Stereochemistry of Organometallic Compound Addition to Ketones

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I. Introduction

A. Organometallic Reagents: Composition, Reaction Mechanisms, Stereochemistry

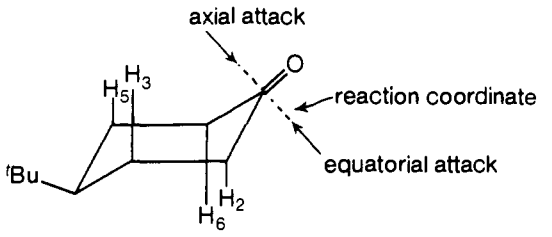
Detailed knowledge concerning the composition of organolithium, organomagnesium, and organoaluminum compounds in solution, accumulated in the past ten years, has rekindled an intense interest in the mechanisms by which these reagents add to various organic substrates. Owing to a determined effort on the part of several research groups, the mechanisms by which methyllithium, dimethylmagnesium, methylmagnesium bromide, diethylzinc, and trimethylaluminum add to ketones are reasonably well understood at the present time. It is generally thought that the mechanisms of CH_3M addition to ketones (where M = Li, Mg, or Al) are representative of the mechanisms of main group organometallic compound addition to ketones in general, except where compelling evidence exists to the contrary (e.g., allyl Grignard reagents).

Research concerning the steric course of addition of organometallic compounds to ketones to give (on hydrolysis) isomeric alcohols has lagged far behind the much larger effort afforded the steric course of reduction of these compounds by metal hydrides. However, recent structural and mechanistic information concerning main group organometallic compounds has caused interest in the stereochemistry of addition of these compounds to cyclic ketones to mushroom. Investigations have had two principal objectives: (1) to develop a unifying theory concerning the factors involved which lead to observed isomer ratios in organometallic compound addition to cyclic ketones and (2) to discover ways in which organometallic compounds can be influenced to react with cyclic ketones to produce predominantly either of the two possible alcohols.

B. Theories Concerning Stereoselectivity of Addition and Reduction of Cyclic Ketones

All theories concerning stereoselective addition and reduction of cyclic ketones assume that an entering group (R or H) approaches the carbonyl carbon on a line perpendicular to the plane of the carbonyl group in order to effect maximum orbital overlap in the transition state. This imaginary line of approach (see 1) is known as the reaction coordinate. Steric approach control was considered by Dauben and coworkers[1] to be an important factor in the steric course of reduction of cyclic ketones by complex metal hydrides. Steric approach control implies an early, reactant-like, transition state in which the entering group approaches the least hindered side of the ketone. In the case of cyclohexanones, the least hindered path of approach of an entering group to the carbonyl is the equatorial side since approach along the reaction coordinate from the axial side encounters steric hindrance from the 3,5-axial hydrogens. Dauben and coworkers[1] have formulated a second important factor known as product development control since hydride reductions of 4-*tert*-butylcyclohexanone involve predominant axial attack. Product development control implies a late, product-like transition state in which the observed isomer ratio reflects the stability of the product. Thus, for 4-*tert*-butylcyclohexanone, the predominant isomer predicted by steric approach control is the axial alcohol (**2**) and that predicted by product development control is the equatorial alcohol (**3**).

The principal objection of many workers to the Dauben concept is that transition states should be similar for fundamentally similar reactions. For example, hydride reduction of 4-*tert*-butylcyclohexanone is said to have a product-like transition state leading to isomer **3**; however, hydride reduction of 3,3,5-trimethylcyclohexanone (**4**) is said to have a reactant-like transition state leading to isomer **5**. Because the environment about the carbonyl (C-1, C-2, C-6) is identical in both ketones, many workers argue that the nature of the transition



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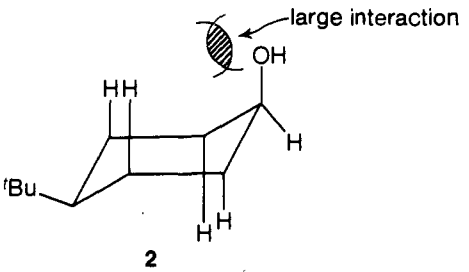
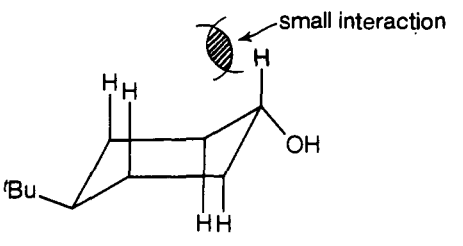
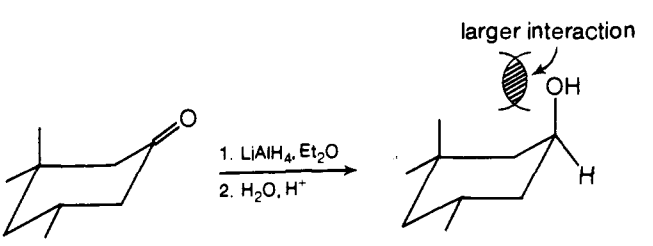


2
less stable isomer



3
more stable isomer

states resulting from reduction of the two ketones should be similar rather than entirely different.

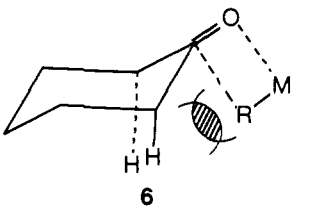


4 5
less stable isomer

Pioneering work by Eliel and coworkers[2,4] has produced convincing arguments against the importance of product development control in hydride reductions. They note that in $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone a 92:8 ratio of equatorial:axial alcohol (**3:2**) is obtained, whereas equilibration of a mixture of 4-*tert*-butylcyclohexanols produces a 79:21 ratio of **3:2**.[3,4] Thus, a significantly larger percentage of **3** is produced than would be predicted by product development control. In addition, competitive rate experiments involving various metal hydrides and several 3,5-di-, tri-, and tetramethyl-substituted cyclohexanones have shown that an axial methyl group in the 3 and/or 5 position retards the rate of axial attack compared to 4-*tert*-butylcyclohexanone, whereas the rate of equatorial attack remains essentially unchanged.[2] This observation is not consistent with that predicted by product development control in which an axial methyl substituent would be expected to retard equatorial attack.

Marshall and Carroll considered the steric course of reaction of cyclohexanones to be due to steric factors alone.[5] They suggested that when the carbonyl carbon entering group transition state bonding distance is greater than 1.6 Å, a steric strain involving the entering group and the 3,5-diaxial hydrogens is greater than that involving the 2,6-diaxial hydrogens. On the other hand, when the transition state bonding distance is less than 1.6 Å, steric strain by the 2,6-diaxial hydrogens is greater. Thus, an entering hydride ion which would be expected to have a relatively short bond to the carbonyl carbon in the transition state would be expected to attack along the reaction coordinate preferentially from the axial side. On the other hand, an alkyl group would be expected to attack along the reaction coordinate preferentially from the equatorial side owing to an expected longer bond length in the transition state. Unfortunately, there is no way of determining exact transition state bond lengths. It seems that a decision is usually made as to the transition state bond length after the isomer ratio has been determined, and therefore this model is of questionable predictive value. In addition one might consider that a number of reductions of 4-*tert*-butylcyclohexanone are known in which hydride attack takes place preferentially from the equatorial side and a number of organometallic addition reactions are known where an alkyl group attacks preferentially from the axial side.

Cherest and Felkin[6-8] considered the stereoselectivity of organometallic compound addition to cyclohexanones to be influenced by two factors: (1) the steric interaction of the incoming group with the 3,5-axial substituents and (2) the torsional strain of the incoming group with the 2,6-axial substituents (**6**). Torsional strain implies bond repulsion between the forming C–R bond and the 2,6-axial hydrogen bonds. Torsional strain is not a steric phenomena but an interaction similar to that experienced in ethane involving C–H single bond repulsion when rotation about C_1–C_2 takes place (**7**). In addition of



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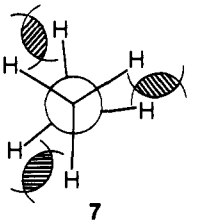


7
torsional strain
in elipsed ethane

organometallic compounds to cyclohexanones, torsional strain opposes steric strain. Torsional strain hinders equatorial attack whereas steric strain hinders axial attack. The actual stereochemistry of addition depends upon which factor is greater in a particular case. For a cyclohexanone with no 3- or 5-axial substituent larger than hydrogen, small entering groups (hydride) are opposed more strongly by torsional strain; thus attack occurs predominantly from the axial side.[5,6] If the cyclohexanone contains one or more larger axial substituents (e.g., methyl or ethyl) at the 3 or 5 position, steric strain is more important regardless of the size of the incoming group, and thus attack occurs predominantly from the equatorial side.

The abnormally high percentage of axial attack observed when $(CH_3)_3Al$ is allowed to react with 4-*tert*-butylcyclohexanone in a 2:1 ratio in benzene cannot be explained by any of the theories presented thus far. Investigation of several ketones having varied steric requirements has shown this to be due to a compression of the complexed carbonyl group against the 2,6-equatorial hydrogens in the transition state. This new concept of stereochemical control will be discussed in detail in section IV.

The principal factors governing the steric course of addition of cyclic ketones have been derived from considerations involving reduction and alkylation of 4-*tert*-butylcyclohexanone. The same principles can be generalized to include reactions of all cyclic ketones examined to date with organometal-

lic reagents. Detailed examination of cases selected to show how these principles operate will be presented. The importance of the conformation of the ketone, the solution composition of the organometallic reagent, the solvent, and the mechanism by which the ketone is alkylated, will be discussed.

II. Organolithium, Organosodium, and Organopotassium Compounds

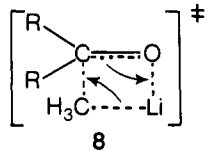
A. Solution Composition of Organolithium Compounds and Their Mechanism of Reaction with Ketones

Molecular weight measurements of a number of organolithium compounds demonstrate that the molecular aggregation depends to a large extent on the nature of the R group and the solvent. Ethyllithium and *n*-butyllithium are hexameric in both benzene and cyclohexane,[9,10] whereas *n*-butyllithium is tetrameric in diethyl ether.[11] Although phenyllithium is dimeric[11,12] in both diethyl ether and tetrahydrofuran, methyllithium is reported to be tetrameric.[11]

The reaction of *n*-butyllithium with benzonitrile has been kinetically examined and found to be 0.33 order in *n*-butyllithium.[13] The difference between 0.33 order and the 0.25 order expected for reaction through monomer was ascribed to medium effects on the monomer–tetramer equilibrium.[13]

The reaction of methyllithium with 2,4-dimethyl-4′-mercaptomethylbenzophenone is reported to be first order in ketone and 0.25 order in methyllithium.[14,15] The data were adequately described in terms of a tetrameric reagent in equilibrium with monomer (eq 1). No evidence for a CH_3Li–ketone complex was found. Although no transition state was suggested, it is reasonable to assume that **8** represents the expected four-center transition state.

$$(CH_3Li)_4 \rightleftharpoons 4CH_3Li$$
$$CH_3Li + K \longrightarrow P \qquad (1)$$



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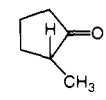
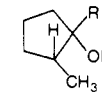
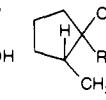
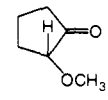
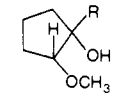
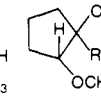
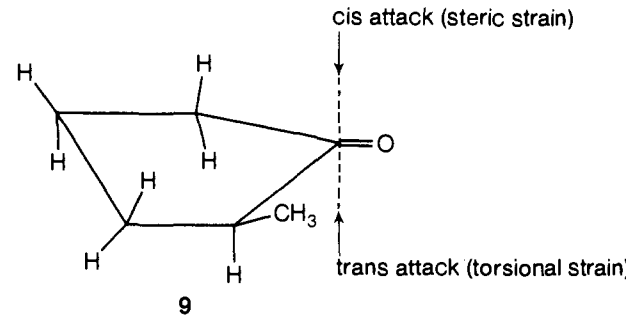
B. Stereochemistry of Addition of Organoalkali Compounds to Cyclic Ketones

The amount of information available concerning the steric course of organolithium compound addition to cyclic ketones far exceeds that available for organosodium and organopotassium reagents. Table I illustrates the observed stereochemistry in addition reactions of organoalkali compounds to cyclopentanones. The alcohol isomer ratios were found to be independent of the reactant ratios and concentrations in those instances where these factors were investigated. On the other hand, alcohol isomer ratios were dependent on the nature of the reagent and, in some cases, the solvent.[16–18] As expected, CH_3Li and C_6H_5Li preferentially attack 2-methylcyclopentanone from the least hindered side, demonstrating the importance of steric approach control. However, HC≡CLi and HC≡CNa attack preferentially from the more hindered cis side. The reason for this unusual stereochemistry appears to be the following. Ethynyl reagents are linear with but a single other atom bonded to the entering groups. The preferred conformation of 2-methylcyclopentanone is that in which the 2-methyl group occupies a pseudoequatorial position while C-3 and C-4 are twisted with respect to each other in such a way that their hydrogens are staggered (**9**). Approach of a large reagent along the reaction coordinate from

TABLE I. Reactions of Organoalkali Compounds with 2-Substituted Cyclopentanones

Organoalkali compd	Ketone	Solvent	Isomer percentage[a] Cis alcohol	Trans alcohol	Ref
					
CH_3Li		Diethyl ether	70	30	16, 17
n-C_4H_9Li		Hexane	86	14	21
C_6H_5Li		Diethyl ether	95	5	17
HC≡CLi		THF–NH_3	21	79	16, 17
HC≡CNa		Benzene–toluene	9	91	16, 17
					
HC≡CLi		NH_3(liq)	98	2	18
HC≡CLi		THF	26	74	18

[a] Normalized as % cis alcohol + % trans alcohol = 100%.



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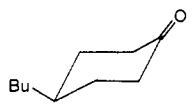
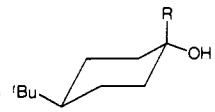
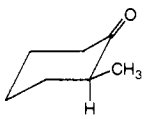
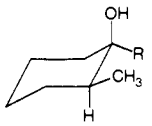
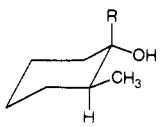
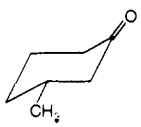
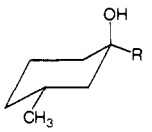
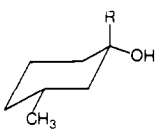
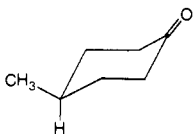
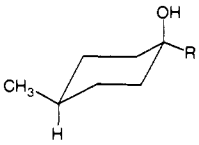
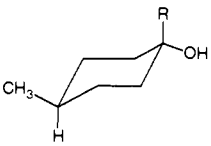
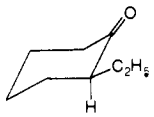
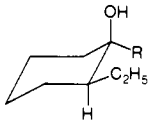
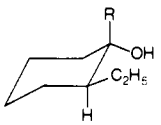
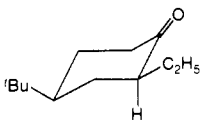
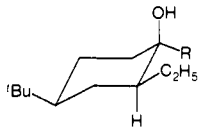
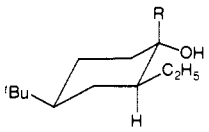
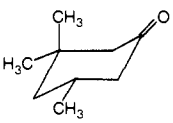
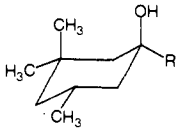
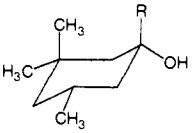
the cis side should experience significant steric interaction in its encounter with the C-2 methyl group and therefore will prefer to attack from the trans side. On the other hand, approach of a small reagent should encounter little steric interaction with the C-2 methyl group in a pseudo-equatorial position; however, it will encounter significant torsional strain from the pseudo-axial C_2–H bond and therefore will prefer to attack from the cis side. A notable exception to cis attack by ethynyllithium reagents on 2-substituted cyclopentanones is the reaction of HC≡CLi with 2-methoxycyclopentanone in liquid ammonia. In liquid ammonia, HC≡CLi is completely dissociated and the entering group $(HC{\equiv}C)^-$ carries a full negative charge. Encounter of this group by the polar 2-CH_3O– group via cis attack results in repulsion and thereby causes predominant trans attack (98%).[18] However in tetrahydrofuran HC≡CLi is not dissociated; therefore, torsional strain controls the stereochemistry and only 26% trans attack occurs.[18]

Table II illustrates the isomer ratios obtained from the reactions of a variety of cyclohexanones with organoalkali reagents. Cyclohexanones are considered to be in the chair conformation with substituents (e.g., CH_3, C_2H_5, etc) occupying equatorial positions whenever possible. In the case of 4-*tert*-butylcyclohexanone, the *tert*-butyl group, by virtue of its larger size, has such a tendency to occupy an equatorial position that the molecule is effectively "locked" in a single chair conformation.[31] The steric course of alkylation will then be controlled by factors discussed in section I.B. Cyclohexanones possessing a substituent smaller than *tert*-butyl will tend to have a small equilibrium concentration of the conformational isomer in the chair form where the substituent is now axial instead of equatorial. The importance of the latter conformation in the steric course of alkylation has been judged not to be significant. Reaction of HC≡CNa with 2-ethylcyclohexanone and *cis*-2-ethyl-4-*tert*-butylcyclohexanone

TABLE II. Reactions of Organoalkali Compounds with Substituted Cyclohexanones

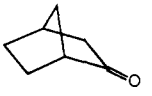
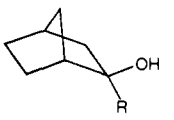
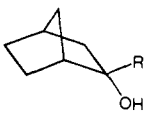
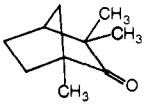
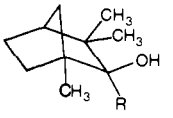
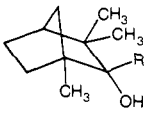
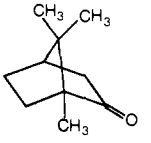
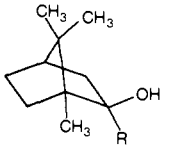
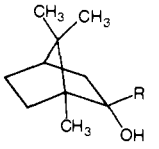
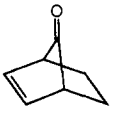
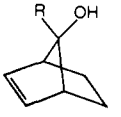
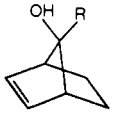
Organoalkali compd	Ketone	Solvent	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
					
CH_3Li		Diethyl ether	65	35	19
C_6H_5Li		Diethyl ether	58	42	20
$n\text{-}C_6H_{13}Li$		Benzene–hexane	75	25	21
$HC{\equiv}CNa$		NH_3–diethyl ether	12	88	22
					
C_6H_5Li		Diethyl ether	88	12[b]	23
$HC{\equiv}CLi$		$THF\text{-}NH_3$	45	55	24
$HC{\equiv}CLi$		THF	42	58	24
$HC{\equiv}CLi$		Benzene	67	33	24
$HC{\equiv}CNa$		$THF\text{-}NH_3$	41	59	24
$HC{\equiv}CNa$		Benzene	53	47	24
$NC{\equiv}CK$		$THF\text{-}NH_3$	44	56	24
					
C_6H_5Li		Diethyl ether	44	56[b]	23
$HC{\equiv}CLi$		$THF\text{-}NH_3$	18	82	24
$HC{\equiv}CK$		$THF\text{-}NH_3$	20	80	24
					
C_6H_5Li		Diethyl ether	53	47[b]	23
					
$HC{\equiv}CLi$		$THF\text{-}NH_3$	53	47	25
$HC{\equiv}CNa$		$THF\text{-}NH_3$	40	60	25
					
$HC{\equiv}CNa$		$THF\text{-}NH_3$	45	55	25
					
CH_3Li		Diethyl ether	100	0	26
C_2H_5Li		Diethyl ether	100	0	26
$i\text{-}C_3H_7Li$		Diethyl ether	100	0	26
$t\text{-}C_4H_9Li$		Diethyl ether	100	0	26

[a] Normalized as % axial alcohol + % equatorial alcohol = 100%. [b] It should be noted that the preferred conformation of these alcohols is that in which the phenyl group is equatorial.

(equatorial ethyl) gave essentially the same percentage of equatorial attack, indicating that the chair conformation of 2-ethylcyclohexanone with the 2-ethyl group axial plays no significant roll in these reactions (Table II).[25]

Table II illustrates the preference of large groups (e.g., CH_3, C_6H_5, $n\text{-}C_4H_9$) to attack from the equatorial side of cyclohexanones (steric approach control) and small groups ($RC{\equiv}C-$) to attack preferentially from the axial side (torsional

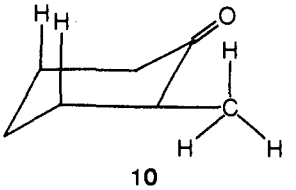
TABLE III. Reactions of Organoalkali Compounds with Bicyclic Ketones

Organoalkali compd	Ketone	Solvent	Isomer percentage[a] Exo alcohol	Endo alcohol	Ref
					
C_6H_5Li		Diethyl ether	0	100	27
					
HC≡CNa		Morpholine	0	100	28
					
CH_3Li		Diethyl ether	100	0	29
HC≡CLi		Morpholine	100	0	29
CH_2=$CHCH_2Na$		Morpholine	100	0	29
HC≡CNa		Morpholine	100	0	29
CH_3C≡CK		Morpholine	100	0	29
			 anti alcohol	 syn alcohol	
CH_3Li		Diethyl ether	77	23	30
n-C_4H_9Li		Diethyl ether	50	50	30
n-C_4H_9Li		n-Hexane	50	50	30
t-C_4H_9Li		n-Hexane	67	33	30
CH_2=$CHLi$		Diethyl ether	30	70	30
C_6H_5Li		Diethyl ether	28	72	30
C_6H_5Li		n-Hexane	28	72	30

[a] Normalized as % endo (syn) alcohol + % exo (anti) alcohol = 100%.

strain controlled).

The reactions of 2-, 3-, and 4-methylcyclohexanones with organoalkali reagents indicate clearly the loss of influence of a substituent as it becomes more remote from the reaction site. 2-Methylcyclohexanone is attacked from the equatorial side to a much larger extent by similar reagents than is 4-*tert*-butylcyclohexanone. It has been suggested that the 2-CH_3 group introduces a pseudo-axial hydrogen into the molecule (**10**) which increases hindrance of attack from the axial side.[32]



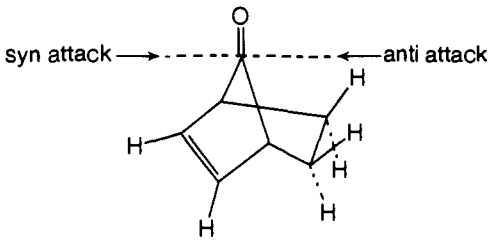
10

The effect on the steric course of addition reactions brought about by introduction of a large group in the 3 and/or 5 axial position of the cyclohexanone ring is clearly illustrated by the reactions of RLi compounds with 3,3,5-trimethylcyclohexanone.[30] In all cases (Table II) 100% equatorial attack occurred. The validity of the steric approach control theory is borne out by these examples and many others reported herein.

Table III illustrates the reactions of organoalkali compounds with several bicyclic ketones. The principal advantage of employing bicyclic ketones in stereoalkylation studies is that these compounds are conformationally stable. Norcamphor[27] and fenchone[28] are attacked 100% from the less hindered exo side by C_6H_5Li[27] and HC≡CNa,[28] respectively. This somewhat surprising result will be discussed in depth, in section III.B.

Addition of several organoalkali reagents to camphor yields a single product, the exo alcohol.[29] The presence of the 7,7-dimethyl groups renders the exo side too hindered for attack along the reaction coordinate, and thus steric approach control completely overrides any other factors even for the smallest entering groups (e.g., HC≡C–).

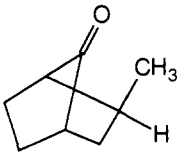
The reaction of 7-norbornenone with organolithium reagents represents a case where steric factors are reported to play a minor roll in addition to the carbonyl group. As illustrated in **11**, the syn face is somewhat less hindered than the



11

anti face to approach along the reaction coordinate. Methyllithium and *tert*-butyllithium gave predominantly syn attack; however, *n*-butyllithium in both diethyl ether and hexane attacks both faces equally.[30] The strong preference for anti attack by C_6H_5Li and CH_2=CHLi was thought to be due to the fact that these compounds are more polar than their saturated analogs and that the negative charge approaching the carbonyl from the syn face encounters a repulsive interaction with the double bond. However, the fact that both *n*-C_4H_9Li and C_6H_5Li give the exact same stereochemistry in both polar and nonpolar solvents is somewhat disturbing since the ionic character of the C–Li bond would be expected to be significantly different in the two different solvents. It would certainly be interesting to study the reaction of this ketone with HC≡CLi in both polar and nonpolar solvents.

Although no one has yet examined the reactions of compounds like 2-*exo*-methyl-7-norbornanone (**12**) with alkylating agents, it would certainly be of interest to do so. Except for



12

steric approach factors, all other factors are either nonexistent or neutralized (torsional strain, electronic factors, etc.). Thus, **12** would be an excellent model for examining the actual steric bulk of entering groups and the effective steric bulk of organometallic compounds work in progress as of this printing).

III. Organomagnesium Compounds

A. Solution Composition of Organomagnesium Compounds and Their Reaction Mechanisms with Ketones

The composition of organomagnesium compounds in ether solvents has been a subject of considerable interest.[33] Dimethylmagnesium, diethylmagnesium, and diphenylmagnesium exist as monomers in tetrahydrofuran at all concentrations and in diethyl ether at concentrations below 0.1 *M*; however, these compounds exhibit increased association in diethyl ether at higher concentrations,[34,35] approaching a limiting dimeric species at concentrations >1 *M*. The degree of association depends on the nature of the alkyl (aryl) group and decreases in the order: methyl > phenyl > ethyl. Equation 2 gives an adequate description of dialkylmagnesium compounds in diethyl ether.

$$2R_2Mg \rightleftharpoons R{-}Mg\begin{matrix}R\\R\end{matrix}Mg{-}R \qquad (2)$$

The Schlenk equilibrium (eq 3) is generally accepted as an adequate description of the composition of Grignard compounds in polar solvents.[33,36,37] The magnitude of the equilibrium constant, K_s, is dependent on the nature of the particular reagent and on the solvent.[38] In very polar solvents such as tetrahydrofuran[35] and tertiary amines,[39] Grignard compounds (except fluorides) are essentially monomeric. In diethyl ether, however, alkylmagnesium bromides and iodides are essentially monomeric at low concentrations, *ca.* 0.1 *M*; however, they exhibit increased association at higher concentrations.[34,35] Alkylmagnesium chlorides are stable dimers at all concentrations in diethyl ether.[35] Association measurements demonstrate that in general magnesium halides are more strongly associated than the corresponding dialkylmagnesium compounds, indicating that association occurs predominantly through halogen rather than alkyl or aryl bridges. Equation 4

$$R_2Mg + MgX_2 \overset{K_s}{\rightleftharpoons} 2RMgX \qquad (3)$$

$$\text{trimer} \rightleftharpoons R{-}Mg\begin{matrix}X\\X\end{matrix}Mg{-}R \rightleftharpoons 2RMgX \rightleftharpoons$$

$$R_2Mg + MgX_2 \rightleftharpoons \begin{matrix}R\\R\end{matrix}Mg\begin{matrix}X\\X\end{matrix}Mg \rightleftharpoons \text{trimer} \qquad (4)$$

adequately describes the composition of alkylmagnesium bromides and iodides in diethyl ether whereas **13** describes the composition of alkylmagnesium chlorides and fluorides.

$$R{-}Mg\begin{matrix}X\\X\end{matrix}Mg{-}R$$

13

Allyl- and 3-substituted-allylmagnesium halides[40] have the possibility of existing in two forms, **14** and **15**, in addition to more highly associated forms. NMR evidence has been presented that such compounds are best described as rapidly equilibrating pairs with the equilbrium lying far toward the side of form **14**.[41,42]

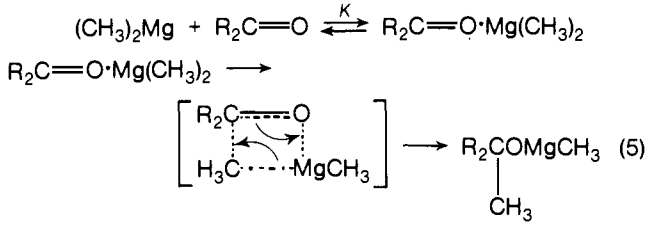
$$\underset{\mathbf{14}}{RCH{=}CHCH_2MgX} \rightleftharpoons \underset{\mathbf{15}}{RCHCH{=}CH_2 \\ \quad | \\ \quad MgX}$$

The composition of CH_3MgOR' compounds in diethyl ether has been shown to be primarily a function of R'. In those alkoxides in which R' is small (e.g., C_2H_5) the compounds are predominantly tetrameric, whereas in those cases in which R' is large, e.g., $(C_2H_5)_3C$–, the compounds are predominantly dimeric.[43]

Investigations of the mechanisms of organomagnesium compound addition to ketones have revolved about the following four points: (1) the kinetic order of these reactions in the organomagnesium compound; (2) the nature of the reactive species in those cases where several species exist in equilibrium; (3) the exact nature of the alkyl transfer step, whether it occurs by complex formation or by direct bimolecular collision; and (4) whether the reaction proceeds by a single electron transfer or polar mechanism.

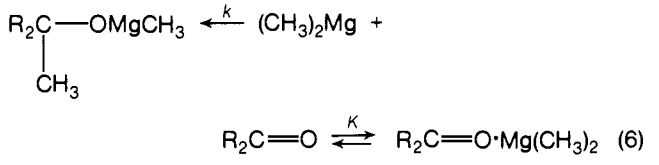
The kinetics of the reaction of dimethylmagnesium with large excesses of 2-methylbenzophenone has been studied. By using the ketone in large excess, the kinetic order of the organomagnesium species was determined unambiguously to be first order. No evidence of complex formation between dimethylmagnesium and ketones was found; however, evidence was presented for complex formation in the reaction of dimethylmagnesium with 4-methylmercaptoacetophenone.[45] There is general agreement by recent workers con-

cerning the mechanism of dimethylmagnesium addition to ketones[44-46] illustrated by eq 5. The equilibrium constant gov-



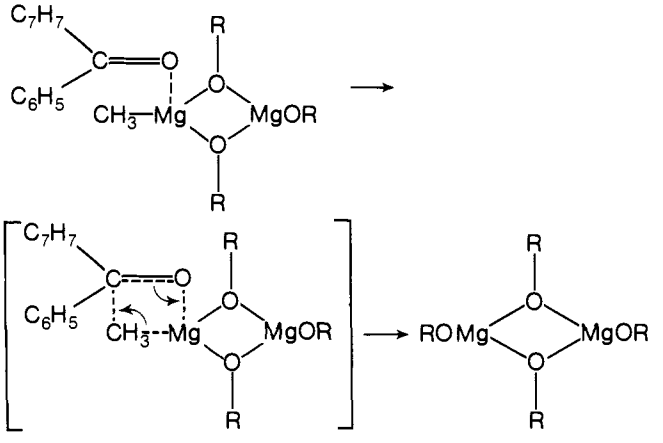
(5)

erning complex formation, K, is smaller than the equilibrium constants involving Grignard reagents and alkylmagnesium alkoxides with the same ketone.[44,45] it must be pointed out that, although eq 5 depicts the reaction as proceeding through a complex, it is possible that reaction can also occur via bimolecular collision not involving complex[44,45] (eq 6). The inability to determine by kinetics whether reaction proceeds through complex (eq 5) or by bimolecular collision not involving complex (eq 6) is general and applies to the remaining organomagnesium compounds to be discussed.



(6)

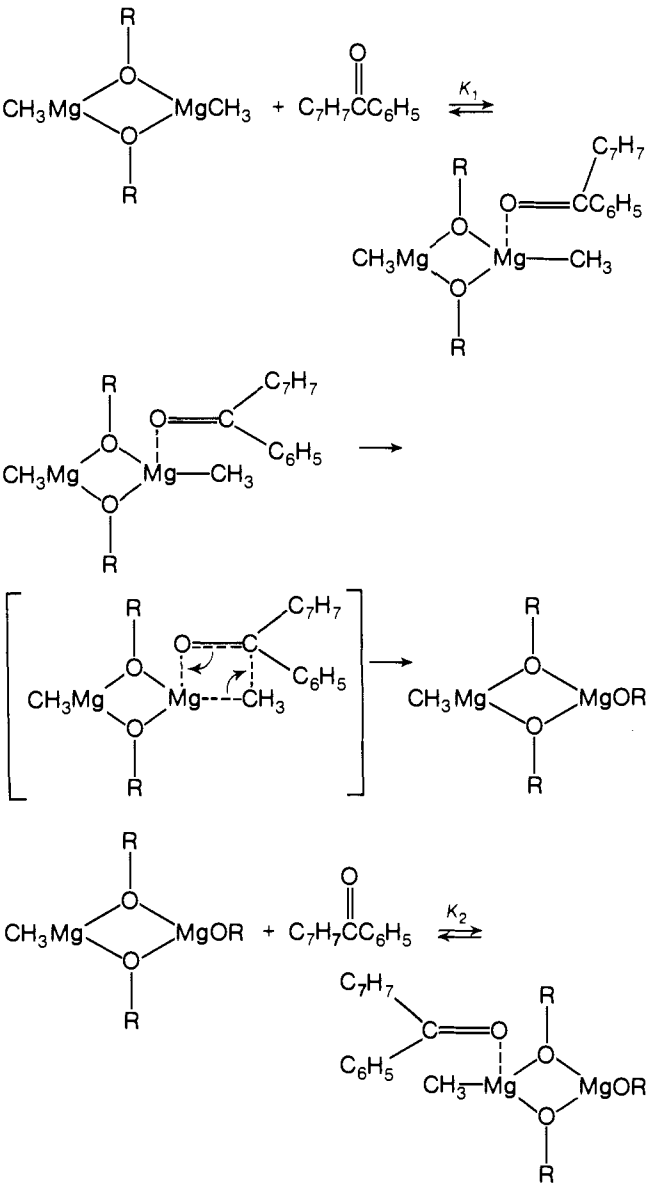
The only detailed mechanistic study involving the addition of an alkylmagnesium alkoxide to a ketone reported thus far involves the reaction of methylmagnesium methylphenyl(o-tolyl)methoxide, $CH_3MgOC(C_6H_5)(C_7H_7)CH_3$, with 2-methylbenzophenone (Scheme I).[44] The alkoxide, formed by the reaction of $(CH_3)_2Mg$ with 2-methylbenzophenone, rapidly dimerizes, and each active methyl group of the dimer reacts with the ketone in a first-order fashion according to eq 7.

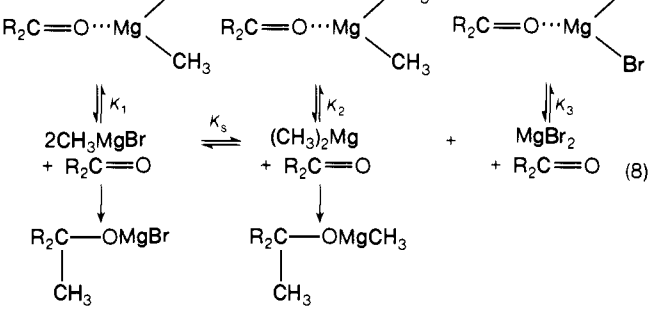


$$R = -C(C_6H_5)(C_7H_7)CH_3 \qquad (7)$$

Although numerous conflicting reports concerning the mechanism of Grignard reagent addition to ketones have appeared in the literature,[33] there appears to be general agreement concerning at least one aspect of this reaction at the present time. Current workers appear to agree that the transition state contains one molecule of organomagnesium reagent and one molecule of ketone.[47-50] Although there is considerable evidence that methyl Grignard reagents add to ketones via a polar mechanism,[49-51] there is some evidence that branched Grignard reagents (e.g., *tert*-butylmagnesium chloride) react via one-electron transfer.[51] Although several workers have demonstrated that determination of the rate law cannot distinguish between the reaction proceeding via rearrangement of complex or by bimolecular collision.[44,47-50] at least one recent report offers kinetic evidence that reaction proceeds by bimolecular collision not involving complex.[52] In a recent study involving the reaction of methylmagnesium bromide with 2-methylbenzophenone, a detailed description of the reaction was presented (eq 8) which demonstrates that both CH_3MgBr and $(CH_3)_2Mg$ react in a first-order fashion.

SCHEME I



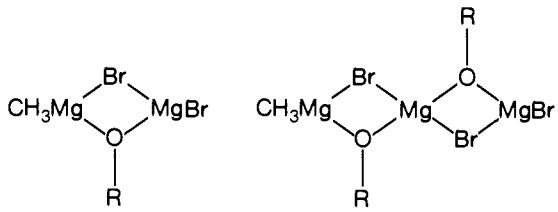


(8)

The product of dimethylmagnesium addition to ketone, $ROMgCH_3$, has but fleeting existence in the Grignard reaction as it undergoes immediate and essentially complete exchange with $MgBr_2$ via eq 9. At low Grignard reagent to ke-

$$ROMgCH_3 + MgBr_2 \longrightarrow ROMgBr + CH_3MgBr \quad (9)$$

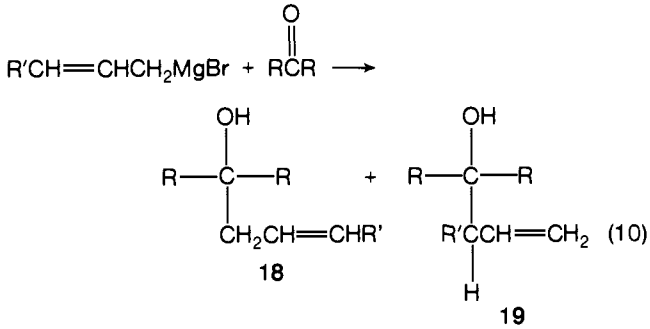
tone ratios, a significant concentration of product, ROMgBr, is formed compared to remaining Grignard reagent which then ties up the remaining CH_3MgBr in the forms of **16** and **17**.



16 **17**

These species further react with ketone via four-centered transition states in a manner exactly analogous to the other organomagnesium reagents presented.[50]

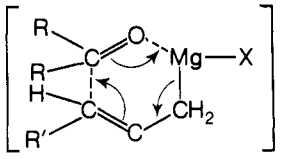
Reaction of 3-substituted allyl Grignard reagents with ketones have the possibility of giving products **18** and **19** (eq 10). Reaction of several ketones having varied steric require-



(10)

18 **19**

ments with crotylmagnesium bromide demonstrate that the ratio of **18** to **19** is greatly dependent on the steric environment of the ketone. Relatively unhindered ketones give almost exclusively the rearranged product **19** whereas highly hindered ketones give almost exclusively the normal product **18**.[53] The rearranged product is thought to arise via a six-center transition state, **20**, whereas the normal product apparently arises via rearrangement of the magnesium salt of **19**. Thus, **18** arises primarily via thermodynamic control



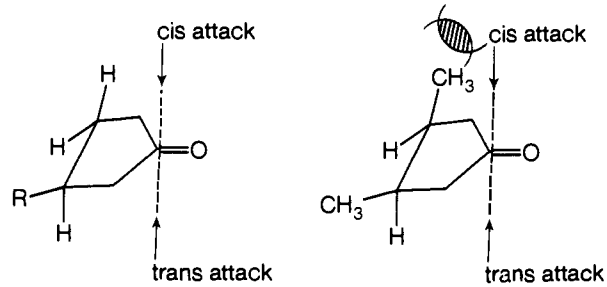
20

whereas **19** arises primarily via kinetic control.[54,55] The principal feature here, whose importance will be discussed in the following section, is that the ratio **18**:**19** is a measure of the steric hindrance to addition offered by a ketone.

B. Addition of Organomagnesium Compounds to Cyclic Ketones

More reactions concerning the addition of organomagnesium compounds to cyclic ketones have been reported than by all other organometallic compounds combined. The objectives of these reactions have been the following: (1) to produce a particular isomeric alcohol to be used further in a synthetic sequence, (2) to gain knowledge concerning the composition of a particular organomagnesium compound, (3) to discover the optimum conditions (solvent, concentration, halide of RMgX, etc.) for producing a desired isomer in maximum yield, and (4) to explore in a theoretical sense the driving force behind the steric course of alkylation. The data in Tables IV–VI, while not comprehensive, are extensive enough to reveal the important discoveries reported to date. Table IV illustrates the reactions of organomagnesium compounds with several cyclopentanones. In reactions involving organomagnesium compounds with 2-alkylcyclopentanones, attack occurs predominantly from the least hindered trans side (steric approach control) in the case of alkylmagnesium compounds and predominantly from the more hindered cis side (torsional strain) in the case of ethynylmagnesium compounds. In general, greater trans attack occurs as the size of the entering group increases ($C_6H_6 > n\text{-}C_3H_7 > C_2H_5 > CH_3$) in accordance with predictions based on steric approach control.

Although 3-alkylcyclopentanones are attacked by organomagnesium reagents with a slight preference for trans entry, examination of the data in Table IV demonstrates that this is not due to steric approach control. If steric approach control is the predominant factor, the stereochemistry would not be insensitive to the steric requirement of the reagent, which it appears to be. Also similar stereochemistry was observed with 3-methyl- and 3-*tert*-butylcyclopentanone, indicating an insensitivity to the steric requirement of the substrate. In the case of both 3-methylcyclopentanone and 3-*tert*-butylcyclopentanone, all reagents, both alkyl and ethynyl compounds, give approximately the same percentage of trans attack. Indeed, Table IV reveals that ethynylmagnesium compounds give a slightly greater percentage of trans attack than do alkylmagnesium reagents. Examination of the conformation of 3-alkylcyclopentanone (**21**) shows that the 3-alkyl group prefers to occupy a pseudo-equatorial position, and therefore it is not at all clear whether cis or trans entry along the reaction coordinate would encounter greater steric strain.



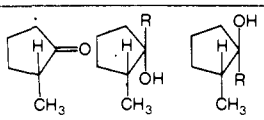
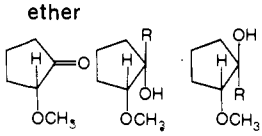
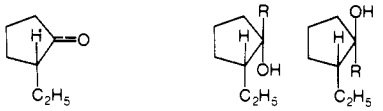
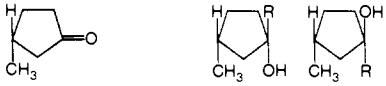
21 **22**

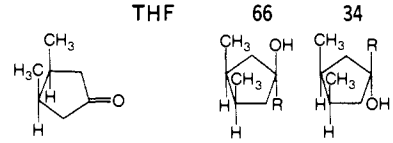
Preference for trans attack by Grignard reagents on *cis*-3,4-dimethylcyclopentanone is high. In this ketone one methyl group must occupy a pseudo-axial position (**22**) leading to significant steric hindrance to cis attack.

Table V lists the isomer ratios obtained from the addition of organomagnesium reagents to cyclohexanones. One general feature of these reactions and of all other organometallic additions to cyclic ketones is that solvent has no great effect on the observed isomer ratio obtained by reaction with a particular organometallic compound. For example, if the solvent is varied from diethyl ether[19,58] to tetrahydrofuran[88] to triethylamine[88] in the addition of $(CH_3)_2Mg$ to 4-*tert*-butylcyclohexanone, the amount of equatorial attack increases by only 14%. Likewise, the addition of CH_3MgI to 2-methylcyclohexanone in diethyl ether and benzene gives essentially the same results.[59,63] Numerous other examples to substantiate this point can be found throughout the tables in this review. In general, the percentage of attack by a particular organometallic reagent from the least hindered side of a cyclic ketone will increase slightly in more polar solvents. This is apparently due to the fact that solvents of greater polarity coordinate the organometallic more strongly and increase the effective steric bulk of the molecule.

It should be noted that addition to cyclohexanones is gov-

TABLE IV. Reactions of Organomagnesium Compounds with Cyclopentanones

Organomagnesium compd	Ketone	Solvent	Isomer percentage[a] Cis alcohol	Trans alcohol	Ref
					
CH_3MgI		Diethyl ether	45	55	17
CH_3MgBr		Diethyl ether	60	40	90
C_2H_5MgBr		THF	75	25	16, 17
n-C_3H_7MgBr		Diethyl ether	80	20	17
$C_6H_{13}MgBr$		Diethyl ether	80	20	17
C_6H_5MgBr		THF	99	1	17
C_6H_5MgBr		Diethyl ether	100	0	90
$HC{\equiv}CCH_2MgBr$		Diethyl ether	60	40	17
$CH_2{=}CHMgCl$		THF	92	8	16, 17
$HC{\equiv}CMgBr$		THF	50	50	16, 17
$CH_3C{\equiv}CMgBr$		THF	33	67	16, 17
$(CH_3)_3CC{\equiv}CMgBr$		THF	50	50	17
$C_6H_5C{\equiv}CMgBr$		THF	50	50	16, 17
$CH_2{=}CHCH_2MgCl$		Diethyl ether	77	23	17
					
C_2H_5MgBr		Diethyl ether	75	25	18
n-C_3H_7MgBr		Diethyl ether	87	13	18
$HC{\equiv}C{-}CH_2MgX$		Diethyl ether	95	5	18
$HC{\equiv}CMgX$		THF	42	58	18
$CH_3C{\equiv}CMgX$		THF	44	56	18
$C_6H_5C{\equiv}CMgX$		THF	46	54	18
$CH_2{=}CHCH_2MgX$		Diethyl ether	82	18	18
					
C_2H_5MgBr		THF	80	20	56
n-C_3H_7MgBr		Diethyl ether	80	20	56
$CH_3C{\equiv}CMgBr$		THF	36	64	56
					

Organomagnesium compd	Ketone	Solvent	Isomer percentage[a] Cis alcohol	Trans alcohol	Ref
CH_3MgI		Diethyl ether	60	40	56
CH_3MgBr		Diethyl ether	58	42	90
n-C_3H_7MgBr		Diethyl ether	61	39	56
C_6H_5MgBr		Diethyl ether	58	42	90
$CH_3C{\equiv}CMgBr$		THF	65	35	56
$CH_2{=}CHCH_2MgCl$		Diethyl ether	65	35	56
					
$(CH_3)_2Mg$		Diethyl ether	53	47	57
$(CH_3)_2Mg$		THF	52	48	57
$(CH_3)_2Mg$		Anisole	54	46	57
$(C_2H_5)_2Mg$		Diethyl ether	57	43	57
$(i$-$C_3H_7)_2Mg$		Diethyl ether	62	38	57
CH_3MgBr		Diethyl ether	54	46	56, 57
CH_3MgBr		THF	53	47	57
CH_3MgBr		Anisole	54	46	57
CH_3MgI		Diethyl ether	51	49	57
C_2H_5MgCl		Diethyl ether	55	45	57
C_2H_5MgBr		Diethyl ether	56	44	56, 57
C_2H_5MgI		Diethyl ether	59	41	57
i-C_3H_7MgCl		Diethyl ether	62	38	57
i-C_3H_7MgBr		Diethyl ether	61	39	56, 57
i-C_3H_7MgI		Diethyl ether	67	33	57
n-C_3H_7MgBr		Diethyl ether	55	45	56
$HC{\equiv}CCH_2MgBr$		Diethyl ether	64	36	56
$HC{\equiv}CMgBr$		THF	65	35	56
$CH_3C{\equiv}CMgBr$		THF	66	34	56
					
CH_3MgBr		Diethyl ether	92	8	90
C_6H_5MgBr		Diethyl ether	92	8	90

[a] Normalized as % cis alcohol + % trans alcohol = 100%.

erned by steric approach control. Large reagents tend to attack cyclohexanones from the least hindered (equatorial) side of the molecule and equatorial entry increases in a regular way as the size of the entering group increases ($CH_3 < C_2H_5 < n$-$C_3H_7 < i$-C_3H_7, etc.). An exception to this is the high percentage of axial entry by phenyl organometallic compounds on 4-*tert*-butylcyclohexanone.[20,60,90] For example, comparison of the reaction of methyl- and phenylmagnesium bromide with both 2-methylcyclopentanone[17,90] and 4-*tert*-butylcyclohexanone[19,58,60] reveals that the phenyl group behaves as a larger entering group than the methyl group toward 2-methylcyclopentanone and as a smaller entering group than methyl toward 4-*tert*-butylcyclohexanone. No satisfactory explanation for this anomaly has been offered to date, but it may lie in the exact orientation of the phenyl group on entry. If the phenyl group enters a cyclohexanone axially with the face of the phenyl ring perpendicular to the 3,5-axial hydrogens (**23**) considerable steric interference will occur. However, if the phenyl

TABLE V. Reaction of Organomagnesium Compounds with Cyclohexanones

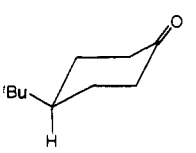
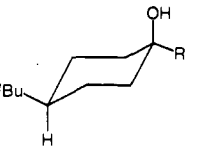
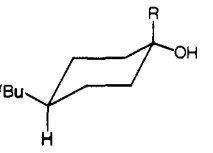
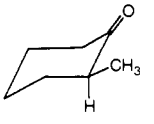
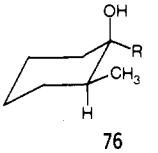
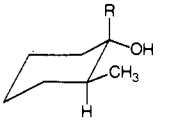
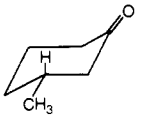
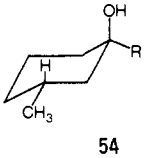
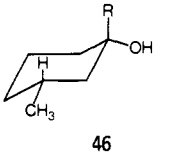
Organomagnesium compd	Ketone	Solvent	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
					
$(CH_3)_2Mg$		Diethyl ether	62	38	19, 58[b]
$(CH_3)_2Mg$		THF	74	36	88
$(CH_3)_2Mg$		Triethylamine	76	24	88
$(n\text{-}C_3H_7)_2Mg$		Diethyl ether	75	25	102
$(CH_2{=}CHCH_2)Mg$		Diethyl ether	44	56	99, 102
$(CH_3CH{=}CHCH_2)_2Mg$		Diethyl ether	70	30	102
CH_3MgI		Diethyl ether	53	47	19, 59, 60[b], 100
CH_3MgI (0.1 %)		Diethyl ether	62	38	100
CH_3MgI (0.8 %)		Diethyl ether	54	46	100
CH_3MgBr		Diethyl ether	60	40	19, 58
CH_3MgBr (0.1 M)		Diethyl ether	68	32	100
CH_3MgBr (0.8 M)		Diethyl ether	62	38	100
$(CH_3)_2Mg + MgBr_2$		Diethyl ether	60	40	58
$CH_3MgBr +$ $CH_3(C_2H_5)_2COMgBr$		Diethyl ether	56	44	58
CH_3MgBr		THF	69	31	19
CH_3MgBr		Anisole	61	39	19
CH_3MgBr		Benzene	62	38	19
CH_3MgCl		Diethyl ether	59	41	19
C_2H_5MgBr		Diethyl ether	71	29	22, 60[b]
$n\text{-}C_3H_7MgBr$		Diethyl ether	68	32	101
$n\text{-}C_3H_7MgI$		Diethyl ether	67	33	101
$i\text{-}C_3H_7MgBr$		Diethyl ether	82	18	60
$t\text{-}C_4H_9MgBr$		Diethyl ether	100	0	60
C_6H_5MgBr		Diethyl ether	49	51	60
$C_6H_5CH_2MgCl$		Diethyl ether	76	20	60
$CH_3MgOC(C_2H_5)_2CH_3 +$ $MgBr_2$		Diethyl ether	60	40	58
$CH_3MgOC(C_2H_5)_2CH_3$		Diethyl ether	74	26	58
$CH_3MgO\text{-}n\text{-}C_3H_7$		Diethyl ether	76	24	61
$CH_3MgO\text{-}n\text{-}C_3H_7$		Benzene	78	22	61
$CH_3MgO\text{-}i\text{-}C_3H_7$		Diethyl ether	79	21	71
$CH_3MgO\text{-}i\text{-}C_3H_7$		Benzene	85	15	61
$CH_3MgOC_6H_5$		Diethyl ether	60	40	61
$CH_3MgOC_6H_5$		Benzene	53	47	61
$CH_3MgN(i\text{-}C_3H_7)_2$		Diethyl ether	73	27	62
$CH_3MgN(i\text{-}C_3H_7)_2$		Benzene	63	37	62
					
$(CH_2{=}CHCH_2)_2Mg$		Diethyl ether	76	24	99
CH_3MgCl		THF	88	12	63
CH_3MgI		Diethyl ether	84	16	59, 63
CH_3MgI		Benzene	82	18	63
C_2H_5MgI		Diethyl ether	90	10	59
C_2H_5MgBr		Diethyl ether	95	5	59
$n\text{-}C_3H_7MgBr$		Diethyl ether	94	6	59
$i\text{-}C_3H_7MgBr$		Diethyl ether	98	2	59
C_6H_5MgBr		Diethyl ether	91	9[c]	23, 59[b]
$HC{\equiv}CMgBr$		THF	45	55	24
					
$(CH_2{=}CHCH_2)_2Mg$		Diethyl ether	54	46	99
C_2H_5MgBr		Diethyl ether	68	32	24

TABLE V (Continued)

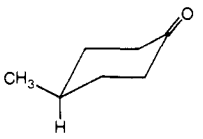
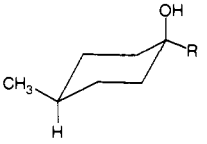
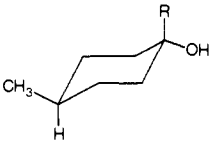
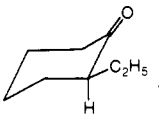
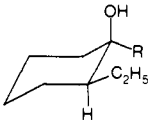
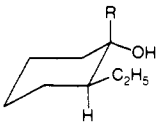
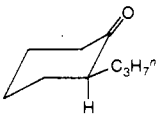
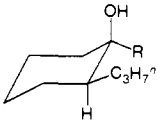
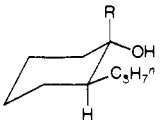
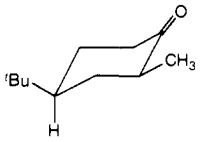
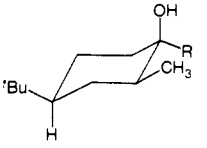
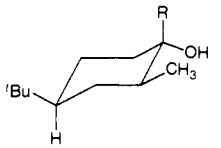
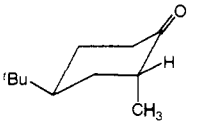
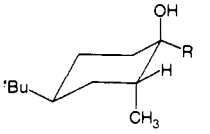
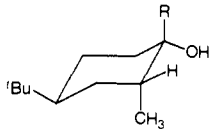
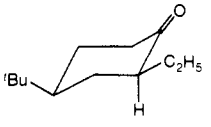
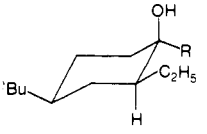
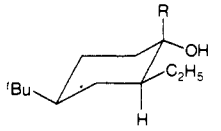
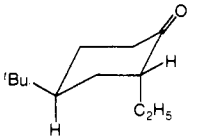
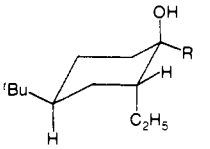
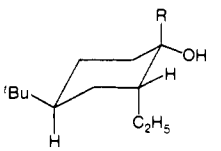
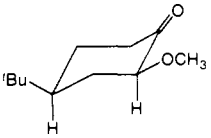
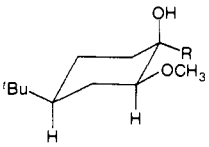
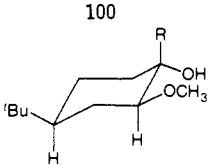
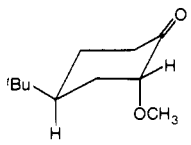
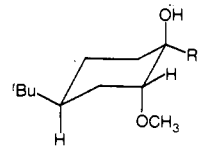
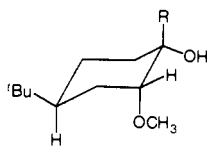
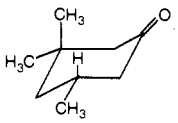
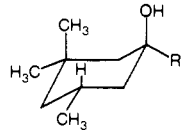
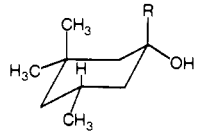
Organomagnesium compd	Ketone	Solvent	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
C_2H_5MgBr		THF	72	28	24
C_2H_5MgBr		Toluene	73	27	24
C_2H_5MgBr		Pyridine–diethyl ether	80	20	24
C_6H_5MgBr		Diethyl ether	59	41[c]	23
					
$(CH_2{=}CHCH_2)_2Mg$		Diethyl ether	44	56	99
C_6H_5MgBr		Diethyl ether	54	46[c]	23
					
CH_3MgI		Diethyl ether	84	16	25, 59
C_2H_5MgBr		THF	95	5	25
n-C_3H_7MgBr		Diethyl ether	93	7	25
$HC{\equiv}CCH_2MgBr$		Diethyl ether	85	15	25
$HC{\equiv}CMgBr$		THF	50	50	25
$CH_3C{\equiv}CMgBr$		THF	43	57	25
$CH_2{=}CHCH_2MgCl$		Diethyl ether	80	20	25
					
CH_3MgCl		THF	81	19	63
CH_3MgI		Diethyl ether	75	25	63
					
CH_3MgI		Diethyl ether	83	17	59
					
CH_3MgI		Diethyl ether	20	80	59
					
n-C_3H_7MgBr		Diethyl ether	92	8	25
$CH_3C{\equiv}CMgBr$		THF	28	72	25
					
$CH_3C{\equiv}CMgBr$		THF	0	100	25
					
$CH_2{=}C{=}CHMgBr$		Diethyl ether	94	6	64

TABLE V (Continued)

Organomagnesium compd	Ketone	Solvent	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
					
$CH_2{=}C{=}CHMgBr$		Diethyl ether	25	75	64
					
CH_3MgI		Diethyl ether	100	0	26
C_2H_5MgBr		Diethyl ether	100	0	26
n-C_3H_7MgBr		Diethyl ether	100	0	27
i-C_3H_7MgBr		Diethyl ether	100	0	26
t-C_4H_9MgBr		Diethyl ether	100	0	26
$HC{\equiv}CCH_2MgBr$		Diethyl ether	100	0	26
$H_2C{=}CHMgBr$		Diethyl ether	100	0	26, 65[d]
C_6H_5MgBr		Diethyl ether	100	0	90
$HC{\equiv}CMgBr$		Diethyl ether	100	0	26
$H_2C{=}CHCH_2MgBr$		Diethyl ether	100	0	26

[a] Normalized as % axial alcohol + % equatorial alcohol = 100%. [b] Average of slightly conflicting values. [c] It should be noted that the preferred conformation of these alcohols is that in which the phenyl group is equatorial. [d] In THF.

TABLE VI. Reactions of Organomagnesium Compounds with Bicyclic Ketones

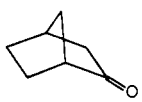
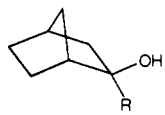
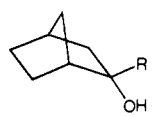
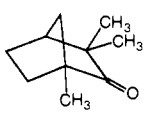
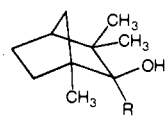
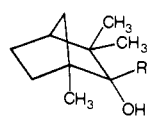
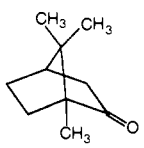
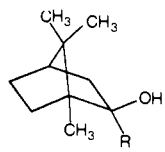
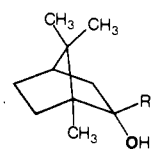
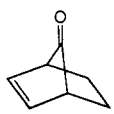
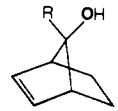
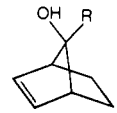
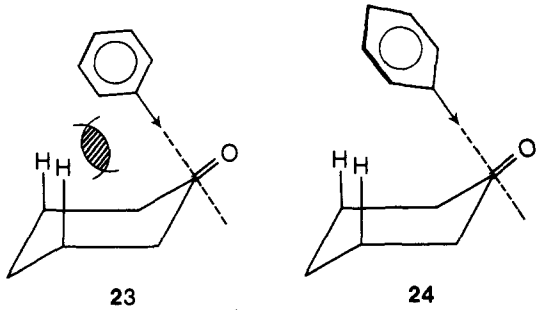
Organomagnesium compound	Ketone	Solvent	Isomer percentage[a] Exo alcohol	Isomer percentage[a] Endo alcohol	Ref
					
CH_3MgI		Not given	0	100	66, 67
C_6H_5MgBr		Not given	0	100	68
p-$CH_3C_6H_4MgX$		Diethyl ether	0	100	27
p-ClC_6H_4MgX		Diethyl ether	0	100	27
p-$CH_3OC_6H_4MgX$		Diethyl ether	0	100	27
					
$HC{\equiv}CMgBr$		THF	0	100	28
$CH_3C{\equiv}CMgBr$		THF	0	100	28
$C_5H_5C{\equiv}CMgBr$		THF	0	100	28
					
CH_3MgX		Diethyl ether	100	0	29
$CH_2{=}CHMgCl$		Diethyl ether	97	3	29, 65[b]
C_6H_5MgBr		Diethyl ether	100	0	69
p-$CH_3OC_6H_4MgBr$		THF	100	0	70
$HC{\equiv}CCH_2MgX$		Diethyl ether	100	0	29
$HC{\equiv}CMgX$		THF	100	0	29
$CH_3C{\equiv}CMgX$		THF	100	0	29
$CH_2{=}CHCH_2MgX$		Diethyl ether	100	0	29
			 (anti alcohol)	 (syn alcohol)	

TABLE VI (Continued)

Organomagnesium compound	Ketone	Solvent	Isomer percentage[a] Exo alcohol	Endo alcohol	Ref
CH_3MgI		Diethyl ether	96	4	71
CH_3CH_2MgI		Diethyl ether	100	0	71
$(CH_3)_2CHMgI$		Diethyl ether	100	0	71
$(CH_3)_3CCH_2MgI$		Diethyl ether	100	0	71
$CH_2{=}CHMgBr$		Not given	80	20	72
C_6H_5MgBr		Diethyl ether	74	26	30

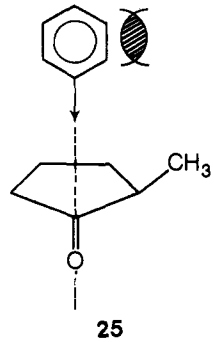
[a] Normalized as % endo (syn) alcohol + % exo (anti) alcohol = 100%. [b] Average of slightly conflicting values.

group enters axially with the face of the phenyl ring parallel to the 3,5-axial hydrogens (**24**) little steric interference would be expected to occur owing to the flatness of the phenyl ring. Similar cis entry into 2-methylcyclopentanone (**25**) would be accompanied by severe steric strain between the 2-methyl group and the phenyl group. Reaction of methyl and phenyl



23

24



25

organometallics with *cis*-2-methyl-4-*tert*-butylcyclohexanone (eq 2-Me) should yield a higher percentage of equatorial attack by the phenyl reagents if the preceding explanation is correct. Unfortunately, such reactions with phenylmetallic compounds have not been reported.

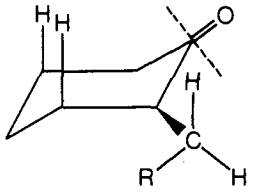
Ethynylmagnesium compounds tend to give more axial attack on cyclohexanones than magnesium alkyls, and the steric course of the reaction is controlled by torsional strain as noted in section II.B.

The halide of a Grignard reagent has little effect on the steric consequence of the reaction. Methylmagnesium chloride and bromide, for example, yield essentially the same isomer ratio in reaction with cyclopentanones[17,56,57,99] and cyclohexanones,[19,58,100] whereas methylmagnesium iodide tends to give a slightly higher percentage of attack from the more hindered side of the ketones.[17,19,59,60,100]

There appears to be little correlation between the association of the organomagnesium reagent and the stereochemistry of its reactions with cyclic ketones. In general, little change in isomer ratio occurs with change in concentration of the organomagnesium reagent. In the case of organolithium reagents this is understandable in terms of the reactive species being monomeric RLi regardless of the association of the reagent.[13-15] The mechanistic studies concerning the addition of organomagnesium reagents have been carried out both in dilute solution, where only monomeric species exist,[44,49,50] and in concentrated solution, where the organomagnesium species are predominantly associated. There is no general agreement yet concerning the relative reactivities of monomeric and more highly associated species.[45,47,48] However, organomagnesium compounds would be expected to give a higher percentage of attack from the less hindered side of a cyclic ketone in concentration ranges where the organomagnesium compound is associated owing to the greater steric bulk of the active associated species compared to the monomer species, yet the evidence is to the contrary. Methylmagnesium bromide and iodide both give a slightly higher percentage of equatorial attack on 4-*tert*-butylcyclohexanone when the concentration of the Grignard reagent is 0.1 *M* (monomer) than at 0.8 *M* (associated).[100] The reason for this may be that, regardless of the concentration, it is the monomeric species that is reacting and/or that a disolvated monomer can have a similar or greater steric bulk in addition to cyclic ketones compared to a monosolvated associated form. The latter reasoning is similar to that given in noting that reagents appear to have a greater effective steric bulk in more polar solvents.

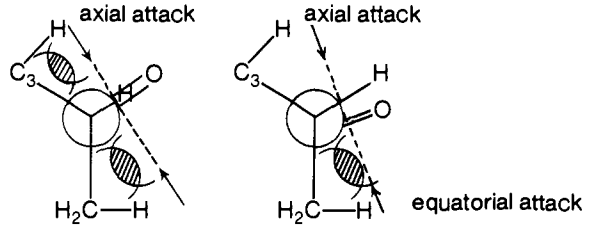
If the entering R group of an organometallic compound is held constant and the metal is varied, approximately the same stereochemistry is observed in addition to cyclic ketones. Thus the reactions of CH_3Li, $(CH_3)_2Mg$, CH_3MgCl, CH_3MgBr, $CH_3MgO\text{-}i\text{-}C_3H_7$, and $CH_3MgN(i\text{-}C_3H_7)_2$ in diethyl ether give an amount of equatorial attack on 4-*tert*-butylcyclohexanone which does not vary by greater than 19% among the compounds.[19,58,61,62] Trimethylaluminum in diethyl ether gives a slightly greater percentage of equatorial attack than any of the above, indicating the importance of direct branching on the metal atom either by alkyl groups or by solvent molecules (Table VIII).[90] An important generalization can be made at this point. *The observed steric course of alkylation of a cyclic ketone is primarily a function of the entering R group (regardless of the nature of the metal to which it is attached) and of the steric requirement of the particular ketone as controlled by steric strain and torsional strain in the transition state.* Other factors such as solvent, reactant ratio, reactant concentration, and the type and total bulk of the organometallic molecule result in only minor changes in the overall observed stereochemistry.

Concerning the steric requirement of the ketone, the percentage of axial attack on methyl-substituted cyclohexanones increases as the methyl group is shifted from C-2 to C-4 (Table V). Thus, the further away a substituent on a cyclic ketone exists, relative to the reaction site, the less influence it has on the steric course of reaction. It should be noted that addition to 2-methyl-, 2-ethyl-, and 2-*n*-propylcyclohexanone gives approximately the same ratio of axial to equatorial alcohol. Although a larger substituent might be expected to hinder axial attack to a greater extent, the primary steric strain in all of these cases is due to interaction of the entering group with a pseudo-axial hydrogen (**10, 26**).



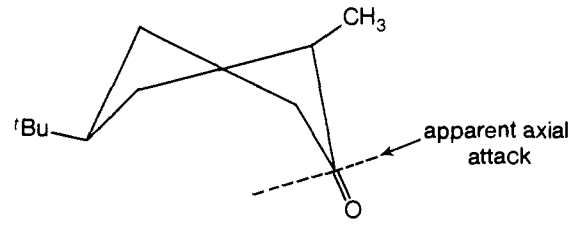
26

The reaction of CH_3MgI with *cis*-2-methyl-4-*tert*-butylcyclohexanone (equatorial 2-Me) and *trans*-2-methyl-4-*tert*-butylcyclohexanone (axial 2-Me) have been studied.[59] The results with the former ketone were essentially the same as with 2-methylcyclohexanone.[59,63] However, axial entry into *trans*-2-methyl-4-*tert*-butylcyclohexanone (axial 2-Me) was an unusually high 80%. The results cannot be explained if the conformation of the ketone is such that the carbonyl group exactly eclipses the 2,6-equatorial hydrogens (**27a**). If this were the



27a **27b**

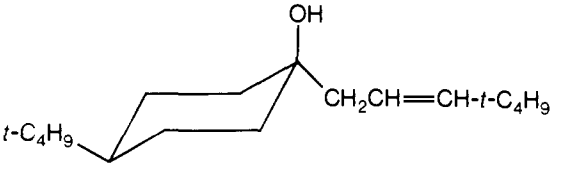
case, the entering methyl group would encounter steric strain with the one pseudo-axial hydrogen in the case of equatorial attack and with the two 3,5-axial hydrogens in the case of axial attack (**27a**). Since two interactions occur in axial attack and only one in equatorial attack, equatorial attack should be preferred. However, if the conformation of the ketone is such that the carbonyl group lies below the 2,6-equatorial hydrogens (**27b**), equatorial attack would hindered by the proximity of the pseudo-axial hydrogen to the reaction coordinate and axial attack should be favored. Conformational analysis calculations indicate that the carbonyl group in cyclohexanones does lie below the 2,6-equatorial hydrogens with an $H_{eq}C—C=O$ dihedral angle of about 5°.[31,73] Another explanation of the large amount of axial attack observed with *trans*-2-methyl-4-*tert*-butylcyclohexanone is the possibility that an axial methyl group is so unstable in a chair conformation that the ketone prefers to react through a twist boat conformation (**28**). Attack from the least hindered exo side results in the formation of the same product expected from axial attack.



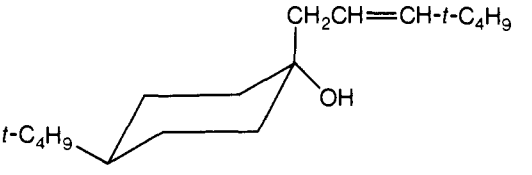
28

The reactions of allylmagnesium bromide and *n*-propylmagnesium bromide with 4-*tert*-butylcyclohexanone in diethyl ether have been compared.[6] *n*-Propylmagnesium bromide reacts via a four-center transition state (eq 5), whereas allylmagnesium bromide reacts via a six-center transition state (**20**) in which the entering carbon atom is not bonded to magnesium. Thus, although the two reagents appear similar in size, the allyl Grignard reagent should have less effective bulk as an entering group than the propyl group and therefore should give more axial attack. The results, which show that *n*-propylmagnesium bromide gives only 26% axial attack whereas allylmagnesium bromide gives 52% axial attack, demonstrate the importance of both torsional strain[6] and steric approach control.

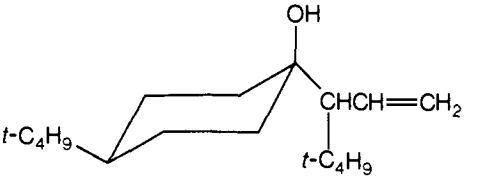
Analysis of the reaction of *tert*-butylallylmagnesium bromide with 4-*tert*-butylcyclohexanone confirmed experimentally that which had been theorized from calculations and study of models, namely that approach from the equatorial side of 4-*tert*-butylcyclohexanone encounters less steric strain than approach from the axial side. It has already been pointed out that 3-substituted allyl Grignard reagents give a sensitive measurement of the steric environment about a ketone.[7,53-55] Reaction of *tert*-butylallylmagnesium bromide with 4-*tert*-butylcyclohexanone has the possibility of giving four products (**29–32**). These are shown along with the percentage of each actually found.[8]



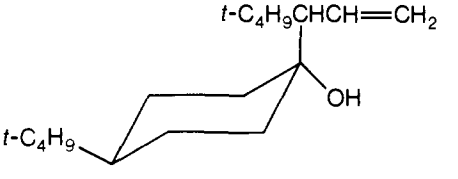
29, 33%



30, 41%



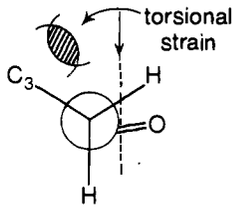
31, 26%



32, 0%

The only equatorial alcohol formed (**30**) is the nonrearranged product, demonstrating that attack from the axial side encounters steric strain.[7,53-55] The rearranged product is formed exclusively by equatorial attack as expected for such a large entering group.[8] However, the nonrearranged alcohol[54,55] is found to consist predominantly of equatorial alcohol.[8] This is consistent with the steric course of reactions involving small entering groups being controlled by torsional strain.

It should be noted that, although the literature contains only references to torsional strain involving the entering group and the 2,6-axial hydrogens during equatorial attack, a group entering from the axial side encounters torsional strain in the transition state between its partially formed bond and the C_2-C_3 and C_5-C_6 bonds of the cyclohexanone (**33**). This is similar to the torsional strain encountered in the eclipsed conformation of propane (**34**). If the carbonyl group of cyclohexanones perfectly eclipsed the 2,6-equatorial hydrogens, then torsional strain hindering both axial attack and equatorial attack would be approximately the same (**35**). Torsional strain



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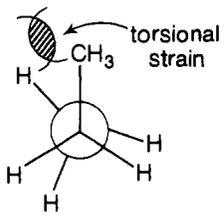


34

has been demonstrated to be more severe for a group attacking the equatorial side of a cyclohexanone, providing further evidence that the carbonyl group lies below the plane of the 2,6-equatorial hydrogens (**33**). If this were not the case, there would be no tendency for any group, including hydride, to attack a cyclohexanone preferentially from the axial side.

Table VI provides stereochemical data concerning the reaction of organomagnesium compounds with bicyclic ketones. Norcamphor undergoes essentially 100% attack from the exo side by all organomagnesium compounds thus far reported.[27,66-68] An entering group approaching norcamphor from the exo side encounters steric strain involving one hydrogen from the methylene bridge and one pseudo-axial hydrogen on C-3. Attack from the endo side is sterically hindered by three pseudo-axial hydrogens on C-3, C-4, and C-5. Examination of the norcamphor model indicates that attack from the endo side is more sterically hindered than attack from the exo side. However, steric strain alone does not appear to be sufficient to explain the enormously large percent of oxo attack observed. A group approaching norcamphor from the exo side encounters no torsional strain, but a group approaching from the endo side encounters torsional strain involving the partially formed entering group–carbonyl carbon bond and the C_1–C_6 bond of the ketone (**36**). In contrast to the cyclohexanone and cyclopentanone cases, torsional strain and steric approach control reinforce one another in the norcamphor molecule to provide a strong directional influence for exo attack.

Fenchone is analogous to norcamphor. The 3-exo and the 3-endo methyl groups offset each other from a steric and torsional point of view. The introduction of a pseudo-axial hydrogen from the C_1 methyl group which provides steric hindrance to exo attack does not appear to offset the directional influence of combined steric strain and torsional strain encountered in endo attack, and fenchone undergoes attack 100% from the exo side.[28]

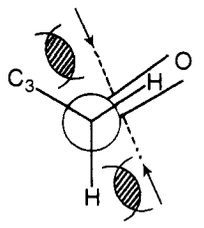
The methyl group bonded to C_7 of camphor encounters such severe steric strain with groups attempting to enter the molecule from the exo direction that essentially 100% endo attack on camphor is observed.[29,65,69,70]

Grignard reagents attack 7-norbornenone almost exclusively from the less hindered syn face, in sharp contrast to organolithium reagents which give a large percentage of anti attack.[30,71,72] In the case of phenyl and vinyl entering groups, for example, a large percentage of the syn alcohol can be obtained by use of the appropriate lithium reagents, whereas a large percentage of the anti alcohol can be obtained by use of the appropriate Grignard reagents.

IV. Organoaluminum Compounds

A. Solution Composition of Organoaluminum Compounds and Their Reaction Mechanisms with Ketones

The solution composition of organoaluminum compounds and the mechanisms by which they alkylate ketones are perhaps known with greater certainty and in greater detail than similar information concerning any other class of organometallic compounds. Organoaluminum compounds exist as mo-



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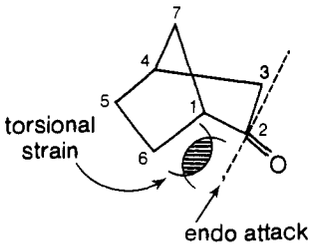
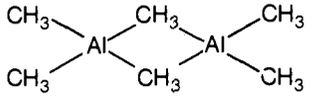


36

nomers in polar solvents such as diethyl ether[74,75] with the vacant orbital strongly coordinated by a solvent molecule.[76] On the other hand, molecular weight determinations of several organoaluminum compounds in benzene have been interpreted in terms of a monomer–dimer equilibrium in which the position of the equilibrium is a function of the nature of the alkyl group. Of the compounds reported, trimethylaluminum[77] and triphenylaluminum[75] were essentially dimeric, whereas triisopropylaluminum was the least associated, being essentially monomeric in benzene.[77]

Evidence from infrared spectroscopy,[78] X-ray analysis,[79] and nuclear magnetic resonance spectroscopy[80,81] demonstrate that trimethylaluminum exists as a dimeric molecule held together by a double methyl bridge (**37**). The NMR spec-



37

trum of trimethylaluminum at room temperature in hydrocarbon solvent shows a single proton resonance signal.[80,81] As the temperature is lowered to −65°, two separate signals are observed (in 2:1 ratio). The upfield signal corresponds to the protons of the terminal methyl groups, and the downfield signal corresponds to the protons of the bridging methyl groups. The variable-temperature NMR data indicate that trimethylaluminum is undergoing very rapid exchange of terminal and bridging methyl groups at room temperature. Since dissociation to monomer and recombination is thought to be the mechanism for rapid exchange of alkyl groups,[81] it is clear that each dimer, as a stable entity, is very short lived. This indicates that although the amount of monomer present at any instant is very small, a large amount of monomer is available for reaction in a relatively short period of time.

The reaction of trimethylaluminum and benzophenone in diethyl ether was studied kinetically over a wide range of reactant ratios and concentrations.[82] The reaction was found to be second order overall, first order in trimethylaluminum and first order in ketone. Evidence for complex formation between $(CH_3)_3Al$ and benzophenone in low concentration was obtained by ultraviolet spectroscopy. Equation 11 describes the mechanism of reaction. As in the case with organolithium and organomagnesium compounds (except allyl Grignard reagents), the transition state is described as being four-centered (**38**).[82]

$$(C_6H_5)_2C{=}O + (CH_3)_3Al{\cdot}O(C_2H_5)_2 \rightleftharpoons (C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3 + (C_2H_5)_2O$$

$$(C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3 \longrightarrow \left[(C_6H_5)_2C{=}O \cdots H_3C{-}Al(CH_3)_2\right]^{\ddagger} \longrightarrow (C_6H_5)_2C(CH_3){-}OAl(CH_3)_2 \quad (11)$$

38

A rate study involving the reaction of trimethylaluminum with benzophenone in benzene demonstrates that the reac-

tants, $(CH_3)_3Al$ and ketone, form a complex whose formation is essentially complete.[83] The half-life of disappearance of this 1:1 complex is about 2900 sec when it is present alone at 0.0883 *M* concentration, but decreases to about 50 sec when trimethylaluminum is also present at the same concentration. Detailed analysis of the kinetic data revealed a finding unique in organometallic reaction mechanisms, namely, that the reaction mechanism changes as the initial ratio of reactants is increased from 1:1 to 2:1. In 1:1 ratio the transition state contains one molecule of $(CH_3)_3Al$ and ketone, whereas in 2:1 ratio the transition state involves two molecules of $(CH_3)_3Al$ and one of ketone.[83] Equation 12 describes the mechanism of reaction in 1:1 reactant ratio. The reaction is analogous to that observed in diethyl ether except that the position of the equilibrium governing complex formation lies almost completely to the left in diethyl ether and almost completely to the right in benzene.[82,83] The exact nature of the

$$(CH_3)_3Al + (C_6H_5)_2C{=}O \rightleftharpoons (C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3$$

$$(C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3 \longrightarrow \left[(C_6H_5)_2C\cdots O \;\; H_3C\cdots Al(CH_3)_2\right]^{\ddagger} \longrightarrow (C_6H_5)_2C(CH_3)OAl(CH_3)_2 \quad (12)$$

38

four-center transition state (**38**) will be discussed in greater detail shortly. Equation 13 illustrates the mechanism by which $(CH_3)_3Al$ adds to benzophenone in a 2:1 or greater ratio in benzene solvent.[83] Although the rate-determining step can be represented by attack of the $(CH_3)_3Al$-ketone complex by $(CH_3)_3Al$ *monomer* via a six-center transition state (**39**),[83] it is also possible to represent the reaction as proceeding via a consecutive bimolecular reaction.

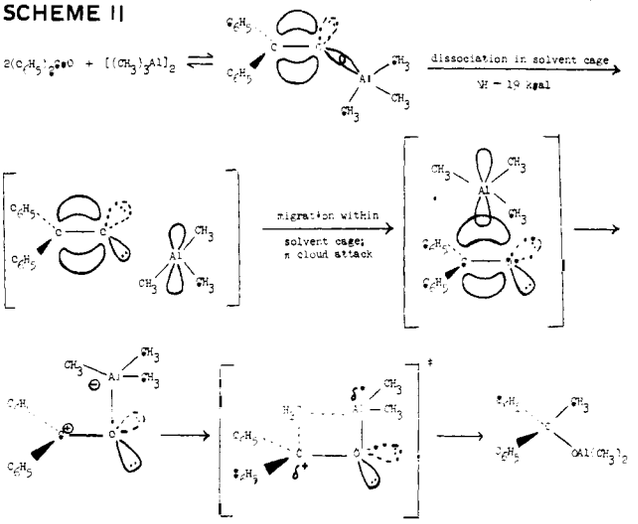
$$(CH_3)_3Al + (C_6H_5)_2C{=}O \rightleftharpoons (C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3 \quad (13)$$

$$(C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3 + (CH_3)_3Al \longrightarrow \left[(C_6H_5)_2C(O{\cdot}Al(CH_3)_2)\,H_3C{-}Al(CH_3)_2{-}CH_3\right] \longrightarrow (C_6H_5)_2C(CH_3)OAl(CH_3)_2{\cdot}Al(CH_3)_3$$

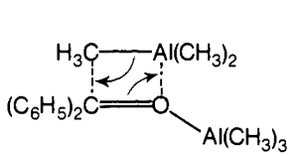
39

As noted in section II.A, the rate law describing the reaction of $(CH_3)_3Al$ with ketone in 1:1 ratio cannot be used to distinguish between rearrangement of the complex and simple bimolecular collision. However, critical analysis of the activation parameters for the reaction of $(CH_3)_3Al$ and benzophenone in diethyl ether and benzene in a 1:1 reactant ratio reveals the nature of the detailed alkyl transfer step in these systems.[84] The activation energies in both ether and benzene were essentially the same, ca. 20 kcal. Internal rearrangement of the complex with distortion of the carbonyl π bond should require at least twice this much energy; therefore an alternate pathway was suggested.[84] The observed activation energy in both solvents is essentially the same as the energy required to dissociate both $(C_6H_5)_2C{=}O{\cdot}Al(CH_3)_3$ and $(C_2H_5)_2O{\cdot}Al(CH_3)_3$. The detailed path most consistent with these results, which indicate a common transition state, arises from the reactants being held in a solvent cage, followed by bimolecular reaction of $(CH_3)_3Al$ with ketone. The activation energy observed consists predominantly of the energy required to dissociate the $(CH_3)_3Al$–ketone complex (in diethyl ether the $(CH_3)_3Al{\cdot}O(C_2H_5)_2$ solvate) plus a small, ca. 1 kcal. energy for addition. The mechanism is illustrated in Scheme II.[84]

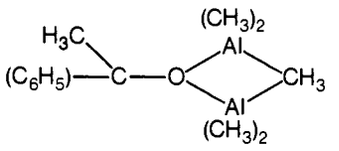
SCHEME II



A four-center transition state, **40**, has been suggested for the reaction of $(CH_3)_3Al$ with benzophenone in 2:1 ratio in benzene[85] since the product of the reaction is "hemialkoxide" (**41**).[85,86] A clear choice between **39** and **40** is not possible at this time, and it has already been pointed out that close



40



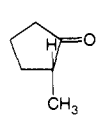
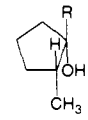
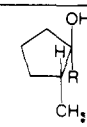
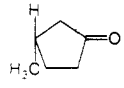
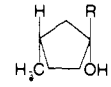
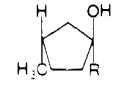
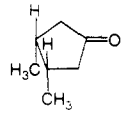
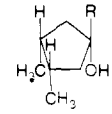
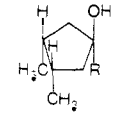
41

scrutiny of the two transition states indicates little difference between the two.[84] Since it is not necessary for the purposes of the following discussion to chose between the two suggestions, the transition state describing the reaction of $(CH_3)_3Al$ and benzophenone in benzene in 2:1 ratio will be designated as six centered in section IV.B for purposes of convenience.

B. Addition of Organoaluminum Compounds to Cyclic Ketones

Since the mechanism by which organoaluminum compounds add to ketones in benzene solvent is a function of reactant stoichiometry, it was considered to be of interest to add R_3Al compounds to cyclic ketones and study the effect of stereochemistry with stoichiometry. A most unusual observation was made when it was found that reaction of $(CH_3)_3Al$ in benzene[87,88] and hexane[88,89] with 4-*tert*-butylcyclohexanone in 2:1 or greater ratio results in 90% axial attack, whereas in 1:1 ratio or in the case of all other main group metal alkyls, predominant equatorial attack (~70%) is observed. Steric approach control favors direction of an entering group (larger than H) to the equatorial side of 4-*tert*-butylcyclohexanone, while torsional strain favors direction of an entering group to the axial side. Since steric strain always dominates torsional strain in the transition state in reactions involving methyl entry (Tables II and V), neither of these modern theories of stereoalkylation is sufficient to explain the results described above. In a recent study involving reaction of several organoaluminum compounds with ketones having varied steric requirements, a satisfactory explanation of the unusual behav-

TABLE VII. Reaction of Organoaluminum Compounds with Cyclohexanones

Organoaluminum compd	Ketone	Solvent	Ratio AlR_3/ketone	Isomer percentage[a] Cis alcohol	Trans alcohol	Ref
						
$(CH_3)_3Al$		Benzene	1.0	60	40	90
$(CH_3)_3Al$		Benzene	2.0	23	77	90
$(CH_3)_3Al$		Benzene	3.0	22	78	90
$(CH_3)_3Al$ then n-C_4H_9Li[b]		Benzene–hexane	1.0	86[c]	14[c]	21
$(C_6H_5)_3Al$		Benzene	1.0	100	0	90
$(C_6H_5)_3Al$		Benzene	2.0	94	6	90
$(C_6H_5)_3Al$		Benzene	4.1	84	16	90
						
$(CH_3)_3Al$		Benzene	1.0	61	39	90
$(CH_3)_3Al$		Benzene	2.0	57	43	90
$(CH_3)_3Al$		Benzene	4.0	56	44	90
$(C_6H_5)_3Al$		Benzene	1.0	58	42	90
$(C_6H_5)_3Al$		Benzene	2.0	63	37	90
						
$(CH_3)_3Al$		Benzene	1.0	92	8	90
$(CH_3)_3Al$		Benzene	2.0	91	9	90
$(CH_3)_3Al$		Benzene	4.0	90	10	90
$(C_6H_5)_3Al$		Benzene	1.0	91	9	90
$(C_6H_5)_3Al$		Benzene	2.0	100	0	90

[a] Normalized as % cis alcohol + % trans alcohol = 100%. [b] $(CH_3)_3Al$ and ketone added in 1:1 ratio followed in 10 sec by addition of one equiv of n-C_4H_9Li. [c] Butylation percentages.

ior of excess $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone was presented.[90]

Table VII lists the isomer percentages obtained in the reaction of organoaluminum compounds with cyclopentanones. In the case of 2-methylcyclopentanone a drastic change in the ratio of the product isomers occurs as the initial ratio of AlR_3/ketone is varied from 1:1 to 2:1. The change occurs with both trimethyl- and triphenylaluminum and is so pronounced in the case of trimethylaluminum that methyl attack takes place to the extent of 80% from the more hindered side. As noted previously, the transition state describing the 1:1 reactant ratio is four-center, and that describing the 2:1 reactant ratio involves attack of a molecule of trimethylaluminum on the ketone–$Al(CH_3)_3$ complex. Reactions proceeding through a four-center transition state (1:1 ratio R_3Al:ketone) give the product expected for a reaction controlled by steric strain in the transition state. This is true in the case of all cyclopentanones examined as was the case in all cyclohexanones and bicyclic ketones examined. These reactions are analogous to those of organolithium compounds (section II.B) and organomagnesium compounds (section III.B) discussed previously. A second generalization can now be made. *Insofar as it is possible to determine, the stereochemical course of addition reactions which proceed through a four-center transition state is controlled mainly by steric strain and torsional strain in the transition state as determined primarily by the nature of the entering group and the ketone.*

Examination of Table VII reveals that the stereochemical course of addition of R_3Al compounds to 3-methylcyclopentanone and *cis*-3,4-dimethylcyclopentanone is independent of reaction ratio. Therefore, the unusual stereochemistry observed with 2-methylcyclopentanone and 4-*tert*-butylcyclohexanone is not inherent in the change from a four- to six-center transition state. That is, a six-center transition state does not always lead to addition of a substrate from the opposite side when compared to a four-center transition state.

Table VIII tabulates the isomer ratios obtained on reaction of organoaluminum compounds with substituted cyclohexanones in benzene and diethyl ether. It should be noted that all reactions in diethyl ether and 1:1 reaction ratios in benzene result in organoaluminum attack of these ketones preferentially from the least hindered side. These reactions proceed through four-center transition states and follow the generalization previously stated.

All cyclohexanones show a large change in product isomer ratio with reactant ratio. Comparison of the reactions in 2:1 or greater R_3Al:ketone ratios in benzene of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone demonstrate

SCHEME III

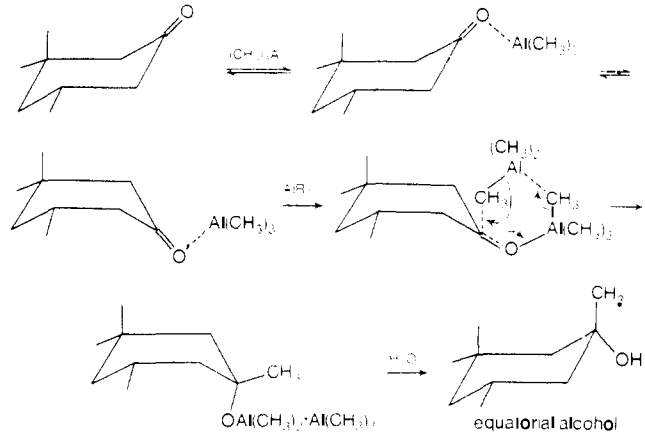
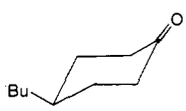
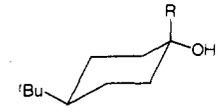
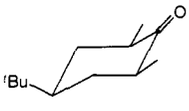
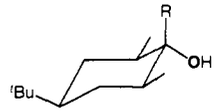
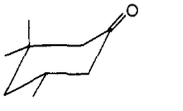
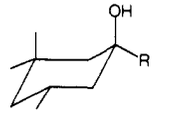
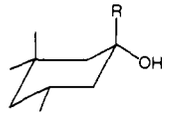


TABLE VIII. Reaction of Organoaluminum Compounds with Cyclohexanones

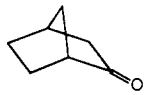
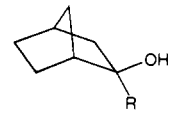
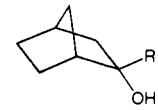
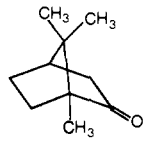
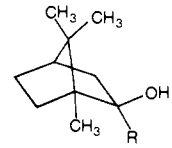
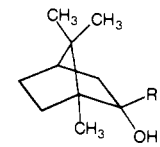
Organoaluminum compd	Ketone	Solvent	Ratio AlR_3/ketone	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
						
$(CH_3)_3Al$		Benzene	0.5	80	20	90
$(CH_3)_3Al$		Benzene	1.0	76	24	90
$(CH_3)_3Al$		Benzene	1.5	53	47	90
$(CH_3)_3Al$		Benzene	2.0	17	83	90
$(CH_3)_3Al$		Benzene	3.0	12	88	90
$(CH_3)_3Al$		Diethyl ether	1.0	85	15	90
$(CH_3)_3Al$		Diethyl ether	3.0	87	13	90
$(C_2H_5)_3Al$		Benzene	1.0	88	12	90
$(C_2H_5)_3Al$		Benzene	2.0	17	83	90
$(C_2H_5)_3Al$		Benzene	4.0	14	86	90
$(C_2H_5)_3Al$		Diethyl ether	1.0	88	12	90
$(C_2H_5)_3Al$		Diethyl ether	3.0	88	12	90
$(C_6H_5)_3Al$		Benzene	1.0	51	49	90
$(C_6H_5)_3Al$		Benzene	2.0	27	73	90
$(C_6H_5)_3Al$		Benzene	4.0	8	92	90
$(C_6H_5)_3Al$		Diethyl ether	1.0	44	56	90
$(C_6H_5)_3Al$		Diethyl ether	3.0	44	56	90
$(CH_3)_2AlC_2H_5$		Benzene	1.0	80(71)[b]	20(29)[b]	21
$(CH_3)_2AlC_2H_5$		Benzene	3.0	12(12)[b]	88(88)[b]	21
$(CH_3)_3Al$ then $(C_2H_5)_3Al$[d]		Benzene	2.0	31(35)	71(65)	21
$(CH_3)_3Al$ then n-C_4H_9Li[d]		Benzene-hexane	1.0	75[c]	25[c]	21
						
$(CH_3)_3Al$		Benzene	1.0	99	1	61
$(CH_3)_3Al$		Benzene	3.0	59	41	61
						
$(CH_3)_3Al$		Benzene	1.0	100	0	90
$(CH_3)_3Al$		Benzene	2.0	81	19	90
$(CH_3)_3Al$		Benzene	4.0	60	40	90
$(CH_3)_3Al$		Diethyl ether	1.0	100	0	90
$(C_2H_5)Al$		Benzene	1.0	100	0	90
$(C_2H_5)_3Al$		Benzene	2.0	89	11	90
$(C_2H_5)_3Al$		Benzene	4.0	78	22	90
$(C_2H_5)_3Al$		Diethyl ether	1.0	100	0	90
$(C_2H_5)_3Al$		Diethyl ether	3.0	100	0	90
$(C_6H_5)_3Al$		Benzene	1.0	100	0	90
$(C_6H_5)_3Al$		Benzene	2.0	100	0	90
$(C_6H_5)_3Al$		Benzene	4.0	100	0	90
$(C_6H_5)_3Al$		Diethyl ether	1.0	100	0	90
$(C_6H_5)_3Al$		Diethyl ether	2.0	100	0	90

[a] Normalized as % axial alcohol + % equatorial alcohol = 100%. [b] Parenthesized percentages are ethylation products. [c] Butylation percentages. [d] $(CH_3)_3Al$ and ketone added in 1:1 ratio followed in 10 sec by addition of $(C_2H_5)_3Al$ or n-C_4H_9Li.

that the unusually high percentage of axial attack does not arise by reaction through the boat conformation of either ketone. Scheme III illustrates that in order for the C-3 axial methyl group to be important sterically, the complexed ketone must be in the chair conformation. Alkylation proceeding through boat conformations of both 3,3,5-trimethylcyclohexanone (Scheme III) and 4-*tert*-butylcyclohexanone would be expected to give about the same percentage of equatorial alcohol for alkylation of each ketone. However, axial attack on 3,3,5-trimethylcyclohexanone occurs to a much smaller extent than on 4-*tert*-butylcyclohexanone, indicating the steric influence of the C-3 axial methyl group which could only be important if the reaction proceeds through the chair conformation. Since an axial methyl group is known to destabilize the chair conformation relative to flexible forms,[92] addition to 4-*tert*-butylcyclohexanone must proceed through the chair conformation to at least as great an extent as 3,3,5-trimethylcyclohexanone.

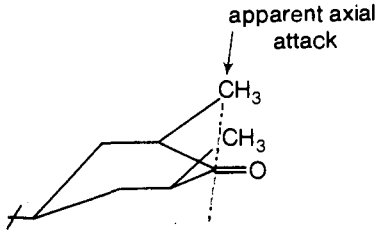
Organoaluminum addition proceeding through cyclohexanone conformations other than the boat and chair are ruled out by the fact that *cis*-2,6-dimethyl-4-*tert*-butylcyclohexanone (equatorial dimethyl) is attacked almost exclusively from the equatorial side by $(CH_3)_3Al$ in a 1:1 reactant ratio in benzene but is attacked over 40% from the axial side when the

TABLE IX. Reactions of Organoaluminum Compounds with Bicyclic Ketones

Organoaluminum compd	Ketone	Solvent	Ratio AlR_3/ketone	Isomer percentage[a] Exo alcohol	Endo alcohol	Ref
						
$(CH_3)_3Al$		Benzene	0.5	5	95	90
$(CH_3)_3Al$		Benzene	1.0	5	95	90
$(CH_3)_3Al$		Benzene	2.0	5	95	90
$(CH_3)_3Al$		Benzene	4.0	5	95	90
						
$(CH_3)_3Al$		Benzene	1.0	0	0[b]	91
$(CH_3)_3Al$		Benzene	2.0	0	0[b]	91

[a] Normalized as % exo alcohol + % endo alcohol = 100%. [b] No reaction after 15 days at room temperature.

ratio of $(CH_3)_3Al$:ketone is 3:1.[61] Reaction via a half-chair (**42**) or twist boat (**43**) would be even more hindered to apparent axial attack than the chair conformation because of the fact that one (twist boat) or both (half chair) of the methyl groups would lie directly above the carbonyl group.



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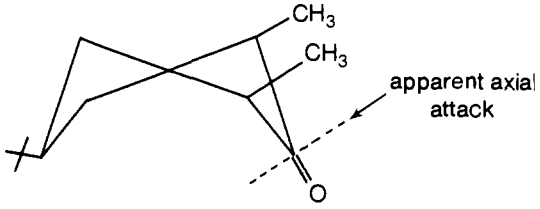

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Table IX tabulates the isomer percentages found for the reaction of bicyclic ketones with $(CH_3)_3Al$ in benzene. No change in product isomer ratio with reactant ratio was found in the case of norcamphor,[90] and camphor failed to react after 15 days.[91]

The following explanation satisfied the stereochemistry observed with each ketone. Figure 1 represents the various orientations of the carbonyl oxygen relative to substituents on adjacent carbon atoms for each ketone studied. It should be noted that Figure 1 represents the cyclohexanones to be in perfect chair conformations and the cyclopentanones to be planar: although this is not exactly the case, it is a reasonable approximation. Figure 1A illustrates the angle between the carbonyl oxygen and the hydrogens on adjacent carbon atoms for 4-*tert*-butylcyclohexanone–AlR_3 complex. It can be seen that equatorial attack by a second molecule of R_3Al compresses the complexed carbonyl against the 2,6-equatorial hydrogens in the transition state. On the other hand, axial attack leads to a staggered arrangement between the complexed carbonyl and the 2,6-equatorial hydrogen atoms. Thus, in the case of the cyclohexanones, this "compression effect"

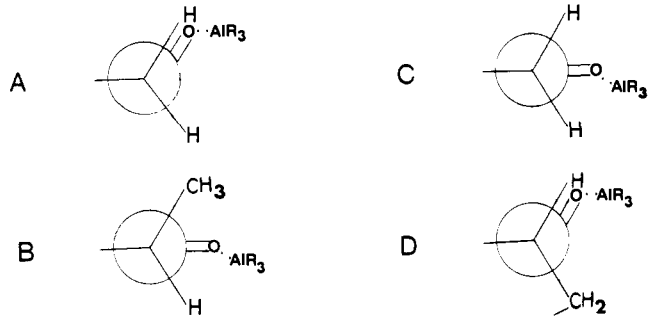


Figure 1. Orientation of the complexed carbonyl oxygen to substituents on adjacent carbon atoms for (A) 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone; (B) 2-methylcyclopentanone; (C) norcamphor, 2-methylcyclopentanone, 3-methylcyclopentanone, *cis*-3,4-dimethylcyclopentanone; (D) norcamphor.

favors attack from the more hindered side of the molecule in the 2:1 R_3Al:ketone ratio. This same effect explains the stereochemistry observed with the other ketones. In the case of 2-methylcyclopentanone, Figure 1B shows the orientation between the carbonyl oxygen and the substituents on the 2-carbon atom, and Figure 1C shows the orientation between the carbonyl oxygen and the substituents on the 5-carbon atom. Trans attack by a second organoaluminum molecule compresses the complexed carbonyl into a methyl group and a hydrogen in the transition state, whereas cis attack compresses the complexed carbonyl between two hydrogens. Thus the "compression effect" favors attack by a second molecule of organoaluminum compound from the most hindered side of the ketone, the cis side.

In the above cases the "compression effect" and the "steric approach factor" oppose each other. Thus a reversal of stereochemistry is anticipated when the ratio of organoaluminum compound to ketone is increased from 1:1 to 2:1 since steric approach control is dominant in the former case resulting in trans attack, whereas the compression effect is dominant in the latter case, resulting in cis attack. Norcamphor represents a different case. Figure 1C represents the orientation of the carbonyl group of norcamphor with the hydrogens on the 3-carbon atom. It can be seen that the complexed carbonyl will be compressed against the exo or endo hydrogens equally, regardless of whether exo or endo attack occurs. On the other hand, endo attack on norcamphor will compress the complexed carbonyl against the hydrogen on the 1 carbon atom, whereas exo attack does not (Figure 1D). Thus, in the

case of norcamphor, the "steric approach factor" and the "compression effect" operate in the same direction. Thus, as anticipated exo attack to give endo alcohol is highly favored regardless of the R_3Al:ketone ratio, and a reversal in stereochemistry is not observed.

Figure 1C also represents the orientation between the complexed carbonyl oxygen and the hydrogens on adjacent carbons for 3-methylcyclopentanone and *cis*-3,4-dimethylcyclopentanone. Attack on these molecules from either side by a second organoaluminum molecule compresses the complexed carbonyl oxygen against nearly equivalent hydrogens. Thus, unlike previous examples, complexes involving these ketones exhibit little net "compression effect", and the stereochemistry will be controlled by other factors. It should be noted that the product isomer ratio remains essentially the same with both ketones regardless of R_3Al:ketone ratio.

Microwave and NMR studies have shown that in the case of acetaldehyde the preferred conformation is one in which a hydrogen atom eclipses the carbonyl group[93] and propionaldehyde exists mainly in the conformation in which a methyl group is eclipsed by the carbonyl group.[94] Thus the forces between single and double bonds appear to be attractive. *Since ultraviolet studies of the benzophenone–$Al(CH_3)_3$ complex indicate that the carbonyl double bond remains intact,*[84] *we believe that the "compression effect" is a steric effect. The effective bulk of the carbonyl group is increased to such an extent by complexation with an organoaluminum compound that severe interaction with groups on adjacent carbons can occur in the transition state. Hence, this effect is called a "compression effect" as opposed to an "eclipsing effect" or "torsional strain effect" which, as previously stated, denoted single bond repulsion.*

From a synthetic point of view, the ability to introduce a large group into the more hindered position of a ketone is very important. Unfortunately, all organoaluminum compounds except trimethyl- and triphenylaluminum give large amounts of reduction. Attempts to use the "compression effect" to cleanly introduce other groups (e.g., ethyl and *n*-butyl) have not been highly successful thus far as the following experiments indicate. An equivalent amount of $(C_2H_5)_3Al$ was added to the complex formed between $(CH_3)_3Al$ and 4-*tert*-butylcyclohexanone within 10 sec after formation of the complex in an attempt to effect ethyl group addition without the normal amount of reduction (36% in 1:1 reactant ratio) and also to effect ethylation over methylation. The results indicate that reduction is decreased from 36 to 20%; however, redistribution of the alkyl group occurs more rapidly than ethylation, and the results are similar to addition with a mixture of $(CH_3)_3Al$ and $(C_2H_5)_3Al$.[21]

Addition to complexes of $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone and 2-methylcyclopentanone in benzene with *n*-butyllithium gave results similar to those observed for addition to the uncomplexed ketone (Tables I, II, VII, VIII).[21] Reaction of these ketones with the ate complex, $LiAl(CH_3)_3$-*n*-C_4H_9, demonstrate that reaction in the former case occurred more rapidly than ate complex formation. The ate complex gave a much higher percentage of methylation and reduction than that found for reaction of *n*-butyllithium with the $(CH_3)_3Al$–ketone complex.[21]

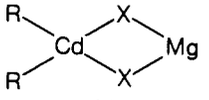
V. Organozinc and Organocadmium Compounds

A. Solution Composition of Organozinc and Organocadmium Compounds and Their Reaction Mechanisms with Ketones

Compared to the previous classes of organometallic compounds discussed in this review, very little is known concerning the solution composition of organozinc and organocadmium compounds and their reaction mechanisms with ketones. Organozinc and organocadmium reagents are generally prepared "in situ" by allowing Grignard reagents to react with zinc and cadmium halides. A description of the solution composition of the products obtained by allowing Grignard reagents to react with $CdCl_2$ and $CdBr_2$ in 1:1 and 2:1 molar ratios in diethyl ether is given by eq 14.[95] Compounds analyzing

$$\begin{aligned} &RMgX + CdX_2 \longrightarrow RCdX + MgX_2 \rightleftharpoons RCdX{\cdot}MgX_2 \\ &2RMgX + CdX_2 \longrightarrow R_2Cd + 2MgX_2 \rightleftharpoons \\ &\qquad R_2Cd{\cdot}MgX_2 + MgX_2 \\ &R_2Cd + CdX_2 \rightleftharpoons 2RCdX \end{aligned} \qquad (14)$$

as $RCdX{\cdot}MgX_2$ have been isolated from the 1:1 reaction mixture. Structures consistent with infrared data for $R_2Cd{\cdot}MgX_2$ are represented by **44** and **45**.[95,96]



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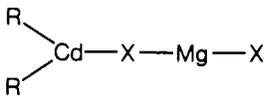
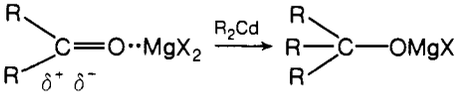


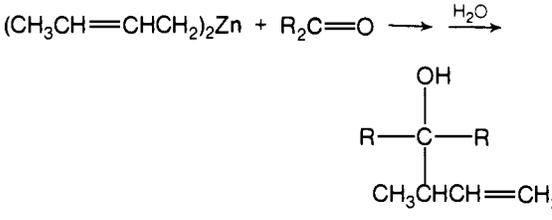
45

Pure dialkylcadmium compounds show almost no reactivity toward ketones; however, addition of magnesium salts, such as $MgBr_2$, greatly increases their reactivity.[97] This increase in reactivity has been interpreted in terms of prior complexation of the carbonyl group by MgX_2 followed by attack on the resulting complex by R_2Cd (eq 15). It has been suggested that complexation increases the partial positive charge on the carbonyl carbon atom, thereby aiding carbanion transfer.[98]



(15)

While dialkylcadmium and dialkylzinc compounds show very little reactivity toward carbonyl compounds in the absence of magnesium halides, diallylzinc and cadmium compounds react readily with carbonyl compounds in the absence of magnesium salts.[99] Dicrotylzinc and -cadmium were found to add to ketones via allylic rearrangement (eq 16).[99,103] In view of the meager information available concerning these compounds, discussion of their stereoalkylation of small ring ketones will be somewhat speculative.



(16)

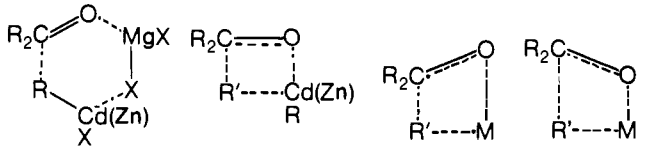
B. Stereochemistry of Addition of Organocadmium and Organozinc Compounds to Cyclohexanones

The only information available concerning the steric course of addition of organozinc and cadmium reagents to small ring ketones involves their reaction with cyclohexanones. The data are summarized in Table X. Two pieces of evidence demonstrate that these reagents behave much differently from other organometallic compounds discussed thus far. (1) Dimethyl- and di-*n*-propylzinc and -cadmium compounds give a much higher percentage of axial attack on 4-*tert*-butylcyclohexanone than do the corresponding organolithium, organomagnesium, and organoaluminum compounds in diethyl ether. (2) In strong contrast to the corresponding organomag-

nesium compounds, diallylzinc and -cadmium compounds give a much higher percentage of equatorial attack on 4-*tert*-butylcyclohexanone than do di-*n*-propylzinc and -cadmium compounds.[6,8,99,101,102]

With respect to the first observation, two transition states were considered (**46** and **47**). It was noted that a comparison of two six-center transition states (one for Mg (X = Br) and Cd (X = I)) reveals that the Mg (X = Br) transition state should be tighter.[100] This assumption was apparently based on the shorter distance of the Mg–Br bond as compared to the Cd–I bond. On the other hand, a comparison of two similar four-center transition states (**47**) shows that the Cd (X = I) transition state should be "tighter."[100] It was also pointed out that since the Zn–O bond distance is shorter than the Cd–O bond distance, alkylations involving zinc alkyls should lead to a "tighter" four-center transition state than similar reactions involving cadmium alkyls. It was reasoned that, on the basis of the Marshall and Carroll model, reactions involving "tighter" transition states should give more axial attack. Therefore the four-center transition (**47**) best describes alkylations of ketones involving organozinc and cadmium reagents.[100]

This line of reasoning can be constructively criticized on several points. The Marshall and Carroll model involves only

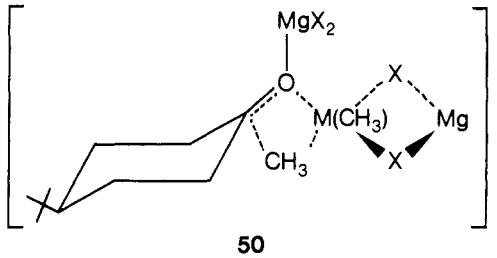


46 **47** **48** **49**

the transition state bonding distance of the entering group as it approaches the carbonyl carbon atom along the reaction coordinate. Thus, the bonding distances of other atoms in the transition state are not intimately involved in the determination of the stereochemistry. Indeed, although four-center transition states are drawn as squares (**47**) for the sake of convenience, a more realistic representation would be as trapezoids (**48** and **49**), in which the minimum transition state bond distance could be approximated by the R′–C and M–O bond distances in the product.[84] Thus, the fact that the Zn–O bond distance is shorter than the Cd–O bond distance cannot be used as guide to the length of the R′–C transition state bond distance in addition of R'_2Cd or R'_2Zn to ketones. It should also be pointed out that, according to the Marshall and Carroll model, strictly steric considerations show that equal amounts of axial and equatorial attack should occur at transition state bond lengths of 1.6 Å. At distances shorter than 1.6 Å, more axial attack should occur. It must be noted that the break-even distance, 1.6 Å, is nearly the same as the average C–C single bond distance, 1.54 Å. Thus, it would appear that in some $(CH_3)_2Zn$ reactions with 4-*tert*-butylcyclohexanone, in which as much as 64% axial attack occurs (Table X),[100] the methyl–carbonyl carbon transition state bond length would have to be shorter than the final methyl–carbon bond distance in the product, an unlikely situation.

Two transition states have been suggested for the addition of zinc and cadmium alkyls to ketones **50**[100] and **51**.[98] It is immediately apparent that these transition states are similar to those involving addition of excess aluminum alkyls to ketones in benzene (section IV.B) in that they involve attack of an organometallic compound on a ketone–Lewis acid complex. Thus, a compression effect between the complexed carbonyl and the 2,6-equatorial hydrogens in the case of 4-*tert*-butylcyclohexanone would be expected. The fact that the percentage of axial attack is not as high as in the aluminum alkyl case is possibly due to the smaller size of the complexing agent (MgX_2 vs. R_3Al). Although the ionic radii of Cl^- (1.8 Å), Br^- (1.96 Å), and I^- (2.19 Å) are not vastly different,[104] a trend toward higher axial attack is found as the percentage of the larger halide ion in the reactions is increased. This is especially evident in those reactions involving di-*n*-propylzinc and -cadmium. In those reactions involving dimethylzinc and -cadmium, the presence of $MgCl_2$ or IMgCl gives an unusually large percentage of axial attack. Perhaps the magnitude of the compression effect is determined by both the size of the complexing group and the strength with which it complexes.

The compression effect also provides a satisfactory answer to the fact that allylzinc and -cadmium compounds give more equatorial attack on 4-*tert*-butylcyclohexanone than do *n*-propylzinc and -cadmium compounds, whereas allylmagnesium compounds give less equatorial attack than do *n*-propylmagnesium compounds. In the latter case, less steric hindrance is encountered by an entering allyl group than by an



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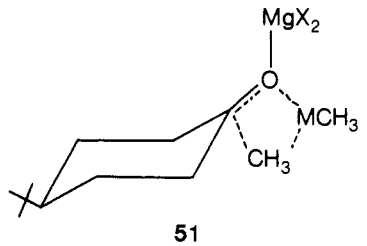


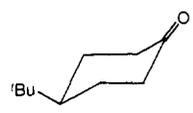
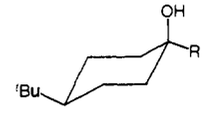
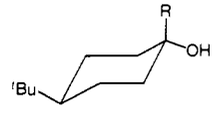
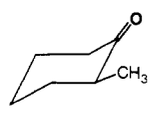
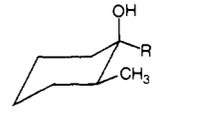
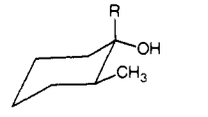
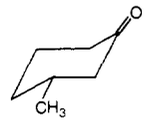
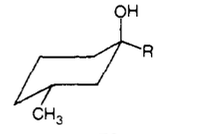
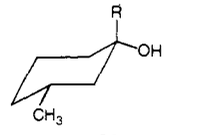
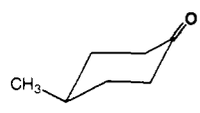
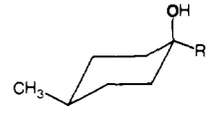
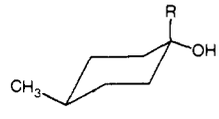
51

entering propyl group. Since the degree of torsional strain should be about the same for each group, the allyl reagent gives a higher percentage of axial attack. Convincing evidence for the concept of torsional strain is provided by comparison of the observed stereochemistry of addition via a four-center transition state (*n*-propylmagnesium bromide) and via allylic rearrangement (allylmagnesium bromide).[6,8] Reaction of di-*n*-propylzinc and -cadmium with 4-*tert*-butylcyclohexanone requires the presence of magnesium halides. The suggested transition state (**50** and **51**) should give a compression effect promoting axial attack. However, diallylzinc and -cadmium react with 4-*tert*-butylcyclohexanone via allylic rearrangement without the presence of magnesium halides, and thus a compression effect is not expected. Although the mechanism for allyl entry by magnesium, zinc, and cadmium reagents is thought to be similar, the mechanism for propyl entry via magnesium reagents is quite different from that for zinc and cadmium reagents. In the latter cases, a compression effect promoting axial attack is operative and the observed results are not surprising.

A detailed study involving addition of $(CH_3)_2Mg$, $(CH_3)_2Zn$, and $(CH_3)_2Cd$ to certain ketones (similar to that conducted with aluminum alkyls[90]) should provide convincing evidence as to whether or not the suggested compression effect with zinc and cadmium alkyls is correct.

A final generalization corcerning the steric course of addition to small ring ketones can now be made. *In those alkylations of small ring ketones in which the mechanism of addition involves attack of the organometallic compound on a complex, either by six-center (**46, 39**) or four-center (**50, 51, 40**) transition states, the stereochemistry of addition will be controlled by steric strain, torsional strain, and compression strain in the transition state, as determined primarily by the*

TABLE X. Reactions of Organozinc and -cadmium Compounds with Cyclohexanones in Diethyl Ether

Organozinc and -cadmium compounds	Ketone	Isomer percentage[a] Axial alcohol	Isomer percentage[a] Equatorial alcohol	Ref
				
$CH_3MgI + CdCl_2$[b]		38	62	100
$2CH_3MgBr + CdCl_2$[c]		50	50	100
$2CH_3MgI + CdCl_2$[c]		42	58	100
$2CH_3MgBr + CdBr_2$[c]		52	48	100
$2CH_3MgI + CdBr_2$[c]		53	47	100
$2CH_3MgI_2 + CdI_2$[c]		52	48	100
$(CH_3)_2Cd + MgBr_2$[d]		49	51	100
$(CH_3)_2Cd + MgBr_2$[d]		47	53	100
$(CH_3)_2Cd + MgI_2$[d]		53	47	100
$2(CH_3)_2Cd + MgI_2$[d]		38	62	100
$2n\text{-}C_3H_7MgI + CdCl_2$[c]		61	39	100
$2n\text{-}C_3H_7MgBr + CdBr_2$[c]		78	22[e]	99, 101, 102
$2n\text{-}C_3H_7MgI + CdBr_2$[c]		55	45	101
$2n\text{-}C_3H_7MgI + CdI_2$[c]		52	48	101
$(CH_2{=}CH{-}CH_2)_2Cd$[f]		78	22	99, 102
$CH_3MgI + ZnI_2$[b]		49	51	100
$2CH_3MgBr + ZnCl_2$[c]		44	56	100
$2CH_3MgI + ZnCl_2$[c]		38	62	100
$2CH_3MgBr + ZnBr_2$[c]		44	56	100
$2CH_3MgI + ZnBr_2$[c]		47	53	100
$2CH_3MgI + ZnI_2$[c]		47	53	100
$(CH_3)_2Zn + MgI_2$[d]		47	53	100
$2(CH_3)_2Zn + MgI_2$[d]		36	64	100
$2n\text{-}C_3H_7MgBr + ZnBr_2$[c]		72	28[e]	99, 101, 102
$2n\text{-}C_3H_7MgI + ZnBr_2$[c]		57	43	101
$2n\text{-}C_3H_7MgI + ZnI_2$[c]		54	46	101
$(CH_2{=}CHCH_2)_2Zn$[f]		84	16	99, 102
$(CH_3CH{=}CHCH_2)_2Zn$[f]		94	6	102
				
$(CH_2{=}CHCH_2)_2Cd$[f]		89	11	99
$(CH_2{=}CHCH_2)_2Zn$[f]		89	11	99
				
$(CH_2{=}CHCH_2)_2Cd$[f]		76	24	99
$(CH_2{=}CHCH_2)_2Zn$[f]		80	20	99
				
$(CH_2{=}CHCH_2)_2Cd$[f]		65	35	99
$(CH_2{=}CHCH_2)_2Zn$[f]		76	24	99

[a] Normalized as % axial alcohol + % equatorial alcohol = 100%. [b] $CH_3Cd(Zn)X$ prepared and used in situ by reaction of $CH_3MgX + Cd(Zn)X_2$. Gilman test for active CH_3Mg was negative. [c] $R_2Cd(Zn)$ prepared and used in situ by reaction of $2RMgX + Cd(Zn)X_2$. Gilman test for active CH_3Mg was negative. [d] $(CH_3)_2Cd(Zn)$ purified. Magnesium halide salts added to ketone solution immediately prior to alkylation. [e] Average of slightly conflicting values. [f] Magnesium halide free allyl- and crotylcadmium and -zinc reagents.

ketone, the entering group, and steric bulk of the complexing agent. Other factors, such as reactant ratio and concentration, solvent, and the nature of the molecule possessing the entering group will result only in minor differences in the observed stereochemistry. It should be noted that solvent and reactant ratio may be crucial in determining whether or not a consecutive bimolecular mechanism is operative as in the case of aluminum alkyls.[90] When it is operative, however, the solvent and reactant ratio do not exert a primary influence on the stereochemistry.

VI. Ate Complexes

A. Composition of Ate Complexes

Ate complexes are the result of interaction between an electron-deficient metal alkyl and a Lewis base.[105] Dimethyl-

magnesium, for example, is a highly polymeric solid with the methyl groups bridge-bonding in such a way that the coordination around the magnesium atom is tetrahedral. In ether solution the methyl bridge bonds are broken and dimethylmagnesium is monomeric; however, magnesium associates with two ether molecules. If methyllithium is added to the solution, the ether molecules are replaced by methyl anions to form ate complexes of the type $Li_nMg(CH_3)_{2+n}$. In general, the tendency toward complex formation and the stability of the complex depend to a large degree on the particular metal and to a lesser degree on the ligand size and charge. For example, the tendency of the adducts $LiMPh_3$ to dissociate into phenyllithium and diphenylmetal increases in the order: $LiBePh_3 < LiZnPh_3 < LiMgPh_3 < LiCdPh_3 < LiHgPh_3$. In general, the smaller the metal, the more stable the adduct. Indeed, the largest metal, mercury, shows no tendency to form an adduct.

B. Stereochemistry of Addition of Ate Complexes to Small Ring Ketones

A recent study involving reactions of ate complexes with 4-*tert*-butylcyclohexanone shows that ate complexes of all metals except aluminum give stereochemistry that is similar to the stereochemistry of the separate organometallics species from which they are made.[106] Since nothing is known about the mechanisms by which ate complexes add to ketones, the reason for the higher percentage of axial attack by $LiAl(CH_3)_4$ and $LiAl(i\text{-}C_4H_9)_3CH_3$ is not known.

The stereochemistry of addition of ate complexes to small ring ketones does not violate the generalizations described in this review.

TABLE XI. Reactions of Ate Complexes with 4-*tert*-Butylcyclohexanone in Diethyl Ether

Ate complex	% axial alcohol	% equatorial alcohol
$LiMg(CH_3)_3$	69	31
$Li_2Mg(CH_3)_4$	68	32
$Li_3Mg(CH_3)_5$	71	29
$LiB(CH_3)_4$[a]	70	30
$LiAl(CH_3)_4$	42	58
$LiAl(i\text{-}C_4H_9)_3CH_3$	30[b]	70[b]
$LiZn(CH_3)_3$	64	36

[a] In refluxing benzene. [b] Methylation products.

VII. Closing Remarks

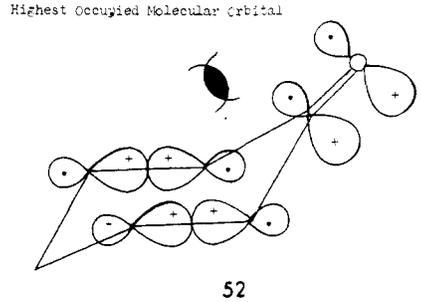
A. Theoretical Considerations

Theory concerning the steric course of addition of organometallic compounds to cyclic ketones is presently in the stage of early development. The concepts of steric approach control, torsional strain, and compression effect appear to be adequate to explain the observed stereochemistry in a majority of cases. In general, if the ketone, the entering group, and the mechanism of addition are known, a reasonable judgment as to which isomeric alcohol will predominate can be made. As refinements in theory are developed and the exact magnitude of the above-mentioned concepts are determined for a variety of cases, it may eventually be possible to make a reasonably good prediction as to the percentage of each isomeric alcohol in an individual case. Such a state of development, which would be extremely valuable for synthetic purposes, appears to be several years in the future.

Further stereochemical studies may take the form of precise mathematical calculations such as those concerning the reduction of a variety of ketones of the type $RC_6H_4COCHR_1CR_2R_3R_4$ with $LiAlH_4$.[107] The percentages of diastereomeric products were calculated by estimating the free energies of the various transition states leading to the isomeric products as referenced against a hypothetical transition state with no steric interactions of the kind that differentially unstabilizes each of the actual transition states. The values for steric interactions considered in free energy calculations of actual transition states are parameters which had been experimentally determined or accurately estimated. Agreement between the calculated percentages of diastereomeric alcohols and those experimentally found are in general good.[107]

Other recent articles suggest that orbital factors may be important in the determination of the percentages of isomeric alcohols formed in reduction and alkylation of ketones. Ab inito (STO-36) calculations have been performed on a variety of carbonyl compounds possessing asymmetric centers.[108] These calculations demonstrate the following: (1) A σ–π mixing occurs in the carbonyl group giving the π orbital significant 2s character and (2) the π-electron cloud becomes dissymmetric, i.e., the electron density is greater on one diastereotopic face than on the other.[108] Thus, nucleophilic reagents would be expected to attack preferentially on the positive face. The calculations predict the same predominant isomer in every case reported as would be predicted by steric approach control.

A new orbital hypothesis concerning the stereoselectivity of alkylation and hydride reduction of cyclohexanones has been recently presented.[109] Hyperconjugative interaction among the β C–C bonds and the π electrons of substituted cyclohexanones gives rise to two bonding and two antibonding orbitals of different energies. The bonding orbital of highest energy (HOMO) has antibonding interaction of the carbonyl with the β C–C bonding orbitals resulting in a decrease of electron density on the axial face and an increase on the equatorial face (**52**).[109] Thus in the absence of steric factors, attack by electrophiles (borane, protons) will occur predominantly at the equatorial face.[109]



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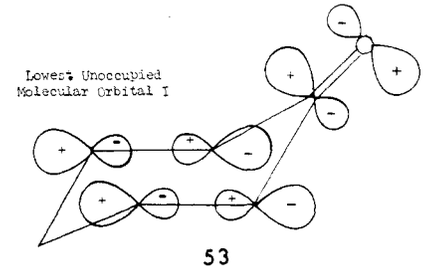
Two depictions of the antibonding orbital of lowest energy.



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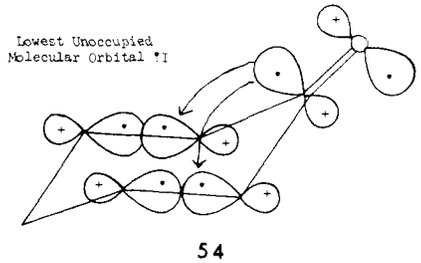

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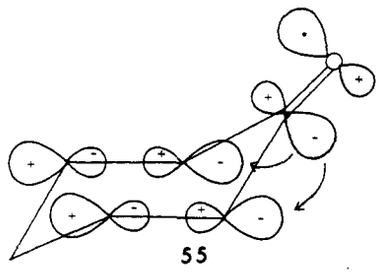
LUMO, have been presented. The first (**53**) involves symmetrical $\sigma^*-\pi^*$ interaction.[109] LUMO I was said to be distorted toward the axial face, thus "avoiding electron repulsion."[109] The second LUMO (**54**) represents the interaction of the symmetrical β C–C σ orbital with the π^* orbital.[109,110] LUMO II would also be distorted toward the axial face. Therefore nucleophiles (hydride, methyl carbanion, etc.) will tend to attack the LUMO from the axial side to effect maximum orbital overlap.[109,110]

The judgments made concerning the bonding modes and predominant equatorial attack by electrophiles appear to be sound. Judgments concerning axial attack by nucleophiles do not appear so clear-cut. It is questionable that LUMO I is distorted toward the axial face to "avoid electronic repulsion" since no electrons exist in this orbital. In fact, it appears more likely that distortion would be toward the equatorial face (**55**) to effect maximum overlap with β C–C antibonding orbitals. Nucleophiles might therefore be expected to attack the equatorial face in the absence of steric factors (not observed).



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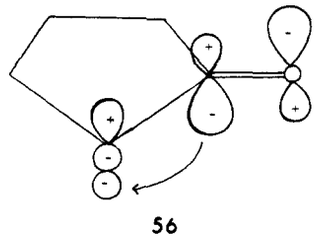
The high percentage of axial attack on 4-*tert*-butylcyclohexanone by zinc and cadmium alkyls and by excess trimethylaluminum in benzene has been explained by considering these reactions to be nucleophilic attack on the LUMO of the ketone.[110] The concepts of the "compression-effect" or the Marshall and Carroll model to explain these reactions was considered to be unsatisfactory.[110]

It must be pointed out that excess trimethylaluminum in benzene attacks 2-methylcyclopentanone (**9**) predominantly from the cis direction. Hyperconjugative interaction between the π^* carbonyl orbital and the β C–C σ^* (LUMO I) or σ (LUMO II) orbitals are not likely since the relatively flat geometry of this molecule (**9**) is insufficient to permit effective overlap of this type. Since the 2-H on 2-methylcyclopentanone is forced into a pseudoaxial position as the 2-CH_3 seeks a pseudoequatorial position (**9**), the geometry is favorable for overlap between the carbonyl π^* orbital and the 2 C–H σ orbital (LUMO II type) (**56**). The possible importance of carbonyl π^*



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orbital and β C–H σ orbital overlap in cyclohexanone systems has been pointed out.[110] The application of this type of overlap to 2-methylcyclopentanone (**56**) predicts trans attack by nucleophiles. Since excess trimethylaluminum in benzene gives predominantly cis attack on this ketone and predominantly axial attack on cyclohexanones, it appears that orbital distortion arguments alone do not offer satisfactory explanations for both ketones.

Concerning orbital distortion arguments to explain the stereochemistry of alkylation of small ring ketones, the following areas of investigations appear crucial. A determination of what actually is the lowest unoccupied molecular orbital (LUMO) must be made. A good estimation of the magnitude of orbital effects must be determined to see if they are significant enough to bring about the changes in stereoalkylation observed with various reagents under various conditions. The orbital arguments should be extended from cyclohexanones to other ketones using a consistent set of π,π^* and σ,σ^* molecular orbitals to predict the HOMO and LUMO, and the direction of their distortion in each case. The steric course of alkylation predicted for these ketones should then be compared with experimental data such as those found in the tables of this review to determine how well orbital theory fits the facts in *all* cases. Concerning cyclohexanones, the importance of β C–C σ,σ^* vs. β C–H σ,σ^* orbital interaction with carbonyl π,π^* orbitals must be determined with some certainty since they predict opposite results.[110] The former appears to be more important because C–C σ,σ^* orbitals are more polarizable than C–H σ,σ^* orbitals,[110] but the C–H σ,σ^* orbitals have a somewhat better geometry to effect overlap with the carbonyl π,π^* orbitals.

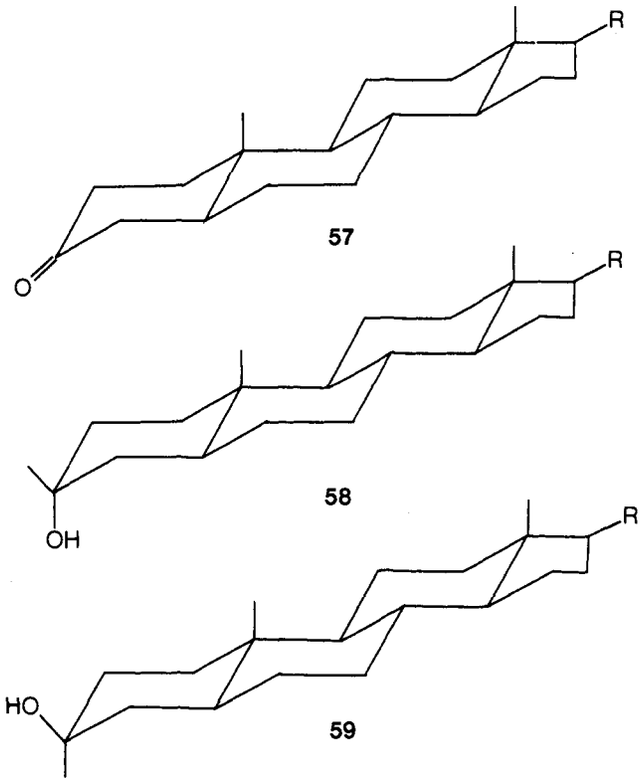
Finally, it must be pointed out that in the cyclohexanone case symmetrical β C–C σ^* orbital interaction with the π orbital (not pictured)[109–111] and symmetrical β C–C σ orbital interaction with the π orbital (**52**) both predict the HOMO to be distorted toward the equatorial side.[109–111] Perhaps the preference for small nucleophiles to attack the axial face is *partially* to avoid electronic repulsion with the electron pair in the HOMO.

The generalizations presented in this review are valid almost without exception in addition of organometallic compounds to ketones. *It must be emphasized that these generalizations are not valid in consideration of the stereochemical course of reduction of cyclic ketones by organometallic reagents or metal hydrides.* In these cases the nature of the molecule possessing the entering hydride often plays a crucial role in the determination of the observed stereochemistry. This is probably due to a combination of the small size of the hydride ion relative to an alkyl group and to the shorter hydrogen–substrate bond relative to an alkyl–substrate bond which allows the substrate to approach the reaction site much closer in the case of reduction.

B. Synthetic Considerations

Perhaps the most exciting aspect of stereoalkylation reactions will be the development of highly selective reagents which can be used to obtain a higher percentage of a desired alcohol isomer in alkylation of a complex cyclic ketone. For example, reaction of CH_3MgI with 3-cholestanone (**57**) gives predominantly 3β-methylcholestan-3α-ol (**58**) (steric approach control),[112] whereas alkylation of this ketone with $(CH_3)_3Al$ in benzene gives predominantly 3α-methylcholestan-3β-ol (**59**) (compression effect).[113]

Although the primary concern of this review has been the stereochemistry of organometallic addition to small ring ketones, it should be pointed out that many of these reagents give other by-products. The two principal reactions which compete with alkylation are reduction of the ketone by organometallic compounds which posses β hydrogens and enolization of the ketone which, on hydrolysis, yields unreacted ketone. In general reduction decreases in the following order: $R_3Al > LiAlR_4 > R_2Zn > R_2Mg = RMgX > R_2Cd > RLi$.[26,90,101,106] For a particular class of organometallic compounds, reduction increases as the length of the alkyl carbon chain increases and as branching increases. Thus, in reaction of Grignard reagents with 2-methylcyclohexanone reduction decreases in the following order: *t*-$C_4H_9MgCl > i$-$C_4H_9MgBr > i$-$C_3H_7MgBr > n$-$C_3H_7MgBr > C_2H_5MgBr$.[114] Enolization



decreases in exactly the same order as reduction for the Grignard reagents listed.[114] In general, more basic compounds give larger percentages of enolization; e.g., methylmagnesium alkoxides usually give >50% enolization[61] as well as condensation products.[58] More polar solvents usually enhance the enolization reaction.

VIII. Addendum

Simple rules for predicting the stereochemical course of nucleophilic and electrophilic attack based on orbital distortion theory have been presented.[115] For electrophilic reactions the direction of attack is controlled by the highest occupied molecular orbital, and for nucleophilic reactions the direction of attack is controlled by the lowest unfilled molecular orbital.[115]

A semiquantitative model which gives an estimate of steric congestion about a reaction center has been reported.[116] The model correlates reasonably well with the observed direction of addition to bicyclic ketones such as norcamphor and 7,7-dimethyl-2-norbornanone but does not work well with substituted cyclohexanones. A method for accommodating the latter cases by correcting steric congestion for torsional strain has been developed.[116]

Conformational analyses of 2-alkylcyclohexanones[117] and 2-alkyl-4-*tert*-butylcyclohexanones[118], have been studied employing lanthanide shift reagents. In the former case, complexation by shift reagents did not appear to change the conformational equilibrium of these ketones a measurable amount.[117,118]

A detailed study concerning the addition of $(CH_3)_3Al$ in toluene to methyl-substituted cyclohexanones and decalonones has been presented.[119] Results obtained with *cis*-2-methyl-4-*tert*-butylcyclohexanone and other α-C substituted cyclohexanones were interpreted as indicating that the 2-equatorial methyl substituent hindered axial attack to a greater extent in a 2:1 $(CH_3)_3Al$:ketone reactant ratio than in a 1:1 ratio.[119] In order to explain the results[119] arising from the 2:1 reactant ratio, a half-chair conformation of the $(CH_3)_3Al$:ketone complex was invoked in which the 2-equatorial methyl group is forced up to the carbonyl plane in the transition state. However, close scrutiny of the data presented[119] does not justify this interpretation of the results. Calculation of transition state free energies ($\Delta G^{\ddagger}$ axial attack $-$ $\Delta G^{\ddagger}$ equatorial attack) from the data reported[119] gives values for addition to 4-*tert*-butylcyclohexanone of 0.786 kcal (1:1 ratio) and -0.975 kcal (2:1 ratio) and for addition to *cis*-2-methyl-4-*tert*-butylcyclohexanone of 1.74 kcal (1:1 ratio) and -0.374 kcal (2:1 ratio). Thus a 2-equatorial methyl group destabilizes axial attack in the 1:1 reactant ratio by 0.954 kcal and by 0.601 kcal in the 2:1 reactant ratio. Calculations carried out on data for other 2-substituted cyclohexanones[119] gave analogous results. Thus correct interpretation of the data shows that axial attack is hindered more by a 2-equatorial methyl group in the 1:1 reactant ratio than in the 2:1 reactant ratio.

Enolates prepared by reaction of diisopropylmagnesium with 2,2-dimethyl-3-butanone and 2,2-dimethyl-3-pentanone have been reported to give ca. 50% axial attack on 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone.[120] The surprisingly large percentage of axial attack on the latter ketone led to the conclusion that the cyclohexanones must exist as nonchair conformers in the transition states of these reactions.[120]

A study involving the addition of methyllithium and methylmagnesium iodide to norbornanones and norbornenones concluded that, in general, there is little difference in the stereochemistry observed when the double bond is present.[121] The results given for fenchone (ca. 98% exo attack) and camphenilone (100% exo attack)[121] indicates that the C_1 methyl group of fenchone has little influence on the steric course of alkylation of this ketone.

The stereochemistry of alkylation of 2-methoxycyclopentanones and α-methoxyalicyclic ketones by a variety of organometallic compounds has been reported.[122] The steric course of alkylation in these reactions was governed primarily by repulsive forces between the methoxy group and the entering nucleophile. The abnormally high percentage of trans attack on 2-methoxycyclopentanone by 2-propynylmagnesium bromide relative to *n*-propylmagnesium bromide was explained by invoking a transition state in which complexation of the 2-methoxy group stabilized a conformation of the ketone in which the cis C-3 hydrogen is locked in a pseudo-axial position, thereby hindering cis attack.[122]

The stereochemistry of Grignard reagent addition to *cis*- and *trans*-3,4-dimethylcyclohexanone has been investigated.[123,124] The percentage of equatorial attack on *trans*-3,4-dimethylcyclohexanone is nearly identical with that found for 4-*tert*-butylcyclohexanone, indicating that the preferred transition state conformation of this ketone is that in which both methyl groups occupy an equatorial position.[124] The observed stereochemistry of addition to *cis*-3,4-dimethylcyclohexanone was interpreted in terms of a conformer equilibrium in which 70% of alkylation proceeds through the conformer with the 4-methyl group in the axial position (3-Me eq) and 30% of alkylation proceeds through the conformer with the 4-methyl group in the equatorial position (3-Me ax).[124]

The reaction of CH_3MgI and *n*-C_3H_7MgBr with 4-*tert*-butylcyclohexanone was studied in the presence of added $LiClO_4$ and $(C_4H_9)_4NCl$.[124] The addition of $LiClO_4$ had no effect on the observed stereochemistry, but the addition of the ammonium salt resulted in greater equatorial attack.[125] The latter reaction probably proceeds through the more bulky ate complex $(C_4H_9)_4NMgCl(CH_3)I$.

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