couloamperometry[21] for constants higher than 5×10^3 M^{-1} s^{-1} and potentiometry[22] and UV spectroscopy[23] for the smaller ones. In all these methods, an excess of bromide ions is necessary to fix equilibrium 4. The experimental rate constant, k_{exptl}, combines

$$Br_2 + Br^- \rightleftarrows Br_3^- \quad (4)$$

the two elementary rate constants related to the two discrete processes:[24] addition of free bromine, k_{Br_2}, and that of the electrophilic tribromide ion, $k_{Br_3^-}$.

k_{Br_2} Determination. Relationship 5[24] relates the rate constants

$$k_{exptl}(1 + K[Br^-]) = k_{Br_2} + Kk_{Br_3^-}[Br^-] \quad (5)$$

k_{exptl}, k_{Br_2}, and $k_{Br_3^-}$. Therefore, we measure k_{exptl} at several (three or four) bromide ion concentrations. According to eq 5, the plot of k_{exptl} $(1 + K[Br^-])$ against $[Br^-]$ gives a straight line whose intercept is k_{Br_2}.

Registry No. 1, 74-85-1; 2, 115-07-1; 3, 115-11-7; 4, 590-18-1; 5, 624-64-6; 6, 513-35-9; 7, 563-79-1; 8, 558-37-2; 9, 594-56-9; 10, 762-63-0; 11, 690-08-4; 12, 107-40-4; 13, 30436-14-7; 14, 5857-68-1; 15, 692-47-7; 16, 692-48-8; 17, 28923-90-2.

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Stereochemistry of the Reaction of Lithium Aluminum Hydride and of Methyllithium with Methyl-Substituted Cyclopentanones, Cyclohexanones, and Norbornanones. Evidence for a Linear Combination of Steric Strain and Product Stability Control in the Stereochemical Course of the Addition Reactions

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Methyl-substituted cyclopentanones, cyclohexanones, and norbornanones were reacted with methyllithium in ether and with lithium aluminum hydride in tetrahydrofuran at 0 °C. The stereochemical course of these reactions is reported and analyzed. The stereochemistry is best explained by a linear combination of both steric strain and product stability controls, $\Delta(\Delta G^{\ddagger}) = \Delta\sigma + \Delta\pi$. While diastereomeric secondary alcohols show significant differences in thermodynamic stability ($\Delta G°_H$), tertiary diastereomeric 1-methylcycloalkyl alcohols show little difference in stability. Hence, the stereochemical course of the reaction of methyllithium with cyclic ketones is little affected by the product stability and $\Delta\pi = 0$. In the case of lithium aluminum hydride reduction, however, the stereochemistry is dictated *simultaneously* and *linearly* by both steric strain and product stability controls. It was found that if product stability control can be cancelled, both methyllithium and lithium aluminum hydride have about equal steric demand in their transition state complexes. Accordingly, an empirical equation, $\Delta(\Delta G^{\ddagger})_H = \Delta(\Delta G^{\ddagger})_{Me} + 1.4(\Delta G°)_H$, was obtained. Here, $\Delta(\Delta G^{\ddagger})_H$ and $\Delta(\Delta G^{\ddagger})_{Me}$, respectively, are the transition state energy differences leading to two diastereomers in the reactions of ketone with lithium aluminum hydride and with methyllithium. The equation provides a qualitative as well as a quantitative treatment of the stereochemical course of the reaction of lithium aluminum hydride with cyclic ketones.

In their recent publications, Eliel[1] and Ashby[2] have presented a general explanation for the observed stereochemistry of the reaction products obtained from cyclic ketones with lithium aluminum hydride or with alkylmetal. Earlier, Cherest and Felkin[3] attributed the observed stereochemistry to the torsional effect of the neighboring C–H or C–R bond during the alcohol formation from the corresponding ketones. Recently, Wipke and Gund[4] have provided a new concept and an empirical equation to incorporate the effect of steric congestion and torsional contribution on the stereoselectivity of the reaction. All these proposals tend to enhance the importance of steric approach[5a] or steric strain[5b] control on the stereochemistry of the hydride reduction of the simple cyclic ketone at the expense of product development[5a] or product stability control.[5b]

In simple cyclic ketones such as 4-*tert*-butylcyclohexanone or 2-methylcyclopentanone, hydride reduction of the ketone produces preferentially the more stable trans alcohol whose formation implies the approach of a hydride (or C–H bond formation) from the more hindered axial side of the ring. This mechanistic implication has been a point of argument among the researchers in this field because the percentage of more stable alcohol formed is higher than the amount allowed by thermodynamic equilibrium.

After careful analysis of the stereochemistry of the reaction products of 12 cyclic ketones with methyllithium and with lithium aluminum hydride, we have concluded that the stereochemistry is controlled *simultaneously, if not in equal proportion, by product stability and steric strain in the transition state.* We, therefore, propose a

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(3) (a) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); (b) M. Cherest and H. Felkin, *ibid.*, 2205 (1968).
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0022-3263/79/1944-2760$01.00/0

Table I

the starting ROH	products composition after 7 days: % *cis*-ROH	% *trans*-ROH	cis/trans
cis-ROH	97	7	13.8
trans-ROH	73	27	2.81
25% *cis*- + 75% *trans*-ROH	73	27	2.81

new concept to explain the dichotomous theory of the original proposals of Dauben[5a] and of Brown[5b] and present an empirical relation to predict the stereochemistry of the reaction.

Experimental Section

Materials. All the methyl-substituted cyclohexanones and norbornanones, with the exception of 1-methylnorbornanone, were purchased from Chemical Sample Co. The rest of the chemicals used have been described in an earlier publication.[6]

Equilibration of 2-Methylcyclopentanol. Equilibrations of various cyclopentanols were carried out according to the literature method;[7] the following example is a typical one. *trans*-2-Methylcyclopentanol (0.4 g, 4 mmol) was mixed with a 2-propanol solution[7] of aluminum 2-propoxide (8 mL, 6 mmol) and was sealed in ampules under a nitrogen atmosphere. Samples after equilibration at 100 °C were analyzed by GLC after hydrolysis, extraction (ether), salting out, and drying. The percentage of the trans alcohol changed from 100 (0 h) to 77.3 (71 h), 76.1 (118 h), and 76.7% (147 h). The final trans/cis ratio (3.25) gave ΔG° = 870 cal/mol.

Equilibration of 1,2,4,4-Tetramethylcyclopentanols. The alcohol, as either an isomeric mixture or pure cis or trans in heptane (0.1 M, 10 mL), was equilibrated with an equal volume of perchloric acid (0.2 M) until a constant ratio of cis/trans alcohol was reached. In general, 7 days at 25 °C were required to reach a constant composition. The cis alcohol, however, did not attain a constant ratio even after 7 days. The results are shown in Table I.

1-Methylnorbornanone. 1-Methylnorbornan-2-*endo*-ol (51 g, 41 mmol) was oxidized at 90 °C by sodium dichromate (107 g) in concentrated sulfuric acid (274 g) and water (840 mL) for 3 h.[9] 1-Methylnorbornan-2-one (32 g) was isolated by steam distillation in 64% yield. The pure ketone (25.4 g) was obtained after redistillation in vacuum, n^{20}_D 1.4676 (lit.[9] 1.4674), and checked with an authentic sample by GLC.

Results

Twelve cyclic ketones[10] (Table II) were reacted at 0 °C for 3 h with methyllithium (MeLi) in ether and lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF). Under these reaction conditions,[5b] the ketones were converted essentially quantitatively to secondary alcohols by $LiAlH_4$. In the reactions with MeLi,[6] all the ketones except camphor were converted to the corresponding tertiary alcohols in more than 80% yield; in the case of camphor, ketones half of the unreacted ketone was recovered.

In general, the major reaction product in the hydride reactions was the more stable of the two diastereomeric alcohols. In the MeLi addition, the major reaction product was the one which required the MeLi to complex on the less hindered side of the carbonyl plane. The results are summarized in Table II.

Diastereomeric alcohols were assumed to have equal area response in the GLC analysis using a flame ionization detector.[11] Dehydration of alcohol during the GLC analysis was not observed judging from the absence of olefinic peaks in the chromatograms. The composition of the reaction products was analyzed by GLC without isolation of the products.

To obtain the stability difference of the two diastereomeric secondary alcohols in the cyclopentyl system, alcohols (single isomer or isomeric mixtures) were equilibrated with aluminum 2-propoxide in 2-propanol at 100 °C.[7] The reaction was monitored by GLC analysis of aliquots until the ratio of the two alcohols reached a constant value; this value was taken as the stability ratio of these two isomeric alcohols at equilibrium. Isoborneol was equilibrated under the same condition to check the present procedures; borneol was found in the final equilibrium mixture to the extent of 70%, in agreement with the report by Wilcox and co-workers.[7]

Under the same equilibration conditions as above, *c*-2, *t*-5-dimethylcyclopentan-*r*-1-ol isomerized to *c*-2,*c*-5-dimethyl- and *t*-2,*t*-5-dimethylcyclopentan-*r*-1-ol; the equilibration of the reaction products containing all three isomers never reached a constant ratio even in a 150-h period. The percentage of *cis*,*cis*-2,5-dimethylcyclopentanol increased rapidly from 3.8 to 11.0% at the end of 150 h. The stability ratio of these alcohols is, therefore, not available.

The free-energy differences (ΔG°) of the cyclohexanols and those of the norborneols were available in the literature and are tabulated together with those of 2-methyl-, 2,2,5-trimethyl-, and 2,4,4-trimethylcyclopentanols in Table II.

Structural Assignment and Stereochemistry. The reaction products from the cyclohexanones are all well characterized in the literature and the stereochemistry of the reactions of these ketones under similar conditions are also available in the literature. The product distributions in the literature under similar conditions are comparable to experimental results. Structural determinations of the products were, therefore, achieved by comparing the observed product distributions with those of the corresponding literature data. Thus in the addition of $LiAlH_4$[1] and of MeLi[12] to 4-*tert*-butylcyclohexanone, we obtained the same results as those reported.

In the case of 3-methylcyclohexanone, 15% of the trans alcohol was obtained by $LiAlH_4$ reduction; this is consistent with the 13% obtained by Varma.[13] This ketone, when reacted with MeLi, yielded 66% of the trans alcohol; in the reaction with methylmagnesium iodide in ether, Kamernitskii and Akhrem[14] reported 60% of the trans alcohol from the same ketone. *trans*-3-*tert*-Butylcyclohexanol was obtained in 16.5% by the $LiAlH_4$ reduction of the corresponding ketone in THF at 0 °C; Varma[13] reported a comparable result (18%). The reaction of the ketone with ethylmagnesium bromide in refluxing ether was reported by Akhrem and co-workers[15] to give 86% of the trans alcohol. Based on this, the major reaction product (80%) of MeLi and 3-*tert*-butylcyclohexanone was assigned to *t*-3-*tert*-butyl-1-methylcyclohexan-*r*-1-ol. This

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(11) E. L. Eliel, S. H. Shroeter, T. J. Brett, F. J. Biros, and J.-C. Richer, *J. Am. Chem. Soc.*, 88, 3327 (1966).
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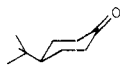
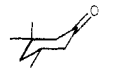
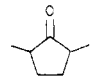
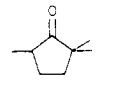
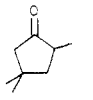
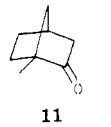
(14) A. A. Akhrem and A. V. Kamernitskii, *Izv. An. SSSR. Otd. Khim.*, 748 (1959); *Zh. Obshch. Khim.*, 28, 754 (1959).
(15) A. M. Prokhoda, A. V. Kamernitskii, and A. A. Akhrem, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1060 (1964).

Table II. Stereochemistry of the Reactions of Methyl-Substituted Cyclic Ketone with MeLi and with $LiAlH_4$ at 0 °C

	MeLi in ether		$LiAlH_4$ in THF				
ketones	% *trans*- or *endo*-OH	$\Delta(\Delta G^{\ddagger})^a$ or $\Delta\sigma_{Me}$	% *trans*- or *endo*-OH	$\Delta(\Delta G^{\ddagger})_H{}^a$	$\Delta\sigma_H{}^a$	$\Delta\pi_H{}^b$	$\Delta G°{}^a$
 1	35[d]	−0.34	88.5[e]	1.11	−0.34	1.45	0.94[f]
 2	66.0	0.36	15.4	−0.92	0.36	−1.28	−0.87[f]
 3	78.5	0.70	16.5	−0.88	0.70	−1.58	−1.20[f]
 4	16.0	−0.90	75[g]	0.60	−0.90	1.50	1.15[f]
 5	99.7	3.17	79.8	0.74	3.17	−2.43	−2.06[f] −1.96[i]
 6	33.0	−0.38	79[g]	0.72	−0.38	1.10	0.87
 7	11.6	−1.10	86.7	1.02	−1.10	2.12	(1.51)[h]
 8	3.0	−1.40	71.0	0.49	−1.40	1.89	1.29
 9	67.0	0.38	91.0	1.26	0.38	0.88	0.90
 10	99.3	2.69	89[k]	1.13	2.69	−1.56	−1.08[j]
 11	98.0	2.11	92.7	1.38	2.11	−0.73	−0.51[l]
 12	2.0	−2.11	8[k]	−1.33	−2.11	0.78	0.66

[a] $\Delta(\Delta G^{\ddagger}) = (\Delta G^{\ddagger})_{cis} - (\Delta G^{\ddagger})_{trans}$ or $\Delta G° = \Delta G°_{cis} - \Delta G°_{trans}$, kcal/mol. [b] Calculated according to eq 6. [c] The starting ketones contain 67% of *trans*-dimethyl ketone. [d] Reference 10. [e] Reference 1. [f] Reflux temperature of 2-propanol; E. L. Eliel et al., *J. Am. Chem. Soc.*, 91, 5487 (1969). [g] Reference 16. [h] Calculated according to eq 7. [i] Reflux temperature of 2-propanol, ref 31. [j] Reference 7. [k] Reference 5. [l] D. L. Vander Jagt, Ph.D. Thesis, Purdue University, West Lafayette, Indiana, 1968.

preferential formation of a trans alcohol is in agreement with the result in the 3-methylcyclohexanone system.

Hydride reduction of 2-methylcyclohexanone in THF at 0 °C was reported to give 75% of the trans alcohol by Brown and Varma.[16] Addition of MeLi to the ketone yields 16% of 1,*t*-2-dimethylcyclohexan-*r*-1-ol which was synthesized by the hydroboration–oxidation of 1,2-dimethylcyclohexene.[6]

The reaction of 3,3,5-trimethylcyclohexanone with $LiAlH_4$ in THF at 0 °C was reported to yield 79.8% of trans alcohol according to Eliel and Senda.[1] With MeLi, two groups had claimed to have obtained trans alcohol stereospecifically.[17,18] Henbest,[19] on the other hand, reported 97% of the trans alcohol. We carried out the

(16) H. C. Brown and V. J. Varma, *J. Am. Chem. Soc.*, 88, 2871 (1966).

(17) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1353 (1965).

(18) S. R. Landor, P. W. O'Connor, A. R. Tatehell, and I. Blain, *J. Chem. Soc., Perkin Trans. 1*, 473 (1973).

(19) H. B. Henbest *Chem. Soc. Spec. Publ.*, No. 19 (1965).

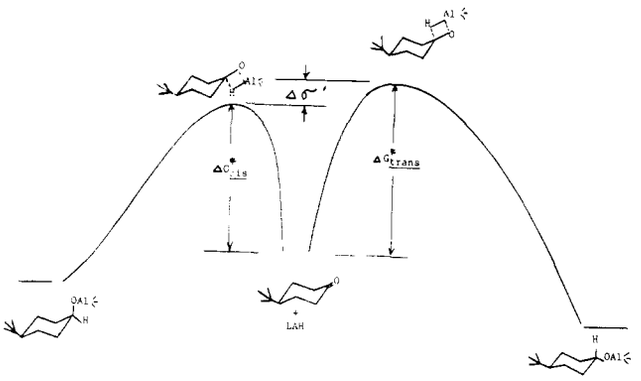


Figure 1. A hypothetical reaction profile with complete steric strain control of reaction transition states.

reaction in ether at 0 °C and confirmed the former result by obtaining the trans alcohol in greater than 99.7% selectivity.

In the cyclopentyl system, the product mixture from the hydride reduction of 2-methylcyclopentanone[5b] was made available by Professor H. C. Brown for comparison in the GLC analysis.

Except for the 2,4,4-trimethylcyclopentanols, all the six remaining trans alcohols in the cyclopentyl system were prepared via hydroboration–oxidation of the corresponding olefins. 2,4,4-Trimethylcyclopentan-*cis*- and -*trans*-ols were characterized by proton NMR spectroscopy.[6]

Characterization of these cyclopentanols including elemental analyses, proton NMR data, refractive index, and melting points of their *p*-nitrobenzoates have been reported separately.[6]

According to Brown and Deck,[5b] the reaction of norbornanone with $LiAlH_4$ in THF at 0 °C yielded 89% of norbornan-2-*endo*-ol. With MeLi in ether at 0 °C, 99.3% of the reaction products from the ketone was 2-methylnorbornan-2-*endo*-ol.[20] The $LiAlH_4$ reduction of 1-methylnorbornanone was highly selective in giving 92.7% of 1-methylnorbornan-2-*endo*-ol.[9] With MeLi, however, reaction of the ketone was less stereoselective than in the case of the parent ketone; only 98% of the product alcohol was the endo alcohol.[9] According to Brown and Deck,[5b] $LiAlH_4$ reduction of camphor produced 8% of borneol (2-*endo*-OH). Camphor reacted with MeLi to give 2% of the endo alcohol.[21]

Discussion

Two Hypothetical Extreme Cases. Strictly speaking, the steric strain control (SSC) and the product stability control (PSC) proposed by Brown and Deck,[5b] or the original terms steric approach control and product development control used by Dauben, Fonken, and Noyce,[4] are best considered to be two hypothetical extremes in the hydride reduction of cyclic ketones. In such a hypothetical extreme where SSC alone is operative (Figure 1) the transition state complexes are assumed to resemble the starting ketone. The free-energy difference of the two transition states leading to cis and trans alcohols, $\Delta(\Delta G^{\ddagger})$, will not be affected by the difference in product stability, $\Delta G°$, but by the net difference in the steric strain, $\Delta\sigma'$, of the two transition state complexes of the metal hydride and the starting ketone. On the other hand, in the case of PSC where the transition states of the reaction have developed well along the reaction coordinate and resembled the structures of reaction products (Figure 2), the energetics of the two transition states differing by $\Delta\pi'$ will then approach the value of the product stability difference, $\Delta G°$.

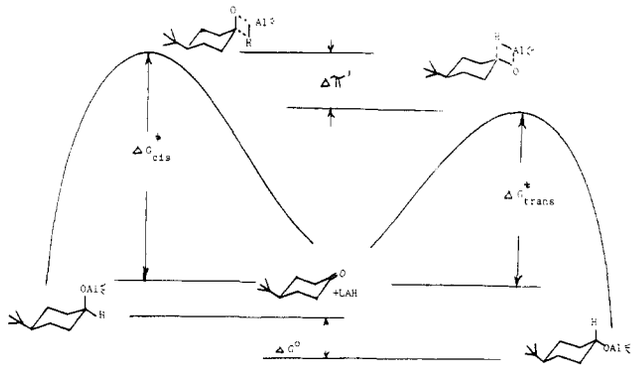


Figure 2. A hypothetical reaction profile with complete product stability control of reaction transition states.

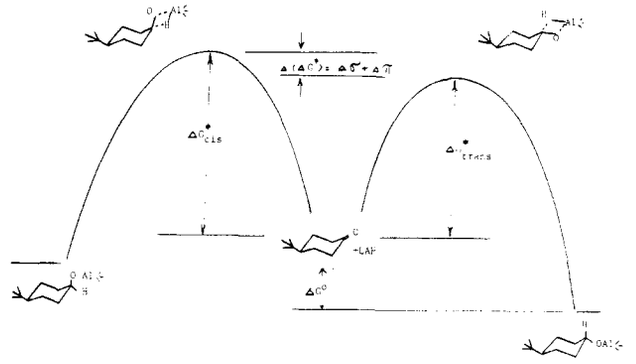


Figure 3. An actual reaction profile with transition states controlled by the steric strain and product stability.

In the real situation, it is proposed that an actual transition state of this type of reaction would be better represented by a superimposed picture of the two extremes as shown in Figure 3. Accordingly, the energy difference of the two transition states in an actual reaction, $\Delta(\Delta G^{\ddagger})$, becomes a combined function of the corresponding energy differences in the two hypothetical extreme cases, $\Delta\sigma'$ and $\Delta\pi'$. This relation is expressed in eq 1 as a linearly additive function.

$$\Delta(\Delta G^{\ddagger}) = a\Delta\sigma' + b\Delta\pi' \quad (1)$$

The relative contribution to an actual reaction from these two hypothetical extremes, $\Delta\sigma'$ and $\Delta\pi'$, would then be regulated by two coefficients, a and b, respectively. For convenience, $\Delta(\Delta G^{\ddagger})$, $\Delta\sigma'$, and $\Delta\pi'$ are calculated by subtracting the energy term leading to the formation of a trans alcohol from that of a cis alcohol, i.e., $\Delta(\Delta G^{\ddagger}) = \Delta G^{\ddagger}_{cis} - \Delta G^{\ddagger}_{trans}$.

The two coefficients, a and b, determine the locations of the actual transition states along the reaction coordinate between the two hypothetical transition states of SSC and PSC. This means that both a and b are related to the bonding nature of the transition-state complex of ketone and $LiAlH_4$ (or MeLi). In this study, the effect of solvent was kept constant, and the carbonyl groups are believed to differ from each other only slightly in bonding characters because of the absence of unsaturated bonds or heteroatoms such as oxygen or nitrogen. Therefore, within the range of the reaction conditions covered in this study, the a/b ratio may be assumed constant. (However, movement of transition states along the reaction coordinate

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(21) H. H. Zeiss and D. A. Peare, *J. Am. Chem. Soc.*, 78, 3182 (1956).
(22) H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, 88, 2811 (1966).

was reported when the nature of the nucleophile was allowed to vary widely as reported by Geneste and coworkers.[23]) The assumption of a constant a/b ratio was experimentally validated as seen in the latter part of the discussion, $a\Delta\sigma'$ and $b\Delta\pi'$ in eq 1 are then simplified to become $\Delta\sigma$ and $\Delta\pi$, respectively, if a constant ratio of a/b is assumed. Accordingly, the stereochemistry of the reaction becomes a linear combination of the two hypothetical cases of PSC and SSC as implied in eq 2.

$$\Delta(\Delta G^{\ddagger}) = \Delta\sigma + \Delta\pi \quad (2)$$

Quantitative Estimate of $\Delta\sigma$ and $\Delta\pi$. Without sound knowledge of the precise nature and the bonding of the transition complexes in these two hypothetical cases, direct evaluation of $\Delta\sigma$ and $\Delta\pi$ would be fruitless. Empirical evaluation of $\Delta\sigma_{Me}$ for the reaction between MeLi and cyclic ketone, however, can be easily obtained.

The reaction between cyclic ketones and MeLi to yield two diastereomeric methylcycloalkyl alcohols possesses a unique character. The difference in the steric requirements of a methyl group and of a solvated hydroxyl group is expected to be small; the stability difference of these two diastereomeric tertiary alcohols can thus be expected to be small. This conclusion is indeed supported by the following experimental results.

Two isomeric *cis*- and *trans*-4-*tert*-butyl-1-methylcyclohexanols were reported to differ only by 0.23 kcal/mol. Differences of 0.15 and 0.56 kcal/mol between 2-methylnorbonan-*exo*- and -*endo*-ols and between 1,2-dimethylnorbonan-*exo*- and -*endo*-ols, respectively, have been reported by Rei and Brown.[25] Likewise, the two isomeric 2-methylbicyclo[3.3.1]octan-*r*-2-*exo*- and -*endo*-ols and 3-methylbicyclo[3.3.1]octan-*r*-3-*exo*- and -*endo*-ols differ only by 0.34 and −0.34 kcal/mol, respectively.[26] The small stability difference between the two diastereomeric tertiary cycloalkyl alcohols appears to be a general phenomenon in the various ring systems. Furthermore, due to solvation, the difference of the steric bulk between the methyl group and the OM group of an alkoxide would become smaller than that between the methyl group and the hydroxyl group of a free alcohol. The above mentioned small stability difference would tend to decrease further since the primary reaction product is a metal alkoxide rather than a free alcohol.[27]

As a result of this diminishing stability difference between the two diastereomeric methylcycloalkyl alkoxides, the effect of product stability control on the stereochemistry of the reaction between MeLi and cyclic ketone becomes negligible, e.g., $\Delta\pi_{Me} = 0$. This leads to further simplification of eq 2. Equation 3 provides a simple

$$\Delta(\Delta G^{\ddagger})_{Me} = \Delta\sigma_{Me} + \Delta\pi_{Me} = \Delta\sigma_{Me} \quad (3)$$

method to evaluate steric strain difference in an addition reaction of MeLi to a cyclic ketone. No such simplification, however, can be made in the case of the secondary alcohol system where significant differences in product stabilities do exist as shown in the last column of Table II.

In general, direct comparison of product distribution of two reactions will not disclose relative magnitude of $\Delta\sigma$ in these two reactions. Therefore, to compare $\Delta\sigma_H$ with $\Delta\sigma_{Me}$, which can be evaluated directly from $\Delta(\Delta G^{\ddagger})_{Me}$, one has to find two systems in which either the contributions of $\Delta\pi_H$ to the stereochemistries of the two reactions are constant or the contributions from $\Delta\sigma_{Me}$ constitute the major variants to the observed difference in the stereochemistries of these two reactions. In other words, for the reactions of a pair of ketones, A and B, only when their reaction products have similar thermodynamic stability difference, $(\Delta G^{\circ})^A = (\Delta G^{\circ})^B$, comparison of $\Delta(\Delta G^{\ddagger})$ will thus lead to the direct evaluation of $\Delta\sigma$ in these two reactions.

$$\Delta(\Delta G^{\ddagger})^B - \Delta(\Delta G^{\ddagger})^A = \Delta\sigma^A - \Delta\sigma^B + \Delta\pi_H{}^A - \Delta\pi_H{}^B = \Delta\sigma^A - \Delta\sigma^B = \Delta(\Delta\sigma) \quad (4)$$

In eq 4, the effects of product stabilities, $\Delta\pi_H{}^A$ and $\Delta\pi_H{}^B$, are mutually cancelled out, and the effects of steric strain, $\Delta\sigma^A$ and $\Delta\sigma^B$, are calculated directly from $\Delta(\Delta G^{\ddagger})^B - \Delta(\Delta G^{\ddagger})^A$. As long as $(\Delta G^{\circ})^A$ equals $(\Delta G^{\circ})^B$, this equation enables one to compare not only $\Delta(\Delta\sigma)$ of the reactions of two ketones with the same nucleophile, but also that of two nucleophiles with the same ketone. In case that $\Delta\pi_H{}^A$ and $\Delta\pi_H{}^B$ or $(\Delta G^{\circ})^A$ and $(\Delta G^{\circ})^B$ have different signs, $\Delta(\Delta\sigma)$ becomes $\Delta(\Delta G^{\ddagger})^B + \Delta(\Delta G^{\ddagger})^A$ in order to cancel out the effect of $\Delta\pi$'s.

Table III compares the steric strain difference of the reactions of $LiAlH_4$ with two ketones, $\Delta(\Delta\sigma_H)$, and that of MeLi with the same two ketones, $\Delta(\Delta\sigma_{Me})$. Comparisons are made from the reactions of two ketones in which ΔG°'s of the resultant alcohols from these two ketones are roughly equal (accordingly $\Delta\pi^A = \Delta\pi^B$); under this constraint, $\Delta(\Delta\sigma)$ becomes the sole or the major controlling factor in the differentiation of the stereochemistry of the two reactions. As shown in the last two columns, $\Delta(\Delta\sigma_H)$ from $LiAlH_4$ with two ketones is approximately equal[28a] to $\Delta(\Delta\sigma_{Me})$ from MeLi with the same two ketones. *This leads to a conclusion that both $LiAlH_4$ and MeLi under a given reaction condition must have about equal steric requirements in their reaction with a cyclic ketone. Accordingly, if product stability control can be neutralized, both $LiAlH_4$ and MeLi under the given reaction conditions would react with equal stereoselectivity.*[28b] From eq 3, one obtains eq 5.

$$\Delta\sigma_H = \Delta\sigma_{Me} = \Delta(\Delta G^{\ddagger})_{Me} \quad (5)$$

Thus, eq 2 is further simplified and after rearrangement it becomes

$$\Delta\pi_H = \Delta(\Delta G^{\ddagger})_H - \Delta(\Delta G^{\ddagger})_{Me} \quad (6)$$

Since the two variables on the right hand side of eq 6 can be obtained through reactions of a ketone with $LiAlH_4$ and with MeLi, $\Delta\pi_H$ can thus be calculated experimentally. Moreover, according to the definition given earlier, it is expected to be linearly correlated with (ΔG°), the stability difference of the two diastereomeric secondary alcohols at ground states, which can be obtained independently via

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(28) (a) In fact, $\Delta(\Delta\sigma_{Me}) = 1.03\Delta(\Delta\sigma_H) + 0.03$ with a correlation coefficient of 0.973 exists when these two parameters are plotted in a regression line with a TI-59 calculator of Texas Instrument Co. (b) According to Sicher and Tichy, the two secondary alcohols from 2-*trans*-methyl-4-*tert*-butylcyclohexanone have roughly equal thermodynamic stability in the ground states. Consequently, the stereochemistry of the reaction of this ketone with $LiAlH_4$ or MeLi would be expected to be equally stereospecific. J. Sicher and M. Tichy, *Collect. Czech. Chem. Commun.*, **32**, 3687 (1967). (c) A regression line of $\Delta\pi_H = 1.31\Delta G^{\circ} - 0.015$ with a correlation coefficient 0.997 was obtained from $\Delta\pi_H$ and ΔG° in Table II. However, $\Delta\pi_H = 1.4\Delta G^{\circ}$ from Figure 4 also provides an equally well linear relationship and accuracy in predicting the product distributions (Table IV). Therefore, $\Delta\pi_H = 1.4\Delta G^{\circ}$ is adopted for its simplicity and convenience.

Table III. Steric Requirement of $LiAlH_4$ and of MeLi, kcal/mol

ketones	nucleophile	$\Delta(\Delta G^{\ddagger})$	ΔG°	$\Delta(\Delta\sigma)^a = \Delta(\Delta G^{\ddagger})^A \pm \Delta(\Delta G^{\ddagger})^E$ ketones involved	$LiAlH_4$ $\Delta(\Delta\sigma_H)$	MeLi $\Delta(\Delta\sigma_{Me})$
1	$LiAlH_4$	1.12	0.93	1 + 2	0.20	
	MeLi	−0.34				0.02
2	$LiAlH_4$	−0.92	−0.89	2 + 6	−0.20	
	MeLi	0.36				−0.02
3	$LiAlH_4$	−0.88	−1.20	3 + 4	−0.28	
	MeLi	0.70				−0.20
4	$LiAlH_4$	0.60	1.15	4 + 10	1.73	
	MeLi	−0.90				1.79
6	$LiAlH_4$	0.72	0.87	9 − 6	0.54	
	MeLi	−0.38				0.76
8	$LiAlH_4$	0.49	1.29	8 + 3	−0.39	
	MeLi	−1.40				−0.70
9	$LiAlH_4$	1.26	0.90	9 + 2	0.34	
	MeLi	0.38				0.74
10	$LiAlH_4$	1.13	−1.08	10 − 3	2.01	
	MeLi	2.69				1.99
11	$LiAlH_4$	1.38	−0.51	11 + 12	0.05	
	MeLi	2.12				0.01
12	$LiAlH_4$	−1.33	0.66			
	MeLi	−2.13				

[a] Comparison of steric requirement of $LiAlH_4$ with that of MeLi is made between two ketones represented by the corresponding numbers shown in the sixth column. The ketones are selected so that they produce two pairs of isomeric secondary alcohols having approximately equal ΔG°. When two ΔG°'s have different signs, such as the case in ketones 3 and 4, $\Delta(\Delta\sigma_H) = \Delta(\Delta G^{\ddagger}_H)^3 + \Delta(\Delta G^{\ddagger}_H)^4 = -0.88 + 0.60 = -0.28$ and $\Delta(\Delta\sigma_{Me}) = 0.70 + (-0.90) = -0.20$. When two ΔG°'s have the same sign, such as the case in ketones 10 and 3, $\Delta(\Delta\sigma_H) = 1.13 - (-0.88) = 2.01$ and $\Delta(\Delta\sigma_{Me}) = 2.69 - 0.70 = 1.99$.

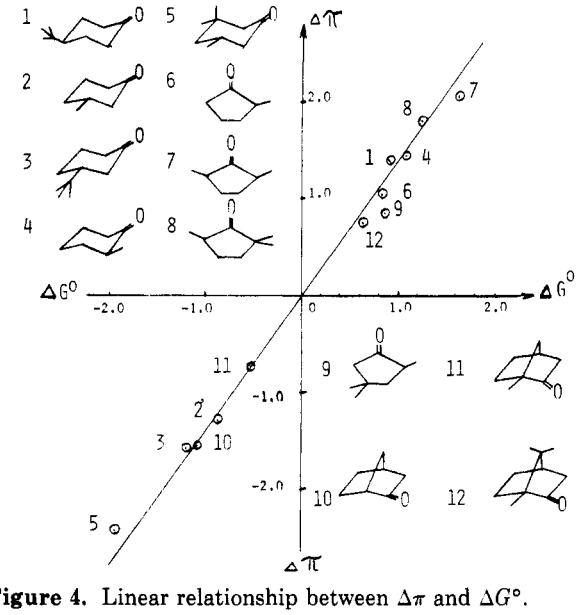

Figure 4. Linear relationship between $\Delta\pi$ and ΔG°.

equilibration of the two alcohols. This provides an independent test of the validity of the assumption made to derive eq 2 from eq 1. *A linear correlation between* ΔG° *and* $\Delta\pi_H$ *indeed exists as shown in Figure 4. The assumption of a constant a/b ratio is, therefore, justified, and the approximation of* $\Delta\sigma_H = \Delta\sigma_{Me}$ *appears to hold.* The slope of the line is 1.4. This gives us a convenient estimation of $\Delta\pi_H = 1.4(\Delta G^{\circ})_H$[28c] and a further simplification to eq 7 from eq 2.

$$\Delta(\Delta G^{\ddagger})_H = \Delta(\Delta G^{\ddagger})_{Me} + 1.4(\Delta G^{\circ})_H = \Delta\sigma_{Me} + 1.4(\Delta G^{\circ})_H \quad (7)$$

Equation 7 clearly illustrates the interlocking effects of the steric strain and the product stability on the stereochemistry of the addition reaction of $LiAlH_4$ and cyclic ketone. Futhermore, all the three parameters are experimentally measurable from three independent reactions, and thus, with any two of the three parameters available one should be able to estimate the third one. A test of eq 7 was indeed provided in the evaluation of ΔG° for the isomeric *cis*- and *trans*-2-methylcyclopentanols. The reported value of $\Delta G^{\circ} = 0.23$ kcal/mol[29] failed to fit with eq 7. Therefore, we measured it experimentally, and a $\Delta G^{\circ} = 0.87$ kcal/mol was obtained. The calculated value from eq 7 was 0.78 kcal/mol which agreed well with the experimental value.

The argument[1] that product stability control is of no importance because that (1) k_a^1/k_a^5 is only 1/2 (in THF) instead of 15 or 100, and (2) in the cyclohexyl system the hydride reduction forms more equatorial alcohol than is allowed by thermodynamics, can perhaps be treated differently as follows.

Equation 7 indicates that direct comparison of $\Delta(\Delta G^{\ddagger})^A$ with $\Delta(\Delta G^{\ddagger})^B$ of two ketones, i.e., **1** and **5**, would not represent a measure of $\Delta(\Delta\pi)$, the effect of product stability difference, or that of $\Delta(\Delta\sigma)$, the effect of steric strain difference in these two ketones. Only when one is sure that $\Delta(\Delta\pi)$ is negligible relative to $\Delta(\Delta\sigma)$ or vice versa, one can then use $\Delta(\Delta G^{\ddagger})$ to measure either the steric strain or the product stability difference of the reactions in these two ketones.

As shown in Table II, the difference in the product stability difference, $\Delta(\Delta\pi)$, of the above mentioned compounds (**1** and **5** in Table II) is 1 kcal/mol whereas the corresponding difference in the steric strain, $\Delta(\Delta\sigma)$, is 2.7 kcal/mol in the opposite direction. Consequently, it is not surprising that k_a^1/k_a^5 is smaller than 15 (or 100) as expected from the effect of the product stability difference alone;[1] the ratio measures neither $\Delta(\Delta\sigma)$ nor $\Delta(\Delta\pi)$ as intended.

In contrast to the implication of eq 7, current explanations[1-4] discount the importance of product stability control in favor of steric strain control of stereochemistry by avoiding an eclipsing strain between the nucleophile and the neighboring hydrogen (2,5-diaxial hydrogen in the case cyclohexyl system). Although the

(29) J. B. Umland and B. W. Williams, *J. Org. Chem.*, **21**, 1302 (1956).

Table IV. Stereochemistry of the Reduction by Lithium Aluminum Hydride as Treated by Equations 5 and 7

ketones	$\Delta\sigma_H$,[a] kcal/mol	$1.4\Delta G^\circ_H$,[a] kcal/mol	$\Delta(\Delta G^\ddagger)$ calcd, kcal/mol	% *trans*- or *endo*-ROH	
				calcd	obsd
1	−0.34	1.32	0.98	84	88.5[b]
2	0.36	−1.22	−0.86	17	15.4
3	0.70	−1.69	−0.99	14	16.5
4	−0.90	1.51	0.61	75	75.0[c]
5	3.17 ± 0.3	−2.74	0.43 ± 0.3	69 ± 1	79.8[b]
6	−0.48	1.22	0.74	80	79.0[c]
8	−1.40	1.81	0.41	68	71.0
9	0.38	1.26	1.64	95	91.0
10	2.69	−1.51	1.18	90	89.0[d]
11	2.11	−0.71	1.40	93	92.7
12	−2.11	0.92	−1.19	10	8.0[d]

[a] Energy to the formation of cis or exo alcohol is subtracted by that of trans or endo alcohol. [b] Reference 1. [c] Reference 16. [d] Reference 5.

eclipsing or torsional strain might be able to explain some stereochemical phenomena in the cyclohexyl system, it fails to explain the preferential formations of trans alcohols in the 2-methyl-[4] 2,5-dimethyl-, and 2,2,5-trimethylcyclopentyl systems. This preferential formation of trans alcohol would require an unlikely assumption of smaller eclipsing strain between the nucleophile (hydride in the case $LiAlH_4$ reduction) and the neighboring *cis*-methyl group than that of the nucleophile and the hydrogen atoms.

As shown in Figure 4, the effect of product stability control, $\Delta\pi$, is 1.4 times larger than ΔG°. This would explain why more than the thermodynamically predicted quantities of equatorial alcohols are obtained in the hydride reduction in the cyclohexyl system.

Finally the result that $\Delta\pi_H$ is larger than $(\Delta G^\circ)_H$ can probably be attributed to the greater degree of molecular aggregation and solvation of $LiAlH_n(OR)_m$ $(n + m = 4)$, the primary hydride reduction product, than that of the free alcohol.

Application of Equation 7 to MeLi as Nucleophile. As mentioned earlier, the effect of product stability control can generally be neglected in the reaction of MeLi and a cyclic ketone. The stereochemistry of this reaction is controlled primarily by the steric strain in the transition state complex.

In the cyclohexyl system, in order to avoid severe steric strain between the methyl group of MeLi and the two axial H's at C-3 and C-5, complexation of MeLi with the carbonyl group on the axial side would be less favorable. The complexation of MeLi on the equatorial side brings about the preferential formation of axial alcohol as observed. Stereoselectivity in favor of the axial alcohol would increase further with the increasing congestion on the axial side such as in 3,3,3-trimethylcyclohexanone.

In the cyclopentyl system, methyl substituents cause greater steric strain on the cis side of the ring; therefore, cis alcohol from the addition of MeLi on the trans side becomes the preferred product. 2,4,4-Trimethylcyclopentanone appears to be an exception[6] because the *trans*-methyl group of the *gem*-dimethyl groups at C-4 apparently becomes the controlling factor on stereoselectivity rather than the sole methyl group at C-2. Hence, trans alcohol becomes the preferred product in this system.

Stereoselectivity increases greatly in the case of norbornanone as a result of relatively large increase of steric strain ($\Delta\sigma_{Me}$ = 2.60 kcal/mol) in the endo side of the molecule. Presence of a methyl group at the bridgehead increases steric strain on the exo side of the carbonyl group and decreases $\Delta\sigma_{Me}$ to 2.12 kcal/mol. This results in the formation of a smaller quantity of endo alcohol. Further introduction of two methyl groups at C-7 apparently adds 4.25 kcal/mol of steric strain on the exo side and reverses the stereochemistry of the reaction. Only 2% of endo alcohol is formed in this case.

Application to other Alkylmetals. In the reactions with other alkylmetals, stereochemistry may again be controlled by the dual factors as $\Delta\pi$ increases. Depending upon the relative bulkiness of the alkyl group and of metal alkoxide (OM), $\Delta\sigma$ and $\Delta\pi$ may or may not have the same sign. In the case where the alkyl group is a small acetylene group, $\Delta\pi$ would be similar to that of hydrogen ($\Delta\pi_H$) and differ in sign with $\Delta\sigma$. Consequently, the stereochemistry of this reaction would be similar to that of $LiAlH_4$. Experimentally, Hennion and O'Shea[30] reported 89% of equatorial alcohol in the addition of sodium acetylide to 4-*tert*-butylcyclohexanone in ammonia. This result indeed resembles that of $LiAlH_4$ reduction (88–92%). In the case where the alkyl group is bulkier than a methyl group, $\Delta\pi$ would have the same sign as would $\Delta\sigma$ and the two contributions may be expected to converge to bring about higher stereoselectivity.

In the case of methylmagnesium iodide where no systematic analysis has been carried out for its stereochemical course of the reaction, the available data[6,10] indicate a gradual increase of the trans alcohol when MeLi is replaced by methylmagnesium iodide. This could be attributed tentatively to the increasing importance of $\Delta\pi_{Me}$ in the methylmagnesium iodide system. With MeLi, $\Delta\pi = 0$ has been assumed; in this system, however, due to greater aggregation of magnesium salt, steric requirement of $-OMg_n$ might be greater than that of a methyl group. Hence $\Delta\pi_{Me} = 0$ and $\Delta\pi \times \Delta\sigma < 0$ in the present system.

Application to Lithium Aluminum Hydride as Nucleophile. Since the overall transition state energy difference, $\Delta(\Delta G^\ddagger)$, or the stereochemistry of the reaction is a linear combination of $\Delta\sigma$ and $\Delta\pi$, any change in the magnitude or sign of $\Delta\sigma$ or $\Delta\pi$ brings about a corresponding change in the $\Delta(\Delta G^\ddagger)$. Thus, in simple cyclic ketones, such as cyclopentanone or cyclohexanone derivatives where $\Delta\sigma$ is generally small, $\Delta(\Delta G^\ddagger)$ or the stereochemistry of the reaction would receive a relatively high proportion of contribution from $\Delta\pi$, i.e., one is prone to observe the product stability control.

A classical example of product stability controlled stereochemistry could be observed when $\Delta\pi$ is greater than $\Delta\sigma$ yet different in sign. Under such condition any influence of $\Delta\sigma$ on the overall stereochemistry would be opposed and subdued by that of $\Delta\pi$, and the net result is the preferential formation of the more stable of the two possible diastereomers.

(30) G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, 80 614 (1958).

A gradual increase in $\Delta\sigma$ by making a ketone more rigid or crowded would gradually tilt the stereochemistry of the reaction toward the realm of steric strain control.[22] Upon further increase of $\Delta\sigma$ to a point where it becomes greater than $\Delta\pi$ or $1.4\Delta G°$, stereochemistry of the reaction becomes reversed from product stability to the steric strain controlled pattern.

In Table IV, the stereochemistry of reduction of methyl-substituted cyclic ketones by $LiAlH_4$ is treated quantitatively by the use of eq 5 and 7. Both $\Delta\sigma_H$ and $\Delta\pi_H$ or $1.4\Delta G°$ were obtained by using eq 5 and Figure 4 from two independent reactions. The overall differences of the free energy of activation, $\Delta(\Delta G^{\ddagger})$, were then calculated from eq 7. From the energy differences, the percentage of trans or endo alcohols were calculated and compared with the actual results. The agreements between the two numbers are striking. The only deviation appears in the case of 3,3,5-trimethylcyclohexanone, whose secondary alcohol derivatives show a widely spread value of $\Delta G°_H$ ranging from 1.47 in cyclohexane to 1.96 kcal/mol in 2-propanol. A number of 1.73 kcal/mol for $\Delta G°_H$ will give a perfect fit with the observed result.

In the case of 2,2-dimethyl-4-*tert*-butylcyclohexanone, an unusually high stereoselectivity (95.9% of equatorial alcohol) has been reported. This high stereoselectivity is believed to be brought about not because of a high $\Delta\sigma_H$ but because of the converging contributions from both $\Delta\sigma_H$ and $\Delta\pi_H$. By the use of the two known parameters, $\Delta G°_H$ (0.87 kcal/mol)[28] and $\Delta(\Delta G^{\ddagger})_H$ (1.7 kcal/mol),[1] the steric strain of the reaction, $\Delta\sigma_H$ or $\Delta\sigma_{Me}$ is estimated to be only 0.49 kcal/mol according to eq 7. This allows one to predict the formation of 71% of 1,2,2-trimethyl-*trans*-4-*tert*-butylcyclohexan-*r*-1-ol from the reaction of MeLi and the ketone in ether at 0 °C. Should this prediction be confirmed, it would mean a reversal of steric congestion from the axial side to the equatorial side of the ring by the introduction of a *gem*-dimethyl group at C-2. A similar phenomenon was observed in the hydride reduction of 2,4,4-trimethylcyclopentanone. The formation of 91% of trans-2,4,4-trimethylcyclopentanol[6] is the most stereospecific in the present cyclopentanones system. While $\Delta\sigma_H$ = 0.38 kcal/mol in this system is not unusually high, the mutually enhanced contributions of $\Delta\sigma_H$ and $\Delta\pi_H$ in the same direction result in a high stereoselectivity. The $LiAlH_4$ reduction of ketone **11** is more stereospecific than that of ketone **10**, 92.7 vs. 89%, due to a decreased contribution from $\Delta G°$ in the former case. This demonstrates the importance of $\Delta\pi_H$ (or $\Delta G°$) on the stereochemical courses of $LiAlH_4$ reductions even though these reductions have been cited as classical examples of SSC.[5b]

In acyclic systems, $LiAlH_4$ reduction of an unsymmetrical ketone follows Cram[32] or Prelog's rule.[33] The stereochemical course is predictable on the basis of steric strain control alone. This absence of product stability control may be attributed to the negligible difference in the product stabilities of the two diastereomers. Hence, in the acyclic system, only steric strain control or $\Delta\sigma$ is important, and the stereochemistry of the reaction can be predicted without taking into account the effect of the product stability difference.

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Registry No. 1, 98-53-3; 2, 591-24-2; 3, 936-99-2; 4, 583-60-8; 5, 873-94-9; 6, 1120-72-5; *cis*-7, 6672-39-5; *trans*-7, 32476-60-1; 8, 4573-09-5; 9, 4694-12-6; 10, 497-38-1; 11, 10218-04-9; 12, 76-22-2; *cis*-4-*tert*-butyl-1-methylcyclohexanol, 16980-56-6; *trans*-4-*tert*-butyl-1-methylcyclohexanol, 16980-55-5; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; *cis*-3-methylcyclohexanol, 5454-79-5; *trans*-3-methylcyclohexanol, 7443-55-2; *cis*-1,3-dimethylcyclohexanol, 15466-94-1; *trans*-1,3-dimethylcyclohexanol, 15466-93-0; *cis*-3-*tert*-butyl-1-methylcyclohexanol, 57279-17-1; *trans*-3-*tert*-butyl-1-methylcyclohexanol, 57279-18-2; *cis*-3-*tert*-butylcyclohexanol, 10488-10-5; *trans*-3-*tert*-butylcyclohexanol, 16201-66-4; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *cis*-1,2-dimethylcyclohexanol, 19879-11-9; *trans*-1,2-dimethylcyclohexanol, 19879-12-0; *cis*-3,3,5-trimethylcyclohexanol, 933-48-2; *trans*-3,3,5-trimethylcyclohexanol, 767-54-4; *cis*-1,3,3,5-tetramethylcyclohexanol, 2952-06-9; *trans*-1,3,3,5-tetramethylcyclohexanol, 2815-49-8; *cis*-1,2-dimethylcyclopentanol, 16467-13-3; *trans*-1,2-dimethylcyclopentanol, 16467-04-2; *cis*-2-methylcyclopentanol, 25144-05-2; *trans*-2-methylcyclopentanol, 25144-04-1; *c*-2,*c*-5-dimethylcyclopentan-*r*-1-ol, 65404-79-7; *c*-2,*t*-5-dimethylcyclopentan-*r*-1-ol, 65378-78-1; *t*-2,*t*-5-dimethylcyclopentan-*r*-1-ol, 63057-29-4; *cis*,*cis*-1,2,5-trimethylcyclopentan-*r*-1-ol, 65378-81-6; *cis*,*trans*-1,2,5-trimethylcyclopentan-*r*-1-ol, 65378-82-7; *trans*,*trans*-1,2,5-trimethylcyclopentan-*r*-1-ol, 65378-83-8; *cis*-1,2,2,5-tetramethylcyclopentanol, 65378-84-9; *trans*-1,2,2,5-tetramethylcyclopentanol, 65378-85-0; *cis*-2,2,5-trimethylcyclopentanol, 65378-79-2; *trans*-2,2,5-trimethylcyclopentanol, 65378-80-5; *cis*-2,4,4-trimethylcyclopentanol, 57905-84-7; *trans*-2,4,4-trimethylcyclopentanol, 57905-83-6; *cis*-1,2,4,4-tetramethylcyclopentanol, 58493-56-4; *trans*-1,2,4,4-tetramethylcyclopentanol, 58493-55-3; *endo*-2-methylbicyclo[2.2.1]heptan-2-ol, 3212-16-6; *exo*-2-methylbicyclo[2.2.1]heptan-2-ol, 3212-15-5; *endo*-bicyclo[2.2.1]heptan-2-ol, 497-36-9; *exo*-bicyclo[2.2.1]heptan-2-ol, 497-37-0; *endo*-1-methylbicyclo[2.2.1]heptan-2-ol, 3588-21-4; *exo*-1-methylbicyclo[2.2.1]heptan-2-ol, 766-25-6; *endo*-1,2-dimethylbicyclo[2.2.1]heptan-2-ol, 13429-45-3; *exo*-1,2-dimethylbicyclo[2.2.1]heptan-2-ol, 23351-29-3; *endo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 507-70-0; *exo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 124-76-5; *endo*-1,2,7,7-tetramethylbicyclo[2.2.1]heptan-2-ol, 28405-88-1; *exo*-1,2,7,7-tetramethylbicyclo[2.2.1]heptan-2-ol, 2371-42-8; MeLi, 917-54-4; $LiAlH_4$, 16853-85-3.

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