aldehyde and benzophenone, quantitatively to the corresponding alcohols. However, acetone was reduced in only 40% yield to 2-propanol with 35% of the starting ketone being recovered presumably because of enolization. This alane also reduced 4-tert-butylcyclohexanone to provide 18% axial alcohol and 92% equatorial alcohol in 45% yield with 30% recovered ketone. The relative ratio of alcohols is approximately the same as that observed using AlH_3[36] in THF (19% axial alcohol). However, in benzene, $HAl(N(i-Pr)_2)_2$ in a 2:1 ratio of reagent to ketone provided 30% of the axial alcohol and 70% of the equatorial alcohol in 45% yield with 30% the ketone recovered. These experiments served as controls for the reactions which followed in which the hydrometalation product containing catalyst was reacted with a series of ketones.

When 1-octene was added to $HAl(N(i-Pr)_2)_2$ and catalyst and allowed to react under hydrometalation conditions, and then the reaction mixture was added to acetone or vice versa, it produced only 5% 2-propanol, 2% of the addition product (2-methyl-2-decanol), and 70% recovered acetone. When benzaldehyde was allowed to react with the hydrometalated species formed from the reaction of 1-octene with $HAl(N(i-Pr)_2)_2$ and Cp_2TiCl_2, the major product was benzyldiisopropylamine (90%). When $HAl(NEt_2)_2$ was used as the hydrometalating agent, 90% benzyldiethylamine was produced. When benzophenone was allowed to react with $HAl(NEt_2)_2$ or $HAl(N(i-Pr)_2)$, 62–65% of the corresponding amine (Ph_2CHNR_2) was formed in addition to 38% benzhydrol. Only a trace of the expected addition product was observed. Since the normal addition products were observed only in low yields in these reactions, they will not be discussed further, except that this reaction type is being pursued as a route to tertiary amines.

Reaction of the Hydrometalation Product with Oxygen or Carbon Dioxide. R_3Al compounds undergo rapid oxidation in the presence of O_2 to produce, on hydrolysis, alcohols[19] or with CO_2 to produce tertiary alcohols or carboxylic acids, depending on the reaction conditions.[37]

When oxygen or carbon dioxide was passed through the hydrometalation reaction mixture of 1-octene and $HAl(N-(i-Pr)_2)_2$ in the presence of Cp_2TiCl_2, only octane was observed by GLC after workup with saturated ammonium chloride or 10% HCl. The reason for the lack of oxidation can be argued on the basis of inductive effect where nitrogen withdraws electron density from the adjacent carbon atom thereby strengthening the aluminum–carbon compared to R_3Al compounds. The electron-donating ability of the NR_2 group by resonance is diminished because the orbital size different between aluminum and nitrogen prohibits good overlap; thus the overall effect of the NR_2 group on $Al–NR_2$ compounds is one of electron withdrawal.

(36) K. Ziegler, F. Krupp, K. Weyer, and W. Larbig, *Justus Liebigs Ann. Chem.*, **629**, 251 (1960).

Concerning the Effects of Added Salts on the Stereoselectivity and Rate of Organometallic Compound Addition to Ketones

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The addition of CH_3Li to 4-tert-butylcyclohexanone in the presence of $LiClO_4$ increased the formation of the axial alcohol from 65 to 92% compared to the reaction in the absence of $LiClO_4$. This result was attributed to complexation of the ketone by $LiClO_4$ followed by the addition of CH_3Li to the carbonyl group rather than by addition of a $CH_3Li–LiClO_4$ complex directly to the uncomplexed ketone. To complete a more detailed investigation of this unusual result, other organometallic compounds, ketones, and salts were studied in a similar manner. In addition to CH_3Li, t-BuLi, PhLi, $(CH_3)_2Mg$, and $(CH_3)_3Al$ were also allowed to react with 4-tert-butylcyclohexanone, 2-methylcyclohexanone 3,3,5-trimethylcyclohexanone, and norcamphor in the presence of equalmolar ratios of ten different salts in order to study their effect on the stereochemistry of the alcohol products. In addition to stereochemical effects, a major result of the reactions with RLi and R_2Mg in the presence of $LiClO_4$ was a dramatic increase in the rate of reaction.

Recently, it was reported that a mixture of CH_3Li and $LiCu(CH_3)_2$ provides unusually high rate enhancement and

stereoselectivity (92% equatorial attack in diethyl ether) in the methylation of 4-tert-butylcyclohexanone compared

to the reaction of CH_3Li alone.[1] Four possible explanations for the stereoselectivity have been suggested:[2] (1) CH_3Li reacts with $LiCu(CH_3)_2$ to form a complex (e.g., $Li_2Cu(CH_3)_3$ or $Li_3Cu(CH_3)_4$) which then reacts with the ketone;[1] (2) CH_3Li reacts with LiI to form a complex, a reaction known to produce $Li_4(CH_3)_3I$,[3] which then reacts with the ketone; (3) $LiCu(CH_3)_2$ and LiI react to form a complex which then reacts with the ketone; and (4) $LiCu(CH_3)_2$ reacts with the ketone to form a σ complex followed by reaction of the complexed carbonyl compound with CH_3Li.

The first suggestion was discounted on the basis that molecular weight measurements indicated that $Li_2Cu(CH_3)_3$ is monomeric in diethyl ether[2] and THF, whereas CH_3Li is tetrametric[4] and therefore $LiCu(CH_3)_2$[5] or $Li_2Cu(CH_3)_3$ should not be considered more bulky than a tetrametric molecule such as CH_3Li. Also, $Li_2Cu(CH_3)_3$ is only slightly more reactive than $LiCu(CH_3)_2$ in the conjugate addition of enones[6] in both diethyl ether and THF and is more stereoselective. Since $LiCu(CH_3)_2$ reacts very slowly with ketones and the $CH_3Li-LiCu(CH_3)_2$ mixture reacts with ketones more than 1000 times faster than CH_3Li alone, it is highly unlikely that $Li_2Cu(CH_3)_3$ is the reactive species.

Recently, low-temperature ^1H NMR evidence[7] was reported supporting the existence of an equilibrium mixture of CH_3Li, $LiCu(CH_3)_2$, and $Li_2Cu(CH_3)_3$ (eq 1) in dimethyl ether, THF, and diethyl ether; however, no evidence of any higher order complexes such as $Li_3Cu(CH_3)_4$ was found.

$$LiCH_3 + LiCu(CH_3)_2 \rightleftharpoons Li_2Cu(CH_3)_3 \qquad (1)$$
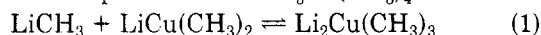
The third possibility was overruled due to the fact that when a halide-free mixture of CH_3Li and $LiCu(CH_3)_2$ was allowed to react with 4-*tert*-butylcyclohexanone, the same high stereoselectivity was observed.

The only reasonable possibility remaining then is that CH_3Li reacts with a complex between $LiCu(CH_3)_2$ and ketone (eq 2). This complex represents an activated ke-

$$LiCu(CH_3)_2 - R_2C=O \rightarrow R_2C=O \atop {\displaystyle \cdots \atop LiCu(CH_3)_2} \qquad (2)$$
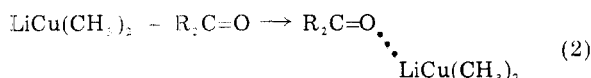
tone which then proceeds to react much more rapidly with CH_3Li than when the ketone is not complexed. In addition, the stereochemistry of CH_3Li addition to the complex would be expected to be different than CH_3Li addition to the free ketone due to the difference in hybridization of the carbonyl carbon in each case. This suggestion also explains why there is no rate enhancement or increase in stereoselectivity when the same reaction is conducted in THF; i.e., the ketone would not be expected to compete effectively with THF solvent molecules for coordination sites on lithium. The unusual rate enhancement in diethyl ether is explained on the basis that the concentration of ketone complexed to $LiCu(CH_3)_2$, LiI, etc., would be expected to be considerably higher in ether than in THF, and certainly the complexed carbonyl compound would be much more reactive than the uncomplexed carbonyl. Recently reports involving ^{13}C NMR have confirmed that no complex formation exists between CH_3Li and $LiClO_4$;

however, complex formation does take place between $LiClO_4$ and the carbonyl group[7,8] in diethyl ether, and yet a dramatic increase in stereoselectivity is observed when CH_3Li is allowed to react with 4-*tert*-butycyclohexanone in the presence of an equal molar amount of $LiClO_4$ just as in the case of $LiCu(CH_3)_2$.

In order to complete a more detailed study of the unusual stereoselectivity found in the alkylation of cyclohexanones with CH_3Li in the presence of lithium salts, several metal salts were added to the reaction of CH_3Li and 4-*tert*-butylcyclohexanone. In an attempt to expand the scope of the reaction, other ketones (e.g., 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and norcamphor) and other organolithium reagents (e.g., *tert*-butyl- and phenyllithium) were also allowed to react in the presence of $LiClO_4$. Similar studies were also conducted with organomagnesium and aluminum reagents.

Experimental Section

All reactions were performed under nitrogen or argon at the bench, using Schlenk tube techniques, or in a glove box equipped with a recirculating system, using manganese oxide to remove oxygen and dry ice–acetone traps to remove solvent vapors.[9,10] Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Glassware and syringes were flamed and cooled under a flow of nitrogen or argon. Ketones, metal salts, and solutions of internal standards were prepared by weighing the reagent in a tared volumetric flask and diluting it with the appropriate solvent.

Analysis. GLC analyses were carried out on an F and M Model 700 or Model 720 gas chromatograph. Flame photometry was conducted on a Colman Model 21 flame photometer. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10, using Eriochrome-Black T as an indicator. Aluminum was determined by adding excess standard EDTA solution to hydrolyzed samples and then back titrating with standard zinc acetate solution at pH 4, using dithizone as an indicator. Lithium reagents were analyzed by the standard Gilman double titration method (titration of total base followed by titration of total base after reaction with benzyl chloride)[11] or by flame photometry. The amount of active C–Mg and C–Li was determined by titrating the active reagent with dry 2-butanol in xylene, using 2,2'-diquinoline as an indicator.

Materials. Solvents. Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen from $NaAlH_4$ and diethyl ether (Fisher Reagent Grade) from $LiAlH_4$ prior to use.

Organometallic Compounds. Methyllithium in THF or diethyl ether was prepared by the reaction of $(CH_3)_2Hg$ with excess lithium metal dispersion (Alfa), 30% in petrolatum, which was washed repeatedly with ether/pentane until clean under argon atmosphere prior to use. Both solutions were stored at −78 °C until used.

Diethylmagnesium was prepared[12] by the reaction of diethylmercury with magnesium metal (ROC/RIC) at 40–60 °C in the absence of solvent. The resulting $(CH_3CH_2)_2Mg$ was extracted from the gray solid with ether and the resulting solution standardized by magnesium analysis. Trimethylaluminum (Ethyl Corporation) was distilled under vacuum in a glove box, and standard solutions were prepared in diethyl ether and THF. The resulting solutions were standardized by aluminum and methane analyses. Lithcoa *tert*-butyllithium and *n*-butyllithium, MC/B methyllithium, and PCR Incorporated phenyllithium were analyzed prior to use for active C–Li by the Watson and Eastman procedure described in the analytical section. The methyllithium

(1) T. L. MacDonald and W. C. Still, *J. Am. Chem. Soc.* **97**, 5280 (1975).

(2) E. C. Ashby and J. J. Watkins, *J. Chem. Soc., Chem. Commun.*, 784 (1976).

(3) D. P. Novak and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 3793 (1972).

(4) P. West and R. Waack, *J. Am. Chem. Soc.*, **89**, 4395 (1967).

(5) R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.*, **98**, 4098 (1976).

(6) E. C. Ashby, J. J. Lin, and J. J. Watkins, *J. Org. Chem.*, **42**, 1099 (1977).

(7) E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.*, **99**, 5312 (1977).

(8) A. Pull and D. Poolock, *Trans. Faraday Soc.*, 1709 (1977).

(9) D. F. Schriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, 1969.

(10) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, **51**, 65 (1974).

(11) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(12) E. C. Ashby and R. C. Arnott, *J. Organomet. Chem.*, **14**, 1 (1968).

reagent was also analyzed by methane gas analysis, using standard vacuum line techniques. All reagents were hydrolyzed prior to use and the organic fractions subjected to GLC analysis.

Ketones. Norcamphor, 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 4-*tert*-butylcyclohexanone were obtained from Aldrich Chemical Co. or Chemical Samples Co. and sublimed or distilled and stored over 4A molecular sieves prior to use.

Metal Salts. Lithium salts (lithium perchlorate, lithium iodide, and lithium bromide) were purchased from Alfa Inorganics and dried under vacuum at 100 °C overnight. Sodium tetraphenylborate and tetramethylammonium iodide were purchased from Fisher and used without further purification. Lithium methoxide and *tert*-butoxide were prepared by the reaction of *n*-butyllithium in hexane with a stoichiometric amount of the appropriate alcohol under anhydrous conditions, using an argon atmosphere. Magnesium methoxide and *tert*-butoxide as well as bis(diisopropylamino)magnesium were prepared in diethyl ether by the reaction of dimethylmagnesium with a stoichiometric amount of the appropriate alcohol or amine under an argon atmosphere. Aluminum methoxide and isopropoxide and tris(diisopropylamino)alane were prepared in THF by the reaction of alane with a stoichiometric amount of the appropriate alcohol or amine under an argon atmosphere.

If the lithium, magnesium, or aluminum salts were desired in another solvent, the original solvent was removed under vacuum and replaced by the desired solvent which was freshly distilled. This procedure was repeated three times in order to remove the last traces of the original solvent.

General Reactions of Ketones. A 10-mL Erlenmyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under argon or nitrogen. The flask was then sealed with a rubber serum cap and connected by means of a syringe needle to an argon- or nitrogen-filled manifold. The amount of organometallic reagent (ca. 0.1–1.0 mmol) in THF or diethyl ether was added to the flask, using a syringe, and the addition of the metal salt solution followed, if needed. The temperature was controlled by a dry ice–acetone bath; then the calculated amount of ketone in THF or diethyl ether was added to the stirred mixture.

The reverse addition (organometallic reagent added to a mixture of ketone, internal standard, and metal salt at -78 °C) produced the same results. After the designated time, the reaction was quenched with the slow addition of methanol and dried over anhydrous MgSO₄. A 12 ft 20% FFAP on Diatoport S column (column temperature, 150 °C; helium flow rate, 60 mL/min) was used to separate the products of 4-*tert*-butylcyclohexanone. The retention time was 13.0 min for *n*-C₁₄H₃₀, 33.0 min for *cis*-1-methyl-4-*tert*-butylcyclohexanol, 38.0 min for 4-*tert*-butylcyclohexanone, and 41.5 min for *trans*-1-methyl-4-*tert*-butylcyclohexanol. A 14 ft 10% diglycerol on Diatoport S column at 80 °C was used to separate the products of 2-methylcyclohexanone. The retention time was 4.4 min for the ketone, 5.2 min for the cis alcohol, 9.5 min for the trans alcohol, and 16.1 min for *n*-C₁₄H₃₀. A 10 ft column of 20% SAIB on Chromosorb W at 180 °C and with a flow rate of 60 mL/min gave the following retention times for ketone, axial alcohol, and equatorial alcohol for the methylation of 3,3,5-trimethylcyclohexanone: 5.0, 4.3, and 6.0 min.

The isomeric alcohols resulting from the methylation of norcamphor could not be separated by GLC. In addition, the isomeric alcohols resulting from the phenylation of all ketones studied could not be determined by GLC because of dehydration. Therefore, the isomer ratios in these cases were determined by NMR analysis. We had previously[13] determined the methyl singlet for the resulting exo alcohol from the methylation of norcamphor to be 73 Hz in benzene and that from the endo alcohol methyl group singlet to be 74 Hz. These results were confirmed.

The identification of the phenylation products of all ketones was determined by NMR spectroscopy utilizing the peak areas of the hydroxyl protons of the alcohols in Me₂SO-*d₆*. In these cases, workup of reaction mixtures was carried out as follows. After the reaction was complete, distilled water was added in order

Table I. Reactions of CH₃Li–Metal Salts with 4-*tert*-Butylcyclohexanone in Diethyl Ether Solvent for 2 h at -78 °C in a 2:1:1 Ratio

expt no.	salt	% of axial alcohol[a]	% of equat alcohol[a]	% yield[b]
1	none	65	35	97
2	NaBPh₄	68	32	97
3	Al(N(*i*-Pr)₂)₃	64	36	80
4	Al(O-*i*-Pr)₃	64	36	85
5	Mg(OCH₃)₂	68	32	83
6	Mg(O-*i*-Pr)₂	69	31	85
7	Me₄NI	70	30	92
8	LiBr	76	24	99
9	LiI	81	19	98
10	LiO-*t*-Bu	75	25	73
11	LiClO₄	92	8	96

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%. [b] The yield was determined by GLC and based on an internal standard. No ketone was recovered in any of the experiments.

Table II. Reactions of CH₃Li–LiClO₄ with Various Ketones in Et₂O Solvent for 2 h at -78 °C

expt no.	ketone	LiClO₄/ ketone	% of axial or endo alcohol[a]	% of equat alcohol[a]
12		0	65	35
13		1	92	8
14		0	100	0
15		1	100	0
16		0	88	12
17		1	96	4
18		0	100	0
19		1	100	0

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%. No ketone was recovered in any of the experiments.

to effect hydrolysis. The solution was then transferred to a separatory funnel and washed several times with distilled water. The ether layer was separated and allowed to evaporate and Me₂SO-*d₆* added to the sample. The sample was then dried over Linde 4A molecular sieves and transferred to an NMR tube. This procedure minimized dehydration and equilibration. Benzaldehyde was added as the internal standard.

In the case of phenylation of 4-*tert*-butylcyclohexanone, the chemical shifts for the axial and equatorial hydroxyl protons are 4.56 and 4.73 ppm, respectively. The assignment of each alcohol hydroxyl peak to a particular isomer was based on several reports in the literature concerning their chemical shifts in Me₂SO and Me₂SO-*d₆*.[14] The identification of the phenylation products of 2-methylcyclohexanone was accomplished according to the procedure of Luderer and co-workers.[15] The ¹H NMR showed the methyl doublet of the axial alcohol to be at 0.60 ppm and the methyl doublet associated with the equatorial alcohol to be at 0.62 ppm. Identification of the *tert*-butylation products of 4-*tert*-butylcyclohexanone was accomplished according to the method of Meakins.[14c] The axial hydroxyl proton in Me₂SO-*d₆* is

(13) E. C. Ashby, J. Laemmle, and P. V. Roling, *J. Org. Chem.*, 38, 2526 (1973).

(14) (a) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, 86, 1256 (1964); (b) R. J. Ouellette, *J. Am. Chem. Soc.*, 86, 4378 (1964); (c) G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc.* C, 1106 (1968); (d) J. Battioni, W. Chodkiewicz, and P. Cadiot, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 264, 991 (1967); (e) J. Battioni, M. Chapman, and W. Chodkiewicz, *Bull. Soc. Chim. Fr.*, 976 (1969); (f) J. Battioni and W. Chodkiewicz, *ibid.*, 981 (1969); (g) J. Battioni and W. Chodkiewicz, *ibid.*, 1824 (1971).

(15) J. R. Luderer, J. E. Woodall, and J. L. Pyle, *J. Org. Chem.*, 36, 2909 (1971).

Table III. Rate of Reaction of Ketones with CH$_3$Li–LiClO$_4$ at –78 °C in Diethyl Ether Solvent[a]

expt no.	ketone	time	% of recov ketone	% of endo or axial alcohol[a]	% of equat alcohol[a]
20		1 min	56	65	35
		3 min	45	65	35
		5 min	36	65	35
		15 min	15	65	35
	no LiClO$_4$	30 min	6	65	35
		60 min	0	65	35
21	with LiClO$_4$	5 s	0	92	8
		10 s	0	92	8
22		1 min	60	87	13
		3 min	40	88	12
		5 min	33	88	12
		15 min	20	87	13
	no LiClO$_4$	30 min	7	88	12
		60 min	0	88	12
23	with LiClO$_4$	5 s	5	95	5
		10 s	0	96	4
24		1 min	70	100	0
		5 min	55	100	0
		15 min	31	100	0
		30 min	15	100	0
	no LiClO$_4$	60 min	3	100	0
		120 min	0	100	0
25	with LiClO$_4$	5 s	5	100	0
		10 s	0	100	0

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%.

Table IV. Reactions of RLi–LiClO$_4$ with 4-*tert*-Butylcyclohexanone in Et$_2$O Solvent for 2 h at –78 °C

expt no.	reagent	LiClO$_4$/ ketone	% of recov ketone	% of additional products — axial alcohol	% of additional products — equat alcohol	% of reduction — equat alcohol
26	MeLi	0	0	65	35	
27		1	0	92	8	
28	*t*-BuLi	0	30	100	0	7
29		1	37	100	0	<1
30	PhLi	0	0	58	42	
31		1	0	69	31	

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%.

3.49 ppm. Finally, the identification of the *tert*-butylation products of 2-methylcyclohexanone was accomplished by the method of Ficini and Maujean.[16]

Results and Discussion

Organolithium Reactions. The detailed results of stereoselective methylation in diethyl ether of 4-*tert*-butycyclohexanone (eq 3) by CH$_3$Li in the presence of equi-

molar amounts of various metallic salts [e.g., LiBr, LiI, LiClO$_4$, NaBPh$_4$, Me$_4$NI, LiO-*t*-Bu, Mg(O-*i*-Pr)$_2$ Al(O-*i*-Pr)$_3$, and Al(N-*i*-Pr)$_2$)$_3$] are reported in Tables I–III. When CH$_3$Li was allowed to react with 4-*tert*-butylcyclohexanone in diethyl ether solvent, 65% of the axial alcohol was formed. However, when either LiO-*t*-Bu, LiBr, LiI, or LiClO$_4$ (Table I) was added to an ether solution of CH$_3$Li before it was added to the ketone, the amount of axial alcohol formed increased to 75, 76, 81, and 92%,
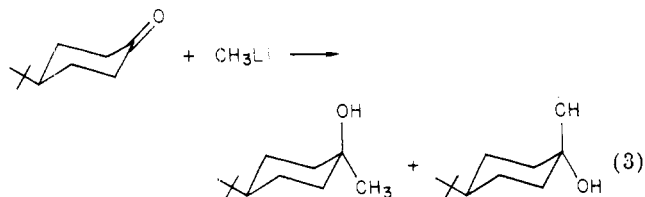
respectively. When the diethyl ether solvent was replaced by THF, no increase in stereoselectivity was observed on the addition of the above lithium salts. A number of other salts (experiments 2–7) produced no effect or only a slight increase (~5%) in the formation of axial alcohol. When Al(N(*i*-Pr)$_2$)$_3$, Al(O-*i*-Pr)$_3$, Mg(OCH$_3$)$_2$, Mg(O-*i*-Pr)$_2$, and LiO-*t*-Bu were present, the total product yield decreased to 80, 85, 83, and 73, respectively (compared to ≥96% for the lithium salts presumably due to enolization of the ketone).

Because LiClO$_4$ had the greatest effect on the stereochemistry of this reaction, it was decided to study the scope of similar reactions, using LiClO$_4$, but varying the nature of the ketone and the organolithium reagent. When ketones other than 4-*tert*-butylcyclohexanone (Table II) were allowed to react with CH$_3$Li in the presence of LiClO$_4$, only 2-methylcyclohexanone showed an increase in the production of the axial alcohol (88% without and 96% with LiClO$_4$ added). The energy difference in changing the stereochemistry from 88 to 96% is, of course, quite significant (1.9 kJ/mol vs. 3.0 kJ/mol), even compared to the change from 65 to 92%. The other ketones, 3,3,5-trimethylcyclohexanone and norcamphor, did not show any increase in the formation of the axial alcohol since only the axial or endo alcohol was observed in the absence of LiClO$_4$. However, even these ketones showed a pronounced rate enhancement when allowed to react[a] with CH$_3$Li in the

(16) J. Ficini and A. Maujean, *Bull. Soc. Chim. Fr.*, 219 (1971).

Table V. Reactions of *tert*-Butyllithium with Ketones in the Presence and Absence of LiClO$_4$ at $-78\ °$C in Et$_2$O Solvent in a 2:1:1 Ratio

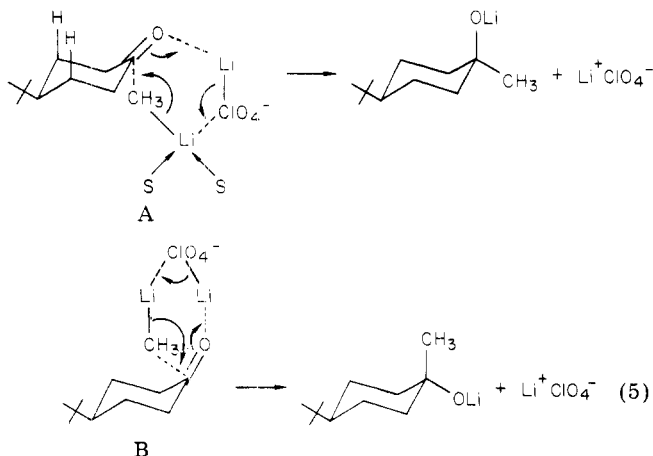| expt no.	ketone	time	% of re-cov ketone	% of axial alcohol[a]	% of equat alcohol[a]
38		5 min	45	100	0
		10 min	35	100	0
		15 min	30	100	0
		30 min	30	100	0
	no LiClO$_4$	60 min	30	100	0
		120 min	30	100	0
39	with LiClO$_4$	5 s	37	100	0
		10 s	37	100	0
		60 s	37	100	0
		120 s	37	100	0
40		2 min	50	100	0
40		5 min	35	100	0
		10 min	26	100	0
		15 min	13	100	0
		30 min	14	100	0
	no LiClO$_4$	60 min	13	100	0
		120 min	14	100	0
41	with LiClO$_4$	5 s	13	100	0
		10 s	13	100	0
		60 s	13	100	0
		120 s	13	100	0

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%.

presence of LiClO$_4$ (Table III). In the absence of LiClO$_4$, the reaction of CH$_3$Li with 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, or norcamphor was essentially over in 1 h; however, when LiClO$_4$ was present, the reaction was complete in less than 10 s at $-78\ °$C. The substantial rate enhancement is probably due to the increased reactivity of the newly formed complex between the carbonyl group and LiClO$_4$ (eq 4 and 5).

Equation 4 illustrates the proposed transition state for the reaction of CH$_3$Li with 4-*tert*-butylcyclohexanone which provides 65% of the axial alcohol on hydrolysis.

(4)
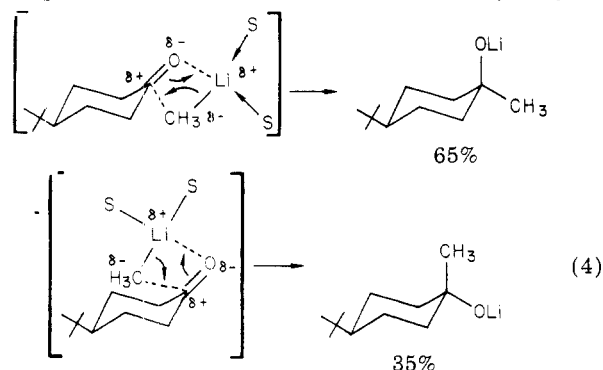
If LiClO$_4$ is introduced (eq 5), complexation between

(5)

Table VI. Reactions of RLi-LiClO$_4$ with 2-Methylcyclohexanone in Et$_2$O Solvent for 2 h at $-78\ °$C

expt no.	reagent	LiClO$_4$/ketone	% of recov ke-tone	% of axial alco-hol[a]	% of equat alco-hol[a]
32	MeLi	0	0	88	12
33		1	0	96	4
34	*t*-BuLi[b]	0	13	100	0
35		1	14	100	0
36	PhLi	0	0	88	12
37		1	0	94	6

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%. [b] Without LiClO$_4$, 1% of the *trans*-2-methylcyclohexanol was detected by GLC. With LiClO$_4$, only a trace of the *trans*-2-methylcyclohexanol was detected by GLC.

Table VII. Reactions of Me$_2$Mg-Salt with 4-*tert*-Butylcyclohexanone in Et$_2$O Solvent for 2 h at $-78\ °$C in a 2:1:1 Ratio

expt no.	salt	% of axial alco-hol[a]	% of equat alco-hol[a]	% yield[b]
42	none	62	38	96
43	LiClO$_4$	65	35	96
44	NaBPh$_4$	60	40	97
45	LiBr	65	35	95
46	LiI	65	35	94
47	LiO-*t*-Bu	65	35	70
48	Mg(O-*i*-Pr)$_2$	74	26	89
49	MeMgO-*i*-Pr (only)	75	25	91

[a] The normalized percent of axial alcohol + percent of equatorial = 100%. [b] The yield was determined by GLC, using an internal standard. No ketone was recovered in any experiment.

LiClO$_4$ and the carbonyl group takes place, increasing the bonyl group increases the rate of reaction with CH$_3$Li since rate of subsequent attack by CH$_3$Li and also influencing the subsequent stereochemistry of the reaction. It is not surprising that complexation between LiClO$_4$ and the car-

Table VIII. Reactions of Me₂Mg–LiClO₄ with Ketones in Et₂O Solvent for 2 h at −78 °C in a 2:1:1 Ratio

expt no.	ketone	LiClO₄/ ketone	% of re- cov ketone	% of endo or axial alcohol[a]	% of equat alcohol[a]
50		0	0	62	38
51		1	0	69	31
52		0	0	85	15
53		1	0	89	11
54		0	0	80	20
55		1	0	84	16
56		0	0	100	0
57		1	0	100	0

[a] The normalized percent of axial alcohol + percent of equatorial alcohol = 100%.

the complexed carbonyl group should be highly polarized as in other cases of acid catalysis of carbonyl compounds. This complexation also accounts for the increase in the amount of axial alcohol because complex A has less serious 3,5-diaxial hydrogen interactions than those exhibited in complex B. The complexation also explains the results obtained when THF is the solvent: namely, no rate enhancement or increase in the stereoselectivity. Tetrahydronfuran is more basic than diethyl ether and therefore the carbonyl group can no longer compete for complexation of LiClO₄.

These results of enhanced rate and stereochemistry bear an amazing resemblance to the results observed some time ago in the case of 4-*tert*-butylcyclohexanone alkylation by (CH₃)₃Al in 1:1 and 1:2 ratios.[17] In benzene solvent, the reaction proceeds approximately 1,000 times faster when the reactants are in a 2:1 ratio than a 1:1 ratio. The mechanisms of these reactions have been studied and the conclusions reached that the 1:1 reaction proceeds via a 4-center transition state whereas the 1:2 reaction proceeds via a 6-center transition state.

When phenyllithium was allowed to react with 4-*tert*-butylcyclohexanone and 2-methylcyclohexanone (Tables IV and V, respectively) in the presence of an equalmolar amount of LiClO₄ in diethyl ether, only a slight increase in the formation of the axial alcohols was observed compared to the reaction without LiClO₄. One can assume that the phenyl group presents an even lesser steric requirement than the methyl group, as has been shown earlier for the reactions of organomagnesium compounds with 4-*tert*-butylcyclohexanone;[18] therefore less of a stereochemical change is expected. In addition, phenyllithium is known to be dimeric in ether, whereas methyllithium is tetrameric.

An interesting observation concerning the reaction of *tert*-butyllithium with 4-*tert*-butylcyclohexanone is that in the absence of LiClO₄, 7% of the product is the equatorial alcohol produced by reduction of the ketone (experiment 28) and 30% of the product is recovered ketone. On the other hand, in the presence of LiClO₄, the reduction product was only 1%, but the amount of recovered ketone increased to 37%. From Table V it can be seen that without the addition of LiClO₄ (experiment 38), the reaction is essentially over in 15 min, but in the presence of LiClO₄ (experiment 39), the reaction is over in less than 5 s. Evidently, the complexation of the ketone with LiClO₄ increases the rate of the addition reaction substantially without affecting the β-hydrogen reduction pathway and hence the 1,2-addition product increases relative to reduction product in the presence of LiClO₄.

When *tert*-butyllithium was allowed to react with 2-methylcyclohexanone (Table VI experiments 34 and 35),

13% of the ketone was recovered in the absence of LiClO₄ and 14% of the ketone was recovered when an equalmolar amount of LiClO₄ was present. When comparing this result with that of the 4-*tert*-butylcyclohexanone reaction (30% 4-*tert*-butylcyclohexanone recovered when LiClO₄ is absent), an explanation can be suggested in terms of enolization intermediates. 4-*tert*-Butylcyclohexanone has four hydrogen atoms available for abstraction, with the two equatorial ones being the most accessible. 2-Methylcyclohexanone has three hydrogens available for abstraction, but the most stable enolate predominates in an 89:11 ratio (eq 6).[19] Based on these points, it is expected that

(6)

89%   11%
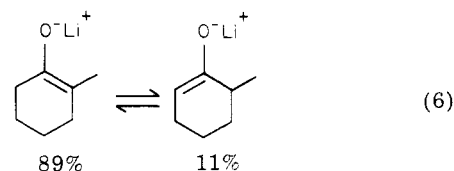
4-*tert*-butylcyclohexanone would have roughly twice as many hydrogens available for abstraction as 2-methylcyclohexanone, and this is indeed reflected in the amounts of recovered starting ketones for the two reactions (30:13) after hydrolysis.

It was also observed that only the axial alcohol, *cis*-1,2-dimethylcyclohexanol, was produced whether LiClO₄ was present or not. However, just as for the 4-*tert*-butylcyclohexanone reaction (Table V), it appears that *tert*-butyllithium is sufficiently bulky that attack takes place from the least hindred side of the molecule to the exclusion of the more hindered side (axial attack).

Organomagnesium Reactions. Chastrette and Amouroux[20] reported that the presence of LiClO₄ or *n*-Bu₄NCl in the reaction of Grignard reagents with 4-*tert*-butylcyclohexanone has no effect on the sterochemistry of the reaction of R₂Mg compounds with 4-*tert*-butylcyclohexanone; however, the addition of these salts did increase the amount of enolization product. Our work in this area was carried out in order to verify these results as well as investigate the influence of other salts and ketones in the reaction of organomagnesium compounds with cyclohexanones. The results are recorded in Tables VII and VIII.

In general, we observed only slight increases (4–7%) in the formation of the axial alcohols over the equatorial alcohols compared with the reactions without the addition of LiClO₄. We did observe that when Mg(O-*i*-Pr)₂ (Table VII experiment 48) was present in equalmolar ratio with (CH₃)₂Mg, the stereochemistry of the product increased from 62% axial alcohol when no salt was present (experi-

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(18) E. C. Ashby and J. Laemmle, *Chem. Rev.*, **75**, 521 (1975).

(19) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).
(20) M. Chastrette and R. Amouroux, *Bull. Soc. Chim. Fr.*, 1955 (1974).

Table IX. Reactions of Me_2Mg with
4-*tert*-Butylcyclohexanone in the Presence and Absence of
$LiClO_4$ in Et_2O Solvent at $-78\ °C$ in a $2:1:1$ Ratio

expt no.	time	% of re-cov ketone	% of axial alco-hol[a]	% of equat alco-hol[a]
		No $LiClO_4$		
58	2 min	50	62	38
	5 min	35	62	38
	10 min	20	61	39
	15 min	13	62	38
	30 min	5	63	37
	60 min	0	62	38
	120 min	0	62	38
		$LiClO_4$ Added		
59	10 s	5	69	31
	20 s	0	70	30
	40 s	0	70	30
	60 s	0	68	32
	120 s	0	69	31
	120 min	0	69	31

[a] The normalized percent of axial alcohol + percent of
equatorial alcohol = 100%.

ment 42) to 75% (experiment 48) when salt was present.
A similar result was obtained when MeMgO-*i*-Pr was al-
lowed to react with the same ketone. Therefore it may be
assumed that a redistribution reaction according to eq 7
took place, which accounts for the so-called salt effect.

$$Mg(OR)_2 + Mg_2Mg \rightleftharpoons 2MeMg(OR) \qquad (7)$$
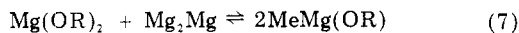
The other salts ($NaBPh_4$, LiBr, and LiI) had little effect
on the stereochemistry of the reactions studied. LiO-*t*-Bu
did not increase the stereoselectivity of the reaction, but
it did increase the amount of enolization (30%) (experi-
ment 47), a result similar to the observation of Georgoulis[21]
using KO-*t*-Bu.

The reactions of 4-*tert*-butylcyclohexanone, 3,3,5-tri-
methylcyclohexanone, and 2-methylcyclohexanone with
$(CH_3)_2Mg$ in the absence of $LiClO_4$ resulted in the forma-
tion of the corresponding cis alcohols in 62, 85, and 80%,
respectively. With $LiClO_4$ present, the amount of cis al-
cohols increased to 69, 89, and 84%, respectively (Table
VIII experiments 50–57). Although this is not much en-
hanced stereochemistry, the numbers are real. However,
the major effect of the addition of $LiClO_4$ to the reactions
was a pronounced rate enhancement. A rate study was
conducted with and without $LiClO_4$ on the reaction of
Me_2Mg with 4-*tert*-butylcyclohexanone at $-78\ °C$ (Table
IX). It was found that the presence of $LiClO_4$ increased
the rate approximately 180 times over that observed for
the reaction without $LiClO_4$. It can be reasoned, as for the
CH_3Li reactions, that the increased polarization resulting
from the complexation of the carbonyl group with $LiClO_4$
enabled the rate of reaction to increase with a slight in-

crease in enhanced stereoselectivity as well. Therefore, the
effect of added $LiClO_4$ is profound in altering the rate of
the reaction but not the stereoselectivity.

Organoaluminum Reactions. Chastrette and Amour-
oux[22] have reported that the addition of salts, such as NaF,
KF, or n-Bu_4NX where X = I, Br, Cl, or F, slows down the
reaction of R_3Al compounds with benzaldehyde in the
order I > Br > Cl > F and NaF > KF > n-Bu_4NF. In no
case was the reaction faster in the presence of a salt than
in its absence. They suggested that this result was proba-
bly due to the deactivating nature of a newly formed com-
plex C between R_3Al and the salt.[23]
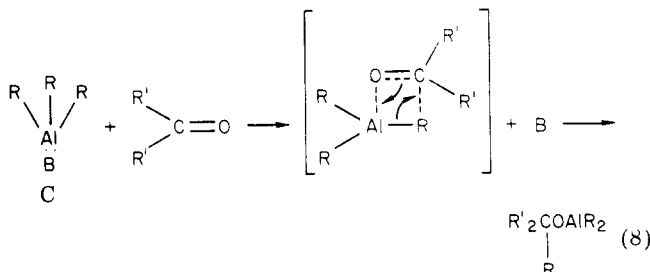
With this report as precedence, we decided to study
further any change in the stereochemistry of the products
of reaction of Me_3Al with 4-*tert*-butylcyclohexanone in the
presence of various salts in diethyl ether.

The salts studied were $LiClO_4$, $NaBPh_4$, LiBr, LiI, and
LiO-*t*-Bu. All reactions were complete after 12 h at -78
°C. Only a slight increase (85 to 88%) in the formation
of the axial alcohol was observed in the case of $LiClO_4$ and
$NaBPh_4$. The other salts produced no effect at all. All
of the salts slowed down the rate of reaction, presumably
by complexation with Me_3Al as suggested earlier by Chas-
trette.[23]

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