; MS calcd for $C_{14}H_{17}F_3O$ 258.1231, found 258.1226.

***cis*-3-(2,3,4,5,6-Pentafluorophenyl)-1-methylcyclohexanol**: white crystalline solid; mp 125.5–126.5 °C; IR (CCl_4) 3612, 2936, 1614, 1596, 990, 978 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60–3.40 (m, 1 H), 2.00–1.30 (m, 8 H), 1.29 (s, 3 H), 1.18 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 69.79, 42.71, 38.00, 31.93, 30.26, 30.05, 21.81. Anal. Calcd for $C_{13}H_{13}F_5O$: C, 55.72; H, 4.68. Found: C, 55.96, H, 4.87.

***trans*-3-(2,3,4,5,6-Pentafluorophenyl)-1-methylcyclohexanol**: white crystals; mp 90.5–92.5 °C; IR ($CHCl_3$) 3614, 2936, 1538, 1496, 990, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20–3.00 (m, 1 H), 2.05–1.40 (m, 9 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 70.90, 44.39, 39.76, 32.55, 30.14, 25.37, 23.87. Anal. Calcd for $C_{13}H_{13}F_5O$: C, 55.72; H, 4.68. Found: C, 55.99; H, 4.75.

Catalytic Osmylation.[28] A solution of OsO_4 in THF (0.5 mL, 0.039 mmol) was added to a solution of the alkene (1.0 mmol) and trimethylamine *N*-oxide dihydrate (0.167 g, 1.5 mmol) in 10 mL of THF and 5 mL of water at room temperature. Stirring was continued until TLC indicated no more starting material. The reaction mixture was diluted with 10 mL of water and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with saturated aqueous sodium sulfite (Na_2SO_3, 10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated. Analysis of the diasteriomeric diols was achieved by integration (^{1}H NMR signal) of the

methylene protons. To confirm the ^1H NMR data the diols were converted into the corresponding acetonide and analyzed by HPLC or GC.

***cis*-1-(Hydroxymethyl)-3-(trimethylsilyl)cyclohexanol (major) and *trans*-1-(hydroxymethyl)-3-(trimethylsilyl)cyclohexanol (minor)**: IR ($CDCl_3$) 3580, 3436, 2930, 1450, 1244, 858, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ [3.62, 3.57 (AB q, J = 12 Hz, major 1.86 H), 3.36 (s, minor 0.14 H)], 2.00–0.80 (m, 10 H), 0.70–0.50 (m, 1 H), –0.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) major δ 72.65, 65.67, 35.96, 35.26, 26.17, 24.95, 22.75, –3.72; minor δ 71.91, 70.94, 34.27, 33.55, 26.64, 22.24, 19.40, –3.72.

***cis*-1-(Hydroxymethyl)-3-phenylcyclohexanol (major) and *trans*-1-(hydroxymethyl)-3-phenylcyclohexanol (minor)**: IR ($CHCl_3$) 3577, 3425, 2933, 1601, 1488, 1448, 1072, 1063, 1042, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.10 (m, 5 H), [3.70 (s, major), 3.44 (s, minor), 2 H], 3.20–2.50 (m, 3 H), 2.20–1.20 (m, 8 H); ^{13}C NMR ($CDCl_3$) major δ 145.92, 128.37, 126.64, 126.14, 73.01, 65.74, 42.23, 41.13, 34.42, 33.51, 23.31; minor δ 146.81, 128.50, 126.82, 126.43, 125.95, 72.11, 71.46, 38.60, 33.74, 32.94, 21.31.

***cis*-1-(Hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]cyclohexanol (major) and *trans*-1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-cyclohexanol (minor)**: IR ($CDCl_3$) 3576, 3420, 2935, 1618, 1324, 1157, 1120, 1061, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), [3.73, 3.67 (AB q, J = 11.5 Hz, major), 3.42 (q, J = 11.5 Hz, minor), 2 H], [2.95–3.15 (m, minor), 2.55–2.75 (m, major), 1 H], 2.30–1.00 (m, 10 H); ^{13}C NMR ($CDCl_3$, 300 MHz) major δ 149.88, 127.18, 127.07, 125.31, 73.00, 65.86, 41.92, 41.07, 34.54, 33,22, 23.20; minor δ 150.77, 128.29, 125.52, 122.41, 72.08, 71.54, 40.90, 38.59, 33.50, 32.98, 21.18.

Acetonides from Diols.[116] To a 10-mL reaction vessel were added the diol (1.0 mmol), acetone (5.0 mL), and 2,2-dimethoxypropane (0.61 mL, 5.0 mmol). After 5 min, p-toluenesulfonic acid monohydrate (0.020 g, 0.1 mmol) was added. Progress of the reaction was monitored by TLC. The reaction was completed after 2 h at room temperature. The reaction mixture was poured into aqueous 10% $NaHCO_3$ (25 mL) and extracted with ether (3 × 75 mL). The combined extracts were washed with brine (25 mL) and dried ($MgSO_4$), and the solvent was evaporated. The acetonide was dissolved in ether (3 mL) and analyzed by GC or HPLC.

2,2-Dimethyl-7-(trimethylsilyl)-1,3-dioxaspiro[4.5]decane: IR ($CDCl_3$) 2926, 1450, 1245, 1053, 861, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ [3.70 (d, J = 2 Hz, minor) 3.85, 3.82 (AB q, J = 8.5 Hz, major) 2 H], [1.40 (s, major) 1.39 (s, minor) 6 H], 2.0–0.70 (m, 8 H), 0.60–0.40 (m, 1 H), –0.04 (s, 9 H); ^{13}C NMR ($CDCl_3$) major δ 108.23, 82.13, 72.03, 37.55, 37.11, 27.46, 27.36, 26.46, 25.76, 24.34, –3.68; MS calcd for $C_{13}H_{26}O_2Si$ 242.1703, found 242, 277 (M – 15).

2,2-Dimethyl-7-phenyl-1,3-dioxaspiro[4.5]decane: IR ($CHCl_3$) 2933, 2858, 1601, 1450, 1368, 1243, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.10 (m, 5 H), [3.94, 3.92 (AB q, J = 9 Hz, major), 3.74 (q, J = 9 Hz, minor) 2 H], [2.90–3.11 (m, minor), 2.40–2.55 (m, major) 1 H], 1.41 (s, 3 H), 1.37 (s, 3 H), 2.12–1.21 (m, 8 H); ^{13}C NMR ($CDCl_3$) major δ 145.79, 128.44, 126.67, 126.23, 125.95, 72.11, 71.46, 38.60, 33.74, 32.94, 21.31; minor δ 128.35, 126.79, 125.97, 109.36, 75.19, 43.47, 39.80, 35.51, 33.37, 29.64, 22.46. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.88; H, 9.10.

2,2-Dimethyl-7-[4-(trifluoromethyl)phenyl]-1,3-dioxaspiro[4.5]decane: IR ($CDCl_3$) 2988, 2935, 1615, 1320, 1246, 1140, 1055, 826, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), [3.96, 3.93 (AB q, J = 8.5 Hz, major), 3.78, 3.73 (AB q, J = 8.5 Hz, minor), 2 H], [3.22–3.01 (m, minor), 2.65–2.45 (m, major), 1 H], 1.41 (s, 3 H), 1.38 (s, 3 H), 2.11–1.21 (m, 8 H); ^{13}C NMR ($CDCl_3$) major δ 150.10, 127.71, 126.06, 126.01, 109.07, 82.32, 72.72, 44.52, 43.50, 36.87, 33.55, 27.89, 24.94; minor δ 151.23, 127.79, 127.24, 123.09, 110.09, 80.99, 75.72, 43.87, 40.43, 35.99, 33.78, 27.99, 22.96. Anal. Calcd for $C_{17}H_{21}F_3O_2$: C, 64.96; H, 6.73. Found: C, 64.56; H, 6.77.

Conversion of the Diols to Methylcarbinols. To a solution of diol (1.0 mmol) in pyridine (3.0 mL) at room temperature was added p-toluenesulfonyl chloride (0.191 g, 1 mmol). The reaction mixture was stirred until no diol was detected by TLC (6 h) and the reaction mixture worked up by pouring the solution into water (25 mL). The monotosylate was extracted from the aqueous phase with ether (3 × 100 mL), and the combined extracts were washed with water (2 × 25 mL). The organic extracts were dried ($MgSO_4$), concentrated, and flash chromatographed (10:1 hexane/EtOAc).

The monotosyl alcohols (1.0 mmol) were dissolved in dry THF (2.0 mL), and Super-Hydride[117] ($LiEt_3BH$, 1 M, 2 mL, 2 mmol) was added. After 2 h at room temperature the TLC showed no starting material. To the reaction mixture was added 1 mL of 3 N NaOH and then 0.5 mL of 30% aqueous H_2O_2. The mixture was extracted with ether (3 × 100 mL), and the extracts were washed with 10% $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated.

***m*-Chloroperoxybenzoic Acid Epoxidations.** To a solution of alkene (1 mmol) in dichloromethane (4 mL) at 0 °C was added m-chloroperoxybenzoic acid (0.259 g, 1.5 mmol) in dichloromethane (2 mL). The reaction was stirred for 2 h at 0 °C. The excess peroxide was destroyed by adding 10 mL of 10% Na_2SO_3. Saturated aqueous $NaHCO_3$ (25 mL) was added and the mixture extracted with diethyl ether (3 × 75 mL). The combined extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. The resulting mixture of oxiranes were subsequently reduced with $LiAlH_4$ by the same procedure previously described.

Oxymercuration.[27] To a 25-mL reaction flask were added $Hg(OAc)_2$ (0.325 g, 1 mmol), water (2 mL), and THF (2 mL). The yellow solution was stirred at room temperature for 5 min and then at 0 °C for 5 min. Alkene (1 mmol) in THF (2 mL) was added dropwise. Upon stirring for 1 h at 0 °C 1 mL of 3 N NaOH and 1 mL of 0.5 M $NaBH_4$ in 3 N NaOH were added, respectively. The mixture was extracted with ether (3 × 75 mL), and the combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$) and evaporation, the alcohols were dissolved in 3 mL of ether and analyzed by GC or HPLC.

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