Spring 1969

REACTIVITY AND STEREOCHEMISTRY OF ORGANOZINC REAGENTS WITH VARIOUS SIMPLECARBONYL FUNCTIONS

EDWIN JOHN GOLLER

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation
https://scholars.unh.edu/dissertation/904

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.
REACTIVITY AND STEREOCHEMISTRY OF ORGANOZINC REAGENTS WITH VARIOUS SIMPLE CARBONYL FUNCTIONS

Keywords
Chemistry, Organic
GOLLER, Edwin John, 1940-
REACTIVITY AND STEREOCHEMISTRY OF ORGANOZINC REAGENTS WITH VARIOUS SIMPLE CARBONYL FUNCTIONS.

University of New Hampshire, Ph.D., 1969
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan
REACTIVITY AND STEREOCHEMISTRY OF ORGANOZINC REAGENTS WITH VARIOUS SIMPLE CARBONYL FUNCTIONS

by

EDWIN J. GOLLER
B.S., Merrimack College, 1961
M.S., Northeastern University, 1964

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
The Requirements for the Degree of
Doctor of Philosophy

Graduate School
Department of Chemistry
June, 1969
This thesis has been examined and approved.

\[\underline{\text{Paul R. Jones}}\]
Thesis director, Paul R. Jones
Professor of Chemistry

\[\underline{\text{Kenneth K. Andersen}}\]
Kenneth K. Andersen
Associate Professor of Chemistry

\[\underline{\text{James D. Morrison}}\]
James D. Morrison
Associate Professor of Chemistry

\[\underline{\text{Alexander R. Amell}}\]
Professor of Chemistry

\[\underline{\text{James A. Stewart}}\]
Assistant Professor of Biochemistry

\[\text{May 23, 1969}\]

Date
ACKNOWLEDGMENT

I wish to express my sincere gratitude and appreciation to Dr. Paul R. Jones for his understanding and guidance throughout the course of this investigation, and for his assistance in the preparation of this manuscript. The many thoughtful considerations he has extended have made working with him a distinct pleasure.

The author would also like to acknowledge the collaboration of William J. Kauffman in the preparation of various materials, and to express his appreciation for the many helpful discussions and suggestions.

A special note of thanks is extended to Dr. James D. Morrison for his assistance in the preparation of this manuscript. His contagious enthusiasm has served as an added incentive during the course of this work.


[Signature]

Edwin J. Sollin
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>viii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>SURVEY OF RECENT LITERATURE</td>
<td>3</td>
</tr>
<tr>
<td>EXPERIMENTIAL</td>
<td>19</td>
</tr>
<tr>
<td>Generation of Anhydrous Zinc Bromide in Solution</td>
<td>20</td>
</tr>
<tr>
<td>Reaction of in situ Ethylzinc Bromide (Br,Br) and Benzoyl Chloride in THF</td>
<td>22</td>
</tr>
<tr>
<td>Reaction of in situ Ethylzinc Bromide (Br,Br) and Benzoyl Chloride in Ether</td>
<td>23</td>
</tr>
<tr>
<td>Reaction of in situ &quot;Diethylzinc&quot; (Br,Br) and Propanoyl Bromide</td>
<td>24</td>
</tr>
<tr>
<td>Attempted Reaction of in situ Ethylzinc Bromide (Br,Br) with Benzaldehyde in THF</td>
<td>25</td>
</tr>
<tr>
<td>Reaction of in situ &quot;Diethylzinc&quot; (Br,Br) with Benzaldehyde in Ether</td>
<td>26</td>
</tr>
<tr>
<td>Attempted Reaction of in situ &quot;Diethylzinc&quot; (Br,Br) with Acetophenone</td>
<td>27</td>
</tr>
<tr>
<td>Reaction of in situ Phenylzinc Bromide (Br,Br) with Benzaldehyde</td>
<td>28</td>
</tr>
<tr>
<td>Reaction of in situ Diphenylzinc (Br,Br) with Benzaldehyde</td>
<td>29</td>
</tr>
<tr>
<td>Reaction of in situ Ethylzinc Ethoxide (Br,Br) with Benzaldehyde</td>
<td>29</td>
</tr>
<tr>
<td>Generation of Anhydrous Zinc Iodide in Solution</td>
<td>30</td>
</tr>
<tr>
<td>Reaction of in situ Dimethylzinc (I,I) with Benzaldehyde</td>
<td>31</td>
</tr>
<tr>
<td>Reaction of in situ Dimethylzinc (Br,Br) with Cyclohexanone</td>
<td>31</td>
</tr>
</tbody>
</table>
Reaction of in situ Methylcyclohexoxyzinc (I, Br) with Cyclohexanone ............ 32
Reaction of in situ Diphenylzinc (Br, I) with Carbon Dioxide .................. 33
Preparation of Anhydrous Magnesium Iodide Dietherate .......................... 34
Reaction of Methylmagnesium Bromide and Iodide with 4-t-Butylcyclohexanone 34
Reaction of in situ Dimethylzinc (I, Br) with 4-t-Butylcyclohexanone ........... 36
Preparation and Analysis of "Purified" Dimethylzinc ............................. 37
Reaction of "Reconstituted" Dimethylzinc with 4-t-Butylcyclohexanone .......... 38
Reaction of "Purified" Dimethylzinc with 4-t-Butylcyclohexanone·MgI₂ ........... 39
1-Methyl-4-t-butylcyclohexene .............................................. 39
Attempted Equilibration of (Z)- and (E)-1-Methyl-4-t-butylcyclohexanols: Control Experiment .......................... 40
Reaction of n-Propylmagnesium Bromide with Heptanal .......................... 40
Reaction of in situ Di-n-propylzinc (Br, Br) with Heptanal ....................... 41
Reaction of n-Propylmagnesium Bromide and Iodide with 4-t-Butylcyclohexanone 42
Reaction of in situ Di-n-propylzinc (I, I) with 4-t-Butylcyclohexanone .......... 44
Effect of Extraction Procedure on Product Ratios: Control Experiment .......... 46
Trimethylamine Borane Reduction of 4-t-Butylcyclohexanone ...................... 46
Equilibration of (Z)-4-t-Butylcyclohexanol: Control Experiment ................. 46
Attempted Equilibration of (E)-4-t-Butylcyclohexanol: Control Experiment ..... 48

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
# LIST OF TABLES

| Table I. | Reactivity of Organozincs | 10 |
| Table II. | Reactivity of *in situ* bis-(*α*-Ethoxymethyl)-zinc with Aldehydes, Ketones, and Acid Chlorides | 13 |
| Table III. | Reactivity of "salt-free" Diallylzinc | 15 |
| Table IV. | Reactivity of 2-Phenylethynylzinc Bromide | 16 |
| Table V. | Reaction of Organozincs, -Cadmiums, and -Magnesiums with 4-*t*-Butylcyclohexanone | 18 |
| Table VI. | Glpc Analysis of *threo-* and *erythro-* Alcohols | 57 |
| Table VII. | Reaction of *in situ* Ethylzinc Bromide with Acid Halides | 67 |
| Table VIII. | Reaction of *in situ* Zinc Reagents with Benzaldehyde in Ether | 68 |
| Table IX. | Reaction of *in situ* Alkylzinc Reagents with Ketones in Ether | 69 |
| Table X. | Reaction of *in situ* Organometallic Reagents in Ether with 4-*t*-Butylcyclohexanone | 76 |
| Table XI. | Reaction of Reconstituted Dimethylzinc and -Cadmium Reagents with 4-*t*-Butylcyclohexanone in Ether | 79 |
| Table XII. | Reaction of "Purified" Dimethylzinc and -Cadmium Reagents in Ether with 4-*t*-Butylcyclohexanone·MgX₂ | 81 |
| Table XIII. | Reaction of *in situ* Organometallic Reagents in Ether with Acyclic Aldehydes | 96 |
| Table XIV. | Reaction of *in situ* *n*-Propyl Organometallic Reagents with 4-*t*-Butylcyclohexanone | 109 |
ABSTRACT

REAKIVITY AND STEREOCHEMISTRY OF ORGANOZINC REAGENTS WITH VARIOUS SIMPLE CARBONYL FUNCTIONS

by

EDWIN J. GOLLER

An investigation into the true reactivity of in situ organozinc reagents toward acid halides, aldehydes, and ketones has been undertaken. Because of the difficulties encountered in obtaining and handling anhydrous zinc halides, an alternate approach to the preparation of in situ reagents has been explored. Zinc bromide and iodide have been generated in anhydrous ether or THF by the interaction of elemental zinc and the appropriate halogen. In situ zinc reagents prepared from such solutions or by the conventional method with the commercially available salt, contain magnesium or lithium halide. Only those containing magnesium salts were found to be highly reactive toward acid halides, aldehydes, and to a lesser degree toward ketones. In the few cases studied, the reactivity of in situ reagents was found to be considerably lower in THF than in ether. Reagents prepared from the commercially available salt were somewhat less reactive.
In an attempt to elucidate the mechanism of the addition reaction, and in particular the role of magnesium or lithium halides, a study of the stereochemistry of addition of in situ dimethylzinc to 4-t-butylcyclohexanone, 2-phenylpropanal, 2-phenylbutanal, and 2-phenyl-3-methylbutanal has been carried out. The results have been compared with those obtained for the corresponding reaction of methyl Grignard and cadmium reagents. The lower stereoselectivity observed with the zinc reagents is rationalized as arising from a tighter four-center transition state for the zinc and cadmium reactions. The results obtained with the first three substrates fit a steric-approach control consistent with the models proposed by Marshall and Felkin. The results obtained for the addition of organometallic species to 2-phenyl-3-methylbutanal are anomalous and represent a clear violation of the postulates of Cram, Karabatsos, and Felkin.

The stereochemistry of the competing addition and reduction reactions of 4-t-butylcyclohexanone with n-propylmagnesium and di-n-propylzinc reagents was explored. The reactivity of the propyl zinc reagents was extremely low, and the major reaction path in one instance was that of reduction. The results of the addition reactions were in agreement with those obtained with the analogous methyl reagents. The stereochemistry of the reduction reaction was dependent on the particular magnesium halide present and in general appears to be highly sensitive to slight variations in steric and electronic influences.
INTRODUCTION

Organozinc reagents were among the first organometallics to be prepared and characterized. The reagents employed in these early investigations were prepared through the interaction of the appropriate alkyl iodide and metallic zinc, followed by distillation of the desired dialkylzinc from the reaction mixture. The chemistry of these "purified" reagents was extensively investigated prior to the discovery of the Grignard reagent in 1900. The latter reagent was found to be considerably more reactive and quickly replaced the organozincs as an important tool of the synthetic organic chemist. However, the reaction of organozincs with acid halides to produce ketones continued to be of considerable synthetic value.

The discovery of the highly reactive organomagnesium and -lithium compounds led to a new method of preparing organozinc reagents. In situ dialkylzincs prepared through the reaction of a Grignard reagent with anhydrous zinc halide differ from the "purified" reagents in that they contain two molar equivalents of magnesium halide. As demonstrated in the present investigation, these in situ reagents possess properties quite distinct from those of the "purified" organozincs.

The first indication that the chemical properties of in situ and "purified" reagents may be quite different was seen in the work of Kollonitsch with organocadmiums.
He observed that the in situ dialkylcadmiums were considerably more reactive toward both aldehydes and acid chlorides than the analogous "purified" compounds. Indeed, their reactivity rivaled that of the Grignard reagents; and the increased reactivity was ascribed to the presence of magnesium and/or lithium halide.

The purpose of the present investigation was two-fold: first, to ascertain whether an analogous difference in reactivity could be found between the "purified" and in situ organozinc reagents. Second, if such differences were noted, what is the role of magnesium and/or lithium halides in the reaction?
SURVEY OF RECENT LITERATURE

A. Preparation and Composition.

Since the time of Frankland (1849), the principal method of preparing dialkylzincs has been the thermal disproportionation of alkylzinc iodides obtained by the direct interaction of zinc or a zinc-copper couple and alkyl iodides.

\[
\begin{align*}
RI + Zn-Cu & \rightarrow RZnI \\
2RZnI & \xrightarrow{\Delta} R_2Zn + ZnI_2
\end{align*}
\]

Solutions of dialkyl- or diarylzincs are more conveniently prepared by addition of anhydrous zinc halides to solutions of Grignard or lithium reagents. Some of the practical difficulties encountered in handling anhydrous zinc halides have been overcome through the preparation of zinc bromide from its elements in anhydrous ether. Organomercury and organoaluminum compounds have also found some limited use as precursors for organozinc reagents.

Thiele and coworkers have recently reported a convenient method for the preparation of the somewhat less stable allylzinc reagents from boron derivatives.
The compounds are only slightly soluble in nonpolar solvents but dissolve readily in ether or THF.

\[ 3(CH_3)_2Zn + 2B(CH_2CH=CH_2)_3 \rightarrow 3(CH_2=CHCH_2)_2Zn + 2(CH_3)_3B \]  \hspace{1cm} (5)

Perhaps as a result of the many investigations into the composition of the Grignard reagent,\(^\text{10}\) considerable attention has been directed at the problem concerning the composition of organozinc halide solutions. Of primary interest has been the determination of the position of equilibrium 6 and the association of the reagents in solution.

\[ R_2Zn + ZnX_2 \rightleftharpoons 2RZnX \]  \hspace{1cm} (6)

Boersma and Noltes\(^\text{11}\) have concluded, on the basis of nmr and ebullioscopic studies, that equilibrium 6 lies almost totally to the right for solutions of ethylzinc chloride and bromide. They also reported tetrameric association of these reagents in benzene but found them to be essentially unassociated in donor solvents. Abraham and Rolfe\(^\text{12a,b}\) have found the association factor for chloride, bromide, and iodide to be low (ca. 1.25) and independent of concentration over the range 0.03-0.41 M in THF and 0.02-0.11 M in ether. The liquid dialkyls are covalently bonded, monomeric substances, the bonds formed by zinc being co-linear. Dimethylzinc is one of the most volatile organometallic compounds known.\(^\text{13}\)

The rate of exchange of ethyl groups in ether or THF solutions of ethylzinc iodide according to equilibrium 6 is reported to be slow, while the situation
for ethylzinc chloride and bromide is not as certain.\textsuperscript{12b} Dessy and Coe\textsuperscript{14} have reported complete random exchange of Zn\textsuperscript{65} when labeled zinc chloride was added to distilled diethylzinc in ether or THF after equilibration for five days. However, analysis of Zn\textsuperscript{65} was accomplished by precipitation of a ZnCl\textsubscript{2}·Bipy complex from solution. In view of the present evidence supporting the existence of EtZnCl species in ether and THF,\textsuperscript{11,12a,b} precipitation of the zinc chloride complex would appear to indicate a rapid exchange of alkyl groups (displacement of equilibrium 6).

Nmr evidence has been obtained which indicates no alkyl group exchange in Et\textsubscript{2}Zn-Me\textsubscript{2}Zn mixtures, but points to rapid exchange of ethyl groups in toluene solutions of diethylzinc-ethylzinc halide (halide = Cl, Br, I).\textsuperscript{15} The fact that rapid exchange was observed with the iodide system in toluene but not in ether or THF as noted above, is not surprising since bridged structures similar to \textsuperscript{1} are known to be more important in nondonor solvents.\textsuperscript{11,16}

\[
\begin{align*}
\text{R-Zn} & \quad \text{Zn-X} \\
\downarrow & \quad \downarrow \text{X} \\
\text{X} & \quad \text{X} \\
\end{align*}
\]

Diallylzincs are monomeric in nondonor solvents. On the basis of its nmr spectrum in benzene, Thiele\textsuperscript{9} has concluded that dimethallylzinc is best represented as a rapidly equilibrating mixture of 2\textsubscript{a} and 2\textsubscript{b}, rather than
as an ionic species such as 3.

\[
1 \quad | \quad 3 \\
\text{CH}_3 - \text{Zn} - \text{CH}_2 - \text{C} = \text{CH}_2 \quad \leftrightarrow \quad 1 \quad | \quad 3 \\
\text{CH}_2 = \text{C} - \text{CH}_2 - \text{Zn} - 
\]

(7)

Most alkylzinc alkoxides are tetrameric in solvents such as benzene or toluene. A cubane structure (4) has been proposed for methylzinc methoxide\textsuperscript{17} on the basis of X-ray diffraction studies. With increasing bulk of the alkoxide group, however, the degree of association decreases.\textsuperscript{18}

In solution the situation is somewhat complicated by the following equilibrium:\textsuperscript{19}
Isolation of 5 has been accomplished and an average molecular weight of 755 (calcd 796) obtained. The temperature-dependent nmr spectrum was best accounted for by an equilibrium between the following six-coordinate (5a) and four-coordinate (5b) zinc species.

Recently, unsymmetrical diarylzincs have been prepared through the interaction of an arylzinc halide and aryl Grignard reagent in ether. Upon addition of dioxane the unsymmetrical organozinc was precipitated before disproportionation could occur.
B. Reactivity.

The reactivity of organozinc reagents toward various carbonyl functions was extensively investigated prior to 1900.\textsuperscript{21} These "distilled" or "purified" reagents are known to be quite inert toward simple ketones and esters. While the reaction with aldehydes is slow and inefficient, the "purified" organozincs do react readily with acid halides and anhydrides to form ketones, and with activated carbonyl compounds, \textit{e.g.}, \(\text{\(\alpha\)}}\)-keto esters, to give alcohols.

With the advent of highly reactive organometallics, the use of Grignard or lithium reagents for the preparation of organozincs has become standard procedure.\textsuperscript{3} However, unlike the "purified" reagents, these \textit{in situ} dialkyl- and diarylzincs contain two molar equivalents of magnesium or lithium halide. Until recently,\textsuperscript{7} however, the two reagents have generally been accepted as equivalent; thus, the possibility that they possess different chemical properties remained untested for some time.

The work of Pinson and Fries\textsuperscript{22} will serve to illustrate this point. In an attempt to prepare methyl cyclobutyl ketone through the interaction of excess \textit{in situ} dimethylzinc or -cadmium and cyclobutanecarboxylic acid chloride (6) the authors reported the major product to be dimethylcyclobutylcarbinol (7). They attributed the
formation of carbinol to the "highly reactive" intermediate, methyl cyclobutyl ketone, rather than to the reactivity of the in situ reagent. Thus, it was generally accepted that the success in the preparation of ketones from acid halides was due to the low reactivity of the zinc reagents toward the keto function.\(^3\)

Following the observation of Kollonitsch\(^3\) regarding the greater reactivity of in situ dialkylcadmiums, Freon and coworkers\(^7\) have recently compared the reactivity of "purified", in situ, and "reconstituted" organozinc reagents. The results, presented in Table I, serve to dispel the notion\(^3\) that the reagents are chemically equivalent and unreactive toward aldehydes and ketones.

The apparent order of reactivity is: "reconstituted" > in situ > "purified". However, when zinc bromide was generated in anhydrous ether from elemental bromine and zinc, the reactivity of the resultant in situ zinc reagents was equivalent to that of the "reconstituted". This variable reactivity of in situ reagents probably reflects the difficulty encountered in preparing and handling anhydrous zinc halides.

In view of the above noted differences in reactivity, a recent report by Marx\(^23\) concerning the kinetics of the

\(\text{(CH}_3\text{)}_2\text{Zn(MgX}_2\text{)} + \begin{array}{c} \text{O} \\ \text{H} \end{array} \text{C-Cl} \rightarrow \begin{array}{c} \text{OH} \\ \text{C(CH}_3\text{)}_2 \end{array} \) (11)
<table>
<thead>
<tr>
<th>Aldehyde or Ketone</th>
<th>Organozinc Reagent</th>
<th>Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>(C$_2$H$_5$)$_2$Zn</td>
<td>40</td>
</tr>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>(n-C$_4$H$_9$)$_2$Zn</td>
<td>15</td>
</tr>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>2C$_2$H$_5$MgBr + ZnBr$_2$</td>
<td>55</td>
</tr>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>2n-C$_4$H$_9$MgBr + ZnBr$_2$</td>
<td>70</td>
</tr>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>(C$_2$H$_5$)$_2$Zn + 2MgBr$_2$</td>
<td>70</td>
</tr>
<tr>
<td>C$_6$H$_5$CHO</td>
<td>(n-C$_4$H$_9$)$_2$Zn + 2MgBr$_2$</td>
<td>70</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>(C$_2$H$_5$)$_2$Zn</td>
<td>5</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>(n-C$_4$H$_9$)$_2$Zn</td>
<td>5</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>2C$_2$H$_5$MgBr + ZnBr$_2$</td>
<td>50</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>2n-C$_4$H$_9$MgBr + ZnBr$_2$</td>
<td>40</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>(C$_2$H$_5$)$_2$Zn + 2MgBr$_2$</td>
<td>60</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>(n-C$_4$H$_9$)$_2$Zn + 2MgBr$_2$</td>
<td>55</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>(C$_2$H$_5$)$_2$Zn</td>
<td>0</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>(n-C$_4$H$_9$)$_2$Zn</td>
<td>0</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>2C$_2$H$_5$MgBr + ZnBr$_2$</td>
<td>45</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>2n-C$_4$H$_9$MgBr + ZnBr$_2$</td>
<td>30</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>(C$_2$H$_5$)$_2$Zn + 2MgBr$_2$</td>
<td>60</td>
</tr>
<tr>
<td>C$_2$H$_5$COCH$_3$</td>
<td>(n-C$_4$H$_9$)$_2$Zn + 2MgBr$_2$</td>
<td>55</td>
</tr>
<tr>
<td>Aldehyde or Ketone</td>
<td>Organozinc Reagent</td>
<td>Alcohol (%)</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td>------------</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>((C_2H_5)_2Zn)</td>
<td>0</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>((n-C_4H_9)_2Zn)</td>
<td>0</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>(2C_2H_5MgBr + ZnBr_2)</td>
<td>51</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>(2n-C_4H_9MgBr + ZnBr_2)</td>
<td>45</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>((C_2H_5)_2Zn + 2MgBr_2)</td>
<td>55</td>
</tr>
<tr>
<td>( C_6H_5COCH_3 )</td>
<td>((n-C_4H_9)_2Zn + 2MgBr_2)</td>
<td>50</td>
</tr>
</tbody>
</table>
reaction of "purified" diethylzinc and benzaldehyde in refluxing diethyl ether is of interest. The reaction was found to be first order in organometallic and first order in aldehyde \( k = 1 \times 10^{-2} \text{ mol}^{-1} \text{ min}^{-1} \). The kinetics were repeated and measured with varying amounts of zinc bromide, zinc chloride, or magnesium bromide added. While the presence of the salts gave rise to an increase in reaction rate, the reaction order remained unchanged. No explanation of the role of salt in the reaction was offered.

The addition reactions of in situ dialkylzincs and -cadmiums have recently been extended to include the imino function. As expected, the cadmium reagents proved to be of superior reactivity.

![Diagram](image)

\[
\begin{align*}
  &\text{a) } R = \text{H}, 55\%; \quad \text{b) } R = \text{Cl}, 63\%
\end{align*}
\]

Freon et al. have prepared in situ bis(\(\alpha\)-ethoxy-methyl)-zinc and -cadmium reagents, and found them to be highly reactive toward aldehydes. They offer an advantage over the corresponding Grignard reagent in their greater thermal stability.

\[
\begin{align*}
  \text{ClCH}_2\text{OC}_2\text{H}_5 + \text{Mg} &\xrightarrow{\text{THF} \ -15^\circ} \text{ClMgCH}_2\text{OC}_2\text{H}_5 \\
  &\xrightarrow{\text{ZnI}_2 \ -15^\circ} \text{Zn(\text{CH}_2\text{OC}_2\text{H}_5)}_2
\end{align*}
\]
Table II

Reactivity of \textit{in situ} bis (\(\alpha\)-Ethoxymethyl)-zinc with Aldehydes, Ketones, and Acid Chlorides\textsuperscript{25}

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Products</th>
<th>Ketone (%)</th>
<th>Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{C}_2\text{H}_5\text{COC}_2\text{H}_5)</td>
<td></td>
<td>--</td>
<td>0.35</td>
</tr>
<tr>
<td>(\text{C}<em>6\text{H}</em>{13}\text{COCH}_3)</td>
<td></td>
<td>--</td>
<td>0.0</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{COCH}_3)</td>
<td></td>
<td>--</td>
<td>0.0</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{CHO})</td>
<td></td>
<td>--</td>
<td>70</td>
</tr>
<tr>
<td>(\text{n-C}_4\text{H}_9\text{CHO})</td>
<td></td>
<td>--</td>
<td>36</td>
</tr>
<tr>
<td>(\text{n-C}_4\text{H}_9\text{COCl})</td>
<td></td>
<td>60</td>
<td>--</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{COCl})</td>
<td></td>
<td>1</td>
<td>--</td>
</tr>
</tbody>
</table>

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
In contrast to the usual alkyl- and arylzincs, allyl reagents—and to a lesser extent benzylzincs—prepared from the appropriate halide and metallic zinc react readily with aldehydes, ketones, anhydrides, esters, nitriles, and carbon dioxide.\textsuperscript{26} Freon et al.\textsuperscript{27} have found the reactivity of diallylzincs, prepared according to the method of Thiele,\textsuperscript{9} to be comparable to that of the corresponding Grignard reagents (Table III). Somewhat unexpectedly, the reactivity of the "salt-free" diallylzinc is slightly lower than that of diallylcadmium.

Alkynylzinc halides prepared through the reaction of allylzinc halides and the appropriate alkyne are reactive toward aldehydes and to a lesser degree toward ketones. The results of Golse et al.\textsuperscript{28} obtained with 2-phenylethynylzinc bromide and a variety of aliphatic ketones and aldehydes are given in Table IV.

The stereochemistry of addition of various zinc reagents to 4-\textsuperscript{t}-butylcyclohexanone has been studied.\textsuperscript{29a,b} The major product of the reaction of di-n-propylzinc results from β-reduction of the ketone; however, the ratio of isomeric reduction products could not be determined (glpc). The stereochemical results of the addition reaction showed the major isomer resulted from equatorial attack, i.e., the axial alcohol (8). Unexpectedly, diallyl- and dicrotylzinc

\[
\begin{align*}
\text{CH}_2\text{=CHCH}_2\text{Br} + \text{Zn} & \xrightarrow{\text{THF}} \text{CH}_2\text{=CHCH}_2\text{ZnBr} & \text{RC=CH} & \xrightarrow{\text{RC=CZnBr}} \\
\text{RC=CZnBr} + \text{R'CR''} & \xrightarrow{\text{THF}} \text{RC=C-CR'CR''} \\
\end{align*}
\]
Table III

Reactivity of "salt-free" Diallylzinc\textsuperscript{27}

<table>
<thead>
<tr>
<th>Aldehyde or Ketone</th>
<th>Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C\textsubscript{3}H\textsubscript{7}CHO</td>
<td>65</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}CHO</td>
<td>75</td>
</tr>
<tr>
<td>C\textsubscript{2}H\textsubscript{5}COCH\textsubscript{3}</td>
<td>71</td>
</tr>
<tr>
<td>C\textsubscript{2}H\textsubscript{5}COC\textsubscript{2}H\textsubscript{5}</td>
<td>83</td>
</tr>
</tbody>
</table>
Table IV

Reactivity of 2-Phenylethynylzinc Bromide

<table>
<thead>
<tr>
<th>Aldehyde or Ketone</th>
<th>Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butanal</td>
<td>63</td>
</tr>
<tr>
<td>Pentanal</td>
<td>56</td>
</tr>
<tr>
<td>Hexanal</td>
<td>57</td>
</tr>
<tr>
<td>Heptanal</td>
<td>60</td>
</tr>
<tr>
<td>2-Butenal</td>
<td>22</td>
</tr>
<tr>
<td>2-Propanone</td>
<td>8</td>
</tr>
<tr>
<td>2-Pentanone</td>
<td>5</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>23</td>
</tr>
</tbody>
</table>
gave a greater proportion of equatorial attack than the n-propyl reagent; yet in the case of the crotylzinc reagent, the addition product is that which would result from an $S_{E2}'$ transfer (allylic rearrangement) of the crotyl group. The corresponding allyl and crotyl Grignard reagents give a greater percentage of axial attack than n-propylmagnesium bromide. The results are summarized in Table V.

The Reformatskii reaction has been and continues to be of considerable synthetic importance. Although a detailed review of the recent literature is beyond the scope of the present work, a recent report by Palmer and Ried concerning a novel approach to the generation of the zinc enolate is of interest. Metallic zinc was replaced by di-n-propylzinc in the reaction between (-)-menthyl bromoacetate (10) and acetophenone; and after the appropriate workup, optically active (+)-3-hydroxy-3-phenylbutanoic acid (11) was obtained.

\[
\begin{align*}
\text{(-)-MenthyloCCH}_2\text{Br} & \quad \text{C}_6\text{H}_5\text{COCH}_3 & \quad \text{(n-C}_3\text{H}_7)_2\text{Zn} \\
\text{0} & \quad \text{10} & \quad \text{11}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Reagent</th>
<th>% Reaction</th>
<th>% [9]</th>
<th>% [10]</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C₃H₇MgBr</td>
<td>--</td>
<td>75</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>(n-C₃H₇)₂Zn(MgBr₂)</td>
<td>--</td>
<td>75</td>
<td>25</td>
<td>53</td>
</tr>
<tr>
<td>(n-C₃H₇)₂Cd(MgBr₂)</td>
<td>--</td>
<td>80</td>
<td>20</td>
<td>17.5</td>
</tr>
<tr>
<td>CH₂=CHCH₂MgBr</td>
<td>&gt;99</td>
<td>44.5</td>
<td>55.5</td>
<td>--</td>
</tr>
<tr>
<td>(CH₂=CHCH₂)₂Zn</td>
<td>35</td>
<td>84</td>
<td>16</td>
<td>--</td>
</tr>
<tr>
<td>(CH₂=CHCH₂)₂Cd</td>
<td>55</td>
<td>77.5</td>
<td>22.5</td>
<td>--</td>
</tr>
<tr>
<td>CH₃CH=CHCH₂MgBr</td>
<td>&gt;99</td>
<td>70</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>(CH₃CH=CHCH₂)Zn</td>
<td>15</td>
<td>86</td>
<td>14</td>
<td>--</td>
</tr>
</tbody>
</table>

Table V

Reaction of Organozincs, -Cadmiums, and -Magnesiums with 4-tert-Butylcyclohexanone²⁹ (Equation 16).
EXPERIMENTAL

The infrared spectra were recorded with a Perkin-Elmer Model 337 grating spectrophotometer; nmr spectra, obtained with a Varian A-60 spectrometer, are reported in ppm ($\delta$) downfield from tetramethylsilane (0.0 ppm) used as an internal standard. Gas liquid phase chromatographic (glpc) analyses and separations were accomplished with a Varian Model 90-P gas chromatograph using helium as the carrier gas. The various liquid phases employed: i.e., Apiezon L (10%, 10'), Carbowax 20 M (10%, 10'), FFAP (10%, 10'), SAIB (20%, 10'), SE-30 (20%, 5'), and STAP (10%, 10'), were all deposited on 60/80 mesh chromosorb W. Areas under the peaks were determined as the product of the height and half-height peak width, and no correction made for differences in response ratios unless otherwise stated. Both nmr and ir spectra, as well as the chromatographic charts, are described by a file number.

Melting points, determined with a Hoover Capillary Melting Point Apparatus, and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories of Knoxville, Tennessee.

Grignard reagents employed in all stereochemical studies were prepared from singly-sublimed magnesium (Dow Chemical Co.) in a dry nitrogen atmosphere and stored in serum-capped bottles. Their concentrations were checked periodically by titration with standard sec-butyl alcohol.
in xylene using either 1,10-phenanthroline or 2,2'-biquinoline as indicator. All stereochemical investigations involving the use of organometallic reagents were carried out under an atmosphere of dry nitrogen in ether solution unless otherwise stated. Each organozinc reagent employed gave a negative Gilman test for the presence of Grignard reagent before use.

**Generation of Anhydrous Zinc Bromide in Solution.**

A one-liter, three-necked flask was fitted with a mechanical stirrer, reflux condenser, and dropping funnel (Teflon stopcock). To the flask, containing a suspension of 37.7 g (0.58 mol) of powdered zinc in 500 ml of anhydrous ether or THF was added 80 g (0.50 mol) of bromine. Although the reaction is exothermic, it required periodic heating so as to maintain a gentle reflux. After approximately half the bromine had been added, the reaction became sluggish, so that continuous heating and rapid, efficient stirring became essential. The addition of bromine was complete in about 10 hr, and stirring was continued overnight to insure maximum reaction. The entire operation was carried out under an atmosphere of dry nitrogen, and repeated testing with moist litmus indicated no hydrogen bromide was evolved during bromination.

The final solution was centrifuged under nitrogen to remove the excess zinc and the final volume of solution measured. Calculation of the concentration of zinc bromide (generally 1 M) was based on the volume of solution and the weight of recovered zinc metal. Although several variations of the above procedure were tried, the final solution always contained residual bromine as evidenced...
by its yellow-orange color. After storage for several days in serum-capped bottles the solution became dark brown. The zinc reagents prepared from these zinc bromide solutions and their subsequent reaction products were generally highly colored.

The initial yellow-orange color was observed to lighten slightly when a portion of the solution was extracted with sodium bisulfite. The nmr spectrum (4648) of the ethereal solution indicated ether as the only organic component. Glpc analysis on FFAP after precipitation of zinc bromide dioxonate indicated 98% ether (minimum) with a maximum of 2% of a component whose retention time was identical to that of ethanol. No high-boiling components could be detected.

The dioxonate was precipitated by addition of dioxane, recrystallized from chloroform, and dried.

**Anal. Calcd for C₄H₈O₂·ZnBr₂:** C, 15.33; H, 2.57; Br, 51.01. Found: C, 15.12; H, 2.59; Br, 50.84.

Ethereal solutions of anhydrous zinc bromide and chloride were also prepared by dissolving the fused salts (commercially available as "dry" salts) in anhydrous ether. In order to avoid a two-phase system with the chloride, it was necessary to prepare a concentrated solution (4-5 M). At this concentration a one-phase liquid was obtained. The zinc bromide prepared by this method was clear and colorless.* These solutions were also stored over molecular sieves in serum-capped bottles.

*Ethereal solutions of zinc bromide prepared by the interaction of zinc and bromine were employed in all reactions unless otherwise stated.
Reaction of in situ Ethylzinc Bromide (Br,Br)* and Benzoyl Chloride.

In THF.

Ethylmagnesium bromide was prepared in the usual manner from 5.0 g (0.21 mol) of magnesium and 20.7 g (0.19 mol) of ethyl bromide in 150 ml of THF. Then 250 ml of 0.8 M zinc bromide (0.2 mol) in THF was added slowly with stirring and cooling. The resultant two-phase liquid system gave a negative Gilman test for the presence of Grignard reagent. The 60 MHz-nmr spectrum (4078-a and 4078-b) of the in situ reagent was identical to that reported by Abraham and Rolfe:12b nmr (THF) \( \delta \) 1.1 (t, 3, \( \text{CH}_3\text{CH}_2\text{-} \)) and 0.1 ppm (q, 2, \( \text{CH}_2\text{Zn} \)).

Benzoyl chloride (27.7 g, 0.19 mol) in 50 ml of THF was added slowly with stirring over a 30-min period at room temperature. This solution was refluxed for one hour and then stirred at room temperature overnight. The reaction mixture was poured onto crushed ice, acidified with 100 ml of 2 N hydrochloric acid, and the resultant two layers were separated. THF was removed from both on a rotary evaporator, and the residues combined and extracted twice with 100-ml portions of ether. The combined ether layers were in turn extracted with saturated sodium bicarbonate, water, dried (MgSO\(_4\)), and concentrated to yield 24 g of a dark, sweet-smelling liquid (ir 7025-a). The bicarbonate extracts yielded 1.8 g of benzoic acid (mp 120.5-122°, ir 7025-b) after acidification.

The liquid was distilled at reduced pressure to give three fractions and 16 g of a solid polymeric residue. The lowest boiling fraction [2.1 g, bp 43-67°]

*Halogens in parentheses indicate, respectively, the alkyl halide from which RMgX was prepared and the zinc halide used for the exchange.
(0.45 mm)] was identified (comparison with authentic samples) by ir (7036-a), nmr (3496-a), and glpc (1 and 2) on STAP; and found to contain mostly ethyl benzoate (75%) and propiophenone (25%). Ir (neat) 1690 (keto C=O) and 1725 cm\(^{-1}\) (benzoate C=O). Fractions 2 [1.0 g, bp 67-111\(^\circ\) (0.45 mm)] and 3 [6.7 g, bp 112-123\(^\circ\) (0.45 mm)] were combined after inspection of their ir (7036-c and 7036-d) and nmr (3547) spectra. This material gave a positive Beilstein test.

The precipitate obtained after treatment with sodium iodide in acetone\(^{33}\) was subsequently treated with concentrated nitric acid and carbon tetrachloride,\(^{34}\) identifying the halide as bromide. This evidence when coupled with the following spectral data allowed tentative identification of 4-bromobutyl benzoate (14%): ir (neat) 1720 (benzoate C=O) and 1275 cm\(^{-1}\) (C-O); nmr (CCl\(_4\)) \(\delta\) 8.0 (m, 2, aromatic), 7.4 (m, 3, aromatic), 4.31 (t, 2, CH\(_2\)OBz), 3.43 (t, 2, CH\(_2\)Br), and 1.94 ppm [t, 4, BrCH\(_2\)(CH\(_2\))\(_2\)CH\(_2\)OBz].

Treatment of the bromo ester with phthalimide and potassium carbonate in dimethylformamide gave the 4-phthalimidobutyl benzoate derivative, mp 96-97\(^\circ\) (lit.\(^{35}\) mp 97-98\(^\circ\)). A mixture of 4-bromobutyl benzoate and 4-chlorobutyl benzoate was prepared according to the method of Cloke et al.\(^{36}\) The 4-phthalimidobutyl benzoate obtained from this mixture showed no melting point depression when mixed with the above sample.

In Ether.

The procedure and amounts of reagents employed were the same as those employed in THF except that the reaction time was reduced to three hours in refluxing ether. Hydrolysis was accomplished by pouring the reaction mixture onto crushed ice. Subsequently the mixture
was acidified with dilute hydrochloric acid and the aqueous layer extracted with two 100-ml portions of ether. The combined ether layers were extracted with saturated sodium bicarbonate, dried (MgSO₄), and freed of solvent in vacuo to yield 23.4 g of crude product. Distillation at 39-46° (0.4 mm) gave 19.7 g of a light yellow liquid whose ir spectrum (6820) indicated the presence of propiophenone and ethyl benzoate: ir (neat) 1690 (keto C=O) and 1725 cm⁻¹ (benzoate C=O). The yields of ketone (22%) and ester (68%) were determined by nmr (3315) spectroscopy with dioxane as the internal standard. Authentic samples of the ketone and ester were available.

**Reaction of in situ "Diethylzinc" (Br,Br) and Propanoyl Bromide.**

Ethylmagnesium bromide was prepared in the usual manner from 2.5 g (0.1 mol) of magnesium and 10.9 g (0.1 mol) of ethyl bromide in 35 ml of ether. To this solution was added 0.5 molar equivalent of zinc bromide (38 ml of 1.3 M) with stirring and cooling.

Propanoyl bromide (13.7 g, 0.1 mol) in 10 ml of ether was added slowly at room temperature and the solution stirred overnight. The reaction was quenched with 100 ml of 2 N hydrochloric acid. After saturation of the aqueous layer with sodium chloride, it was extracted with three 100-ml portions of ether. The ether layers were combined, extracted with sodium bicarbonate solution, dried over magnesium sulfate, and the solvent removed at reduced temperature and pressure to yield 9.5 g of crude product. The ir (7462-a) and nmr (4286-d) spectra indicated the
presence of diethyl ketone and ethyl propionate: ir (neat) 1745 (ester C=O) and 1720 cm\(^{-1}\) (keto C=O); nmr (neat) \(\delta\) 3.90 (q, 2, CH\(_2\)CO) and 2.30 ppm [q, 4, (CH\(_2\))\(_2\)C=O]. Glpc analysis (12) was performed on Carbowax 20 M at a column temperature of 65° and a flow rate of 45 ml/min. The yield and retention times of diethyl ketone and ethyl propionate were 28% (1.47 min) and 35% (1.30 min), respectively. Retention times and spectra of both ketone and ester corresponded to those of authentic samples.

**Attempted Reaction of in situ Ethylzinc Bromide (Br,Br) with Benzaldehyde in THF.**

The Grignard reagent (0.2 mol) was prepared in the usual manner from ethyl bromide under an atmosphere of dry nitrogen in THF. One molar equivalent of zinc bromide (200 ml of 1 M) was added slowly with stirring to give a two-phase liquid system. Addition of 10.6 g (0.1 mol) of benzaldehyde produced no noticeable evolution of heat or change in the appearance of the mixture. A 2-ml aliquot was removed and hydrolyzed (NH\(_4\)Cl) after two hours of stirring at room temperature. The remainder of the reaction mixture was hydrolyzed after four hours (total) with 100 ml of 2 N ammonium chloride solution, the THF removed in vacuo on a rotary evaporator, and the aqueous residue extracted with several portions of ether. The ether extracts were combined, dried (MgSO\(_4\)), and the solvent removed to yield 21.6 g of crude product. The nmr spectrum (4244, CCl\(_4\)) given below indicated the major component may have resulted from cleavage and subsequent polymerization of the reaction solvent (THF). The two major areas of absorption [\(\delta\) 3.4 (m) and 1.6 ppm (m)] were broad and occurred at slightly higher field than the multiplets of THF (\(\delta\) 3.65 (m) and 1.73 ppm (m)].
The crude product was analyzed by glpc (10) on Apiezon L at a column temperature of 180° and flow rate of 40 ml/min. The amount of THF polymer (major product) was not determined as it remained on the column. However, the identity and relative amounts of the major volatile products were determined since samples of the authentic materials were available. Thus, benzaldehyde (70%), ethylphenylcarbinol (10%), propiophenone (20%) and traces of benzyl alcohol were observed at retention times of 1.68 min, 2.15 min, 3.42 min, and 2.50 min, respectively. Essentially the same results were obtained from analysis of the aliquot removed after two hours except that a somewhat larger amount of unchanged benzaldehyde was noted.

Reaction of in situ "Diethylzinc" (Br,Br) with Benzaldehyde in Ether.

Ethylmagnesium bromide was prepared in the usual manner from 4.8 g (0.2 mol) of magnesium and 21.8 g (0.2 mol) of ethyl bromide in 70 ml of ether. To this solution was added 0.5 molar equivalent of zinc bromide (38 ml of 1.3 M) with stirring and cooling. The reaction was carried out under an atmosphere of dry nitrogen. Addition of 5.3 g (0.05 mol) of benzaldehyde, with stirring, was complete in 5 min. A slight warming occurred, and a second, paste-like "liquid" phase appeared. While the mixture was stirred for two hours at room temperature, 2-ml aliquots were removed and hydrolyzed (NH₄Cl) at 0.5-hr intervals. Hydrolysis of the remaining solution was accomplished with 100 ml of 2 N ammonium chloride solution. After the usual work-up procedure, 6.8 g of crude product was obtained.
Glcpc analysis of this material was performed at a column temperature of 170° with Apiezon L at a flow rate of 40 ml/min. The ir (7598-c) and nmr (4318) spectra are essentially identical to those obtained with an authentic sample of ethylphenylcarbinol: ir (neat) 1095 (C-O) and ~3400 cm⁻¹ (OH); nmr (neat) δ 6.83 (s, 5, aromatic), 1.5 (m, 2, CHCH₂CH₃), and 0.71 ppm (t, 3, CH₂CH₃). The yield of carbinol (78%) was determined by nmr analysis with dioxane as the internal standard. Analysis of the various aliquots revealed the reaction to be essentially complete after 1.5 hr. The identical reaction was run with diethylzinc prepared from commercially available zinc bromide, which had been rendered anhydrous by the standard fusion technique. In this case the yield of ethylphenylcarbinol was 60%.

** Attempted Reaction of in situ "Diethylzinc" (Br,Br) with Acetophenone. In Ether. 

Ethylmagnesium bromide was prepared from 4.8 g (0.2 mol) of magnesium and 21.8 g (0.2 mol) of ethyl bromide in 50 ml of ether. To this solution was added 77 ml of 1.3 M zinc bromide solution (0.1 mol) with stirring at room temperature.

Addition of acetophenone (6.0 g, 0.05 mol) caused no evolution of heat nor change in the appearance of the reagent. The solution was stirred under an atmosphere of dry nitrogen for six hours, hydrolyzed with ammonium chloride solution, and worked up in the usual manner to give 5.2 g of crude product. From a comparison of the ir (7598-b) and nmr (4286-g) spectra of the crude product
with those of an authentic sample of methylethylphenylcarbinol, it was concluded that no addition product had formed in the reaction (87% acetophenone recovered).

In THF.

Ethylmagnesium bromide was prepared from 4.8 g (0.2 mol) of magnesium and 21.8 g (0.2 mol) of ethyl bromide in 60 ml of THF. The molarity of the reagent was determined by titration (5 ml aliquot) of its 1,10-phenanthroline charge transfer complex with standard (1.0 M) sec-butyl alcohol according to the method of Watson and Eastham. To the remaining Grignard reagent (55 ml of 1.8 M) was added 0.5 molar equivalent of zinc bromide (50 ml of 1.0 M, 0.05 mol) with stirring at room temperature.

Addition of acetophenone (3.0 g, 0.025 mol) caused no evolution of heat nor change in the appearance of the reagent. The remainder of the reaction procedure and work-up were carried out as described above and gave 4.2 g of crude product. Ir (7642) and nmr (4325-a) analysis of the recovered material established that it was mostly unchanged acetophenone and THF polymer.

Reaction of in situ Phenylzinc Bromide (Br,Br) with Benzaldehyde.

Phenylmagnesium bromide was prepared in 60% yield from 2.4 g (0.1 mol) of magnesium and 15.7 g (0.1 mol) of bromobenzene in 100 ml of ether. After titration of the reagent one molar equivalent (0.06 mol) of zinc bromide in ether was added. Then 3.0 g (0.028 mol) of benzaldehyde was added, and the mixture stirred overnight at ambient

*The molarity of Grignard reagents employed in all subsequent reactions was determined before use by the titration method of Watson and Eastham.
temperature. Hydrolysis ($\text{NH}_4\text{Cl}$) and subsequent work-up of the reaction mixture gave 5.1 g of a brown liquid. The nmr spectrum (4516-a) of the neat liquid disclosed the presence of unchanged benzaldehyde [$\delta$ 9.88 ppm (s, 1, H$_{\text{Bz}}$)] and benzhydrol [$\delta$ 5.35 (s, 1, H$_{\text{COH}}$) and 4.45 ppm (s, 1, H$_{\text{COH}}$)]. Quantitative determination of the benzhydrol (15%) was accomplished by nmr analysis with dioxane as internal standard.

**Reaction of in situ Diphenylzinc (Br,Br) with Benzaldehyde.**

The procedure and quantities of reagents employed were the same as above except that 0.5 molar equivalent of zinc bromide was employed (relative to phenylmagnesium bromide) and the reaction time was 15 hr. Nmr analysis (4701) of the crude product indicated a 65% conversion of benzaldehyde to benzhydrol. Similarly, analysis of aliquots removed after two and five hours showed the reaction was essentially complete after five hours.

**Reaction of in situ Ethylzinc Ethoxide (Br,Br) with Benzaldehyde.**

An ethereal solution of diethylzinc (125 ml of 0.26 M) was prepared as previously described. To this solution was added one molar equivalent (1.5 g, 0.033 mol) of absolute ethanol, followed by 1.7 g (0.016 mol) of benzaldehyde in 10 ml of ether. The reaction was carried out at room temperature with stirring. Aliquots were removed and quenched after 0.5 and 1.0 hr, and the remaining mixture hydrolyzed after 1.5 hr with ammonium chloride solution. After acidification, the aqueous layer was extracted several times with ether. The ether layers were combined, washed with sodium bicarbonate solution, dried ($\text{MgSO}_4$), and eventually yielded 2.0 g of crude product.
spectrum (4697) compared favorably with that of an authentic sample of ethylphenylcarbinol. The ir spectrum (7351) is consistent with this assignment and showed only weak absorption at 1705 cm\(^{-1}\) (C=O). The yield of ethylphenylcarbinol (65%) was determined by nmr analysis with dioxane as the internal standard.

Glcpc analyses (18) of samples quenched after 0.5, 1.0, and 1.5 hr were performed under the conditions previously described (see p. 27). The results indicated the reaction was essentially complete after 1.0 hr.

**Generation of Anhydrous Zinc Iodide in Solution.**

A one-liter, three-necked flask was fitted with a mechanical stirrer and a pressure-equalizing addition funnel. The flask contained a suspension of 37.7 g (0.58 mol) of powdered zinc in 500 ml of anhydrous ether. A piece of glass wool placed in the funnel served to support 126.9 g (0.5 mol) of iodine. A reflux condenser, connected above the addition funnel, served to condense the ether vapors generated from heating the contents of the flask. The condensed solvent then passed over the iodine on its return to the reaction vessel, thus bringing the iodine in contact with the zinc. Although the reaction is exothermic, it was necessary to adjust the external heat periodically so as to maintain a gentle reflux. The addition of iodine was complete in 8 hr, but vigorous stirring was continued overnight to insure maximum reaction. The entire process was carried out under an atmosphere of dry nitrogen.

The final solution was centrifuged under nitrogen to remove the excess zinc and the final volume of the solution measured. Calculation of the concentration of zinc
iodide (generally 1 M) was based on the volume of solution and the weight of zinc metal recovered. The colorless solution was stored over molecular sieves (3A) in a serum-capped bottle and used as required.

**Reaction of in situ Dimethylzinc (I,I) with Benzaldehyde.**

An ethereal solution of 10.6 ml of 2.08 M methylmagnesium bromide (0.022 mol) was added, by means of a 20-ml syringe,* to 5 ml of ether. Then 10.0 ml of 1.1 M zinc iodide (0.011 mol) was added slowly with stirring and cooling. The reagent was cooled to 0° and 1.2 g (0.011 mol) of benzaldehyde in 15 ml of ether added while the internal temperature was maintained below 5°. The ice bath was removed immediately and the reaction mixture stirred for three hours at ambient temperature. Hydrolysis was accomplished with 25 ml of sodium bicarbonate solution; and after the usual work-up, 1.4 g of crude product was obtained.

The crude product was analyzed by glpc (33) on FFAP (10%, 10') at a column temperature of 180° and a flow rate of 40 ml/min. The identification of unchanged benzaldehyde and methylphenylcarbinol (77%) was accomplished by comparison of their retention times (3.39 min and 6.90 min, respectively) with those of authentic samples.

**Reaction of in situ Dimethylzinc (Br,Br) with Cyclohexanone.**

The following procedure will serve to illustrate the reaction of the *in situ* dimethyl- and diethylzinc reagents with cyclohexanone.

*All subsequent transfers of Grignard and zinc reagents were carried out with the aid of a 20-ml syringe.*

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
An ethereal solution of 28.0 ml of 1.85 M methylmagnesium bromide (0.052 mol) was added to 40 ml of ether. Then 17.4 ml of 1.5 M zinc bromide \(^{38}\) (0.026 mol) was added slowly with stirring and cooling. To this reagent was added 1.3 g (0.013 mol) of cyclohexanone at room temperature. After being stirred overnight, the mixture was hydrolyzed with 25 ml of sodium bicarbonate, the ether layer separated, and the aqueous layer extracted with ether. The ether layers were combined; dried (MgSO\(_4\)), and concentrated to yield 1.4 g of crude product.

Glpc analysis (24-a) was performed with Apiezon L at a column temperature of 145° and a flow rate of 40 ml/min. Identification of 1-methylcyclohexanol and cyclohexanone was accomplished by comparison of retention times of alcohol and ketone (5.40 min and 4.22 min, respectively) with those of authentic samples. Results of the dialkylzinc-cyclohexanone reaction series are given in Table IX.

**Reaction of in situ Methylcyclohexoxyzinc (I,Br) with Cyclohexanone.**

Dimethylzinc reagent (0.038 mol) in ether was prepared as described above. To this was added 3.8 g (0.038 mol) of cyclohexanol with the subsequent formation of a second paste-like liquid phase. Then 1.0 g (0.01 mol) of cyclohexanone in ether was added rapidly and vigorous stirring continued at room temperature overnight. After the usual work-up 3.4 g of crude product was obtained. Glpc (21) analysis on Apiezon L revealed a 27% conversion to 1-methylcyclohexanol.
Reaction of in situ Diphenylzinc (Br,I) with Carbon Dioxide.

Run I.

An ethereal solution of diphenylzinc (0.015 mol) was prepared in the usual manner from 15.6 ml of 1.92 M phenylmagnesium bromide and 11.5 ml of 1.3 M zinc iodide. The solution was cooled to -78° and 5.0 g of crushed dry ice added. The reaction mixture was stirred for two hours at -78° and additional quantities of dry ice added at 0.5 hr intervals.

After being warmed to 0°, the mixture was hydrolyzed with 25 ml of dilute hydrochloric acid (0-5°), the ether layer separated, and the aqueous layer extracted with three 20-ml portions of ether. The combined ether layers were subsequently extracted with saturated sodium bicarbonate solution, and the resultant aqueous layer acidified with concentrated hydrochloric acid before extraction with several 20-ml portions of benzene. The benzene layers were combined, dried (MgSO₄), and the solvent removed on a rotary evaporator to yield 1.0 g (27%) of a slightly yellow solid, mp 114-118°. Recrystallization from water gave 0.5 g (13%) benzoic acid, mp 120.5-121.5° (lit. 122.4°).

Run II.

An ethereal solution of 0.3 M diphenylzinc (Br,I; 0.030 mol) was prepared in the usual manner, and carbon dioxide bubbled into the solution at room temperature over a 15-hr period. The resultant cloudy solution was hydrolyzed and worked up as described above, to yield 1.5 g (41%) of benzoic acid, mp 120-121°. On the assumption that only one of the phenyl groups of the diphenylzinc reagent is reactive, the yield is 82%.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Preparation of Anhydrous Magnesium Iodide Dietherate.

The procedure employed was identical to that described previously for the preparation of zinc iodide. The final solution, however, consisted of two phases which, if allowed to cool, yielded a third, solid phase \((\text{MgI}_2 \cdot 2\text{C}_4\text{H}_10\text{O})\). Generally the liquid became colored after a few hours, apparently because of the liberation of iodine.

The colorless two-phase system was filtered before cooling through a glass wool plug under a current of dry nitrogen. Removal of solvent was effected at room temperature and aspirator pressure, in the presence of both calcium chloride and phosphorus pentoxide to insure anhydrous conditions. The residual solid magnesium iodide dietherate was placed in a dry box and transferred to a tightly sealed container under dry nitrogen. This material could be stored for several days before appreciable iodine color developed.

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 by means of a 20-ml syringe 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

*The volume of ether varied depending on the concentration (0.8 or 0.1 M) of Grignard reagent desired.
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 in 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.

Glpco analysis and separation were accomplished at a column temperature of 190° on FFAP (20%, 10') at a flow rate of 75 ml/min. The retention times were as follows: (Z)41-1-methyl-4-t-butylcyclohexanol (5.54 min), (E)41-1-methyl-4-t-butylcyclohexanol (6.69 min) and 4-t-butylcyclohexanone (7.46 min). The order of elution on SAIB42 was the same. Analyses were carried out on crude, isolated product and no correction made for mass balance.* Areas under the peaks were determined as the product of the height and half-height peak width. The results are given in Table X. Values for the relative amounts of product alcohols were reproducible within ±1% and those of unchanged ketone within ±5% in separate reaction runs. The response ratios of the two alcohols are known to be the same.43

*Normalized %; %Z + %E = 100; Yield of alcohols = 100 - % ketone.
Reaction of in situ Dimethylzinc (I,Br) with 4-t-Butyl-cyclohexanone.

The following procedure will serve to illustrate the reaction of the in situ zinc reagents with 4-t-butyl-cyclohexanone.

An ethereal solution of 27.4 ml of 1.90 methyl-magnesium iodide (0.052 mol) was added to 24.0 ml of anhydrous ether. Then 20.0 ml of 1.3 M zinc bromide (0.026 mol) was added slowly with stirring and cooling, to give a two-phase liquid system. After the reagent was cooled, 2.0 g (0.013 mol) of 4-t-butylcyclohexanone in 15 ml of ether was added at 0-5°. At the start of the reaction, the solution was 0.3 M in dimethylzinc. The ice-salt bath was removed and the reaction mixture stirred for 3 hr at room temperature.

Hydrolysis was accomplished at 0-5° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, dried over magnesium sulfate, and concentrated on a rotary evaporator at room temperature. The residual crude product amounted to 2.3 g.

Glpc analysis on FFAP of the crude reaction mixtures indicated that in some instances a considerable amount of zinc salt was carried through the work-up procedure, as evidenced by the presence of variable amounts of 1-methyl-4-t-butylcyclohexene (see below) in addition to the desired alcohols. The % olefin increased drastically unless the injector port of the chromatograph was cleaned regularly. In such cases the crude product was taken up in benzene and any solid zinc salts which precipitated were removed. It was later found that extraction
of the crude reaction mixture with ammonium hydroxide<sup>44</sup> removes the undesirable salts. Infrared and nmr spectra gave no evidence of olefin in the samples prior to injection. Redissolving the precipitated zinc salts in ether gave a solution whose glpc analysis showed no trace of alcohols or olefin. For all values reported in Table X, the % olefin did not exceed 5%. Values for the relative amounts of product alcohols were reproducible within ±1% in separate reaction runs.

**Preparation and Analysis of "Purified" Dimethylzinc.**

A procedure similar to that described by Krug and Tang<sup>45</sup> was used. Zinc powder (65 g, 1.0 mol) and 13 g of cupric citrate were mixed in a 250-ml three-necked flask. The contents were heated under a current of dry nitrogen, over a free flame, with occasional shaking, until the evolution of moisture and other gases had ceased. The flask was allowed to cool and the mixture used immediately for the preparation of dimethylzinc.

The flask was fitted with a condenser, mechanical stirrer, and dropping funnel; and the condenser was in turn connected to a gas absorption trap containing toluene. After the flask had been flushed with dry nitrogen, 71 g (0.5 mol) of methyl iodide was added dropwise over a period of 2-3 hr. The reaction was sluggish and required occasional warming on a water bath. The reaction was carried out under an atmosphere of dry nitrogen, and the contents stirred overnight at room temperature.

Before removal of the addition funnel, condenser, and stirrer was attempted, the flask was cooled to -78° in a dry ice-acetone bath. The flask was then fitted for
distillation of the dimethylzinc under an atmosphere of dry nitrogen. A Dewar condenser was used containing a mixture of ethanol and crushed ice (1:1, v/w) at a temperature of -15°, and the collection flask immersed in a dry ice-acetone bath. Distillation yielded 15.7 g (0.164 mol, 65%) of dimethylzinc collected at 44-50° (760 mm). Sufficient ether was then added to prepare a 1.0 M solution of "purified" dimethylzinc, and the reagent was refrigerated in a serum-capped amber bottle until required.

The concentration was checked 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. Precipitation of zinc salts occurred immediately after the end point was reached.

Reaction of "Reconstituted" Dimethylzinc with 4-<t>Butyl-cyclohexanone.

The following procedure will serve to illustrate the reaction of "reconstituted" dimethylzinc reagents with 4-<t>Butylcyclohexanone. An ethereal solution of 12.0 ml of 1.0 M dimethylzinc (0.012 mol) was added to 12 ml of ether containing 9.9 g (0.023 mol) of anhydrous magnesium iodide dietherate.* This mixture was stirred for 20-30 min at room temperature and then cooled to 0°. One gram (0.006 mol) of 4-<t>Butylcyclohexanone in 15 ml of ether was added at such a rate that the temperature did not exceed 5°. The concentration at the start of the

*The amount of salt varied depending on the molar ratio (2:1, 1:1, 1:2) of salt to dimethylzinc desired.
reaction was 0.3 M in dimethylzinc. The ice-salt bath was removed and the reaction stirred for 3 hr at room temperature. The reaction mixture was cooled to 0°, hydrolyzed, and worked up as described above. The crude product, usually amounting to 0.8-1.2 g, was analyzed as described above. The reproducibility of the results reported in Table XI was comparable to that obtained with the in situ reagents.

Reaction of "Purified" Dimethylzinc with 4-t-Butylcyclohexanone-MgI₂.

The following procedure will serve to illustrate the reaction of "purified" dimethylzinc with prior coordinated 4-t-butylcyclohexanone. A solution of 1.0 g (0.006 mol) of ketone, 9.9 g (0.023 mol) of magnesium iodide dietherate, and 34 ml of anhydrous ether was stirred for 15 min at room temperature. The mixture was cooled to 0° and 12.0 ml of 1.0 M (0.012 mol) dimethylzinc added as rapidly as possible below 5°. Addition time normally was 15-30 sec. The ice-salt bath was removed and the reaction stirred for 3 hr at room temperature. As in the previous reactions, the concentration of dimethylzinc was 0.3 M. Hydrolysis and work-up were the same as previously described. The reproducibility of the values reported in Table XII was comparable to that obtained with the in situ reagents.

l-Methyl-4-t-butylcyclohexene.

l-Methyl-4-t-butylcyclohexene was collected by preparative glpc. The injector port of the chromatograph was coated with salt by injection of ether solutions of
zinc iodide. Subsequent injection of the mixture of alcohols obtained from reaction of methylmagnesium iodide with ketone produced mainly 1-methyl-4-t-butylcyclohexene. Its nmr spectrum determined in carbon tetrachloride was essentially the same as that recently reported by Allinger. Its infrared spectrum (7451-a) was also consistent 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.

**Attempted Equilibration of (Z)- and (E)-1-Methyl-4-t-butylcyclohexanols: Control Experiment.**

The isolated product obtained from the reaction of methylmagnesium bromide (0.1 M) with 4-t-butylcyclohexanone (Table X) was dissolved in 10 ml of ether and added to dimethylzinc reagent under the conditions previously described for the reaction of in situ reagent with ketone. After hydrolysis and work-up, percentages obtained by glpc on FFAP were unchanged within experimental error.

**Reaction of n-Propylmagnesium Bromide with Heptanal.**

An ethereal solution of 8.6 ml of 2.32 M n-propylmagnesium bromide (0.02 mol) was added to 60 ml of ether. The reagent was cooled in an ice-salt bath and stirred until the internal temperature reached 0°. A solution of 1.1 g (0.01 mol) of heptanal 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 15 min at 0°; then the ice bath was removed and stirring continued at ambient temperature for an additional 1.5 hr.

The solution was cooled by an ice-salt bath and slowly hydrolyzed with 25 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 successively with 25- and 15-ml portions of ether. The ether layer was then dried over magnesium sulfate and concentrated at room temperature on a rotary evaporator to give 1.2 g of crude product.

Glcpc analysis was carried out at a column temperature of 160° and flow rate of 40 ml/min on Apiezon L. The chromatogram (57) showed only traces of heptanal (3.05 min), 1-heptanol (3.74 min), and 4-decanone (8.90 min), indicating a nearly quantitative conversion (> 95%) to 4-decanol* (10.22 min). For identification of peaks see below.

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

An ethereal solution of 13.0 ml of 2.32 M n-propylmagnesium bromide (0.03 mol) was added to 12 ml of ether. Then 10.0 ml of 1.5 M (0.015 mol) zinc bromide was added slowly with stirring and cooling. The mixture was cooled to 0° and 1.1 g (0.01 mol) of heptanal in 15 ml of ether was added at such a rate that the internal temperature remained below 5°. At the start of the reaction the solution was 0.3 M in di-n-propylzinc. The ice

*Normalized %; % heptanal + % 1-heptanol + % 4-decanone + % 4-decanol = 100.
bath was removed after 15 min and the reaction mixture stirred for 2.0 hr at room temperature.

Hydrolysis was accomplished with 25 ml of saturated sodium bicarbonate solution. The ether layer was separated, and the aqueous layer extracted twice with 25 and 15 ml of ammonium hydroxide solution (1 part concentrated ammonia and 2 parts water, v/v), which had previously been saturated with sodium chloride. The ether layer was then dried over magnesium sulfate and removed at room temperature on a rotary evaporator to yield 1.3 g of product.

This material was analyzed by glpc (55) on Apiezon L under the conditions described above. In addition to the expected 4-decanol (37.7%) and 1-heptanol (17.6%), significant amounts of 4-decanone (12%) and heptanal (5%) were detected. The reaction was repeated several times under identical conditions, but the results could not be reproduced; i.e., the amount of 4-decanol varied from 10-57%.

1-Heptanol was identified by comparison of its retention time with a sample obtained from the lithium aluminum hydride reduction of heptanal. 4-Decanone was isolated by preparative glpc and identified by its ir spectrum (7997) which is essentially identical to that reported for 4-decanone by Sadtler (23658). The nmr spectrum (5418) is also consistent with the assignment.

Reaction of n-Propylmagnesium Bromide and Iodide with 4-t-Butylcyclohexanone.

The procedure described here for the reaction of n-propylmagnesium bromide will also serve to illustrate that employed with n-propylmagnesium iodide.
To a reaction flask containing 7 ml of anhydrous ether was added an ethereal solution of 11.2 ml of 2.32 M n-propylmagnesium bromide (0.026 mol). The contents were cooled to 0° by means of an ice bath prior to the addition of a solution of 1.0 g (0.006 mol) of 4-tert-butylcyclohexanone in 15 ml of ether. The temperature remained below 5° during addition. After a total of 15 min at ice-bath temperature, the bath was removed and stirring continued at ambient temperature for 2.75 hr. The Grignard concentration was initially 0.8 M, and the reaction was carried out under an atmosphere of dry nitrogen.

Hydrolysis of the mixture was carried out at 0-10° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, the aqueous layer extracted once with 20 ml of ether, and the organic layers combined and dried over magnesium sulfate. The ether was removed at room temperature on a rotary evaporator to yield 1.1 g of crude product.

Glcpc analysis was carried out at a column temperature of 140° and a flow rate of 100 ml/min on STAP (10%, 10') with the crude product, and no correction was made for mass balance. The chromatogram (61) showed a nearly quantitative conversion of ketone to alcohols via both reduction and addition processes. Analysis of an aliquot removed after 0.25 hr was essentially identical to the one obtained after 3.0 hr. The results with the Grignard reagents given in Table XIV were reproducible within ±1% for the product alcohols.*

*Normalized %; % (Z) + % (E) = 100 for both addition and reduction products.
The products were identified as (Z)- and (E)-4-tert-butylcyclohexanol (retention time 14.90 min and 17.88 min, respectively, and (Z)- and (E)-1-n-propyl-4-tert-butylcyclohexanol (retention time 24.10 min and 26.37 min, respectively). Identification of the addition products was based on a previous literature report that the major isomer resulted from equatorial attack of the propyl group. Identification of the reduction products was accomplished by independent synthesis through reduction of 4-tert-butylcyclohexanone with trimethylamine borane and separation of the isomers on neutral alumina (see below).

Reaction of in situ Di-n-propylzinc (I,1) with 4-tert-Butylcyclohexanone.

Preliminary experiments carried out with di-n-propylzinc in 2- and 4-M excess in ether indicated poor yields of alcohols, and the crude products contained large quantities of zinc salts carried through the work-up. The following procedure proved the most satisfactory and will serve to illustrate the reaction of in situ n-propylzinc reagents with 4-tert-butylcyclohexanone.

An ethereal solution of 23.6 ml of 2.2 M n-propylmagnesium iodide (0.052 mol) was added by means of a syringe to 29 ml of benzene. Then 20.0 ml of 1.3 M zinc iodide (0.026 mol) was added with stirring and cooling. The resultant reagent was cooled to 0° and 1.0 g (0.006 mol) of 4-tert-butylcyclohexanone added at such a rate that the temperature did not exceed 5°. The solution was stirred at ice-bath temperature for 15 min and then at room temperature for 2.75 hr. The initial concentration of di-n-propylzinc was 0.3 M.
Hydrolysis with a saturated sodium bicarbonate solution and work-up as described above provided 1.4 g of crude product. However, glpc analysis on STAP (column 135°, flow rate 100 ml/min) indicated that in some cases zinc salts had been carried through the work-up as evidenced by a considerable quantity of dehydration product. In such cases, two new peaks appeared at slightly longer retention times than the solvent benzene. This behavior is analogous to that observed in the dehydration of (Z)- and (E)-1-methyl-4-t-butylcyclohexanols reported above. The reaction product obtained from the (Br,Br) reagent did not show any dehydration at this stage and could be analyzed without further treatment.

Removal of the zinc salts was accomplished by dissolving the crude product in 50 ml of benzene and extracting with two 10-ml portions of aqueous ammonia as previously described. This aqueous ammonia was subsequently extracted with 20 ml of benzene and all benzene layers combined. After drying (MgSO₄) and removal of solvent, 1.1 g of crude product was obtained and analyzed on STAP as before. The results from this (chromatogram 98) and related experiments involving di-n-propylzinc, given in Table XIV, were reproducible within ± 2%* for the addition product alcohols and ± 5% for unchanged ketone.

*The per cent (Z)- and (E)-4-t-butylcyclohexanol was reproducible within ± 3%.
Effect of Extraction Procedure on Product Ratios: Control Experiment.

The product (1.1 g) obtained from the above reaction was again dissolved in 50 ml of benzene and the extraction procedure repeated. GLPC analysis of the resultant mixture agreed within ±1.5% with that reported above (Table XIV).

Trimethylamine Borane Reduction of 4-t-Butylcyclohexanone.

This reaction gave approximately equal amounts of (Z)- and (E)-4-t-butylcyclohexanols, which were separated on neutral alumina with pentane as solvent.

Equilibration of (Z)-4-t-Butylcyclohexanol: Control Experiment.

Di-n-propylzinc (Br,I; 0.052 mol) was prepared in the manner described above. A solution was prepared by dissolving 0.5 g (0.0032 mol) of 4-t-butylcyclohexanone and 0.5 g (0.003 mol) of (Z)-4-t-butylcyclohexanol (96.7% isomeric purity) in 15 ml of benzene, and the precise composition determined by GLPC analysis on STAP. This solution was added to the zinc reagent as previously described for the reaction of in situ n-propylzinc reagents.

The reaction was allowed to proceed for 24 hr, with an aliquot taken for analysis after 3 hr. Assuming that the (Z)/(E) ratio of reduction alcohols given in Table XIV represents essentially the kinetically controlled isomer distribution, it was found that some equilibration had occurred after 3 and 24 hr. This was evidence by an increase in the amount of the thermodynamically more

*This assumption is probably valid since the extent of equilibration as noted below was not very great even after 24 hr.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
stable (E)-alcohol over that required by the above mentioned (Z)/(E) ratio. The results are tabulated below.

<table>
<thead>
<tr>
<th>Reaction time (hr)</th>
<th>0</th>
<th>3</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)/(E) [Reduction products]</td>
<td>-</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>% Reaction</td>
<td>0</td>
<td>25</td>
<td>74</td>
</tr>
<tr>
<td>% Reduction</td>
<td>0</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>% (Z)-4-t-Butylcyclohexanol</td>
<td>Calcd</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>Obs</td>
<td>96.7</td>
<td>88.8</td>
<td>73.3</td>
</tr>
</tbody>
</table>

A sample calculation of the % (Z)-4-t-butylcyclohexanol to be expected after 3 hr (93%) is given below.

Wt. of ketone reacted = 0.5 g x 0.25 (fraction reacted) = 0.12 g.

Wt. of ketone giving reduction products = 0.12 g x 0.28 (fraction reduced) = 0.035 g.

Wt. of reduction product formed = 0.035 g x \( \frac{156 \text{ g alcohol}}{154 \text{ g ketone}} \) = 0.035 g.

Wt. of (Z)-alcohol formed = 0.035 g x \( \frac{1.07}{2.07} \) = 0.018 g.

Wt. of (E)-alcohol formed = 0.018 g.

Wt. of (Z)-alcohol after 3 hr = 0.48 g + 0.02 g = 0.50 g.

Wt. of (E)-alcohol after 3 hr = 0.02 g + 0.02 g = 0.04 g.

0.54 g total

% (Z)-Alcohol after 3 hr = \( \frac{0.50 \text{ g}}{0.54 \text{ g}} \times 100 = 93 \).
Attempted Equilibration of (E)-4-t-Butylcyclohexanol: Control Experiment.

The above experiment was repeated with a mixture composed of 0.5 g (0.0032 mol) of 4-t-butylcyclohexanone and 0.5 g (0.003 mol) of (E)-4-t-butylcyclohexanol (90.4% isomeric purity) in benzene. Glpc analysis on STAP showed no equilibration had occurred after 24 hr. The results are tabulated below.

<table>
<thead>
<tr>
<th>Reaction time (hr)</th>
<th>0</th>
<th>3</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)/(E) [Reduction Products]</td>
<td>-</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>% Reaction</td>
<td>0</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>% Reduction</td>
<td>0</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>% (E)-4-t-Butylcyclohexanol</td>
<td>Calc</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>Obs</td>
<td>90.4</td>
<td>89.4</td>
<td>88.5</td>
</tr>
</tbody>
</table>

Reaction of Ethylmagnesium Iodide with 4-t-Butylcyclohexanone.

An ethereal solution of 13.7 ml of 1.90 M ethylmagnesium iodide (0.026 mol) was added as described previously to 5 ml of ether. The reagent was cooled to 0°, and 1.0 g (0.006 mol) of 4-t-butylcyclohexanone in 15 ml of ether was added dropwise over a 5 min period. The reaction mixture, initially 0.8 M in Grignard, was stirred at ice-bath temperature for 10 additional minutes and then at ambient temperature for 4 hr. The mixture was hydrolyzed with 25 ml of saturated sodium bicarbonate solution and worked up as previously described to provide 1.0 g of crude product. Glpc analysis (79) of this mixture indicated a quantitative conversion of ketone to alcohol was achieved. However, it was impossible to separate the isomeric addition.
and reduction products on all column materials tested: i.e., Apiezon L, Carbowax 20 M, FFAP, SAIB, SE-30, STAP, and XF-1150. Generally the products of reduction and addition appeared as two peaks, and each peak represented the total response from the two axial (Z)-alcohols (addition and reduction) or the two equatorial (E)-alcohols (addition and reduction). Thus, the relative amount of addition to reduction as well as the ratios of (Z)/(E) addition and/or reduction alcohols could not be calculated.

The best separation was achieved at a column temperature of 130° with Carbowax 20 M and a flow rate of 100 ml/min. Identification of the (Z)- and (E)-1-ethyl-4-t-butylcyclohexanols (11.8 min and 14.1 min, respectively) was made on the assumption that the major product resulted from equatorial attack, analogous to the methyl- and n-propylmagnesium halide reactions. A small shoulder (shorter retention time) appeared on the side of the (E)-1-ethyl-4-t-butylcyclohexanol peak due to the presence of (E)-4-t-butylcyclohexanol (reduction product). The presence of (Z)-4-t-butylcyclohexanol was not actually detected since its retention time was essentially the same as that of (Z)-1-ethyl-4-t-butylcyclohexanol. The retention times of the reduction products were obtained by glpc analysis of authentic samples (see page 46).

Preparation of 2-Phenylbutanoyl Chloride.

Thionyl chloride (224 g, 1.9 mol) was added slowly with stirring to 50 g (0.31 mol) of 2-phenylbutanoic acid. The mixture was refluxed for 1.5 hr and stirred for an additional 0.5 hr at room temperature. After removal of excess thionyl chloride at reduced pressure, 54 g (97%) of 2-phenylbutanoyl chloride was collected at 84-87° (3.7 mm) [lit.51 bp 97-98° (14 mm)].
Preparation of the Imidazolide of 2-Phenylbutanoic Acid.\textsuperscript{53}

To a solution of imidazole (40.4 g, 0.59 mol) in 300 ml of anhydrous THF was added, over a period of 30 min at room temperature, a solution of 54 g (0.29 mol) of 2-phenylbutanoyl chloride in 200 ml of THF. The contents were refluxed for one hour and stirred at room temperature for an additional 4 hr. Then the solution was cooled to 0° and the imidazole hydrochloride removed by filtration. After removal of the solvent \textit{in vacuo}, the solid residue was washed with cold benzene and 45 g of white imidazolide collected by suction filtration. The benzene washings were extracted with dilute hydrochloric acid, saturated sodium bicarbonate, dried over magnesium sulfate, and the benzene removed \textit{in vacuo} on a rotary evaporator. The solid residue was washed with an ice-cold petroleum ether-benzene (3:1, v/v) solution, and 10 g of white imidazolide obtained. The combined product, mp 86.5-89° (lit.\textsuperscript{52} mp 87-89), weighed 55 g (87%). The ir spectrum (8417) of the imidazolide is characterized by a carbonyl band at 1730 cm\textsuperscript{-1} in agreement with that reported by Long.\textsuperscript{52}

Preparation of 2-Phenylbutanal.

A procedure similar to that described by Staab\textsuperscript{53} was employed. A solution of 55 g (0.26 mol) of the imidazolide of 2-phenylbutanoic acid in 250 ml of ether was cooled to -20° in an ethanol-snow bath. Then 2.7 g (0.07 mol) of lithium aluminum hydride in 200 ml of ether was added, with stirring, at such a rate that the temperature did not exceed -15°. After completion of the addition the reaction mixture was stirred at -20° for 0.5 hr and then allowed to reach ambient temperature. The reaction
was carried out under an atmosphere of dry nitrogen. Hydrolysis was accomplished with 100 ml of dilute hydrochloric acid. The aqueous layer was extracted twice with ether; the ether layers were combined, dried over magnesium sulfate, and the solvent removed on a rotary evaporator. Distillation of the crude product gave 20.0 g (0.13 mol, 50%) of 2-phenylbutanal, bp 50.5-59° (0.7 mm) [lit.54 bp 97-99° (15 mm)]. GPC analysis on FFAP at 150° indicated the material was homogeneous, and the IR spectrum (8423-b) is consistent with the assigned structure. Preparation of 2-Phenyl-3-methylbutanonitrile.49

2-Phenyl-3-methylbutanonitrile [bp 110° (7 mm)] was prepared in 59% yield from phenylacetonitrile and isopropyl bromide in 50% aqueous sodium hydroxide according to the method of Makosza and Serafin.55 The final product contained approximately 22% unchanged phenylacetonitrile. Attempted Preparation of 2-Phenyl-3-methylbutanal.

A procedure similar to that described by Brown and Garg56 was employed. To a slurry of 11.4 g (0.3 mol) of lithium aluminum hydride in 300 ml of anhydrous ether was added 39.6 g (0.45 mol) of ethyl acetate over a period of 1.25 hr, the temperature being maintained at 3-7°. The solution was stirred at 0° for an additional 0.5 hr before a mixture of 2-phenyl-3-methylbutanonitrile (33.2 g, 0.21 mol) and phenylacetonitrile (6.8 g, 0.06 mol) was added (5 min). The temperature reached a high of 8° before the mixture was cooled to 0° with stirring under nitrogen. After 1 hr reaction time the mixture was decomposed with 300 ml of 5 N sulfuric acid.
The ether layer was separated; and after extraction of the aqueous layer with three 50-ml portions of ether, all ether layers were combined, washed with sodium bicarbonate, and with eight 30-ml portions of water to remove ethanol. The ether layer was dried over magnesium sulfate and concentrated on a rotary evaporator to yield 42.1 g of crude product. The ir spectrum (8473-a) indicated that the product consisted mostly of unchanged starting material as evidenced by absorption at 2240 cm$^{-1}$ (C≡N) with only very weak absorption at 1725 cm$^{-1}$ (aldehyde C=O).

**Attempted Preparation of Ethyl Phenylisopropylglycidate.**

The procedure followed was similar to that described by Allen, Van Allan, Drake, and Blumenstein. To a mixture of 100 g (0.61 mol) of isobutyrophenone, 74.8 g (0.61 mol) of ethyl chloroacetate, and 150 ml of dry benzene was added, over a period of two hours, 27.3 g (0.7 mol) of powdered sodium amide at such a rate as to maintain the temperature between 15-20°. A slight evolution of ammonia was noted. After the mixture had been at room temperature for 0.5 hr, one molar equivalent (0.61 mol) of ethyl bromoacetate was added; again only a small quantity of ammonia was evolved.

After an additional 3 hr at room temperature, the mixture was cautiously poured onto 500 g of crushed ice. The organic layer was separated and the aqueous layer extracted once with 150 ml of benzene. The combined benzene solutions were washed with three 300-ml portions of water, the last one containing 10 ml of acetic acid. The solution was dried over magnesium sulfate, benzene removed on a rotary evaporator, and the residue fractionally
distilled at reduced pressure. The fraction boiling below 80° (7 mm) consisted mainly of unchanged ethyl chloro- and bromoacetate. The second fraction, 80-86° (7 mm), weighed 85 g and consisted mainly of unchanged isobutyroph- phenone; 2,4-dinitrophenylhydrazone, mp 162-163° (lit. mp 163°). No glycidic ester was detected (ir no. 8509-c).

Basic Hydrolysis of 2-Phenyl-3-methylbutanenitrile.

The procedure of Cram was employed. The nitrile (40.0 g, 0.25 mol) was added to a solution of 56 g (1.0 mol) of potassium hydroxide in 300 ml of diethylene glycol (DEG) and the solution stirred at 107° for 72 hr. The mixture was poured onto 200 g of crushed ice and 200 ml of water added. The mixture was stirred and 20 g (45%) of solid 2-phenyl-3-methylbutanamide (mp 109-110.5°, lit. 111-112°) recovered by filtration. The ir spectrum (8565-b) is consistent with the assigned structure.

When the basic filtrate was acidified with concentrated hydrochloric acid, a highly colored paste-like material settled to the bottom of the flask. The contents were refrigerated overnight, but the viscous material did not solidify. After the aqueous DEG solution was decanted, the residue was taken up in ether, dried over magnesium sulfate, and the solvent removed on a rotary evaporator to yield 16 g of crude acid. Distillation at 109-115° (0.7 mm) [lit. bp 159-160° (14 mm)] gave 10.0 g (22%) of 2-phenyl-3-methylbutanoic acid. The ir spectrum (8565-a) is consistent with the assigned structure.
Hydrolytic Deamination of 2-Phenyl-3-methylbutanamide.  

2-Phenyl-3-methylbutanoic acid was prepared in 65% yield by treatment of the corresponding amide with aqueous nitrous acid.

Preparation of 2-Phenyl-3-methylbutanoyl Chloride.

The procedure described by Cram was employed. 2-Phenyl-3-methylbutanoic acid (24.1 g, 0.135 mol) and 19.2 g (0.16 mol) of thionyl chloride were stirred overnight at room temperature. The excess thionyl chloride was removed at room temperature (20 mm). The desired acid chloride (23.7 g, 89%) was collected at 75-79° (1.4 mm) [lit. bp 125° (13 mm)]. The ir spectrum (8661) is consistent with the assigned structure.

Preparation of 2-Phenyl-3-methylbutanal.

The procedure described by Brown for the reduction of acid chlorides to aldehydes was employed. To a solution of 15.2 g (0.077 mol) of 2-phenyl-3-methylbutanoyl chloride in 50 ml of diglyme, cooled to -78° in a dry ice-acetone bath, was added 20.3 g (0.08 mol) of lithium aluminum tri-<sub>t</sub>-butoxyhydride in 100 ml of diglyme over a period of 1 hr in a nitrogen atmosphere. No major rise in temperature occurred during addition. The dry ice-acetone bath was removed and the mixture allowed to warm to room temperature (ca. 1 hr). Hydrolysis was accomplished by pouring the contents onto crushed ice, and the resultant mixture was extracted several times with ether.

Extraction of the combined ether layers with aqueous sodium bisulfite failed to remove any of the aldehyde.

The combined ether layers were then dried over magnesium sulfate, the solvent was removed on a rotary evaporator, and the residue distilled at 70-73° (1.6 mm)
lit. 62 bp 72–73° (1.0 mm), to yield 5.0 g (33%) of 2-phenyl-3-methylbutanal. Glpc analysis on SAIB at a column temperature of 150° and a flow rate of 50 ml/min showed the product consisted of ca. 85% of the desired aldehyde (retention time 22.58 min) and ca. 15% of isobutyrophenone (retention time 17.00 min). An ir spectrum (8758) of the ketone, collected by preparative glpc, was virtually identical to that of a commercial sample of isobutyrophenone (8759).

**Reaction of Methylmagnesium Bromide with 2-Phenylpropanal.**

The following procedure will serve to illustrate the reaction of the various Grignard reagents with 2-phenylpropanal, 2-phenylbutanal, and 2-phenyl-3-methylbutanal.

An ethereal solution of 14.5 ml of 2.07 M methylmagnesium bromide (0.03 mol) was added by means of a 20-ml syringe to 39 ml of anhydrous ether with stirring. The reagent was then cooled with an ice-salt bath and stirred until the internal temperature reached 0°. A solution of 2.0 g (0.015 mol) of 2-phenylpropanal in 15 ml of ether was added at such a rate that the temperature did not exceed 5°. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layers were dried (MgSO₄) and the solvent removed at room temperature on a rotary evaporator to give 1.9 g of crude product.

Glpc analysis was carried out at a column temperature of 150° and a flow rate of 100 ml/min on FFAP (10%, 10') deposited on 60/80 mesh Chromosorb W. The chromatogram (42) indicated a nearly quantitative conversion of aldehyde...
to a mixture of threo- and erythro-alcohols. The results obtained with the Grignard reagents (Table XIII) were reproducible within ±1% in separate reaction runs.

Identification of the threo- and erythro-alcohols obtained from addition of methyl Grignard reagents to 2-phenylpropanal and 2-phenylbutanal, as well as of threo- and erythro-alcohols obtained from addition of 2-propylmagnesium bromide to 2-phenyl-3-methylbutanal, is based on previous literature reports\textsuperscript{63} that the major product is the erythro isomer. The identification of threo- and erythro-3-phenyl-4-methyl-2-pentanols (Table VI, entries 10 and 11) resulting from addition of methylmagnesium iodide to 2-phenyl-3-methylbutanal is based on their order of elution on STAP and FFAP and on their relative rates of dehydration (see below).

Dehydration of threo- and erythro-Alcohols.

From an inspection of Table VI it is clear that for all threo-erythro pairs, the threo isomer possesses the shorter retention time (entries 3, 5, and 8). On this basis entry 10 is tentatively assigned the threo configuration.

The relative rates of dehydration of the various diastereomeric pairs of addition products were monitored by glpc analysis on STAP. The injector port of the chromatograph (265°) was coated with salt by injection of ether solutions of zinc bromide. Subsequent injection and analysis of the various diastereomeric product pairs (Table VI) showed the appearance of several new peaks (presumably olefin) with retention times slightly longer than that of the ether solvent, and an accompanying decrease in the amount of threo- and erythro-alcohols.
Table VI

Glcpe Analyses of *threo*- and *erythro*-Alcohols

<table>
<thead>
<tr>
<th>Compound</th>
<th>Column</th>
<th>Temp °C</th>
<th>Flow Rate (ml/min)</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{OCHCHO}$</td>
<td>FFAP</td>
<td>150</td>
<td>67</td>
<td>9.5</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_3\text{a}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>threo</em>- $\text{CH}_2\text{CH}_2\text{OH}$</td>
<td>FFAP</td>
<td>150</td>
<td>67</td>
<td>17.2</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_3\text{a}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>erythro</em>- $\text{CH}_2\text{CH}_2\text{OH}$</td>
<td>FFAP</td>
<td>150</td>
<td>67</td>
<td>20.6</td>
</tr>
<tr>
<td>$\text{Et}$ $\text{CH}_3\text{a}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>threo</em>- $\text{CH}_2\text{CH}_2\text{OH}$</td>
<td>FFAP</td>
<td>150</td>
<td>67</td>
<td>16.1</td>
</tr>
<tr>
<td>Compound</td>
<td>Column</td>
<td>Temp °C</td>
<td>Flow Rate (ml/min)</td>
<td>Retention Time (min)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>---------</td>
<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>6. **erythro-**CHOEtCHOH iPr</td>
<td>FFAP</td>
<td>150</td>
<td>67</td>
<td>19.8</td>
</tr>
<tr>
<td>7. <strong>CHOCHO</strong> iPr iPr</td>
<td>FFAP</td>
<td>160</td>
<td>67</td>
<td>9.0</td>
</tr>
<tr>
<td>8. **threo-**CHOCHOI I</td>
<td>STAP</td>
<td>160</td>
<td>70</td>
<td>9.8</td>
</tr>
<tr>
<td>9. **erythro-**CHOCHOI I</td>
<td>Carbowax 20M</td>
<td>150</td>
<td>70</td>
<td>42.6</td>
</tr>
<tr>
<td>10. **threo-**CHOCHOI I</td>
<td>Carbowax 20M</td>
<td>150</td>
<td>70</td>
<td>47.1</td>
</tr>
<tr>
<td>Compound</td>
<td>Column</td>
<td>Temp °C</td>
<td>Flow Rate (mL/min)</td>
<td>Retention Time (min)</td>
</tr>
<tr>
<td>----------------</td>
<td>--------</td>
<td>---------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>iPr CH$_3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. erythro-CH$_3$-CHOH</td>
<td>FFAP</td>
<td>160</td>
<td>67</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>STAP</td>
<td>160</td>
<td>70</td>
<td>27.6</td>
</tr>
</tbody>
</table>

*Infrared spectra of threo- and erythro-alcohols collected by preparative GLPC are available under the following file numbers: (8777), (8778), (8779), (8780), (8781), (8782).*
Comparison of the isomeric composition of the addition alcohols before and after dehydration revealed that the alcohol of longer retention time (erythro) in each instance underwent dehydration faster than that of shorter retention time (threo). The results support the tentative assignment made above for threo- and erythro-3-phenyl-4-methyl-2-pentanols (entries 10 and 11).

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

The following procedure will serve to illustrate the reaction of the various in situ zinc reagents (Table XIII) with 2-phenylpropanal, 2-phenylbutanal, and 2-phenyl-3-methylbutanal.

An ethereal solution of 15.0 ml of 2.0 M methylmagnesium bromide (0.03 mol) was added to 10 ml of anhydrous ether. Then 10.0 ml of 1.5 M zinc bromide (0.015 mol) was added slowly with stirring and cooling. The reagent was cooled and 2.0 g (0.015 mol) of 2-phenylpropanal in 15 ml of ether was added at 0-5°. At the start of the reaction, the solution was 0.3 M in dimethylzinc. The ice-salt bath was removed and the reaction stirred for 2.5 hr at room temperature.

Hydrolysis was accomplished at 0-5° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, dried over magnesium sulfate, and concentrated on a rotary evaporator at room temperature. The residual crude product amounted to 2.3 g.

Glpc analysis on FFAP of the crude reaction mixtures indicated that in some instances a considerable amount of
zinc salt was carried through the work-up procedure, as evidence by the presence of variable amounts of olefin in addition to the expected threo- and erythro-alcohols. The % olefin increased unless the injector port of the chromatograph was cleaned regularly. The nmr spectrum (5103) gave no evidence of olefin in the samples prior to injection.

In cases where the presence of zinc salt was suspected, the crude product was taken up in benzene and a small amount of petroleum ether added until the solution became cloudy. The flask was cooled to 0° and allowed to stand for several minutes. Generally, a quantity of zinc salt settled out, and additional amounts of petroleum ether were added until no more solid separated. The salts were removed by filtration, the solution concentrated on a rotary evaporator, and the residue analyzed by glpc as outlined above. Values denoting the relative amounts of threo- and erythro-alcohols (Table XIII) were reproducible within ± 1%* and those of unchanged aldehyde with ± 5% in separate reaction runs.

Attempted Equilibration of erythro-3-Phenyl-2-pentanol: Control Experiment.

Dimethylzinc (I, 0.015 mol) was prepared in the manner described above. A solution was prepared containing 1.0 g (0.007 mol) of erythro-3-phenyl-2-pentanol (79.2% isomeric purity) and 1.0 g (0.008 mol) of 2-phenylpropanal in 15 ml of ether, and the precise composition determined

*Normalized %; % threo + % erythro = 100.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
by glpc analysis on FFAP. This solution was added to the zinc reagent as previously described for the reaction of in situ methylzinc reagents.

The reaction was allowed to proceed for 24 hr, an aliquot being taken for analysis after 3.0 hr. Assuming that the threo/erythro ratio obtained from Table XIII represents essentially the kinetically controlled isomer distribution it was found that no measurable equilibration had occurred after 3 and 24 hr. This was evident from the fact that there was no increase in the amount of the thermodynamically more stable threo-alcohol over that predicted by the above mentioned threo/erythro ratio.
The results are tabulated below.

<table>
<thead>
<tr>
<th>Reaction time (hr)</th>
<th>0</th>
<th>3</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threo/Erythro</td>
<td>0.85</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>% Reaction</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>% erythro-3-Phenyl-2-pentanol</td>
<td>66</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>79.2</td>
<td>66.8</td>
<td>67.6</td>
</tr>
</tbody>
</table>

A sample calculation of the % erythro-3-phenyl-2-pentanol to be expected after 3 hr (66%) is given below.

Wt. of aldehyde reacted = 1.0 g.
Wt. of addition product formed = 1.0 g aldehyde x $\frac{150 \text{g alcohol}}{134 \text{g aldehyde}} = 1.12$ g.
Wt. of threo-alcohol formed = $1.12 \text{ g} \times \frac{0.85}{1.85} = 0.52$ g.
Wt. of erythro-alcohol formed = $1.12 \text{ g} - 0.52 \text{ g} = 0.60$ g.
Initially 0.79 g erythro- and 0.21 g threo-alcohol were present.

Wt. of threo-alcohol after 3 hr = 0.21 g + 0.52 g = 0.73 g.

Wt. of erythro-alcohol after 3 hr = 0.79 g + 0.60 g = 1.39 g.

% erythro-alcohol after 3 hr = \( \frac{1.39}{2.12} \times 100 = 65.7 \)

Attempted Equilibration of threo-3-Phenyl-2-pentanol:
Control Experiment.

The above experiment was repeated with a mixture composed of 0.8 g (0.0053 mol) of threo-3-phenyl-2-pentanol (90.5% isomeric purity) and 0.8 g (0.0060 mol) of 2-phenylpropanal in ether. GLPC analysis on FFAP showed no equilibration had occurred after 24 hr. The results are tabulated below.

<table>
<thead>
<tr>
<th>Reaction time (hr)</th>
<th>0</th>
<th>1.25</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threo/Erythro (predicted from reaction)</td>
<td>-</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>% Reaction</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Calcd</td>
<td>-</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>% threo-3-Phenyl-2-pentanol</td>
<td>Obs</td>
<td>90.5</td>
<td>67.2</td>
</tr>
</tbody>
</table>
DISCUSSION OF RESULTS

As pointed out earlier, a considerable amount of confusion has existed concerning the reactivity of organo-zinc reagents. Although the utility of these reagents is well known for the synthesis of ketones, their use in the preparation of alcohols became obsolete with the advent of the Grignard reagent. The mechanism of the reaction of various carbonyl functions with organozinc reagents has never been elucidated.

It has become evident from the work of Kollonitsch\(^{4a,b}\) that \textit{in situ} dialkylcadmiums are considerably more reactive toward aldehydes, ketones, and acid chlorides than the corresponding "purified" compounds. Kollonitsch ascribed the increased reactivity of the \textit{in situ} reagents to the presence of magnesium halide. Although both "purified" and \textit{in situ} zinc reagents are known to react with acid halides, the question concerning their relative reactivity toward simple aldehydes and ketones remained unanswered.

The use of \textit{in situ} zinc reagents in synthesis has been somewhat impaired because of the practical difficulty of obtaining and handling anhydrous zinc halides. Thus, before investigating their reactivity, it seemed desirable to explore alternate approaches to the synthesis of the \textit{in situ} reagents. In particular, anhydrous zinc halides were generated by halogenation of the metal in ether and in THF, a reaction which has been shown to occur in the presence of coordinating solvents.\(^{64a,b}\)
Previous workers have encountered difficulty in the preparation of anhydrous zinc bromide in ether. It had been reported that the final solutions contained a considerable amount of unchanged bromine, rendering them unsatisfactory for present purposes. In an attempt to eliminate this problem, the original procedure was modified to include rapid and efficient stirring in the presence of excess powdered zinc. However, the final solutions still contained residual bromine as evidenced by their yellow-orange color which darkened considerably after storage for several days. The zinc reagents prepared from these solutions, although highly colored, proved to be comparable to the conventional in situ reagents in reactivity toward acid halides (Table VII). No attempt was made to determine the optimum reaction conditions.

Somewhat surprisingly, solutions of zinc iodide prepared from the elements contained no noticeable traces of residual iodine. These solutions remained colorless on storage for several months, a result in conflict with that observed in the preparation of ethereal solutions of anhydrous magnesium iodide.

Inspection of the results presented in Tables VIII and IX clearly illustrates the high yield of alcohols obtained through the interaction of in situ zinc reagents with simple aldehydes and aliphatic ketones. Entries 2 and 3 of Tables VIII and IX seem to point up the lower yield of addition products obtained with the conventional in situ reagents relative to those reagents prepared from freshly generated zinc halide. With the exception of
entry 1 of Table IX, these results are in agreement with those recently reported by Freon et al. (see Table I). However, neither the method of analysis nor a report of physical constants for the expected product, methylethylphenylcarbinol, was included by Freon.

From a consideration of entry 4 of Table VIII and 6 of Table IX, it is apparent that the second alkyl group of dimethyl- and diethylzinc is transferable, although its reactivity appears to depend somewhat on the nature of the alkoxy group and the carbonyl being attacked. The higher reactivity of ethylethoxyzinc (12) over methylcyclohexoxyzinc (13) may reflect the fact that the former reagent is

\[
\text{C}_2\text{H}_5\text{ZnOC}_2\text{H}_5 \quad \text{CH}_3\text{ZnOC}_6\text{H}_{11}
\]

homogeneous in ether whereas the latter is not. The relative reactivity of the two alkyl groups is of particular interest to the stereochemical studies to be discussed later.

Although only a limited amount of data is available (entry 2 of Tables VII and VIII), it appears that the reactivity of alkylzincs in THF solution may be considerably lower than that observed in ether. Reference to this fact will be made later in connection with the reaction mechanism.

Diphenylzinc (Br,I) was found to react slowly with carbon dioxide and benzoic acid was isolated in 41% yield.

*An 82% yield is calculated assuming only one aryl group is transferable.
Table VII

Reaction of in situ Ethylzinc Bromide with Acid Halides

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ratio of EtZnBr:RCOX</th>
<th>Solvent</th>
<th>Present Work</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Benzoyl chloride</td>
<td>1:1</td>
<td>ether</td>
<td>$C_6H_5COC_2H_5$ (22)</td>
<td>30$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$C_6H_5CO_2C_2H_5$ (68)</td>
<td>--</td>
</tr>
<tr>
<td>2. Benzoyl chloride</td>
<td>1:1</td>
<td>THF$^b$</td>
<td>$C_6H_5COC_2H_5$ (trace)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$C_6H_5CO_2(CH_2)_4Br$ (14)</td>
<td>--</td>
</tr>
<tr>
<td>3. Propionyl bromide</td>
<td>1:1</td>
<td>ether</td>
<td>$C_2H_5COC_2H_5$ (28)</td>
<td>&gt;30$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$C_2H_5CO_2C_2H_5$ (35)</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$A. Michael, *Amer. Chem. J.*, 25, 419 (1901). $^b$A considerable amount of polymeric by-product was also formed.
Table VIII

Reaction of in situ Zinc Reagents with Benzaldehyde in Ether

<table>
<thead>
<tr>
<th>Zinc Reagent</th>
<th>Ratio of Zinc Reagent to Aldehyde</th>
<th>Reaction Time (hr)</th>
<th>Products (% Yield)</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₂Zn (I, I)</td>
<td>2:1</td>
<td>3</td>
<td>C₆H₅CHOH(CH₃) (77)</td>
<td>--</td>
</tr>
<tr>
<td>(C₂H₅)₂Zn (Br, Br)</td>
<td>2:1</td>
<td>2</td>
<td>C₆H₅CHOH(C₂H₅) (78)</td>
<td>70⁴</td>
</tr>
<tr>
<td>(C₂H₅)₂Zn(Br, Br)</td>
<td>2:1</td>
<td>2</td>
<td>C₆H₅CHOH(C₂H₅) (60)</td>
<td>55⁴</td>
</tr>
<tr>
<td>C₂H₅ZnOC₂H₅ (Br, Br)</td>
<td>2:1</td>
<td>1.5</td>
<td>C₆H₅CHOH(C₂H₅) (65)</td>
<td>--</td>
</tr>
<tr>
<td>C₆H₅ZnBr</td>
<td>2:1</td>
<td>15</td>
<td>(C₆H₅)₂CHOH (15)</td>
<td>--</td>
</tr>
<tr>
<td>(C₆H₅)₂Zn (Br, Br)</td>
<td>2:1</td>
<td>15</td>
<td>(C₆H₅)₂CHOH (65)</td>
<td>--</td>
</tr>
</tbody>
</table>

aThe reaction of EtZnBr with benzaldehyde in THF gave only traces of the addition alcohol.
bPrepared from a fused sample of commercially available zinc bromide.
**Table IX**

Reaction of *in situ* Alkylzinc Reagents with Ketones in Ether

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Zinc Reagent</th>
<th>Ratio of Zinc Reagent to Ketone</th>
<th>Reaction Time (hr)</th>
<th>Alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetophenone</td>
<td>((C_2H_5)_2Zn) (Br,Br)</td>
<td>2:1</td>
<td>6</td>
<td>(C_6H_5CHOH(C_2H_5)) (0)(^a)</td>
</tr>
<tr>
<td>2. Cyclohexanone</td>
<td>((C_2H_5)_2Zn) (Br,Br)</td>
<td>2:1</td>
<td>12</td>
<td>(C_6H_{11}OH(C_2H_5)) (40)</td>
</tr>
<tr>
<td>3. Cyclohexanone</td>
<td>((CH_3)_2Zn) (Br,Br)(^b)</td>
<td>2:1</td>
<td>12</td>
<td>(C_6H_{11}OHCH_3) (32)</td>
</tr>
<tr>
<td>4. Cyclohexanone</td>
<td>((CH_3)_2Zn) (I,Br)</td>
<td>2:1</td>
<td>15</td>
<td>(C_6H_{11}OHCH_3) (43)</td>
</tr>
<tr>
<td>5. Cyclohexanone</td>
<td>((CH_3)_2Zn) (I,I)</td>
<td>2:1</td>
<td>15</td>
<td>(C_6H_{11}OHCH_3) (50)</td>
</tr>
<tr>
<td>6. Cyclohexanone</td>
<td>(CH_3ZnOC_6H_{11}) (I,B)</td>
<td>4:1</td>
<td>15</td>
<td>(C_6H_{11}OHCH_3) (27)</td>
</tr>
</tbody>
</table>

\(^a\)The same result was obtained in THF. \(^b\)Prepared from a fused sample of commercially available zinc bromide.
This result is particularly interesting in view of the fact that carbon dioxide has been used as an inert atmosphere in the preparation and distillation of "purified" dialkylzincs. Gilman and Marple obtained an 18% yield of benzoic acid through the interaction of diphenylzinc ("salt-free") and carbon dioxide after a 24-hr reflux in xylene.

Once it has been established that the presence of magnesium halide imparts a greater reactivity to the systems studied, an obvious question arises as to the role of the salt in the reaction mechanism. There are at least three a priori modes of influence. The salt may exert an activating influence on the carbonyl substrate, on the organometallic reagent, or on both.

One approach to an understanding of the reactions of zinc reagents with various functional groups is to compare their behavior with that of the Grignard reagent. In view of the careful studies of the stereochemistry of the addition of methyl Grignard reagents to 4-\textit{t}-butylcyclohexanone and various acyclic aldehydes, a detailed investigation of these reactions, where the additive reagent is a dimethylzinc compound, was undertaken. A similar study of the mechanism of organocadmium reactions has been carried out in these laboratories, and the results obtained with both zinc and cadmium reagents are included in the remaining tables.

As shown in eq. 18, the reaction between a methyl reagent and 4-\textit{t}-butylcyclohexanone is expected to lead to a mixture of \textit{cis}(Z) and \textit{trans}(E)-1-methyl-4-\textit{t}-butylcyclohexanols, 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 axial alcohol (15). 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 have proposed a model (Fig. 1) for the transition state, by which one could estimate semi-quantitatively the magnitude of the steric effect on the basis of transition state bond lengths. From this model it has been rationalized that 1,3-(diazial) interactions are less important than 1,2-(equatorial axial) interactions in the formation of a C-H bond; while, with the longer C-C bond being formed during Grignard additions, the importance of the interactions is reversed. A corollary of this hypothesis is the prediction that, within certain
Figure 1

Marshall Model

\[
\begin{align*}
A & \quad \text{EO or AO} \\
\alpha \beta & \quad 1.2 \text{Å} \\
\alpha & \quad 1.6 \\
\beta & \quad 2.0 \\
\alpha & \quad 2.4 \\
\end{align*}
\]

\[
\begin{align*}
\text{C-C Bond} & \quad 1.54 \text{Å} \\
\text{C-H Bond} & \quad 1.07 \text{Å}
\end{align*}
\]
rather narrow limits of bond distances, the amount of axial attack will increase as the transition state bond distance decreases.

Cherest and Felkin have pointed out the importance of considering torsional effects (17a and 17b). They have attempted to show that interpretation of the steric outcome of the nucleophilic addition reaction can encompass both open chain systems and cyclohexanones, based on the following four premises:

1. "The transition states in these reactions are in all cases essentially reactant-like."
2. "Torsional strain (Pitzer strain) involving partial bonds (in transition states) represents a substantial 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 as assumed by Cram and Karabatsos."
4. "Polar effects stabilize those transition states in which the separation between R' and an electronegative group is greatest and destabilize the others."

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Thus in the cyclohexanone system the steric course of the reaction is the result of a balance between the magnitude of torsional strain developed between the group approaching equatorially (17a) and the 2,6-axial groups, and the magnitude of the steric strain developed between the group approaching axially (17b) and the 3,5-axial groups. Recent results on hydride reductions can best be explained with the Marshall and Felkin models.

The 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 were introduced 2 moles of (CH₃)₂Zn or (CH₃)₂Cd; 4 moles of CH₃MgX, CH₃ZnX, or CH₃CdX. Under these conditions the reaction can be considered to involve R₂M or RMX but not RMOR'. As noted previously (Table IX) methylcyclohexoxyzinc (13) was considerably less reactive than dimethylzinc toward cyclohexanone. In a few instances olefin formation caused by the presence of zinc salts was observed, but the amount was well below the level required to affect the ratio of alcohols (see page 37).

From the experimental results, presented in Tables X, XI, and XII, several general observations can be made.

1. On the basis of the values of unchanged ketone in comparable experiments, the following reactivity series can be written: CH₃Li, CH₃MgX > (CH₃)₂Cd > (CH₃)₂Zn > CH₃CdX, CH₃ZnX.

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 MgI₂
rather than MgBr\(^2\) was present.

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

5. Monomeric CH\(_3\)MgX (0.1 M) gives more (Z)-alcohol, resulting from equatorial attack, than the corresponding associated species (0.8 M). At the same concentration, CH\(_3\)MgBr shows a greater preference for equatorial attack than does CH\(_3\)MgI. By contrast, there is no appreciable change in reactivity or stereochemistry when the concentration of (CH\(_3\))\(_2\)Cd (I,Cl) is increased from 0.4 M to 0.9 M, or when the concentration of (CH\(_3\))\(_2\)Zn (I,Cl) is decreased from 0.3 M to 0.1 M.

6. Preference for axial attack follows the series: (CH\(_3\))\(_2\)Zn > (CH\(_3\))\(_2\)Cd > CH\(_3\)MgX.

7. Contrary to the Grignard reagents, in all cadmium and zinc reagents except R\(_2\)M (I,Cl), the stereochemistry of addition was independent of the halogens or of their source. For R\(_2\)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 XI and XII.
Table X

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conc,M</th>
<th>Unchanged ketone(%)</th>
<th>(Z)-Alcohol(%)</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CH₃MgI</td>
<td>0.8</td>
<td>1</td>
<td>53.8d</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>61.8d</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>63.7d</td>
<td>1.8</td>
</tr>
<tr>
<td>6. (CH₃)₂Zn(I,I)</td>
<td>0.3</td>
<td>20</td>
<td>46.5</td>
<td>0.87</td>
</tr>
<tr>
<td>7. (CH₃)₂Zn(Br,Br)</td>
<td>0.3</td>
<td>85</td>
<td>44.4f</td>
<td>0.80</td>
</tr>
<tr>
<td>8. (CH₃)₂Zn(I,Br)</td>
<td>0.3</td>
<td>20</td>
<td>46.8f</td>
<td>0.88</td>
</tr>
<tr>
<td>9. (CH₃)₂Zn(Br,Cl)</td>
<td>0.3</td>
<td>97</td>
<td>44</td>
<td>0.8</td>
</tr>
<tr>
<td>10. (CH₃)₂Zn(I,Cl)</td>
<td>0.3</td>
<td>60</td>
<td>38.3</td>
<td>0.62</td>
</tr>
<tr>
<td>11. (CH₃)₂Zn(I,Cl)</td>
<td>0.1</td>
<td>65</td>
<td>38.7</td>
<td>0.63</td>
</tr>
<tr>
<td>12. (CH₃)₂Zn(CH₃Li,ZnI₂)</td>
<td>0.3</td>
<td>99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reagent</td>
<td>Conc., M</td>
<td>Unchanged ketone (%)</td>
<td>(Z)-Alcohol (%)</td>
<td>(Z)/(E)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>13. (\text{CH}_3\text{ZnI(I,I)})</td>
<td>0.3</td>
<td>90</td>
<td>49.0(^f)</td>
<td>0.96</td>
</tr>
<tr>
<td>14. (\text{CH}_3\text{ZnX(I,Cl)})</td>
<td>0.3</td>
<td>99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15. ((\text{CH}_3\text{)}_2\text{Cd(I,I)})(^e)</td>
<td>0.4</td>
<td>7.5</td>
<td>51.6(^f)</td>
<td>1.1</td>
</tr>
<tr>
<td>16. ((\text{CH}_3\text{)}_2\text{Cd(Br,Br)})</td>
<td>0.4</td>
<td>50</td>
<td>51.5(^f)</td>
<td>1.1</td>
</tr>
<tr>
<td>17. ((\text{CH}_3\text{)}_2\text{Cd(I,Br)})</td>
<td>0.4</td>
<td>5</td>
<td>53.5</td>
<td>1.2</td>
</tr>
<tr>
<td>18. ((\text{CH}_3\text{)}_2\text{Cd(Br,I)})</td>
<td>0.4</td>
<td>5</td>
<td>53.1(^f)</td>
<td>1.1</td>
</tr>
<tr>
<td>19. ((\text{CH}_3\text{)}_2\text{Cd(Br,Cl)})</td>
<td>0.4</td>
<td>55</td>
<td>50.2</td>
<td>1.0</td>
</tr>
<tr>
<td>20. ((\text{CH}_3\text{)}_2\text{Cd(I,Cl)})</td>
<td>0.4</td>
<td>5</td>
<td>42.4(^f)</td>
<td>0.74</td>
</tr>
<tr>
<td>21. ((\text{CH}_3\text{)}_2\text{Cd(I,Cl)})</td>
<td>0.9</td>
<td>5</td>
<td>40.7</td>
<td>0.69</td>
</tr>
<tr>
<td>22. ((\text{CH}_3\text{)}_2\text{Cd(CH}_3\text{Li,Cl)}_2)</td>
<td>0.4</td>
<td>99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23. ((\text{CH}_3\text{)}_2\text{Cd(CH}_3\text{Li,ClBr}2)</td>
<td>0.4</td>
<td>99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24. (\text{CH}_3\text{CdX(I,Cl)})</td>
<td>0.8</td>
<td>90</td>
<td>37.7(^f)</td>
<td>0.61</td>
</tr>
</tbody>
</table>
The results obtained with cadmium reagents are taken from the Ph.D. Thesis of W. J. Kauffman, University of New Hampshire, 1969.

\[ b\% = \frac{\text{area (ketone)}}{\text{area (ketone) + area (Z)+(E) alcohols)}} \times 100. \]

Normalized \%; \( \%(Z) + \%(E) = 100 \); Yield alcohols = 100 - \%ketone.

For comparable results at similar concentrations see Ref. 4.

Halogen in parentheses indicate, respectively, the methyl halide from which RMgX was prepared and the metal halide used for the exchange (eq. 2).

Result of at least two separate runs with a maximum deviation of \( \pm 1\% \).

Reaction time was 8 hours, and 3 molar equivalents of zinc reagent were used. The reactivity of the in situ reagent prepared from commercially available zinc bromide was virtually nil.
Table XI\textsuperscript{a}

Reaction of "Reconstituted" Dimethylzinc and -Cadmium Reagents with 4-\textsuperscript{t}-Butylcyclohexanone (1 Molar Equiv.) in Ether\textsuperscript{b}

<table>
<thead>
<tr>
<th>Reagent (concen)</th>
<th>Salt</th>
<th>Unchanged ketone(%)</th>
<th>(Z)-Alcohol(%)</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. $2(CH_3)_2Zn(0.3M)$</td>
<td>4 MgI\textsubscript{2}</td>
<td>67</td>
<td>45.2</td>
<td>0.83</td>
</tr>
<tr>
<td>2. $2(CH_3)_2Zn(0.3M)$</td>
<td>2 MgI\textsubscript{2}</td>
<td>80</td>
<td>46.6</td>
<td>0.87</td>
</tr>
<tr>
<td>3. $2(CH_3)_2Zn(0.3M)$</td>
<td>1 MgI\textsubscript{2}</td>
<td>88</td>
<td>44.1\textsuperscript{c}</td>
<td>0.79</td>
</tr>
<tr>
<td>4. $2(CH_3)_2Cd(0.4M)$</td>
<td>8 MgBr\textsubscript{2}</td>
<td>66</td>
<td>52.4\textsuperscript{c}</td>
<td>1.1</td>
</tr>
<tr>
<td>5. $2(CH_3)_2Cd(0.4M)$</td>
<td>4 MgBr\textsubscript{2}</td>
<td>68</td>
<td>52.6\textsuperscript{c}</td>
<td>1.1</td>
</tr>
<tr>
<td>6. $2(CH_3)_2Cd(0.4M)$</td>
<td>2 MgBr\textsubscript{2}</td>
<td>67</td>
<td>51.5\textsuperscript{c}</td>
<td>1.1</td>
</tr>
<tr>
<td>7. $2(CH_3)_2Cd(0.4M)$</td>
<td>1 MgBr\textsubscript{2}</td>
<td>80</td>
<td>50.1\textsuperscript{c}</td>
<td>1.0</td>
</tr>
<tr>
<td>8. $2(CH_3)_2Cd(0.4M)$</td>
<td>2 MgI\textsubscript{2}</td>
<td>60</td>
<td>50.4</td>
<td>1.0</td>
</tr>
<tr>
<td>9. $2(CH_3)_2Cd(0.4M)$</td>
<td>1 MgI\textsubscript{2}</td>
<td>75</td>
<td>44.2\textsuperscript{c}</td>
<td>0.79</td>
</tr>
<tr>
<td>10. $2(CH_3)_2Cd(0.1M)$</td>
<td>2 MgI\textsubscript{2}</td>
<td>75</td>
<td>53.5</td>
<td>1.2</td>
</tr>
<tr>
<td>11. $2(CH_3)_2Cd(0.4M)$</td>
<td>$2 MgI_2 + 2 MgF_2$</td>
<td>76</td>
<td>49.8</td>
<td>0.99</td>
</tr>
</tbody>
</table>
a Same as Table X.
b Columns 3, 4, and 5 defined as in Table X.
c Results of at least two separate runs with a maximum deviation of ± 1%.
Table XII<sup>a</sup>

Reaction of "Purified" Dimethylzinc and -Cadmium Reagents in Ether with 4-<i>t</i>-Butylcyclohexanone (1 molar Equiv.)·MgX<sub>2</sub><sup>b</sup>

<table>
<thead>
<tr>
<th>Reagent (Concn)</th>
<th>Salt</th>
<th>Unchanged ketone (%)</th>
<th>(Z)-Alcohol (%)</th>
<th>(Z)/(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Zn(0.3M)</td>
<td>4 MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>60</td>
<td>47.3</td>
<td>0.90</td>
</tr>
<tr>
<td>2. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Zn(0.3M)</td>
<td>2 MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>66</td>
<td>46.7</td>
<td>0.88</td>
</tr>
<tr>
<td>3. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Zn(0.3M)</td>
<td>1 MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>90</td>
<td>36.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.57</td>
</tr>
<tr>
<td>4. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>8 MgBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>47</td>
<td>51.7</td>
<td>1.1</td>
</tr>
<tr>
<td>5. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>4 MgBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>66</td>
<td>52.1</td>
<td>1.1</td>
</tr>
<tr>
<td>6. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>2 MgBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>66</td>
<td>49.1</td>
<td>0.97</td>
</tr>
<tr>
<td>7. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>1 MgBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>87</td>
<td>46.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.88</td>
</tr>
<tr>
<td>8. 3.6(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>2 MgBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>62</td>
<td>50.0</td>
<td>1.0</td>
</tr>
<tr>
<td>9. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>2 MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>50</td>
<td>52.8</td>
<td>1.1</td>
</tr>
<tr>
<td>10. 2(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(0.4M)</td>
<td>1 MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>71</td>
<td>37.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Same as Table X.

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

Results of at least two separate runs with a maximum deviation of ±1%.
Three mechanistic pathways for the addition of dimethylzinc and dimethylcadmium to 4-t-butylcyclohexanone will be considered: 1) addition of the Grignard reagent, present in small concentration in the reaction mixture (eq. 4); 2) addition of the zinc or cadmium reagent by way of some six-center transition state; and 3) addition of the zinc or cadmium reagent by way of some four-center transition state.

An important factor when considering any reaction mechanism is the degree of association of the reagents. On the basis of earlier work\textsuperscript{12b,72a} it is assumed that the Grignard reagents in 0.1 M concentration and the zinc and cadmium reagents in 0.3-0.4 M concentrations are monomeric. Magnesium halides present in the zinc and cadmium reagents (0.6-0.8 M) are undoubtedly polymeric.\textsuperscript{72b}

The zinc and cadmium reagents were prepared from the Grignard reagent according to the stoichiometry represented in eq. 4. Although it can be argued that $\text{RMgX}$ might be present by a reversal of eq. 4, this is

\[2\text{RMgX} + \text{MX}_2 \rightarrow \text{R}_2\text{M} + 2\text{MgX}_2 \]  \hspace{1cm} (4)

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.\textsuperscript{73}

Qualitative tests indicate that at most the Grignard reagent is present in very low concentration. The characteristic color of a charge-transfer complex between either 2,2'-biquinoline or 1,10-phenanthroline\textsuperscript{31}...
and Grignard reagent was not observed with the zinc or cadmium reagents. The familiar Gilman color test for RMgX was negative in every experiment. Although the increased reactivity of zinc and cadmium reagents in the presence of magnesium halide would be compatible with attack by the Grignard reagent, the stereochemical results do not support this mechanism. Inspection of Tables X, XI, and XII reveals that both zinc and cadmium reagents give more (E)-alcohol (less thermodynamically stable)\(^{43,46}\) resulting from axial attack, than do the Grignard reagents at low concentration. Indeed, the zinc reagents gave (E)-alcohol as the major product. The leveling effect of \((Z)\)-alcohol with increasing magnesium halide concentration shown in Tables XI and XII would not be expected if the added salt were shifting eq. 4 to the left.

If \(R_2M\) is the attacking reagent, it might be involved in a six-center or four-center transition state, by analogy with systems already studied. Thus, Ashby\(^{10}\) obtained kinetic evidence consistent with the six-center transition state \(^{18}\), which had been proposed previously for the reaction of RMgX with ketone. An analogous transition state \(^{19}\), as well as others, can easily be visualized for zinc and cadmium reagents, \(\text{MgX}_2\) being an important part of the structure.
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 20 involving a pentacoordinate magnesium. A similar structure for zinc and cadmium reagents is shown in 21. (In structures 18-21 solvent molecules are omitted for simplicity).

Although the choice between transition states 19 and 21 is a subtle one, it is felt that the results summarized above are better accommodated by a four-center transition state similar to 21.
In accord with Felkin's suggestion and the recent results on hydride reduction by Eliel et al.\textsuperscript{11} it is reasonable to consider reactant-like rather than product-like transition states. This conclusion is supported in the present work by consideration of entries 6, 7, 15, and 16 in Table X. It can be seen that a decrease in the reactivity of the reagent because of a variation of halide present generally is not accompanied by any change in stereochemistry. The less reactive zinc reagent typically leads to more of the less stable (E)-alcohol. Application of the Hammond Principle\textsuperscript{75} and the hypothesis of "product-development" control predicts the opposite stereochemical result.

Although the activating effect of the magnesium salts would be accounted for by a six-center process such as (19), the pronounced tendency of cadmium and especially zinc, to form stable complexes with oxygen (C=O)\textsuperscript{76} leads one to question the likelihood of transition state 19.

We can conclude that steric interference to axial attack is diminished in both zinc and cadmium reactions, as compared to the magnesium 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 zinc and cadmium. If one compares the two six-center transition states 18 and 19 where X represents Br and I, respectively, 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 zinc (and presumably Cd) reactions were proceeding through four-center transition states, these may 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 21 when M=Zn.

The stereochemistry of addition of RMgX is sensitive to changes in concentration of reagent, as is evident from Table X. If the addition of zinc and cadmium reagents were to involve a similar transition state 19 containing MgX₂, one might expect a similar effect. In fact, the stereochemistry of addition of both zinc and cadmium in situ reagents is independent of concentration changes, in ranges where the association of MgX₂ is changing drastically.⁷³b No change in stereochemistry is observed in the prior coordination experiments (Table XII) until the amount of MgI₂ is reduced to one molar equivalent per equivalent of ketone. The change is toward more axial attack, the opposite of the trend in dilution of the Grignard reagent.

The activating effect of MgX₂ may be ascribed to activation of the ketone and/or the organometallic through coordination with magnesium salt. Of particular interest in this regard is a recent report by Freon et al., who have obtained infrared evidence for the existence of 22 in ether.

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

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
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, thus facilitating transfer of the alkyl group. The lack of reactivity of RMX and of \( R_2M \) derived from lithium reagents may reflect the inability of monodentate ligands (LiX) to form complexes similar to 22. The inferior reactivity of \( RZnX \) and \( RCdX \) solutions containing magnesium halide may also reflect the lowered tendency of such compounds to form electron-donor complexes similar to 22.

Although all other mechanistic alternatives can not be excluded at present, it is felt that the sequence of steps shown in Scheme 1 is consistent with the results obtained here. In view of the molar excess of magnesium halide one might expect both ketone and \( R_2M \) to be substantially associated with magnesium salt (eq. 19 and 20). The four-center transition state 24, written for equatorial attack, still contains strongly associated magnesium halide. The coordination of the central metal atom in 24 may vary for zinc and cadmium, for it is well known that cadmium exhibits a greater tendency than zinc toward formation of octahedral complexes. On the other hand, there is ample precedent for the octahedral configuration of organozincs. House has recently pointed to the possibility of a pentacoordinate magnesium species in additive reactions of dimethylmagnesium.
As noted earlier, the reactivity of zinc reagents is lower than that of the corresponding cadmium compounds, in line with the fact that zinc is known to coordinate more strongly to oxygen than cadmium. Cadmium halide complexes are also known to be stronger than the corresponding zinc complexes, hence Equilibrium 20 should lie farther to the left for \( R_2Zn \) species than for \( R_2Cd \). This competition between solvent and \( MgX_2 \) for \( R_2M \) would also explain the lower reactivity of both zinc and cadmium reagents in THF.
Evidence supporting this mechanism has been obtained recently by Marx, who has found the reaction between diethylzinc and benzaldehyde in ether to be first order in aldehyde and first order in diethylzinc.

The difference in stereochemistry observed with 0.8 M and 0.1 M Grignard reagents (Table X) suggests a tighter six-center transition state for the associated reagents (more axial attack). It is noteworthy that the stereochemical results with 0.1 M CH₃MgBr in ether are close to those obtained for 1 M THF solutions, which are also monomeric. Dependency of the stereochemistry of RMgX addition on the halogen present can be explained by consideration of the association. If we assume that methylmagnesium bromide is less highly associated than methylmagnesium iodide, as is the case for the corresponding ethyl reagents, we should predict more axial attack with methylmagnesium iodide. This is indeed the case.

Dehydration of (Z)- and (E)-1-methyl-4-t-butylcyclohexanols (15 and 16) to 1-methyl-4-t-butylcyclohexene occurred when zinc salts were carried through the work-up procedure. Variable amounts of ether solutions of zinc bromide were injected into the chromatograph and the injector port coated with salt. Subsequent injection of the mixture of (Z)- and (E)-alcohols allowed a study of the course of the dehydration reaction. 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 faster than the (Z)-alcohol. Such a result
would be consistent with an $E_1$ elimination with the magnesium halide acting as a Lewis acid catalyst.

The fact that no equilibration of the (Z)- and (E)-1-methyl-4-$t$-butylcyclohexanols was noted is not surprising, since the addition products are tertiary alcohols and incapable of undergoing a Meerwein-Pondorff-Verley oxidation-reduction process. Hydrolysis of the reaction mixtures was accomplished with aqueous base ($\text{NaHCO}_3$); thus an elimination-addition sequence is also unlikely.

In order to test further the conclusions reached concerning the mechanism of addition, the stereochemistry of addition of dimethylzinc and -cadmium to acyclic aldehydes was investigated and compared to the behavior of the corresponding magnesium compounds. As in the previous-4-$t$-butyl-cyclohexanone series, determination of the per cent stereo-selectivity obtained with the various organometallic reagents was accomplished by glpc analysis with racemic materials.

The reaction between a methyl reagent and the various 2-phenylalkanals (25) should lead to a mixture of threo- and erythro-alcohols as illustrated by equation 22.

\[
\begin{align*}
\text{25} \quad & R' = \text{CH}_3 \\
\text{b} \quad & R' = \text{C}_2\text{H}_5 \\
\text{c} \quad & R' = \text{t-}\text{C}_3\text{H}_7 \\
M = \text{Mg, Zn, Cd}
\end{align*}
\]
Classically such reactions have been rationalized on the basis of a kinetic control mechanism, where the transition state resembles reactants rather than products. Interpretation of the fact that the pair of diastereomeric products (26 and 27) are not formed in equal amounts has, for a number of years, been explained by Cram's rule.79

The rule empirically states that when a carbonyl function is flanked by the two smaller groups (M and S) attached to the adjacent chiral carbon atom, the reagent (R'-M) preferentially approaches the carbonyl group from the side of the group S. The rule, which applies only to reactions which are kinetically controlled, can be illustrated by the Newman projection* 28. The rule as stated does not apply to situations where the small group, S, is hydroxy, alkoxy, amino, halide, etc.

Although the diastereomeric product distribution for a large number of nucleophilic addition reactions has been correctly predicted qualitatively by the Cram model, Karabatsos has recently pointed out a number of shortcomings from a quantitative standpoint. The Karabatsos treatment, somewhat less empirical than that of Cram, is

*Transition states are drawn for only one of the enantiomeric structures throughout the discussion.
based on two initial assumptions. \(^6^3\) (1) "Little bond breaking and making has occurred at the transition state. Consequently, the arrangement of groups around the asymmetric carbon atom with respect to the carbonyl group is similar to that about the \(sp^3\)-\(sp^2\) carbon-carbon bonds." (2) "The diastereomeric transition states that control product stereospecificity have the smallest group, S, closest to the incoming bulky group R'" (29 and 30).

After consideration of the various interactions present in 29 and 30, the energy difference represented by the approach of the reagent from the right in 29 and the left in 30 reduces to the difference in the magnitude of interactions O-M and O-L, the former generally being smaller.

Karabatsos has considered only those conformations where the carbonyl group is eclipsed. Recent nmr and microwave evidence indicates that the eclipsed-carbonyl ground state is generally more stable than the alternate staggered-carbonyl conformation. Unlike Cram, Karabatsos predicts the degree of stereoselectivity of the addition reactions to be independent of the steric bulk of the attacking reagent R', but to decrease as the steric bulk of R increases.
Felkin and coworkers have attempted to show that the interpretation of the steric outcome of the nucleophilic addition reactions can encompass both open-chain carbonyls and cyclohexanones, based on the four premises mentioned above (see page 73). These premises lead to the choice of $31$ as the lowest energy transition state.

Contrary to that predicted by the Karabatsos model, one would expect on the basis of $31$, $32$, and $33$ an increase in the stereoselectivity of the reaction as the steric bulk of $M$, $L$, or $R$ increases. The Felkin model also predicts an increase in stereoselectivity as the steric bulk of the reagent, $R'$, increases (destabilize $33$).

Again the experiments were carried out in such a way that the number of transferable methyl groups was held constant. Thus, for each mole of aldehyde, there was introduced one mole of $(\text{CH}_3)_2\text{Zn}$ or $(\text{CH}_3)_2\text{Cd}$; two moles of $\text{CH}_3\text{MgX}$, $\text{CH}_3\text{ZnX}$, or $\text{CH}_3\text{CdX}$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
The results that follow will be discussed in terms of the three models and the assumptions inherent in each. It is hoped that a greater understanding of the addition mechanism and the relationship of the various models to the actual transition states has been achieved.

From the experimental results, presented in Table XIII, several general observations can be made.
1. The reactivity of in situ organozinc and -cadmium reagents toward aldehydes is greater than toward cyclohexanone.
2. On the basis of unchanged aldehyde, the reactivity of \((\text{CH}_3)_2\text{M} \ (\text{M} = \text{Zn, Cd})\) toward the various aldehydes is essentially equivalent to that of the Grignard reagents.
3. On the basis of unchanged aldehyde, the reactivity of organozinc reagents prepared from methyllithium is extremely low. Organozincs designated as \((\text{I,Cl})\) are the least reactive of those reagents containing magnesium halide.
4. The stereochemistry of addition of Grignard reagents to acyclic aldehydes is independent of concentration (association). However, \(\text{CH}_3\text{MgBr}\) is more stereoselective than \(\text{CH}_3\text{MgI}\).
5. Contrary to the magnesium compounds, the stereochemistry of addition of all zinc and cadmium reagents, except those designated as \((\text{I,Cl})\), is independent of halide. Anomalous behavior of the \((\text{I,Cl})\) reagents was noted in the cyclohexanone reaction series as well.
6. Except for the 2-phenyl-3-methylbutanal reaction series, the % erythro-alcohol decreases according to the series:

\[
\text{CH}_3\text{MgX} > (\text{CH}_3)_2\text{Cd}, \text{CH}_3\text{CdX} > (\text{CH}_3)_2\text{Zn}, \text{CH}_3\text{ZnX}
\]
Table XIIia

Reaction of in situ Organometallic Reagents in Ether with Acyclic Aldehydes

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Organometallic</th>
<th>Conc, M</th>
<th>% Erythro&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Threo/Erythro</th>
<th>% Unchanged Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅CHCHO</td>
<td>CH₃MgI</td>
<td>0.8</td>
<td>64.3</td>
<td>0.55</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>CH₃MgI</td>
<td>0.1</td>
<td>65.6</td>
<td>0.52</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>CH₃MgBr</td>
<td>0.8</td>
<td>69.8</td>
<td>0.43</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</td>
<td>54.7</td>
<td>0.83</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>(CH₃)&lt;sub&gt;2&lt;/sub&gt;Zn(Br,Br)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.3</td>
<td>56.9</td>
<td>0.77</td>
<td>1</td>
</tr>
<tr>
<td>C₆H₅CHCHO</td>
<td>(CH₃)&lt;sub&gt;2&lt;/sub&gt;Zn(I,Cl)</td>
<td>0.3</td>
<td>51.5</td>
<td>0.94</td>
<td>8</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃ZnI(I,I)</td>
<td>0.3</td>
<td>54.3</td>
<td>0.84</td>
<td>1</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Organometallic</td>
<td>Conc, M</td>
<td>% Erythro&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Threeo/Erythro</td>
<td>% Unchanged Aldehyde</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>--------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnBr(Br,Br)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.3</td>
<td>56.0</td>
<td>0.79</td>
<td>2</td>
</tr>
<tr>
<td>9. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnX(Br,I)</td>
<td>0.3</td>
<td>54.1</td>
<td>0.85</td>
<td>2</td>
</tr>
<tr>
<td>10. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnX(I,Cl)</td>
<td>0.3</td>
<td>59.7</td>
<td>0.68</td>
<td>40</td>
</tr>
<tr>
<td>11. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnX(Li,I)</td>
<td>0.3</td>
<td>53.5</td>
<td>0.87</td>
<td>75</td>
</tr>
<tr>
<td>12. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnX(Li,Br)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.3</td>
<td>--</td>
<td>--</td>
<td>90</td>
</tr>
<tr>
<td>13. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(I,I)</td>
<td>0.4</td>
<td>61.1</td>
<td>0.64</td>
<td>1</td>
</tr>
<tr>
<td>14. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(Br,Br)</td>
<td>0.4</td>
<td>59.8</td>
<td>0.67</td>
<td>1</td>
</tr>
<tr>
<td>15. C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCHO</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(I,Cl)</td>
<td>0.4</td>
<td>60.4</td>
<td>0.66</td>
<td>1</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Organometallic</td>
<td>Conc., M</td>
<td>% Erythro</td>
<td>Three/Erythro</td>
<td>% Unchanged Aldehyde</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------</td>
<td>----------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>CH₃</td>
<td>(CH₃)₂Cd(I,Cl)</td>
<td>0.4</td>
<td>62.1</td>
<td>0.61</td>
<td>1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃CdI(I, I)</td>
<td>0.8</td>
<td>60.8</td>
<td>0.64</td>
<td>1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃CdBr(Br,Br)</td>
<td>0.8</td>
<td>62.2</td>
<td>0.61</td>
<td>1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃CdX(I,Cl)</td>
<td>0.8</td>
<td>56.8</td>
<td>0.76</td>
<td>1</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>CH₃MgI</td>
<td>0.8</td>
<td>65.2</td>
<td>0.53</td>
<td>1</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>CH₃MgBr</td>
<td>0.8</td>
<td>69.2</td>
<td>0.44</td>
<td>1</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>(CH₃)₂Zn(I, I)</td>
<td>0.3</td>
<td>54.5</td>
<td>0.83</td>
<td>1</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>(CH₃)₂Cd(Br,Br)</td>
<td>0.4</td>
<td>58.4</td>
<td>0.71</td>
<td>1</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Organometallic</td>
<td>Conc. M</td>
<td>% Erythro&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Threo/Erythro</td>
<td>% Unchanged Aldehyde</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>---------</td>
<td>-------------------------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt; MgBr</td>
<td>0.8</td>
<td>64.2</td>
<td>0.57</td>
<td>1</td>
</tr>
<tr>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Zn(I,I)</td>
<td>0.3</td>
<td>36.3</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(I,I)</td>
<td>0.4</td>
<td>32.5</td>
<td>2.1</td>
<td>1</td>
</tr>
<tr>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Cd(I,Br)</td>
<td>0.4</td>
<td>29.3</td>
<td>2.4</td>
<td>1</td>
</tr>
</tbody>
</table>

The results obtained with cadmium reagents are taken from the Ph.D. Thesis of W. J. Kauffman, University of New Hampshire, 1969.

<sup>b</sup> Normalized %; % _threo_ + % _erythro_ = 100.

<sup>c</sup> Results reproducible within ± 1% in separate reaction runs.

<sup>d</sup> Organometallic in 2:1 molar ratio.

<sup>e</sup> See reference 38. <sup>f</sup>(Li,X) ≡ (CH<sub>3</sub>Li,ZnX<sub>2</sub>).
However, for all aldehyde reactions the dimethylzinc reagents are less stereoselective than are the cadmium.

7. The stereochemistry of addition to 2-phenylpropanal (1-19) and 2-phenylbutanal (20-23) is dependent on the organometallic reagent but independent of aldehyde. An inversion in stereoselectivity is observed in the addition of methyl reagents (not with \( i-C_3H_7MgBr \)) to 2-phenyl-3-methylbutanal (24, 26-28).

8. Changing the magnesium reagent from methyl to \( i\)-propyl in reactions with 2-phenyl-3-methylbutanal causes an inversion in stereoselectivity (44.9% erythro vs. 64.2% erythro, respectively).

The significant increase in reactivity of the various in situ zinc and cadmium reagents toward aldehydes has for the first time allowed the comparison of the behavior of both \( (CH_3)_2M \) and \( CH_3MX \) (\( M = Zn, Cd \)) reagents. Indeed the reactivity toward aldehydes is sufficiently high that the previously observed dependence on the electronegativity of halide was noted only with those reagents containing chloride (I, Cl). The apparent lack of reactivity of those reagents prepared from methylthiium (Table XIII, entries 11 and 12) is in agreement with the earlier results and represents further supporting evidence for the inclusion of bridged structure 22 in the transition state.

The stereochemistry of addition of the methylzinc and -cadmium reagents to 2-phenylpropanal (25a) is essentially independent of halide. The trend in stereoselectivity observed in such reactions as a function of the organometallic reagent \( [CH_3MgX > (CH_3)_2Cd > (CH_3)_2Zn] \) is consistent with the earlier results and with the proposed four-center transition state for alkyl group transfer. Characteristically, the stereochemistry of the Grignard addition reactions is dependent on the nature of the halide,
bromide being more selective than iodide.

As illustrated by entries 1 and 2 of Table XIII, the stereochemistry of Grignard addition is independent of concentration, thus the change in stereoselectivity of Grignard addition with halide (entries 1 and 3, Table XIII) cannot be explained on the basis of association differences of the reagents. One possible explanation may be the existence of a polar effect in the transition state between the α-phenyl substituent and the more electronegative bromide causing a greater destabilization of conformer 33 (Felkin model) when X=Br relative to I.

\[
\begin{align*}
\text{CH}_3 \\
\text{Mg} \\
\text{X} \\
\text{Ph} \\
\text{O} \\
\text{CH}_3 \\
\text{Mg} \\
\text{X} \\
\text{CH}_3 \\
\text{H} \\
\text{H} \\
\end{align*}
\]

In order to test further the validity of the four-center transition state for alkyl group transfer, the addition reactions of the various in situ organometallics with 2-phenylbutanal (25b) and 2-phenyl-3-methylbutanal (25c) were investigated. The stereochemical outcome of such a reaction series should reflect the changes in steric
interactions as the size of the "medium" group M is varied from methyl to ethyl to i-propyl. Both the Cram and Felkin treatments predict greater selectivity (increase in % erythro) while that of Karabatsos predicts a lower selectivity (decrease in % erythro).

Within a given organometallic series, the stereochemistry of addition was essentially insensitive to the change of M from methyl to ethyl. However, an inversion in stereoselectivity was observed for the addition of methyl reagents to 2-phenyl-3-methylbutanal (25c; M = i-C₃H₇), the major product being threo-3-phenyl-4-methyl-2-pentanol (27c). On the assumption that the assignment of threo and erythro isomers is correct, this result represents a clear violation of Cram's and Felkin's postulates. While the Karabatsos treatment would predict a decrease in the % erythro-alcohol as M varies from ethyl to i-propyl, the major product should still be erythro-3-phenyl-4-methyl-2-pentanol (26c). Thus it appears that none of the three models offers a satisfactory explanation of the results for the reactions of 25c with the methyl reagents. The reaction of i-propylmagnesium bromide with

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C} & \text{H} \rightarrow \text{C}_6\text{H}_5\text{C} \text{OH} \\
\text{H} & \text{H} \qquad \text{H} \text{H} \\
i\text{C}_3\text{H}_7 & \text{CH}_3 \\
i\text{C}_3\text{H}_7 & \text{CH}_3 \\
25c & 26c & 27c
\end{align*}
\]
25c gives erythro-alcohol as the major isomer (64%), in qualitative agreement with the prediction of Cram, Karabatsos, and Felkin.

In view of the recent success of the Felkin approach for explaining the stereochemistry of addition reactions in cyclic and acyclic systems, the above results will be discussed in terms of the Felkin model.

According to Felkin, the importance of torsional strain in the transition states for acyclic systems requires that staggered (31, 32, and 33) rather than eclipsed conformations be considered.* The important steric interactions involve $R'$ and $R(H)$. The interaction between complexed carbonyl oxygen and the substituent attached to the $\alpha$-carbon is believed to be insignificant.

\[ M = \text{CH}_3, \text{C}_2\text{H}_5, \text{i-C}_3\text{H}_7; R' = \text{CH}_3, \text{i-CH}_3\text{H}_7; R = \text{H} \]

*Conformer 31 leads to erythro-alcohol; conformers 32 and 33 lead to threo-alcohol.
Inspection of transition state conformers 31a-33a and 31b-33b reveals that, while interactions between a magnesium-coordinated carbonyl group and the α-carbon substituent M may be small, this need not be the case for the zinc or cadmium coordinated species. If the four-center transition state is tighter, as was previously postulated to explain the results obtained with 4-tert-butylcyclohexanone, then zinc and cadmium reactions may be more sensitive to the steric bulk of M destabilizing 31a relative to 31b. Thus modification of the Felkin model to include the M—O interactions would account for the greater proportion of threo-alcohol obtained with zinc and cadmium reagents, and explain the observed stereoselectivity series Mg > Cd > Zn for reactions involving 25a and 25b. Both the Cram and Karabatsos models would predict the opposite for a tighter four-center transition state.

The fact that no change in stereoselectivity was observed as M varies from methyl to ethyl for all comparable organometallic reagents tested, implies that either the M-H steric interactions (32a and 32b) do not increase significantly or that any increase which does occur is counterbalanced by a similar increase in the magnitude of the M—O steric interactions (for uncomplexed C=O, $\Delta G^+ = 0.1$ kcal for Et—O vs. Me—O).\textsuperscript{63}

The enormous increase in the per cent threo-alcohol when M becomes i-propyl is somewhat difficult to explain. The results are in violation of the basic postulates of Cram, Karabatsos, and Felkin. According to Felkin there should be an increase rather than a decrease in the
per cent erythro-alcohol as the steric bulk of M is increased. However, modification of the Felkin model to include consideration of the M—O interactions may lead one to predict (qualitatively) an increase in the per cent threo-alcohol if the i-Pr—O interaction should become dominant.

As noted above, in reactions where zinc and cadmium are the attacking reagents, the stereochemical outcome should be more sensitive to changes in the steric bulk of M than when RMgX is the reagent. Inspection of Table XIII reveals that the change in stereochemistry was approximately the same for the Grignard and zinc reagents (entries 20 and 24 vs. 22 and 26); however, the change was significantly greater for the cadmium reagents (entries 23, 27, and 28). When M = i-propyl, the cadmium reagent yields the greatest amount of threo-alcohol (27c) and is therefore the most stereoselective reagent tested.

While the results agree qualitatively with the modified Felkin analysis, quantitatively they are less appealing. The threo/erythro ratio (0.83) obtained when \((\text{CH}_3)_2\text{Zn (I, I)}\) adds to 2-phenylpropanal (25a) corresponds to a \(\Delta G^\#\) of 0.11 kcal. Changing M from methyl to i-propyl should destabilize conformer 31a on the basis of the M—O interactions, eclipsed* \(\text{CH}_3—0\) being favored over i-Pr—O by 0.40 kcal for a free carbonyl oxygen. The resultant \(\Delta\Delta G^\#\) (0.40-0.11) favoring 32a by 0.29 kcal, must

\*\(\Delta G\) values for eclipsed interactions are used for calculations involving partially eclipsed conformers only as a means of determining approximate values for steric interactions.
be counterbalanced to a considerable extent by the increased steric interactions (M-H) in 32a as methyl is replaced by i-propyl. Thus, although an increase in the per cent threo-alcohol might occur, the experimentally determined free energy difference, ΔG° = 0.31 kcal, calculated from the threo/erythro ratio of 1.8, appears to be excessive.

An alternate suggestion might be that when M = i-propyl the phenyl group on the α-carbon may rotate such that steric and electronic interactions are reduced considerably toward the attacking methyl reagent. Thus i-propyl may act as the larger group as in 33a and 34a. Although such a model would predict threo-alcohol as the major product from all organometallic reagents, one would expect the order of stereoselectivity of reagents to remain as Mg > Cd > Zn and not the observed Cd > Zn > Mg. Also it would then be difficult to explain why, when M = i-propyl, it behaves as the large group toward methyl reagents but not toward i-propylmagnesium bromide.

When i-propylmagnesium bromide attacks 2-phenyl-3-methylbutanal (25c), the stereoselectivity more closely resembles that obtained with the methyl reagents and 2-phenylpropanal or 2-phenylbutanal. The modified Felkin model might predict a slight decrease in stereoselectivity...
as the steric bulk of M increased, which would be counter-balanced by a predicted increase in selectivity as the bulk of the attacking reagent is increased. Thus the value of 64.2% erythro-alcohol appears to conform with the theory quite well.

It is evident that additional experimental evidence is essential before a clearer understanding of the data obtained with 2-phenyl-3-methylbutanal can be achieved. In particular, the reactions of di-i-propylzinc, di-i-propylcadmium, diethylzinc, diethylcadmium, and ethylmagnesium bromide with 25c should prove informative.

The reaction between an n-propyl organometallic reagent and 4-t-butylcyclohexanone (14) should yield a mixture of (Z)- and (E)-1-n-propyl-4-t-butylcyclohexanols (35 and 36, respectively) via an addition process, as well as (Z)- and (E)-4-t-butylcyclohexanols (37 and 38, respectively) resulting from β-reduction of the ketone.29a,b
The experiments were carried out in such a way that for each mole of ketone there were introduced four moles of Grignard reagent or two moles of di-n-propylcadmium. Because of the low reactivity of the zinc reagents it was necessary to employ a 4:1 molar ratio of di-n-propylzinc: ketone.

Contrary to the results obtained with the methyl reagents, significant differences in the behavior of di-n-propylzinc and -cadmium reagents have been noted in their reactions with 4-t-butylcyclohexanone. Some generalizations can be made from inspection of Tables X and XIV.

1. Based on the amount of unchanged ketone in comparable experiments, the following reactivity series can be written:

\[ \text{n-PrMgX} > (\text{n-Pr})_2\text{Cd} > (\text{n-Pr})_2\text{Zn} \]

2. The overall reactivity of in situ di-n-propylzinc and -cadmium reagents toward 4-t-butylcyclohexanone is lower than that observed with the methyl reagents.

3. Based on the amount of unchanged ketone, the di-n-propylzinc and -cadmium reagents are more reactive when MgI\(_2\) rather than MgBr\(_2\) is present.

4. The per cent reduction obtained with n-propylmagnesium bromide increases as the concentration decreases. At comparable concentrations, n-propylmagnesium bromide and iodide show no difference in the per cent reduction obtained. The stereochemistry of their reduction products is independent of concentration but is dependent on the halide present. The stereochemistry of their addition products is independent of concentration and halide present.
5. The per cent reduction varies with the nature of the organometallic reagent and decreases according to the series:

\[(n-Pr)_2Zn \succ n-PrMgX \succ (n-Pr)_2Cd\]

6. In the case of organocadmiums, the per cent reduction and the stereochemistry of reduction are independent of halide present. With organozinc reagents, the per cent reduction and the stereochemistry of the reduction products varied according to the halide present. The least reactive zinc reagent gave the greatest proportion of reduction product.

7. No equilibration of epimeric reduction products was noted in the cadmium reactions \(((I,Br) \text{ reagent})\), but a significant amount of equilibration was detected in the zinc reactions \(((I,Br) \text{ reagent}; \text{ see Experimental})\).

8. The addition reactions of the \(n\)-propylmagnesium, -zinc, and -cadmium reagents proceed with a greater percentage of equatorial attack than do the analogous methyl reagents.

9. Except for the \((Br,Br)\) reagents, the stereochemistry of the addition reactions showed only a slight dependence on halide.

Although the relative order of reactivity \((Mg \succ Cd \succ Zn)\) remains unchanged from that observed with the methyl reagents on 4-t-butylcyclohexanone, the reactivity of the zinc reagents is extremely low even when present in 4:1 excess. This lack of reactivity not only posed problems for analysis of the reaction products, but also raises questions concerning the significance of several of the above observations. The large quantity of unchanged ketone was undoubtedly responsible for the carry-over of a significant
Table XIV\textsuperscript{a,b}

Reaction of \textit{in situ} n-Propyl Organometallic Reagents with 4-t-Butylcyclohexanone

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conc,M</th>
<th>Unchanged Ketone</th>
<th>% Addn \textsuperscript{g}</th>
<th>(Z)Addn \textsuperscript{h}</th>
<th>% Reduction \textsuperscript{h}</th>
<th>% (E)Red \textsuperscript{i}</th>
<th>Addn/Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. n-PrMgBr\textsuperscript{d}</td>
<td>0.8</td>
<td>&lt; 1</td>
<td>68.6</td>
<td>69.8</td>
<td>31.4</td>
<td>94.2</td>
<td>2.2</td>
</tr>
<tr>
<td>2. n-PrMgBr\textsuperscript{d}</td>
<td>0.1</td>
<td>&lt; 1</td>
<td>60.4</td>
<td>70.6</td>
<td>39.6</td>
<td>95.3</td>
<td>1.5</td>
</tr>
<tr>
<td>3. n-PrMgI\textsuperscript{d}</td>
<td>0.8</td>
<td>4</td>
<td>68.6</td>
<td>69.0</td>
<td>31.4</td>
<td>86.6</td>
<td>2.2</td>
</tr>
<tr>
<td>4. (n-Pr)\textsubscript{2}Zn(I,I)\textsuperscript{d}</td>
<td>0.3</td>
<td>77</td>
<td>67.9</td>
<td>55.6</td>
<td>32.1</td>
<td>74.3</td>
<td>2.1</td>
</tr>
<tr>
<td>5. (n-Pr)\textsubscript{2}Zn(I,Br)\textsuperscript{d}</td>
<td>0.3</td>
<td>77</td>
<td>56.7</td>
<td>59.0</td>
<td>43.3</td>
<td>48.4\textsuperscript{e}</td>
<td>1.3</td>
</tr>
<tr>
<td>6. (n-Pr)\textsubscript{2}Zn(Br,Br)\textsuperscript{d,k}</td>
<td>0.3</td>
<td>87</td>
<td>31.4</td>
<td>70.5</td>
<td>68.6</td>
<td>19.4</td>
<td>0.46</td>
</tr>
<tr>
<td>7. (n-Pr)\textsubscript{2}Cd(I,I)\textsuperscript{c}</td>
<td>0.4</td>
<td>10</td>
<td>87.7</td>
<td>55.1</td>
<td>12.3</td>
<td>71.8</td>
<td>7.1</td>
</tr>
<tr>
<td>8. (n-Pr)\textsubscript{2}Cd(Br,Br)\textsuperscript{c,j}</td>
<td>0.4</td>
<td>62</td>
<td>90.3</td>
<td>76.8</td>
<td>9.7</td>
<td>73.7</td>
<td>9.3</td>
</tr>
<tr>
<td>9. (n-Pr)\textsubscript{2}Cd(I,Br)\textsuperscript{c}</td>
<td>0.4</td>
<td>20</td>
<td>90.9</td>
<td>58.4</td>
<td>9.1</td>
<td>71.9\textsuperscript{f}</td>
<td>10.0</td>
</tr>
<tr>
<td>10. (n-Pr)\textsubscript{2}Cd(I,Cl)\textsuperscript{c}</td>
<td>0.4</td>
<td>20</td>
<td>91.4</td>
<td>62.9</td>
<td>8.6</td>
<td>69.7</td>
<td>10.6</td>
</tr>
</tbody>
</table>
aThe results obtained with cadmium reagents are taken from the Ph.D. Thesis of W. J. Kauffman, University of New Hampshire, 1969.

bAll values except those reported as % Unchanged Ketone are normalized; % Addn + % Red = 100; % (Z)Addn + % (E)Addn = 100; % (Z) Red + % (E) Red = 100.

cReactions were run with 2 molar equivalents of Cd reagent.

dReactions were run with 4 molar equivalents of Zn and Mg reagents.

eNo equilibration of epimeric reduction products was noted.

fEquilibration of epimeric reduction was noted.

gValues were reproducible within ± 5% in separate reaction runs.

hValues were reproducible within ± 2% in separate reaction runs.

iValues were reproducible within ± 2% for Mg and Cd; ± 3% for Zn in separate reaction runs.

jValue unchanged in ether-benzene (1:2) solvent.

kPrepared from commercial sample of zinc bromide.
amount of zinc salts through the work-up procedure. The problem was alleviated to a large degree by carrying out the reactions in ether-benzene solvent and extracting the aqueous hydrolysis layer with benzene rather than ether. Any remaining salt was removed by ammonium hydroxide extraction (see Experimental).

The values reported in Table XIV under the heading \"% (E) Red\", were reproducible to \(\pm 3\%\) in the case of the organozinc reactions. The following factors probably contributed most to the lack of reproducibility. (1) Because of the large amount of unchanged ketone, the glpc analysis proved to be difficult; resolution of the ketone peak from that of \((Z)\)-4-\(\eta\)-butylcyclohexanol (37) was generally less than complete. (2) Equilibration of reduction products was shown to occur.

The observation that the addition reaction with propyl reagents gives a greater proportion of equatorial attack relative to the corresponding methyl reagents, can be rationalized on the basis of the models proposed by Marshall\(^69\) and Felkin\(^47,70\). It is expected that as \(R'\) increases from methyl to \(n\)-propyl, a corresponding increase in steric interactions involving \(R\) and \(R'\) in 17b should occur giving rise to a greater proportion of axial alcohol (35). A detailed analysis of the system is best achieved by reference to the transition state models 39 and 40.

\[
\begin{align*}
39 & \quad 40
\end{align*}
\]
It is likely that the C-2 carbon atom in 40 would be rotated so as to minimize the steric interactions between the incoming reagent and the substituents of the cyclohexanone ring. One of the more strain-free conformations appears to place one of the C-2 protons above and between (bisecting) the 3,5-axial protons. However, even under the most favorable circumstances, it would appear unlikely that the propyl reagent could approach the top side of the cyclohexanone ring as closely as the methyl reagent.

The significant drop in reactivity of the di-n-propylzinc and -cadmium reagents relative to their methyl counterparts may reflect a significant degree of sensitivity of the reactions to these steric factors. In line with this conclusion is the observation that the least reactive (most bulky) zinc and cadmium reagents, \((\text{n-Pr})_2\text{M (Br,Br)}\), give much larger percentages of \((Z)-1\text{-n-propyl-4-t-butyl-cyclohexanol (35)}\). This poses the question as to why the \((\text{n-Pr})_2\text{M (Br,Br)}\) reagent should behave as if it were bulkier than \((\text{n-Pr})_2\text{M (I,I)}\).

The answer may lie in the ability or inability of the propyl group to occupy the most favorable conformation in the transition state for addition. Inspection of models reveals that the most favorable conformation may be that where the alkyl chain is "bent" back away from the cyclohexyl ring such that the terminal methyl group (C-3) is in the vicinity of the coordinated magnesium halide. Thus, in the case where X=I, one might expect the more polarizable (sponge-like) iodide to tolerate this situation more readily than bromide.
The ratio of addition to reduction may also depend to some extent on steric factors. Thus, \((n-Pr)_2Zn(Br,Br)\), the bulkiest zinc reagent, gives the greatest per cent reduction. Again inspection of models reveals that the transition state for reduction (41) should be more strain-free than that for addition (40). If the transition state for addition with zinc is tighter than that for cadmium, then this could conceivably contribute to the preference of zinc reagents for reduction. That steric factors cannot be dominant is clear, however. For example, no increase in the per cent reduction is observed with \((n-Pr)_2Cd(Br,Br)\), and the difference in stereoselectivity (transition state bond distances) of addition reactions of propylzinc and -cadmium is too small to account for the large differences in the addition: reduction ratios.

Since addition and reduction reactions are undoubtedly in competition with one another, if the addition reaction is retarded (or the reduction process activated) one should observe a greater proportion of reduction products. The apparent superior reactivity of cadmium reagents relative to zinc toward addition may preclude any serious competition of the reduction process with the former reagent.
Although such arguments may explain to a considerable extent the addition-reduction ratios observed with zinc and cadmium, they can not explain why Grignard reagents give addition-reduction ratios which are intermediate between zinc and cadmium. Consider the fact that the magnesium compounds are the most reactive in addition and yield a stereochemistry of addition which would indicate they are the bulkiest reagent (most equatorial attack). It would appear then that the nature of the carbon-metal bond also has a significant influence on the addition-reduction ratio.

In this regard the nature of the halide coordinated to the metal should also influence the addition-reduction ratio. Mosher et al. noted in the reaction of n-propyl magnesium halide with diisopropyl ketone that the per cent reduction decreased according to the series I > Br > Cl, the total spread being 18%. However, in the reaction of i-propylmagnesium halides with the same ketone no change in the per cent reduction was noted. Thus, it is not without precedent that essentially no difference was noted for the n-propylmagnesium bromide and iodide reduction of 4-t-butylcyclohexanone. As expected, the per cent reduction obtained with the di-n-propylcadmiums did not change significantly with halide. In marked contrast, the addition-reduction ratio varied enormously with halide in the reactions with organozinc reagents.

Assuming the previous conclusion is correct regarding the four-center transition state for the addition reactions of zinc and cadmium reagents, one would expect the addition-reduction ratio to be more sensitive to halide for
Grignard reactions than for those of zinc. The halogen does not occupy a primary position in either the four-center transition state to addition or the six-center process for reduction. The transition state for Grignard addition (18), however, involves the making and breaking of halogen bonds, while the Grignard reduction mechanism (42) does not. Clearly, the observed results do not fit this analysis. Thus one is left with the previously noted possibilities of steric influences, and other activating or retarding influences such as inductive effects of the halide on the nature of the carbon-metal bond. Electronic factors have been observed to be important when highly electronegative substituents are located in the alkyl chain of the Grignard reagent. 2-Phenyl-3,3,3-trifluoromethylpropylmagnesium chloride (43) was found to be a poor reducing agent, for example.

\[
\begin{align*}
\text{CF}_3 & \quad \text{H} \\
\phi & \quad \text{CH}_2\text{MgCl}
\end{align*}
\]
The addition-reduction ratio in the Grignard reactions was observed to change slightly with dilution of the reagents; yet the stereochemistry of their addition or reduction reactions is independent of concentration. This probably reflects a lower degree of sensitivity of the addition and reduction reactions involving the bulkier propyl reagent (relative to methyl) to changes in association. Thus, no differences in the stereochemistry of addition between n-propylmagnesium bromide and iodide were observed. It appears that the ratio of addition to reduction is somewhat more sensitive to solvation effects. This is in agreement with some recently published data of Ashby and Walker,\textsuperscript{82} where the per cent reduction was found to increase significantly when Grignard reactions are carried out in amine rather than ether solvent.

In the few cases studied, the stereoselectivity of \(\beta\)-reduction reactions of Grignard reagents has been found to be independent of halide. Mosher \textit{et al.}\textsuperscript{83a,b} have studied the variation in stereoselectivity of the reduction of methyl \(t\)-butyl ketone with (+)-1-halo-2-methylbutylmagnesium reagents and found the per cent asymmetric induction to vary as chloride (13%); bromide (12%); and iodide (8%). The reduction reactions of n-propyl Grignard and -cadmium reagents with 4-\(t\)-butylcyclohexanone proceed to give (E)-4-\(t\)-butylcyclohexanol (38) as the major isomer via axial attack. The observation that Grignard reagents give a greater proportion of 38 via axial attack implies a tighter transition state, according to Marshall. The results are in accord with
the expected metal-oxygen bond distances (Mg—O vs. Cd—O). The stereoselectivity of the reduction reactions with di-n-propylcadmiums was independent of halide, as expected, while n-propylmagnesium bromide gave a slightly greater amount of (E)-alcohol than the iodide. No equilibration of reduction products via a Meerwein-Pondorff-Verley process was detected.

If the metal-oxygen bond distances were the controlling factor in the stereoselectivity of the reduction process, then the data should reveal only slight differences between organomagnesium and the analogous organozinc reagents. This is not the case, however, for the per cent (E)-4-tert-butylcyclohexanol (38) decreased drastically from magnesium to zinc.

It can be pointed out that the reagent which behaves as the bulkiest in the addition reaction, (n-Pr)_2Zn(Br,Br), also yields the major reduction product via equatorial attack. However, it is unlikely that steric effects alone could explain the observed change from predominant axial attack of hydride with (n-Pr)_2Zn(I,I) to predominant equatorial attack with (n-Pr)_2Zn(Br,Br), giving the thermodynamically less stable alcohol. As noted earlier, the transition state leading to reduction should be less sensitive to steric factors than the four-center transition state leading to addition. Because a small amount of equilibration was noted with (n-Pr)_2Zn(I,Br) reagent, it must be assumed that the values reported in Table XIV as "% (E) Red" Represent a maximum for the amount of (E)-alcohol produced (minimum amount of equatorial attack). While the value obtained with (n-Pr)_2Zn(I,I) is in close agreement with that of (n-Pr)_2Cd(I,I) (ca. 70%), the remaining values

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
are clearly out of line. Abenhaim has recently carried out the reduction of 4-t-butylcyclohexanone with (n-Pr)\(_2\)Zn(Br,Br)\(^{29a,b}\) and, although he was unable to determine the stereochemistry of reduction products, the addition-reduction ratio (0.89) reported is in substantial agreement with that reported here (0.46).
BIBLIOGRAPHY

1. (a) E. Frankland, Ann., 71, 171 (1849); (b) E. Frankland, ibid., 71, 213 (1849); (c) E. Frankland, ibid., 85, 329 (1853); (d) E. Frankland, ibid., 99, 333 (1856).

2. V. Grignard, Compt. Rend., 130, 1322 (1900).


21. Reference 6, Chapters 4 and 5.


38. Zinc bromide solution was prepared from the commercially available salt.


58. Reference 39, p. 100.


64. (a) M. A. Raynaud and M. Moureu, Compt. Rend., 181, 1069 (1925); (b) D. S. Crocket and H. M. Haendler, J. Amer. Chem. Soc., 82, 4158 (1960).

65. Reference 6, p. 46.


