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Stereoselective Organometallic Alkylation Reactions. III. "Ate" Complex Addition to Cyclic and Bicyclic Ketones[1]

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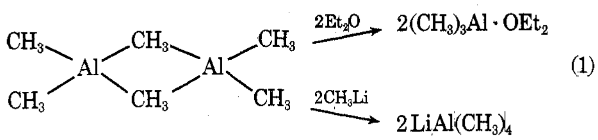
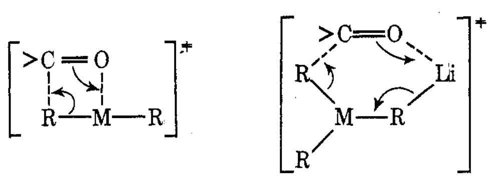
The stereochemistry of addition of a variety of "ate" complexes with such ketones as 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, norcamphor, and camphor has been studied. The reaction of $LiAl(CH_3)_4$ and $LiAl(i\text{-}C_4H_9)_3CH_3$ with 4-*tert*-butylcyclohexanone in benzene, diethyl ether, tetrahydrofuran, and dimethoxyethane results in predominant axial attack to form equatorial alcohol (*via* methylation), regardless of reactant ratio or reaction time. However, the reaction of other "ate" complexes such as $LiB(CH_3)_4$ and $Li_nM(CH_3)_{2+n}$ compounds (where M = Mg and Zn and n = 1, 2, or 3) with 4-*tert*-butylcyclohexanone yields predominantly equatorial attack in diethyl ether. Reaction of all ate complexes studied with 3,3,5-trimethylcyclohexanone yields 100% axial alcohol. Reaction of norcamphor and camphor with all ate complexes studied yields 95% endo alcohol and 99% exo alcohol, respectively, regardless of reactant ratio.

Ate complexes are the result of interaction between an electron-deficient metal alkyl and a Lewis base.[2] Trimethylaluminum, for example, exists as a dimer with two methyl groups bridge bonded in such a way that the coordination about the aluminum atom is tetrahedral.[3] In ether solution the weak methyl bridge bonds are broken in favor of ether solvation of the trimethylaluminum. If methylithium is added to the solution, the ether molecule is replaced by a methyl carbanion to form the ate complex $LiAl(CH_3)_4$. Basically these are simply acid–base reactions where the Lewis acid $[Al(CH_3)_3]$ reacts with a base (*e.g.*, ether or CH_3Li) to form a salt. In general, the tendency toward ate complex formation and the stability of the complex depend to a large degree on the particular metals involved and to a lesser degree on the ligand size and charge. For example, the tendency of the adducts $LiM(C_6H_5)_3$ to dissociate into phenyllithium and $M(C_6H_5)_2$ increases in the order $LiBe(C_6H_5)_3 < LiZn(C_6H_5)_3 < LiMg(C_6H_5)_3 < LiCd(C_6H_5)_3 < LiHg(C_6H_5)_3$. In general, the smaller the central metal atom and the more electropositive the group I metal the more stable is the adduct. Indeed, in the above series the largest metal, mercury, shows no tendency to form an adduct.



(1)

No reports concerning either the mechanism or stereochemistry of ate complex addition to ketones has appeared in the literature. Since the central metal atom of ate complexes such as $LiAl(CH_3)_4$ or $Li_2Mg(CH_3)_4$ do not have available orbitals for complexation with a carbonyl group as do $(CH_3)_3Al$ and $(CH_3)_2Mg$, there is reason to believe that the mechanism and hence stereochemistry of reaction should be different. In addition it was felt that since lithium is capable of complexing with carbonyl compounds, possibly ate complexes of the type $Li_nM(CH_3)_{2+n}$ might react by complexation of the lithium atom with the carbonyl oxygen atom. Such possibilities, in addition to recent reports concerning the composition of ate complexes in solution,[4] have prompted us to investigate these compounds as stereoselective alkylating agents.



Experimental Section

Materials. Methyllithium was obtained from Foote Mineral Co. and was used without further purification. Analysis of CH_3Li gave CH_3:Li ratios ranging from 0.95:1 to 1:1 and essentially no halide was detected. Solutions of CH_3Li were refrigerated in serum capped bottles and their concentrations were checked prior to use. Dimethylmagnesium was prepared from dimethylmercury by reaction with Dow Chemical Co. doubly sublimed magnesium turnings.[5] Trimethylborane was prepared by reaction of $BF_3 \cdot O(C_2H_5)_2$ with methylmagnesium bromide. The trimethylborane was distilled from the reaction vessel and collected at Dry Ice–acetone temperature. Dimethylzinc was prepared by reaction of methylmagnesium bromide with anhydrous zinc chloride followed by distillation of the dimethylzinc under reduced pressure. Potassium *tert*-butoxide was prepared by reaction of potassium metal with excess *tert*-butyl alcohol. Excess *tert*-butyl alcohol was removed under vacuum at 80°.[6] Trimethyl- and triisobutylaluminum, obtained from Texas Alkyls, were purified by vacuum distillation.

4-*tert*-Butylcyclohexanone (Frinton) was distilled under vacuum and found by glpc to be 99.9% pure. Tetradecane (99.9% pure, Chemical Sample Co.) was used as an internal standard. 3,3,5-Trimethylcyclohexanone (99% pure, Chemical Sample Co.) was distilled over 4A molecular sieves at 1 mm at 80°. Norcamphor (97% pure, Aldrich Chemical Co., Milwaukee, Wis.) was sublimed at 1.8 mm at 53° and found by glpc to be 99% pure. Camphor (Fisher Scientific Co.) was sublimed at 2 mm at 75° twice and found by glpc to be 99% pure.

Preparations. $LiB(CH_3)_4$ and $LiAl(CH_3)_4$ were prepared by addition of CH_3Li to an excess of trimethylborane and trimethylaluminum, respectively, in diethyl ether.[7] The products were purified by removal of all solvent and excess boron or aluminum alkyl by gentle heating (70°) under vacuum followed by redissolution in the appropriate solvent. Ether solutions of $LiAl(i\text{-}C_4H_9)_3CH_3$ were prepared by adding a benzene solution of $(i\text{-}C_4H_9)_3Al$ to ether Analysis after removal of ether indicated the product to be $LiAl(i\text{-}C_4H_9)_3CH_3 \cdot O(C_2H_5)_2$. Even mild heating results in the elimination of isobutylene. Benzene solutions of $LiAl(i\text{-}C_4H_9)_3CH_3$ were prepared by adding a benzene solution of $(i\text{-}C_4H_9)_3Al$ to ether desolvated (90°, 100 μ, 24 hr) CH_3Li.

Tri-*n*-octylpropylammonium bromotrimethylaluminate was prepared by addition of an appropriate amount of $(CH_3)_3Al$ in ether or benzene to dry tri-*n*-octylpropylammonium bromide. In the ether case, ate complex formation was indicated by the fact that the ammonium salt, which shows little solubility in diethyl ether, immediately dissolved on addition of trimethylaluminum. Preparation of ate complexes such as $KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$, $KAl(CH_3)_3O\text{-}t\text{-}C_4H_9$, $LiMg(CH_3)_3$, $Li_2Mg(CH_3)_4$, $Li_2Zn(CH_3)_4$, etc., were prepared by mixing the appropriate alkali metal alkyl or alkoxide to the appropriate alkaline earth metal alkyl in the appropriate ratios. No attempt was made to characterize these ate complexes since information concerning their formation and stability exists in the literature.[2,4]

Reactions. All reactions were carried out on a vacuum manifold equipped with three-way glass stopcocks attached to ₸ 24/40 inner joints. Round-bottom flasks equipped with ₸ 24/40 outer joints were attached to the manifold and the system was evacuated, flamed, and refilled with nitrogen three times prior to use. Standard solutions of reagents were introduced into the reaction vessel *via* syringes equipped with stainless steel needles. Mixing was accomplished *via* rapid stirring with a Teflon stirring bar. After a desired amount of time had elapsed, the reaction mixtures were hydrolyzed with distilled water or saturated ammonium chloride and prepared for analysis.

Analysis. Product analysis for the isomeric alcohols resulting from methylation of 4-*tert*-butylcyclohexanone,3,3,5-trimethylcyclohexanone, and norcamphor have been previously described.[8] Products resulting from methylation of camphor were analyzed by glpc. The identity of the peaks was determined by comparison of the hydrolyzed products formed on reaction of camphor with methyllithium and methylmagnesium bromide.[9]

Aluminum analysis was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. Magnesium and zinc analysis were carried out by EDTA titration at pH 10 using Eriochrome Black T as an indicator. Potassium and lithium analysis were carried out employing flame photometry. Gas analysis was carried out on a high vacuum line.

Results and Discussion

The stereochemistry of reaction of ate complexes of magnesium, boron, and zinc with several ketones is illustrated in Table I. The stereochemistry of addition of CH_3Li, $(CH_3)_2Mg$, and $(CH_3)_2Zn$ is also shown for comparison. The data in Table I represents only a fraction of the total data collected, but demonstrates all factors discussed. The principle feature of all these reactions is that attack by the ate complex occurs predominantly at the less hindered side of the carbonyl group in every case. In addition, the ratio of isomeric alcohols obtained by alkylation with ate complexes is essentially the same as that found for alkylation by the separate reagents which compose the ate complex. Thus, the following general reaction scheme, employing $Li_2Mg(CH_3)_4$ as a specific example, can be written for ate complex addition to ketones. The fact that the separate reactants in each case [CH_3Li, $(CH_3)_2Mg$, and $(CH_3)_2Zn$] give the same stereochemistry as the ate complex appears to indicate that ate complex alkylation may occur *via* paths II and III rather than path I. To investigate this more fully, the ate complex $LiMg(C_6H_5)_2CH_3$ was prepared. The separate reactants CH_3Li which attacks 4-*tert*-butylcyclohexanone predominantly from the equatorial side and $(C_6H_5)_2Mg$ which attacks 4-*tert*-butylcyclohexanone to a slightly greater extent from the axial side might form an ate complex from which the stereochemistry of methyl transfer would be considerably different from that observed with CH_3Li. If the latter proved to be the case, it would strongly indicate that path I is the correct description of ate complex alkylation. Unfortunately, $LiMg(C_6H_5)_2CH_3$ methylates 4-*tert*-butylcyclohexanone with essentially the same stereochemistry as CH_3Li. Thus, a clear choice between path I and paths II and III cannot be made, although it appears that these reactions are proceeding by path I.

$$\begin{tikzcd} \mathrm{Li_2Mg(CH_3)_4} \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, "\substack{\text{ketone}\\ \text{path I}}"] & \mathrm{2CH_3Li} \arrow[r, phantom, "+"] \arrow[d, "\substack{\text{ketone}\\ \text{path II}}"] & \mathrm{Mg(CH_3)_2} \arrow[d, "\substack{\text{ketone}\\ \text{path III}}"] \\ \text{products} & \text{products} & \text{products} \end{tikzcd} \qquad (2)$$

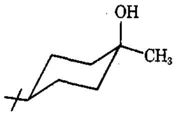
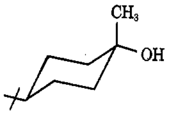
The presence of a salt, tri-*n*-octylpropylammonium bromide, in the reaction of CH_3MgBr with 4-*tert*-butylcyclohexanone had negligible effect on the stereochemistry. Ate complex formation was definitely indicated in this case since the ammonium salt itself is insoluble in diethyl ether but dissolves on addition of an equivalent amount of CH_3MgBr [or $(CH_3)_3Al$]. The addition of a strong base, potassium *tert*-butoxide, in the reaction of $(CH_3)_2Mg$, $(CH_3)_3Al$, and CH_3MgBr with the same ketone has no effect on the stereochemical results.

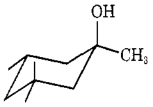
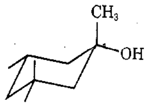
Special mention must be made of alkylation involving $LiB(CH_3)_4$ with 4-*tert*-butylcyclohexanone.This ate complex, as previous reports indicate,[7] is stable in a variety of polar solvents, *e.g.*, water, isopropyl alcohol, diethyl ether, and benzene.[10] Attempted alkylation of 4-*tert*-butylcyclohexanone using $LiB(CH_3)_4$ in diethyl ether, isopropyl alcohol, or benzene at room temperature failed to yield any evidence of the expected alcohols even after prolonged reaction times. Although no reaction was observed in isopropyl alcohol at reflux temperature, reaction did occur slowly in benzene at reflux temperature to yield 48% total alcohol products after 3 days at a 5:1 reagent:ketone reactant ratio. Although it is not clear whether reaction occurred *via* path I or path II in this case, it is noteworthy that to our knowledge this is the first reported alkylation of a ketone by a saturated alkylborane.

The isomer ratios in all reactions reported in this paper are independent of reaction time. Consequently, isomer equilibrium is not a factor under the conditions of these reactions.

The ate complexes of aluminum are considered separately due to the unusual stereochemistry observed in their reaction with 4-*tert*-butylcyclohexanone (Tables II and III). Lithium tetramethylaluminate alkylates 4-*tert*-butylcyclohexanone predominantly from the most hindered axial side in diethyl ether, tetrahydrofuran, and dimethoxyethane. This is an unusual result because all reagents except excess $(CH_3)_3Al$ in benzene[7] and $(CH_3)_2Zn$ and $(CH_3)_2Cd$ in the presence of magnesium halide[11] attack this ketone from the less hindered equatorial side. The per cent equatorial alcohol formed (~58%) is essentially the same in all solvents and is independent of reactant concentrations and ratios. In the more basic solvents, a greater amount of ketone is recovered indicating a larger percent-

Table I
Reaction of Ate Complexes of Boron, Magnesium, and Zinc with Ketones in Diethyl Ether

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone[a]	% axial alcohol[b] 	% equatorial alcohol[b] 
CH_3Li	0.76	4.0	A	65	35
$(CH_3)_2Mg$	0.44	4.0	A	70	30
$(CH_3)_2Zn$	0.20	4.0	A	No reaction	
$LiB(CH_3)_4$	0.20	1.0	A	No reaction after 4 days	
$LiB(CH_3)_4$	0.20	3.0	A	No reaction after 4 days	
$LiB(CH_3)_4$	0.20	5.0	A	67[c]	33[c]
$LiMg(CH_3)_3$	0.22	1.0	A	69	31
$LiMg(CH_3)_3$	0.36	4.0	A	70	30
$Li_2Mg(CH_3)_4$	0.14	2.0	A	69	31
$Li_3Mg(CH_3)_5$	0.14	2.0	A	71	29
$LiMg(C_6H_5)_2CH_3$	0.10	1.0	A	65[d]	35[d]
$LiZn(CH_3)_3$	0.23	1.0	A	64	36
$LiZn(CH_3)_3$	0.37	4.0	A	70	30
$Li_2Zn(CH_3)_4$	0.14	2.0	A	68	32
$Li_3Zn(CH_3)_5$	0.14	2.0	A	69	31
$KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$	0.027	4.0	A	71	29
$[(n\text{-}C_8H_{17})_3C_3H_7N]Mg(CH_3)_2Br$	0.132	3.0	A	75	25

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% axial alcohol[b] 	% equatorial alcohol 
CH_3Li	0.19	1.0	B	100	0
$(CH_3)_2Mg$	0.21	1.0	B	100	0
$(CH_3)_2Zn$	0.16	1.0	B	No reaction	
$LiMg(CH_3)_3$	0.36	4.0	B	100	0
$Li_2Mg(CH_3)_4$	0.21	1.0	B	100	0
$Li_3Mg(CH_3)_5$	0.27	4.0	B	100	0
$LiZn(CH_3)_3$	0.25	1.0	B	100	0
$Li_2Zn(CH_3)_4$	0.30	4.0	B	100	0
$Li_3Zn(CH_3)_5$	0.25	4.0	B	100	0

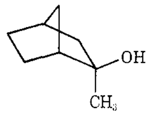
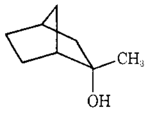
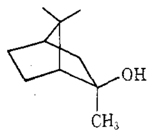
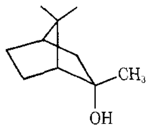
Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% exo alcohol[b] 	% endo alcohol[b] 
CH_3Li	0.80	4.0	C	5	95
$(CH_3)_2Mg$	0.46	3.0	C	5	95
$(CH_3)_2Zn$	0.28	3.0	C	No reaction	
$LiMg(CH_3)_3$	0.33	3.0	C	5	95
$Li_2Mg(CH_3)_4$	0.28	1.0	C	5	95
$Li_3Mg(CH_3)_5$	0.27	3.0	C	5	95
$LiZn(CH_3)_3$	0.32	1.0	C	5	95
$Li_2Zn(CH_3)_4$	0.32	3.0	C	5	95
$Li_3Zn(CH_3)_5$	0.27	3.0	C	5	95

Table I
(Continued)

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% exo alcohol 	% endo alcohol 
CH_3Li	0.23	1.0	D	99	1
$(CH_3)_2Mg$	0.51	4.0	D	99	1
$(CH_3)_2Zn$	0.22	4.0	D	No reaction	
$LiMg(CH_3)_3$	0.37	4.0	D	99	1
$Li_2Mg(CH_3)_4$	0.22	1.0	D	99	1
$Li_3Mg(CH_3)_5$	0.27	4.0	D	99	1
$LiZn(CH_3)_3$	0.39	4.0	D	99	1
$Li_2Zn(CH_3)_4$	0.22	1.0	D	99	1
$Li_3Zn(CH_3)_5$	0.26	4.0	D	99	1

[a] A, 4-*tert*-butylcyclohexanone; B, 3,3,5-trimethylcyclohexanone; C, norcamphor; D, camphor. [b] Normalized as % axial (exo) alcohol + % equatorial (endo) alcohol = 100%. [c] Reaction was carried out in refluxing benzene for 3 days. Total yield of alcohol products was 48%. Reaction in benzene at room temperature was not carried out owing to low solubility of $LiB(CH_3)_4$ in benzene. [d] Methylation products.

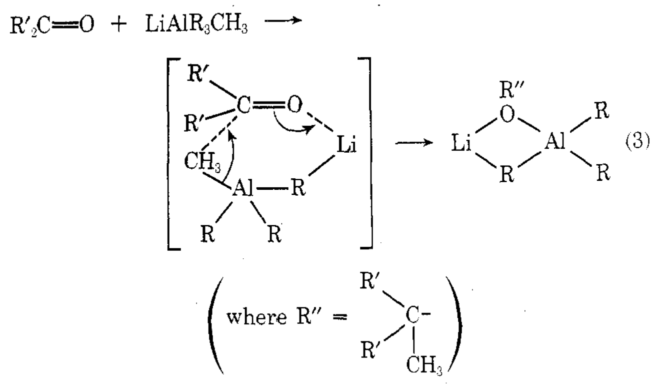
age of enolization. Lithium triisobutylmethylaluminate yields even larger percentages of equatorial alcohol *via* methylation, although large amounts of reduction product are formed.

The reason for the unusually high percentage of axial attack in these cases is not immediately obvious. The normal controlling factors of the stereochemistry of alkylation, steric approach control, and torsional strain are not sufficient to explain the observed isomer ratios in these reactions.[12] The "Compression Effect," which was shown to be the controlling factor in the alkylation of 4-*tert*-butylcyclohexanone with excess $(CH_3)_3Al$ in benzene and proposed for the $(CH_3)_2Zn$ and $(CH_3)_2Cd$ reactions,[12] may also be the controlling factor in the $LiAl(CH_3)_4$ reactions. However, nothing is known about the mechanism of ate complex addition to ketones and the exact way in which a compression effect might operate is not clear.

The stereochemistry of addition of aluminum ate complexes to 4-*tert*-butylcyclohexanone in benzene is illustrated in Table III. In 1:1 reactant ratio $LiAl(CH_3)_4$ gives slightly less axial attack on 4-*tert*-butylcyclohexanone in benzene (48%) than in polar solvents (58%). In addition, the observed isomer ratio of the product is dependent on reactant ratio with the percentage of axial attack increasing as the ate complex:ketone ratio increases.

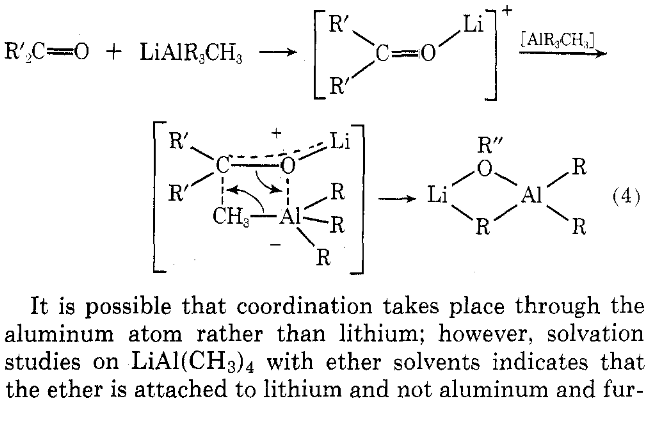
The reaction of $LiAl(i\text{-}C_4H_9)_3CH_3$ with 4-*tert*-butylcyclohexanone in benzene yields no methylation product, whereas in diethyl ether a significant percentage of methylation product (~30%) is observed. In addition, the percentage of equatorial alcohol formed *via* reduction of the ketone increases significantly in going from diethyl ether (52%) to benzene (69%) at the higher reagent:ketone ratios. The mechanism of reduction of ketones by these types of ate complexes is not known, but is expected to be significantly different from that proposed for aluminum alkyls[13] since all primary coordination sites on the aluminum atom are occupied. However, we found that lithium triisobutylmethylaluminate prepared in ether is isolated as the monoetherate $[LiAl(i\text{-}C_4H_9)_3CH_3 \cdot O(C_2H_5)_2]$ even after the liquid compound is subjected to vacuum (100 μ, 24 hr, room temperature). Thus, it appears that one molecule of ether is specifically solvated to each molecule of ate complex and therefore it is possible that complexes such as $LiAl(CH_3)_4$–ketone play an important role in the mechanisms of both alkylation and reduction.

If coordination of the ketone takes place at lithium, it is possible to draw a reasonable transition state for the reaction. Coordination of the carbonyl oxygen atom by lithium followed by a rate-determining carbanionic attack at the carbonyl carbon atom is somewhat reminiscent of the reac-



(3)

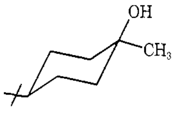
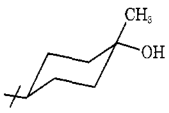
tion of ketones with R_3Al compounds in 1:2 ratio where the first molecule coordinates the carboxyl oxygen and the second attacks the carbonyl carbon. The fact that the stereochemistry of ate complex alkylation reveals predominant axial attack rather than the usual 30:70 (axial:equatorial) ratio observed by those reactions that proceed through a four-center transition lends some support to the proposed mechanism. It is not necessary that the transition state be cyclic; indeed one could picture a consecutive bimolecular reaction in which the lithium ion complexed carbonyl group is then attacked by the tetraalkylaluminate ion.

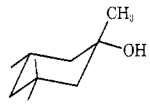
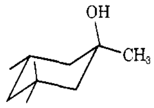


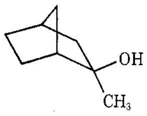
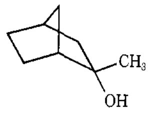
(4)

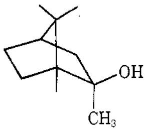
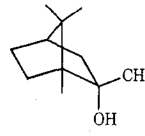
It is possible that coordination takes place through the aluminum atom rather than lithium; however, solvation studies on $LiAl(CH_3)_4$ with ether solvents indicates that the ether is attached to lithium and not aluminum and fur-

Table II
Reaction of Ate Complexes of Aluminum with Ketones in Polar Solvents[a]

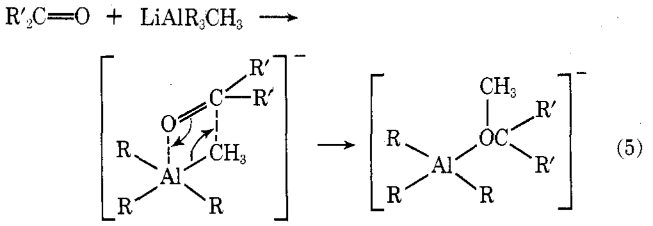
Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% axial alcohol[b] 	% equatorial alcohol[b] 
$LiAl(CH_3)_4$	0.15	1.0	A	42	58
$LiAl(CH_3)_4$	0.21	4.0	A	42	58
$LiAl(CH_3)_4$	0.18	1.0	A	44[c]	56[c]
$LiAl(CH_3)_4$	0.37	4.0	A	43[c]	57[c]
$LiAl(CH_3)_4$	0.39	1.0	A	43[d]	57[d]
$LiAl(CH_3)_4$	0.63	4.0	A	44[d]	56[d]
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.10	1.0	A	18[e]	82[e]
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.30	3.0	A	31[e]	69[e]
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.355	1.0	A	31[e]	69[e]
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.461	3.0	A	33[e]	67[e]
$(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$	0.044	1.0	A	81	19
$(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$	0.132	3.0	A	77	23

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% axial alcohol[b] 	% equatorial alcohol[b] 
$LiAl(CH_3)_4$	0.40	1.0	B	100	0
$LiAl(CH_3)_4$	0.54	4.0	B	100	0

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% exo alcohol 	% endo alcohol 
$LiAl(CH_3)_4$	0.19	1.0	C	5	95
$LiAl(CH_3)_4$	0.61	4.0	C	5	95

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	Ketone	% exo alcohol 	% endo alcohol 
$LiAl(CH_3)_4$	0.36	1.0	D	99	1
$LiAl(CH_3)_4$	0.58	4.0	D	99	1

[a] Diethyl ether unless otherwise noted. [b] Normalized as % axial (exo) alcohol + % equatorial (endo) alcohol = 100%. [c] Tetrahydrofuran. [d] Dimethoxyethane. [e] Methylation product. The major product of these reactions was the reduction product (66 to 75%). In all cases the reduction product was composed of 48% axial alcohol and 52% equatorial alcohol.



(5)

thermore the observed stereochemistry is not consistent with this suggestion.

Similar mechanistic suggestions could be made to explain the reduction reactions; however, there is even less justification than exists for the alkylation reactions to discuss these reactions at this time.

As was noted in the ether case, the addition of an equivalent amount of tri-*n*-octylpropylammonium bromide to $(CH_3)_3Al$ in benzene does not alter the stereochemistry observed in the 1:1 $(CH_3)_3Al$·ketone:reactant ratio. However, in a 3:1 reactant ratio, $Al(CH_3)_3$ yields 90% axial attack on 4-*tert*-butylcyclohexanone,[7] whereas $(n\text{-}C_4H_9)_3\text{-}C_3H_7NAl(CH_3)_3Br$ gives 76% equatorial attack, providing strong evidence that the principle species in solution in the latter case is the proposed ate complex. In every case the ate complexes involving the R_4N^+ cation attacked 4-*tert*-butylcyclohexanone more from the less hindered equatorial side than the corresponding Li^+ cation complexes. This result could be interpreted simply as a steric effect; however, the possibility also exists that the difference is due to the fact that the Li^+ cation can complex the carbonyl oxygen, whereas the NR_4^+ cation cannot and therefore one might

Table III
Reaction of Ate Complexes of Aluminum with 4-*tert*-Butylcyclohexanone in Benzene

Reagent	Initial concentration, *M*	Ratio of reagent:ketone	% axial alcohol[a]	% equatorial alcohol[a]
$LiAl(CH_3)_4$	0.012	1.0	52	48
$LiAl(CH_3)_4$	0.012	4.0	42	58
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.085	1.0	Trace[b]	0[b]
$LiAl(i\text{-}C_4H_9)_3CH_3$	0.26	3.0	0[b]	0[b]
$(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$	0.044	1.1	75	25
$(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$	0.132	3.1	76	24

[a] Normalized as −% axial alcohol + % equatorial alcohol = 100%. [b] Methylation product. The only product of these reactions was reduction product with no recovered ketone. The reduction product was composed of 39–31% axial alcohol and 61–69% equatorial alcohol at the low and high ratios, respectively.

Table IV
Stereochemistry of Alkylation of 4-*tert*-Butylcyclohexanone by $LiAl(CH_3)_4$ as a Function of Temperature[a]

Temp, °C	Solvent	$[LiAl(CH_3)_4]$, *M*	$LiAl(CH_3)_4$/ketone	% yield of alcohol products	% yield of axial products
25	Benzene	0.012	1.0	79	52
25	Benzene	0.012	4.0	99	42
5	Benzene	0.0093	1.0	14	48
5	Benzene	0.0098	4.0	20	49
25	Ether	0.15	1.0	87	42
25	Ether	0.21	4.0	97	42
0	Ether	0.24	1.0	40	35
0	Ether	0.48	4.0	61	32
−75	Ether	0.091	1.0	8	36
−75	Ether	0.11	4.0	11	37

[a] All reaction times, 20 hr. [b] Normalized as −% ketone + % alcohol = 100%. [c] Normalized as −% axial alcohol + % equatorial alcohol = 100%.

Table V
Per Cent Recovered Ketone from Reaction of a Variety of Metal Alkyls and Ate Complexes with 4-*tert*-Butylcyclohexanone under Identical Reaction Conditions[a]

Ate complex	% recovered ketone
$Li_3Mg(CH_3)_5$	6
$Li_2Mg(CH_3)_4$	8
CH_3Li	10
$LiMg(CH_3)_3$	19
$Li_3Zn(CH_3)_5$	19
$Li_2Zn(CH_3)_4$	22
$(CH_3)_2Mg$	28
$LiZn(CH_3)_3$	33
$LiAl(CH_3)_4$	33
$(CH_3)_3Al$	59
$(CH_3)_2Zn$	99

[a] Conditions: time, 2 hr; temperature, 25°; organometallic reagent concentration, 0.2 *M*; reagent:ketone ratio, 2:1.

expect' substantial differences in the respective transition states.

Owing to the unusually high percentage of axial attack observed in the alkylation of 4-*tert*-butylcyclohexanone by $LiAl(CH_3)_4$, a study of the temperature dependence of the observed isomer ratio obtained from this reaction was undertaken. It was felt that, if the activation enthalpies leading to axial and equatorial alcohol were significantly different, the isomer ratio might be controlled simply by controlling the temperature. The results, illustrated in Table IV, demonstrate that temperature has a noticeable, but small, effect on the observed isomer ratio.

Finally, to evaluate various organometallic reagents in terms of their use as alkylating agents, a series of reactions involving reaction of these reagents with 4-*tert*-butylcyclohexanone was carried out to determine their relative yields. The results, shown in Table V, should not be considered a representation of relative reactivities since recovery of ketone occurs *via* enolization as well as *via* lack of addition.

Registry No.—CH_3Li, 917-54-4; $(CH_3)_2Mg$, 2999-74-8; $(CH_3)_2Zn$, 544-97-8; $LiB(CH_3)_4$, 2169-38-2; $LiMg(CH_3)_3$, 52225-42-0; $Li_2Mg(CH_3)_4$, 15679-76-2; $Li_3Mg(CH_3)_5$, 14040-22-3; $LiMg(C_6H_5)_2CH_3$, 52196-04-0; $LiZn(CH_3)_3$, 52196-05-1; $Li_2Zn(CH_3)_4$, 15691-62-0; $Li_3Zn(CH_3)_5$, 14040-23-4; $KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$, 52196-06-2; $[(n\text{-}C_8H_{17})_3C_3H_7N]Mg(CH_3)_2Br$, 52196-07-3; $LiAl(CH_3)_4$, 14281-94-8; $LiAl(i\text{-}C_4H_9)_3CH_3$, 52196-08-4; $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$, 52196-09-5; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; norcamphor, 497-38-1; camphor, 76-22-2.

References and Notes

(1) We are indebted to the National Science Foundation (Grant No. GP-31550X) for partial support of this work.

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(10) Special caution should be exercised on acid hydrolysis of $LiB(CH_3)_4$ in any of the solvents mentioned since the $B(CH_3)_3$ released is spontaneously flammable.

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(12) For a recent review concerning the stereochemistry of alkylation of ketones, see E. C. Ashby and J. Laemmle, *Chem. Rev.*, in press.

(13) E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **35**, 1034 (1970).