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Stereoselective Organometallic Alkylation Reactions. IV. Organolithium and Organoaluminum Addition to Trimethyl-, Triphenyl-, and Trichloroaluminum Complexes of 4-*tert*-Butylcyclohexanone and 2-Methylcyclopentanone[1]

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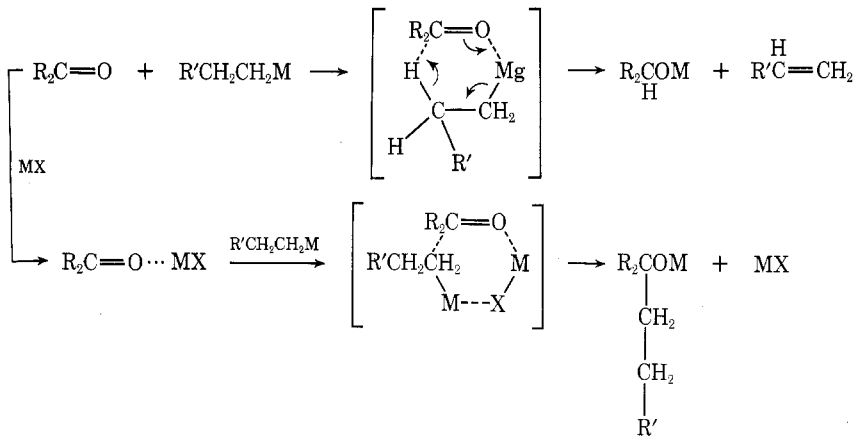
Reaction of $(C_2H_5)_3Al$ with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ complex gave significant percentages of ethylation, methylation, and reduction. The similarity between this reaction and the addition of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ in 1:1 ratio to 4-*tert*-butylcyclohexanone as well as the similarity of the predominant isomer (equatorial alcohol) arising from methylation and ethylation in both cases indicates that in the first case redistribution of the alkyl groups between $(C_2H_5)_3Al$ and ketone–$Al(CH_3)_3$ is much faster than alkylation. Triethylaluminum addition to ketone–$AlCl_3$ complex leads to ethyl entry predominantly from the axial side (compression effect) accompanied by a much larger percentage of reduction than $(C_2H_5)_3Al$ addition to uncomplexed ketone. Compounds of the type $(C_2H_5)_nAlX_{3-n}$ give larger ethylation:reduction ratios than $(C_2H_5)_3Al$ when X is electron donating (CH_3) and smaller ratios when X is electron withdrawing (Cl). Attempts to introduce *n*-butyl groups into 4-*tert*-butylcyclohexanone and 2-methylcyclopentanone from the more hindered side by reaction of *n*-butyllithium with ketone–AlR_3 and ketone–$AlCl_3$ complexes were not successful. Alkylation of these complexes gave about the same ratio of isomeric alcohols as did *n*-butyllithium. Analysis of the results of these latter reactions indicates that the reactions did not occur via the corresponding ate complexes, $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n*, since the latter gave a significantly larger percentage of methylation and reduction, respectively.

One of the more potentially fruitful recent developments in the area of stereoselective alkylation of ketones has been the discovery that reaction of $(CH_3)_3Al$ with alicyclic ketones in 2:1 ratio in hydrocarbon solvent causes attachment of the methyl group at the carbonyl site predominantly (90%) from the most hindered side.[3,4] Unfortunately, the method is limited in those cases where the organoaluminum reagent possesses β hydrogens in that reduction products are formed.

The present work involves a study of reactions of $(C_2H_5)_3Al$ and *n*-C_4H_9Li with aluminum alkyl and aluminum chloride complexes of 4-*tert*-butylcyclohexanone and 2-methylcyclopentanone (ketones displaying a large compression effect)[3c] in order to investigate the possibility of bonding groups other than methyl or phenyl, particularly those that possess a β hydrogen, to the more hindered side of the ketones in high yield. The object of adding the RLi or R_3Al compounds to a complexed ketone was not only to direct the R group to the most hindered side of the carbonyl group (compression effect), but also to hinder the possibility of reduction by the ethyl or butyl group via β-hydrogen transfer. In addition, the potential of compounds such as $(CH_3)_nAl(C_2H_5)_{3-n}$, $(CH_3)_nAlCl_{3-n}$, and $(C_2H_5)_n$-$AlCl_{3-n}$ were investigated as stereoselective alkylating agents. In each case, special attention was given to the total percentages of the various possible alkylation–reduction products as well as to the ratio of isomeric alcohols obtained from alkylation and reduction.



Experimental Section

Materials. Trimethylaluminum and triethylaluminum were obtained from Texas Alkyls, Inc., and distilled through a 12-in. glass helix packed column at reduced pressure. *n*-Butyllithium, obtained from Foote Mineral Co. as a clear hexane solution, was used without further purification. 2-Methylcyclopentanone, obtained from Chemical Samples Co., was dried over activated 4-A molecular sieve prior to use. Frinton Laboratories 4-*tert*-butylcyclohexanone and Fisher reagent grade anhydrous aluminum chloride were sublimed under nitrogen prior to use. Fisher Certified thiophene-free benzene was distilled from $NaAlH_4$ prior to use.

Apparatus and Procedure. Transfers of materials used in this study were carried out in a glove box described elsewhere.[5] Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Deliveries could be reproduced to better than ±0.5%. Solutions of ketones were prepared by weighing out a known amount of ketone in a calibrated volumetric flask and diluting to the mark with benzene. Solutions of ketone–$AlCl_3$ complexes were prepared by adding an appropriate amount of ketone solution in benzene to a weighed amount of $AlCl_3$ in a volumetric flask and diluting to the mark with benzene.[3c] These solutions were used within 24 hr of preparation in every case. Solutions of organoaluminum compounds were prepared by diluting known amounts of the standard reagents with benzene. The concentrations of organoaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis which was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. Solutions of *n*-butyllithium were hydrolyzed and lithium analysis was carried out by flame photometry.

Preparations. "Mixed aluminum alkyls" [$(C_2H_5)_2AlCH_3$, $(CH_3)_3Al_2(C_2H_5)_3$, etc.] were prepared by mixing appropriate volumes of standard trimethyl- and triethylaluminum solutions in a volumetric flask and diluting to the mark.[6] Dimethylaluminum *n*-propoxide was prepared by addition of an appropriate amount of *n*-propyl alcohol to standard $(CH_3)_3Al$ solution. Alkylaluminum chlorides were prepared by adding an appropriate amount of standard aluminum alkyl solution to a weighed amount of $AlCl_3$ in a volumetric flask and diluting to the mark. Reaction was indicated by the fact that all the aluminum chloride dissolved. $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* were prepared by adding an appropriate amount of *n*-butyllithium in hexane to the standard solution of aluminum alkyl in benzene. Ate complex formation was indicated by the immediate appearance of a white precipitate.

Reactions. All reactions were carried out in 6 × 0.625 in. test tubes equipped with 12/30 ground glass joints and stoppers. The test tubes were flamed, taken under vacuum through the glove box entry port, and flushed with high-purity nitrogen once inside the glove box.

In those cases involving the addition of alkylating agent to ketone–$Al(CH_3)_3$ and ketone–$Al(C_6H_5)_3$ complexes, the following procedure was used. An appropriate amount of ketone was placed in the test tube followed by addition of a sufficient amount of complexing agent to yield a 1:1 ketone–aluminum alkyl complex. The test tube was shaken briefly to ensure mixing and an appropriate amount of alkylating agent was added. The time elapsed between addition of the complexing agent and addition of the alkylating agent was about 10–15 sec and never more than 25 sec.

In those reactions involving addition of alkylating agents to ketone or ketone–$AlCl_3$ complex, appropriate amounts of alkylating agent were added to the ketone or ketone–$AlCl_3$ when a 1:1 ratio was desired and ketone or ketone–$AlCl_3$ was added to alkylating agent when a 2:1 or greater alkylating agent:substrate ratio was desired.

All reaction mixtures were immediately stoppered after addition of reagents and although the addition process generally resulted in thorough mixing, the tubes were shaken. In those reactions involving a solid alkylating agent, i.e., $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n*, and in those in which a precipitate immediately formed, i.e., additions of *n*-C_4H_9Li to ketone–$Al(CH_3)_3$, ketone–$Al(C_6H_5)_3$, and ketone–$AlCl_3$ complexes, continuous stirring was accomplished via a Teflon stirring bar. All reaction mixtures were allowed to stand stoppered overnight in the glove box and were removed and hydrolyzed about 20 hr after mixing. The solvent in all reactions was benzene except those involving organolithium compounds, when the solvent was benzene–hexane.

Product Analysis. All reactions were hydrolyzed with distilled water and after hydrolysis 3,3,5-trimethylcyclohexanone was added as an internal standard. Those mixtures involving alkylations of 4-*tert*-butylcyclohexanone were all analyzed by GLC employing a 22 ft × 0.125 in. stainless steel column of 10% FFAP on Diatoport-Sat (115°). The following order of emergence of the standard and all possible products occurs under these conditions: 3,3,5-trimethylcyclohexanone (standard) > axial alcohol (methylation) > 4-*tert*-butylcyclohexanone > equatorial alcohol (methylation) > axial alcohol (reduction) > axial alcohol (ethylation) > equatorial alcohol (reduction) > equatorial alcohol (ethylation) > axial alcohol (butylation) > equatorial alcohol (butylation). The axial alcohols from reduction and ethylation and the equatorial alcohols from reduction and ethylation do not completely separate under these conditions, although the separation is good. In order to estimate the area associated with each alcohol, a straight line was dropped from the trough between the two peaks perpendicular to the base line and was considered to be the separation point of the peaks. Overlap between the two butylation isomers is even more serious. The butylation products take an extremely long time to emerge under these conditions (about 6 hr) and have very long frontside slopes which drop rapidly to the base line after the peak is reached. The area corresponding to each butylation isomer was estimated in the following fashion. The total area for both isomers was measured. The forward slope corresponding to the equatorial alcohol (second peak) was extrapolated to the base line and the area measured. This area was considered to be the area corresponding to the equatorial alcohol. Substraction of this area from the total area then gave the area corresponding to the axial alcohol. A sample of the butylation isomers obtained by reaction of 4-*tert*-butylcyclohexanone with *n*-butyllithium was analyzed by both GLC and NMR in DMSO-d_6. In the NMR, the equatorial OH protons and the axial OH protons are completely separated with the axial OH protons absorbing at higher field.[3] The isomer percentage obtained by NMR and the GLC method described agreed within 2%. All remaining samples involving butylation of 4-*tert*-butylcyclohexanone were analyzed by GLC.

Those mixtures involving alkylation of 2-methylcyclopentanone were analyzed by GLC employing a 15 ft × 0.125 in. stainless steel column of 10% diglycerol on Chromosorb W at 80°. The order of emergence of the standard and all products analyzed is the following: 2-methylcyclopentanone > cis alcohol (methylation) > 3,3,5-trimethylcyclohexanone (standard) > trans alcohol (methylation) = cis alcohol (reduction) > trans alcohol (reduction) > cis alcohol (butylation) > trans alcohol (butylation). Since it was impossible to separate the cis alcohol (reduction) from the trans alcohol (methylation), the total amount of both methylation and re-

duction is reported in those reactions where both occurred; however, no isomer ratios are given (Table VI). The isomeric butylation products gave broad peaks under the conditions cited but separated completely from all other products and from one another.

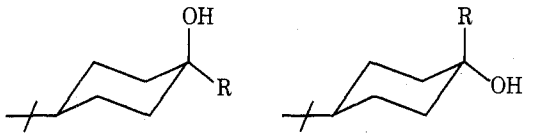
The material balances for all reactions reported were essentially 100% except for those reactions involving alkylaluminum chlorides or alkylations of 4-*tert*-butylcyclohexanone–$AlCl_3$ complexes. In the latter cases, the material balances were ~80% and a number of small unidentified peaks appeared in the GLC. No attempt was made to measure isomer ratios due to phenylation of the ketones because of decomposition of these alcohols under GLC conditions.

Results and Discussion

Table I reports on the results of the reaction of trimethylaluminum with 4-*tert*-butylcyclohexanone and 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ complex. Two possible paths were envisioned for the latter reaction. Path I assumes that only ethylation would be observed if (1) alkyl exchange between $(C_2H_5)_3Al$ and the ketone–$Al(CH_3)_3$ is slow compared to ethylation and (2) methylation via intramolecular rearrangement of the $R_2C{=}O{\cdots}Al(CH_3)_3$ complex is slow compared to ethylation.[7] Reduction should not be possible via this scheme, since the organoaluminum compound possessing the β hydrogens is not complexed to the carbonyl oxygen.[8]

The results in Table I indicate that redistribution of alkyl groups between $(C_2H_5)_3Al$ and ketone–$Al(CH_3)_3$ complex occurs much faster than alkylation. In these reactions methylation, ethylation, and reduction all occur to a significant extent and in about the same ratios as alkylations with the corresponding $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds.

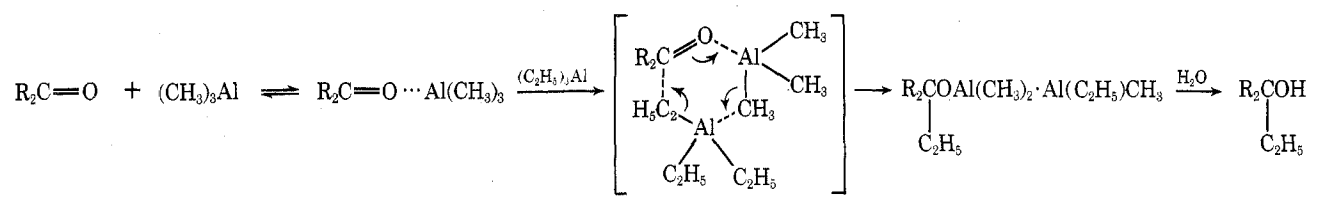
Several other interesting facts are demonstrated by the data in Table I. First, in all cases of alkylation (methylation and ethylation) where the ratio of organoaluminum compound to ketone was 1:1, the predominant attack was from the equatorial side to give predominantly the axial alcohol (steric approach control), whereas when excess organoaluminum compound was employed the preferred attack was from the more hindered axial side, giving predominantly equatorial alcohol (compression effect). Second, while



axial alcohol equatorial alcohol

methyl and ethyl groups are transferred at about the same rate from $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds, statistical correction of the data to account for the methyl:ethyl ratio indicates that ethyl groups are transferred more rapidly than methyl groups when the organoaluminum:ketone ratio is 1:1, whereas methyl groups are transferred more rapidly than ethyl groups when excess organoaluminum compound is used. Third, the ethylation:reduction ratio is somewhat higher in alkylations with $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds than with triethylaluminum itself. For example, in a 1:1 reactant ratio, the ratio of ethylation to reduction is 1.7:1 for triethylaluminum and averages 2.3:1 for $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds, whereas employing excess organoaluminum compound the ethylation:reduction ratio is 2.8:1 for triethylaluminum and averages 3.6:1 for $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds. Finally, it should be pointed out that the ratio of axial to equatorial alcohol for the reduction reaction does not change significantly regardless of the organoaluminum compound employed. This re-

Path I. Redistribution Slow Compared to Ethylation



Path II. Redistribution More Rapid Than Ethylation

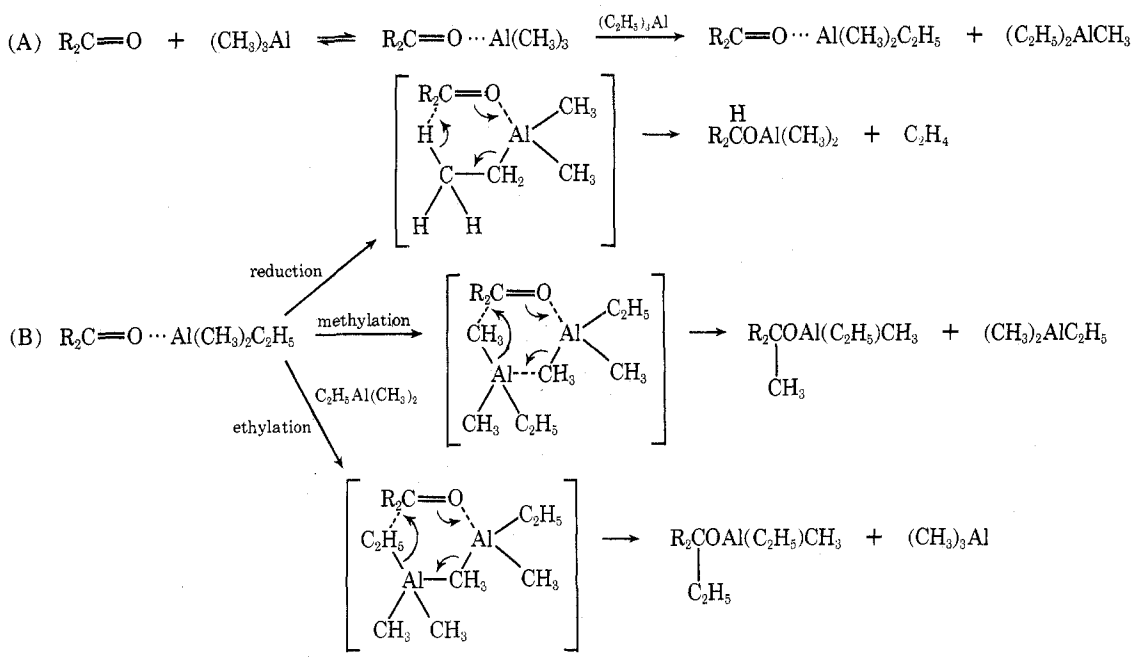


Table I
Reaction of $(C_2H_5)_3Al$ with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone–$Al(CH_3)_3$ Complex.[a] Reaction of $(C_2H_5)_3Al_2(CH_3)_3$, $(C_2H_5)_2AlCH_3$, and $C_2H_5Al(CH_3)_2$ with 4-*tert*-Butylcyclohexanone

Reagent	Substrate	Reagent concn, *M*	Reagent:substrate ratio	Methylation %			Ethylation %			Reduction %			Recovered[d] ketone, %
				Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial alcohol	
$(C_2H_5)_3Al$	Ketone	0.179	1.0				64	79	21	36	19	81	46
$(C_2H_5)_3Al$	Ketone	0.204	2.9				74	12	88	26	25	75	0
$(C_2H_5)_3Al$	Ketone–$Al(CH_3)_3$	0.094	1.0	54	31	71	37	35	65	9	23	77	6
$(C_2H_5)_3Al$	Ketone–$Al(CH_3)_3$	0.151	2.9	26	23	77	53	12	88	21	27	73	2
$(C_2H_5)_3Al_2(CH_3)_3$	Ketone	0.050	0.5	35	79	21	42	79	21	23	21	79	51
$(C_2H_5)_3Al_2(CH_3)_3$	Ketone	0.098	1.5	50	11	89	38	12	88	12	22	78	0
$C_2H_5Al(CH_3)_2$	Ketone	0.170	1.0	58	80	20	29	71	29	13	24	76	39
$C_2H_5Al(CH_3)_2$	Ketone	0.191	3.0	66	12	88	27	12	88	7	24	76	0
$(C_2H_5)_2AlCH_3$	Ketone	0.174	1.0	21	73	27	60	79	21	19	26	74	48
$(C_2H_5)_2AlCH_3$	Ketone	0.198	3.1	30	11	89	56	10	90	14	23	77	0

[a] Complexes formed by $(CH_3)_3Al$ addition to ketone followed in 10–20 sec by addition of $(C_2H_5)_3Al$. [b] Normalized as % methylation alcohols + % ethylation alcohols + % reduction alcohols = 100%. [c] Normalized as % axial alcohol + % equatorial alcohol = 100%. [d] Normalized as % total alcohol + % ketone = 100%.

Table II
Reaction of $(CH_3)_3Al$ with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone–$AlCl_3$ Complex. Reaction of $(CH_3)_3Al_2Cl_3$, $(C_2H_5)_3Al_2Cl_3$, $(CH_3)_2AlCl$, and $(C_2H_5)_2AlCl$ with 4-*tert*-Butylcyclohexanone

Reagent	Substrate	Reagent concn, *M*	Reagent:substrate ratio	Alkylation %			Reduction %			Recovered[c] ketone, %
				Total[a]	Axial[b] alcohol	Equatorial[b] alcohol	Total[a]	Axial[b] alcohol	Equatorial[b] alcohol	
$(CH_3)_3Al$	Ketone–$AlCl_3$	0.182	0.98	100	10	90	0			76
$(CH_3)_3Al$	Ketone–$AlCl_3$	0.202	1.94	100	11	89	0			11
$(C_2H_5)_3Al$	Ketone–$AlCl_3$	0.193	1.00	0			100	19	81	56
$(C_2H_5)_3Al$	Ketone–$AlCl_3$	0.214	2.00	17	20	80	83	28	72	8
$(CH_3)_3Al_2Cl_3$	Ketone	0.113	0.50	100	54	46	0			77
$(CH_3)_3Al_2Cl_3$	Ketone	0.127	1.00	100	13	87	0			52
$(CH_3)_2AlCl$	Ketone	0.217	1.00	100	56	44	0			69
$(CH_3)_2AlCl$	Ketone	0.244	2.00	100	9	91	0			15
$(C_2H_5)_3Al_2Cl_3$	Ketone	0.115	0.50	35	57	43	65	27	73	80
$(C_2H_5)_3Al_2Cl_3$	Ketone	0.121	0.93	43	23	77	57	17	83	32
$(C_2H_5)_2AlCl$	Ketone	0.223	1.00	31	65	35	69	20	80	31
$(C_2H_5)_2AlCl$	Ketone	0.250	2.00	41	27	73	59	26	74	6

[a] Normalized as % alkylation alcohols + % reduction alcohols = 100%. [b] Normalized as % axial alcohol + % equatorial alcohol = 100%. [c] Normalized as % total alcohol + % ketone = 100%.

sult is consistent with the cyclic six-center transition state proposed for the reduction reaction.[8]

Table II illustrates the reactions of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ with 4-*tert*-butylcyclohexanone–$AlCl_3$ complex as well as the reactions of methyl- and ethylaluminum chloride with 4-*tert*-butylcyclohexanone. Addition of the organoaluminum compounds to the ketone–$AlCl_3$ complex leads to predominantly axial attack, indicating operation of the compression effect, as expected.

Compounds such as $(CH_3)_nAlCl_{3-n}$ and $(C_2H_5)_nAlCl_{3-n}$ alkylate with little discrimination in 1:1 aluminum alkyl:ketone ratio (steric approach control); however, alkylation takes place predominantly from the axial side in 2:1 ratio. The percentage of equatorial attack in 1:1 ratio is considerably less than that formed from the corresponding aluminum alkyls, whereas the percentage of axial attack in a 2:1 ratio is about the same as that formed from the corresponding aluminum alkyls.

One striking observation (Table II) is the large percentage of reduction product formed in reactions involving $(C_2H_5)_nAlCl_{3-n}$ compounds as compared to $(C_2H_5)_3Al$ (see Table I). This is consistent with the observation by Mole that in alkylation of benzophenone, the ethylation:reduction ratio greatly decreases when $(C_2H_5)_2AlC_6H_5$ is employed rather than $(C_2H_5)_3Al$.[6a] Thus, it appears that in compounds of the type $(C_2H_5)_nAlX_{3-n}$, the ethylation is enhanced when X is electron donating (CH_3), thus increasing the reactivity of the Al–C_2H_5 bond, whereas reduction is enhanced when X is electron withdrawing (Cl) as expected for groups that decrease the reactivity of the Al–C_2H_5 bond. Another interesting observation is that the addition of 2 mol of $(C_2H_5)_3Al$ to 1 mol of ketone–$AlCl_3$ complex gave 83% reduction. This result is sufficiently different from the addition of 2 mol of $(C_2H_5)_2AlCl$ to 1 mol of ketone (59% reduction) that a clear choice between paths I and II cannot be made in these cases.

Table III illustrates the reaction of $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone in the presence of $(CH_3)_2AlOC_3H_7$-*n*. Since dimethylaluminum alkoxides are formed during the course of alkylation of ketones by $(CH_3)_3Al$, it was of interest to observe the effect of this type of compound on the steric course of alkylation when present initially. Surprisingly, $(CH_3)_2AlOC_3H_7$-*n* alkylated the ketone in very small yield with predominantly equatorial attack (85%). Isomer ratios obtained from alkylations in the presence of $(CH_3)_2AlOC_3H_7$-*n* were essentially the same as those obtained with $(CH_3)_3Al$ alone. This result may appear surprising in view of the reports that $(CH_3)_2AlOR$ compounds

Table III
Reaction of $(CH_3)_2AlOC_3H_7$-*n* with 4-*tert*-Butylcyclohexanone. Reaction of $(CH_3)_3Al$ with 4-*tert*-Butylcyclohexanone in the Presence of $(CH_3)_2AlOC_3H_7$-*n* and with 4-*tert*-Butylcyclohexanone–$Al(C_6H_5)_3$ Complex

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Product isomer ratio[a]		Relative % yield[b]
				Axial alcohol	Equatorial alcohol	
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.158	1.0	85	15	5.2
$(CH_3)_2AlOC_3H_7$-*n*		0.172	2.0	86	14	10
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.088	1.0	78	32	49
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.122	2.0	14	86	100
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.141	3.0	10	90	100
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.044	1.0	36	64	0.6[c]
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.072	2.0	27	73	2.2[c]

[a] Methylation product. [b] Normalized as % ketone + % alcohols = 100%. [c] Methylation % as determined by an internal standard. The major product of these reactions is apparently phenylation.

Table IV
Reaction of $(CH_3)_2AlOC_3H_7$-*n* with 2-Methylcyclopentanone. Reaction of $(CH_3)_3Al$ with 2-Methylcyclopentanone in the Presence of $(CH_3)_2AlOC_3H_7$-*n* and with 2-Methylcyclopentanone–$Al(C_6H_5)_3$ Complex

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Product[a] of		Relative % yield[b]
				Trans attack	Cis attack	
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.185	1.0	Trace[c]		0
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.187	2.0	Trace[c]		0
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.096	1.0	53	47	50
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.129	2.0	34	66	75
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.147	3.0	18	82	100
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.046	1.0	32	68	2.7[d]
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.074	2.0	9	91	11[d]

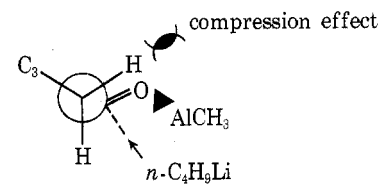
[a] Methylation or phenylation product. [b] Normalized as % alcohol + % ketone = 100%. [c] Cis alcohol predominates. [d] Methylation % as determined by an internal standard. The major product of these reactions is apparently phenylation.

form stable complexes with $(CH_3)_3Al$ of the type $(CH_3)_2AlOR{\cdot}Al(CH_3)_3$,[8,9] which renders $Al(CH_3)_3$ relatively unreactive.[8] However, Mole has pointed out that these complexes are formed in high yield only by addition of $(CH_3)_3Al$ to ketone in 2:1 ratio and are formed in very low yield by addition of $(CH_3)_3Al$ to a solution of $(CH_3)_2AlOR$.[9a] Also, $(CH_3)_2AlOC_3H_7$-*n* may have less tendency to complex $(CH_3)_3Al$ compared to those alkoxides previously studied.[9]

Table III also illustrates the reaction of $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone–$Al(C_6H_5)_3$ complex. In these reactions the equatorial alcohol (methylation) predominates (compression effect). The extremely small yield of methylation product indicates rapid exchange with ketone–$Al(C_6H_5)_3$ to give compounds of the type $(CH_3)_n$-$Al(C_6H_5)_{3-n}$ (path II). Mole has shown that reaction of $(CH_3)_2AlC_6H_5$ with benzophenone yields triphenylcarbinol as the exclusive product;[6a] thus the major product of the reaction via path II is expected to arise via phenylation.

Table IV illustrates the results of the reaction of 2-methylcyclopentanone with the same reagents employed in Table III. The results are analogous.

Table V illustrates the reactions of *n*-butyllithium with 4-*tert*-butylcyclohexanone and with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$, –$Al(C_6H_5)_3$, and –$AlCl_3$ complexes in hydrocarbon solvent. It was expected that attack on the complexes might lead to a compression effect, yielding a high



degree of axial attack by the butyl group. Reaction of *n*-butyllithium with 4-*tert*-butylcyclohexanone in all ratios in the presence or absence of $(CH_3)_2AlOC_3H_7$-*n* gave about 66% equatorial attack (steric approach control).

Reaction of *n*-butyllithium with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ and –$Al(C_6H_5)_3$ complexes at 1:1 and 3:1 lithium alkyl:complex ratios gave about 80% equatorial attack. Thus, contrary to expectation, axial attack was even less favored in the presence of the complexing agents. These reactions were characterized by the immediate formation of a precipitate upon addition of the n-C_4H_9Li solution to the complex, suggesting that the reaction may have proceeded via ate complex formation ($LiAlR_3C_4H_9$-*n*) followed by alkylation of the ketone. However, the results shown in Table V indicate that this explanation cannot be the case. For example, when n-C_4H_9Li was added to $(CH_3)_3Al$–ketone complex in a 1:1 ratio the methylation: butylation ratio was 18:82 and the percent axial alcohol (butylation) was 79%, whereas when a suspension of $LiAl(CH_3)_3C_4H_9$-*n* was stirred overnight with ketone in a

Table V
Reaction of *n*-Butyllithium with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone–$AlCl_3$, $-Al(CH_3)_3$, and $-Al(C_6H_5)_3$ Complexes[a] in Benzene–Hexane. Reaction of $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* with 4-*tert*-Butylcyclohexanone in Benzene–Hexane

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Methylation %			Butylation %			Reduction %			Recovered[d] ketone, %
				Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	
n-C_4H_9Li	Ketone	0.149	1.04				100	67	33	0	0	0	8.2
n-C_4H_9Li	Ketone	0.369	3.02				100	63	37	0	0	0	1.3
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.149	1.04	1.5	75	25	98.5	70	30	0	0	0	10.5
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.369	3.02	1.1	80	20	98.9	65	35	0	0	0	4.1
n-C_4H_9Li	Ketone–$Al(CH_3)_3$	0.155	1.03	18	53	47	82	79	21	Trace			8.0
n-C_4H_9Li	Ketone–$Al(CH_3)_3$	0.382	3.03	9.7	68	32	90.3	81	19	0	0	0	5.5
n-C_4H_9Li	Ketone–$Al(C_6H_5)_2$	0.053	0.96					81	19	0	0	0	*d*
n-C_4H_9Li	Ketone–$Al(C_6H_5)_3$	0.155	3.04					77	23	0	0	0	*d*
n-C_4H_9Li	Ketone–$AlCl_3$	0.263	1.00				35	67	33	65	40	60	42
n-C_4H_9Li	Ketone–$AlCl_3$	0.452	1.97				60	65	35	40	33	77	16
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.156	1.05	86	43	57	14	65	35	Trace	0	0	37
$LiAl(C_6H_5)_3C_4H_9$-*n*	Ketone	0.052	1.06					65	35		34	66	*d*

[a] Complexes formed by organoaluminum reagent to ketone followed in 10–20 sec by addition of n-C_4H_9Li. [b] Normalized as % methylation alcohols + % butylation alcohols + % reduction alcohols = 100%. [c] Normalized as % axial alcohol + % equatorial alcohol = 100%. [d] Normalized as % total alcohol products + % ketone = 100%. % phenylation not directly determined.

Table VI
Reaction of *n*-Butyllithium with 2-Methylcyclopentanone and Complexes[a] of 2-Methylcyclopentanone with $(CH_3)_3Al$ and $(C_6H_3)_3Al$ in Benzene–Hexane. Reaction of $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* in Benzene–Hexane

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Butylation %			Methylation + reduction %	Recovered[d] ketone, %
				Total[b]	Trans[c] attack (cis alcohol)	Cis[c] attack (trans alcohol)		
n-C_4H_9Li	Ketone	0.172	1.05	100	87	13		18
n-C_4H_9Li	Ketone	0.416	3.04	100	78	22		6.2
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.172	1.05	100	82	18	Trace	12.0
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.416	3.04	100	80	20	0	20.0
n-C_4H_9Li	Ketone–$Al(CH_3)_3$	0.179	1.03	95.7	86	14	4.3	17
n-C_4H_9Li	Ketone–$Al(CH_3)_3$	0.432	3.02	100	79	21	0	0.5
n-C_4H_9Li	Ketone–$Al(C_6H_5)_3$	0.056	.97		76	24	Trace redn	*d*
n-C_4H_9Li	Ketone–$Al(C_6H_5)_3$	0.155	3.02		77	23		*d*
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.177	1.04	90.3	78	22	9.7	50
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.058	1.00		80	20	Measurable redn	*d*

[a] Complexes formed by rapid addition of organoaluminum reagent to ketone followed by addition in 10–20 sec of n-C_4H_9Li. [b] Normalized as % methylation alcohol + % butylation alcohol + % reduction alcohol = 100%. [c] Normalized as % cis alcohol + % trans alcohol = 100%. [d] Normalized as % total alcohol products + % ketone = 100%. % phenylation not directly determined.

1:1 ratio the methylation:butylation ratio was 86:14 and the percent axial alcohol (butylation) was 65%. These results are far too different to suggest that alkylation occurred via the ate complex in both cases. Since the mechanism of addition of n-C_4H_9Li to ketone–AlR_3 complexes is not known, no judgment can be made as to why the observed isomer ratio is obtained.

Addition of n-C_4H_9Li to 4-*tert*-butylcyclohexanone–$AlCl_3$ complex gives large amounts of reduction as well as butylation. This result is presumably due to redistribution via path II to produce $(C_4H_9)_nAlCl_{3-n}$ compounds, which would be expected to react predominantly as reducing agents. This was the only case where a significant amount of reduction occurred except for addition of $LiAl(C_6H_5)_3C_4H_9$-*n* to ketone. These reactions all give the same ratio of axial to equatorial alcohol (butylation) as did simple addition of n-C_4H_9Li to ketone. Reactant ratio did not appear to be a factor in the observed isomer ratio obtained in any of these reactions.

Table VI illustrates the reaction of 2-methylcyclopentanone with the reagents described in Table V. In every case the percent axial alcohol formed was ~80%. Thus, n-C_4H_9Li attacking ketone or complex and ate complex attacking ketone gave essentially identical results. It is interesting that in the reaction of $LiAl(CH_3)_3C_4H_9$-*n*, 90% of the reaction proceeds via butylation and <10% via methylation, whereas in the case of reaction with 4-*tert*-butylcyclohexanone, 86% methylation and only 14% butylation were observed.

Registry No.—$(C_2H_5)_3Al$, 97-93-8; $(C_2H_5)_3Al_2(CH_3)_3$, 54617-81-1; $(C_2H_5)_2AlCH_3$, 13197-84-7; $C_2H_5Al(CH_3)_2$, 13197-83-6; $(CH_3)_3Al$, 75-24-1; $(CH_3)_3Al_2Cl_3$, 15455-52-4; $(C_2H_5)_3Al_2Cl_3$, 12075-68-2; $(CH_3)_2AlCl$, 1184-58-3; $(C_2H_5)_2AlCl$, 96-10-6;

$(CH_3)_2AlOC_3H_7$-*n*, 54549-33-6; $LiAl(CH_3)_3C_4H_9$-*n*, 54549-40-5; $LiAl(C_6H_5)_3C_4H_9$-*n*, 54549-45-0; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclopentanone, 1120-72-5; *n*-butyllithium, 109-72-8; 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$, 54549-41-6; 4-*tert*-butylcyclohexanone–$Al(C_6H_5)_3$, 54549-44-9; 2-methylcyclopentanone–$Al(C_6H_5)_3$, 54549-43-8; 4-*tert*-butylcyclohexanone–$AlCl_3$, 54549-39-2; 2-methylcyclopentanone-$Al(CH_3)_3$, 54549-42-7.

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Abnormal Products Obtained during an Attempted Substitution of 3α,5-Cyclo-6β-methoxy-5α-23,24-bisnorcholan-22-ol Tosylate with a Grignard Reagent Involving γ,γ-Dimethylallyl Bromide

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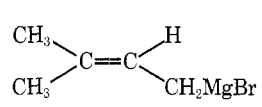
Attempted coupling of 6β-methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-yl tosylate (**2a**) with γ,γ-dimethylallyl bromide (**1**) in the presence of magnesium leads to the formation of 22,22′-bis-6β-methoxy-3α,5-cyclo-5α-bisnorcholanyl (**6**), a novel disteroid, and 3α,5-cyclo-5α-23,24-bisnorcholan-6β-yl methyl ether (**5**) rather than to the expected desmosterol derivatives. The formation of these products has been attributed to a common 22-bisnorcholanylmagnesium bromide intermediate which undergoes Wurtz-type coupling or is hydrolyzed to an alkane during work-up.

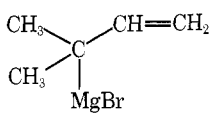
In our recently reported synthesis of desmosterol,[1] we tested the utility of allylic organometallics as synthons for construction of the steroid side chain. Recent communications[2,3] along similar lines prompted us to report the results of our experiments.

The chemistry of allyl Grignard and allyllithium reagents has been well documented.[4,5] Notable problems associated with the use of these reagents are self-coupling and allylic rearrangements of the Grignard reagents, which leads to mixtures of isomeric products. Unsymmetrical allylic Grignard reagents react with unhindered electrophilic substrates, such as carbonyl compounds[6] and epoxides,[7,8] to afford branched products. Less branched carbinols are preferentially formed, however, in reactions with relatively hindered ketones. This phenomenon, as suggested by Felkin and coworkers,[9,10] is due to the differences in the steric strain in the two possible allylic transition states.

A NMR study of γ,γ-dimethylallylmagnesium bromide[11] has indicated that the reagent exists as a rapidly equilibrating pair of classical structures (**1a** and **1b**) with the



1a



1b

equilibrium well on the side of form **1a**. Reaction of **1** with carbon dioxide[12] and with cyclohexanone[5] has been reported to give a tertiary acid and a tertiary carbinol, respectively, suggesting the predominance of form **1b**. γ,γ-Dimethylallyllithium, however, when treated with an equimolar amount of the allylic bromide in a cross-coupling reaction, gives rise to mixtures[5] of direct and transposed products with allylic transposition limited to the allylic portion derived from either **1a** or **1b**.

It was therefore of interest to determine whether 3α,5-cyclo-22-tosyloxy-5α-23,24-bisnorcholan-6β-ol 6-methyl ether (**2a**) could be successfully substituted with the allyl Grignard reagent **1**. Coupling of aryl Grignard reagents with alkyl sulfates and sulfonates is well known and has been reviewed by Kharasch.[13] Earlier, it was observed that the tosylate **2** could be easily displaced with sodium iodide[1,3] or with sodium salts of activated methylene compounds.[14] Recently it has been also shown[3] that the tosylate **2** undergoes a smooth nucleophilic displacement with the lithium salt of 3-methyl-1-butyn-3-ol tetrahydropyranyl ether. Our specific interest in the attempted allyl Grignard reaction, however, was to examine the reaction products for the presence of compound **3** and the product of allylic transposition **4**. The latter was envisaged as a key intermediate for the preparation of 23,23-dimethylcholesterol, a substance desirable to us for biological oxidation studies.

The coupling experiment was carried out under the conditions described by Seyferth[15,16] for magnesium-induced condensation of triphenyltin chloride with allyl bromide. The reaction mixture was separated by column chromatography, but none of the products could be identified as the expected structures **3** or **4**. Instead, two crystalline steroidal products differing in their respective mobility on thin layer chromatography were isolated.

The less polar product showed infrared spectral bands at 1090, 1010, and 970 cm^{-1}, indicating the presence of a 6-methoxy *i*-steroid moiety. This was supported by the appearance of signals at 3.32 (3 H), 2.77 (1 H), and broad multiplets at 0.33–0.67 ppm in the NMR spectrum, confirming the presence of a methyl ether residue, 6α-H, and cyclopropyl hydrogens, respectively. The other characteristic methyl proton signals, besides the two singlets at 0.72 (3 H) and 1.01 (3 H) ppm due to 18- and 19-methyls, were three sharp peaks at 0.78, 0.89, and 0.99 ppm (J = 6 Hz, 6 H). The latter three signals would seem to represent a pair of overlapping doublets for two methyls which could be due to 21 and 22 secondary methyls. This speculation was con-