in the dark. The resulting solution was evaporated and the residue purified (alumina, CCl_4) and recrystallized (CCl_4) to give spiro compound 32 (0.046 g, 82%).

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Registry No. 1, 789-24-2; 2, 88180-04-5; 6, 88180-05-6; 7, 88180-06-7; 9, 88180-07-8; 10, 88180-08-9; 11, 29972-98-3; 12, 88180-11-4; 14, 88180-10-3; 16, 88180-12-5; 17, 88180-09-0; 19, 17165-86-5; 20, 88180-13-6; 21, 17926-66-8; 22, 88180-14-7; 24, 1705-89-1; 25, 88180-15-8; 26, 88180-16-9; 27, 88180-17-0; 28, 88180-18-1; 29, 67665-44-5; 30, 159-66-0; 31, 88180-19-2; 32, 88180-20-5; 33, 88180-21-6; 34, 88180-23-8; 35, 88180-22-7; PTM, 4070-01-3; PPF, 32390-14-0; C_6Cl_6, 118-74-1.

Asymmetric Induction in Carbonyl Analogues: Comments on Models

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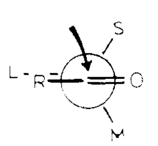
Organometallic reagent additions to certain carbonyl analogues are reported. The compounds in question have $C{=}C(CN)_2$ or $C{=}C(CO_2R)_2$ in place of CO. The ground-state conformation of these analogues is quite specific. Some of the additions obey the Cram et al. rules for asymmetric induction but require that approach of the organometallic reagent occurs over the L group in the ground-state conformation. This is taken as an indication that the ground-state conformation is not relevant, in agreement with the Curtin–Hammett principle. In other cases, little asymmetric induction is observed. A third type of behavior concerns opposite modes of addition to the dicyanide vs. the diester substrates. The variability of the data are discussed in terms of the validity of rules for asymmetric induction. Secondary isotope effects are explored in an attempt to resolve the dichotomy between additions to cyclic vs. acyclic ketones. The suggestion is made that the dichotomy in stereochemistry of addition may be related to a kinetically significant conformational change in cyclohexanones vs. acyclic substrates or cyclopentanones.

In recent years, a variety of approaches to asymmetric induction has resulted in systems showing high enantiomeric purities in the reaction products.[1-3] These striking successes have shifted interest from consideration of the fundamental bases of the phenomenon. Studies on the steric course of additions to carbonyl date from the 1950's when Barton codified the major findings for cyclohexanones. In acyclic systems, Cram and ElHafez established the rule for asymmetric induction (cf. model 1), a model that still is widely used for predictive purposes.[4]



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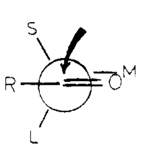

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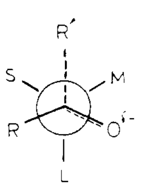

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Later, Leitereg and Cram extended this work to include 1,3-asymmetric induction.[5] Cram emphasized the growing space demands of the carbonyl oxygen as charge develops in the course of addition, a factor often disregarded in more recent work.

In 1967, Karabatsos formulated an alternative approach (model 2) based on extensive studies of the conformations of carbonyl compounds.[6] Approach to carbonyl was considered most likely to occur over the small group (usually hydrogen) in the conformation in which the medium-sized group is eclipsed with carbonyl. However, subsequent work on substrates with large R groups was interpreted in terms of a different model.[6c] In 1968, Chêrest, Felkin, and Prudent suggested a third approach (cf. 3). This model emphasizes the transition state, not the ground state, as seems reasonable on the basis of the Curtin–Hammett principle.[7-9] These workers agree with Karabatsos and others that the transition state is "early"; i.e., it resembles the starting structure rather than the product with regard to the extent of bond formation. However, torsional interactions in the developing bond to

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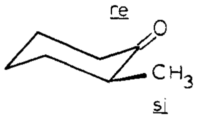
0022-3263/84/1949-0778$01.50/0 © 1984 American Chemical Society

carbonyl are regarded as significant. The studies of Chêrest et al. remain one of the few attempts to correlate cyclic and acyclic substrates.[10]

Regarding the dichotomy between cyclic and acyclic substrates, the authoritative commentators Morrison and Mosher wrote "...the Cram rule does not apply to the cyclic system, nor did Cram attempt to apply it to cyclic systems. The intriguing question is why should it fail in its application to this system which on the surface appears to be the best possible example for testing this model."[11] In general, small reagents attack the *re* face of carbonyl (cf. **4**), whereas large reagents attack the *si* face.[12,13] Models **1-3** have no provision for change in mode of attack, and until recently, this did not appear to be an important consideration in acyclic reactions.[14] In the cyclic system, Chêrest et al. considered the steric interaction between the attacking reagent and H_{3ax} and H_{5ax} to impede *re* approach. With large reagents, the enhanced steric interactions lead to a change to *si* approach. *si* approach is inhibited by torsional interactions between the developing bond and H_{2ax} and H_{6ax}. Thus, it is worthwhile to consider briefly the fundamental basis of torsional interactions. Torsional interactions are quantum mechanical phenomena associated with electrons delocalized in σ orbitals encompassing several classical "bonds". Some of the filled orbitals move upward in energy upon eclipsing of classical bonds, and others move downward, but the net effect is usually destabilizing.[15] Since the size of atoms plays no direct role in torsional interactions, the size of the reagent is not a factor. The moot point regarding this ingenious explanation concerns whether steric effects should not also occur in *si* attack. Indeed, Marshall, Richer, and others consider steric effects to be of importance.[16]



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An interesting study by Huet et al. on 6-substituted α,β-unsaturated cyclohexanones showed that the product spread was not dissimilar to that of the saturated analogues.[17] The lesser steric interactions due to the absence of H_{3ax} in the unsaturated molecule must approximately cancel the lesser torsional/steric effects due to the absence of H_{2ax}. In a force-field calculation model of ketone reductions, Wipke and Gund were able to account for the product ratios only by incorporation of a torsional correction,[18] although the direction chosen for hydride approach to carbonyl remains open to question. Houk believes that torsional effects are *more* pronounced in the transition state than in the product.[19] Thus, torsional effects would appear to have an undeniable influence, although the dimension of their influence is not entirely clear at present.

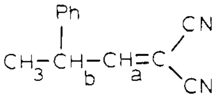
The objectives of the present study were twofold: (1) to study the effect of size and the (lack of) metal coordinating ability at the charge migration terminus and (2) to study ketone additions in cyclic vs. acyclic systems with similar substitution patterns.

Carbonyl Analogues

In previous work, the effect on asymmetric induction of varying the groups at chiral carbon, the effect of varying the nonchiral R group at carbonyl, and the effect of various reagents have been thoroughly studied. To the best of our knowledge, the effect of structure at the charge migration terminus (i.e., oxygen in the case of ketones) has not been investigated.

Wallenfels et al. has demonstrated the similarity of $C{=}C(CN)_2$ and $C{=}C(CO_2R_2)$ groups to $C{=}O$ in many types of reactions.[20] In these carbonyl analogues, the steric requirements of the dicyanide and diester functions are obviously much greater than oxygen. On the other hand, the charge that develops in the course of reaction is delocalized in the case of the carbonyl analogues, and solvation demands and cation association effects are reduced.

In the asymmetric induction studies reported herein, the groups at chiral carbon are L = Ph, M = CH_3, and S = H; i.e., the same groups as were present in Cram's original studies.[4] The dicyanide and diester substrates **5** and **6** are much more conformationally pure than 2-phenylpropanal, the original substrate.[4] For **5** and **6**, the very large NMR coupling constants ($^3J_{ab}$ = 11.0 Hz for **5** and 10.5 Hz for **6**) indicate a strong tendency for trans hydrogens. Thus, H_b is eclipsed with $C{=}C$.[21] This conformation is reasonable, considering the steric requirements of the dicyanide or diester functions. In 2-phenylpropanal, Karabatsos and Hsi found that the trans conformer had a small weight, ca. 23%.[22] Using Bothner-By's estimate of ^3J = 11 Hz as the maximum value for ^3J, the weight of the trans conformer must be ≥90% for **5** and **6**.[21] Theoretical treatments also indicate that a bond (like the $C{-}H_b$ bond in **5** and **6**) should be eclipsed with $C{=}C$.[23] The reason



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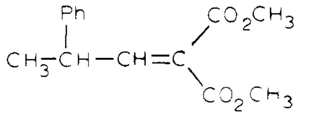

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[10] (a) The most attractive approach, the LFER approach of Ruch and Ugi (Ruch, E.; Ugi, I. *Top. Stereochem.* **1969**, *4*, 99; *Theor. Chim. Acta* **1970**, *4*, 287), has not been successfully applied to 1,2-asymmetric induction, to the best of the writer's knowledge. (b) Salem, L. *J. Am. Chem. Soc.* **1973**, *95*, 94.

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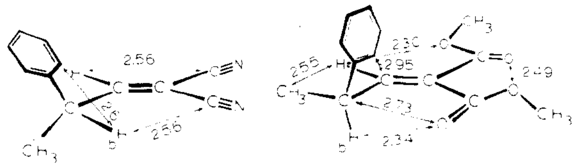
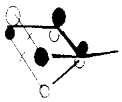
Scheme I



5 6

for this preference is not because eclipsing is favorable but because this arrangement avoids an antibonding interaction of orbitals involving the other two bonds to the sp^3 carbon (cf. 7).



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On the other hand, molecular mechanics calculations[24] on **5** indicate a minimum of energy for a H_a–C–C–H_b dihedral angle of 117° (using the parameterization "built-in" the program). In this conformation, H_a is eclipsed with CH_3. The conformation indicated by NMR (and also favored on theoretical grounds[23]) could be duplicated by incorporating some ad hoc changes in the parameterization. Principal among these is a rather high V_1 torsional constant for HCC=C (0.9 kcal/mol), which then favors a 0° dihedral angle (eclipsed conformation), plus inclusion of a lower bending constant for C=CCN (0.41 mdyne Å rad^{-2}) and a lower bending constant for H_bC=C (0.40 mdyne Å rad^{-2}). The resulting "steric energy" (a term used in the MM2 program indicating the sum of all interactions) is quite low, 0.8 kcal/mol. However, this low figure results from a cancellation of terms [van der Waals (steric), 6 kcal/mol, vs. torsional interactions, −9 kcal/mol]. The latter, of course, is a consequence of the exact figure chosen in the parameterization changes. The various energy terms are listed in the Experimental Section.

In the subsequent discussions of the reactions of **5**, it will become of interest to know the energy required to rotate phenyl out-of-the-way of a reagent approaching the *re* face of the C=C. This energy is of the order of 2 kcal.

The calculations on the diester **6** could not be induced to reproduce the geometry indicated by NMR (H_b eclipsed with C=C). The total energy under a variety of parameterization conditions was much higher for **6** than **5** (ca. 23 vs. 0.8 kcal/mol), undoubtedly due to the greater steric requirements of the ester functions. The H_a–C–C–H_b dihedral angle was 148° in this particular calculation. Other details of the calculated geometry of **5** and **6** are shown in Scheme I.

The difficulty with **6** may be due to the parameterization of MM2, which requires both ester functions to be coplanar with C=C. In actuality, as long as one ester function is coplanar, the loss of resonance stabilization taken by moving the other ester out-of-plane is more than made up by improved steric interactions.

Table I lists the results of various types of addition reactions to these carbonyl analogues. Three types of addends were studied: alkyl(aryl) Grignards, alkyllithiums, and lithium dialkyl(diaryl)cuprates. The second class of reagents was least successful, giving all manner of products save the desired ones.[25] The results of the few successful runs are given in Table I. In general, good reproducibility was observed in the various additions. Quantitative ^{13}C NMR spectroscopy proved to be a good tool for product analysis.[26] The peak intensities for the isomeric products could be compared carbon by carbon.

Table I. Product Ratios in Addition Reactions of the Carbonyl Analogues 5 and 6

substrate	addend	reaction conditions	product ratios[b] (parf:pref)
5	$CH_3MgI \cdot Et_2O$	normal addition, RT[c]	35:65
5	$CH_3MgI \cdot Et_2O$	inverse addition, RT	39:61
5	$CH_3MgI \cdot Et_2O$	normal, −78 °C	36:64
5	i-$PrMgBr \cdot Et_2O$	normal, RT	53:47
5	i-$PrMgBr \cdot Et_2O$	inverse, RT	45:55
5	$PhMgBr \cdot Et_2O$	normal, RT	9:91
5	$PhMgBr \cdot Et_2O$	inverse, RT	25:75
5	$PhMgBr \cdot Et_2O$	normal, −78 °C	10:90
6[a]	$CH_3MgI \cdot Et_2O$	normal, RT	48:52[a]
6	$CH_3MgI \cdot Et_2O$	normal, −78 °C	48:52
6	$PhMgBr \cdot Et_2O$	normal, RT	73:27
6	$PhMgBr \cdot Et_2O$	normal, −78 °C	75:25
5	CH_3Li	normal, RT	53:47
5	CH_3Li	normal, ca. 0 °C	49:51
5	CH_3Li	normal, −78 °C	50:50
5	$(CH_3)_2CuLi$	normal, RT	39:61
5	Ph_2CuLi	normal, RT	44:56
5	Ph_2CuLi	normal, −78 °C	40:60
6	$(CH_3)_2CuLi$	normal, RT	43:57
6	Ph_2CuLi	normal, RT	88:12
6	Ph_2CuLi	normal, −78 °C	88:12

[a] The ethyl ester gave similar results to the methyl ester. [b] The C-K-C rules predict the pref isomer. [c] Room temperature.

The stereochemistry of addition proved to be variable. Methyl Grignard addition to the dicyanide **5** gave a modest excess of the isomer eventually assigned the "pref" configuration (cf. Experimental Section).[27] Little difference was noted in normal vs. inverse additions or in additions at low temperature. The dominance of the pref isomer is in accord with the predictions of the C–K–C rules but not in agreement with predictions based on simple steric effects, which were the basis of two of the three rules. If the ground-state conformation has any significance, formation of the pref product requires approach over the L = Ph group, the one possibility that previous investigators agree is unlikely.[4,6,7] Of course, the ground-state conformation need not be significant.[8] As the molecule gains energy in its approach to the transition state, different weightings of conformers may occur. Of greater importance is the approach and development of bonding to the addend. However, if the ground-state conformation is not significant in the additions to **5** and **6**, it may also not be significant in additions to carbonyls themselves. If not significant, of what value are predictions of reaction stereochemistry based on quantum calculations involving ground-state conformations?[28]

Other additions were irregular (cf. Table I). Methyllithium gave a slight preference for the parf diastereomer, but lithium dimethylcuprate again gave the pref isomer. Isopropyl Grignard on **5** showed little specificity. Major degrees of asymmetric induction occurred only for phenyl

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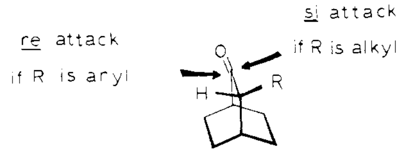
Grignard and lithium diphenylcuprate. However, the pref product is dominant from **5** and the parf is dominant from **6**.

These results are unsatisfying from the standpoint of scientific inquiry. The correlation of behavior, which is the first step in establishing cause–effect relationships, is absent. The minimum statement is that the C–K–C rules are applicable to these carbonyl analogues in some cases, but not others. When the C–K–C rules do appear to apply, the approach of the addend is contrasteric on the basis of the ground-state conformation. As stated earlier, the C–K–C rules do not apply to cyclic ketones. Among cyclic ketones themselves, the reactions of cases such as **8** are not easily understood; a contrasteric approach again is involved.[8] In acyclic ketones, Spanish workers have recently shown that differing organometallic addends gave products of opposite stereochemistry, not unlike the data of Table I.[14] In view of the increasing array of discordant results, the possibility must be faced that the C–K–C rules may have no strong fundamental bases.



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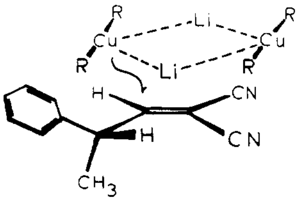
To attempt to perceive why certain substrates have a common mode of reaction, e.g., Karabatsos' results showing a reaction stereochemistry that parallels ground-state conformation, it is perhaps instructive to review the dynamics of the reaction. These simple ketones have barriers to internal rotation on the order of 2 kcal, which leads to a rate of conformational interconversion of ca. 10^{11} s^{-1}. This rate is as large or faster than diffusion. Thus, even if molecules having sufficient energy to react approach on a collision course, internal rotation occurs during the encounter. Since some orientations of the ketone are more favorable than others for reaction, a product-forming collision becomes a matter of probabilities. The stereochemistry of product formation is often not highly temperature dependent (low $\delta\Delta H^{\ddagger}$) and strongly affected by $\delta\Delta S^{\ddagger}$. Since the transition state involves energized molecules, conformational weights may vary. In simple cases, the probabilities of reaction "may be" (not "must be") proportional to the ground-state conformational weights by scaled factors. However, it is a matter of similar intramolecular interactions being important in the transition state as in the ground state, not that a certain ground-state conformation uniquely gives reaction.[8] In the present cases, i.e., substrates **5** and **6**, the much greater steric effects may lead to different interactions in the transition state than in the ground state and thus no apparent correlation with ground-state conformation.

Alternatively, it is also possible that the mechanism of reaction of **5**, of **6**, and of the original ketones may be different. Cuprate reagents are planar and dimeric in character.[30] Charge-transfer processes have been suggested as important in cuprate additions to substrates similar to **5** or **6**.[31] In certain cases, *E*/*Z* isomerization of the substrate occurs, possibly due to electron transfer from cuprate to alkene, internal rotation, and then back-donation of the odd electron. Substrates similar to **5** have been shown to participate in reactions proceeding by electron-transfer mechanisms, e.g., with superoxide.[32] It is conceivable that an electron-transfer (ET) process might occur to a greater degree for the dicyanide **5**, in contrast to greater nucleophilic addition for the diester **6**. Ashby and co-workers have found strong evidence for ET processes in certain types of Grignard additions to ketones.[33] Thus, similar mechanisms for Grignard and cuprate additions to **5** are not out of the realm of possibility. In contrast, the steric effect of the nonplanar ester function in **6** may inhibit complexation and ultimate electron transfer.



6a

The cyclic analogues of **5** and **6** were not studied, since Zefirov and co-workers have shown that the C_2 substituent is axial. This substituent would inhibit *si* attack by any mechanism.[34]

Cyclic vs. Acyclic Systems

One difficulty in assessing the dichotomy between cyclic vs. acyclic substrates is that the data are not available for similarly substituted cases. In acyclic systems, the degree of asymmetric induction is rather small if the M and L groups are both alkyl groups.[11] High degrees of asymmetric induction are most often observed when L is aromatic. For cyclic substrates, only scattered reports exist on the reactions of 2-phenylcyclohexanone.[35] The prior work suggests no unusual effect for the phenyl substituent.

Table II lists the stereochemistry of reduction of phenyl-substituted cyclic and acyclic substrates, using some of the newer hydride reducing agents. Prior indications are upheld for 2-phenylcyclohexanone. The classic response to the size of the reductant is found;[12] small reagents give *re* attack and large reagents give *si*. The data are similar for 2-phenylcyclohexanone and 2-alkylcyclohexanones (cf. Table III). On the other hand, the acyclic substrate is much less sensitive to the size of the reductant. In our hands, K-Selectride (Aldrich) gave about the same results as other hydrides. Thus, the dichotomy between cyclic and acyclic substrates is broadened. Cyclic substrates do not appear to be highly sensitive to the nature of the C_2 substituent, but the steric course of the reaction is sensitive to the type of reagent; acyclic substrates show the reverse.

In order to account for the effect of phenyl in acyclic cases, Chĕrest et al. have suggested a polar effect of phenyl.[7] Although phenyl is slightly electron withdrawing (group moment, 0.3 D),[36] phenyl is hardly the epitome of

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(30) Stewart, K. R.; Lever, J. R.; Whangbo, M. H. *J. Org. Chem.* **1982**, *47*, 1472.

(31) (a) Cabaret, D.; Welvaert, Z. *J. Organomet. Chem.* **1979**, *177*, 75. (b) Solladie-Cavallo, A.; Tsamo, E. *Ibid.* **1979**, *172*, 1165. (c) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 288. (d) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141. (e) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721.

(32) Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Lett.* **1978**, 1143.

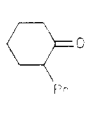
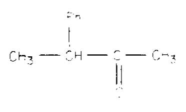
(33) Ashby, E. C.; Weisemann, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 189, 3101.

(34) Zefirov, N. S.; Baranenkov, I. M. *Tetrahedron Lett.* **1979**, 4875. Also see ref 15a.

(35) (a) Cense, J. M. *Tetrahedron Lett.* **1972**, 2153. (b) Thomas, T. L.; Davison, T. A.; Griffith, R. C.; Scott, F. L. *Ibid.*, **1976**, 1465. (c) Reference 12c; ref 18.

(36) Minkin, V. I.; Osipov, O. A.; Zhdanov, Y. A. "Dipole Moments in Organic Chemistry"; Plenum Press: New York, 1970; p 89.

Table II. Stereochemistry of Addition of Various Hydrides to Cyclic vs. Acyclic Ketones

hydride (solvent)	 cyclic substrate, % trans product	 acyclic substrate,[g] % parf product
potassium tri-*sec*-butylhydridoborate[d] (THF)	2.0	85.4
potassium tri-*sec*-butylhydridoborate (THF, 18-C-6)	2.0	
aluminum isopropoxide[a] (*i*-PrOH)	16.8	61.5
lithium tri-*t*-butoxyhydridoaluminate (Et_2O)	35.3	
sodium hydridotrimethoxyborate (Et_2O)	44.1	67.1
sodium hydridotrimethoxyborate (THF)	55.9	
9-borabicyclononane (THF)	55.5	53.7
diborane (THF)	58.1	
sodium tetrahydridoborate (Et_2O, aqueous OH^-)	71.6	67.3
PmHS/DbTO[b] (EtOH)	71.4	59.9
sodium bis(1,4-dioxapentyl)dihydridoaluminate[c] (C_6H_6)	73.2	69.5
sodium bis(1,4-dioxapentyl)dihydridoaluminate (Et_2O)	61.6	
sodium bis(1,4-dioxapentyl)dihydridoaluminate (Et_2O, 18-C-6)	69.6	
sodium cyanotrihydridoborate (CH_3OH, HCl)	75.6	81.1
lithium tetrahydridoaluminate (Et_2O)[e]	78.3	81.1
lithium tetrahydridoaluminate (Et_2O)[f]	73.2	75.1
lithium tetrahydridoaluminate (C_6H_6)[e]	56.2	69.2
lithium tetrahydridoaluminate (TMEDA, C_6H_6)	70.6	72.6

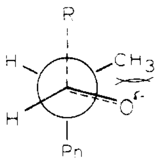
[a] Kinetic conditions (not equilibrium). [b] Polymethylhydrogensiloxane/tetrabutyldiacetoxytin oxide dimer. [c] Commercial name is Red-Al (Aldrich). [d] Commercial name is K-Selectride (Aldrich). [e] Not homogeneous. [f] Homogeneous. [g] C–K–C rules predict the parf isomer.

Table III. Effect of Substituent on Stereochemistry of LAH Reduction

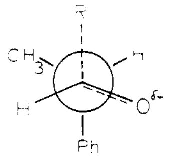
cyclic ketone	trans product, %
2-methylcyclohexanone	76[b]
2-methylcyclopentanone	75–82[a]
2-isopropylcyclohexanone	71[b]
2-phenylcyclohexanone	78

[a] Reference 11. [b] Reference 35a.

a polar group. Anh and co-workers recast the findings of Chérest et al. in terms of an antiperiplanar effect (cf. model **3** in which the attacking reagent and L = Ph are trans).[29] Although theoretical calculations have lent credence to the general idea, it is not easy to discern why phenyl should be antiperiplanar to the approaching reagent more than another group or why the effect should not occur in 2-phenylhexanone. Furthermore, in moving from ketones to aldehydes as substrate, it is unclear why the preference for **9a** over the sterically preferred **9b** persists. On the other hand, Karabatsos' data indicate that phenyl has an antipathy for carbonyl in the ground state.[22] Phenyl prefers a dihedral angle of 120° with respect to CO, whereas methyl and ethyl, etc., tolerate an eclipsed conformation with respect to CO to a greater extent. To the extent that this orientation is relevant in the transition state, phenyl would be opposed to the approaching reagent.



9a



9b

In cyclohexanones, Anh emphasizes the likelihood of ring flattening in order to enhance antiperiplanarity between the incoming reagent and H_{2ax} and H_{6ax}.[29] Earlier, Doyle and co-workers had postulated ring flattening in cases where coordination between carbonyl and metallic reagents occurs.[37] In early work, Landor and Regan had suggested the importance of nonchair forms in the course of additions to carbonyl.[38] This idea was originally unpopular,[39] but Ashby discussed these possibilities at some length in a review of carbonyl additions.[40,41] Recently, Wigfield demonstrated that the ground-state geometry of cyclohexanone does not necessarily pertain in the transition state.[42] In view of the number of papers that postulate flattening or distortion of the ring, force-field calculations were carried out on representative systems. The problem has become exacerbated by recent findings concerning the direction of approach toward carbonyl. Recent investigations favor an approach "behind" carbonyl (**10**) rather than colinear with the p orbital.[27,43,44]

The object of these calculations was to estimate the energy requirements for various types of changes. Hydride reductions of cyclic ketones proceed with very low enthalpy of activation, and a highly distorted ring may not be possible for a low energy activation process. Alternatively, distortion may occur, but it could then also be kinetically significant and account for some of the difference between cyclic and acyclic systems.[8]

Calculations were performed on 2-methylcyclopentanone and 2-methylcyclohexanone. The corresponding 2-phenyl compounds would have been preferable, but these would have required much greater calculation times. The behavior of the five-membered ring is not similar to the six.[11] The five-membered ring does not show the *re* to *si* change in mode of attack as the bulk of the reagent increases. In other aspects, the five-membered ring resembles acyclic

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(37) (a) Doyle, M. P.; McOsker, C. C.; Ball, N.; West, C. T. *J. Org. Chem.* **1977**, *42*, 1922. (b) Doyle, M. P.; West, C. T. "Stereoselective Reductions"; Halstead: New York, 1976.

(38) Landor, S. R.; Regan, J. P. *J. Chem. Soc. C* **1967**, 1159.

(39) Chauviere et al. (Chauviere, G.; Welvaert, Z.; Eugene, D.; Richer, J. C. *Can. J. Chem.* **1969**, *47*, 3285) strongly favor a retained chair conformation in the transition state.

(40) Ashby, E. C. *Chem. Rev.* **1975**, *75*, 521.

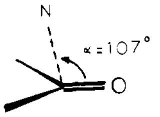
(41) Hirsl-Starcevik et al. (Hirsl-Starcevik, S.; Majerski, Z.; Sunko, D. E. *J. Am. Chem. Soc.* **1974**, *96*, 3659) have provided strong indications of a retained chair form in another type of reaction course.

(42) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.

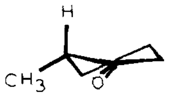
(43) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(44) Bürgi, H. B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

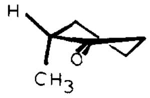
substrates.[11] The cyclopentanone ring upheld the reputation of its class and proved to be rather mobile.[45] Two minima of energy were found (11 and 11') and perhaps more exist as yet undetected. Each minimum was rather shallow; a rotation of 20° on either side of the minimum led to a maximum increase in energy of 1.6 kcal (usually less.)



10



11, SE 9.2 kcal/mol

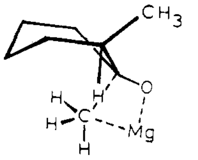


11', SE 9.2

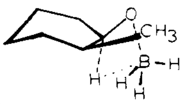
The six-membered ring proved to be somewhat more rigid. Full flattening of the carbonyl group (leaving only C_4 out-of-plane) required on the order of 5 kcal/mol. A partial flattening such that C_1 lay about 30° out of the C_2–C_3–C_5–C_6 plane cost only 1.6 kcal. A change to the most stable twist–boat form that could be conveniently located also cost ca. 5 kcal,[46] although the intermediate points on the way to this local minimum are likely to be much higher in energy.[24] It is evident from these trial calculations that conformational adjustment would require significant energy in terms of the 5 kcal/mol activation enthalpy.[47]

In the second approach, the hydride or Grignard reagent is included in the calculations at a range of distances from carbonyl. Several angles of approach of the reagent were investigated for *re* attack. The reacting centers were held in a rigid geometry similar to that determined by Eisenstein et al.[29] The calculation minimized the energy of the nonreacting groups. In the simulation of the borohydride reduction of 2-methylcyclohexanone, little tendency for ring distortion was found either in the *si* or the experimentally favored *re* mode of approach. However, the calculations did not include bonding between hydride and carbonyl carbon. The interactions present were mainly steric effects. Even with a hydride position 25° "behind" the carbonyl p orbital at a hydride to carbonyl carbon distance of 1.6 Å, distortion of the ring was minimal, although distortion of borohydride was severe due to the closeness of oxygen. The latter may not be a real effect in cases where borohydride interacts with solvent rather than the ketone oxygen. The calculations brought out a factor in four-center reactions that we had not suspected, namely, that the interactions of atoms 1 with 3 and of 2 with 4 are repulsive (by about 4 kcal between boron and carbonyl carbon, in this particular simulation). The actual reacting system may be forced to adopt a rather looser geometry than the simulation. This also may be one reason that four-center mechanisms are rather rare in organic chemistry.

In the simulation of the addition of methyl Grignard, little tendency for ring distortion was found in the approach of methyl to the *re* face of carbonyl in the geometries tested. However, the Grignard methyl was highly distorted. In the favored *si* attack, some distortion of the ring toward a pseudo-boat form was noted, cf. structure **12**. This effect arises from an avoided repulsion between the Grignard methyl and H_{2ax} and H_{6ax}, which become splayed outward. It is not known how relevant this geometry is to the true transition state, but it does show that steric effects can be significant.



12



13

The final approach concerns a simulation of the later stages of the reaction by incorporating a hydride to carbonyl carbon bond that is intact but stretched (1.6 Å). The erstwhile hydride is maintained along the reaction trajectory. In these cases, *re* approach again gives near normal geometry, but *si* attack now leads to flattening in the carbonyl region (cf. **13**). Thus, in one case, product-like geometry gives rise to an apparent ring distortion not present in the analogous reactant-like state. For this and other reasons it is of interest to study the position of the transition state along the reaction coordinate.

A difference in the position of the transition state could explain some of the dichotomy between cyclic and acyclic ketones. The relative insensitivity of acyclic ketones to the type of hydride could be due to an early transition state in which hydride is distant from substrate. The apparent dependence of the steric course of reaction on ground-state conformation[6] could also be explained by a relatively unperturbed carbonyl in the transition state. The insensitivity of cyclic ketones to the type of C_2 substituent could be due to a later transition state in which the nonreacting parts of the original reagent have largely departed. However, this interpretation is in opposition to the Hammond postulate, as the cyclic ketones are more reactive.[42,47]

The technique applied to investigate this question was secondary isotope effects. Geneste and Lamaty have provided a detailed discussion of the factors that affect secondary isotope effects in reduction of α-deuterated ketones.[48,49] Notable among these is hyperconjugation, which gives rise to a greater stabilization of the ground state for the protic ketone and a slower reaction. In late transition states, the hyperconjugative properties of the carbonyl are largely destroyed, leading to a relatively large differentiation in rates of reaction between isotopically substituted ketones. Geneste and Lamaty found k_H/k_D values for borohydride reduction clustered from 1.0 to 0.88, with cyclohexanones generally showing pronounced isotope effects.[49] In reaction of ketones, a range of locations of the transition state along the reaction coordinate has been postulated.[6,7,12,16,29,35] Wigfield has suggested that the position is dependent upon the hydride used, ranging from product-like in the case of tetrahydridoborate to reactant-like for LAH.[42]

Our attempts to study borohydride reductions were hampered by exchange of the label with the basic solvent. Thus, LAH reductions in the nonprotic solvent ether were investigated. Even in these cases, a degree of mixing of labels was noted in the competition reactions between labeled and unlabeled ketones. Using high-resolution mass spectrometry, only the masses of fully deuterated (alpha positions) vs. undeuterated were monitored due to lack of

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(45) Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1.

(46) (a) Jensen, F. R.; Bek, B. H. *Top. Stereochem.* **1968**, *90*, 1066; a 5-kcal barrier is suggested. (b) Lamaty and Rogue (Lamaty, G.; Rogue, J. P. *Tetrahedron Lett.* **1970**, 5011, 5015) quote a somewhat smaller value of 3.7 kcal/mol. (c) Older work by Allinger et al. (Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999) quotes the boat form of cyclohexanone as ca. 3.3 kcal/mol above the chair. The barrier to interconversion would be expected to be somewhat larger.

(47) (a) Brown, H. C.; Wheeler, O. H.; Ichikawa, K. *Tetrahedron* **1957**, 1, 214. (b) Brown, H. C.; Bernheimer, R.; Morgan, K. J. *J. Am. Chem. Soc.* **1965**, *87*, 1280.

(48) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. (b) See also: Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755. (c) Giese, H. *Angew Chem., Int. Ed. Engl.* **1977**, 125.

(49) Geneste, P.; Lamaty, G. *Bull. Soc. Chim. Fr.* **1968**, 669.

knowledge of the stereochemistry of deuterium in partially deuterated substrates. The competition reactions were run to ca. 20% completion. The isomeric alcohols were isolated and individually analyzed, and the deuterium content was compared to that of the starting mixture of ketones. For the cyclic substrate, k_H/k_D was calculated to be 1.08 for the major product, *trans*-2-phenylcyclohexanol (**20**), and 0.96 for the minor isomer *cis*-**20**. For the acyclic substrate, k_H/k_D is 0.88 for the major product, *parf*-3-phenyl-2-butanol (**21**), compared to the less believable figure of ca. 0.6 for *pref*-**21**. The latter is perhaps adversely affected by the difficulties in handling small quantities of product. However, the results generally seem in accord with the Hammond postulate in that the more endothermic process leading to the minor product is associated with a more pronounced isotope effect and a later transition state.[49,50]

The present results suggest that quite a different transition-state position pertains for cyclic and acyclic ketones. However, these isotope effects should not be closely interpreted in view of the differences with Geneste and Lamaty's results for borohydride reduction. However, Geneste and Lamaty noted several instances in which torsional barriers were larger for deuterium-substituted molecules, an observation of importance where conformational changes are of importance to the overall kinetics. The complexity of secondary isotope effects is underscored by the results of Halevi who found k_H/k_D values that moved above and below unity as temperature varied in studies of ester hydrolyses.[51]

In conclusion, a reasonable case can be made that reductions of six-membered cyclic ketones may not obey the Curtin–Hammett principle in certain instances. In borohydride reductions, quite different activation parameters exist for substrates such as acetone ($\Delta H^{\ddagger}$ = 8.8 kcal/mol; $\Delta S^{\ddagger}$ = −39 eu) compared to the more reactive cyclohexanone ($\Delta H^{\ddagger}$ = 5.1 kcal/mol; $\Delta S^{\ddagger}$ = −48 eu).[47] LAH reductions may involve even lower activation enthalpies. If so, the activation enthalpy would be of roughly the same magnitude as the energy required for a conformational change such as a ring flattening. It is noteworthy that $\Delta S^{\ddagger}$ is 10 eu less than that for the mobile acetone or cyclopentanone cases. The change in the geometry of the cyclohexanone as part of the reaction course would then be a significant factor in the reaction energetics. The reason for a more rapid reaction of cyclohexanones under such conditions is not understood. Even though a deformation of the ring may be involved, the C_2 alkyl or phenyl groups are virtually held out of the path of an approaching reagent. If the cyclohexanone must suffer a deformation in the course of reaction, a slight additional deformation may adjust the nonbonded interactions from repulsive to attractive [significant negative energy (attractive) van der Waals terms were noted in some MM2 calculations involving sizeable distances between the reactants]. The onset of the attractive region vis-â-vis the repulsive region is quite sudden.[52] However, it should be recognized that transition-state models such as **1**–**3** and **12** and **13** are hardly unique. A range of geometries is highly probable.[53]

With regard to quantum mechanical interpretations of reaction stereochemistry, we fail to see why the systems studied by this technique should be uniquely exempt from Curtin–Hammett considerations. The stereochemistry is determined by the relative transition-state energies for the two stereochemical paths. The ground-state energy is a common factor for both processes. If the ground state and its energy are irrelevant, it is hard to see how the orbital characteristics, which determine the energy, should dominate the course of reaction.[54] These orbital characteristics should be important only to the extent that they are also present in the transition state. Cases have been reported in which transition-state orbital characteristics are quite different from the ground state.[54c]

Experimental Section

Spectral Methods. ^{1}H NMR spectra were taken on a Varian A-60D or a EM-390 spectrometer vs. tetramethylsilane as internal standard, on recently calibrated instruments. ^{13}C NMR spectra were taken on a Varian XL-100 spectrometer with the center peak of $CDCl_3$ taken as 76.9 ppm from Me_4Si, the ultimate standard against which all chemical shifts are reported. For quantitative ^{13}C NMR spectra, $Cr(acac)_3$, ca. 100 mg, was added to the 10–20% (w/v) solutions of the substances in $CDCl_3$.[26] The spectral width was 5000 Hz, using a 1-s pulse repitition rate. A full data table was used (8K), resulting in error in line position of ±1.25 Hz. From 5 to 15 K of pulses were collected, the latter common for quantitative runs. The tip angle was ca. 45°, or slightly less for quantitative runs. Coupling constants were taken from suitable large expansions (180 Hz for ^{1}H, and 1000 Hz for ^{13}C NMR), the latter using the gated mode of decoupler operation (error ±0.25 Hz). For the quantitative ^{13}C NMR runs, the ratios of peak intensities for equivalent carbons in the two isomers were determined for all differentiated carbons and averaged. Repetitive runs were in good agreement between different workers, with ^{1}H integration data, and with earlier work, when available.[4]

Mass spectra were taken on an AEI-MS-50 mass spectrometer operating at 70 eV in the high-resolution mode. For the isotope effect studies, mass analysis of the starting ketone mixture was done at low resolution, monitoring the d_3 (or d_4) and unlabeled masses. Corrections for ^{13}C were done as needed. Analysis of the separated reduction products was done at high resolution (ca. 50 000) in order to separate the masses of interest from interfering peaks. In this mode of operation, no correction for ^{13}C was necessary. The "peak switch" mode of operation was used where the d_3 (or d_4 in the acyclic substrate) and the unlabeled peaks were alternately read. The traces of at least five "switches" were averaged and used to calculate the relative ratio of undeuterated vs. fully deuterated alcohol. These data, divided by similar data for the starting ketone mixture, gave k_H/k_D.

Addition Reactions. In a flame-dried three-necked flask, equipped with condenser, addition funnel, and magnetic stirrer

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(50) Primary isotope effects were not attempted due to the repeated observation of *inverse* isotope effects, whose interpretation is not straightforward. (a) Wigfield, D. C.; Phelps, D. J.; Pottie, R. F.; Sander, R. *J. Am. Chem. Soc.* **1975**, *97*, 897. (b) Howarth, O. W.; McAteer, C. H.; Moore, P.; Morris, G. E. *J. Chem. Soc., Chem. Commun.* **1982**, 745. (c) Pasto et al. (Pasto, D. J.; Lepeska, B.; Cheng, T.-C. *J. Am. Chem. Soc.* **1972**, *92*, 6083) report large and normal isotope effects in the hydroboration of alkenes. (d) Morrison et al. (Morrison, J. D.; Tomazewski, J. E.; Mosher, H. S.; Dale, J.; Miller, D.; Elsenbaumer, R. L. *Ibid.* **1977**, *99*, 316) report normal isotope effects in hydride transfer between carbons. (e) Reference 48. (f) Davis, R. E.; Carter, J. *Tetrahedron* **1966**, *22*, 495.

(51) Halevi, E.; Margolin, Z. *Proc. Chem. Soc.* **1964**, 174. (b) Sass, W. *Diss. Abstr. Int. B* **1971**, *32*, 185–186.

(52) Lennard-Jones, J. E. In "Statistical Mechanics"; Fowler, R. H., Ed., Cambridge Univ. Press: Cambridge, England, 1935; Chapter 10.

(53) Menger, F. M.; Grossman, J.; Liotta, D. C. *J. Org. Chem.* **1983**, *48*, 906.

(54) (a) A similar argument has been set by Inagaki et al. (Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4055) with regard to the anomalous reactions of norbornene. An initial charge-transfer interaction of electrophiles and the orbitals of greater coefficient (exo) is considered to dominate the course of the reaction. However, the second step of additions of, say, HX, is a nucleophilic addition. It was not discussed why the same stereochemistry (exo) often occurs. (b) See also: Ito and Kakehi (Ito, S.; Kakehi, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1869) for another type of interpretation. (c) If consideration only of ground-state orbitals were sufficient, it would appear that nucleophilic addition should occur more readily for ethylene than for acetylene, but it does not due to other effects that develop in the course of the addition; cf.: Stozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1342. (d) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Tran Huu Dau, M.-E. *Ibid.* **1973**, *95*, 6147. (e) Munstorer et al. (Munstorer, H.; Kresze, G.; Brechbiel, M.; Kwart, H. *J. Org. Chem.* **1982**, *47*, 2677) consider initial complexation as a factor in reactions ultimately showing high specificity. If so, the ground-state orbitals would be significant.

(other runs used a power stirrer), 0.41 g (0.017 mol) of magnesium, crystal of iodine, and a small amount of anhydrous ether were added. The mixture was gently heated for 5 min, and the ether was decanted. After ensuring that traces of ether were absent, the apparatus was gently heated with a flame until the magnesium took on a slightly white coloration. The flask was cooled, and 0.020 mol of the alkyl or aryl halide in 75 mL of dry ether was added dropwise over 1.0–1.5 h. The resulting mixture was gently refluxed for 30 min to 2 h.

In method 1, the substrate **5** or **6** (0.01 mol) was dissolved in 75 mL of dry ether and added dropwise to the Grignard (normal addition), with 30 min of additional stirring. The reaction was worked up by adding ca. 100 mL of 10% hydrochloric acid in water dropwise with stirring. The layers were separated and the aqueous layer was washed with 3 × 150 mL of ether. The combined ether layers were washed twice with a dilute sodium bicarbonate solution and twice with water and dried ($MgSO_4$), and the ether was evaporated under vacuum. Traces of ether were removed by adding small amounts of CCl_4 and evaporating to dryness. The resulting oil was analyzed by NMR.

In method 2, the Grignard solution, prepared as above, was added dropwise to the ether solution of the carbonyl analogue (0.010 mol in 75 mL of ether) (inverse addition). Workup proceeded as above.

Organolithium reagents were prepared in a three-necked flask, under nitrogen, by cutting small pieces of lithium wire (ca. 1 mm) (0.10 g., 0.00143 mol) so that they fell directly into the flask containing the solvent of choice, 75 mL of ether or hexane. A solution of 0.0070 mol of alkyl or aryl halide in 75 mL of dried solvent was added over 1–1.5 h with stirring. It was necessary to reflux some of the less reactive reaction mixtures. These also necessitated a change from lithium wire to lithium powder (30% dispersion in mineral oil, with 1% sodium, from Alfa Inorganics). Commercially prepared *tert*-butyllithium (Alfa Inorganics) was also used. The "end point" method of following the reaction course was used (observation of a pronounced change in the nature or color of the solution). Hydrolysis and workup proceeded as for the Grignard reactions.

The lithium organocuprate reagents were prepared from the organolithium reagents, cooled to 0 °C, and treated with cuprous iodide, and the resulting solution was stirred for 15 min. The best reagent molar ratios were found to be organic halide, 2; lithium, 3; cuprous iodide, 4; and substrate, 1. The substrate **5** or **6** in 75 mL of solvent was added to the organocuprate in a "normal addition" manner, the solution was stirred briefly and then worked up by addition of dilute hydrochloric acid, an extraction cycle, as before, plus an additional extraction with sodium bisulfite solution. Mixed organocuprate reagents were briefly investigated but were not successful, in our hands.

The substrates **5** and **6** were prepared in a round-bottomed flask equipped with a Dean–Stark water separator and condenser. To the round-bottomed flask were added 5.04 g (0.044 mol) of 2-phenylpropanal, 29.07 g (0.044 mol) of malononitrile, 9.05 g of acetic acid, and 2.5 g (0.024 mol) of piperidine along with 150 mL of sodium-dried benzene. The mixture was refluxed until no further water formation was noted, ca. 3 h. Water (100 mL) was added to the cooled solution, it was separated, and the aqueous layer was extracted with benzene (2 × 150 mL). The combined organic layers were washed with saturated ammonium chloride solution (2 × 100 mL) and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The resulting dark red oil was vacuum distilled. The dicyanide **5** was collected at 116–118 °C (0.26 mm) 60 g (76% yield); ^1H NMR ($CDCl_3$) 1.44 (d, 3, CH_3), 4.05 (dq, 1, $Ph(CH_3)CH$), 7.25 ppm (m, 6, Ph plus $CH{=}C(CN)_2$); ^{13}C NMR ($CDCl_3$) 19.3 (CH_3), 42.6 (CH), 87.3 ($C(CN)_2$), 110.2, 111.6 (CN), 126.6, 127.6, 128.9, 138.9 (Ph), 171.2 ppm ($CH{=}C(CN)_2$).

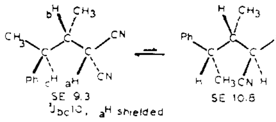
The diester substrate **6** was prepared with some difficulty due to facile rearrangement on the nonconjugated β,γ-unsaturated diester. A 3.5-h reflux period was found to be most advantageous. The product was purified by the same extraction cycle as noted above and by vacuum distillation with the cut taken at 135–137 °C (0.22 mm) collected (69% yield): ^1H NMR ($CDCl_3$) 1.43 (d, 3, CH_3), 3.70 (s, 3, OCH_3), 7.13 ppm (m, 6, Ph and $CH{=}C(CO_2CH_3)_2$; ^{13}C NMR ($CDCl_3$) 20.0 (CH_3), 39.4 ($Ph(CH_3)CH$), 52.0 (OCH_3), 126.6 ($C(CN_2)$), 126.7, 127.2, 128.4, 141.9 (Ph), 152.2 ($-CH{=}C$), 163.9, 165.3 ppm (CO).

Purification of the Diastereomeric Products. The reaction mixture was analyzed by NMR directly after workup to avoid the possibility of fractionation. The isomers were also separated, when possible, and their spectral characteristics individually determined. For the methyl adducts **14** either flash chromatography[55] or preparative-scale liquid chromatography could be used. The LC system used was homebuilt from a design of Altex Scientific, Inc., and utilized either 15- or 25-mm i.d. glass columns.[56] The system operated at ca. 40 psi, using either silica gel 60, 70–230 mesh, or else Aluminoxide 90, neutral (Activitatsstufe I), 70–230 mesh, both from E&M Reagents, Inc.). The progress of the separation was followed by TLC using Eastman chromagram sheets, which had similar characteristics to the column separation. The eluent was technical grade pentane, washed with sulfuric acid and then with sodium hydroxide solution and water, dried ($MgSO_4$), and distilled from sodium metal. More polar eluents were made from this pentane plus anhydrous ethyl ether, the latter having been distilled from LAH. The methyl adduct **14** was separated by a single pass through silica, either flash or liquid chromatography. Of 0.50 g of crude product formed by method 1, 0.10 g (14% yield) of the parf isomer and 0.14 g (20% yield) of the pref isomer could be isolated in pure form. Intermediate fractions were cycled through a second time, as necessary, to obtain greater quantities. The spectral data for these and other compounds are listed in Table IV.

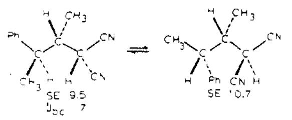
***pref*-1,1-Dicyano-2-methyl-3-phenylbutane (14):** mass spectrum, calcd for $C_{13}H_{14}N_2$ m/e 198.1158, obsd 198.1159.

***parf*-1,1-Dicyano-2-methyl-3-phenylbutane (14):** mass spectrum, calcd for $C_{13}H_{14}N_2$ m/e 198.1158, obsd 198.1164.

The decision regarding relative configuration rests on NMR coupling constants, chemical shifts, and MM2 calculations of relative energies. For the parf isomer, MM2 indicates the energies shown for the two main conformers. MM2 also shows that in **14a** the Ph group lies face-on toward H_a, which would result in a strong shielding of this proton compared to that in the major pref isomer **14r**. The coupling constants for the parf isomer are quite pronounced, $^3J_{ab}$ = 3.6 Hz and $^3J_{bc}$ = 9.9 Hz, compared to $^3J_{ab}$ = 5.7 Hz and $^3J_{bc}$ = 7.2 Hz for the pref isomer. MM2 predicts the parf isomer to be somewhat more conformationally pure favoring **14a** as observed. The data for the phenyl adducts **16** were analyzed similarly, vide infra.



14a (parf)



14c (pref)

The isopropyl adduct **15** or **5** was separable although two columns were needed. The pref isomer was separable on a flash column apparatus with silica support, and ether/pentane (1:15) as eluent; but a reduction product, 1,1-dicyano-3-phenylbutane, came off with the parf isomer. These were separated on a LC alumina column with ether/pentane (3:15) as eluent. The parf isomer was recrystallized to purity. Of 0.56 g of crude material in a typical run, 0.17 g (29%) parf and 0.269 (45%) pref was isolated plus 0.11 g of reduction product. The configuration assignment is tentative, as too much time was required to calculate the geometry of these complex molecules. However, as nearly 50% of each was formed in the reaction, the interpretation does not depend upon assignment.

***parf*-2-Phenyl-3-(dicyanomethyl)-4-methylpentane (15):** mp 87–88 °C; mass spectrum calcd for $C_{15}H_{18}N_2$ m/e 226.1471, obsd 226.1469.

***pref*-15:** a pale yellow oil (film dried); mass spectrum, calcd for $C_{15}H_{18}N_2$ m/e 226.1471, obsd 226.1468.

Attempted addition of *tert*-butyl Grignard, *tert*-butyllithium, or the analogous cuprate was unsuccessful. The reduction product 1,1-dicyano-3-phenylbutane was the major product, with only very small amounts of addition product.

The phenyl adducts was operationally the most successful, although a clean separation was unsuccessful. A combination of

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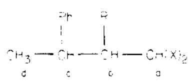
[55] Still, W. C.; Kahn, K.; Mitra, A. *J. Org. Chem.* **1978**, *3*, 2923.

[56] Formulated with plans supplied by Prof. A. I. Meyers, Colorado State University.

Table IV. ^{1}H and ^{13}C NMR Chemical Shifts of Addition Products 14–19


$CH_3-CH(Ph)-CH(R)-CH(X)_2$

			^{1}H					^{13}C					
	X	R	R	H_a	H_b	H_c	H_d	R	X	C_a	C_b	C_c	C_d
parf-14	CN	CH_3	1.35	3.36	2.20	2.67	1.45	14.6	110.9 112.7	28.0	43.3	42.4	19.5
pref-14	CN	CN	1.12	3.70	2.35	2.90	1.38	14.7	111.4 112.5	27.4	41.4	42.3	19.1
parf-15	CN	*i*-Pr	1.16 1.21	3.53	2.20	3.20	1.37	20.2[a] 20.6 22.7	108.1 109.2	28.5	52.0	40.3	18.6[a]
pref-15	CN	*i*-Pr	1.01 1.03	3.77	2.00	3.23	1.45	18.1[a] 20.5 21.4	112.9 113.4	28.7	53.2	40.3	17.5[a]
parf-16	CN	Ph	*b*	3.55	3.18	3.48	1.12	*b*	111.3 111.9	28.6	53.3	41.9	20.5
pref-16	CN	Ph	*b*	4.06	~3.4	~3.4	1.43	*b*	111.8 112.2	27.4	52.2	41.5	19.9
parf-17	CO_2CH_3	CH_3	1.00	3.28	2.50	2.80	1.22	13.1	168.8 169.5 51.9 52.0	54.9	41.9	39.9	16.9
pref-17	CO_2CH_3	CH_3	0.81	3.43	2.50	2.77	1.30	14.0	168.9 169.4 52.3 52.0	54.8	42.5	39.5	19.6
parf-18	CO_2CH_3	Ph	*b*				0.95	*b*	167.9 168.4 51.9	56.0	52.1	42.8	18.5
pref-18	CO_2CH_3	Ph	*b*	3.50	~3.2	~3.2	1.22	*b*	168.0 169.0 52.1 52.3	55.7	51.3	41.9	19.6
parf-19	CN CO_2CH_3	Ph	*b*	3.32	~3.4	~3.4	1.06	*b*	115.3 165.7 52.9	52.6	42.6	43.1	20.8

[a] Tentative assignment. [b] The usual phenyl absorptions were observed.

Table V. Calculations of Alkene Conformation (kcal/mol)

	$Ph(CH_3)CHCH{=}C(CN)_2$ 5	$Ph(CH_3)CHCH{=}C(CO_2CH_3)_2$ 6
final "steric energy"	0.79	20.4
compression	0.60	2.4
bending	0.99	5.1
stretch-bend	0.05	0.35
van der Waals' 1,4-energy	6.28	14.8
other	−1.41	2.8
torsional	−9.05	−10.7
dipole	3.34	5.5

flash and liquid chromatography and finally recrystallization of the partially purified isolable isomer was used. The product of one run, 0.54 g (crude), provided 0.18 g of the minor isomer *parf*-**16** and 0.29 g of the major product *pref*-**16**.

***parf*-1,1-Dicyano-2,3-diphenylbutane (16)**: mp 144.0–144.5 °C, obtained as colorless well-formed crystals; mass spectrum, calcd for $C_{18}H_{16}N_2$ *m/e* 260.1315, obsd 260.1318.

***pref*-16**: a pale golden oil; mass spectrum, calcd for $C_{18}H_{16}N_2$ *m/e* 260.1315, obsd, 260.1324.

The methyl adducts of the diester **6** were prepared as described above. As separations were very difficult, some of the dicyanides isolated above were converted to the diester addition products, e.g., by the following procedure.

In a three-necked flask with condenser, addition funnel, and magnetic stirrer, 0.26 g (1.3 mmol) of *parf*-**14** was added along with 250 mL of methane. Hydrochloric acid gas was bubbled through for 12 h. Water (100 mL) was then added, and the mixture was stirred for 30 min, and then the methanol was distilled off. Sodium chloride was added till saturated, and the mixture was extracted with (3 × 150 mL) of ether. The combined organic layers were extracted with saturated sodium bicarbonate solution (2 × 100 mL) and with water, dried ($MgSO_4$), and evaporated, giving the crude product in 64% yield. This parf diester **17** was purified by flash chromatography with ether/pentane (1:5) as eluent. This product proved to be identical in ^{13}C NMR chemical shifts with one of the two products (e.g., the minor product of addition of lithium dimethylcuprate to **6**). The pref isomer was similarly prepared from *pref*-**14** and was identical with the other addition product.

***parf*-1,1-Dicarbomethoxy-2-methyl-3-phenylbutane (17)**: obtained as a pale yellow oil; mass spectrum, calcd for $C_{15}H_{20}O_4$ *m/e* 264.1362, obsd (very small intensity) 264.1376. The McLafferty rearrangement peaks at *m/e* 132.0941 and the base peak *m/e* 105.0693 were consistent with structure.

***pref*-17**: a pale yellow oil; mass spectrum, parent ion not observed. Strong peaks at *m/e* 132.0937 (McLafferty rearrangement) and at *m/e* 105.0689 [$PhCH(CH_3)^+$] were consistent with structure.

***parf*-16**, on attempted conversion to the diester, gave instead the half-cyanide–half-ester **19**.

***parf*-1-Carbomethoxy-1-cyano-2,3-diphenylbutane (19)** was obtained as a yellow oil; mass spectrum; parent ion not found; McLafferty rearrangement peak at *m/e* 194.1064 (very low intensity) and the base peak at 105.0683 were consistent with structure as were the NMR spectra (Tables IV and V).

Conversion of *pref*-**16** to the corresponding diester *pref*-**18** was successful, giving a product that was identical with one of the products of addition of phenyl Grignard to **6** (the major adduct to **5** was converted into the minor adduct from **6**).

***pref*-18**: mass spectrum, parent ion at m/e 302 not observed, but the McLafferty rearrangement peak at m/e 194.12 was consistent with structure as were the NMR spectra.

Ketone Reductions. The ketone reductions utilized hydride reagents obtained from commercial sources and were used as received. However, aluminum isopropoxide and diborane were prepared locally. Solvents used in the reductions were dried by distillation from LAH, in cases where dryness was critical. Sodium tetrahydrioborate, lithium tetrahydrioridoaluminate, sodium hydridotrimethoxyborate, sodium cyanotrihydridoborate, and the tetramethylenediamine complex of LAH were obtained from Alfa-Ventron Corp. Sodium bis(2-methoxyethoxy)dihydridoborate, polymethylhydrosiloxane (PMHS), tetrabutyldiacetoxytin dimer (DABTO), and 9-borabicyclo[3.3.1]nonane (9-BBN) were products of Aldrich Chemical Co., as was 2-phenylcyclohexanone. The latter was purified by repeated recrystallization from petroleum ether.

The instrumentation used is as described previously; except for the isotope effects, separations on a Waters Associates ALC-201 liquid chromatography were performed with monitoring by an ISCO UA4 ultraviolet detector.

Preparation of 3-Phenyl-2-butanone. In a 1-L round-bottomed flask, equipped with stirrer, condenser, and addition funnel, 80.4 g (0.6 mol) of 2-phenylpropanal in 100 mL of dry ether were added to methyl Grignard prepared from 99.4 g (0.7 mol) of methyl iodide and 20g (0.8 mol) of magnesium turnings in the usual manner. The final reaction mixture was refluxed gently for 1 h and hydrolyzed by being poured into 75 ml of 15% H_2SO_4 solution. The aqueous layer was extracted with 2 × 100 mL portions of ether, and the combined ether layers were washed with 10% sodium thiosulfate solution, dried ($MgSO_4$), and evaporated, giving 95 g of the crude alcohol **20** as product. A portion of this product was distilled through a short-pass column at 54–56 °C (0.3 mm). The bulk of **20** was oxidized to the ketone by dissolving **20** in 500 mL of benzene and adding this to a 5-L flask with 300 g (1.01 mol) of sodium dichromate, 200 mL of glacial acetic acid, 400 mL of H_2SO_4, and 1300 mL of water. The layers were separated, and the aqueous layer was washed with an additional 500 mL of benzene. The combined organic layers were washed with water, a 10% sodium carbonate solution, and again with water, dried ($MgSO_4$), evaporated, and distilled with the cut boiling at 42–44 °C (0.3 mm) collected: 51.7 g, 53%, lit. bp 97–98 °C (11 mm).

Hydride Reduction Procedure. The following is typical of most reductions. In a dried round-bottomed flask, 0.1 g (2.5 mmol) of LAH and 30 mL of anhydrous ether were distilled from LAH directly into the reaction vessel. After a short period of stirring (ca. 5 min), 0.2 g. (4 mmol) of 2-phenylcyclohexanone was added in 5 mL of anhydrous ether over 15 min. The final mixture was stirred overnight and hydrolyzed by the dropwise addition of a saturated sodium sulfate solution. The ether layer was decanted and the residue washed with ether; the combined ether layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was freed from solvent, then 1–1.5 mL of $CDCl_3$ plus 50–75 mg of chromium tris(acetylacetonate) was added, and the solution was filtered into an NMR tube. The ^{13}C NMR data acquisition proceeds as previously described.

The DABTO/PMHS reduction, however, required a different procedure: to a 100-mL three-necked flask equipped with stirrer, condenser, and a rubber septum inlet were added 0.2 of ketone, 0.014 g of DABTO, and 4 mL of 95% ethanol. The stirred reagents were heated to reflux, and then 0.1 g of PMHS was slowly added through the septum by syringe, with continued heating for 1 h. The solution was allowed to cool, and 3 mL of water were added, giving a gel. The gel was filtered and washed with 10 mL of ether. The combined organic solvents were evaporated to near dryness under vacuum; the residue was redissolved in ether, dried (Na_2SO_4), and analyzed by ^{13}C NMR.

The aluminum isopropoxide reduction was carried out in the following manner to ensure kinetic, as opposed to equilibrium, conditions. In a 500-mL round-bottomed flask equipped with drying tube and condenser, 18 g (0.67 mol) of aluminum shavings, 200 mL of isopropyl alcohol, and 0.35 g, of mercuric chloride were added. The mixture was heated on a water bath until the solution came to reflux, and then 1 mL of carbon tetrachloride was added whereupon the solution continued to boil on its own. The reflux rate was controlled by occasional cooling. External heating was finally necessary to dissolve the remainder of the aluminum. The excess isopropyl alcohol was removed under vacuum, and the residue was distilled at ca. 145 °C (15 mm), giving 89 g (64%) of aluminum iospropoxide, which solidified on cooling. An acetone test solution was prepared from 0.12 g of 2,4-DNP, 25 mL of water, and 21 mL of concentrated HCl, with final dilution of the mixture to 125 mL, making a 1% solution.

In a 10-mL round-bottomed flask, fitted with reflux condenser, provision was made to be able to collect samples of the distillate from the top of the condenser. A 1-mmol quantity of the 0.44 M aluminum isopropoxide solution in isopropyl alcohol was added, along with 2 mL of dried isopropyl alcohol and 0.2 g of ketone. The solution was stirred magnetically at reflux (uncooled condenser). Periodically, samples were taken from the top of the condenser and tested for the presence of acetone. When a negative test occurred, cooling water was run through the condenser. Isopropyl alcohol was added as necessary to provide a constant volume. The solution was refluxed for an additional 5 min and again tested for acetone. If negative, 2 mL of water was added to quench the reaction. The precipitate was filtered, the supernatant was evaporated to near dryness, and the residue taken up with ether, dried (Na_2SO_4), and analyzed by ^{13}C NMR.

The K-Selectride reductions were carried out by combining 2 mL of 0.5 M potassium tri-*sec*-butylhydridoborate in THF plus 10 mL of additional dried THF in a round-bottomed flask. To this solution was added 0.2 g of ketone dissolved in 5 mL of dried THF dropwise by syringe. The final mixture was stirred for 1 h, and then 3 mL of 3 N NaOH solution was added and the mixture stirred for 10 min, followed by addition of 3 mL of 30% hydrogen peroxide solution. After no further reaction occurred upon peroxide addition, the aqueous layer was saturated with K_2CO_3 and the organic layer decanted; the aqueous layer was washed with 10 mL of ether, and the combined organic layers were dried ($MgSO_4$), evaporated and analyzed as before.

The cyanoborohydride reductions were carried out by placing 0.7 g of ketone in 10 mL of methanol in a round-bottomed flask and then adding 0.125 g of sodium cyanoborohydride along with several drops of 1% methyl orange indicator, which turned yellow. The solution was stirred for several minutes, and then a methanol–HCl solution (prepared by passing HCl gas through 50 mL of methanol for 2 min) was added dropwise until a red color resulted. Stirring was continued with additional "titration" by adding the acid solution as necessary. After the solution remained red in color for 1 h without further addition of HCl, solvent was evaporated under vacuum. The residue was mixed with 5 mL of water and 10 mL of ether, and NaCl was added to saturate the aqueous layer with stirring. The layers were separated, and the aqueous layer was washed with ether. The combined organic layers were dried ($MgSO_4$), etc.

The diborane reductions were carried out essentially by the procedure of Brown and SubbaRao.[57]

The 9-BBN reductions were carried out in a round-bottomed flask by adding 0.2 g of ketone to 20 mL of dried THF and 0.24 g (2 mmol) of 9-borabicyclononane. The mixture was stirred for 4 h, and the solvent was removed by passing a stream of nitrogen over the solution. Traces of THF were removed under vacuum, and then 20 mL of dried hexane was added along with 0.15 g of 2-amino-1-propanol, which gave a white precipitate (boron comlex). The precipitate was filtered and washed with ether, and the combined organic layers were washed with 5% HCl solution and dried ($MgSO_4$), etc.

Acknowledgment. The donors to the Petroleum Research Fund, administered by the American Chemical Society, are thanked. The advice of Dr. R. L. Schowen of the University of Kansas on isotope effects is acknowledged with appreciation. Mr. Kerry Johnson is thanked for assistance with the calculations.

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(57) Brown, H. C.; SubbaRao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681.

Registry No. **5**, 88106-71-2; **6**, 38323-04-5; *parf*-**14**, 88106-72-3; *pref*-**14**, 88106-73-4; *parf*-**15**, 88106-74-5; *pref*-**15**, 88106-75-6; *parf*-**16**, 88106-76-7; *pref*-**16**, 88106-77-8; *parf*-**17**, 88106-78-9; *pref*-**17**, 88106-79-0; *parf*-**18**, 88106-80-3; *pref*-**18**, 88130-58-9; *parf*-**19**, 88106-81-4; **20**, 2362-61-0; PMHS, 26403-67-8; DBTO, 17068-56-3; TMEDA, 110-18-9; 18-crown-6, 17455-13-9; CH_3MgI, 917-64-6; *i*-PrMgI, 920-39-8; PhMgBr, 100-58-3; CH_3Li, 917-54-4; $(CH_3)_2CuLi$, 15681-48-8; Ph_2CuLi, 23402-69-9; D_2, 7782-39-0; potassium tri-*sec*-butylhydridoborate, 54575-49-4; lithium tri-*tert*-butylhydridoaluminate, 17476-04-9; sodium hydridotrimethoxyborate, 16940-17-3; 9-borabicyclononane, 280-64-8; sodium bis(1,4-dioxapentyl)dihydroaluminate, 22722-98-1; sodium cyanotrihydroborate, 25895-60-7; 2-phenylpropanal, 93-53-8; malononitrile, 109-77-3; dimethyl malonate, 108-59-8; 2-phenylcyclohexanone, 1444-65-1; 3-phenyl-2-butanone, 769-59-5; aluminum isopropoxide, 555-31-7; diborane, 19287-45-7; sodium tetrahydridoborate, 16940-66-2; lithium tetrahydridoaluminate, 16853-85-3; 2-methylcyclopentanone, 1120-72-5; 2-isopropylcyclohexanone, 1004-77-9; *tert*-butyllithium, 594-19-4; 2-methylcyclohexanone, 583-60-8.

Reactivity-Selectivity in the Swern Oxidation of Alcohols Using Dimethyl Sulfoxide-Oxalyl Chloride[1]

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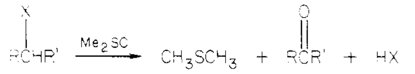
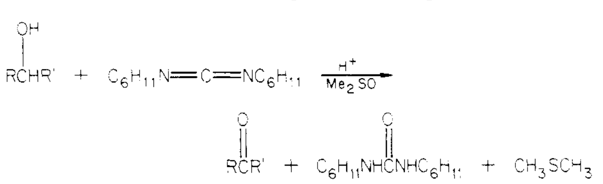
The competitive oxidation of a mixture of two alcohols by less than an equivalent amount of oxidant under the conditions developed by Swern (reaction of the alcohol at -60 °C with $Me_2SCl^+Cl^-$ (**4**) generated from $(COCl)_2$ and Me_2SO in CH_2Cl_2 followed by reaction with Et_3N) shows significant selectivity, with crowded alcohols and those bearing electron-withdrawing substituents being less reactive. Experiments in which the order of mixing of the alcohols and the oxidant are changed and the time of reaction varied establish that the process involves initial fast formation of a mixture of alkoxydimethylsulfonium ions $ROSMe_2^+$ (**1**), which equilibrate at a slower rate with the residual alcohols. Addition of Et_3N rapidly converts the existing mixture of **1** to carbonyl products. Intramolecular and intermolecular H/D isotope effects are consistent with this mechanistic scheme. In a practical application of these reactivity principles the steroid **33** with a crowded 11β-OH group was oxidized smoothly in 58% yield to the 11-ketone **34**, whereas the 9α-fluoro substituent present in **36** inhibited the reaction, and ketone was formed in only 5% yield.

The first use of dimethyl sulfoxide (Me_2SO) as an oxidizing agent was by Kornblum and co-workers,[2] who showed that alkyl halides and tosylates are converted to carbonyl compounds by Me_2SO at room temperature or with heating (eq 1). A variety of procedures using Me_2SO with electrophilic "activators" have subsequently been developed and reviewed.[3]

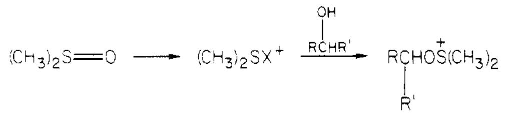


$$\overset{\displaystyle \mathrm{X}}{\mathrm{RCHR'}} \xrightarrow{\mathrm{Me_2SO}} \mathrm{CH_3SCH_3} + \overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{RCR'}}} + \mathrm{HX} \qquad (1)$$

The widely used Moffatt[3b] procedure involves reaction of the alcohol, Me_2SO, dicyclohexylcarbodiimide (DCC), and an acid at room temperature (eq 2). Some of the electrophilic activators used with Me_2SO in the other procedures include acetic anhydride, trifluoroacetic anhydride, SO_3-pyridine, P_2O_5, *t*-BuOCl, halogens, *N*-halosuccinimides, and oxalyl chloride. These latter reactions evidently all proceed through the formation of activated dimethylsulfonium species Me_2SX^+, which react with the alcohol to form an alkoxysulfonium ion **1** (eq 3), which then reacts with base to give an ylide **2** that reacts intramolecularly to form the carbonyl product (eq 4). The Moffatt procedure evidently also involves the ylide **2**, but this is formed in an intramolecular reaction in which a nitrogen of the DCC acts as the base.[3b] Formation of (methylthio)methyl esters **3**, a common side reaction in these procedures, evidently also occurs through the intermediacy of **2** (eq 5).

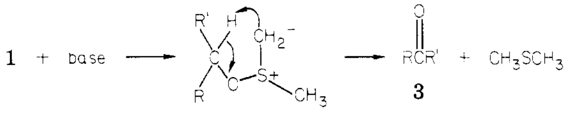


$$\overset{\displaystyle \mathrm{OH}}{\mathrm{RCHR'}} + \mathrm{C_6H_{11}N{=}C{=}NC_6H_{11}} \xrightarrow[\mathrm{Me_2SO}]{\mathrm{H^+}} \overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{RCR'}}} + \mathrm{C_6H_{11}NH}\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NHC_6H_{11}} + \mathrm{CH_3SCH_3} \qquad (2)$$



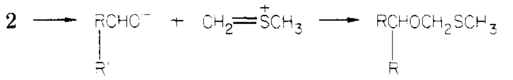
$$\mathrm{(CH_3)_2S{=}O} \longrightarrow \mathrm{(CH_3)_2SX^+} \xrightarrow{\overset{\displaystyle \mathrm{OH}}{\mathrm{RCHR'}}} \underset{\displaystyle \mathrm{R'}}{\mathrm{RCHO\overset{+}{S}(CH_3)_2}} \qquad (3)$$

1



$$\mathbf{1} + \mathrm{base} \longrightarrow \mathbf{2} \longrightarrow \overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{RCR'}}} + \mathrm{CH_3SCH_3} \qquad (4)$$

2 **3**



$$\mathbf{2} \longrightarrow \underset{\displaystyle \mathrm{R'}}{\mathrm{RCHO^-}} + \mathrm{CH_2{=}\overset{+}{S}CH_3} \longrightarrow \underset{\displaystyle \mathrm{R}}{\mathrm{RCHOCH_2SCH_3}} \qquad (5)$$

3

Particularly convenient reaction conditions developed by Swern[3c,4] involve reaction of Me_2SO with oxalyl chloride

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[1] Contribution No. 663 from the Institute of Organic Chemistry. This article is dedicated to the memory of the late Professor Swern.

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