AN INQUIRY INTO THE NATURE AND MECHANISM OF ADDITION OF ORGANOCADMIUM REAGENTS TO SIMPLE CARBONYL COMPOUNDS

WILLIAM J. KAUFFMAN

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Keywords
Chemistry, Organic

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AN INQUIRY INTO THE NATURE AND MECHANISM OF ADDITION OF
ORGANO CADMIUM REAGENTS TO SIMPLE CARBONYL COMPOUNDS

by

WILLIAM J. KAUFFMAN
B.S., Juniata College, 1966

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ABSTRACT

AN INQUIRY INTO THE NATURE AND MECHANISM OF ADDITION OF ORGANOCADMIUM REAGENTS TO SIMPLE CARBONYL COMPOUNDS

by

WILLIAM J. KAUFFMAN

The addition of in situ organocadmium reagents to simple carbonyl compounds has been investigated. Reaction was observed to occur rapidly in diethyl ether when iodide ion (MgI₂) was present. The amount of addition was considerably diminished when tetrahydrofuran was used as solvent, or if iodide ion was not present. The alkylcadmium halides were unreactive toward ketones, but were as reactive as the in situ dialkylcadmiums toward aldehydes. The aldehydes studied reacted almost quantitatively with in situ dialkylcadmium or alkylcadmium halide reagents regardless of the halide present.

The stereochemistry of addition of in situ and "reconstituted" dimethylcadmium reagents to 4-t-butylcyclohexanone was independent of the halide present, except in the case of (I,Cl). More axial attack was noted for the dimethylcadmium reagents than for the comparable Grignard reagents. The stereochemistry of addition of the dimethylcadmium reagents was found to be independent of the amount of halide (MgX₂) present, until the amount was reduced to one
equivalent, when more axial attack occurred. The stereochemistry of the Grignard reactions was observed to be dependent both on the halide present and on concentration. These differences between the dimethylcadmium and Grignard reagents are rationalized by considering a four-center mechanism for the cadmium reactions and a six-center mechanism for the Grignard reactions.

The reaction of di-n-propylcadmium reagents with 4-tert-butylcyclohexanone differed from that of the methyl reagents in several ways. For example, the stereochemistry of the addition products was dependent on the halide present for the propyl cadmium reactions but not for the propyl Grignard reactions. The ratio of addition/reduction was found to vary from 1.5-2.2 for the Grignard reactions, while that of the cadmium reactions varied from 7.7-10.0. This indicated that the addition pathway was preferred in the reactions of the cadmium reagents. The reduction product stereochemistry was dependent on the halide present in the Grignard reactions but was independent of halide for the cadmium reactions. More axial alcohol resulting from equatorial reduction was observed with the cadmium reactions than with the Grignard reactions. No equilibration of the reduction alcohols was observed in the reactions.

The stereochemistry of addition of in situ dimethylcadmium reagents to a series of acyclic aldehydes (2-phenylpropanal, 2-phenylbutanal, 3-methyl-2-phenylbutanal) was investigated. The cadmium reactions were observed to be less stereoselective than the Grignard reactions except in the case of addition to 3-methyl-2-phenylbutanal. The erythro isomer was the major product.
except in the reactions with the 3-methyl-2-phenylbutanal (45% threo- with methylmagnesium iodide; 70% threo- with dimethylcadmium). The results do not fit the conventional models for addition to acyclic aldehydes, by which the erythro product is favored; they can be rationalized on the basis of increased oxygen-isopropyl interaction in the Felkin model.
INTRODUCTION

Since 1936, organocadmium reagents have been known to react with acid chlorides to produce ketones. Early experiments indicated that the "purified" organocadmium reagents did not add to simple aldehydes and ketones. This fact explained the utility of organocadmium reagents for preparing ketones. Kollonitsch refuted this generalization in 1960, but the statement that organocadmium reagents are typically unreactive toward aldehydes and ketones appears even in some recent references.

Comparing the "purified" organocadmium reagent with the in situ reagent, Kollonitsch observed that the latter was considerably more reactive than the former, and did indeed add readily to benzaldehyde and acetophenone. The present investigation was undertaken to study extensively the factors affecting the reactivity and stereochemistry in the addition of cadmium reagents to simple carbonyl compounds. The factors affecting the addition of organocadmium reagents were to be compared to those of other organometallic reagents, whose mechanism of addition has been investigated. These comparisons might shed light on the mechanism of organocadmium addition to carbonyl compounds and explain the activating effect of magnesium halide.
HISTORICAL BACKGROUND

The first synthesis of organocadmium compounds was reported by E. Mahler in 1916. The usual method of preparation consists of an exchange reaction between cadmium salts and Grignard or lithium reagents. At the present time, three types of organocadmium compounds are known: the symmetrical compounds (R₂Cd), the asymmetrical compounds (RR'Cd), and the alkyl- or arylcadmium halides (RCdX).

\[
\begin{align*}
2\text{RMgX} + \text{CdX}_2 &\rightarrow \text{R}_2\text{Cd} + 2\text{MgX}_2 \quad (1) \\
\text{RMgS} + \text{CdX}_2 &\rightarrow \text{RCdX} \quad (2) \\
\text{R'MgX} + \text{RCdX} &\rightarrow \text{RR'Cd} + \text{MgX}_2 \quad (3)
\end{align*}
\]

As indicated in Equation 3, the RCdX species cannot be considered to be \( \text{R}_2\text{Cd} \cdot \text{CdX}_2 \) because only the asymmetrical organocadmium compound is produced and isolated.

Dialkylcadmium compounds can be distilled and freed from the magnesium halide. This is known as the "purified" organocadmium reagents. Undistilled dialkylcadmiums prepared according to Equation 1 are known as "in situ" reagents. The purified dialkylcadmium compounds are monomeric liquids and less volatile than the corresponding dialkylzinc and dialkylmercury compounds. This has been attributed to the enhanced van der Waals forces arising from the anomalously long cadmium-carbon bond (2.11 Å in dimethylcadmium compared to 2.09 Å in dimethylmercury and 1.94 Å in dimethylzinc). Dialkylcadmium compounds are known to form various 1:1 electron-donor complexes with organic ligands such as bipyridyl,
dioxane, and tetrahydrofuran. The dioxanate complex of dimethylcadmium is largely dissociated in solution, but it can be isolated in the crystalline state. It has been noted that complexes with bidentate ligands are more stable than those of monodentate ligands.

The nature of the in situ reagent has not been definitely clarified. Infrared evidence has been recently obtained for a bridged electron-donator complex involving magnesium bromide and dimethylcadmium in ether solution.

The alkylcadmium halides, on the other hand, have been isolated and examined. They are infusible solids which soften and decompose above 100° with no definable melting point. No precise determination of their structure has been reported, but it is known that they are monomeric in dimethylsulfoxide solution. Because ethereal ethylzinc
iodide and alkylmercury halides are monomeric, it is expected that alkylcadmium halides are also monomeric in ether solution. It is interesting to note that alkylcadmium halides do not form electron-donator complexes as do the symmetrical organocadmium compounds.

L. Le Guilly and F. Tatibouet have observed that magnesium bromide precipitated when ethereal, in situ di-n-propylcadmium (MgBr₂) was cooled, leaving 1/6 of the normal amount in solution. Cooling of an in situ n-propylcadmium bromide solution in ether caused formation of crystals whose composition corresponded to n-PrCdBr·MgBr₂·2(C₂H₅)₂O. Both of these reagents were comparable to the normal in situ di-n-propylcadmium in reactivity toward aldehydes. (Table 1, no. 17,18).

New methods of preparing organocadmium compounds have been reported recently. Thiele and Zdunneck devised a preparation for diallylcadmium from an exchange reaction between dimethylcadmium and triallylboron. Both cadmium

\[ 3(CH₃)₂Cd + 2B(CH₂-CH=CH₂)₃ \rightarrow 2B(CH₃)₃↑ + 3Cd(CH₂-CH=CH₂)₂ \]  

and zinc reagents, prepared free of halide by this method, were found to be quite reactive species. As shown by P. Freon et al., these reagents add to aldehydes and ketones readily (Table 1, no. 36-39). Thiele and Freon both concluded that the allyl structures are ionic in nature. Unlike the "purified" alkyl and aryl reagents, diallylcadmium was more reactive toward addition than diallylzinc.
The preparation of organocadmium compounds from the reaction of metallic cadmium and alkyl halides, reported to be unsuccessful in ether solution,\(^1\) was recently reported by J. Chenault and F. Tatibouet.\(^{23,24}\) They observed that an exothermic reaction took place when alkyl iodides and cadmium metal were mixed in dimethylsulfoxide, dimethylformamide, or hexamethylphosphoramidate (HMPT). Alkyl bromides could not be used, but allylic or propargylic bromides underwent exothermic reaction with cadmium metal. It was later determined that hexamethylphosphoramidate was the solvent of choice because of side reactions in the other two solvents.

The reaction with alkyl halides reportedly led to precipitation of a cadmium halide-hexamethylphosphoramidate complex. After removal of the cadmium halide complex, a dialkylcadmium-hexamethylphosphoramidate complex could be isolated. Infrared, Zerewitinoff, and polarographic analysis

\[
\text{Cd}^0 + \text{RX} \xrightarrow{\text{HMPT}} \frac{1}{2}\text{R}_2\text{Cd(S)}_2 + \frac{1}{2}\text{CdX}_2(S)_n
\]

\[S = \text{HMPT}\]
\[n = 2, X = \text{I}\]
\[n = 4, X = \text{Br}\]

confirmed the presence of dialkylcadmium compounds. By a careful distillation procedure, it was possible to break up the dialkylcadmium complex into the pure dialkylcadmium. The diethyl-, dipropyl-, and dibutylcadmium reagents were prepared by this method.
Reaction of the reagents prepared in hexamethylphosphoramide with acid chlorides was investigated and these reagents were shown to have the same reactivity as the normal "purified" reagents.\(^\text{24}\) (Table 1, no. 40-45).

It was observed that addition of hexamethylphosphoramide to the "in situ" (Br,Br) reagents prepared in ether caused precipitation of a magnesium bromide-hexamethylphosphoramide complex. After removal of the precipitate, the filtrate was shown to contain dialkylcadmium reagent which could be purified by the method of Krause.\(^\text{9}\) It is interesting to note that no evidence was found of alkylcadmium halide under these conditions.

The first extensive investigation into the reactivity of organocadmium reagents was conducted by Gilman and Nelson\(^\text{1}\) in 1936. They reported that addition of an acid chloride to "in situ" organocadmium reagents produced ketones in good to excellent yields. The preparation of ketones from acid chlorides and anhydrides with organocadmium reagents has been extensively reviewed.\(^\text{25,26}\) Gilman observed that "purified" organocadmium reagents did not react with aldehydes or ketones. For example, "purified" diethylcadmium was shown to react very slowly with benzaldehyde and Michler's ketone. It

\[
\begin{align*}
  \text{C}_6\text{H}_5\text{CHO} + (\text{C}_2\text{H}_5)_2\text{Cd} & \quad \text{\((C_2\text{H}_5)_2\text{O}\)} \quad \text{\(\text{C}_6\text{H}_5\text{CHC}_2\text{H}_5\)} \quad \text{(very slow)} \\
  \text{\(\text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{N(C}_6\text{H}_4\text{C}-\text{C}_6\text{H}_4\text{N(CH}_3)_2\text{)-P} + (C_2\text{H}_5)_2\text{Cd} \quad \text{\((C_2\text{H}_5)_2\text{O}\)} \quad \text{\(\text{C}_2\text{H}_5\)}
\end{align*}
\]

\(\text{(8)}\)
was generally believed that the utility of the preparation of ketones from acid chlorides was due to the extremely slow reactivity of the organocadmium reagent with the keto group. On the basis of this work by Gilman and Nelson, it was assumed that the organocadmium compounds in general did not react with simple aldehydes or ketones.

However, addition of organocadmium reagents to activated aldehydes and ketones—\(\alpha\)-diketones, \(\alpha\)-ketosteres, \(\alpha\)-keto aldehydes,\(^{27}\) \(\alpha\)-halo aldehydes and ketones\(^{28}\)—has been reported in the literature. For example, in situ dialkyl- and diarylcadmium reagents have been shown to react with buta-2,3-dione, producing the respective alkyl- or arylmethylacetyl carbinols (38-70\%).\(^{29}\)

\[
\begin{align*}
\text{CH}_3\text{C}_2\text{CCH}_3 + \text{R}_2\text{Cd} & \rightarrow \text{CH}_3\text{(R)C} - \text{CCH}_3 \quad (9) \\
\text{R} &= \text{C}_2\text{H}_5 \quad 68\% \\
&= \text{C}_4\text{H}_9 \quad 70\% \\
&= \text{C}_6\text{H}_{11} \quad 38\% \\
&= \text{C}_6\text{H}_{15} \quad 44\%
\end{align*}
\]

Reaction of diphenylcadmium with phenylglyoxal has been reported to afford benzoin in 51\% yield.\(^{30}\)

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}-\text{CH} + (\text{C}_6\text{H}_5)_2\text{Cd} \quad \text{MgBr}_2 \quad (\text{C}_2\text{H}_5)_2\text{O} & \rightarrow \text{C}_6\text{H}_5\text{C}-\text{CH}-\text{C}_6\text{H}_5 \quad (10)
\end{align*}
\]

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The reactivity toward activated carbonyls can be seen in the attempted preparation of an α-keto ester from the appropriate acid chloride. If the chloride of monoethyl oxalate is treated with diethylcadmium, the keto ester is not isolated, but the reaction proceeds a stage further with the formation of an α-hydroxy ester containing a tertiary carbon atom. Numerous examples can be found in the literature of the addition to activated carbonyl compounds by organocadmium reagents.

\[
\begin{align*}
&\text{O} \quad \text{O} \\
&\text{ClC-C-OC}_2\text{H}_5 + (\text{C}_2\text{H}_5)_2\text{Cd} \xrightarrow{\text{MgBr}_2} (\text{C}_2\text{H}_5)_2\text{C} - \text{C-OC}_2\text{H}_5
\end{align*}
\]

The addition of cadmium enolates to carbonyl compounds—analogous to the well-studied Reformatsky reaction—has been reported in a few instances. J. Cason and R. Fessenden reported preparation of cadmium enolates by treating in situ organocadmium reagents with α-halo esters. They observed that the cadmium enolates could be condensed with simple carbonyl compounds in a manner analogous to the Reformatsky reaction. The solvent affected the yield of condensation product; it was found that a 1:1 mixture of benzene-ether served best when a nonreactive carbonyl was attacked. It was noted that under the same conditions, the zinc Reformatsky reagent was generally slightly more reactive.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Bromo ester</th>
<th>Yield of β-Hydroxy ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}<em>3\text{CC} _6 _\text{H}</em>{13})</td>
<td>(\text{CH}_3\text{CH-CO}_2\text{C}_2\text{H}_5)</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>(\text{Br})</td>
<td>79%</td>
</tr>
<tr>
<td>(\text{CH}_3\text{CH-CH}_2\text{C-CH}_2-\text{CH}_3)</td>
<td>(\text{CH}_3\text{CH-CO}_2\text{C}_2\text{H}_5)</td>
<td>47%</td>
</tr>
<tr>
<td>(\text{O})</td>
<td>(\text{Br})</td>
<td>68%</td>
</tr>
</tbody>
</table>
M. Palmer and J. Reid later investigated zinc and cadmium enolates containing optically active ester substituents. These enolates afforded partially active condensation products with acetophenone.

In 1960 Kollonitsch undertook a comparison of the "purified", in situ, and "reconstituted" organocadmium reagents. The last reagent was prepared by addition of magnesium halide to "purified" dialkylcadmium. He discovered that the reactivity of the organocadmium compounds was greatly affected by the presence of magnesium (and other) halides. Because the in situ and the "reconstituted" reagents were comparable in reactivity toward acid chlorides, they were assumed to be the same.

Noting that almost all the ketone syntheses reported in the literature had been carried out with the in situ reagent, he investigated the reaction of acid chlorides with the "purified", in situ, and "reconstituted" reagents. Benzoyl chloride was found to react only very slowly with the "purified" organocadmium reagents but gave acetophenone in 68% yield with dimethylcadmium in the presence of lithium bromide. The same order of reactivity was noted with acetyl chloride, whose reaction with purified diethylcadmium was shown to be 20% complete after twenty minutes at 28°, but was 97% complete under the same conditions when magnesium bromide was present. The activating effect of magnesium halide in these reactions was shown to vary with the halogen in the order: MgI₂ > MgBr₂ > MgCl₂.

Kollonitsch also investigated the reactivity toward aldehydes and ketones. Reaction of benzaldehyde with "purified" diethylcadmium in ether was 20% complete after one hundred hours at 25°, but was 86% complete in one hour.
in the presence of magnesium bromide. Acetophenone was also observed to react with diethylcadmium in the presence of magnesium bromide. (Table 1, no. 1-4).

In the light of Kollonitsch's observations, P. Freon and his collaborators have investigated the reactivity of various organocadmium reagents with aldehydes and ketones. They reported that benzaldehyde reacted generally with \textit{in situ} organocadmium reagents, producing the secondary alcohols in good yields. (See Table 1, no. 5-8). Comparable yields were noticed from the organocadmium reagents and formaldehyde, acetaldehyde, and propionaldehyde. Yields were reported slightly improved when a 25\% excess of the \textit{in situ} reagent was employed. G. Soussan also studied the addition of dialkylcadmium reagents to aldehydes, and observed that an oxidation-reduction side reaction occurred, which in some cases predominated.

In the addition reaction of \textit{in situ} diethylcadmium to diethyl ketone, it was observed that, as the molar equivalency of either the organocadmium reagent or the ketone was increased, the yield of the alcohol was enhanced.

\[
\text{C}_2\text{H}_5\text{COC}_2\text{H}_5 + (\text{C}_2\text{H}_5)_2\text{Cd} \rightarrow (\text{C}_2\text{H}_5)_3\text{COH} \quad (13)
\]

<table>
<thead>
<tr>
<th>moles \text{C}_2\text{H}_5\text{COC}_2\text{H}_5</th>
<th>moles \text{(C}_2\text{H}_5)_2\text{Cd}</th>
<th>\text{(C}_2\text{H}_5)_3\text{COH}</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10-15</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>20-25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

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Using three molar equivalents of organocadmium reagent to one of ketone, Freon et al. reported\(^{36}\) addition of \textit{in situ} diethyl-, dibutyl-, and diphenylcadmium reagents to a series of ketones (Table 1, no. 9-16). Although the yields are below those reported from the Grignard reagents, it is evident that ketones are not inert under mild conditions.

In order to determine whether alcohols could be produced during the ketone synthesis from the reaction of an organocadmium reagent with an acid chloride, the reaction of \textit{in situ} diethylcadmium with propionyl chloride was investigated in detail.\(^{36}\) As the molar equivalence of diethylcadmium was increased, the amount of tertiary alcohol increased. This demonstrated that the intermediate in the ketone synthesis was capable of reacting further with the diethylcadmium reagent.

<table>
<thead>
<tr>
<th>moles $\text{C}_2\text{H}_5\text{COCl}$</th>
<th>moles $(\text{C}_2\text{H}_5)_2\text{Cd}$</th>
<th>$(\text{C}_2\text{H}_5)_3\text{COH}$</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

(14)

A more general investigation into the comparative reactivity of \textit{in situ} and purified organocadmium reagents was conducted by J. Michel \textit{et al.}\(^{37}\) It was observed that in all reactions the \textit{in situ} reagent was considerably more reactive than the purified reagent. (Table 1, no. 19-35). These results and those previously mentioned demonstrate
that "in situ" organocadmium reagents are reactive organometallic reagents and do readily react with simple aldehydes and ketones.

Since the reactivity studies mentioned above, the work reported in the literature has been mainly concerned with new methods of preparation and novel reactions of organocadmium compounds. The only recently reported addition of organocadmium reagents to aldehydes or ketones involved that of bis-(ethoxymethyl)-cadmium. Preparation involved formation of the corresponding Grignard reagent by reaction of 1-chloromethyl ethyl ether with magnesium and mercuric chloride in tetrahydrofuran at -15°. The cadmium reagent was then formed by an exchange reaction between the Grignard and cadmium iodide. These in situ reagents were found to react readily

\[
\text{ClCH}_2\text{OC}_2\text{H}_5 + \text{Mg} \xrightarrow{\text{THF}} \text{ClMgCH}_2\text{OC}_2\text{H}_5 \xrightarrow{\text{HgCl}_2} \text{CdI}_2 \xrightarrow{-15°} \text{Cd(CH}_2\text{OC}_2\text{H}_5)_2 + 2\text{MgX}_2
\]

with aldehydes, activated carbonyls, and acid chlorides, but not as readily with ketones. (See Table 1, no. 40-45). The corresponding zinc reagents, prepared similarly, were found to be less reactive.

The addition of organocadmium reagents to N-benzylideneaniline has been recently reported. It was observed that addition of diethylcadmium to three structurally similar anils occurred when the in situ reagent was employed but not with "purified" diethylcadmium. It was also noted that the corresponding zinc reagents were less reactive.
A new reaction of normal in situ organocadmium reagents with isocyanates in ether solution has been reported recently. Grignard reagents are known to produce amides upon reaction with isocyanates, while the reaction of in situ dialkylcadmium reagents was shown to induce trimerization of the isocyanate. Investigations into the nature of this reaction are now being conducted in French laboratories.

\[ \text{R'}\text{NCO} + \text{R}_2\text{Cd} \rightarrow \text{R'NCO} \quad (17) \]

\[
\begin{align*}
\text{R} & = \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{C}_4\text{H}_9 \\
\text{R'} & = \text{C}_2\text{H}_5, \text{C}_4\text{H}_9, \text{C}_6\text{H}_5, \text{C}_{10}\text{H}_7
\end{align*}
\]
The kinetics of the reaction of "purified" diethylcadmium with substituted benzylic alcohols has been recently investigated. The kinetics was found to be second order: first order each in diethylcadmium and in benzyl alcohol, in ether at 34-35°C. The $\rho$ for the reaction was +0.35.

The kinetics of the reaction of "purified" dimethylzinc with benzaldehyde has also been reported. This reaction was also found to be second order: first order each in dimethylzinc and benzaldehyde. Although the addition of metal salts (MgBr$_2$, ZnBr$_2$, ZnCl$_2$) increased the rate, the kinetic order was unchanged.

The only stereochemical investigation into the addition of organocadmium reagents to carbonyl compounds—that of in situ di-$n$-propyl- and diallylcadmium and -zinc to 4-$t$-butylcyclohexanone—was published by Abenhaim in 1968. Although the stereochemistry of the addition was reported, the composition of the reduction products was not determined.

\[
\begin{align*}
\text{Pr} & \hspace{1cm} \text{A (E)} \\
\text{Pr} & \hspace{1cm} \text{A (Z)} \\
\text{OH} & \hspace{1cm} \text{R (E)} \\
\text{OH} & \hspace{1cm} \text{R (Z)}
\end{align*}
\]
The di-n-propyl organocadmium reagent was reported to produce the Z addition alcohol ($A_Z$) in 80% normalized yield. The ratio of addition/reduction was 4.66 for this reaction.

<table>
<thead>
<tr>
<th></th>
<th>Mg</th>
<th>Zn</th>
<th>Cd</th>
<th>(n-propyl reagents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_Z$</td>
<td>73</td>
<td>75</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Add/Red</td>
<td>2.3</td>
<td>0.89</td>
<td>4.66</td>
<td></td>
</tr>
</tbody>
</table>

This work will be further examined in the discussion.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Product</th>
<th>% in situ</th>
<th>&quot;purified&quot;</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C₆H₅COCl</td>
<td>(CH₃)₂Cd</td>
<td>C₆H₅COCH₃</td>
<td>68 (LiBr)</td>
<td>trace</td>
<td>4</td>
</tr>
<tr>
<td>2. CH₃COCl</td>
<td>(C₂H₅)₂Cd</td>
<td>CH₃COC₂H₅</td>
<td>97 (MgBr₂)</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>3. C₆H₅CHO</td>
<td>(C₂H₅)₂Cd</td>
<td>C₆H₅CH(OH)C₂H₅</td>
<td>86 (MgBr₂)</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>4. C₆H₅COCH₃</td>
<td>(C₂H₅)₂Cd</td>
<td>C₆H₅CCH₃(OH)C₂H₅</td>
<td>---</td>
<td>---</td>
<td>4</td>
</tr>
<tr>
<td>5. C₆H₅CHO</td>
<td>(CH₃)₂Cd</td>
<td>C₆H₅CH(OH)CH₃</td>
<td>55 (MgBr₂)</td>
<td>---</td>
<td>34</td>
</tr>
<tr>
<td>6. C₆H₅CHO</td>
<td>(C₂H₅)₂Cd</td>
<td>C₆H₅CH(OH)C₂H₅</td>
<td>60 (MgBr₂)</td>
<td>---</td>
<td>34</td>
</tr>
<tr>
<td>7. C₆H₅CHO</td>
<td>(C₄H₉)₂Cd</td>
<td>C₆H₅CH(OH)C₄H₉</td>
<td>65 (MgBr₂)</td>
<td>---</td>
<td>34</td>
</tr>
<tr>
<td>8. C₆H₅CHO</td>
<td>(C₆H₅)₂Cd</td>
<td>C₆H₅CH(OH)C₆H₅</td>
<td>35 (MgBr₂)</td>
<td>---</td>
<td>34</td>
</tr>
<tr>
<td>9. CH₃COCH₃</td>
<td>(C₂H₅)₂Cd</td>
<td>CH₃COH(CH₃)C₂H₅</td>
<td>40 (MgBr₂)</td>
<td>---</td>
<td>36</td>
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<tr>
<td>Product</td>
<td>CH₃COH(CH₃)CH₃</td>
<td>CH₃(CH₃)₂COH(C₂H₅)₂</td>
<td>C₂H₅COH(C₂H₅)₂</td>
<td>C₂H₅CH(OH)C₆H₅</td>
<td>C₆H₅CH₂(OH)C₃H₇</td>
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<tr>
<td>---------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>In situ</td>
<td>35 (MgBr₂)</td>
<td>25 (MgBr₂)</td>
<td>40 (MgBr₂)</td>
<td>40 (MgBr₂)</td>
<td>58 (MgBr₂)</td>
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<tr>
<td>% purified</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
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</table>

| Reagent | (C₄H₉)₂Cd  | (C₆H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  | (C₂H₅)₂Cd  |

| Substrate | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  | CH₃COCH₃  |

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<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Product</th>
<th>% in situ</th>
<th>&quot;purified&quot;</th>
<th>Ref.</th>
</tr>
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<tr>
<td>22. C₆H₅CH-CH₂</td>
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<td>C₆H₅CH₂CHC₂H₅</td>
<td>65 (MgBr₂)</td>
<td>trace</td>
<td>37</td>
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<tr>
<td>23. HCO₂C₂H₅</td>
<td>(C₆H₅)₂Cd</td>
<td>(C₆H₅)₂CHOH</td>
<td>45 (MgBr₂)</td>
<td>trace</td>
<td>37</td>
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<tr>
<td>24. C₂H₅O₂C-CO₂C₂H₅</td>
<td>(C₂H₅)₂Cd</td>
<td>(C₂H₅)₂COH-CO₂C₂H₅</td>
<td>85 (MgBr₂)</td>
<td>trace</td>
<td>37</td>
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<tr>
<td>25. (CH₃CO)₂-O</td>
<td>(C₄H₉)₂Cd</td>
<td>CH₃COC₄H₉</td>
<td>55 (MgBr₂)</td>
<td>trace</td>
<td>37</td>
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<tr>
<td>26. OHC-N(CH₃)₂</td>
<td>(C₆H₅)₂Cd</td>
<td>C₆H₅CHO</td>
<td>40 (MgBr₂)</td>
<td>trace</td>
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<tr>
<td>27. C₆H₅CH=CHNO₂</td>
<td>(C₄H₉)₂Cd</td>
<td>(C₆H₅)C₄H₉CH-CH₂NO₂</td>
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<td>37</td>
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<tr>
<td>28. i-C₃H₇COCH₂NO₂</td>
<td>(C₄H₉)₂Cd</td>
<td>i-C₃H₇COH-CH₂NO₂</td>
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<td>trace</td>
<td>37</td>
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<tr>
<td>29. i-C₃H₇CH₂CH₂OH</td>
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<td>C₂H₆</td>
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<td>30. C₆H₅COCl</td>
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<td>C₆H₅COC₂H₅</td>
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<td>31. CH₃COCl</td>
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<td>32. C₆H₅COC₂H₅</td>
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<td>(C₂H₅)₂COHCH₂OC₂H₅</td>
<td>5 (MgI₂,MgCl₂)</td>
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<tr>
<td>33. C₆H₅CHO</td>
<td>(C₂H₅OCH₂)₂Cd</td>
<td>C₆H₅CHOH(CH₂OC₂H₅)</td>
<td>95 (MgI₂,MgCl₂)</td>
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<td>34. C₄H₉COCl</td>
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<tr>
<td>35. CH₃CO-COCH₃</td>
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<td>CH₃CO-COH(CH₃)</td>
<td>60 (MgI₂,MgCl₂)</td>
<td>--</td>
<td>37</td>
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<tr>
<td>Substrate</td>
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<td>Product</td>
<td>% in situ</td>
<td>% &quot;purified&quot;</td>
<td>Ref.</td>
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<tr>
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<tr>
<td>CH$_3$COC$_2$H$_5$</td>
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<td>CH$_3$C(OH)CH$_2$CH=CH$_2$</td>
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<td>C$_2$H$_5$CO$_2$H$_5$</td>
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<td>(C$_2$H$_5$)$_2$COHCH$_2$CH=CH$_2$</td>
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<tr>
<td>C$_3$H$_7$CHO</td>
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<td>---</td>
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<td>HMPT (C$_2$H$_5$)$_2$Cd</td>
<td>CH$_3$COC$_2$H$_5$</td>
<td>50</td>
<td>---</td>
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<tr>
<td>C$_2$H$_5$COCl</td>
<td>HMPT (C$_2$H$_5$)$_2$Cd</td>
<td>C$_2$H$_5$COC$_2$H$_5$</td>
<td>40</td>
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<tr>
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<tr>
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<td>CH$_3$COCl</td>
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<td>CH$_3$COC$_3$H$_7$</td>
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<tr>
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<td>CH$_3$COC$_4$H$_9$</td>
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</tbody>
</table>
EXPERIMENTAL

Instrumentation.- Infrared spectra were recorded with a Perkin-Elmer Model 337 grating spectrophotometer; nmr spectra, obtained with a Varian A-60 spectrometer, were recorded in ppm downfield from tetramethylsilane used as an internal standard. Gas liquid phase chromatographic (glpc) analysis and separations were accomplished with a Varian Model 90-P gas chromatograph. Areas were determined as the product of the height and the half-height peak width, and percentages reported are normalized. Analyses were carried out on the crude, isolated product and no correction made for mass balance, unless otherwise stated. Melting points, determined with a Hoover Capillary Melting Point Apparatus, are corrected; boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories of Knoxville, Tennessee.

Materials.- The Grignard reagents were prepared in a dry nitrogen atmosphere, from reagent grade magnesium turnings except where noted. In some cases the reagent was prepared from singly sublimed magnesium (Dow Chemical Co.). No difference was noted between reagents as a function of the purity of magnesium used in the preparation. Methylmagnesium bromide in ether was obtained from Arapahoe Chemical Co. and methyllithium from Foote Mineral Co. The solutions were refrigerated in serum-capped bottles and their concentrations checked periodically by titration.
with 1,10-phenanthroline or 2,2'-biquinoline. Anhydrous cadmium chloride (Fisher certified), bromide and iodide (Alfa Inorganics) were used after oven-drying for 48 hours at 110°. The 4-tert-butylcyclohexanone and 2-phenylpropanal were obtained from Aldrich Chemical Co. The glpc column materials [FFAP, STAP, SAIB, Apiezon L, Chromosorb W (60-80 mesh)] were obtained from Varian Aerograph, Inc.

Experimental Apparatus.- The following is a description of the experimental apparatus used for reactions of organocadmium reagents with the various substrates, except where noted in the experimental. A 3-necked, round-bottomed flask was fitted with a mechanical stirrer and a pressure-equalizing addition funnel. To insure dryness, a steady stream of dry nitrogen was allowed to pass through the system via the addition funnel while the entire system was flamed with a Bunsen burner. The flask was stoppered, the nitrogen flow slowed, and the flask allowed to cool. The reagents were then added and the reaction carried out as described in the Experimental Section. An atmosphere of dry nitrogen was maintained during reactions except where noted. Each organocadmium reagent employed gave a negative Gilman test for the presence of Grignard reagent. The transfer of the Grignard reagents from the serum-capped bottles was accomplished by use of a 20-ml syringe.
Reaction of Filtered in situ Diethylcadmium (Br,Cl)* with Benzoyl Chloride in THF.

An ethylmagnesium bromide solution, prepared from 4.8 g of magnesium (0.20 mol), 21.8 g of ethyl bromide (0.200 mol), and 150 ml of anhydrous THF, was added to a stirred mixture of 18.3 g of CdCl₂ (0.100 mol) and 150 ml of anhydrous THF. The solution was stirred for 30 min at gentle reflux after the addition was complete, and the Gilman test was shown to be negative.

The stirred cadmium reagent was filtered through the glass frit into a 1000-ml, 3-necked, round-bottomed flask equipped with a stopper and an aspirator connection, by means of positive nitrogen pressure on one side of the frit and partial vacuum on the other. In some cases when the cadmium reagent contained too much suspended solid, the frit became clogged and this procedure of removing solids was not reliable. The flask containing the filtrate was equipped with a mechanical stirrer, reflux condenser, and a pressure-equalizing addition funnel.

A solution of 14.1 g of benzoyl chloride (0.100 mol) in 50 ml of anhydrous THF was added dropwise to the stirred cadmium reagent and the solution refluxed for 2 hr after the addition was complete. The reaction was then hydrolyzed with 100 ml of saturated ammonium chloride solution and 25 g of ice. The layers were separated and the aqueous layer extracted with 200 ml of ether. The combined ether-THF layer was extracted with saturated NaHCO₃ solution,

*Halogens in the parentheses indicate, respectively, the alkyl halide from which RMgX was prepared and the CdX₂ used for the exchange reaction.
water, dried over MgSO$_4$, and concentrated on a rotary evaporator.

The crude product (22.6 g) was distilled at reduced pressure and two fractions were obtained. The lower-boiling fraction [5.6 g, bp 97-119° (15-16 mm)] was identified by tlc, ir (no. 7065), nmr (no. 3516) and glpc on STAP; and found to contain mostly ethyl benzoate (90%) and propiophenone (10%). The second fraction [5.9 g, bp 182-184° (15-16 mm)] gave a positive Beilstein test. The precipitate obtained after treatment with sodium iodide in acetone was shown to be a bromide by reaction with nitric acid and carbon tetrachloride. Spectral data also indicated that the product was 4-bromobutyl benzoate: ir (no. 7063, neat) 1720 and 1275 cm$^{-1}$ (benzoate C=O); nmr (no. 3497, CCI$_4$) § 8.0 (m, 2, aromatic), 7.4 (m, 3, aromatic), 4.30 (t, 2, -CH$_2$OBz), 3.42 (t, 2, -CH$_2$Br), 1.93 (t, 4, BrCH$_2$(CH$_2$)$_2$CH$_2$OBz).

Reaction of in situ Diethylcadmium (Prepared from Diethylmagnesium) with Benzoyl Chloride in THF.

Ethylmagnesium bromide (0.200 mol) was prepared as described in the previous reaction. A solution of 11.7 g of dioxane in 30 ml of anhydrous THF was added dropwise to the Grignard reagent and the mixture stirred for 1 hr. The precipitate was allowed to settle and the mixture filtered by suction through a glass frit containing a layer of celite into a 500-ml, 3-necked, round-bottomed flask which was cooled in a dry ice-acetone bath. An atmosphere of dry nitrogen was maintained during the filtration. The diethylmagnesium solution was transferred to an addition funnel and added dropwise to a stirred mixture of 18.3 g of CdCl$_2$ (0.1 mol) and 140 ml of anhydrous
THF. The solution was refluxed for 0.5 hr, after which time the Gilman test was negative. The cadmium reagent was then filtered through a glass wool plug under an atmosphere of dry nitrogen into a 500-ml, 3-necked, round-bottomed flask equipped as previously described.

A solution of 14.1 g of benzoyl chloride (0.1 mol) in 50 ml of anhydrous THF was added dropwise to the stirred cadmium reagent and the mixture refluxed for 2 hr after the addition was complete. The reaction was hydrolyzed by pouring the mixture onto 100 ml of saturated ammonium chloride solution and 25 g of ice. The work-up was as previously described.

Distillation of the crude product yielded two fractions. Fraction no. 1 (2.38 g) was identified as ethyl benzoate: bp 49-59° (1 mm), \( n^24°D 1.5035 \) [lit. \( n^25°D 1.5068 \)]; ir (no. 7209, neat) 1720 and 1275 cm\(^{-1} \) (benzoate CO); nmr (no. 3662, CCl\(_4\)) \( 7.45 \) (m, 2, aromatic), 6.81 (m, 3, aromatic), 3.75 (m, 2, \(-\text{CH}_2\text{O}_{-}\text{Bz}\)), 0.71 (t, 3, CH\(_3\)).

Fraction no. 2 was identified as 4-chlorobutyl benzoate (5.3 g): bp 112-114° (1 mm), \( n^24°D 1.5200 \) [lit. \( n^25°D 1.5203 \), bp 112° (1 mm)]; ir (no. 7210, neat) 1720 and 1275 cm\(^{-1} \) (benzoate CO); nmr (no. 3665, CCl\(_4\)) \( 8.0 \) (m, 2, aromatic), 7.40 (m, 3, aromatic), 4.37 (t, 2, \(-\text{CH}_2\text{O}_{-}\text{Bz}\)), 3.65 (t, 2, \(-\text{CH}_2\text{Cl}\)), 1.94 (t, 4, ClCH\(_2\)(CH\(_2\))\(_2\)CH\(_2\)O\(_{-}\text{Bz}\)).

Reaction of Filtered, in situ Diethylcadmium with Benzoyl Chloride in Ether.

The experimental procedure was the same as that described for the filtered diethylcadmium reaction, except anhydrous ether was substituted for THF. The diethylcadmium reagent once formed was filtered through a glass wool plug under an atmosphere of dry nitrogen. A solution
of 14.1 g of benzoyl chloride (0.100 mol) in 50 ml of anhydrous ether was added dropwise to the stirred cadmium reagent in ether and the solution refluxed for 2 hr after the addition was complete. The reaction mixture was hydrolyzed, washed, dried and concentrated as previously described. Distillation yielded one fraction [10.6 g, bp 48-60° (1 mm)], which was identified as a mixture of ethyl benzoate and propiophenone. Glpc analysis on STAP indicated that the mixture was 80% ethyl benzoate, and 20% propiophenone. Ir (no. 6996) and nmr (no. 3518) spectra indicated that ethyl benzoate was the major component.

**Reaction of Diethylcadmium (one-step)** with Benzaldehyde in Ether.

To prepare the one-step reagent, 15 ml of an ethyl bromide solution (21.8 g of ethyl bromide (0.200 mol) in 75 ml of anhydrous ether) was added to a stirred mixture of 4.8 g of magnesium (0.20 mol) and 72 ml of anhydrous ether. Once the reaction had started, 18.3 g of CdCl₂ (0.100 mol) was added. The remaining ethyl bromide solution was added over a period of 45 min. After the addition was complete, the solution was brought to reflux for 2 hr and then stirred for an additional 30 min at ambient temperature. A Gilman test was shown to be negative.

A solution of 10.5 g of benzaldehyde (0.100 mol) in 50 ml of anhydrous ether was added dropwise over a period of 20 min to the stirred cadmium reagent. After the addition was complete, the reaction was gently refluxed for 1 hr and stirred for an additional 30 min at room temperature. The mixture was hydrolyzed by pouring the solution onto 50 g of ice and 60 ml of saturated ammonium
chloride solution. The layers were separated and the aqueous layer extracted twice with ether. The ether layers were combined and dried over MgSO4. Tlc of the concentrated sample on Silica Gel HF plates with CHCl3 as the eluent indicated that the major component was ethylphenylcarbinol. Distillation yielded 7.9 g of ethylphenylcarbinol (59% yield): bp 98-102° (13 mm); nmr (no. 3877, CCl4) δ 0.78 (t, CH3), 1.53 (m, CH2), 4.42 (m, CH and OH), 7.20 (s, aromatic).

Reaction of Diethylcadmium (one-step) with Benzaldehyde in THF.

The experimental procedure was exactly the same as that described above, except that anhydrous THF was used as the solvent. The aqueous layer was extracted twice with ether and the combined ether-THF solution dried and concentrated as before. Tlc on Silica Gel HF plates with CHCl3 as eluent indicated the crude product (12.1 g) was mainly benzaldehyde. Distillation yielded 9.8 g of benzaldehyde (93%); bp 92-96° (18 mm). No trace of ethylphenylcarbinol was observed.

Reaction of Centrifuged, in situ Diethylcadmium (Br,Cl) with Benzaldehyde in Ether.

A. Supernatant:

Ethylmagnesium bromide, prepared from 2.43 g of magnesium (0.100 mol), 40 ml of anhydrous ether, and 10.9 g of ethyl bromide (0.100 mol) in 10 ml of anhydrous ether, was added to a stirred mixture of 9.2 g of CdCl2 (0.050 mol) and 60 ml of anhydrous ether. The Gilman test was negative after 45 min at room temperature. The diethylcadmium reagent was then centrifuged in glass centrifuge tubes.
under an atmosphere of dry nitrogen, and the supernatant reagent was transferred to a reaction flask.

To this was added a solution of 5.3 g of benzaldehyde (0.05 mol) in 10 ml of anhydrous ether dropwise over a period of 5 min, and then the mixture was refluxed for 1 hr. The mixture was cooled in an ice bath and hydrolyzed with 50 ml of saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted twice with ether. The ether layers were combined, dried, concentrated on a rotary evaporator, and the crude product distilled. Two fractions were obtained: Fraction no. 1 [3.1 g, bp 66-70° (1.5 mm)] was identified as 75% ethylphenylcarbinol, 12.5% benzaldehyde, and 12.5% propiophenone by nmr (no. 4122) analysis. Fraction no. 2 [2.3 g, bp 70-73° (1.5 mm)] was shown by nmr (no. 4123) to be ethylphenylcarbinol. The nmr analysis was conducted by integrating the methylene resonances: \( \delta 2.65 \) (m, -C-CH\(_2\)-) and \( 1.61 \) (m, -C-CH\(_2\)-), and the aldehyde resonance at \( 9.87 \) (C-H). Normalized percentages were then calculated after making the required statistical corrections. On the basis of these figures, there was obtained 68.4% ethylphenylcarbinol, 7.3% recovery of benzaldehyde, and 5.7% propiophenone. The infrared spectrum (no. 7257) also indicated the presence of propiophenone in the crude product.

B. Residue:

The residual, solid material after centrifugation of the above reagent was mixed with 75 ml of anhydrous ether and treated with benzaldehyde exactly as described above. After hydrolysis, work-up, and distillation, there was obtained 4.0 g of material, bp 37-45° (1.5 mm). It was identified as benzaldehyde (76% recovery) by its nmr (no. 3878) and ir (no. 7242) spectra.
Reaction of in situ Diethylcadmium (Br,Cl) with Benzaldehyde in Ether.

The Grignard reagent, prepared from 4.8 g of magnesium (0.20 ml), 100 ml ether, and 21.8 g of ethyl bromide (0.200 mol), was added dropwise to a stirred solution of 18.4 g of CdCl$_2$ (0.100 mol) and 120 ml of anhydrous ether. After the addition was complete, the cadmium reagent was stirred at ambient temperature for 45 min. Then 10.6 g of benzaldehyde (0.100 mol) dissolved in 20 ml of anhydrous ether was added dropwise to the stirred cadmium reagent over a period of 10 min. The reaction mixture was refluxed for an additional 60 min, cooled in an ice bath, and hydrolyzed with 100 ml of saturated ammonium chloride solution. The work-up was the same as described previously, two fractions being obtained on distillation: Fraction no. 1 [1.2 g, bp 35-51.5° (0.5 mm)] was identified by nmr (no. 3711) and tlc as benzaldehyde. Fraction no. 2 [7.2 g, bp 52-55.5° (0.5 mm)] was identified by nmr (no. 3712), ir (no. 7233) and tlc to be ethylphenylcarbinol (53% yield).

Reaction of in situ Dimethylcadmium (I,Cl) with p-Nitroacetophenone in Ether.

To a mixture of 7.55 g of CdCl$_2$ (45.4 mmol) and 160 ml of anhydrous ether, cooled in an ice bath, was added 45.4 ml of ethereal 2 M MeMgI (90.9 mmol) at such a rate that no ebullition occurred. The bath was removed and the mixture stirred for 30 min before a Gilman test was taken.

A solution of 5.00 g of p-nitroacetophenone (30.3 mmol) in 20 ml of anhydrous ether was added dropwise to
the dimethylcadmium reagent, which was cooled to 0° by means of an ice bath. The bath was removed after the addition was complete (25 min) and the mixture stirred for 1 hr. The mixture was then cooled and hydrolyzed with saturated NaHCO₃ solution. The layers were separated and the aqueous layer extracted twice with ether. After combining the ether layers, drying over MgSO₄, and concentrating on a rotary evaporator at 25°, there was obtained 5.4 g of crude product: ir (no. 8462, neat) 3450 (OH) and 1530, 1350 cm⁻¹ (NO₂); nmr (no. 6159, CCl₂H₂) δ 1.54 (s, CH₃C(OH)), 7.90 (m, aromatic). Both ir and nmr spectra indicated that very little ketone was left in the crude product. Attempted distillation of the sample at reduced pressure caused decomposition and solidification of the residue. This can be attributed to the presence of cadmium salts which cause dehydration at elevated temperatures during the distillation. Attempted removal of the cadmium salts in other reaction runs by addition of benzene caused precipitation of a gum which was only soluble in methylene chloride. This indicated that the cadmium salts present are held tightly and cannot be precipitated alone. Further purification was not attempted.

Reaction of in situ Diethylcadmium (Br,Cl) with m-Nitrobenzaldehyde in Ether.

To a cold, stirred mixture of 6.13 g of CdCl₂ (33.5 mmol) and 20 ml of anhydrous ether was added 89 ml of ethereal 0.75 M C₂H₅MgBr at such a rate that no ebullition occurred. The resultant mixture was stirred for 30 min at ambient temperature before a Gilman test was shown to be negative.

A solution of 10.1 g of m-nitrobenzaldehyde in 25 ml of THF was added dropwise (15 min) to the stirred
diethylcadmium reagent at ambient temperature. The mixture was stirred for 45 min after the addition was complete. The mixture was then hydrolyzed by pouring onto 20 g of ice and 60 ml of saturated ammonium chloride solution. The organic layer was separated and the aqueous layer extracted twice with ether. After drying and concentrating on a rotary evaporator, the crude product (12.3 g) was distilled under vacuum. Material was collected (5.92 g) whose boiling point ranged from 144° to 159° (1.15 mm). After standing, a solid formed which was removed by suction filtration. This was identified as m-nitropropiophenone: 1.2 g, mp 88-89° [lit. 52 mp 88-89°]; ir (no. 3622, mull) 1695 cm⁻¹ (CO); nmr (no. 4541, CCl₄) δ 0.96 (t, CH₃), 2.80 (m, CH₂), 7.79 (m, aromatic). The residual liquid was tentatively identified as m-nitrobenzyl alcohol: ir (no. 3621, neat) 3475 cm⁻¹ (OH); nmr (no. 4540, CCl₄) δ 4.20 (s, OH), 4.35 (s, CH₂), 7.63 (m, aromatic).

Reaction of in situ Diethylcadmium (Br,Cl) with Cyclohexanone.

Diethyl cadmium was prepared by addition of 77 ml of 0.87 M ethylmagnesium bromide (0.067 mol) to a stirred mixture of 7.13 g of CdCl₂ (0.033 mol) and 60 ml of anhydrous ether. The Gilman test was negative after 15 min at ambient temperature. A solution of 1.0 g of cyclohexanone (0.010 mol) in 15 ml of anhydrous ether was added dropwise to the stirred diethylcadmium reagent over a period of 5 min. The mixture was stirred for 180 min after the addition was complete and then cooled in an ice bath and hydrolyzed with 50 ml of saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted twice with ether. The ether layers were combined and dried over MgSO₄. After removal of the drying agent by filtration and concentration
by use of a rotary evaporator, the crude product weighed 1.0 g. Glpc analysis on Carbowax showed very little of the desired alcohol to be present, cyclohexanone being the major constituent.

Reaction of in situ Diethylcadmium (I,Cl) with Cyclohexanone.

Diethylcadmium was prepared by the addition of 95 ml of 1.50 M ethylmagnesium iodide (0.143 mol) to a stirred mixture of 13.05 g of CdCl₂ (0.071 mol) and 90 ml of anhydrous ether. The Gilman test was negative after 15 min at ambient temperature. A solution of 3.5 g of cyclohexanone (0.036 mol) in 15 ml of anhydrous ether was added dropwise over a period of 5 min. The mixture was stirred for 180 min after the addition was complete, then cooled in an ice bath, and hydrolyzed with 50 ml of saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted with ether. The ether layers were combined and dried over MgSO₄. After removal of the drying agent by filtration and concentration on a rotary evaporator, the crude product weighed 3.5 g. Analysis on Carbowax and FFAP indicated that the entire product was 1-ethylcyclohexanol; no cyclohexanone appeared in the glpc analysis. On this basis the yield of alcohol was 80%.

Reaction of Ethylcadmium Halide (I,Cl) with Cyclohexanone.

Ethylcadmium halide was prepared by the addition of 100 ml of 1.5 M ethylmagnesium iodide (0.15 mol) to a stirred mixture of 27.3 g of CdCl₂ (0.15 mol) and 90 ml of anhydrous ether. The Gilman test was negative after 30 min at ambient temperature. A solution of 3.0 g of cyclohexanone (0.031 mol) in 15 ml of anhydrous ether was added dropwise to the
stirred cadmium reagent. The mixture was stirred for 180 min at ambient temperature, then cooled in an ice bath, and hydrolyzed with 50 ml of saturated ammonium chloride solution. After the layers were worked up as described previously, 2.8 g of crude product was isolated. The sample was shown to contain both cyclohexanone and cyclohexanol from its ir (no. 7390) and nmr (no. 4718) spectra. Glpc analysis on Carbowax indicated that the mixture was 33% 1-ethylcyclohexanol. Based on the amount isolated, this corresponded to a 22.6% yield of alcohol, while 62% of the cyclohexanone was recovered.

Reaction of in situ Dimethylcadmium (I,Cl) with Cyclohexanone.

Dimethylcadmium was prepared by the addition of 85 ml of 1.79 M methylmagnesium iodide (0.152 mol) to a stirred mixture of 13.9 g of CdCl₂ (0.076 mol) and 90 ml of anhydrous ether. The Gilman test was shown to be negative after 15 min at ambient temperature. A solution of 3.7 g of cyclohexanone (0.038 mol) in 15 ml of anhydrous ether was added dropwise to the stirred cadmium reagent over a period of 5 min. The reaction was stirred for 40 min after the addition was complete, then cooled in an ice bath and hydrolyzed with 50 ml of saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted twice with ether, the ether layers being combined and dried over MgSO₄. After removal of the drying agent by filtration and concentration by use of a rotary evaporator, the crude product weighed 4.0 g. Glpc analysis on Apiezon L indicated only 1-methylcyclohexanol, with no trace of cyclohexanone. Yield based on 4.0 g of product was 93%.
Reaction of Methylcyclohexoxycadmium (I,Cl) with Cyclohexa-
none.

Dimethylcadmium reagent was prepared by the addition of 87 ml of 1.83 M methylmagnesium iodide (0.159 mol) to a stirred mixture of 14.5 g of CdCl₂ (0.079 mol) and 90 ml of anhydrous ether. The Gilman test was negative after 15 min at ambient temperature. The cadmium reagent was then cooled in an ice bath, and 7.8 g of freshly distilled cyclohexanol (0.079 mol) dissolved in 15 ml of anhydrous ether was added dropwise. After the addition was complete, the bath was removed and the mixture stirred for 30 min at ambient temperature. A solution of 3.8 g of cyclohexanone (0.0395 mol) in 15 ml of anhydrous ether was added dropwise over a period of 5 min. The reaction mixture was stirred for 40 min, then cooled in an ice bath, and hydrolyzed with 50 ml of saturated ammonium chloride solution. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined, dried, and concentrated on a rotary evaporator; the final crude product weighed 10.4 g. Glpc analysis on Apiezon L and STAP showed that 19.9% of the mixture was 1-methylcyclohexanol (together with cyclohexanone and cyclohexanol). A comparison of the areas under the 1-methylcyclohexanol and cyclohexanone peaks indicated that this ratio corresponded to 40% 1-methylcyclo-
hexanol. The yield of 1-methylcyclohexanol based on isolated product was 19.9% of 10.4 g, or 2.0 g (45% yield): nmr (no. 4711) and ir (no. 7389) spectra indicated that the isolated product was indeed a mixture of the three com-
ponents.
The Reaction of in situ Dimethylcadmium (I,Cl) with Acetophenone.

A solution of 38.8 ml of 1.7 M MeMgI (66 mmol) was added to a stirred, cold mixture of 6.1 g of CdCl₂ (33.3 mmol) and 45 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The solution was then stirred at ambient temperature for 15 min before a Gilman test was taken.

A 2.0-g sample of acetophenone (16.7 mmol), dissolved in 10 ml of anhydrous ether, was added dropwise to the stirred dimethylcadmium reagent. The solution was stirred for 1 hr after the addition was complete. The mixture was cooled in an ice bath and hydrolyzed with 50 ml of saturated NaHCO₃ solution. The ice bath was removed and the mixture stirred for an additional 5 min. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the ether solution concentrated on a rotary evaporator. Final weight of product was 2.3 g. The infrared spectrum (no. 7745) contained only weak carbonyl absorption at 1695 cm⁻¹; nmr (no. 4913, CCl₄) δ 1.46 (s, 6, CH₃), 3.40 (s, 1, OH), 7.29 (m, 5, aromatic).

Reaction of in situ Di-n-propylcadmium (Br,Br) with Heptanal.

A solution of 15.1 ml of 2.32 M n-PrMgBr (35.1 mmol) was added to a stirred, cold mixture of 4.77 g CdBr₂ (17.6 mmol) and 28 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The ice bath was removed and the solution stirred for 15 min before a Gilman test was taken.
A solution of 2.0 g of heptanal (17.6 mmol) in 10 ml of anhydrous ether was added dropwise to the stirred cadmium reagent. After the addition was complete, the reaction mixture was stirred for an additional 90 min. The mixture was cooled in an ice-salt bath and hydrolyzed with 50 ml of saturated ammonium chloride solution such that the temperature did not exceed 20°. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the solution concentrated on a rotary evaporator at 25° or below. Yield of crude product was 2.3 g. Glpc analysis on Apiezon L indicated that there was 1.7% heptanal, 3.6% heptanol, 6.5% 4-decanone, and 88.2% 4-decanol. Heptanol was prepared by LiAlH₄ reduction of heptanal and 4-decanol prepared by reaction of n-PrMgBr on heptanal. The preparation and identification of 4-decanone was done by E. Goller. Reaction of n-Propylcadmium Bromide with Heptanal.

Experimental conditions were the same as those described above, except that in this case 9.54 g of CdBr₂ (35.2 mmol) was used and the solution was stirred for 30 min before a Gilman test was taken. The crude product weighed 2.1 g and was shown by glpc to consist of the following: 5.0% heptanal, 15.4% heptanol, 23.1% 4-decanone, and 56.5% 4-decanol.

Reaction of Phenylmagnesium Bromide with 2-Phenylpropanal.

The experimental procedure was exactly the same as that described below, except no CdCl₂ was added. Nmr analysis (no. 5936) after work-up and isolation indicated that the ratio of the diastereomeric alcohols was 87% erythro and 13% threo, plus or minus 3%. The ratio of the diastereomers was determined by integrating the areas.
under the diastereomeric methyl doublets at a sweep width of 100 cps.

Reaction of in situ Diphenylcadmium (Br,Cl) with 2-Phenylpropanal.

A solution of 15.5 ml of 1.92 M PhMgBr (29.8 mmol) was added to a stirred, cold mixture of 2.74 g of CdCl₂ (14.9 mmol) and 22 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. After the addition was complete, the solution was stirred at ambient temperature for 15 min before a Gilman test was taken.

A solution of 2.0 g of 2-phenylpropanal in 10 ml of anhydrous ether was added dropwise to the diphenylcadmium reagent, while the internal temperature was maintained below 5° by means of an ice bath. After the addition was complete, the mixture was stirred for 15 min at 0°. The bath was removed and the mixture stirred for an additional 105 min. The mixture was cooled to 0° and hydrolyzed with 30 ml of saturated NaHCO₃ solution, the internal temperature being kept below 10°. After the addition was complete, the bath was removed and the mixture stirred for an additional 5 min.

The layers were then separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. After removal of the drying agent and concentration on a rotary evaporator at 25° or below, the final weight of crude product was 3.2 g. Nmr analysis (no. 5937) indicated that all of the starting material had reacted. The results indicated that the ratio was the following: erythro, 90%; threo, 10% (± 3%). These were also determined by integration of the areas under the diastereomeric methyl doublets at a sweep width of 100 cps.
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<tr>
<td>OH</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>1. 10% on Chromosorb W.</td>
<td></td>
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<tr>
<td>(\text{OH} \quad \text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>2. 20% on Chromosorb W.</td>
<td></td>
</tr>
</tbody>
</table>
Preparation of Anhydrous Magnesium Iodide.

This salt was prepared by E. J. Goller. 53

Preparation of Anhydrous Magnesium Bromide.

Magnesium bromide was prepared as previously reported. 56

Reaction of Methylmagnesium Bromide and Iodide with 4-t-Butylcyclohexanone.

The following procedure will serve to illustrate the reaction of the various Grignard and lithium reagents with 4-t-butylcyclohexanone. An ethereal solution of 27.4 ml of 1.90 M methylmagnesium iodide (0.053 mol) was added to 39 ml* of diethyl ether with stirring. The reagent was then cooled with an ice-salt bath and stirred until the internal temperature reached 0-5°. A solution of 2.0 g (0.013 mol) of 4-t-butylcyclohexanone in 15 ml of ether was added at such a rate that the temperature did not exceed 5°. After the addition was complete, the solution was stirred for 30 min more at ice-salt bath temperature. The bath was then removed and the reaction stirred at ambient temperature for an additional 2.5 hr.

The solution was cooled by an ice-salt bath and slowly hydrolyzed with 30 ml of saturated sodium bicarbonate solution such that the internal temperature did not exceed 5°. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layers were dried over magnesium sulfate and concentrated at room temperature on a rotary evaporator, to give 2.0 g of crude product. Analysis was carried out by glpc.

*The volume of ether varied depending on the concentration (0.8 or 0.1 M) of Grignard reagent desired.
Preparation and Analysis of "Purified" Dimethylcadmium.

The preparation of dimethylcadmium was taken from the work of Kraus except extensive fractionation of ether from the cadmium reagent was not performed.

Analysis of the dimethylcadmium was accomplished by treating a 5-ml aliquot of the reagent with 50 ml of 0.58 N sulfuric acid and back titrating with 0.40 N sodium hydroxide. The end point was determined by use of a pH meter and by use of Mallinckrodt "Indicator" (pH range 6-7). Both methods yielded comparable results. No basic cadmium or zinc salts precipitated until after the end point was reached, and values obtained were reproducible. The ether solutions were stored in a refrigerator in serum-capped amber bottles. To check on the possibility of Cd(OH)$_2$ formation in these titrations and its effect on the titration values, control experiments were run. Four times the amount of cadmium present in the above titration was added in the form of CdCl$_2$ to the same amount of standard sulfuric acid solution used in the titrations. This solution was then titrated with standard base under the conditions described above. It was found that the presence of cadmium salt had no effect on the titration values.

Reaction of "Reconstituted" Dimethylcadmium with 4-t-Butyl-cyclohexanone.

The following procedure will serve to illustrate the reaction of "reconstituted" reagent with 4-t-butyl-cyclohexanone. An ethereal solution of 8.9 ml of 1.53 M dimethylcadmium (0.013 mol) was added to a stirred solution of 10.2 ml of 2.64 M magnesium bromide (0.027 mol) and 14 ml of anhydrous ether. Upon complete addition the mixture was
stirred for 15 min at room temperature and then 15 min at 0°. One gram of 4-t-butylcyclohexanone in 5-10 ml of ether was added at such a rate that the temperature did not exceed 5°. The concentration at the start of each reaction was 0.4 M in dimethylcadmium. The mixture was stirred for 30 min at 0° and finally at room temperature for 2.5 hr. The reaction mixture was then cooled, hydrolyzed, and worked up as described above.

Reconstitution with magnesium iodide was accomplished by addition of the solid dietherate to an ethereal solution of dimethylcadmium. The resultant mixture was stirred at room temperature until all the salt had dissolved (ca. 20 min).

Reaction of 4-t-Butylcyclohexanone·MgX₂ with "Purified" Dimethylcadmium.

The following procedure will serve to illustrate the reaction of salt-free dimethylcadmium with prior coordinated 4-t-butylcyclohexanone. A solution of 1.0 g of ketone (0.0065 mol) in 20 ml of anhydrous ether and 10.2 ml of 2.6 M magnesium bromide (0.026 mol) was stirred for 15 min at room temperature. The mixture was cooled to 0° and 8.9 ml of 1.53 M dimethylcadmium added as rapidly as possible below 5°. Addition time normally was 15-30 sec. The reaction mixture was stirred at 0° for 30 min and then at room temperature for 2.5 hr. Hydrolysis and work-up were the same as previously described. As in the earlier reactions, the concentration of dimethylcadmium was 0.4 M.

In cases where iodide salts were used, the solid Mgl₂·2Et₂O was dissolved in the appropriate ethereal
solution of 4-\textit{t}-butylcyclohexanone immediately prior to addition of the organometallic reagent.

**Reaction of \textit{in situ} Dimethylcadmium with 4-\textit{t}-Butylcyclohexanone in Ether.**

The following will serve to illustrate the reaction of the \textit{in situ} dimethylcadmium reagents with 4-\textit{t}-butylcyclohexanone. An ethereal solution of 24.2 ml of 2.2 M methylmagnesium iodide (0.053 mol) was transferred to a stirred mixture of 9.75 g of CdI\textsubscript{2} (0.027 mol) in 42.0 ml of anhydrous ether, which was cooled in an ice bath. The addition was carried out such that no ebullition occurred. The bath was then removed and the solution stirred for 15-30 min before a Gilman test was performed. In all cases the test was negative before the reaction was allowed to proceed.

The reagent was then cooled in an ice bath; and, when the internal temperature reached 0-5°, 2 g of 4-\textit{t}-butylcyclohexanone (0.013 mol) dissolved in 10 ml of anhydrous ether was added and the internal temperature kept below 5°. After the addition was complete, the solution was stirred for 30 min at ice-bath temperature. The bath was then removed and the solution stirred for an additional 150 min.

The solution was cooled and hydrolyzed with 30 ml of saturated NaHCO\textsubscript{3} solution, such that the internal temperature did not exceed 5°. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layer was then dried over MgSO\textsubscript{4} and concentrated on a rotary evaporator at a
temperature of 25° or below. Addition of 75-100 ml of cyclohexane caused precipitation of cadmium salts which were removed by gravity filtration and washed with more cyclohexane. Concentration of the combined filtrates on a rotary evaporator at 25° or below yielded 2.2 g of crude product.

**Reaction of in situ Dimethylcadmium (Br,I) with 4-t-Butylcyclohexanone in THF.**

The procedure was similar to that in ether. In this case 35.9 ml of 1.48 M methylmagnesium bromide (0.053 mol) in THF was transferred to a stirred solution of 9.75 g of CdI₂ (0.027 mol) in 31 ml of anhydrous THF, which was cooled in an ice bath. The bath was then removed and the solution stirred for 30 min, at which time a Gilman test was negative.

The reagent was then cooled in an ice bath; and, when the internal temperature reached 0-5°, 2 g of 4-t-butylcyclohexanone (0.013 mol) dissolved in 10 ml of anhydrous THF was added at such a rate that the internal temperature did not exceed 5°. After the addition was complete, the solution was stirred for 30 min at the ice bath temperature. The bath was then removed and the solution stirred for an additional 150 min.

The solution was then cooled and hydrolyzed with 30 ml of saturated NaHCO₃ solution such that the internal temperature did not exceed 5°. The layers were separated and the aqueous layer extracted three times with ether. The ether and THF layers were combined and dried over MgSO₄. After removal of the drying agent by filtration,
the solution was concentrated on a rotary evaporator at 25° or below. Upon addition of 75 ml of benzene, two liquid phases appeared. Addition of 100 ml more of benzene caused formation of one liquid phase and precipitation of cadmium salts. The salts were removed by filtration and washed with more benzene. The benzene solution was concentrated on the rotary evaporator under the same conditions. Final weight of crude product was 2.1 g. Glpc analysis indicated that traces of salts were left, as evidenced by observation of 3.5% olefin on the chromatogram.

GLPC Analysis of the Reaction Mixtures from in situ Dimethylcadmium and 4-t-Butylcyclohexanone.

Previous work demonstrated that the axial and equatorial alcohols could be separated on a 10' x 1/4" column packed with 20% SAIB on Chromosorb W (60-80 mesh). The response ratios of the two alcohols are known to be the same. The product mixture from reaction of 4-t-butylcyclohexanone with methylmagnesium bromide (0.8 M) was analyzed, and the values obtained compared favorably with those reported. Configurational assignments were made on this basis. It was found that if the ketone was present in an appreciable amount, this column could not be used. Analysis on a 10' x 1/4" 10% FFAP column at 190° and a flow of 75 ml/min could be used in these cases, and the order of elution was the same as on SAIB. All values reported were determined on the FFAP column.

Glpc analysis of the crude reaction mixtures indicated that in some instances a considerable amount of zinc and cadmium salts was carried through the work-up procedure, as evidenced by the presence of variable amounts of 1-methyl-4-t-butylcyclohexene in addition...
to the desired alcohols. The % olefin increased drastically unless the injector port of the chromatograph was cleaned regularly. Infrared and nmr spectra gave no evidence of olefin in the samples prior to injection. Some of the excess salts could be removed by dissolving the sample in cyclohexane or benzene and filtering the mixture.

1-Methyl-4-\textsuperscript{t}-butylcyclohexene was collected by preparative glpc. The ether solutions of zinc salts were injected into the chromatograph and the injector port coated with salt. Subsequent injection of the mixture of alcohols obtained from reaction of methylmagnesium iodide with ketone produced mainly 1-methyl-4-\textsuperscript{t}-butylcyclohexene. Its nmr spectrum ($\text{CCl}_4$) was essentially the same as that recently reported by Allinger.\textsuperscript{58b} Its infrared spectrum was also consistent\textsuperscript{59} with the assigned structure.

By varying the amount of salt on the injector port, the course of the dehydration could be followed. No change in the (Z)/(E) ratio was detected until the amount of olefin exceeded 10%. Above 10% small differences were noted and the values indicated that the (E)-alcohol (equatorial OH) was being dehydrated at a faster rate than the (Z)-alcohol.

Control Experiments.
1. The isolated product obtained from the reaction of methylmagnesium bromide (0.1 M) with 4-\textsuperscript{t}-butylcyclohexanone (Table 4) was dissolved in 10 ml of ether and added to dimethylcadmium reagent under the conditions previously described for the reaction of \textit{in situ} reagents with ketone. After hydrolysis and work-up, percentages obtained by glpc were unchanged within experimental error (± 1%).
2. The precipitated cadmium salts, which occurred when cyclohexane was added, were redissolved in ether and the sample injected into the chromatograph. No trace of olefin or alcoholic products was observed.

Reaction of in situ Di-n-propylcadmium with 4-t-Butylcyclohexanone in Ether.

The following experimental procedure will serve to illustrate the reaction of in situ di-n-propylcadmium reagents with 4-t-butylcyclohexanone. An ethereal solution of 11.5 ml of 2.32 M n-propylmagnesium bromide (26.6 mmol) was added to a stirred mixture of 4.87 g of CdI₂ (13.3 mmol) and 22 ml of anhydrous ether, which was cooled in an ice bath. This addition was carried out such that no ebullition occurred. The ice bath was removed, and the Gilman test was negative after 15 min.

The di-n-propylcadmium reagent was then cooled in an ice bath; and, when the internal temperature reached 0-5°, 1 g of 4-t-butylcyclohexanone (65 mmol) dissolved in 10 ml of anhydrous ether was added such that the internal temperature did not exceed 5° (addition time approximately 5 min). After the addition was complete, the mixture was stirred for 15 min at the ice bath temperature, and then for 105 min at ambient temperature.

The solution was cooled in an ice-bath to an internal temperature of 0° and hydrolyzed with 30 ml of saturated NaHCO₃ solution such that the internal temperature did not exceed 10°. The bath was then removed and the mixture stirred for an additional 5 min. After work-up and removal of cadmium salts, the crude product weighed 1.0 g.
Reaction of n-Propylmagnesium Iodide with 4-t-Butylcyclohexanone in Ether.

The following experimental procedure will serve to illustrate the reaction of n-propyl Grignard reagents with 4-t-butylcyclohexanone. An ethereal solution of 13.3 ml of 2.0 M methylmagnesium iodide (26.6 mmol) was added with stirring to 21 ml of anhydrous ether, which was cooled in an ice bath. The bath was removed and the solution stirred for 15 min.

The Grignard reagent was then cooled in an ice bath to an internal temperature of 0-5°, and a solution of 1 g of 4-t-butylcyclohexanone in 10 ml of anhydrous ether added at such a rate that the internal temperature did not exceed 5° (approximately 5 min). After the addition was complete, the mixture was stirred for 15 min at the ice bath temperature, and then for 105 min at ambient temperature.

The solution was then cooled in an ice bath to an internal temperature of 0° and hydrolyzed with 30 ml of saturated NaHCO₃ solution such that the internal temperature did not exceed 10°. The bath was then removed and the mixture stirred for an additional 5 min. The crude product after work-up weighed 1.0 g.

Trimethylamine Borane Reduction of 4-t-Butylcyclohexanone.

To a stirred solution of 100 ml of dry diglyme, 10 g of 4-t-butylcyclohexanone (65 mmol), and 1.6 g of trimethylamine borane (22 mmol), which was cooled in an ice bath, was slowly added 6.5 ml of boron trifluoride etherate (65 mmol). After the addition was complete, the bath was removed and the mixture stirred for 12 hr. The mixture was then poured into 150 ml of 10% NaHCO₃ solution
and extracted with pentane. After work-up there was obtained 10.1 g of crude product which was shown by glpc to contain 2% 4-t-butylcyclohexanone and about equal amounts of the isomeric reduction alcohols.

**Separation of cis (axial)- and trans-(equatorial)-4-t-Butylcyclohexanols.**

A 4-ft glass column of 1-in diameter was packed with 250 g of neutral alumina (Brockmann Activity no. 1) with pentane as solvent. Then 8 g of the 4-t-butylcyclohexanol mixture from the (CH$_3$)$_3$N·BH$_3$ reduction, dissolved in a minimum amount of pentane, was deposited on the column. Fractions of 125 ml each were collected, concentrated, and analyzed by glpc.

The column was eluted with 6 l. of pentane and no alcohols were obtained. Instead there was obtained a liquid whose retention time was the same as that of the olefin found in some of the analyses where cadmium salts were present. The material was collected by preparative glpc and shown not to be the dehydration product; nmr (no. 5852, CCl$_4$) $\delta$ 1.15 (t), 3.45 (m), 3.5 (s). Identification was not attempted.

Next 1 l. of 1% ether-pentane, 2 l. of 5% ether-pentane, and 2 l. of 10% ether-pentane were used successively. The alcohols were eluted with the last solvent in the following order: axial alcohol (4 g, 98% purity), equatorial alcohol (4 g, 99% purity).

**GLPC Analysis of the Reaction Mixture from Di-n-propylcadmium and 4-t-Butylcyclohexanone.**

Analysis was conducted on a 10% FFAP or 10% STAP (10' x 1/4") column supported on Chromosorb W (60-80 mesh) at a temperature of 130° or 140°, respectively, and a flow rate of 100 ml/min. Under these conditions the reduction
and addition products were nicely separated. Retention times (see Table 2) of the reduction alcohols were compared with those of a commercial sample and one prepared by LiAlH₄ reduction of 4-t-butylcyclohexanone. The configurational assignments were based upon previous work in which it had been shown that the equatorial alcohol predominated substantially. The configurational assignment of the addition products was also based upon previous work where the axial alcohol was the predominant isomer in the reaction of propyl Grignard reagents with 4-t-butylcyclohexanone.

In order to identify dehydration products from the 2° (reduction) and 3° (addition) alcohols, dehydration experiments were performed. A commercial sample of the 2° 4-t-butylcyclohexanol was dehydrated by the action of phosphoric acid and the products distilled at atmospheric pressure. The clear liquid obtained was spectrally similar to 1-methyl-4-t-butylcyclohexene reported previously: ir (no. 4944, neat) 3025, 698, 650 cm⁻¹ (C=C); nmr (no. 5867, CCl₄) δ 0.85 (t, t-butyl), 1.20 (m), 1.60 (s, broad), 5.60 (s, broad), 1.91 (s, broad), 1.01 (s), 5.40 (s, broad). Glpc analysis on FFAP and STAP showed the major component to have a slightly longer retention time than that of benzene. Two minor impurities were also present.

To compare these results to those of dehydration on the column, a commercial mixture of 4-t-butylcyclohexanol in ether was mixed with ethereal ZnI₂. This sample was injected under the same chromatographic conditions normally used for analysis. The amount of dehydration could be increased by addition of more ZnI₂ to the sample. Material appeared whose retention time was the same as that found for the olefin produced by phosphoric acid dehydration. The same
impurities appeared in approximately the same proportions, implying that some rearrangement may have occurred.

To determine where the product from dehydration of the 3° alcohols occurred on the chromatogram, the crude product from a di-n-propylcadmium reaction without treatment with benzene was injected under the same conditions. A major peak appeared with a longer retention time (see Table 2) than that of the dehydration product from the 2° reduction alcohols. After the crude product was treated with benzene as previously described, this peak disappeared or was substantially reduced.

**Attempted Equilibration of cis-(axial)-4-t-Butylcyclohexanol.**

A mixture of 0.6 g of 4-t-butylcyclohexanone and 0.4 g of 4-t-butylcyclohexanol (98% axial) was dissolved in 10 ml of anhydrous ether and added to in situ di-n-propylcadmium (Br,I) under the same reaction conditions as previously described for the reaction of di-n-propylcadmium (Br,I) with 4-t-butylcyclohexanone. Aliquots were taken at 3, 8, 12, and 23 hr and hydrolyzed as previously described. Glpc analysis of the product after 23 hr will be used to demonstrate the method of analyzing the data obtained.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>% Reduction (equatorial OH)</th>
<th>% Add (axial OH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-hr product:</td>
<td>7.4%</td>
<td>41.9% (36.8%)</td>
</tr>
<tr>
<td>% Reaction = 52.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of Add/Red = 10.0</td>
<td>(Previously determined from the reaction of in situ di-n-propylcadmium (Br,I) with 4-t-butylcyclohexanone)</td>
<td></td>
</tr>
</tbody>
</table>
Expected % Red = 5.07% (50.7%/%Red = 10.0)

(Stereochemistry of the reduction product previously determined in the reaction of di-n-propylcadmium with 4-t-butylcyclohexanone: 72% equatorial and 28% axial)

Expected New axial Reduction Product: 28% of 5.07 = 1.42%
Expected New equatorial Reduction Product: 72% of 5.07 = 3.65%

Total equatorial Reduction Product Expected:
3.65%(new) + 1.1%(initial) = 4.75% (observed 5.1%)

Total axial Reduction Product Expected:
1.42%(new) + 39.2%(initial) = 40.6%

Normalized % axial Reduction Product Expected: 90.1%

Observed: 87.5%

The experimental error in all the percentages used in these calculations is ± 2%. Another indication that equilibration did not occur was the observation that the normalized % axial reduction product varied from 89.8% to 87.5% from the 3-hr aliquot to the 23-hr aliquot. A second equilibration experiment afforded similar results. Data from the glpc analysis showed that the stereochemistry of the addition products was the same in every aliquot and equal to that obtained in the original reaction of in situ di-n-propylcadmium (Br,I) with 4-t-butylcyclohexanone.
Attempted Equilibration of trans-(equatorial)-4-t-Butylcyclohexanol.

A mixture of 0.8 g of 4-t-butylcyclohexanol (88.1% equatorial) and 0.2 g of 4-t-butylcyclohexanone was dissolved in 10 ml of anhydrous ether and added to in situ di-n-propylcadmium (Br,I) under the same reaction conditions as described above. Aliquots were taken at 3 and 13.75 hr. Glpc analysis of the product after 3 hr and 13.75 hr indicated that no equilibration had occurred. Analysis of the glpc data was exactly the same as that described above. The normalized % equatorial reduction product expected after 13.75 hr was determined to be 87.9%. The value observed was 88.3% and indicated that no equilibration had occurred. Again the stereochemistry of the addition products was the same as that observed without the presence of the added 2° alcohols, and the experimental error was ± 2%.

Reaction of in situ Dimethylcadmium with 2-Phenylpropanal.

A solution of 15 ml of 2.0 M MeMgI (30 mmol) was added via a 20-ml syringe to a stirred, cold mixture of 2.74 g of CdCl₂ (14.9 mmol) and 22 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The solution was then stirred at room temperature for 20-30 min before the Gilman test was performed. In all cases the test was negative before the reaction was allowed to proceed to the next step.

The dimethylcadmium reagent was then cooled in an ice-salt bath to an internal temperature of 0°; 2 g of 2-phenylpropanal (14.9 mmol) dissolved in 10 ml of anhydrous ether was added at such a rate that the internal temperature did not exceed 5°. The solution was stirred for 15 min after the addition was complete at the ice-salt bath temperature.
The bath was then removed and the reaction mixture stirred for an additional 105 min.

The solution was cooled in an ice-salt bath and hydrolyzed with 30 ml of saturated NaHCO₃ solution at such a rate that the internal temperature did not exceed 10°. The solution was stirred for an additional 5 min after removal of the bath. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the ether solution concentrated on a rotary evaporator at 25° or below. The residue was diluted with 30-60 ml of anhydrous benzene. The resultant precipitated cadmium salts were removed by gravity filtration. The filtrate was concentrated under the same conditions and the residue analyzed by glpc. Final weight of the product after all the benzene was removed was 2.1 g. Olefin formation caused by the presence of cadmium salts was a less serious problem than in the reactions with 4-tert-butylcyclohexanone.

Reaction of Methylmagnesium Iodide with 2-Phenylpropanal.

A solution of 15 ml of 2.0 M MeMgl (30 mmol) was added by means of a 20-ml syringe to 22 ml of anhydrous ether with stirring. To prevent the loss of ether, the flask was cooled during the addition of the MeMgl. The Grignard reagent was then cooled with an ice-salt bath to an internal temperature of 0°. A solution of 2-phenylpropanal (14.9 mmol) in 10 ml of anhydrous ether was added at such a rate that the internal temperature did not exceed 5°. After the addition was complete the solution was stirred for an additional 15 min at the ice-salt bath temperature.
### Table 3

**Formation of in situ Cadmium Reagent for the Reaction with 2-Phenylpropanal.**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Final M</th>
<th>Grignard Reagent (2 M in ether)</th>
<th>Salt</th>
<th>Additional Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(\text{CH}_3)_2\text{Cd (I, I)}$</td>
<td>0.4 M</td>
<td>15 ml MeMgI</td>
<td>5.45 g CdI₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$(\text{CH}_3)_2\text{Cd (I, Cl)}$</td>
<td>0.4 M</td>
<td>15 ml MeMgI</td>
<td>2.74 g CdCl₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$(\text{CH}_3)_2\text{Cd (Br, Br)}$</td>
<td>0.4 M</td>
<td>15 ml MeMgBr</td>
<td>4.06 g CdBr₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CdX (I, Cl)}$</td>
<td>0.8 M</td>
<td>15 ml MeMgI</td>
<td>5.48 g CdCl₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CdBr}$</td>
<td>0.8 M</td>
<td>15 ml MeMgBr</td>
<td>8.12 g CdBr₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CdI}$</td>
<td>0.8 M</td>
<td>15 ml MeMgI</td>
<td>10.9 g CdI₂</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{Cl}_3\text{MgBr}$</td>
<td>0.8 M</td>
<td>15 ml MeMgBr</td>
<td>---</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{Cl}_3\text{MgI}$</td>
<td>0.8 M</td>
<td>15 ml MeMgI</td>
<td>---</td>
<td>22 ml Ether</td>
</tr>
<tr>
<td>$\text{CH}_3\text{MgI}$</td>
<td>0.1 M</td>
<td>15 ml MeMgI</td>
<td>---</td>
<td>285 ml Ether</td>
</tr>
</tbody>
</table>
The bath was removed and the solution stirred at ambient temperature for an additional 105 min.

The solution was then cooled in an ice-salt bath and hydrolyzed with 30 ml of saturated NaHCO₃ solution at such a rate that the internal temperature did not exceed 10°. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined, dried over MgSO₄, and concentrated on a rotary evaporator at 25° or below, yielding 2.1 g of crude product, which was analyzed by glpc.

**GLPC Analysis of the Reaction Mixture from Dimethylcadmium and 2-Phenylpropanal.**

Analysis was conducted on a 101 x 1/4" column packed with 10% FFAP on Chromosorb W (60-80 mesh) at a temperature of 170° and a flow rate of 67 ml/min. The product obtained from the reaction of methylmagnesium iodide with 2-phenylpropanal was subjected to glpc analysis and the two major products collected by preparative glpc. Comparison of the nmr spectra of the two diastereomeric 3-phenyl-2-butanol obtained with those reported in the literature allowed a tentative configurational assignment. The material with the shorter retention time was designated threo and the material with the longer retention time erythro (see Table 2):

\[
\text{nmr (threo)}: \quad \text{(no. 5235, } \text{CCl}_4) \delta 1.10 \text{(d), 1.22 (d), 2.61 (m), 3.70 (m), 7.15 (s).}
\]
\[
\text{nmr (erythro): } \quad \text{(no. 5236, } \text{CCl}_4) \delta 0.92 \text{(d), 1.22 (d), 2.58 (m), 3.74 (m), 7.14 (s).}
\]

After each diastereomer had been isolated as described, glpc analysis and comparison of the retention times confirmed the assignments.
Lithium aluminum hydride reduction of 2-phenylpropanal provided 2-phenyl-1-propanol, which would have to occur by reduction in the system. Glpc analysis indicated that the retention time was longer than that of the additional alcohols so the peaks were well separated. Preparation of 3-phenylbutan-2-one was accomplished by CrO$_3$ oxidation in acetone solution of a crude mixture of the butanols obtained by the reaction of 2-phenylpropanal with methylmagnesium iodide. The ketone was not isolated from the reaction mixture, but the reaction was followed by nmr and glpc. Nmr (no. 5939, CCl$_4$) indicated that a singlet appeared at $\delta$ 2.10, which was assigned to the methyl ketone resonance. Glpc analysis indicated that the ketone had a retention time slightly longer than that of the starting aldehyde. The configurational composition of the remaining 2-phenyl-2-butanols was unchanged after 15% of the alcohols had been oxidized to the methyl ketone. Throughout the experiments with dimethylcadmium and 2-phenylpropanal, the ketone and reduction alcohol totaled no more than 3% of the total product.

Isolation of threo-3-Phenyl-2-butanol.$^{54}$

A mixture of 11 g of isomeric 3-phenyl-2-butanol from the reaction of 2-phenylpropanal with MeMgI, 12.5 g of anhydrous pyridine, and 11.2 g of phthalic anhydride was heated at reflux (oil bath) for 90 min. It was then cooled and dissolved in benzene. The benzene solution was extracted twice with excess dilute sulfuric acid, washed with water, and dried over MgSO$_4$. The solution was concentrated on a rotary evaporator and the residue dissolved in two volumes of ethyl acetate. Petroleum ether (bp 40-60°)
was added until the solution became turbid. The product which crystallized was collected by suction filtration (7.5 g).

This crude monoacid phthalate was placed in a 100-ml round-bottomed flask together with 4 g of sodium hydroxide, 4 g of potassium hydroxide, and 40 ml of water. After being heated at reflux for 16 hr, the solution was cooled and then extracted with low-boiling petroleum ether. The organic layer was washed with water and dried over MgSO₄. The drying agent was removed and the solution concentrated on a rotary evaporator. The final product, weighing 3.4 g, consisted of 90.5% threo isomer (glpc analysis).

Isolation of erythro-3-Phenyl-2-butanol.

A chromatographic column was prepared with 200 g of neutral alumina (Brockmann Activity no. 1) and pentane as solvent. A 6.5 g sample of isomeric alcohols obtained from the reaction of 2-phenylpropanal with MeMgI in a small amount of pentane was placed on the column. The eluent was varied as listed below, 125-ml fractions being collected throughout.

1.5 l. pentane
800 ml 1% ether in pentane
400 ml 5% ether in pentane
200 ml 10% ether in pentane
200 ml 20% ether in pentane
600 ml of ether
Progress of the elution was followed by glpc analysis of the residues after concentration of the fractions. There was obtained 3.2 g of a mixture consisting of 80.4% *erythro* and 19.6% *threo* isomers (glpc) in the first two fractions with ether as eluent.

**Attempted Equilibration of erythro-3-Phenyl-2-butanol.**

A mixture of 1.2 g of 3-phenyl-2-butanol (isomer distribution 80.4% *erythro*, 19.6% *threo*) and 0.9 g of 2-phenylpropanal was dissolved in 10 ml of anhydrous ether. Dimethylcadmium (*in situ*, Br,Br) was prepared as previously described and the above mixture added under the same conditions employed for the reaction of dimethylcadmium reagents with 2-phenylpropanal. Aliquots were taken and hydrolyzed with cold saturated NaHCO₃ solution at 3 and 16 hr. After 3 hr there was less than 1% aldehyde remaining. The data obtained from the 16-hr aliquot will be used to demonstrate the method of analysis.

<table>
<thead>
<tr>
<th></th>
<th>Aldehyde</th>
<th>% <em>erythro</em></th>
<th>% <em>threo</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting mixture:</strong></td>
<td>40.3%</td>
<td>48.0</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>16-hr product:</strong></td>
<td>less than 1%</td>
<td>72.5</td>
<td>27.5</td>
</tr>
</tbody>
</table>

\[
\text{% reaction} = 40\%
\]

(stereochemistry of addition products resulting from reaction with the aldehyde was previously determined: 59.8% *erythro*, 40.2% *threo*)

\[
\text{% New *erythro* Expected: } 59.8\% \text{ of } 40.3 = 24.2\%
\]

\[
\text{% New *threo* Expected: } 40.2\% \text{ of } 40.3 = 16.2\%
\]
Total erythro Product Expected:
\[48.0\% \text{ (initial)} + 24.2\% \text{ (new)} = 72.2\%\]

Total threo Product Expected:
\[11.7\% \text{ (initial)} + 16.2\% \text{ (new)} = 27.8\%\]

Values obtained after 16 hr: erythro = 72.5%

threo = 27.5%

This indicates that no equilibration occurred during the reaction. The erythro content was the same at 3 hr and 16 hr, also indicating no equilibration had occurred. The experimental error was ± 1% on all values reported above.

Attempted Equilibration of threo-3-Phenyl-2-butanol.

A mixture of 1.3 g of 3-phenyl-2-butanol (isomer distribution 90.5% threo, 9.5% erythro) and 0.9 g of 2-phenylpropanal was dissolved in 10 ml of anhydrous ether. In situ dimethylcadmium (Br,Br) was prepared as previously described and the above mixture added under the same conditions employed for the reaction of dimethylcadmium reagents with 2-phenylpropanal. Aliquots were taken at 5 min, 1.5, 9, and 12 hr, and hydrolyzed with cold, saturated NaHCO₃ solution.

<table>
<thead>
<tr>
<th>Aliquot</th>
<th>% threo</th>
<th>% aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>71.4</td>
<td>7</td>
</tr>
<tr>
<td>1.5 hr</td>
<td>70.5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>9.0 hr</td>
<td>71.5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>12.0 hr</td>
<td>71.5</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>
Analysis of the data, as described previously for the equilibration of the erythro isomer, indicated that the total amount of threo expected was 72.2%. The value observed (71.5%) was well within the experimental error (± 1%) and indicates that no equilibration had occurred.

**Preparation of 2-Phenylbutyryl Chloride.**

Fifty grams of 2-phenylbutyric acid (0.305 mol) was placed in a 250-ml three-necked, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. After 135 ml of thionyl chloride (224 g; 1.90 mol) had been added, the mixture was stirred briefly at ambient temperature and the contents stirred at room temperature for an additional 0.5 hr. The excess thionyl chloride was distilled at atmospheric pressure. The 2-phenylbutyryl chloride was distilled, bp 84.5-83°C (3.7 mm). Yield was 54 g (97%).

**Preparation of Imidazolide of 2-Phenylbutyric acid.**

A solution of imidazole (40.4 g; 0.594 mol) in 300 ml of anhydrous THF was placed in a 1-L three-necked, round-bottomed flask equipped with a magnetic stirrer and a dropping funnel. A solution of 54 g of 2-phenylbutyryl chloride (0.297 mol) in 200 ml of anhydrous THF was added over a period of 30 min at room temperature. The contents were then refluxed for 1 hr and stirred at room temperature for an additional 4 hr. The solution was cooled in an ice bath and the imidazole hydrochloride removed by suction filtration. The solvent was removed on a rotary evaporator.
to give a light yellow solid. The solid was extracted with cold benzene and the white solid imidazolide collected by suction filtration. This yielded 45 g of imidazolide, mp 86-89°.

The benzene solution used for extraction was then washed with dilute HCl and saturated NaHCO₃ solution. Next it was dried over MgSO₄. The drying agent was then removed and the solution evaporated to dryness with the rotary evaporator. The solid remaining was washed with a cold petroleum ether-benzene solution (3:1 v/v) and the white solid collected by suction filtration; 10 g, mp 86-89°. The combined fractions amounted to 55 g (0.26 mol) of imidazolide (87%).

Preparation of 2-Phenylbutanal.

Reduction of the above imidazolide was accomplished with LiAlH₄. 53

Reaction of Methylmagnesium Bromide with 2-Phenylbutanal. 54

A solution of 13.5 ml of 1.98 M methylmagnesium bromide (26.8 mmol) was added via a 20-ml syringe to 20 ml of anhydrous ether with stirring. The reagent was then cooled by means of an ice-salt bath to an internal temperature of 0-5°; 2 g of 2-phenylbutanal (13.4 mmol) in 10 ml of anhydrous ether was added and the internal temperature maintained below 5°. The solution was stirred for 15 min at the bath temperature after the addition was complete. The bath was removed and the solution stirred at ambient temperature for an additional 105 min.

The solution was then cooled to an internal temperature of 0° and hydrolyzed with 30 ml of saturated
NaHCO₃ solution at such a rate that the internal temperature did not exceed 10°. The solution was stirred for an additional 5 min after removal of the ice bath. The layers were separated and the aqueous layer extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the solution concentrated on a rotary evaporator at 25° or below. Final weight of crude product was 2.1 g.

Reaction of in situ Dimethylcadmium (Br,Br) with 2-Phenylbutanal.

A solution of 13.5 ml of 1.98 M MeMgBr (26.8 mmol) was added via a 20-ml syringe to a stirred, cold mixture of 3.65 g of CdBr₂ (13.4 mmol) and 20 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The solution was then stirred at ambient temperature for 15 min before the Gilman test was taken. The test was negative before the reaction was allowed to proceed to the next step.

The dimethylcadmium reagent was then cooled to an internal temperature of 0-5°; 2 g of 2-phenylbutanal in 10 ml of anhydrous ether was added at such a rate that the internal temperature did not exceed 5°. The solution was then stirred for 15 min at ice-salt bath temperature after the addition was complete. The solution was stirred at ambient temperature for an additional 105 min.

It was cooled in an ice-salt bath to an internal temperature of 0° and hydrolyzed with 30 ml of saturated NaHCO₃ solution at such a rate that the internal temperature did not exceed 10°. The solution was stirred for an additional 5 min after removal of the bath. The layers were
separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the ether layer concentrated on a rotary evaporator at 25° or below. Addition of 50-75 ml of anhydrous benzene caused precipitation of cadmium salts, which were removed by filtration. The filtrate was concentrated in the same manner and the residue analyzed by glpc. Final weight of crude product after removal of benzene was 2.1 g.

GLPC Analysis of the Reaction Mixtures from 2-Phenylbutanal.

Analysis was conducted on a 10' x 1/4" column packed with 10% FFAP on Chromosorb W (60-80 mesh) at a temperature of 165-170° with a flow rate of 67 ml/min. The chromatogram was very similar to that obtained from the 2-phenylpropanal system. From previous work it was known which of the diastereomers predominated in the Grignard reaction. As in the 2-phenylpropanal system, the threo product had the shorter retention time (see Table 2). Two small peaks appeared in the same positions as the reduction and oxidation products from the 2-phenylpropanal system and these were assigned to the corresponding byproducts. The extent of oxidation and reduction did not exceed 3%.

Preparation of Benzyltriethylammonium Chloride.

A solution of 10.1 g (0.1 mol) of triethylamine in 100 ml of anhydrous benzene was placed in a 250-ml Erlenmeyer flask. Benzyl chloride, 12.7 g (0.100 mol), was then mixed with 30 ml of anhydrous benzene and added slowly to the triethylamine solution which was being stirred magnetically. No noticeable reaction occurred and the flask was gently heated for 2 hrs. The precipitate formed after this time was collected by suction. The
filtrate was then returned to the flask, stoppered, and stirred overnight at ambient temperature.

The reaction was noticeably slow; after 12 hrs more solid was collected. Infrared analysis (no. 4833) of the combined precipitates (9.4 g), after being dried in a vacuum desiccator over P₂O₅, indicated very little if any triethylamine hydrochloride present.

**Preparation of 3-Methyl-2-phenylbutanonitrile.**

A solution of 94.0 g of phenylacetonitrile (0.31 mol) and 123 g of 2-bromopropane (1.0 mol) was added with stirring to a solution of 200 ml of 50% NaOH and 1.4 g of benzyltriethylammonium chloride. The reaction was mildly exothermic and the internal temperature was kept below 45° by use of an ice bath. After the exothermic reaction ceased, the solution was stirred vigorously overnight. The mixture was then diluted with water and the two layers separated. The aqueous layer was extracted with ether, dried, and concentrated on a rotary evaporator. Distillation under vacuum gave 75 g (58%) of the desired nitrile: bp 111.5-115° (7.3 mm).

**Hydrolysis of 3-Methyl-2-phenylbutanonitrile.**

A mixture of 40 g of nitrile (0.25 mol), 56 g KOH (1.0 mol), and 300 ml of diethylene glycol was stirred and heated at 107° for 72 hr. Dilution with cold water precipitated the amide which was collected by filtration and dried. Final weight of crude amide was 20 g. After work-up and distillation of the acidic material, there was obtained 10 g of 3-methyl-2-phenylbutanoic acid, bp 107-115° (0.7 mm). For a detailed description of the experimental procedure, see Reference 53.
Preparation of 3-Methyl-2-phenylbutanoic Acid.

A solution of 20 g (0.11 mol) of the amide obtained above, 60 ml of glacial acetic acid, 60 ml of concentrated HCl, and 20 ml of water was cooled to 0° by means of an ice-salt bath. A solution of 16 g of NaNO₂ (0.23 mol) in 30 ml of water was added dropwise over a period of 1.5 hr with stirring. After the addition was complete, the bath was removed and the mixture stirred for 12 hr. The mixture was then diluted with water and extracted twice with 100-ml portions of ether. The ether extracts were combined and extracted six times with 50 ml of saturated NaCl solution. The ether solution was dried over MgSO₄ and then concentrated on a rotary evaporator. Distillation yielded 13.1 g (65%) of acid product, bp 109-114° (0.7 mm).

Preparation of 3-Methyl-2-phenylbutanal.

Preparation was accomplished by addition of a solution of 20.3 g (0.08 mol) of tri-t-butoxyaluminum hydride in diglyme to a solution of 15.2 g (0.077 mol) of 3-methyl-2-phenylbutanoyl chloride [bp 60-64° (0.7 mm)] in diglyme at -78°. After work-up there was obtained 5.0 g (33%) of 3-methyl-2-phenylbutanal: 70-73° (1.0 mm) [lit. 72-73° (1.0 mm)]. For a detailed description of the experimental procedure, see Reference 53.

Glpc analysis on FFAP and Carbowax indicated that the fraction contained 85% 3-methyl-2-phenylbutanal and 15% isobutyrophenone.

Reaction of "in situ" Dimethylcadmium (I,I) with 3-Methyl-2-phenylbutanal.

A solution of 6.2 ml of 1.98 M MeMgI (12.3 mmol) was added to a stirred, cold mixture of 2.26 g of CdI₂
(6.20 mmol) in 9.5 ml of anhydrous ether. This addition was carried out such that no ebullition occurred. The solution was then stirred at ambient temperature for 15 min before the Gilman test was shown to be negative.

The dimethylcadmium reagent was then cooled to an internal temperature of 0-5°; 1 g of 3-methyl-2-phenylbutanal (85% pure) in 5 ml of anhydrous ether was added at such a rate that the internal temperature did not exceed 5°. The solution was then stirred for 15 min at the ice-salt bath temperature after the addition was complete. The solution was stirred at ambient temperature for an additional 105 min.

It was cooled in an ice bath to an internal temperature of 0° and hydrolyzed with 15 ml of a saturated NaHCO₃ solution at such a rate that the internal temperature did not exceed 10°. The mixture was stirred for an additional 5 min after removal of the ice bath. The layers were separated, the aqueous layer being extracted twice with ether. The ether layers were combined and dried over MgSO₄. The drying agent was removed by filtration and the ether concentrated on a rotary evaporator at 25° or below.

Addition of 20 ml of anhydrous benzene caused precipitation of cadmium salts, which were removed by filtration. The filtrate was concentrated in the same manner and the residue analyzed by GLPC. Final weight of crude product after removal of the benzene was 1.2 g.

GLPC Analysis of the Reaction Mixture from in situ Dimethylcadmium and 3-Methyl-2-phenylbutanal.

Analysis was conducted on a 10' x 1/4" column packed with 10% STAP on Chromosorb W (60-80 mesh) at a temperature
of 160° with a flow rate of 70.5 ml/min. The 3-methyl-2-phenylbutanal was shown to contain 15% of a single impurity. The impurity was isolated by g LPC and identified by E. Gollier and shown to be isobutyrophenone. Addition of MeMgl to a sample of isobutyrophenone allowed g LPC analysis of the methylisopropylphenylcarbinol. GLPC analysis of the reaction mixture obtained from dimethylcadmium and 3-methyl-2-phenylbutanal resulted in two major component peaks which were isolated by preparative g LPC. All the reaction products were nicely separated and identifiable (Table 2). The NMR spectra of the two diastereomeric alcohols were not conclusive in terms of configurational assignment. A tentative assignment was made on infrared comparison with the threo and erythro isomers of 3-phenyl-2-butanol and 3-phenyl-2-pentanol. Again, the order of elution on the GLPC chromatograph indicated that the threo isomer was eluted first.

To test the configurational assignments, dehydration studies were conducted. This involved the dehydration of threo and erythro mixtures of 3-phenyl-2-butanol, 3-phenyl-2-pentanol, and the 3-phenyl-4-methyl-2-pentanol. Addition of an ethereal solution of ZnBr₂ to each of the samples, followed by injection into the chromatograph at 265°, resulted in dehydration, which could be monitored by GLPC readout. By varying the amount of ZnBr₂ present, the extent of dehydration could be controlled. From the GLPC data taken before and after dehydration it was observed that the erythro isomers of 3-phenyl-2-butanol and 3-phenyl-2-pentanol dehydrated at a faster rate.
This is also what has been observed for solvolysis of the 3-phenyl-2-butanols. The glpc data on 3-phenyl-4-methyl-2-pentanol indicated that the isomer which was previously assigned erythro (ir and glpc elution order) did indeed dehydrate at a faster rate. This data indicated that the assignments are correct.
DISCUSSION AND RESULTS

One of the first reactions studied was that between benzoyl chloride and in situ (Br,Cl) diethylcadmium in ether solution. The reaction was found to produce the desired propiophenone, but ethyl benzoate was the major product. The formation of the ethyl benzoate can be considered to arise from cleavage of the diethyl ether. When tetrahydrofuran was used as the solvent, the 6-halobutyl benzoate ester, which resulted from cleavage of the tetrahydrofuran, was the only isolated product. These experiments indicated that the

\[
\begin{align*}
\text{C}_6\text{H}_5\text{COCl} + (\text{C}_2\text{H}_5)_2\text{Cd} & \xrightarrow{\text{ether}} \text{C}_6\text{H}_5\text{CO}_2\text{C}_2\text{H}_5 + \text{C}_6\text{H}_5\text{OCOC}_2\text{H}_5 \\
\text{C}_6\text{H}_5\text{COCl} + (\text{C}_2\text{H}_5)_2\text{Cd} & \xrightarrow{\text{THF}} \text{C}_6\text{H}_5\text{CO}_2\text{C}_2\text{H}_2(\text{CH}_2)_2\text{CH}_2\text{X} (\text{X=Br, Cl})
\end{align*}
\]

reaction of organocadmium reagents and acid chlorides should be carried out in benzene solution. The early reported yields on this reaction may be in error because of the difficulty in separating the ketone and the ester by distillation.

The initial experiments involving addition of organocadmium reagents to simple carbonyls were conducted on benzaldehyde. Both the in situ and "one step"\textsuperscript{51} diethylcadmium reagents were found to react readily with benzaldehyde in ether, producing ethylphenylcarbinol in good yields. When the reaction was carried out in tetrahydrofuran, very little of the 2° alcohol could be detected.
\[
\text{C}_6\text{H}_5\text{CHO} + (\text{C}_2\text{H}_5)_2\text{Cd} \rightarrow \text{C}_6\text{H}_5\text{CH(OH)}(\text{C}_2\text{H}_5)
\]

"one step" \(\rightarrow\) 59\% (ether) 0\% (THF) \(\text{(Br,Cl)}\)  
\(`\text{in situ}\) \(\rightarrow\) 68\% (ether) 0\% (THF)

The addition of organocadmium reagents to acetophenone and cyclohexanone was found to be more sensitive to reaction variables. The extent of addition of dimethyl- and diethylcadmium was observed to be dependent on the halide present. Addition to cyclohexanone did not occur to any appreciable extent in the absence of iodide ion, introduced as MgI\(_2\).

\[
\text{cyclohexanone} + \text{in situ cadmium reagent} \rightarrow \text{ether} \rightarrow 1\text{-alkylcyclohexanol}
\]

- \((\text{C}_2\text{H}_5)_2\text{Cd} \ (\text{Br,Cl}) \rightarrow 0\% \ (\text{R} = \text{C}_2\text{H}_5)\)
- \((\text{C}_2\text{H}_5)_2\text{Cd} \ (\text{I,Cl}) \rightarrow 80\% \ (\text{R} = \text{C}_2\text{H}_5)\)
- \(\text{C}_2\text{H}_5\text{CdX} \ (\text{I,Cl}) \rightarrow 23\% \ (\text{R} = \text{C}_2\text{H}_5)\) \(\text{(21)}\)
- \((\text{CH}_3)_2\text{Cd} \ (\text{I,Cl}) \rightarrow 93\% \ (\text{R} = \text{CH}_3)\)
- \(\text{C}_6\text{H}_{11}\text{O}\text{Cd(CH}_3\text{)} \ (\text{I,Cl}) \rightarrow 45\% \ (\text{R} = \text{CH}_3)\)

It is also interesting to note that the addition of methylcyclohexoxycadmium to cyclohexanone occurs at a slower rate than does the corresponding \text{in situ} dimethylcadmium reagent. This suggests that the first alkyl group in \text{R}_2\text{Cd} is transferred to a carbonyl much more readily than the second one.
The observation that benzaldehyde was more reactive than cyclohexanone has been observed to be a generalized order of reactivity toward organocadmium reagents.

In view of the detailed study of the stereochemistry of the addition of methyl Grignard reagents to 4-t-butyl-cyclohexanone reported in 1962 and 1965, an investigation into the same reaction with the methyl cadmium reagent was undertaken. As shown in equation 22, the reaction is expected to lead to a mixture of trans("Z")- and cis("E")-1-methyl-4-t-butylcyclohexanols (2 and 3) in which the alcohol function is, respectively, axial and equatorial.

From previous work, it has been convincingly demonstrated that magnesium reagents attack 4-t-butyl-cyclohexanone from the less hindered side with preferential formation of the thermodynamic product, the (Z)-alcohol. Addition of hydride from a variety of metal hydride reagents, on the other hand, occurs predominantly via axial approach. These observations have led to two divergent views on the controlling factors in addition: "steric approach" vs. "product development" control.
Marshall and Carroll\(^7\) proposed a model for the transition state, by which one could estimate semiquantitatively the magnitude of the steric effect on the basis of the transition state bond lengths. From this model,

<table>
<thead>
<tr>
<th>EO or AO</th>
<th>a(\beta)</th>
<th>e(\alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2Å</td>
<td>2.2Å</td>
<td>1.8Å</td>
</tr>
<tr>
<td>1.6</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>2.4</td>
<td>2.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

it has been rationalized that the 1,3-(dialxial) interactions are less important than the 1,2-(equatorial axial) interactions in the formation of a C-H bond (1.07Å); while, with the longer C-C bond (1.54Å) being formed during the Grignard addition, the importance of the interactions is reversed. A corollary of this hypothesis is the prediction that, within certain rather narrow limits of bond distances, the extent of axial attack will increase as the transition state bond distance decreases.

Cherest and Felkin\(^6\) have clarified the interactions in the cyclohexanone system and have pointed out the importance of torsional effects as well. Formation of axial alcohol (equatorial attack) implies a partially eclipsed transition state Z*, involving some degree of torsional strain (1,2 interaction). Formation of the equatorial alcohol (axial attack) implies an essentially staggered transition state E* involving some degree of steric strain (1,3 interaction).
They suggest that the reactions proceed via reactant-like transition states and that the stereochemistry observed is determined by the relative magnitudes of torsional and steric strain in the transition states. Consideration of these factors explains the discrepancy between hydride reduction and Grignard addition stereochemistry. Recent results on hydride reduction can best be explained with the Marshall and Felkin models. Because of the supposed insensitivity of torsional strain to the bulk of the attacking reagent and since $R'$ is held constant in the reactions with 4-t-butylcyclohexanone, the present experimental results seem best explained by considering the axial interactions.

These experiments were carried out in such a way that the number of transferable methyl groups was held constant. Thus, for a mole of ketone, there was introduced
2 moles of \((\text{CH}_3)_2\text{Cd}\) or \((\text{CH}_3)_2\text{Zn}\); 4 moles of \text{CH}_3\text{MgX}, \text{CH}_3\text{CdX}, or \text{CH}_3\text{ZnX}. Under these conditions the reaction can be considered to involve dimethylcadmium and not \text{CH}_3\text{CdOR} (based on the reactivity of dimethylcadmium and methylcyclohexylcadmium with cyclohexanone). The same assumption can be made for the organozinc reactions reported. In a few instances olefin formation during glpc analysis, caused by the presence of cadmium salts, was observed, but the amount was well below the level necessary to affect the ratio of alcohols (See Experimental).

Tables 4-6 contain the results of this investigation, and several general observations can be noted from inspection of the Tables.

1. On the basis of the values of unchanged ketone in comparable experiments, the following reactivity series can be written: \text{CH}_3\text{Li}, \text{CH}_3\text{MgBr} > (\text{CH}_3)_2\text{Cd} > (\text{CH}_3)_2\text{Zn} > \text{CH}_3\text{CdX}, \text{CH}_3\text{ZnX}.

2. Reactivity of the reconstituted reagent is lower than that of the comparable in situ reagent and found to be dependent on the amount of halide present.

3. Reagents were more reactive to addition when \text{MgI}_2 rather than \text{MgBr}_2 was present.

4. Reactivity of cadmium and zinc reagents prepared from methyllithium was nil.

5. Monomeric \text{CH}_3\text{MgX} (0.1 M) gives more (Z)-alcohol, resulting from equatorial attack, than the corresponding associated species (0.8 M). At the same concentration, \text{CH}_3\text{MgBr} shows a greater preference for equatorial attack than does \text{CH}_3\text{MgI}.

By contrast, there is no appreciable change in reactivity or stereochemistry when the concentration of \((\text{CH}_3)_2\text{Cd}\) (I,Cl)
is increased from 0.4 M to 0.9 M, or when the concentration of \((\text{CH}_3)_2\text{Zn} (\text{I,Cl})\) is decreased from 0.3 M to 0.1 M.

6. Preference for axial attack follows the series:

\[(\text{CH}_3)_2\text{Zn} > (\text{CH}_3)_2\text{Cd} > \text{CH}_3\text{MgX}\.

7. Contrary to the Grignard reagents, in all cadmium and zinc reagents except \(\text{R}_2\text{M (I,Cl)}\), the stereochemistry of addition was independent of the halogens or of their source. For \(\text{R}_2\text{M (I,Cl)}\), the amount of axial attack was significantly increased \([(Z)/(E)\ decreased]\).

8. The stereochemistry of addition was essentially the same for comparable in situ and reconstituted reagents.

9. Variation of the amount of magnesium salt in the reagent had little effect on the stereochemistry until it was reduced to one molar equivalent relative to ketone (as compared to four molar equivalents in the in situ reagent). The effect was most pronounced in the prior coordination experiments and with magnesium iodide, where the relative amount of axial attack increased \([(Z)/(E)\ decreased]\). See Tables 5 and 6.

Three mechanistic pathways must be considered for the addition of dimethylcadmium to 4-t-butylocyclohexanone:

1) addition of the Grignard reagent, present in small concentration in the reaction mixture;
2) addition of the cadmium reagent by way of some six-center transition state;
and 3) addition of the cadmium reagent by means of some four-center transition state.

An important consideration in any mechanism is the degree of association of the reagents. On the basis of earlier work,\(^{74,75}\) it is assumed that the Grignard reagents in 0.1 M concentration and the cadmium and zinc reagents in
<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conc. M</th>
<th>Unchanged ketone (%)^a</th>
<th>(Z)-Alcohol (%)^b</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CH₃MgI</td>
<td>0.8</td>
<td>1</td>
<td>53.8</td>
<td>1.2</td>
</tr>
<tr>
<td>2. CH₃MgI</td>
<td>0.1</td>
<td>1</td>
<td>61.7</td>
<td>1.6</td>
</tr>
<tr>
<td>3. CH₃MgBr</td>
<td>0.8</td>
<td>1</td>
<td>61.8</td>
<td>1.6</td>
</tr>
<tr>
<td>4. CH₃MgBr</td>
<td>0.1</td>
<td>1</td>
<td>68.4</td>
<td>2.2</td>
</tr>
<tr>
<td>5. CH₃Li</td>
<td>0.8</td>
<td>1</td>
<td>63.7</td>
<td>1.8</td>
</tr>
<tr>
<td>6. (CH₃)₂Cd(I,I)^d</td>
<td>0.4</td>
<td>7.5</td>
<td>51.6</td>
<td>1.1</td>
</tr>
<tr>
<td>7. (CH₃)₂Cd(Br,Br)</td>
<td>0.4</td>
<td>50</td>
<td>51.5</td>
<td>1.1</td>
</tr>
<tr>
<td>8. (CH₃)₂Cd(I,Br)</td>
<td>0.4</td>
<td>5</td>
<td>53.5</td>
<td>1.2</td>
</tr>
<tr>
<td>9. (CH₃)₂Cd(Br,I)</td>
<td>0.4</td>
<td>5</td>
<td>53.1</td>
<td>1.1</td>
</tr>
<tr>
<td>10. (CH₃)₂Cd(Br,Cl)</td>
<td>0.4</td>
<td>55</td>
<td>50.2</td>
<td>1.0</td>
</tr>
<tr>
<td>11. (CH₃)₂Cd(Br,I)^g</td>
<td>0.4</td>
<td>89</td>
<td>21.7</td>
<td>0.29</td>
</tr>
<tr>
<td>12. (CH₃)₂Cd(I,Cl)</td>
<td>0.4</td>
<td>5</td>
<td>42.4</td>
<td>0.74</td>
</tr>
<tr>
<td>Conc., M</td>
<td>Unchanged ketone (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(Z)-Alcohol (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>5</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>99</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>90</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>20</td>
<td>37.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>85</td>
<td>46.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>20</td>
<td>44&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>97</td>
<td>46.8&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>60</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>65</td>
<td>38.3&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>99</td>
<td>38.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>90</td>
<td>49&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reagents:

13. (CH<sub>3</sub>)<sub>2</sub>Cd(1, Cl)<br>
14. (CH<sub>3</sub>)<sub>2</sub>Cd(CH<sub>3</sub>Li, cdI<sub>2</sub>)<br>
15. (CH<sub>3</sub>)<sub>2</sub>Cd(CH<sub>3</sub>Li, cdBr<sub>2</sub>)<br>
16. CH<sub>3</sub>cdX(1, Cl)<br>
17. (CH<sub>3</sub>)<sub>2</sub>Zn(1, I)<br>
18. (CH<sub>3</sub>)<sub>2</sub>Zn(Br, Br)<br>
19. (CH<sub>3</sub>)<sub>2</sub>Zn(1, Br)<br>
20. (CH<sub>3</sub>)<sub>2</sub>Zn(Br, Br, Cl)<br>
21. (CH<sub>3</sub>)<sub>2</sub>Zn(1, Cl)<br>
22. (CH<sub>3</sub>)<sub>2</sub>Zn(1, Cl)<br>
23. CH<sub>3</sub>Zn(1, Cl)<br>
24. CH<sub>3</sub>ZnX(1, Cl)<br>
25. CH<sub>3</sub>ZnX(1, Cl)
\[ a\% = \frac{\text{area (ketone)}}{\text{area (ketone)} + \text{area ((Z)+(E) alcohols)}} \times 100. \]

\[ \text{^b Normalized \%; } \%(Z) + \%(E) = 100; \text{ Yield alcohols} = 100 - \%\text{ketone.} \]

\[ \text{^c For comparable results at similar concentrations see Ref. 57.} \]

\[ \text{^d Halogens in parentheses indicate, respectively, the methyl halide from which RMgX} \]
\[ \text{was prepared and the metal halide used for the exchange (eq. 2).} \]

\[ \text{^e Result of at least two separate runs with a maximum deviation of \pm 1\%.} \]

\[ \text{^f Reaction time was 8 hours, and 3 molar equivalents of zinc reagent were used.} \]

\[ \text{^g THF as solvent.} \]

\[ \text{^h All results with zinc reagents obtained from Ref. 53.} \]
Table 5

Reaction of "Reconstituted" Dimethylzinc and -Cadmium Reagents with 4-t-Butylcyclohexanone (1 Molar Equiv.) in Ether^a

<table>
<thead>
<tr>
<th>Molar Equiv.</th>
<th>Reagent (conc)</th>
<th>Salt</th>
<th>Unchanged ketone(%)</th>
<th>(Z)-Alcohol(%)</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>8 MgBr₂</td>
<td>66</td>
<td>52.4 b</td>
<td>1.1</td>
</tr>
<tr>
<td>2.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>4 MgBr₂</td>
<td>68</td>
<td>52.6 b</td>
<td>1.1</td>
</tr>
<tr>
<td>3.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>2 MgBr₂</td>
<td>67</td>
<td>51.5 b</td>
<td>1.1</td>
</tr>
<tr>
<td>4.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>1 MgBr₂</td>
<td>80</td>
<td>50.1 b</td>
<td>1.0</td>
</tr>
<tr>
<td>5.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>2 MgI₂</td>
<td>60</td>
<td>50.4</td>
<td>1.0</td>
</tr>
<tr>
<td>6.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>1 MgI₂</td>
<td>75</td>
<td>44.2 b</td>
<td>0.79</td>
</tr>
<tr>
<td>7.</td>
<td>2(CH₃)₂Cd(0.1M)</td>
<td>2 MgI₂</td>
<td>75</td>
<td>53.5</td>
<td>1.2</td>
</tr>
<tr>
<td>8.</td>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>2 MgI₂ + 2 MgF₂</td>
<td>76</td>
<td>49.8</td>
<td>0.99</td>
</tr>
<tr>
<td>9.</td>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>4 MgI₂</td>
<td>67</td>
<td>45.2</td>
<td>0.83</td>
</tr>
<tr>
<td>10.</td>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>2 MgI₂</td>
<td>80</td>
<td>46.6</td>
<td>0.87</td>
</tr>
<tr>
<td>11.</td>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>1 MgI₂</td>
<td>88</td>
<td>44.1 b</td>
<td>0.79</td>
</tr>
</tbody>
</table>
a Columns 3, 4, and 5 defined as in Table 4.
b Results of at least two separate runs with a maximum deviation of \( \pm 1\% \).
c All results with zinc reagents obtained from Ref. 53.
<table>
<thead>
<tr>
<th>Reagent (conc.)</th>
<th>Salt</th>
<th>Molar Equiv.</th>
<th>Unchanged ketone(%)</th>
<th>(Z)-Alcohol(%)</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgBr₂</td>
<td>8</td>
<td>47</td>
<td>51.7</td>
<td>1.1</td>
</tr>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgBr₂</td>
<td>4</td>
<td>66</td>
<td>52.1</td>
<td>1.1</td>
</tr>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgBr₂</td>
<td>2</td>
<td>66</td>
<td>49.1</td>
<td>0.97</td>
</tr>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgBr₂</td>
<td>1</td>
<td>87</td>
<td>46.8</td>
<td>0.88</td>
</tr>
<tr>
<td>3.6(CH₃)₂Cd(0.4M)</td>
<td>MgBr₂</td>
<td>2</td>
<td>62</td>
<td>50.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgI₂</td>
<td>2</td>
<td>50</td>
<td>52.8</td>
<td>1.1</td>
</tr>
<tr>
<td>2(CH₃)₂Cd(0.4M)</td>
<td>MgI₂</td>
<td>1</td>
<td>71</td>
<td>37.5</td>
<td>0.60</td>
</tr>
<tr>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>MgI₂</td>
<td>4</td>
<td>60</td>
<td>47.3</td>
<td>0.90</td>
</tr>
<tr>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>MgI₂</td>
<td>2</td>
<td>66</td>
<td>46.7</td>
<td>0.88</td>
</tr>
<tr>
<td>2(CH₃)₂Zn(0.3M)</td>
<td>MgI₂</td>
<td>1</td>
<td>90</td>
<td>36.1</td>
<td>0.57</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction of "Purified" Dimethylzinc and -Cadmium Reagents in Ether with 4-t-Butylcyclohexanone (1 molar Equiv.) • MgX₂

Table 6
Columns 3, 4, and 5 defined as in Table 4.

Results of at least two separate runs with a maximum deviation of ± 1%.

All results with zinc reagents obtained from Ref. 53.
0.3-0.4 M concentrations are monomeric, while the 0.8 M solutions of Grignard reagents are polymeric. Magnesium halides present in the cadmium or zinc reagents (0.6-0.8 M) are undoubtedly polymeric.

The reagents were prepared from the Grignard reagent according to the stoichiometry represented in eq. 25. Although it can be argued that RMgX might be present by reversal of eq. 25, this is contrary to the general observation that a metal-metal exchange between organometallic and metal salt proceeds in the direction of formation of the less reactive organometallic.

\[
2\text{RMgX} + \text{MX}_2 \rightarrow \text{R}_2\text{M} + 2\text{MgX}_2
\]

Qualitative tests support the conclusion that Grignard reagent is present in very low concentration if at all. The familiar Gilman color test for RMgX was negative in every experiment. The characteristic color of a charge-transfer complex between either 2,2'-biquino-line or 1,10-phenanthroline and Grignard reagent was not observed with our reagents. The increased reactivity of cadmium and zinc reagents in the presence of magnesium halide would be compatible with attack by the Grignard reagent. Our stereochemical results, however, do not support this mechanism. Inspection of the Tables reveals that both cadmium and zinc reagents lead to more \((E)\)-alcohol (less thermodynamically stable), resulting from axial attack, than do the Grignard reagents at low concentration. Indeed, the zinc reagents, in all but one case, gave \((E)\)-alcohol as the major product. The leveling effect
of % (Z)-alcohol with increasing MgBr₂ concentration in Tables 5 and 6 would not be expected if the added salt were shifting eq. 2 to the left. Even more convincing is the fact that Houlihan⁵⁷ observed that addition of MgX₂ to the Grignard reagent resulted in more equatorial attack. It would be expected, therefore, that the Grignard produced by reversal of eq. 25 should produce more equatorial attack than seen in the Grignard reactions, because of the excess MgX₂ which would be present. This is just the exact opposite of what is observed (more axial attack).

If R₂M is the attacking reagent, it might be involved in a six-center or four-center transition state, by analogy with systems already studied. Thus, Ashby⁷⁷ obtained kinetic evidence consistent with the six-center transition state 26a, which had been proposed previously for the reaction of RMgX with ketone. An analogous transition state 26b, as well as others, can easily be visualized for cadmium and zinc reagents, MgX₂ being an important part of the structure.

\[
\begin{align*}
\text{R}'' & \quad \text{O} \quad \text{Mg} \\
\text{R}' & \quad \text{C} \\
\text{R} & \quad \text{X} \\
\text{Mg} & \quad \text{X} \\
\text{Cd(Zn)} & \quad \text{R}
\end{align*}
\]

(26)

\[\text{a} \quad \text{b}\]
On the other hand, simple bimolecular kinetics have been observed by House for the addition of salt-free dimethylmagnesium to benzophenone in ether. These results have been interpreted as support for a four-center transition state 27a involving a pentacoordinate magnesium. A similar structure for cadmium and zinc reagents is shown in 27b (solvent molecules are omitted for simplicity).

\[ \begin{align*}
\text{(27)} \\
\text{a} & \quad \text{b}
\end{align*} \]

The choice between transition states 26b and 27b, based on our results reported here, is a subtle one. The activating effect of magnesium salts would be accounted for by a six-center process involving magnesium halide, while it could not be accommodated in a simple four-center mechanism involving only cadmium or zinc reagent. The pronounced tendency of cadmium and, especially, zinc to form stable complexes with oxygen, however, leads one to question the likelihood of transition state 26b.

In accord with Felkin's suggestion, it is reasonable to consider reactant-like rather than product-like transition states. This is supported in our work by the fact that a decrease in reactivity of reagent because of a variation of halide present generally is not accompanied by any change in stereochemistry. In fact, the less reactive zinc reagent typically leads to more of the less
stable (E)-alcohol. (See Table 4).

We can conclude that steric interference to axial attack is diminished in both Cd and Zn reactions, as compared to Mg reactions. Because the alkyl group has remained the same (methyl throughout), this lowering of steric interference can be explained as arising from a tighter transition state for Cd and Zn.\textsuperscript{72} If one compares two six-center transition states for Mg(X=Br) and Cd(X=I), the former should be tighter on the basis of relative metal and halogen covalent bond distances. It would follow that the reaction with Mg should lead to more axial attack, which is exactly the reverse of what is observed. On the other hand, if the Cd (and presumably Zn) reactions were proceeding through four-center transition states, these should be tighter and lead to more axial attack, as is the case. The greater preference for axial attack by Zn over Cd is consistent with expected metal-oxygen bond distances, the shorter Zn-O bond giving rise to a tighter transition state 27b, when M=Zn.

The stereochemistry of addition of RMgX is sensitive to changes in concentration of reagent, as is evident from Table 4. If the addition of cadmium and zinc reagents were to involve a similar transition state 26b containing MgX\textsubscript{2}, one might expect a similar effect. In fact, the stereochemistry of addition of both cadmium and zinc \textit{in situ} reagents is independent of concentration changes, in ranges where the association of MgX\textsubscript{2} is changing drastically.\textsuperscript{74}

Formation of transition state 26b might be facilitated by prior coordination of the ketone with MgX\textsubscript{2}. No change in stereochemistry is observed in the prior coordination
experiments (Table 6) until the amount of MgI₂ is reduced to one molar equivalent per equivalent of ketone, however. The change is toward more axial attack, the opposite of the trend in dilution of the Grignard reagent.

The activating effect on R₂M by addition of MgX₂ may be ascribed to activation of the ketone and/or the organometallic through coordination with magnesium salt. Infrared evidence¹⁴ has been obtained for the existence of R₂Cd·MgBr₂ in ether.

\[
\begin{align*}
R & \quad \text{Cd} \quad \text{Br} \\
\quad & \quad \text{Mg} \\
R & \quad \text{Br}
\end{align*}
\]

(28)

\[R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_4\text{H}_9\]

The superior reactivity of those reagents containing magnesium iodide rather than bromide is in accord with the electronegativity, i.e., the electron donator ability of the halide. Lack of reactivity of RMX and of R₂M derived from lithium reagents may reflect the lowered tendency of RMX or of monodentate ligands (LiX) to form electron-donor complexes.¹²

The sequence of steps shown in 29 is consistent with results being reported here. Thus, both ketone and R₂M are substantially associated with MgX₂ (29a and 29b).
The four-center transition state, written for equatorial attack, still contains strongly associated MgX₂. With reference to the coordination number of the central metal atom in 29c, several precedents are known for the octahedral configuration of organozincs. On the other hand, House has recently pointed to the possibility of a pentacoordinate magnesium species in additive reactions of dimethylmagnesium. The coordination number in 29c may be different for the two metals, for it is known that cadmium exhibits a greater tendency than zinc toward formation of octahedral complexes.

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The mechanism in 29 can be used to explain the increase in axial attack with one equivalent of magnesium halide (Tables 5 and 6). Under these conditions there is insufficient magnesium halide to coordinate with the carbonyl and \( R_2M \) independently, and tightening of the \( MgX_2 \)-deficient transition state is apparently the outcome. This could arise by a shortening of the M-O bond or by a simultaneous coordination of \( MgX_2 \) with carbonyl and the metal, as represented in the following structure. In both sets of experiments (Tables 5 and 6) it is noted

\[
\begin{align*}
\text{Mg} & \quad \text{O} \\
& \quad \text{X} \\
& \quad \text{M(C}_3\text{H}_3) \\
& \quad \text{CH}_3 \\
\end{align*}
\]

(30)

that \( MgI_2 \) causes a greater amount of axial attack than \( MgBr_2 \), in accord with the stronger Lewis acid character of \( MgI_2 \) and the resulting stronger complex. The involvement of structures such as 29c and 30 must eventually be investigated by kinetic experiments.

The difference in stereochemistry observed with 0.8 M and 0.1 M Grignard reagents (Table 4) suggests a tighter six-center transition state 26a for the associated reagents (more axial attack). It is noteworthy that our stereochemical results with 0.1 M \( CH_3MgBr \) in ether are close to those obtained for 1 M THF solutions, which are also monomeric.74

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Dependency of the stereochemistry on the halogen present can be explained by consideration of the association. If we assume that methyl magnesium bromide is less highly associated than methyl magnesium iodide, as is the case for the corresponding ethyl reagents,82 we should predict more axial attack with methyl magnesium iodide. This is indeed the case.

Because of the possibility of reduction and addition in the reaction of di-n-propylcadmium and 4-t-butylcyclohexanone, investigations into the stereochemistry of the products was undertaken. Initial glpc experiments indicated that the stereochemistry of the addition and reduction products could be determined under one set of experimental conditions.

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{A} (\text{Z}) \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{R} (\text{Z}) \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{A} (\text{E}) \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{R} (\text{E}) \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{OH} \]

\[ \text{n-Pr} \]

\[ \text{OH} \]
The reaction was again carried out with two molar equivalents of di-\(\mu\)-propylcadmium to one of ketone. Olefin formation in the chromatographic analysis, due to the presence of cadmium salts, indicated that the 3° addition alcohols were more sensitive to dehydration than the 2° reduction alcohols. By addition of anhydrous benzene to the sample, as described in the Experimental, the salts could be removed and the olefin formation eliminated. The results are recorded in Table 7.

Several general observations can be seen from inspection of the Table.

a. As observed in the reaction of dimethylcadmium and 4-\(t\)-butylcyclohexanone, the reagents are more reactive when iodide ion is present.

b. The stereochemistry of the reduction products in the Grignard reactions is dependent on the halogen present.

c. The ratio of addition/reduction follows the order: Cd > Mg > Zn.

d. The amount of (E)-reduction alcohol, resulting from axial attack, decreases in the order: Mg > Cd > Zn.

e. The stereochemistry of the addition or reduction products in the Grignard reactions is independent of concentration; however, the ratio of addition/reduction is affected.

f. The amount of (Z)-addition product, resulting from equatorial attack, is dependent on the halogen in the cadmium and zinc reactions, but independent in the Grignard reactions.

g. The stereochemistry of the reduction product is independent of halogen in the cadmium series.
Table 7

Reaction of in situ Di-n-propylcadmium and -zinc Reagents with 4-tert-Butylcyclohexanone.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>% Unchanged Ketone</th>
<th>% Reduction</th>
<th>% Addition</th>
<th>% (E)-Reduction</th>
<th>% (Z)-Addition</th>
<th>Ratio Add/Red.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrMgBr (0.8 M)</td>
<td>1.0</td>
<td>31.4</td>
<td>68.6</td>
<td>94.9</td>
<td>69.8</td>
<td>2.2</td>
</tr>
<tr>
<td>PrMgBr (0.1 M)</td>
<td>0.8</td>
<td>39.6</td>
<td>60.4</td>
<td>95.3</td>
<td>70.6</td>
<td>1.5</td>
</tr>
<tr>
<td>PrMgI (0.8 M)</td>
<td>4.0</td>
<td>31.2</td>
<td>68.8</td>
<td>87.2</td>
<td>69.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Pr₂Cd (I, I; 0.4 M)</td>
<td>11.1</td>
<td>12.3</td>
<td>87.7</td>
<td>71.8</td>
<td>55.1</td>
<td>7.3</td>
</tr>
<tr>
<td>Pr₂Cd (I, Cl; 0.4 M)</td>
<td>19.1</td>
<td>8.6</td>
<td>91.4</td>
<td>69.7</td>
<td>62.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Pr₂Cd (I, Bu; 0.4 M)</td>
<td>21.9</td>
<td>9.1</td>
<td>90.9</td>
<td>71.9</td>
<td>58.4</td>
<td>10.0</td>
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<tr>
<td>Pr₂Cd (Br, Br; 0.4 M)</td>
<td>62.7</td>
<td>9.7</td>
<td>90.3</td>
<td>73.7</td>
<td>76.8</td>
<td>9.4</td>
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<td>Pr₂Zn (I, I; 0.3 M)</td>
<td>77.4</td>
<td>32.1</td>
<td>67.9</td>
<td>74.3</td>
<td>55.6</td>
<td>2.1</td>
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<tr>
<td>Reagent</td>
<td>/%</td>
<td>Unchanged Ketone</td>
<td>% Reduction</td>
<td>% Addition</td>
<td>% (E)-Reduction</td>
<td>% (Z)-Addition</td>
</tr>
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<td>---------------</td>
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<tr>
<td>Pr$_2$Zn (I,BR; 0.3 M)</td>
<td>78.0</td>
<td>43.3</td>
<td>56.7</td>
<td>48.4$^f,j$</td>
<td>59.0</td>
<td>1.3</td>
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<tr>
<td>Pr$_2$Zn (BR,BR; 0.3 M)</td>
<td>87.4</td>
<td>68.6</td>
<td>31.4</td>
<td>19.4$^j$</td>
<td>70.5</td>
<td>0.46</td>
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</tbody>
</table>

$^a$Normalized yields: % Addition + % Reduction = 100%

$^b$Normalized yields: % (E)-Reduction + % (Z)-Reduction = 100%

$^c$Normalized yields: % (E)-Addition + % (Z)-Addition = 100%

$^d$Reactions were run with 4 molar equivalents of Pr$_2$Zn and are reported from Ref. 53.

$^e$Reactions were run with 2 molar equivalents of Pr$_2$Cd.

$^f$Equilibration of epimeric reduction products noted.

$^g$No equilibration of epimeric reduction products was noted.

$^h$Values of % unchanged ketone were reproducible within ± 5% in separate reaction runs.

$^i$Values are averages of at least two experiments with deviation of ± 2%.

$^j$Deviation of ± 3% in separate reaction runs.
$k$ values were determined from not less than three glpc injections per reaction run; deviation $\pm$ 2% for glpc injections.

1. The value was unchanged when a mixture of benzene-ether (2:1) was used as solvent.

m Single reaction run.
According to Felkin's model⁶ for addition to cyclohexanone, the torsional effects resulting from equatorial attack are supposedly insensitive to the bulk of the attacking species. Therefore, changing the attacking group from methyl to propyl is not expected to affect the torsional strain substantially. However, the axial steric interaction should definitely change. Because of the increased steric interaction of the propyl group compared to the methyl group, it would be expected that less axial attack would be observed. A comparison of the results with similar methyl and propyl reagents (Tables 4 and 7, respectively) shows that more axial attack did indeed occur with the methyl reagents. Even more striking is the fact that in no case was axial attack preferred over equatorial attack with the propyl reagents. This is the converse to the case for the methylzinc reagents, for which equatorial attack was never the preferred direction.

One exception to these observations can be noted. The per cent axial attack for methylmagnesium bromide (0.1 M) and propylmagnesium bromide (0.1 M and 0.8 M) were identical within experimental error. This seems to indicate that there is very little difference in axial steric interactions for these two reagents. It is interesting to note that methylmagnesium bromide (0.8 M) did give more axial attack than either of the propylmagnesium bromide reagents.

The effect of halogen on the stereochemistry of addition was strikingly different for ethyl and propyl
reagents. The independence of the propyl Grignard reaction to halogen might have some mechanistic implications. The dependency on halogen and concentration noted in the methyl Grignard reaction was explained by consideration of a bridged six-center transition state. The independence of the propyl Grignard reaction on halogen and concentration might indicate that bridging does not occur or is much weaker in the transition state.

In contrast to the observations noted in the methyl reactions, the results with the propyl cadmium and zinc reagents indicate that there was an effect of halogen on the stereochemistry of the addition reaction. It is interesting to note that in the propyl cadmium (I,X) reactions, the % (Z)-addition (equatorial attack) increases as the electronegativity of X increases (I < Br < Cl). When iodide was not present in the system (Br, Br), the % (Z)-addition increased sharply. This indicates that in the (Br, Br) system, and when X is varied in the presence of iodide, the axial steric interactions increase, relative to the case where (I, I) reagent is employed.

Consider the six- and four-center transition states for axial addition drawn below.

\[
\begin{align*}
\text{CH}_3 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qua
Increasing the electronegativity of X (from I to Br) in the six-center transition state could be expected to make the ring tighter because of the decrease in atomic size of Br compared to I. However, increasing the electronegativity of X also decreases the electron-donator ability and could be expected to reduce the extent of bridging in the transition state. Because these two considerations would lead to opposing stereochemistry (Marshall's model), it is impossible to predict the effect of halogen on the transition state.

Increasing the electronegativity of X in the four-center process tends to make the cadmium atom more positive, thus tightening the cadmium-oxygen bond. At first glance, Marshall's model predicts that this would produce more axial attack. Consideration of models indicates that steric interaction between the axial hydrogens and the β-hydrogens of the propyl group could occur. The models indicate that this interaction would increase as the transition state is tightened; and, because of this increase in axial interaction, more equatorial attack would result. This effect could also be expected in tightening of the six-center transition state. A distinction between these two mechanisms seems impossible with the data obtained thus far.

By examining the six-center transition state for axial reduction, one can estimate its relative size by means of Marshall's model. Based on the M-C bond distances in similarly related organometallics \( [\text{C}_2\text{H}_5\text{MgBr}, (\text{CH}_3)_2\text{Mg}, (\text{CH}_3)_2\text{Zn}, (\text{CH}_3)_2\text{Cd}, \text{and C}_2\text{H}_5\text{ZnI}] \), it is expected that
the Mg and Zn metal to carbon (M-C) bond distances would be quite similar (Zn possibly smaller). The Cd-C bond distance is expected to be longer. As the M-C bond distance increases, Marshall's model predicts that the axial steric interactions increase. This would predict that equatorial attack should be relatively favorable in cadmium reduction, and this is borne out by experimental observation. However, the values for the propylzinc reaction are quite anomalous.

Because equilibration occurred in the zinc reduction reaction, any interpretation of the stereochemistry would be quite complicated. The equilibration may possibly be the result of the amount of ketone present because of the low reactivity of the zinc reagents. However, it is interesting to note that the values reported for the zinc reduction are maximum values for the % (E)-reduction product. This indicates that the steric interactions have increased more drastically than with cadmium. This is not expected in terms of the model used above.

The effect of halogen on the stereochemistry of Grignard reduction can be explained on the basis of electronegativities. The magnesium atom in the case of propylmagnesium bromide should be more positive than in
propylmagnesium iodide. This would tend to shorten the Mg-O bond distance and tighten the transition state. Thus, Marshall's model would predict more axial attack with propylmagnesium bromide than with propylmagnesium iodide, and indeed this is the case.

The change in ratio of addition/reduction in the propylmagnesium bromide reaction with a lowering of the concentration may reflect the difference in kinetic order of the two reactions.

\[
\text{rate of reduction} = k_\text{r} [\text{ketone}] [\text{Grignard}]^{R(\text{Z}), R(\text{E})} (34)
\]

\[
\text{rate of addition} = k_\text{a}[\text{ketone}] [\text{Grignard}]^{2 A(\text{Z}), A(\text{E})}
\]

It is seen from the rate equations for addition (assuming termolecular kinetics as observed for the reaction of CH\textsubscript{3}MgBr with benzophenone\textsuperscript{77}) that the effect of lowering the concentration of the Grignard reagent would have a more pronounced effect on the rate of addition. Thus one would predict that the ratio of addition to reduction would decrease as the concentration is lowered.
Because of the effects seen in the 4-\textit{t}-butylcyclohexanone reactions, stereochemical investigations into addition of \textit{in situ} dimethylcadmium reagents to an acyclic aldehyde series were conducted. It is well known that addition of an organometallic compound to an acyclic aldehyde with an adjacent asymmetric carbon can give rise to diastereomeric products.\textsuperscript{54}

\[
\begin{align*}
\text{RC-CH} & + \text{R'M} \rightarrow \text{RC-(H)R'} \\
R & \text{ erythro} \\
S & \text{ threo}
\end{align*}
\]

The systems investigated were 2-phenylpropanal (R=CH\textsubscript{3}), 2-phenylbutanal (R=C\textsubscript{2}H\textsubscript{5}), and 3-methyl-2-phenylbutanal (R=\textit{i}-C\textsubscript{3}H\textsubscript{7}). The reactions were carried out in such a manner that the number of transferable methyl groups was held constant. Thus, for a mole of aldehyde, there was introduced one mole of dimethylcadmium; 2 moles of Grignard or methylcadmium halide. The results of the experiments are listed in Table 8. The values for the reactions of dimethylzinc are reproduced from Reference 53.

Several general observations can be noted from inspection of the Table.
1. In contrast to the ketone reactions studied, the reactivity with aldehydes is independent of halogen, and CH\textsubscript{3}CdX or CH\textsubscript{3}ZnX are as reactive as the corresponding dimethyl reagents.
2. The selectivity in the 2-phenylpropanal and butanal reactions follows the order: Mg > Cd > Zn.
Table 8

Reaction of Organometallic Reagents with Various Acyclic Aldehydes.\(^a\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>M</th>
<th>%-Erythro</th>
<th>%-Threo</th>
<th>% Unchanged Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>CH(_3)MgI</td>
<td>0.8 M</td>
<td>64.3</td>
<td>35.7</td>
<td>1</td>
</tr>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>CH(_3)MgI</td>
<td>0.1 M</td>
<td>65.6</td>
<td>34.4</td>
<td>1</td>
</tr>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>CH(_3)MgBr</td>
<td>0.8 M</td>
<td>69.5</td>
<td>30.5</td>
<td>1</td>
</tr>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>((\text{CH}_3)_2\text{Cd (I,I)})</td>
<td>0.4 M</td>
<td>61.1</td>
<td>38.9</td>
<td>1</td>
</tr>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>((\text{CH}_3)_2\text{Cd (Br,Br)})</td>
<td>0.4 M</td>
<td>59.8</td>
<td>40.2</td>
<td>1</td>
</tr>
<tr>
<td>C(_6)H(_5)CHCHO (\text{CH}_3)</td>
<td>((\text{CH}_3)_2\text{Cd (I,Cl)})</td>
<td>0.4 M</td>
<td>60.4</td>
<td>39.6</td>
<td>1</td>
</tr>
<tr>
<td>Substrate</td>
<td>Reagent</td>
<td>M</td>
<td>%-Erythro&lt;sup&gt;b&lt;/sup&gt;</td>
<td>%-Threo</td>
<td>% Unchanged Aldehyde</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------</td>
<td>----</td>
<td>------------------------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>$\text{C}<em>{6}\text{H}</em>{5}\text{CHCHO}$</td>
<td>$(\text{CH}_3)_2\text{Cd} (\text{I}, \text{Cl})^c$</td>
<td>0.4 M</td>
<td>62.1</td>
<td>37.9</td>
<td>1</td>
</tr>
<tr>
<td>$\text{C}<em>{6}\text{H}</em>{5}\text{CHCHO}$</td>
<td>$\text{CH}_3\text{CdX} (\text{I}, \text{Cl})$</td>
<td>0.8 M</td>
<td>56.8</td>
<td>43.2</td>
<td>1</td>
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<td>$\text{CH}_3\text{CdBr}$</td>
<td>0.8 M</td>
<td>62.2</td>
<td>37.8</td>
<td>1</td>
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<td>$\text{C}<em>{6}\text{H}</em>{5}\text{CHCHO}$</td>
<td>$\text{CH}_3\text{CdI}$</td>
<td>0.8 M</td>
<td>60.8</td>
<td>39.2</td>
<td>1</td>
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<td>$\text{C}<em>{6}\text{H}</em>{5}\text{CHCHO}$</td>
<td>$(\text{CH}_3)_2\text{Zn} (\text{I}, \text{I})$</td>
<td>0.3</td>
<td>54.7</td>
<td>45.3</td>
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<td>$(\text{CH}_3)_2\text{Zn} (\text{Br}, \text{Br})$</td>
<td>0.3 M</td>
<td>56.9</td>
<td>43.9</td>
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<td>Substrate</td>
<td>Reagent</td>
<td>M</td>
<td>%-Erythro&lt;sup&gt;b&lt;/sup&gt;</td>
<td>%-Threeo</td>
<td>% Unchanged Aldehyde</td>
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<td>C₆H₅CHCHO CH₃</td>
<td>CH₃Mgl</td>
<td>0.3 M</td>
<td>51.5</td>
<td>48.5</td>
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<td>C₆H₅CHCHO CH₃</td>
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<td>0.3 M</td>
<td>54.3</td>
<td>45.7</td>
<td>1</td>
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<td>C₆H₅CHCHO Cl₂</td>
<td>CH₃ZnBr</td>
<td>0.3 M</td>
<td>56.0</td>
<td>44.0</td>
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<tr>
<td>C₆H₅CHCHO CH₃</td>
<td>CH₃ZnX (Br,I)</td>
<td>0.3 M</td>
<td>54.1</td>
<td>45.9</td>
<td>2</td>
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<td>C₆H₅CHCHO CH₃</td>
<td>CH₃ZnX (I,Cl)</td>
<td>0.3 M</td>
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<td>40.3</td>
<td>40</td>
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<tr>
<td>C₆H₅CHCHO CH₃</td>
<td>CH₃ZnI (LiI)</td>
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<td>53.5</td>
<td>40.5</td>
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<tr>
<td>Reagent</td>
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<td>%-2-Hydroxypropanoic acid</td>
<td>%-Aldehyde b</td>
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<tr>
<td>CH₃₂ZnBr (LiBr)</td>
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<td>34.8</td>
<td>41.6</td>
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<td>70.8</td>
<td>65.2</td>
<td>58.4</td>
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<td>54.5</td>
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<td>CH₃MgI</td>
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<td>C₆H₅CHO</td>
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<td>C₆H₅CHO</td>
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<td></td>
</tr>
</tbody>
</table>

a. Unchanged Aldehyde.  
b. Unattached Alcohol.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>M</th>
<th>% Erythro&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Threo</th>
<th>% Unchanged Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅CHCHO</td>
<td>(CH₃)&lt;sub&gt;2&lt;/sub&gt;Cd (I, I)</td>
<td>0.4 M</td>
<td>32.5</td>
<td>67.5</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>(CH₃)&lt;sub&gt;2&lt;/sub&gt;Cd (I, Br)</td>
<td>0.4 M</td>
<td>29.3</td>
<td>70.7</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>(CH₃)&lt;sub&gt;2&lt;/sub&gt;Zn (I, I)</td>
<td>0.3 M</td>
<td>36.3</td>
<td>63.3</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>i-PrMgBr</td>
<td>0.8 M</td>
<td>64.2</td>
<td>36.8</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Zn reactions carried out by E. J. Goller (Ref. 53).

<sup>b</sup>Values reproducible within ± 1% on separate reaction runs.

<sup>c</sup>Two molar equivalents of (CH₃)<sub>2</sub>Cd to one of aldehyde.
3. Preferential formation of the erythro isomer was observed with all the methyl reagents, except in the 3-methyl-2-phenylbutanal reactions.
4. The selectivity in the 3-methyl-2-phenylbutanal reactions follows the order: \( \text{Cd} \succ \text{Zn} \succ \text{Mg} \).
5. The stereochemistry of addition in the cadmium and zinc reactions was independent of halogen except in the case of \( \text{CH}_3\text{CdX} (\text{I, Cl}) \), \( \text{CH}_3\text{ZnX} (\text{I, Cl}) \), and \( (\text{CH}_3)_2\text{Zn} (\text{I, Cl}) \).
6. Increasing the number of equivalents of dimethylcadmium present has no effect on the stereochemistry of the addition products.
7. Stereochemistry of Grignard reactions are dependent on halogen but not concentration.
8. Methylzinc reagents prepared from methyllithium are unreactive.

Before any conclusions about the experimental results are sought, the available methods of interpreting the reactions must be understood. The original investigation into the stereochemistry of addition to acyclic ketones and aldehydes was conducted by D. J. Cram and his collaborators. From this early work Cram proposed a transition state model which explained the results he obtained, and this led to what is commonly known as Cram's Rule. The rule states that when an asymmetric carbon atom is so oriented that the carbonyl function is flanked by the two smaller groups (S and M) attached to the asymmetric carbon atom, the reagent \( (R'X) \) preferentially approaches the carbonyl group from the side of S. This model applies only to reactions that are kinetically controlled.
Karabatsos later pointed out discrepancies in the Cram model and presented one of his own, which likewise was based on the assumption that little bond breaking and making had occurred in the transition state (reactant-like). Consequently, he assumed that the conformational arrangement of the groups on the asymmetric carbon atom with respect to the carbonyl was similar to that about sp²-sp³ carbon-carbon bonds. From nmr data of acyclic aldehydes, he suggested that the conformations of the preferred transition states have either M (KA) or L (KB) eclipsing the carbonyl.

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Karabatsos assumed that the incoming $R'$ is closest to $S$ for steric reasons ($KA$ and $KB$). The transition state $KA$ is preferred over $KB$ because it involves the smaller eclipsing interaction of the carbonyl. The correlation between nmr data and the product ratios is quite good in many cases.

Cherest and Felkin have criticized this interpretation, stating that as $R$ becomes progressively more bulky, more strain occurs in $KA$ and hence destabilizes it with respect to $KB$, which leads to the diastereomeric product. This implies that the bulkier $R$ becomes, the less stereoselective the reaction should be. However, LiAlH$_4$ reduction of a series of ketones where $R$ was made more bulky did not become less selective but more selective. To accommodate this information, Cherest and Felkin presented a model based on several assumptions.

1. The reactions are reactant-like and not product-like.

2. Torsional strain involving partial bonds (in the transition state) are assumed to represent a considerable fraction of the strain between fully-formed bonds, even when the degree of bonding is quite low.

3. The important steric interactions involve $R$ and $R'^-$ rather than the carbonyl oxygen.

4. Polar effects stabilize transition states in which separation between $R'^-$ and electronegative groups is greatest and destabilizes others.

These assumptions imply a preferred staggered conformation for the transition states, where the attacking $R'^-$ comes in anti to the largest group $L$. On this basis,
the least strained of the six possible staggered conformations is $A_1$, followed by $B_1$ and then $B_2$. $A_1$ leads to erythro product, while the latter two give three isomer. These models explain the increase in selectivity as $R$ is made more bulky. Transition state $B_2$ is only of minor importance in the systems we have studied because of the electronic repulsion of the phenyl group with the carbonyl and $R$'. Therefore, transition states $A_1$ and $B_1$ must be considered in the analysis of the experimental data observed in the reactions listed in Table 8.

It can be seen from transition states $38A_1$ and $33B_1$ that the interactions of $R^{(-)}$ with $S$ and $M$ are the same in each case. The predominant factors affecting the stereochemistry are the M-O and R-M interactions. This predicts that the stereochemistry would be independent of $R^{(+)}$. The effect of varying $R^{(+)}$ could affect the dihedral angle between $R^{(-)}$ and $S$ or $M$. This would influence the torsional strain of $M$ and $S$ with $R$ and the carbonyl oxygen. Increasing the bulk of $R^{(-)}$ could destabilize $33B_1$ relative to $38A_1$ (M-R interactions considered most important), if the dihedral angles were affected.
The stereochemistry in the Grignard reactions with 2-phenylpropanal was dependent on the halogen present. Methylmagnesium bromide was observed to be more selective (more erythro) than the comparable methylmagnesium iodide. According to the arguments above, this could mean that the methylmagnesium bromide was more bulky than the methylmagnesium iodide. The association data (mentioned in the 4-tert-butylcyclohexanone discussion) indicate that methylmagnesium bromide is less associated than methylmagnesium iodide. This would not at first seem to fit the analysis described above.

Consider the six-center transition states for the Grignard reactions. The results indicate that when X=Br,

\[
\begin{align*}
A_1 \text{ (erythro)} & \quad B_1 \text{ (threo)}
\end{align*}
\]

the preference for transition state \(39_{A1}\) is greater than when X=I. The observations can be explained if one considers that the M-O interaction in methylmagnesium iodide reaction has increased over that for the methylmagnesium bromide. If the methylmagnesium iodide transition state is more associated (based on electron-donator ability and association data), it might be expected that an
interaction involving M could increase when X=I as compared
to that where X=Br. This could be classified as an M-0
interaction.

The results obtained from the cadmium and zinc
reactions can be analyzed in the same manner. The
experimental results indicate that the reactions are
less stereoselective with cadmium and especially zinc
reagents on the 2-phenylpropanal system. Considering
the arguments based on the bulk of R1−, the data indicate
that the cadmium and zinc transition states are less
bulky than with the Grignard reagents. Consider the
six-center transition states for this reaction. For

![Diagram]

the case of cadmium reagents, the transition state would be
expected to be looser because of the increase in atomic size
and increase in bond distances. This effect, in terms of
increasing the bulk of R1− as mentioned in the Grignard sys-
tem, and decreasing the M-0 interaction, would predict that
the reaction should produce more erythro than noted in the
Grignard reactions. A similar analysis of the zinc reactions
for a six-center mechanism does not fit the experimental results. Another indication that the mechanism is not six-center is the observation that the stereochemistry was independent of halogen, which would not be expected.

On the contrary, the results can be explained by a four-center mechanism, with consideration to changes of the M-O interaction. As the M-O interaction increases, it would be predicted from the Felkin model that more three product should be produced (less stereoelective). The four-center mechanism is drawn below. In this transition state the cadmium or zinc metal is coordinating with the carbonyl oxygen and possibly producing interaction with the M group in transition state 41_A relative to 41_B, where the interaction is between cadmium and the small group S.
The less selective reaction with the organozinc reagents indicates that the transition state must be considered either more bulky than with cadmium (R'\textsuperscript{M}) or that the M-O interaction has increased. The analysis of results in the Grignard discussion is not consistent with the six-center mechanism for this case. However, the four-center mechanism predicts that the expected shorter Zn-O bond distance in the transition state could possibly produce more M-O interaction than with the cadmium reagent. This would fit the experimental observations.

Felkin predicts that as M is made bulkier in these systems, where L is phenyl and S is hydrogen, the reaction becomes more selective. Analysis with his model explains why, in the hydride reductions of a series of isopropyl ketones (R=i-Pr), the ratio of isomers increases from 5 where M=CH\textsubscript{3}, to 10 where M=i-Pr.\textsuperscript{84} It is expected that as M is varied to ethyl and isopropyl, the M-R (R=H) interactions in the series listed in Table 8 would increase in 3\textsubscript{B}, and thus more erythro product would result. However, these interactions are not expected to be vastly different, and if the M-O interaction were important, just the opposite effect--loss of stereoselectivity--could be observed.

The experimental results obtained by varying M from methyl to ethyl (Table 8) indicate that there is no difference in the selectivity of either the Grignard, cadmium or zinc reagents for the two aldehydes. The experimental results of the reactions with the aldehyde where M=i-Pr are quite interesting. By use of Cram's Rule, or Karabatsos or Felkin's models, one would predict that the erythro isomer should be the predominant one.
produced. However, it has been observed that the threo isomer was the major product even with the Grignard reagents. It is interesting to notice that now the zinc and cadmium reagents are more stereoselective, producing the threo isomer as the major product.

The only means of explaining these results according to the Felkin model must involve the M-0 interactions as controlling the stereochemistry of addition. In the case where M-i-Pr, the M-0 interaction in the four-center mechanism could be quite great for the $4\Gamma_A$ transition state. This would predict formation of more threo product relative to the Grignard six-center transition state. Because of the formation of threo product even from the Grignard reactions, it can be postulated that the M-0 interaction is important even in the case of the six-center transition state. This reversal of selectivity is not easily explained on the basis of a six-center mechanism.

It is interesting to note that when isopropylmagnesium bromide was allowed to react with 3-methyl-2-phenylbutanal, the erythro isomer was the major product. The values obtained were in good agreement with previously reported percentages. It seems unusual that such a difference between methyl and propyl Grignard reagents occurred, but it is in line with differences between methyl and propyl Grignard reagents in the reactions with 4-tert-butylocyclohexanone as well.


15. Ref. 2, p. 175; Ref. 10, p. 144.


27. Ref. 6, pp. 192, 199.


31. Ref. 6, pp. 125-139.

43. B. Marx, ibid., 267, 1646 (1968).
44. D. Abenhaim, ibid., 267, 1426 (1968).


51. D. A. Walsh, unpublished results.


57. W. J. Houlihan, ibid., 27, 3850 (1962).

58. (a) J. J. Uebel and H. H. Goodwin, ibid., 33, 3317 (1968); (b) N. L. Allinger and C. D. Liang, ibid., 33, 3319 (1969).


