6 *N* hydrochloric acid. Methanol (200 ml) was added and the mixture was stirred at 50° for 2 hr. The solid remaining after evaporation of the methanol was taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31a** obtained by evaporating the dried ($MgSO_4$) solution amounted to 9.1 g (>100%). Recrystallization from 70 ml of acetonitrile yielded 5.25 g (63%) of white needles: mp 180–188°; $[\alpha]^{25}D$ −52.5°; ir (KBr) 1774 cm^{-1}; nmr δ 1.00, 1.07 (d, C-18). C-18 peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.74; H, 7.74. Found: C, 80.97; H, 7.86.

A second crop of **31a** was obtained from 150 ml of ethanol amounting to 1.80 g (22%), mp 160–164°, with C-18 peak heights at δ 1.00 and 1.07 in the ratio 1:1.7. The combined yield amounted to 7.05 g (85%).

2. Isomerization of 31a with Potassium *tert*-Butoxide.—To a solution of 0.70 g (5 × 3.6 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 1.50 g (3.6 mmol) of **31a** with C-18 nmr peaks at 60 and 64 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 16 hr, the cooled mixture was acidified with 2.1 g (10 × 3.6 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. Trituration with 15 ml of ethanol yielded 1.10 g (73%) of isomerized **31a**, mp 153–155°, with C-18 nmr peaks at 61 and 65 Hz in the ratio 1:2.4.

3. 4′-Cyclohexyl-4′,5′-dihydro-3-methoxy-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (31b).—Metalated cyclohexylacetic acid was prepared on a 60-mmol scale as a heterogeneous mixture in 150 ml of THF following general procedure B. A solution of 6.0 g (20 mmol) of **18** in 25 ml of THF was added and the stirred mixture was warmed to 45–50° for 18 hr.

At the conclusion of the reaction period, 150 ml of water and 100 ml of hexane were added to the homogeneous solution. The aqueous layer was separated and the reaction flask and organic layer were washed with a mixture of 100 ml of water and 100 ml of ether. The aqueous layers were combined, back-extracted with 100 ml of ether, and acidified with excess 6 *N* hydrochloric acid. Methanol (200 ml) was added and the warm (50°) mixture was stirred for 2 hr. The solids remaining after removal of the methanol were taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31b** obtained by evaporating the dried ($MgSO_4$) solution amounted to 7.5 g (89%). Recrystallization from ethanol gave white needles: mp 143–146°; $[\alpha]^{25}D$ −16.3°; ir (KBr) 1768 cm^{-1}; nmr δ 0.92, 0.98 (d, C-18). The peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.60; H, 8.80.

4. Isomerization of 31b with Potassium *tert*-Butoxide.—To a solution of 1.0 g (5 × 5 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 2.1 g (5 mmol) of **31b** with C-18 nmr peaks at 55 and 59 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 18 hr, the cooled solution was acidified with 3.0 g (50 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. The pooled crystalline fractions obtained by eluting an alumina column with hexane–benzene amounted to 2.0 g (95%). The pooled material showed C-18 nmr peaks at 55 and 59 Hz in the ratio 1:4.3. The sample displayed mp 143–147° after recrystallization from 90% acetic acid: $[\alpha]^{25}D$ −14.7°; ir (KBr) 1770 cm^{-1}; nmr δ 1.08, 1.15 (d, C-18); peak height ratio, 1:9.4.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.58; H, 8.90.

Registry No.—**2**, 847-75-6; **2** acetate, 34414-55-6; **3a**, 19605-33-5; **3b**, 31552-58-6; **4a**, 19605-34-6; **4b**, 34414-59-0; **5a**, 34414-60-3; **5b**, 34414-61-4; **5c**, 16387-03-4; **5d**, 13934-61-7; **5e**, 34414-64-7; **5f**, 34414-65-8; **5g**, 34414-66-9; **5h**, 34414-67-0; **6a** (M^+ = Li^+), 31509-80-5; **8a**, 34414-69-2; **8b**, 34414-70-5; **8c**, 34414-71-6; **8d**, 976-70-5; **8e**, 34414-73-8; **8f**, 34440-55-6; **9a**, 34440-56-7; **9b**, 34440-57-8; **9c**, 34440-58-9; **10a**, 34440-59-0; **10b**, 34440-60-3; **10c**, 34440-61-4; **12**, 34440-62-5; **13**, 34440-63-6; **14a**, 34440-64-7; **14b**, 18290-18-1; **14c**, 34440-66-9; **15**, 34440-67-0; **16a**, 18290-22-7; **16b**, 34427-52-6; **17**, 20929-21-9; **22**, 34440-70-5; **23**, 34440-71-6; **24**, 34440-72-7; **25**, 34440-73-8; **26**, 34440-74-9; **27**, 20215-55-8; **29**, 34440-76-1; **30**, 34440-77-2; 21*R*-**3a**, 34440-78-3; 21*S*-**31a**, 34440-79-4; 21*R*-**31b**, 34440-80-7; 21*S*-**31b**, 34440-81-8; acetic acid, 64-19-7; lithium diisopropylamide, 34440-82-9.

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Stereoselective Alkylation Reactions. I. Organomagnesium and Organoaluminum Addition to 4-*tert*-Butylcyclohexanone. Unusual Stereoselectivity Involving Trimethylaluminum Alkylation in Benzene

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The stereochemistry of addition of methylmagnesium and methylaluminum compounds to 4-*tert*-butylcyclohexanone in several solvents has been studied. Specifically methylmagnesium fluoride, chloride, bromide, and iodide, dimethylmagnesium, and trimethylaluminum were allowed to react with 4-*tert*-butylcyclohexanone in hexane, benzene, diethyl ether, tetrahydrofuran, diphenyl ether, and triethylamine. Reactions involving organomagnesium compounds and trimethylaluminum in diethyl ether and tetrahydrofuran results in predominant equatorial attack to form the axial alcohol product (~73%) regardless of the halide and the mode of addition. In reactions involving trimethylaluminum in hydrocarbon solvent where the $(CH_3)_3Al$:ketone ratio is 1:1, similar results are observed. However, when the ratio is 2:1 or greater a drastic reversal of the stereochemistry is observed resulting in predominant axial attack to form the equatorial alcohol (~90%). The mechanism and stereochemistry of these reactions are discussed.

The steric course of organometallic alkylation and metal hydride reduction reactions involving cyclic ketones is a very fundamental problem in organic chemistry which does not seem to be well understood. It was originally proposed by Dauben and coworkers[1] that the course of hydride reduction reactions is de-

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termined primarily by the relative stabilities of the two isomeric products in the absence of significant steric influence involving the attacking reagent on the substrate. However, when steric influences are sufficiently large, the reaction path can change from axial attack to equatorial attack, producing the less stable isomer. These reaction paths are termed "product development control" and "steric approach control," respectively. As shown in Table I, for addition reactions involving

TABLE I

ADDITION REACTIONS TO 4-*tert*-BUTYLCYCLOHEXANONE[a]

Reagent	A[b]	Axial alcohol, %
$LiAlH_4$	0	8[c]
$LiAlH[OC(CH_3)_3]_3$	0	10[d]
HCN	0.17	10[e]
HC≡CH	0.18	11[f]
CH_2=$CHCH_2MgBr$		48[g]
CH_3MgBr	1.70	60[h]
C_2H_5MgBr	1.75	69[i]
n-C_3H_7MgBr		74[g]
$(CH_3)_2CHMgBr$	2.15	82[i]
$(CH_3)_3CMgCl$	>4.2	100[i]

[a] In $(C_2H_5)_2O$ except for $LiAlH[OC(CH_3)_3]_3$, HCN, and HC≡CH. [b] See ref 2. [c] See ref 3. [d] See ref 4. [e] See ref 5. [f] See ref 6. [g] See ref 7. [h] See ref 8a. [i] See ref 8b.

4-*tert*-butylcyclohexanone the relative amount of the trans alcohol obtained from equatorial attack increases as the size of the entering groups increases.[2-8]

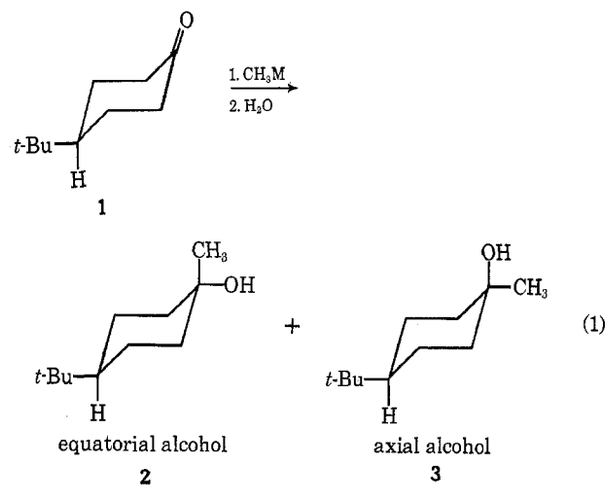
An alternate explanation based on pure steric approach has been suggested.[4] For a small entering group which does not interfere with the 3,5 axial substituents, the reaction will be directed exclusively by the 2,6 axial substituents, which hinder equatorial attack. However, as the size of the entering group becomes larger, the interactions with 3,5 axial substituents increase and the reaction proceeds in favor of equatorial attack. This proposal was later supported and advanced by a consideration of the transition-state geometry.[9] The relative magnitudes of the interaction of 3,5 and 2,6 axial substituents with the entering group is purely based on the transition-state bond lengths; *i.e.*, the extent of axial attack will increase as the bond distance decreases. Therefore, the greater domination by the 3,5 axial substituents in the case of Grignard alkylation reactions can be rationalized on the basis that the transition state for the addition of a Grignard reagent occurs at a greater distance from the carbonyl carbon than the analogous addition of the hydride.

Later, the relative magnitudes of "torsional strain" with respect to equatorial attack and of "steric strain" with 3,5 axial substituents with respect to axial attack in the reactantlike transition state were claimed to be the major factors controlling the stereochemistry of hydride reduction and alkylation reactions.[7] In the reactions between hydrides and unhindered cyclohexanones, the "steric strain" in axial attack is expected to be smaller than the "torsional strain" in equatorial attack; therefore the predominant alcohol is the equatorial one from axial attack. However, as the "effective bulk" of the entering groups or the 3,5 axial substituents become larger, the situation is reversed. It has also been pointed out that the "effective bulk" of the entering reagent depends not only on the "intrinsic bulk" but also on solvation, the bond distance in the transition state, and the mechanism of the reaction.

Although organometallic alkylation reactions have found extensive applications in synthesis, this type of reaction has attracted much less attention in comparison with metal hydride reduction reactions with respect to stereochemical studies. In view of the recent better understanding of both the composition of organometallic compounds in solution and the mechanisms of organometallic alkylation reactions, we feel that a better understanding of the stereochemistry of such reactions is now possible.

An ideal system for investigating the stereochemistry of organometallic alkylation reactions involves the reaction of 4-*tert*-butylcyclohexanone (**1**) with trimethylaluminum and methyl Grignard reagents. Studies involving Grignard reagents are desirable because of the wide scope and versatility of these reagents, and studies involving trimethylaluminum are desirable since this reagent is soluble in both ether and hydrocarbon solvents and thus solvent effects can be evaluated.

As shown in eq 1, the reaction gives a mixture of the



equatorial and axial alcohols. Since alkylation reactions involving trimethylaluminum can give no reduction product and involve reaction of only one of the methyl groups,[10,11] results involving this compound should provide the least complicated data. Furthermore, the mechanisms of trimethylaluminum addition to ketones are well understood both in benzene[10] and in diethyl ether.[11] This reaction is known to proceed *via* two distinct mechanistic paths depending on the ratio of $(CH_3)_3Al$ to ketone. At 1:1 ratio the reaction is first order in $(CH_3)_3Al$ and is presumed to proceed *via* a four-center transition state, whereas at 2:1 ratio (or greater) the reaction is second order in $(CH_3)_3Al$ and is presumed to proceed *via* a six-center transition state.

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TABLE II
REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH TRIMETHYLALUMINUM

Solvent	Expt	$(CH_3)_3Al$/ketone	Concn of $(CH_3)_3Al$, *M*	Time	Recovery of ketone, %	Total yield of alcohol products, %	Yield of axial alcohol, %[a]
Benzene	1	3.00	0.475	1.0 hr	0	89	12[d]
Benzene	2	3.00	0.475	2.0 hr	0	87	17
Benzene	3	2.00	0.448	2.0 hr	0		17
Benzene	4	1.50	0.405	2.0 hr	34		53
Benzene	5	1.00	0.369	2.0 hr	48		73
Benzene	6	1.00	0.0224	2.0 hr	58		74
Benzene	7	1.00	1.205	2.0 hr	44		56
Benzene	8	0.50	0.278	2.5 hr	75		80
Hexane	9	4.50	0.54	2.0 hr	0	90	9
$(C_6H_5)_2O$[c]	10	3.08	0.329	6 days	0	99	15
$(C_6H_5)_2O$	11	1.54	0.269	5 days	3	70	26
$(C_6H_5)_2O$	12	1.03	0.228	6 days	23	56	53
$(C_6H_5)_2O$	13	0.79	0.176	4 min	49	39	72
				5 days	33	37	72
$(C_6H_5)_2O$	14	0.49	0.116	6 days	21	30	72
THF	15	3.02	0.211	3 days	53	12	74
				38 days	20	16	73
THF	16	2.94	0.308	3 days	55	15	74[c]
THF	17	1.03	0.164	3 days	55	10	72[c]
THF	18	1.00	0.176	3 days	53	8	73
THF	19	0.50	0.042	16 days	35	5	73
				38 days	26	7	73
$(C_2H_5)_2O$[c]	20	3.01	0.329	4 days	38	40	75
$(C_2H_5)_2O$	21	0.51	0.141	4 days	20	23	74
$(C_2H_5)_3N$[c]	22	3.08	0.329	6 days	31	0	*b*
$(C_2H_5)_3N$	23	1.03	0.228	6 days	19	0	*b*
$(C_2H_5)_3N$	24	0.49	0.116	6 days	21	0	*b*

[a] Normalized per cent: per cent trans + per cent cis = 100. [b] No measurement was made. [c] The reactions were carried out using benzene solutions of $(CH_3)_3Al$ and ketone containing the polar solvent. [d] Ketone added to $(CH_3)_3Al$.

In addition, numerous stereochemical addition studies[8,12] have already been carried out using ketone **1**, which should make the present studies easier to interpret. Although the importance of the solvent involved in these reactions is well recognized, it is surprising that systematic studies of the solvent effect on stereochemical addition are very limited. Therefore, the reaction of trimethylaluminum and ketone **1** in several selected solvents was undertaken. Since methylmagnesium fluoride has recently been prepared in this laboratory in tetrahydrofuran and shows unique properties,[13] it was decided to investigate the behavior of this particular reagent and other Grignard reagents toward 4-*tert*-butylcyclohexanone under the same conditions involving alkylation with trimethylaluminum. Since trimethylaluminum is known to react with ketones by two different mechanistic paths in benzene solvent, the determination and comparison of equatorial to axial alcohol ratios obtained *via* each mechanistic path and further comparison with ratios found for Grignard reagent alkylation was considered to be most important.

Experimental Section

Materials.—Trimethylaluminum was obtained from Texas Alkyls, Inc., and was purified by distillation under vacuum through a 1-ft packed column, taking the center cut for the present studies. 4-*tert*-Butylcyclohexanone (Frinton) was distilled under vacuum and its purity was estimated by glpc to be at least 99.9%. Tetradecane (99.9% pure, Chemical Samples Co.) was used as an internal standard in the glpc analyses. Methylmagnesium fluoride was prepared as described previously.[13a] Clear and colorless solutions of methylmagnesium chloride and bromide were prepared by reaction of methyl halides with magnesium turnings (doubly sublimed, Dow Chemical Co.) in tetrahydrofuran. Dimethylmagnesium was prepared from the corresponding mercury compound by reaction with magnesium metal.[14] Benzene, hexane, diethyl ether, tetrahydrofuran (THF), diphenyl ether, and triethylamine were distilled from lithium or sodium aluminum hydride prior to use.

Analyses.—The concentrations of trimethylaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis. Aluminum analysis was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. The concentrations of Grignard reagent solutions were determined by hydrolysis of an aliquot followed by magnesium analysis. Magnesium analysis was carried out by EDTA titration at pH 10 using Eriochrome Black T as an indicator.

Glpc analyses were performed using 6-ft matched columns of 10% FFAP on 80–100 mesh Diatoport S. The identity of the peaks was determined by comparison of the hydrolyzed products formed on reaction of ketone **1** with methyllithium and methylmagnesium bromide.[12d] Under the conditions of rate 55 ml/min, injection temperature 200°, and detector temperature 310°, the retention times for tetradecane, cis alcohol, ketone, and trans alcohol are 12, 28, 31, and 36 min at a column temperature of 80°. The two alcohols are known to have the same response ratio.[15] In no case was the presence of 1-methyl-4-*tert*-butylcyclohexanone (from the dehydration of the alcohols) detected.[12d] The amount of the recovered ketone was calculated from the area ratio of ketone to internal standard before and after the reaction.

Reactions.—All the reactions were carried out under a nitrogen atmosphere and the glassware was flash flamed and flushed with nitrogen prior to use. The standard solutions of trimethylaluminum and 4-*tert*-butylcyclohexanone in benzene and in THF

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TABLE III
REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH METHYLMAGNESIUM COMPOUNDS

Reagent	Expt	Solvent	CH_3MgX/ ketone	Concn of CH_3MgX, *M*	Time, hr	Recovery of ketone, %	Total yield of alcohol products, %	Yield of axial alcohol, %[a]
$(CH_3)_2Mg$	25	THF	3.04	0.25	20	2	98	74
$(CH_3)_2Mg$	26	THF	3.04	0.25	20	2	85	75[b]
$(CH_3)_2Mg$	27	THF	0.52	0.06	0.2	75	19	74
					20	53	18	74
$(CH_3)_2Mg$	28	$(C_2H_5)_3N$	1.49	0.10	8	20	56	76
$(CH_3)_2Mg$	29	$(C_2H_5)_3N$	0.55	0.08	1	34	39	76
					8	23	40	77
$(CH_3)_2Mg$	30	Benzene	3.50	0.96	0.5	27	52	72
			0.47	0.15	0.5	48	32	68
CH_3MgF	31	THF	3.2	0.61	20	1	92	73
	32	THF	0.53	0.17	20	55	29	74
CH_3MgBr	33	THF	2.8	0.37	20	0	97	70
	34	THF	0.47	0.10	20	42	26	72
CH_3MgCl	35	THF	3.0	0.49	20	1	100	71
	36	THF	0.52	0.23	20	29	37	71

[a] Normalized per cent: per cent trans + per cent cis = 100. [b] With the addition of 5% of $CoCl_2$.

were stored in a heavy-walled glass bulb sealed with a three-way Teflon stopcock. The reactions were carried out in 15-ml bottles fitted with a rubber septum cap.

The following standard procedure will serve to illustrate the reactions in benzene. A 1.6-ml standard benzene solution of trimethylaluminum (0.985 *M*, 1.58 mmol) was added *via* a syringe into a bottle containing 3 ml of benzene and 1 ml of standard benzene solution of ketone 1 (0.479 *M*, 0.479 mmol) with internal standard at 25°. After the reaction was completed, the solution was cooled in an ice bath and slowly hydrolyzed with 2 ml of saturated ammonium chloride solution. Analysis was carried out by glpc as previously described. The reactions of methylmagnesium compounds were carried out in a similar fashion.

Results

The results of the reactions of 4-*tert*-butylcyclohexanone with trimethylaluminum and methylmagnesium compounds are summarized in Tables II and III. The following observations can be noted by examination of the tables.

1. The stereochemical results of the reactions of trimethylaluminum in benzene and in diphenyl ether are dependent on the ratio of trimethylaluminum to ketone. The amount of axial alcohol decreases from 80% to 12% in benzene and from 72% to 15% in diphenyl ether as the $(CH_3)_3Al$ to ketone ratio increases. On the other hand, the stereochemical results in diethyl ether and tetrahydrofuran are independent of the $(CH_3)_3Al$ to ketone ratio and give a 72–74% yield of axial alcohol in both solvents. The reactions of $(CH_3)_3Al$ and ketone in triethylamine give no addition product.

2. The presence of a weakly coordinating solvent, such as benzene (runs 16 and 17), in the reaction of $(CH_3)_3Al \cdot THF$ with ketone, or addition of a free radical promoter, $CoCl_2$ (run 26), in the reaction of $(CH_3)_2Mg \cdot THF$ with ketone has no effect on the stereochemical results.

3. The stereochemical results of the reactions of methylmagnesium compounds in THF were also independent of the ratio of reactants and the yield of axial alcohol (71–75%) was essentially independent of the particular methylmagnesium compound used. Reaction of dimethylmagnesium with ketone in triethylamine gave results similar to those observed in THF.

4. The isomeric ratios in all reactions studied are independent of reaction time. Consequently, isomer equilibration is not a factor under the conditions of these reactions.

5. The reactions with excess methyl metallic compounds yield predominantly the alcohols with little enolization. However, the reactions with excess ketone and of trimethylaluminum in the more basic solvents appear to produce a considerable amount of higher molecular weight products from aldol condensation.[12b]

Discussion

The results of the present and previous studies concerning the stereochemistry of methyl metallic compound addition to 4-*tert*-butylcyclohexanone are summarized in Table IV. If a true understanding of these stereochemical results is to be forthcoming, one should consider in detail the mechanism of the alkylation reactions involved and the nature of the organometallic species present in solution.

Association of the Organometallic Alkylation Agent. — The composition of methyl metallic compounds in both hydrocarbon and ether solvents is reasonably well understood at the present time. Methyllithium is tetrameric in diethyl ether.[16] Methylmagnesium compounds are best represented by an equilibrium-type association (eq 2) in diethyl ether,[17] except methyl-

$$\text{trimer} \rightleftharpoons \text{dimer} \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \text{dimer} \rightleftharpoons \text{trimer} \quad (2)$$

magnesium fluoride[13b] and $CH_3MgOC(C_2H_5)_2CH_3$,[18] which are dimeric. All methylmagnesium halides and dimethylmagnesium are monomeric in tetrahydrofuran[17c] and triethylamine,[19] except methylmagnesium fluoride, which is dimeric in tetrahydrofuran.[13b] Trimethylaluminum is dimeric in benzene[20] and diphenyl ether,[21] is monomeric in diethyl ether,[22] and is

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TABLE IV

REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH METHYL METALLIC COMPOUNDS

Reagent	Registry no.	$(C_2H_5)_2O$ Association	$(C_2H_5)_2O$ Axial alcohol, %	THF Association	THF Axial alcohol, %
CH_3Li	917-54-4	4	64[a]		
$(CH_3)_2Mg$	2999-74-8	1–2[b]	65[c]	1	74
CH_3MgF	420-09-7			2	74
CH_3MgCl	676-58-4	2	59[d]	1	71
CH_3MgBr	75-16-1	1–2[b]	61[a,c]	1	71
CH_3MgBr		1–2[b]			
CH_3MgBr		1[e]	68[a]		
CH_3MgI	917-64-6	1–2[b]	54[a]		
CH_3MgI		1[e]	62[a]		
$CH_3MgOCCH_3(C_2H_5)_2$	13132-19-9	2	74[c]		
$(CH_3)_3Al$	75-24-1	1	75[f]	1	73
$(CH_3)_2Zn$	544-97-8	1	38–46[a]		
$(CH_3)_2Cd$	506-82-1	1	41–54[a]		

[a] See ref 12d. [b] Monomer ⇌ dimer equilibrium at the concentrations employed. [c] See ref 12b. [d] See ref 12a. [e] Monomeric at 0.1 *M*. [f] Namy, *et al.*,[12c] report 75% at 35°.

expected to be monomeric in tetrahydrofuran and triethylamine. Dimethylzinc and dimethylcadmium are monomeric in diethyl ether.[23]

Importance of the Alkylation Mechanism.—Three mechanisms of addition reactions of organometallic compounds with ketones have been proposed from kinetic studies. In spite of the fact that most organometallic compounds are associated in solution, it is believed that it is the monomeric species (eq 3) that

$$(CH_3M)_n \rightleftharpoons nCH_3M \qquad (3)$$

reacts with the ketone to form a complex **4** in a fast equilibrium step (eq 4).[10,24] The product is then formed either by a relatively slow intramolecular rearrangement of the complex or by a bimolecular attack,[25] both presumably *via* a cyclic four-center transition state **5** (mechanism A), by a relatively slow attack on the complex by a second molecule of monomeric organometallic species, presumably *via* a cyclic six-center transition state **6** (mechanism B), or by a single electron transfer mechanism involving free radical intermediates (mechanism C).

Compared to most organometallic alkylation reactions the mechanism of aluminum alkyl addition to ketones seems to be well understood. The reaction path in benzene is dependent on the ratio of reactants. The reaction proceeds entirely *via* mechanism A when the aluminum alkyl to ketone ratio is 1:1 or less and entirely *via* mechanism B when the aluminum alkyl to ketone ratio is 2:1 or greater.[10] However, the same reaction in diethyl ether proceeds *via* mechanism A independent of the ratio of reactants.[11] Since the reaction of organomagnesium compounds with ketones has proven to be very complex kinetically for a number of reasons, the mechanism has been the subject of considerable controversy for a number of years. Only recently have we determined unequivocally that this reaction is first order in the organomagnesium species.[26]

$$R_2C{=}O + CH_3M \overset{\text{fast}}{\rightleftharpoons} R_2C{=}O{\cdots}MCH_3 \qquad (4)$$

4

Mechanism A

$$R_2C{=}O{\cdots}MCH_3 \text{ or } R_2C{=}O + MCH_3 \xrightarrow{\text{slow}} \left[R_2C{=}O \rightarrow H_3C{-}M\right] \longrightarrow R_2C(CH_3){-}OM \qquad (5)$$

5

Mechanism B

$$R_2C{=}O{\cdots}MCH_3 + CH_3M \xrightarrow{\text{slow}} \left[R_2C(O{\rightarrow}M)(H_3C{-}M{\cdots}CH_3)\right] \longrightarrow R_2C(CH_3){-}OM + CH_3M \qquad (6)$$

6

Mechanism C

$$R_2C{=}O{\cdots}MCH_3 \longrightarrow R_2\dot{C}{-}OM + CH_3\cdot \longrightarrow R_2C(CH_3){-}OM \qquad (7)$$

7

Thus, this reaction does not proceed by mechanism B as originally thought.[27] The existence of mechanism C as a major pathway has been overruled at least in the cases where methyl Grignard reagents prepared from ultrapure magnesium metal[28] are allowed to react with excess benzophenone[26] in diethyl ether. Presumably when Grignard reagents prepared from triply sublimed magnesium or Grignard grade turnings,[28] ketones of low reduction potential,[29] or Grignard reagents capable of easy electron transfer, *e.g.*, *tert*-BuMgBr,[30] are used in the reaction, mechanism C can participate to a significant degree. Since mechanism C presumably represents a side reaction and not a major reaction pathway under the conditions of our studies, only

(23) K. S. Rao, B. P. Stoicheff, and R. Turner, *Can. J. Phys.*, **38**, 1516 (1960).

(24) R. Waack and M. A. Doran, *J. Amer. Chem. Soc.*, **91**, 2456 (1969).

(25) Kinetically it is impossible to distinguish between the reaction as proceeding *via* rearrangement of the complex (1) or by bimolecular attack (2): (1) K + G ⇌ C → P or (2) P ← K + G ⇌ C.

(26) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Amer. Chem. Soc.*, **93**, 4601 (1971).

(27) (a) A. Tuulmets, *Reakts. Sposobnost Org. Soedin.*, **6**, 854 (1969); (b) J. Koppel, L. Margua, and A. Tuulmets, *ibid.*, **5**, 1041 (1968); (c) E. C. Ashby, R. Duke and H. M. Neumann, *J. Amer. Chem. Soc.*, **89**, 1964 (1967).

(28) E. C. Ashby, F. W. Walker, and H. M. Neumann, *J. Chem. Soc. D*, 330 (1970).

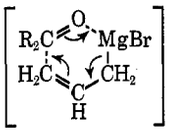
(29) J. F. Fauvarque and E. Rouget, *C. R. Acad. Sci., Ser. C*, 1355 (1971).

(30) T. Holm and I. Crossland, *Acta Chem. Scand.*, **25**, 59 (1971).

mechanism A[26,31] will be considered in discussions of reactions involving methyl Grignard compounds. Since the reactions of organolithium compounds with ketones are extremely fast, there are few reports concerning detailed mechanistic studies of this reaction and thus the mechanism still remains in doubt.

The results of this investigation are represented by the data in Table II. The reactions of $(CH_3)_3Al$ with ketone **1** in diethyl ether and THF give ~73% of the axial alcohol (equatorial attack) regardless of the ratio of alkylating agent to ketone. When the $(CH_3)_3Al$ to ketone ratio in benzene or diphenyl ether was 1:1 or less, similar results were observed (~80% axial alcohol). Likewise the reactions of $(CH_3)_2Mg$, CH_3MgF, CH_3MgCl, and CH_3MgBr in THF give similar results (~73% axial alcohol). On the other hand, the reaction of $(CH_3)_3Al$ in benzene or diphenyl ether with ketone **1** gives substantially different results (~88% equatorial alcohol or 88% axial attack) when the $(CH_3)_3Al$ to ketone ratio is 2:1 or greater.

The unusual stereochemical results found for the reaction of trimethylaluminum with 4-*tert*-butylcyclohexanone in benzene can be explained on the basis that the reaction had previously been shown to proceed by two distinct paths depending on the $(CH_3)_3Al$ to ketone ratio: *via* mechanism A under conditions of excess ketone and *via* mechanism B under conditions of excess aluminum alkyl. Thus, the two different mechanistic paths produce substantially different stereochemical results, namely 88% axial attack when the $(CH_3)_3Al$ to ketone ratio is 2:1 or greater (mechanism B) and 80% equatorial attack when the ratio is 1:1 or less (mechanism A). A previous report[7] concerning the stereochemistry of reactions of ketone **1** with similar "intrinsic bulk" reagents, allyl- and *n*-propylmagnesium bromide, showed that allylmagnesium bromide exhibited considerably more axial attack than the *n*-propyl compound, presumably because of the cyclic six-centered transition state **7**[32] possible in the



7

reaction of the allylic Grignard compound. In this reaction 52% of the equatorial attack (axial attack) is formed using allylmagnesium bromide whereas 26% is formed using *n*-propylmagnesium bromide (Table I). The actual reasons for the unusual stereochemical results obtained from the reactions *via* a six-centered transition state are subtle. However, one of the possible reasons involves the flexibility of the resulting six-centered transition state (**6** and **7**) resulting in a minimization of steric interactions. Thus, axial attack *via* **6** should be a lower energy pathway than that experienced *via* **5**, which is presumably the transition state involved in the reactions involving *n*-propylmagnesium bromide. Clarification of this latter point revolves about the following argument. The results obtained from the reactions of trimethylaluminum and methylmagnesium compounds in diethyl ether and tetrahydrofuran are independent of the ratio of reactants. Therefore, these reactions presumably proceed *via* only one mechanism. Furthermore, since the amount of trans alcohol obtained from these reactions is close to the 75% observed in the reaction of trimethylaluminum in diethyl ether, the present data indicate that the reaction of ketones with Grignard reagents proceeds *via* mechanism A in spite of the controversial results obtained from previous kinetic studies.[26,31]

The answer to the question as to why the six-centered transition produces substantially different stereochemical results than the four-centered transition can also be explained by a mechanism involving a transition state in which the cyclohexane ring is in the boat form. In the boat form, attack should take place preferentially at the position opposite to the flagpole hydrogen. When the ring flips back to the chair form, the alkyl group is in the axial position and the bulky $OAL(CH_3)_2$ group is in the more favorable equatorial position. We have recently determined E_a for the reaction of $(CH_3)_3Al$ with benzophenone in benzene in 1:1 ratio to be 19.2 kcal and in 2:1 ratio to be 10.9 kcal.[33] Assuming that the boat conformation in a cyclohexanone derivative is of somewhat lower energy (3–5 kcal) than a cyclohexane derivative (6 kcal) owing to the absence of 1–4 flagpole interactions, the proposal of a boat conformation is well within the existing energy considerations. There seems to be no preference at this time for either the chair or boat mechanism. It is believed that similar stereochemical studies using *cis*-3-methyl-4-*tert*-butylcyclohexanone should resolve this problem. With an axial 3-methyl group in the 4-*tert*-butylcyclohexanone system, axial attack should be deterred if the reaction proceeds through the chair conformation and should be relatively undisturbed if the reaction proceeds through the boat conformation. Work is in progress to distinguish between these two possibilities.

Importance of Solvent.—Before discussion of the importance of the solvent in determining the stereochemistry of organometallic alkylation reactions, the number of solvent molecules coordinated to the organometallic compound must be considered. Trialkylaluminum compounds have been investigated by nmr and found to coordinate to only 1 mol of solvent [THF, $(C_2H_5)_2O$, and $(C_2H_5)_3N$].[34] A sharp break in the curve produced on plotting chemical shift *vs.* mole fraction at 1:1 ratio in toluene was observed. Furthermore, the monoetherates of trimethylaluminum and diethyl ether or tetrahydrofuran are distillable under vacuum.[22] Organomagnesium compounds are normally coordinated with 2 mol of solvent, as reported by analysis, molecular weights,[35] and nmr[36] studies.

Unfortunately, the role of solvent in the addition reaction is usually neglected in the proposed mechanisms for the sake of simplicity. Recently, however, the importance of solvent in Grignard alkylation reactions has been discussed.[31d] Scheme I, using trimethylaluminum as the alkylating agent and S as the solvent

(31) (a) T. Holm, *ibid.*, **23**, 579 (1969); (b) J. Billet and S. G. Smith, *Tetrahedron Lett.*, 4467 (1969); (c) J. Billet and S. G. Smith, *J. Amer. Chem. Soc.*, **90**, 4108 (1968); (d) H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968); (e) S. G. Smith and J. Billet, *J. Amer. Chem. Soc.*, **89**, 6948 (1967).

(32) H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965).

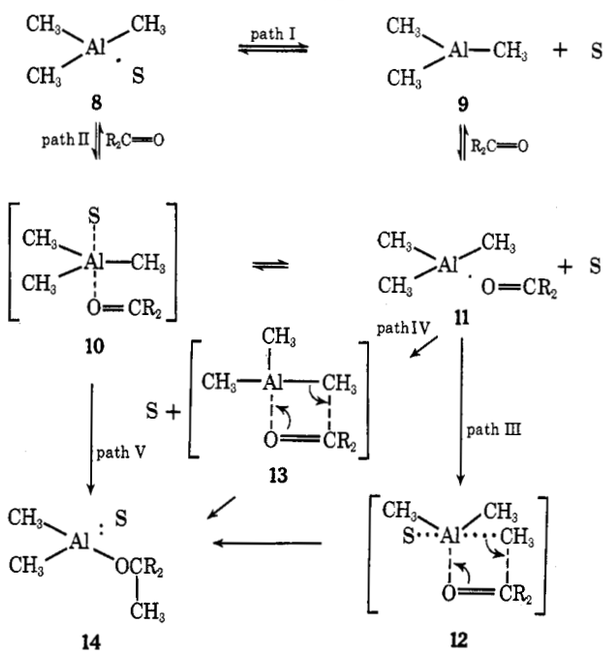
(33) E. C. Ashby and J. Laemmle, work in progress.

(34) Y. Takshi, *Bull. Chem. Soc. Jap.*, **40**, 612 (1967).

(35) G. E. Coates and J. A. Heslop, *J. Chem. Soc. A*, **26** (1966).

(36) J. Ducom, *C. R. Acad. Sci., Ser. C*, **268**, 1259 (1968).

SCHEME I

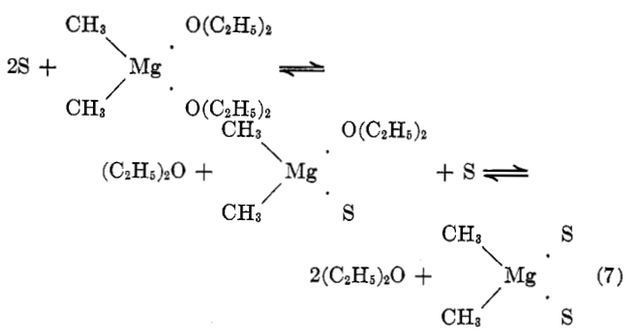


molecule, represents the possible reaction pathways involving alkylation reactions.

The solvent ligand can either be dissociated to form the tricoordinate intermediate **9**[37] (path I) or be displaced by the ketone *via* a pentacoordinate transition state **10** (path II) prior to the formation of the tetracoordinate complex **11**. The product **14** can be formed either with or without the presence of solvent in complex **11** by (1) rearrangement of the methyl group *via* a four-centered transition state involving pentacoordinate aluminum **12**[38] (path III) or (2) tetracoordinate aluminum **13** (path IV).

It appears reasonable to expect that the reaction path which requires the dissociation (path I) or the displacement (path II) of the ligand prior to formation of the complex will be retarded by the presence of a good donor solvent. Actually the decrease in reaction rate as the solvent basicity increases has been observed in the addition reagents of Grignard reagents to nitriles[39] and aluminum alkyls to ketones,[10,11] reduction of ketones with Grignard reagents,[40] abstraction of the acidic hydrogen atom from terminal acetylenes by Grignard reagents,[41] and exchange of alkyl groups between two different metal alkyls.[42]

The effect of solvent on the rate-determining product formation step *via* path III should be considered in some detail. For example, a strong donor solvent may accelerate the rate of alkyl transfer by assisting the dissociation of the carbon–metal bond in transition state **12**. However, in view of the rate retardation observed, if path III is followed, it is more likely that the nature of the ketone, the metal, and the alkyl group have a greater effect on the reaction rate than the solvent. However, the alternative possibility involving formation of a pentacoordinate transition state **10** without dissociation or displacement of the initial solvating ligand (path V) has been recently proposed from kinetic studies involving the reaction of benzophenone and dimethylmagnesium.[14e] Because the addition of monodentate ligands had little effect on reaction rate except on addition of a large excess of ligand and the addition of the bidentate ligands had a substantial effect either to accelerate or to retard the rate of addition reaction in diethyl ether, it was suggested that only the steric bulk properties of the ligand affects the reaction rate *via* transition state **10**. However, the same results can also be rationalized by mechanisms involving the loss of the initial solvating ligand. Equation 7 shows the exchange of ligands in a diethyl ether solution of dimethylmagnesium.



Since diethyl ether itself is a good donor ligand, the addition of a 1- to 2-fold excess of tetrahydrofuran (a better ligand) cannot shift the equilibrium completely to the right. However, since the equilibrium is expected to be very rapid, the reaction probably will proceed *via* the more active diethyl etherate species. Therefore, the significant retardation is only observed with a large excess of tetrahydrofuran. On the contrary, the bidentate ligands form a stable chelate. The addition of a small amount of these ligands can shift the equilibrium completely to the right and thus show a significant change in the reaction rate. The reasons for the different rates of the reaction with the addition of the bidentate ligands does not seem to be well understood. It is possible that the solvent effect on the product formation step (**10**, **12**) becomes important in the presence of the bidentate ligands. Thus, it appears that the relative magnitude of the solvent effects on the complex and product formation steps determines the acceleration or retardation of the reaction.

The stereochemical results obtained in diphenyl ether are similar to the results obtained in benzene. Initially this result might seem strange; however, it is known that trimethylaluminum and diphenyl ether form a weak solvate.[21] Thus, although free trimethylaluminum is present in low concentration (eq 8), the

$$(CH_3)_3Al \cdot O(C_6H_5)_2 \rightleftharpoons (CH_3)_3Al + O(C_6H_5)_2 \quad (8)$$

unsolvated organometallic is so much more reactive than the solvated form that the entire reaction proceeds

(37) R. A. Kovar and G. L. Morgan [*J. Amer. Chem. Soc.*, **91**, 7269 (1969)] have presented evidence through nmr studies for the existence of a monosolvated–disolvated equilibrium in dimethylberyllium dimethyl sulfide. Furthermore, typical magnesium compounds are isolated as monoetherates from solution by vacuum drying at room temperature.

(38) Both pentacoordinate transition states **10** and **12** are assumed to be similar to the transition state in an S$_N$2 reaction; however, the leaving and attacking position of the solvent ligand are different in the two transition states.

(39) (a) H. Edelstein and E. I. Becker, *J. Org. Chem.*, **31**, 3375 (1966); (b) A. A. Scala and E. I. Becker, *ibid.*, **30**, 3491 (1965).

(40) S. V. Vitt, E. I. Khristove, and V. B. Bondorev, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **8**, 1780 (1969).

(41) J. H. Wotiz and G. L. Proffitt, *J. Org. Chem.*, **30**, 1240 (1965).

(42) N. S. Ham and T. Mole, *Progr. Nucl. Magn. Resonance Spectrosc.*, **4**, 91 (1969).

through the unsolvated form. Such is not the case with other ethers such as diethyl ether. The diethyl etherate of trimethylaluminum is so stable that it can be distilled undissociated.

The amount of axial alcohol obtained from the reactions of trimethylaluminum in diethyl ether and tetrahydrofuran is independent of the ratio of reactants (Table II). Therefore, the reactions in tetrahydrofuran are expected to proceed only *via* mechanism A as in diethyl ether. It is interesting to note that the amount of axial alcohol obtained from the reaction with excess ketone in diphenyl ether is the same as in diethyl ether and tetrahydrofuran. The fact that the stereochemistry *via* mechanism A is independent of the nature of the solvent is compatable with the mechanism involving displacement or dissociation of the solvent prior to formation of the product. Without the loss of the solvent (path V), the amount of axial alcohol would be expected to increase as a function of the bulk property of the solvent from tetrahydrofuran to diethyl ether to diphenyl ether. The similar stereochemical results obtained from the reaction of $(CH_3)_3Al$ with excess ketone **1** in benzene (80%) as compared to the reactions in diethyl ether or THF (73%) indicate once again the absence of the solvent ligand in the transition state **13**.

The participation of at least one ether ligand in the transition state involving organomagnesium compounds has been indicated by asymmetric induction studies involving the reaction of dimethylmagnesium and benzaldehyde in the presence of an optically active ether.[43] Therefore, after one of the ligands is displaced, the remaining solvating ligand may affect the stereochemistry of addition in the case of organomagnesium compounds. However, the stereochemistry of the addition reactions of 3-*tert*-butylcyclopentanone with methyl-, ethyl-, and isopropylmagnesium compounds was found to be independent of the solvent [THF, $(C_2H_5)_2O$, and anisole].[44] In the present studies only small differences in stereochemistry are observed in the reactions of methylmagnesium compounds in diethyl ether and in tetrahydrofuran and dimethylmagnesium in triethylamine. These results indicate once again that solvent attachment to the metal in the transition state is not important.

The reaction rate and the product ratio of addition to reduction was found to decrease as the electropositivity of the metal in the organometallic compound varies from lithium to magnesium to aluminum and the halide in the Grignard compound varies from chloride to bromide to iodide. It is surprising to find out that the identity of the halide except iodide and the metal except aluminum in diethyl ether has little effect on the stereochemistry of the addition reaction in both tetrahydrofuran and diethyl ether (Table IV). It is most likely that the stereochemistry of alkylation is dependent on pure steric factors and the electronic factor plays only a minor role. Hence, the same stereochemical results do not imply the nature of the actual reacting species involved as suggested in a previous report.[12b]

Methylmagnesium alkoxide addition to 4-*tert*-butylcyclohexanone has been reported to give a higher axial alcohol yield than the corresponding methylmagnesium halides and the reaction was suggested to involve a different reaction species.[12b] Indeed, recent kinetic studies from this laboratory concerning the reaction of excess benzophenone with dimethylmagnesium show that the alkoxide $[CH_3MgOC(CH_3)(C_6H_5)_2]$ is an intermediate reacting species and it reacts as a dimer.[24a] This result is compatible with the prediction that the bulkier dimer should result in more equatorial attack.

A recent report suggested that the stereochemistry of addition is a function of the association of the reacting species.[12d] According to this suggestion the reactions of methylmagnesium bromide and iodide at 0.1 and 0.8 *M* concentration in diethyl ether should lead to less axial alcohol at the lower concentration, which is exactly the reverse of the observed results (Table IV). Previous studies from this laboratory indicate that the monomer is the reaction species regardless of the degree of association. If the monomer is the reactive species, regardless of the concentration, then the amount of axial product should increase with a decrease in concentration owing to the increased selectivity expected at the lower concentrations. If the dimeric species were to react, it would be expected to do so *via* a six-centered transition state to give predominantly equatorial alcohol; however, the axial alcohol is produced in 68% yield.

Registry No.—**1**, 98-53-3.

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(43) W. French and G. F. Wright, *Can. J. Chem.*, **42**, 2474 (1964).
(44) J. C. Richer and P. Belanger, *ibid.*, **44**, 2067 (1966).