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THE ASYMMETRIC SYNTHESIS OF STYRENE-OXIDE AND ITS REACTIONS WITH DIALKYL MAGNESIUM REAGENTS AND BORON HYDRIDES

RONALD LEROY ATKINS

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Keywords
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THE ASYMMETRIC SYNTHESIS OF STYRENE OXIDE AND ITS REACTIONS WITH DIALKYL MAGNESIUM REAGENTS AND BORON HYDRIDES

by

RONALD L. ATKINS

B. S., The University of Wyoming, 1966
M. S., The University of Wyoming, 1968

A THESIS

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Some Pages have indistinct print. Filmed as received.

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DEDICATION

This thesis is dedicated to my wife Beverly, my son Thomas, and my daughter Andrea for their encouragement, patience and sacrifice which made the attainment of this goal a reality.
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THE ASYMMETRIC SYNTHESIS OF STYRENE OXIDE AND ITS REACTIONS WITH DIALKYL MAGNESIUM REAGENTS AND BORON HYDRIDES

Introduction ........................................... 1
Results ................................................... 16
Reactions of Optically Active Styrene Oxide with Dialkylmagnesium Reagents ....................... 16
Discussion ................................................ 23
Reactions of Optically Active Styrene Oxide with Dialkylmagnesium Reagents ....................... 23
Reaction of Epoxides with Borane ....................... 30
Asymmetric Synthesis of Styrene Oxide .................. 52
Reduction of Phenacyl Chloride with LiAlH₄ Modified with 3-0-Benzyl-1,2-Cyclohexylidene-α-D-Glucofuranose ............................................ 58
Reduction of Phenacyl Chloride with LiAlH₄ Modified with Quinine ............................................ 61
Reductions of Aldehyde with Modified LiAlD₄ .......... 72
Experimental .............................................. 76
General .................................................. 76
Methods ............................................... 76
  Gas Liquid Partition Chromatography .............. 76
  Infrared Absorption Spectra .......................... 76
  Mass Spectra ....................................... 77
R-(-)-2-Phenyl-1,2-Ethanediol (2) ........................................... 78
R-(-)-1-Brosyloxy-2-Phenylethanediol (3) ............................... 79
R-(+)-Styrene Oxide (4) ..................................................... 80

Reaction of Diisopropylmagnesium with R-(+)-Styrene Oxide-4 in the Presence of MgBr$_2$-Dioxane .................. 80
Reaction of R-(+)-Styrene Oxide-4 with Diisobutylmagnesium in the Presence of MgBr$_2$-Dioxane ............. 82
Reaction of R-(+)-Styrene Oxide (4) with Di-t-butylmagnesium in the Presence of MgCl$_2$-Dioxane .......... 83
Reaction of R-(+)-Styrene Oxide (4) with Diethylmagnesium .......................................................... 84

Reaction of R-(+)-Styrene Oxide (4) with Di-t-butylmagnesium .......................................................... 84

Reaction of R-(+)-Styrene Oxide (4) with Diethylmagnesium in the Presence of MgCl$_2$-Dioxane ........... 85

Reaction of R-(+)-Styrene Oxide (4) with Diethylmagnesium in the Presence of MgI$_2$-Dioxane .......... 86

Reaction of R-(+)-Styrene Oxide (4) with BD$_3$ Generated in situ in THF .......................................... 86

Reaction of R-(+)-Styrene Oxide with BD$_3$/BF$_3$·Et$_2$O .......................................................... 87

Preparation of R-(+)-Styrene Oxide-2,2-d$_2$ .......................................................... 88

Reaction of R-(+)-Styrene Oxide-2,2-d$_2$ with BD$_3$/BF$_3$·Et$_2$O .......................................................... 89

Attempted Preparation of Phenylacetaldehyde-1-d .......... 89

Preparation of 1,2:5,6-di-O-Cyclohexyldiene-α-D-Glucofuranose .................................................. 91
Preparation of 3-O-Benzyl-1,2:5,6-di-0-Cyclohexylidene-\(\alpha\)-D-Glucofuranose...............................91
Preparation of 3-O-Benzyl-1,2-0-Cyclohexylidene-\(\alpha\)-D-Glucofuranose.....................................92
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with 3-O-Benzyl-1,2-0-Cyclohexylidene-\(\alpha\)-D-Glucofuranose...........................................92
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Quinine........................................93
Effect of Added Phenylacetaldehyde on the Rotation of Optically Active Styrene Oxide.......................94
Large Scale Reduction of Phenacyl Chloride with LAH•Quinine.................................................95
Repeated Large Scale Reduction of Phenacyl Chloride with LAH•Quinine......................................95
Reaction of Phenacyl Chloride with LAH•Quinine: Inverse Addition.............................................96
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Quinine and One Equivalent of Ethanol......97
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Quinine and Two Equivalents of Ethanol.....97
Repeated Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Quinine and One Equivalent of Ethanol.........................................................98
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Two Equivalents of Quinine...............99
Reaction of Acetophenone with LiAlH\(_4\) Modified with Quinine and Ethanol................................99
Reaction of Phenacyl Chloride with LiAlH\(_4\) Modified with Cinchonine and Ethanol........................100
Reduction of Benzaldehyde with LiAlD\(_4\) Modified with Quinine and One Equivalent of Ethanol........100
Reduction of Phenylacetaldehyde with LiAlD\(_4\) Modified with Quinine and Ethanol........................101
Bibliography....................................................103

vi
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Substituent Effects on Ring Opening Orientation</td>
<td>13</td>
</tr>
<tr>
<td>2. Reagent Effects on Ring Opening Orientation</td>
<td>15</td>
</tr>
<tr>
<td>3. Reaction of R-(-)-Styrene Oxide (4) with Dialkylmagnesium Reagents</td>
<td>20</td>
</tr>
<tr>
<td>4. Effect of Halide Upon Product Distribution</td>
<td>22</td>
</tr>
<tr>
<td>5. Reaction of Epoxides with $\text{B}_2\text{H}_6/\text{BF}_3\cdot\text{Et}_2\text{O}$</td>
<td>32</td>
</tr>
<tr>
<td>6. Reduction of Acetophenone with Alkaloid Modified LiAlH$_4$</td>
<td>54</td>
</tr>
<tr>
<td>7. Reduction of Methyl Ketones with Monosaccharide Modified LiAlH$_4$</td>
<td>56</td>
</tr>
<tr>
<td>8. Reductions of Phenacyl Chloride with LiAlH$_4$ Singly Modified with Quinine</td>
<td>62</td>
</tr>
<tr>
<td>9. Lithium Aluminum Hydride Modified with Quinine and Absolute Ethanol</td>
<td>68</td>
</tr>
<tr>
<td>10. Reduction of Aldehydes with Quinine/Ethanol Modified LiAlD$_4$</td>
<td>73</td>
</tr>
<tr>
<td>11. Asymmetric Syntheses of Benzylalcohol-1-d</td>
<td>74</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Synthesis of Optically Active Styrene Oxide</td>
<td>1</td>
</tr>
<tr>
<td>2. Configuration Correlation Model for the Asymmetric Epoxidation of Styrene by Chiral Peracids</td>
<td>3</td>
</tr>
<tr>
<td>3. Product Distribution from the Reaction of an Oxirane with an Organomagnesium Reagent</td>
<td>7</td>
</tr>
<tr>
<td>4. Mechanism of ( \text{Et}_2\text{Mg/MgBr}_2 ) -Dioxane Addition to ( \text{R}-(\text{+})-4 )</td>
<td>18</td>
</tr>
<tr>
<td>5. Effect of Halide on Mechanism of Addition</td>
<td>28</td>
</tr>
<tr>
<td>6. A Mechanism for the Reaction of ( \text{R}-(\text{+})-4 ) with ( \text{BD}_3/\text{BF}_3 \cdot \text{Et}_2\text{O} )</td>
<td>34</td>
</tr>
<tr>
<td>7. Asymmetric Reduction of Phenylacetaldehyde by ( \text{BD}_3 \cdot \text{Epoxide Complex} )</td>
<td>36</td>
</tr>
<tr>
<td>8. ( \text{BF}_3 ) Catalyzed Rearrangement of Deuterated 1,1-Disubstituted Ethylene Oxides</td>
<td>38</td>
</tr>
<tr>
<td>9. Rearrangement-reduction of ( \text{R}-(\text{+})-\text{Styrene Oxide-1,1-2d} ), 53</td>
<td>42</td>
</tr>
<tr>
<td>10. Asymmetric Reduction of Phenylacetaldehyde by an Alkoxyborane</td>
<td>45</td>
</tr>
<tr>
<td>11. Synthesis of 3-O-Benzyl-1,2-O-Cyclohexylidene-( \alpha-)D-Glucofuranose</td>
<td>60</td>
</tr>
<tr>
<td>12. Mechanisms of Carbinol Formation</td>
<td>64</td>
</tr>
</tbody>
</table>
ABSTRACT

THE ASYMMETRIC SYNTHESIS OF STYRENE OXIDE
AND ITS REACTIONS WITH DIALKYL MAGNESIUM REAGENTS
AND BORON HYDRIDES

by

RONALD L. ATKINS

A new asymmetric synthesis of styrene oxide has been developed. The reduction of phenacyl chloride with the chiral reducing reagent prepared from lithium aluminum hydride, quinine and ethanol followed by treatment with methanolic potassium hydroxide gives optically active styrene oxide. Styrene oxide has been prepared in this manner having 58 to 84% enantiomeric excess (ee) of the S isomer. A second chiral hydride reagent (LiAlH$_4$ modified with cinchonine and ethanol) gave optically active styrene oxide, 29% ee of the R isomer.

The regiospecificity and stereoselectivity of ring opening reactions of optically active styrene oxide with bi-philic reagents is discussed. When R-(+)-styrene oxide is allowed to react with a series of dialkylmagnesium reagents, products are formed by (1) addition of R at the benzylic
position giving chiral carbinols, and (2) addition of R to or reduction of phenylacetaldehyde (rearrangement-addition or rearrangement-reduction) giving achiral carbinols. In the presence of suspended dioxanate-MgX₂ precipitate it was found that product distribution and degree of stereoselectivity were dependent upon the nature of the alkyl group (R = Et, i-Pr, i-Bu and t-Bu), and upon the nature of the halide (X = Cl, Br, and I). In the absence of dioxanate-MgX₂ precipitate only addition at the benzylic position occurs with up to 80% inversion of configuration at the benzylic position. Mechanistic considerations are discussed.

The reaction of R-(+)-styrene oxide with perdeuteroborane/BF₃·Et₂O generated in situ in tetrahydrofuran gives a mixture of S-(-)-2-phenylethanol-2-d and S-(-)-phenylethanol-2-d. When borane/BF₃·Et₂O solution is prepared by addition of BF₃·Et₂O to a tetrahydrofuran solution of diborane, reaction with R-(+)-styrene oxide yields only S-(-)-1-phenylethanol-1-d of 11-14% ee. Mechanistic interpretations are discussed.
Optically active styrene oxide has been prepared by several synthetic routes. All of those giving high optical purity have utilized optically active mandelic acid as the precursor; both isomers being commercially available and of moderate cost. The first synthesis, reported by Eliel and Delmonte¹, involved lithium aluminum hydride reduction of R-(−)-mandelic acid ¹, followed by formation of the p-toluene-sulfonyl derivative of the primary alcohol. Ring closure was effected with aqueous potassium hydroxide to give R-(+)-styrene oxide, ⁴, in approximately 40% overall yield. This synthetic route involves no reaction at the asymmetric center, and is illustrated in Figure 1.

![Figure 1. Synthesis of Optically Active Styrene Oxide.]

The optical purity was reported to be at least 85% based upon the rotation of the phenylmethyl carbinol, ⁵, obtained on opening of the oxirane ring with LiAlH₄, and the optical purity of the starting material, ¹, as shown in
Equation 1.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{R-}(+) & \quad \text{S-}(-) \\
85\% \text{ ee} & \quad 85\% \text{ ee}
\end{align*}
\]

Berti and coworkers\(^2\) synthesized \(\text{R-}(+)\)-styrene oxide by the same route, but effected ring closure using methanolic sodium methoxide. The overall yield of product was improved (50% yield). The oxide had a rotation of \([\alpha]_D^{25} +34.2^\circ\) (neat), the highest reported, and was assumed to be at least 90% optically pure.

In another modification of the Eliel-Delmonte synthesis, Tömösközi\(^3\) prepared the primary brosylate of the 1-phenylethane-1,2-diol, \(2\). The advantage of this method is that the 1-brosyloxy derivative of the diol is more stable than the corresponding tosyl derivative, and can be readily purified by recrystallization. Tömösközi synthesized the oxide in 60% yield. The oxide had a rotation of \([\alpha]_D^{25} +34.2^\circ\) (neat), and was reported to be of 100% optical purity.\(^1\)\(^b\)

Styrene oxide of low optical purity has been prepared from achiral precursors via asymmetric induction. Henbest\(^4\) reported the asymmetric epoxidation of styrene with
(+)-monopercamphoric acid, 6, to give optically active styrene oxide of 2-4% ee. Montanari and coworkers report a detailed study of the asymmetric epoxidation of styrene with a number of chiral peracids. The optical purity of the styrene oxide obtained was low (2-4%).

A configuration correlation model based upon steric considerations has been proposed, and is shown in Figure 2. This model correctly predicts the enantiomer which should be produced in excess from simple, empirically applied, steric arguments. The enantiomer which is produced in excess is that in which the R group of the olefin is disposed trans to the large group L of the peracid. The applicability of this model has yet to be determined for more highly substituted olefins.

Figure 2. Configuration Correlation Model for the Asymmetric Epoxidation of Styrene by Chiral Peracids.

Johnson and coworkers found that the reaction of optically active oxosulfonium methyldis, 7, with aldehydes and ketones yields optically active epoxides (Equation 2).
The optical purity of styrene oxide prepared in this way was low (5%).

In this laboratory, the asymmetric synthesis of styrene oxide has been attempted with a variety of chiral reducing reagents using phenacyl chloride, \( \text{PhCH}_2\text{Cl} \), as the substrate. The reaction sequence is shown in Equation 3.

\[
\begin{align*}
\text{O} \quad & \quad \text{(1) Chiral Reducing Reagent} \quad \text{OH} \\
\text{Ph} \quad & \quad \text{C-CH}_2\text{Cl} \quad \text{Base} \quad \text{(3)}
\end{align*}
\]

A Meerwein-Ponndorf-Verley type reduction using isobornylloxymagnesium bromide proved unsatisfactory due to extensive aldol condensation of the substrate. Di-3-pinanylborane reduction yielded a complex product mixture from which
it was not feasible to separate the desired product. Reduction of 8 with the chiral Grignard reagent, 9, prepared from R-(−)-2-phenylbutyl chloride, 10, provided S-(−)-styrene oxide (39% yield, −14% ee) as shown in Equation 4.

\[
\text{PhCH}_2\text{MgCl} + \text{PhC(O)CH}_2\text{Cl} \xrightarrow{1)} \text{H}_2\text{O} \xrightarrow{2)} \text{Base} \rightarrow \text{PhCH} = \text{CH}_2
\]

The oxirane ring is one of the most extensively studied heterocyclic systems. In our interest in compounds of the general type 11, we felt optically active epoxides might serve as precursors to these reagents. However, the stereochemistry of many reactions which result in opening of the oxirane ring has not been elucidated. Therefore an investigation of the reaction of optically active styrene oxide with a series of biphilic reagents was undertaken. A biphilic reagent is one that is both electrophilic (in the Lewis acid sense) and nucleophilic. Dialkylmagnesium reagents and
borane are two such reagents, and were chosen for preliminary studies.

Since the discovery of organomagnesium reagents by Victor Grignard\textsuperscript{7,8}, these versatile reagents have had great utility in synthetic organic chemistry. It is surprising then that the reaction mechanisms by which Grignard reagents interact with some common organic substrates have yet to be revealed in detail.\textsuperscript{9} There is still considerable debate as to the actual structure of Grignard reagents in solution which makes the task of determining a given reaction mechanism even more difficult.\textsuperscript{10}

The first reported reaction of a Grignard reagent with an oxirane was by Blaise\textsuperscript{11} in 1902. Blaise noted the formation of ethylene bromohydrin upon treatment of ethylene oxide with methylmagnesium bromide. In the years that have passed, research in this area of oxirane chemistry has expanded at a rapid pace.\textsuperscript{12,13,14} From the work reported in the literature, a general pattern has become apparent for the reaction of an oxirane with organomagnesium reagents, and is summarized in Figure 3.\textsuperscript{15}

For a given Grignard reagent and oxirane there are six possible alcohols and two halohydrins that may, in
Figure 3. Product Distribution from the Reaction of Oxirane with an Organomagnesium Reagent

\[
\begin{align*}
\text{MgX}_2 \quad & \xrightarrow{\text{addition}} \quad \text{addition} \\
& \xrightarrow{\text{addition}} \quad \text{addition} \\
& \xrightarrow{\text{addition}} \quad \text{addition} \\
& \xrightarrow{\text{addition}} \quad \text{addition}
\end{align*}
\]
principle, be formed. Fortunately, in most cases only one or two products are formed in significant amounts and it is possible to predict the major product expected from some oxiranes. The factors which govern the course of the reaction, however, are by no means simple.

As mentioned earlier, before it is possible to discuss a mechanism for a given reaction it is of fundamental importance to know the nature of the reactive species involved. There is still some question as to the structure of the reactive species involved in Grignard reactions. Ashby, in an exhaustive and critical review of the literature, advances the argument that typical Grignard reagents in diethyl ether solutions are best represented by Equation 5. (Solvent molecules are also undoubtedly intimately involved, but are not shown in the equation).

\[
R-Mg \quad R-Mg \rightleftharpoons 2 \quad R_{2} \quad Mg \quad + \quad Mg_{2} \quad X \rightleftharpoons \quad R \quad Mg \quad X \quad Mg
\]

(5)

This is a modified version of the well known Schlenk equation which has been expanded to include dimeric forms, and . These dimers become increasingly important at high concentrations, but need not be considered in dilute solution.
The position of the equilibria involved are dependent upon the nature of R, the halide used in preparation of the reagent, the solvent, and the concentration. In dilute solutions of diethyl ether (less than 1 molar) simple alkyl Grignard reagents derived from alkyl iodides and alkyl bromides are monomeric (species 13 and 14), and those derived from alkyl chlorides are only slightly associated. All are highly solvated. For the "normal" case, the equilibrium expressed in Equation 6 lies far to the left \(^9,10,18,19\) and Grignard reagents may be considered as monomers.

\[
2 \text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2 \tag{6}
\]

Dialkylmagnesium compounds can be prepared in nearly quantitative yields by treating ethereal solutions of alkyl Grignard reagents with a molar equivalent of anhydrous 1,4-dioxane.\(^{20}\) The 1,4-dioxane coordinates strongly through oxygen to magnesium halides forming an ether insoluble adduct which precipitates. Filtration of the adduct gives a clear filtrate which is devoid of magnesium halide. Dialkylmagnesium reagents are considered to be monomers in dilute ethereal solutions; like normal Grignard reagents they are highly solvated.

Tiffeneau and Forneau\(^{21}\) reported the reaction of racemic styrene oxide with the Grignard reagents from methyl-
and ethyl bromide to give 1-phenyl-2-propanol, \textit{17}, and 1-phenyl-2-butanol, \textit{18}, respectively (Equation 7).

\[ \text{MeMgBr} \rightarrow \text{Ph-CH}_2\text{CHOHMe} \]

\[ \text{EtMgBr} \rightarrow \text{Ph-CH}_2\text{-CHOHEt} \]

These products are formed by addition of the \textit{R} group of the Grignard reagent to phenylacetaldehyde, \textit{19}, which arises by Lewis acid catalyzed rearrangement of the oxide prior to addition. This rearrangement-addition sequence is shown in Equation 8.
The first report of the addition of a dialkylmagnesium reagent to an oxirane was by Bartlett and Berry. These authors reported that the reaction of cyclohexene oxide with dimethylmagnesium gave trans-2-methylcyclohexanol (Equation 9). Golubic and Cottle reported that the reaction of the same reagent with 1,2-propylene oxide gave only 2-butanol (Equation 10).

\[
\text{MeMgMe} \quad \text{Me}\quad \text{OH}
\]

(9)

\[
\text{CH}_3\text{C} \quad \text{O} \quad \text{CH}_2 \quad \text{MeMgMe} \quad \text{CH}_3\text{CHOH-CH}_2\text{Me}
\]

(10)

Norton and Hass compared the reactions of EtMgBr and Et\textsubscript{2}Mg free of MgBr\textsubscript{2} with a series of epoxyalkanes. The addition of diethylmagnesium prepared from ethyl bromide afforded only 2-methyl-2-pentanol when allowed to react with 2-methyl-1,2-propylene oxide, whereas the reaction of the same epoxide with ethylmagnesium bromide gave only 2-methyl-3-pentanol (Equation 11).
The following conclusions may be drawn from these data:

1. Alkyl substituted oxiranes react with alkyl Grignard reagents via rearrangement intermediates, i.e., carbonyl compounds.

2. Alkyl substituted oxiranes react with dialkyl-magnesium reagents free of magnesium halides to give products resulting from attack at the less hindered carbon atom presumably via an Sn2 type pathway.

From the reaction of racemic styrene oxide and unfiltered diisopropylmagnesium/MgBr$_2$·dioxane, Whitesides and Roberts$^{25}$ isolated only 2-phenyl-3-methyl-1-butanol, 20; that is, attack occurred at the more hindered benzylic position (Equation 12). This result suggests that electronic factors are important in determining the position of attack.
Denian, Henry-Basch and Freon\textsuperscript{26} report a comparative study of the reaction of styrene oxide with alkyl Grignard reagents, dialkylmagnesium reagents, and dialkylcadmium reagents (Equation 13).

\[
\text{PhO} \xrightarrow{\text{H}} \text{C} \xrightarrow{\text{RM}} \text{CH}_2 \quad \xrightarrow{\text{R}} \quad \text{Ph-C-CH}_2\text{OH} + \text{Ph-CH}_2\text{-CHOHR} \quad (13)
\]

R = Me, Et, n-Bu
M = Cd, Mg, Zn

These authors found that alkyl Grignard reagents gave mixtures of alcohols 21 and 22 (\textasciitilde50:50), while dialkylmagnesium reagents gave only the primary alcohols, 21. Organo-cadmium reagents gave only the rearrangement-addition product, 22. They concluded that alkyl Grignard reagents react as mixtures of \text{R}_2\text{Mg} and \text{MgX}_2.

These same authors investigated substituent effects on the orientation of ring opening of substituted trans-stilbene oxide. Their results are summarized in Table 1.\textsuperscript{27}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Compound & X & Yield % & 25 & 26 \\
\hline
23 & Me & 63 & \textasciitilde90 & \textasciitilde10 \\
24 & Cl & 90 & \textasciitilde25 & \textasciitilde75 \\
\hline
\end{tabular}
\caption{Substituent Effects on Ring Opening Orientation}
\end{table}
From these rather limited data, the authors infer that in a 1,2-diphenyl epoxide, reaction of a dialkylmagnesium reagent occurs predominately at the benzylic position that can best accommodate the development of positive charge in the transition state leading to products. Thus in the case of 23, attack is favored at the p-methylphenyl substituted benzylic carbon because of the electron donating methyl group which stabilizes the incipient transition state, and product 25 predominates. Conversely, in the case of the monochloro stilbene oxide 24, the electron withdrawing nature of the chlorine increases the energy of the transition state for attack at the p-chlorophenyl substituted position, and attack is favored at the benzylic carbon atom bearing the unsubstituted phenyl group, giving 26 in excess.

These authors also reported the reaction of racemic styrene oxide with RMgX, R₂Mg/Mgₓ' dioxane, and R₂Mg. These results are given in Table 2.

The data summarized in Table 2 illustrate the marked effect that the nature of the organomagnesium reagent has on the product distribution obtained upon reaction with styrene oxide. Dialkylmagnesium reagents in the presence of MgBr₂·dioxinate give only rearrangement-addition, whereas dialkylmagnesium reagents free of precipitate give only benzylic addition. The "normal" Grignard reagents give a
mixture of benzylic addition and rearrangement-addition.

Table 2.
Reagent Effects on Ring Opening Orientation

\[
\text{Ph} \begin{array}{c}
\text{C} \\
\text{H}
\end{array} \begin{array}{c}
\text{CH}_2 \\
\end{array} + \text{RM} \rightarrow \text{PhCH}_2\text{CHOHR} + \text{PhCHRCH}_2\text{OH}
\]

<table>
<thead>
<tr>
<th>Organomagnesium Reagent</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{R}_2\text{M} + \text{MgBr}_2 \cdot \text{dioxane} )</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>( \text{R}_2\text{M} )</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>( \text{RMgX} )</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

\( \text{R} = \text{Me, Et, n-Bu} \)
\( \text{M} = \text{Mg} \)

From the extensive work of the French\textsuperscript{26,27,28}, the following conclusions concerning the reactions of styrene oxide with organometallic reagents can be drawn:

(1) Oxiranes, and styrene oxide in particular, are very susceptible to rearrangement under the influence of Lewis acids such as magnesium halides.

(2) The magnesium atom of dialkylmagnesium reagents is not a sufficiently strong Lewis acid to promote oxirane rearrangement.
(3) Dialkylmagnesium reagents undergo direct addition to the oxirane ring at the least hindered site in alkyl substituted oxiranes, while in the case of aryl substituted oxiranes addition occurs at the carbon atom which can best stabilize developing positive charge.

(4) When alkyl Grignard reagents are added to styrene oxide two competitive reactions occur: direct addition at the benzylic position, and rearrangement-addition giving secondary alcohols. It is of importance to note that no addition at the β carbon occurs which further emphasizes the importance of the phenyl substituent.

Results: Reactions of Optically Active Styrene Oxide with Dialkylmagnesium Reagents

All of the work thus far discussed has been performed using racemic substrates. With the recent report of an efficient synthetic route to optically active styrene oxide\(^3\), it was thought that a study of the reactions of styrene oxide of known configuration and optical purity would be of interest.

Tomaszewski\(^{29}\), in this laboratory, ran several exploratory reactions involving ring opening of optically active R-(+)-styrene oxide. Among these was the reaction of R-(+)-styrene oxide, 4, (87% ee) with diethylmagnesium in the presence of MgBr\(_2\)·dioxane precipitate. The results obtained
are indicated in Equation 14.

\[
\text{Ph} \text{C}^\text{CH}_2 \xrightarrow{\text{Et}_2\text{Mg}} \text{MgBr}_2 \cdot \text{dioxane} \xrightarrow{} \text{Ph} \text{C}^\text{CH}_2 \text{Et} + \text{OCH}_2\text{CHOEt} (14)
\]

\[
\begin{align*}
\text{R-(+)-4} & \quad 87\% \text{ ee} \\
\text{S-(+)-29} & \quad 43.9\% \text{ ee} \\
& \quad 50\% \text{ yield} \quad 30\% \text{ yield}
\end{align*}
\]

These results do not agree in terms of product distribution with the results obtained by Denian, Henry-Basch and Freon with racemic styrene oxide. Tomaszewski obtained a mixture of benzylic addition (50% yield) and rearrangement-addition (30% yield). The ring opening of the active epoxide occurs with about 50% loss of optical activity. Tomaszewski concluded that these data reflect the formation of an oxide-dialkylmagnesium adduct, 30, shown in Figure 4.

Intermolecular addition of R (Pathway b) leads to products with inversion of configuration at the benzylic position, whereas intramolecular addition (Pathway a) gives products with retention of configuration at the benzylic position. If a free carbonium ion, 31, is formed, racemization occurs via either inter- or intramolecular modes of addition (Pathway c). Since the net result was an excess of inverted product, intermolecular reaction was considered to be the predominant pathway.
Figure 4

Mechanism of Et₂Mg/MgBr₂·Dioxane Addition to R- (+)-4

(a) intramolecular attack
(b) intermolecular attack

4

30

31

racemic benzylic addition products

H₂O

R-(-)-28

S-(+)-28
In the present investigation, we have studied the stereochemistry of ring opening of R-(+)-4 with a number of dialkylmagnesium reagents in the presence of MgX₂·dioxanate precipitate, and filtered dialkylmagnesium reagents free of MgX₂·dioxanate. The data obtained are presented in Table 3.\textsuperscript{30}

We have also investigated the effect of magnesium dihalides upon the product distribution and the stereochemistry of the ring opening. The data obtained are presented in Table 4.
### Table 3
Reaction of R- (+)-Styrene Oxide (4) with Dialkylmagnesium Reagents

![Chemical Structure](image)

\[
\begin{align*}
\text{H} \quad & \text{O} \\
\text{\( R \)} \quad & \text{\( R \text{Me} \)} \\
\text{C} \quad & \text{\( \text{CMe}_2 \)} \\
\text{\( \text{CH}_2 \)} \quad & \text{\( \text{OH} \)} \\
\end{align*}
\]

1) \( R_2 \text{Mg} \)
2) \( \text{H}_2\text{O} \)

\[
\begin{align*}
\text{C} & \longrightarrow \text{CH}_2 \text{OH} + \text{CH}_2 \text{CH(OH)}R + \text{CH}_2 \text{CH}_2 \text{OH} \\
\text{32} & \quad \text{Benzylic Rearrangement} \\
\text{33} & \quad \text{Substitution with Addition} \\
\text{34} & \quad \text{Rearrangement with Reduction} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>% Yield, % ee, Configuration</th>
<th>Stereochemistry of 32 Forming</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Inversion</td>
<td>% Retention</td>
</tr>
</tbody>
</table>

**Filtered Dialkylmagnesium Reagents:**

<table>
<thead>
<tr>
<th>R (Et)</th>
<th>Product (Et)</th>
<th>% Yield, % ee, Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32a</td>
<td>95%, 70% ee, S- (+)</td>
</tr>
<tr>
<td></td>
<td>33a</td>
<td>4%, inactive</td>
</tr>
<tr>
<td>t-Bu</td>
<td>32d</td>
<td>68%, 5% ee, S- (-)</td>
</tr>
</tbody>
</table>

**Dialkylmagnesium Reagents Containing Suspended MgBr₂-Dioxanate:**

<table>
<thead>
<tr>
<th>R (Et)</th>
<th>Product (Et)</th>
<th>% Yield, % ee, Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32a</td>
<td>50%, 50% ee, S- (+)</td>
</tr>
<tr>
<td></td>
<td>33a</td>
<td>30%, inactive</td>
</tr>
<tr>
<td>i-Pr</td>
<td>32c</td>
<td>48%, 53% ee, S- (+)</td>
</tr>
<tr>
<td></td>
<td>33c</td>
<td>20%, inactive</td>
</tr>
<tr>
<td>i-Bu</td>
<td>32d</td>
<td>52%, ( \alpha_{24} + 2.38 \text{ (neat, } \alpha_{26} + 4.25 \text{ (CHCl}_3) )</td>
</tr>
<tr>
<td></td>
<td>33d</td>
<td>23%, inactive</td>
</tr>
<tr>
<td></td>
<td>34d</td>
<td>4%, achiral compound</td>
</tr>
<tr>
<td>t-Bu</td>
<td>32f</td>
<td>3%, 32 and 33 were not separated and no</td>
</tr>
<tr>
<td></td>
<td>33f</td>
<td>18%, rotation data were taken.</td>
</tr>
<tr>
<td></td>
<td>34f</td>
<td>79%, achiral compound</td>
</tr>
</tbody>
</table>
Table 3

Footnotes

(a) Yields were determined by glpc analysis of undistilled reaction mixtures unless otherwise annotated. The difference between the sum of the yields of the reported products and 100% is due to the presence of unreacted starting material and minor by-products, some of which were not identified, but none of which were PhCH(OH)CH₂R.

(b) % ee is the percent enantiomeric excess corrected for the % ee of the oxide used. The latter ranged from 84% to 89%.

(c) Yields computed from glpc analysis following simple distillation.

(d) The maximum rotation is not known.

(e) Suspended MgCl₂-dioxanate in this case.
Table 4

**Effect of Halide Upon Product Distribution**

\[
\begin{align*}
\text{EtMgX} + \text{Dioxane} & \rightarrow \text{EtMgEt/MgX}_2 \cdot \text{Dioxinate} \\
& \overset{R-(+)-4}{\rightarrow} \text{H}_2\text{C}_2\text{OH} + \phi\text{CH}_2\phi\text{CH(OH)Et} \quad 29 \\
& \quad 18
\end{align*}
\]

<table>
<thead>
<tr>
<th>[M]</th>
<th>X</th>
<th>% ee</th>
<th>% Yield</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.48</td>
<td>Cl</td>
<td>89%</td>
<td>82%</td>
<td>69%</td>
<td>3%</td>
</tr>
<tr>
<td>1.04</td>
<td>Br</td>
<td>87%</td>
<td>50%</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>0.37</td>
<td>I</td>
<td>89%</td>
<td>36%</td>
<td>17%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Discussion: Reactions of Optically Active Styrene Oxide with Dialkylmagnesium Reagents.

As stated earlier, dialkylmagnesium reagents in dilute ethereal solutions are monomeric and highly solvated by ether. The ether coordinated to the magnesium atom can be removed only under vigorous conditions (heating \textit{in vacuo}).

There are literature reports concerning the relative basicities of the oxygen in cyclic oxides \((n = \text{ring size} = 3, 4, 5\) and 6) which indicate that the oxygen incorporated in the epoxide ring \((n=3)\) is of unusually low basicity compared to other cyclic oxides and acyclic ethers.\textsuperscript{32,33} It has also been noted that alkyl substitution increases oxygen basicity, whereas aryl substitution decreases oxygen basicity in epoxides.\textsuperscript{34} Therefore, it can be concluded that the oxygen in styrene oxide is considerably less basic than the oxygen in diethyl ether, and the equilibrium represented in Equation 15 must lie to the left, favoring an organomagnesium reagent coordinated by solvent.

\[
\begin{align*}
R\text{Mg} & \quad S + O & \quad \rightleftharpoons & \quad R\text{Mg} & \quad O + S \\
R & \quad \text{S} & \quad & \quad R & \quad \text{S} \\
\end{align*}
\]

\(S = \text{Solvent}\)

\(O = \text{Epoxide}\)
Ashby has shown by variable temperature dynamic nuclear magnetic resonance that the coordinated solvent molecules undergo rapid exchange with free solvent. Therefore, there is opportunity for the oxirane oxygen to enter into the exchange process and become coordinated with the Grignard reagent as in 30 of Figure 4. Reaction can then occur from this complex, or from interaction of the Grignard reagent with uncomplexed epoxide.

The results in Table 3 where dialkylmagnesium reagents free of MgX₂·dioxane precipitate gave exclusively benzylic addition when allowed to react with styrene oxide indicate that dialkylmagnesium reagents are, as earlier observed, of insufficient Lewis acidity to promote rearrangement of styrene oxide to an appreciable degree.

There are two mechanisms which can adequately explain the stereochemical results obtained in the addition of diethyl and di- t-butylmagnesium to R-(+)-4. These are the mechanism advanced by Tomaszewski which involves coordination of a molecule of the epoxide to the magnesium of the dialkylmagnesium reagent followed by intra- or intermolecular addition of the alkyl group at the benzylic position (see Figure 4), or reaction via uncomplexed styrene oxide.

The addition of filtered diethylmagnesium to R-(+)-4 gave S-(+)-2-phenylbutanol, 32a, in 95% yield and 70%
optical purity. The addition of filtered di-t-butylmagnesium to R-(+)-4 gave S-(-)-3,3-dimethyl-2-phenylbutanol, \(32b\), in 50% yield and 5% optical purity. That diethylmagnesium gives a much higher degree of stereoselectivity (85% inversion) than di-t-butylmagnesium (53% inversion) may be a reflection of the large steric bulk of the t-butyl moiety. This steric effect is even more pronounced when considered in the reaction of di-t-butylmagnesium in the presence of magnesium chloride dioxinate precipitate. A different reaction pathway is observed. The predominant course of the reaction is rearrangement followed by reduction. The great difference in the stereoselectivity of the addition of these two reagents to R-(+)-4 reflects a difference in the detailed mechanism of addition of these reagents to R-(+)-4. Since racemization occurs to a degree in both reactions, and electronic factors have been shown to be of great importance, carbon-oxygen bond breaking must occur with, or precede, addition of the alkyl group to the substrate to a significant degree. The addition most likely is occurring through an epoxide that is complexed with a molecule of dialkylmagnesium reagent. A reaction mechanism is shown in Figure 4. The epoxide enters into the exchange equilibrium of the solvated dialkylmagnesium reagent and becomes complexed with a molecule of the dialkylmagnesium as in \(30\). In the complex, because of the Lewis
acid character of the magnesium, the benzylic carbon to oxygen bond becomes polarized and begins to break. A second molecule of dialkylmagnesium reagent can add an alkyl group at the benzylic position with inversion of configuration. If the addition of the alkyl group to the benzylic position is slow, complete carbon oxygen bond breaking occurs and the net result is racemization since the addition then occurs via the achiral carbonium ion \(31\).

In the case of diethylmagnesium, addition of the ethyl moiety, because of its relatively small size, occurs during the breaking of the carbon-oxygen bond. This results in a predominance of inversion at the benzylic position (70%). Only 30% of the reaction proceeds via the open carbonium ion \(31\). On the other hand, the very bulky di-\(t\)-butylmagnesium reagent proceeds with a preponderance of racemization. This means that the addition of the bulky \(t\)-butyl group to the epoxide occurs after the carbon oxygen bond is broken. Addition occurs to the achiral carbonium ion \(31\), leading to nearly completely racemic products.

The reaction of \(R- (+) -4\) with dialkylmagnesium reagents in the presence of suspended magnesium halide/dioxane precipitate shows the expected lack of perturbation as the size of the alkyl group increases, except in the case of the \(t\)-butyl group where there is a dramatic change. It should also be
noted that the size of the alkyl group also has apparently little effect on the degree of stereoselectivity of addition at the benzylic position in that all proceed with a large predominance of inversion, again excluding the t-butyldiethylmagnesium reagent which once again appears to be unique.

Examination of the data in Table IV reveals the marked effect of the halogen used on the product distribution and degree of stereoselectivity. Proceeding through the series Cl, Br, I, there is a pronounced decrease in addition at the benzylic position with a concomitant decrease in stereoselectivity. It is noteworthy that the reaction of diethylmagnesium in the presence of suspended magnesium chloride/dioxane precipitate gives essentially the same results (both with respect to product distribution and stereoselectivity) as did the same reagent free of magnesium-halide/dioxane precipitate. This suggests that if the dialkylmagnesium reagent is prepared using alkyl chlorides, it may be unnecessary to filter the reagent prior to addition.

The reagents derived from ethyl iodide and bromide give less benzylic attack (with more racemization) and more product resulting from rearrangement. These facts are accommodated by the mechanism given in Figure 5. In the case of the diethylmagnesium reagent in the presence of magnesium chloride/dioxane precipitate, the equilibrium ex-
Figure 5

Effect of Halide on Mechanism of Addition

(1) \[ 2 \text{RMg} \rightarrow \text{R}_2\text{Mg} + \text{MgX}_2 \] (1)

(2) \[ \text{MgX}_2 + \text{O} \rightarrow \text{MgX}_2 \text{(2)} \]

(3) \[ \text{MgX}_2 + \text{CH}_2 \rightarrow \text{CH}_2 \text{(3)} \]

(4) \[ \text{H} \rightarrow \left[ \begin{array}{c} \text{H} + \text{MgX}_2 \\ \text{H} \rightarrow \text{CH}_2 \end{array} \right] \rightarrow \text{CH}_2 \text{(4)} \]

Inactive

Inversion

Racemization
pressed in (2) of Figure 5 must lie to the right. This results in there being little or no MgCl₂ remaining in solution to promote rearrangement of the oxide as in (4). Because of the strong Lewis acid character of the MgCl₂, the adduct once formed does not disassociate. The end result is that the diethylmagnesium adds an ethyl group to the oxide with the same product distribution and stereochemical results as was the case of the filtered reagent (see Figure 4).

However, since MgBr₂ and MgI₂ are less Lewis acidic than MgCl₂ because of the relative electronegativities of the halides, the dioxane/MgX₂ adduct in these latter two examples is not as strongly associated and the equilibrium in (2) lies more to the left. This leaves MgX₂ in solution to complex with the styrene oxide. This is manifested in a higher yield of rearrangement-addition product, and with more racemization due to a more "carbonium ion" like character of the ring opening addition reaction.
Reaction of Epoxides with Borane

In 1960, Brown and Subba Rao\textsuperscript{37} reported the reduction of propylene and styrene oxides with borane. The reduction of racemic styrene oxide with borane generated \textit{in situ} from sodium borohydride and boron trifluoride etherate gave 2-phenylethanol (73\%) and 1-phenylethanol (27\%) as shown in Equation 16.

\[
\begin{align*}
\text{Ph} & \quad \text{C} & \quad \text{CH}_2 \\
\text{BH}_3/\text{BF}_3\cdot\text{Et}_2\text{O} & \quad \text{in situ} & \quad \text{PhCH}_2\text{CH}_2\text{OH} + \text{Ph-CH(OH)CH}_3 \\
\end{align*}
\]

Later, Pasto and coworkers\textsuperscript{38} reduced a number of different epoxides with borane-d\textsubscript{3} and determined the deuterium distribution in the products. The reaction was found to be very complex. Besides giving products from direct ring opening of the oxide, rearrangement-reduction occurs, as well as reaction with solvent to give addition product oligomers from oxide and solvent.

In a modification of the reaction of an epoxide with borane, Brown and Yoon\textsuperscript{39} added boron trifluoride as a Lewis acid catalyst. The introduction of the BF\textsubscript{3} produces ring opening of the epoxide and rearrangement. In the rearrangement, a hydride shift occurs, and the major product arises from reduction of the resulting aldehyde or ketone (Equation 17).
A summary of these results is given in Table 5. It is clear that the reduction of epoxides with diborane can be greatly modified by the presence of electrophilic components such as boron trifluoride.

Tomaszewski examined the reaction of R-(+)-styrene oxide with perdeuteroborane generated from lithium aluminum deuteride and BF₃·Et₂O according to the procedure of Brown and Yoon (Equation 18). Surprisingly, he obtained optically active 2-phenylethanol-1-d, 35. The configuration of the

\[ \text{(1) } \text{BD}_3/\text{BF}_3\cdot\text{Et}_2\text{O} \]
\[ \text{(2) } \text{H}_2\text{O} \]

\[ \text{PhCH}_2\text{OH} \]

\[ \text{R-}-(+)-4 \]
\[ 87\% \text{ ee} \]

\[ \text{S}-(-)-35 \]
\[ 78\% \text{ yield} \]
\[ \alpha_D -0.415 \]

((-)-2-phenylethanol-1-d obtained was tentatively assigned by reference to a related configurational assignment for 2-(p-methoxyphenyl)-ethanol-1-d, 38. Belleau and Burba reported the reduction of p-methoxyphenylacetaldehyde, 36, with isobornyloxymagnesium bromide, 37, to give (-)-2-(p-methoxy-
### Table 5

**Reaction of Epoxides with $\text{B}_2\text{H}_6/\text{BF}_3\cdot\text{Et}_2\text{O}$**

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene oxide</td>
<td>2-phenylethanol</td>
<td>98</td>
</tr>
<tr>
<td>$\alpha$-methyl</td>
<td>2-phenyl-1-propanol</td>
<td>100</td>
</tr>
<tr>
<td>styrene oxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-$\beta$-methyl styrene oxide</td>
<td>1-phenyl-2-propanol</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>2-phenyl-1-propanol</td>
<td>3</td>
</tr>
<tr>
<td>$\alpha$-phenyl</td>
<td>2,2-diphenylethanol</td>
<td>95</td>
</tr>
<tr>
<td>styrene oxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-phenylcyclo-</td>
<td>cis-2-phenylcyclopentanol</td>
<td>18</td>
</tr>
<tr>
<td>pentene oxide</td>
<td>trans-2-phenylcyclopentanol</td>
<td>82</td>
</tr>
</tbody>
</table>
phenyl)-ethanol-1-d, \textit{38} (Equation 19).

\begin{align*}
\text{CH}_3\text{O-} & \text{CH}_2\text{CH} \\
\text{OMgBr} & \rightarrow \text{p-MeOPhCH}_2\text{C} & \text{OH} \\
\text{36} & \text{37} & \text{S-(-)-38}
\end{align*}

If the assumption is made that the reduction follows the usually successful stereocorrelation model for reductions with isobornyloxy magnesium bromide, \textit{(-)-38} has the S configuration. It has been shown in related cases that replacement of a phenyl group with a p-methoxyphenyl substituent neither changes the sign nor does it appreciably affect the magnitude of rotation in a pair of related chiral compounds.\textsuperscript{41,42} The maximum rotation of 2-phenylethanol-1-d should be of the same order of magnitude as that of the p-methoxy compound, \textit{38}. The optical purity of \textit{38} from the MFV reduction, which exhibited a rotation of -1.44\(^\circ\), was assumed to be about 40-50\%.\textsuperscript{42} On the basis of this assumption, Tomaszewski estimated that the \textit{(-)-2-phenylethanol-1-d} \((\alpha_D -0.415)\) produced in the reaction of \textit{R- (+)-stilbene oxide with BD\textsubscript{3}/BF\textsubscript{3}·Et\textsubscript{2}O} was about 11-14\% optically pure, and that the reaction proceeded with about 12-16\% transfer of chirality. A possible mechanism for the reaction, advanced by Tomaszewski, is shown in Figure 6.
Figure 6

A Mechanism for the Reaction of R-(+)-4 with BF₃/ED₃BF/Et₂O

$$\text{R-}(+)\text{-4} \xrightarrow{\text{BF}_3} \text{39} \xrightarrow{\text{BF}_3} \text{40}$$

$$\text{D} \xrightarrow{\text{CH}_2\text{Ph}} \text{H}_2\text{O}$$

$$\text{D} \xrightarrow{\text{CH}_2\text{Ph}} \text{OH}$$

$$\text{S-}(-)\text{-35-1-d}$$
This mechanism assumes that there is an initial complexation of the oxide with boron trifluoride followed by essentially complete ring opening to form the secondary carbonium ion, \textsuperscript{39}. The secondary carbonium ion would be formed in preference to the primary because of resonance stabilization of the positive charge by the phenyl group. Ring opening will be accompanied by rotation about the C\textsubscript{1}-C\textsubscript{2} bond to relieve eclipsing of the substituents on C\textsubscript{1} and C\textsubscript{2}. It was further assumed that the favored direction of rotation would be to the right when the oxide is viewed along the C\textsubscript{1}-C\textsubscript{2} bond with C\textsubscript{1} to the front. That is, the -OBF\textsubscript{3} moiety rotates away from the large phenyl group on C\textsubscript{2}. This rotation places H\textsubscript{R} in an orientation more favorable to migration than that of H\textsubscript{S}. A preferential H\textsubscript{R} hydride shift generates \textsuperscript{42}, which may be in resonance with \textsuperscript{43}. Reduction by borane-d\textsubscript{3} would give 2-phenylethanol-1-d upon hydrolysis.

If the mechanism advanced by Tomaszewski approximates the actual chain of events, there must be a high degree of concertedness to the steps a through d. The chirality of the R-(-)-styrene oxide appears to have some measure of control over the process.

Yoon and Brown\textsuperscript{39} and Pasto and coworkers\textsuperscript{38} have also postulated the intermediacy of a carbonyl compound (complex \textsuperscript{43}) in the reduction of an epoxide with borane-d\textsubscript{3}. At first
glance intermediates such as 42 or 43, which are achiral, seem inconsistent in view of the optical activity of the 2-phenylethanol-1-d produced in this reaction.

A second mechanism which can explain the observed results and which is compatible with the formation of achiral intermediates, is the asymmetric reduction of the achiral rearrangement product (phenylacetaldehyde) by a chiral complex of BD₃ and unrearranged epoxide as shown in Figure 7.

Figure 7

Asymmetric Reduction of Phenylacetaldehyde by BD₃·Epoxide Complex

![Chemical structure diagram]
Blackett and coworkers\(^{43}\) have examined the stereo-selectivity of the boron trifluoride catalyzed rearrangement of the cis and trans monodeuterated epoxides 45 and 46, to give 1,3,3-trimethylbutyraldehyde, 47 (Equation 20). It was found that there is a pronounced preference for migration of the group (H or D) cis to the methyl group. For epoxide 46 the ratio of deuteride:hydride migration was 1:0.89, while for epoxide 45 it was 1:2.65. The mechanism advanced to explain these data is similar to that of Tomaszewski (see steps a-c in Figure 6), and involves a concerted breaking of the tertiary carbon to oxygen bond with concomitant rotation of the -OBF\(_3\) moiety away from the bulky t-butyl group followed by hydride (or deuteride) transfer as in 50 to give the aldehyde 47. This mechanism is shown in Figure 8 for epoxide 45.
Figure 8

BF₃ Catalyzed Rearrangement of Deuterated 1,1-disubstituted Ethylene Oxides

![Chemical structures and reactions]

- Complex formation
- Bond rupture
- Rotation
- Preferential deuteride transfer

(+)-45 → 48
49
47
As part of the present investigation, several experiments designed to test the mechanistic proposals advanced by Blackett and by Tomaszewski were carried out.

To be absolutely certain that the results obtained by Tomaszewski were valid, the reaction was repeated exactly as described. The results are shown in Equation 21, and are in excellent agreement with the data reported by Tomaszewski.

\[ \text{BD}_3/\text{BF}_3\cdot\text{Et}_2\text{O} \xrightarrow{\text{THF, } 0^\circ} \text{PhCH}_2\xrightarrow{\text{C}} \text{OH} \]

R-(+)-4  S-(-)-35
90% ee  97% yield

\([\alpha]^{29}_D -0.35^\circ\]

The 2-phenylethanol-1-d, 35, was distilled and isolated in 99+% purity (by glpc and nmr) to ensure that there were no optically active impurities present.

The reaction of R-(+)-4 with BD$_3$/BF$_3$·Et$_2$O generated in situ in tetrahydrofuran from lithium aluminum deuteride and BF$_3$·Et$_2$O was also carried out. The reaction gave S-(−)-1-phenylethanol-2-d, 51 (64%) and S-(−)-2-phenylethanol-2-d, 52 (36%) as shown in Equation 22.
The product distribution observed is in good agreement with those reported by Brown and Subba Rao. The assignment of the S configuration to (-)-52 is based on the stereoselective synthesis of 52 from optically active mandelic acid reported by DePuy and coworkers. The estimated optical purity of S-(-)-52 is based upon a maximum rotation for R-(+)-2-phenylethanol-1,1,2-d3 of 2.14° calculated by Tomaszewski, making the assumption that the deuterium atoms at the primary carbon do not appreciably effect the magnitude or sign of rotation.

These results suggest that borane-d3 generated in situ* from LiAlD4 and BF3·Et2O in THF is of insufficient Lewis acidity to promote rapid rearrangement of R-(+)-4 to phenylacetaldehyde. In the absence of a strong Lewis acid BD3 reacts with R-(+)-4 to give ring opening products. From

*The in situ preparation proceeds as follows:

\[ \text{LiAlD}_4 + \text{BF}_3 \cdot \text{Et}_2\text{O} \rightarrow \text{LiAlF}_4 + \text{Et}_2\text{O} + \text{BD}_3. \]
the stereochemistry of the products, it is evident that attack at the benzylic position proceeds with predominate inversion of configuration. Attack at the primary position gives \( S-(-)-51 \). Assuming that the deuterium atom does not appreciably effect the magnitude of the rotation, the carbinol, \( 51 \), is 89% optically pure (based upon the \([\alpha]_D^\text{max.}\) for \( \text{PhCH(OH)CH}_3 \)), and terminal opening proceeds with no loss of optical activity as would be expected.

A stringent test of both Tomaszewski's and Blackett's mechanistic interpretations would be the reaction of \( R-(+)-\text{styrene oxide} \) doubly labeled with deuterium at the primary position. If the concerted rearrangement-hydride transfer mechanism correctly approximates the actual path followed, reaction of the deuterated oxide with borane-\( d_3 \) should lead to \( S-(-)-2\text{-phenylethanol-}1,1,2-d_3, 54 \). The reaction sequence is shown in Figure 9. Steps a-c would occur at least partially in a synchronous manner with some transfer of chirality.

The required dideuterated epoxide \( R-(+)-53 \) was synthesized from \( R-(-)-\text{mandelic acid, 1} \), as shown in Equation 23. Curiously, the synthesis was less efficacious both in terms of the percent yield and the optical purity of the oxide than the corresponding preparation of the perhydro oxide.
Figure 9

Rearrangement-reduction of R-\((+)-\)styrene oxide-1,1-2\textsuperscript{d}53

\begin{align*}
R-\((+)-\text{53} & \xrightarrow{a} R-\((+)-\text{53} \\
\text{Reduction} \xrightarrow{\text{BD}_3} & \text{S-\((-)-\text{54}}
\end{align*}
R-(-)-53 was allowed to react with BD$_3$/BF$_3$·Et$_2$O in THF at 0°. The only isolable product (70% yield) was 2-phenyl-ethanol-1,1,2-d$_3$, 54. A small amount of 1-phenylethanol was also observed. The trideuterated alcohol was isolated 98% pure (2% of 1-phenylethanol as the only impurity) by preparative gas chromatography. The alcohol obtained was racemic (Equation 24), i.e., no transfer of chirality was observed.

This experiment suggests that the mechanism advanced by Tomaszewski/Blackett (Figure 6) is not the pathway followed in this reaction, since if it were, the product should have been optically active.

A likely explanation for the nonselective transfer is that the incipient carbonium ion, 40 (Figure 6), being
somewhat stabilized by the phenyl substituent through delocalization of the positive charge, has a lifetime of sufficient length to preclude the preferential rotation-transfer. To test the validity of this argument, the optically active 2,2-dideutério-1-methyl-1-ɛ-butyl ethylene oxide should be prepared and subjected to rearrangement under the influence of boron trifluoride.

In the reaction of $\text{R-}$(+)−53 with $\text{BD}_3/\text{BF}_3\cdot\text{Et}_2\text{O}$ a small amount of 1-phenylethanol (terminal opening product) was observed. The presence of this product could account for the asymmetric reduction observed in the manner shown in Figure 10.

In this hypothetical mechanism, the oxide undergoes rearrangement as in (1) to give phenylacetaldehyde, 19. The chiral reducing reagent is generated by terminal opening of $\text{R-}$(+)−4, as in (2), to give the chiral monoalkoxyborane, 55. This chiral reducing agent then reduces 19 to give the dialkoxyborane, 56, which upon hydrolysis gives 52 and S−(−)−51.

To determine if a chiral monoalkoxyborane can function as an asymmetric reducing agent, borane, 60, which has been modified with one equivalent of $\text{R-}$(+)−1-phenylethanol, 58, was used to reduce trifluoromethyl phenyl ketone. The product, trifluoromethylphenylcarbinol, 59, was isolated by
Figure 10

Asymmetric reduction of phenylacetaldehyde
by an alkoxyborane

(1) $R-(+)\text{-}4 \xrightarrow{\text{BF}_3} \phi\text{CH}_2\text{C}-\text{H}$

(2) $R-(+)\text{-}4 \xrightarrow{\text{terminal opening}} \text{D}$

(3) $19 + 55 \rightarrow H\text{-}\text{C-O-BD-O-C-CH}_2\text{Ph}$

(4) $56 \xrightarrow{\text{H}_2\text{O}} S-(\text{-})\text{-}51 \text{ and } S-(\text{-})\text{-}52$
preparative gas chromatography and was racemic (Equation 25).

\[
\ce{CF_3PhC\equivCH\overset{\text{CH}_3}{\text{Me}}} + \ce{H\overset{\text{CH}_3}{\text{Me}}OBH_2} \rightarrow \ce{CF_3PhCH\overset{\text{Me}}{\text{OH}}} + \ce{H\overset{\text{CH}_3}{\text{Me}}OH} \quad (25)
\]

\[\text{From carbinol racemic } [\alpha]^2_{D} +42.8^\circ \text{ with } [\alpha]^2_{25} +42.8^\circ\)

Trifluoromethyl phenyl ketone is very easily reduced, and the optically pure carbinol, 59, has a specific rotation of 31.85°. Since the concentration of asymmetrically modified borane was high (one equivalent) it would be expected that the conditions for asymmetric reduction to occur by 60 are reasonably good. However, since the product of the reduction, 59, was racemic it must be concluded that the chiral monoalkoxyborane, 60, probably does not induce asymmetry upon reduction in the system examined. This result is circumstantial evidence against the hypothesis that asymmetric reduction of 42 or 43 by a chiral alkoxy borane may be occurring in the reaction of R-(+)-4 with BD₃/BF₃·Et₂O.

A remaining mechanism which can account for the formation of optically active product in the reaction of R-(+)-4 with BD₃/BF₃·Et₂O is reduction of phenylacetaldehyde by
a chiral complex as depicted in Figure 7. In this mechanism a \( BF_3 \) complex of the rearrangement product, phenylacetaldehyde is reduced asymmetrically by a chiral \( BD_3/epoxide \) complex, 44, to give optically active 2-phenylethanol-1-d.

A test of this mechanism would be to reduce phenylacetaldehyde-1-d, 61, with \( BH_3/BF_3\cdot Et_2O \) in the presence of \( R-(\text{-})-4 \). Reduction of 61 by \( BH_3 \) complexed with \( R-(\text{+})-4 \) could give optically active 2-phenylethanol-1-d, whereas if \( R-(\text{+})-4 \) undergoes intramolecular rearrangement-reduction, achiral 2-phenylethanol would be produced.

Unfortunately, all attempts to prepare 61 were unsuccessful. The method of Walborsky and coworkers\(^{45}\) employing the formation of the metalloaldimine, 62, from the addition of benzyl lithium or benzylmagnesium bromide to 1,1,3,3-tetramethylbutylisocyanide, followed by hydrolysis with \( D_2O \), was unsuccessful due to difficulty in generation of benzyl lithium. And when benzylmagnesium bromide was employed instead of benzyl lithium, the aldimine was obtained, but deuterium incorporation was only 50% (by nmr) and the aldimine was not readily hydrolyzed (Equation 26).

Deuterated aldehydes have also been prepared by formation of the lithium salt of the 1,3-dithiapropene derivative of the desired aldehyde, 63. Hydrolysis with \( D_2O \) gives the \( C_1 \) labeled aldehyde, 65 (Equation 27). This route to phenyl-
\[
\begin{align*}
\text{CH}_3 \text{CH} = \text{CH}_2 \text{C} = \text{N} = \text{C} + \text{PhCH}_2\text{Li} \quad &\text{or} \quad \text{PhCH}_2\text{MgBr} \\
\rightarrow \quad &\text{PhCH}_2\text{C}^+\text{M}^- \\
\end{align*}
\]
acetaldehyde-1-d was attempted, but failed because the major site of proton abstraction by the butyl lithium reagent was at the benzylic position. Deuterium incorporation (determined by nmr) was apparently a statistical distribution, with 70% incorporation at the benzylic position and 30% incorporation at C₁.

The synthesis was then attempted by an expensive adaptation of the general procedure of Pfitzner and Moffatt for the oxidation of primary alcohols to aldehydes. The mild acid catalyzed oxidation of 2-phenylethanol-1,1-2d, 66, with dimethyl sulfoxide in the presence of dicyclohexylcarbo-diimide (DCC) was attempted (Equation 28). However, this

\[
\text{Ph-CH}_2\text{CD}_2\text{OH} + \text{O} \quad \text{DCC} \quad \text{O} \quad \text{C} \quad + \text{CH}_3\text{-S-CH}_3 \quad (28)
\]

procedure was not applicable in this case because of extensive elimination of the sulfonium intermediate, 67, to give styrene as the major product of the reaction (Equation 29). Once again, the benzylic nature of the substrate led to undesirable side reactions.
As stated earlier, the configurational assignment and estimated optical purity of S-(-)-35 was based upon the related active alcohol S-(-)-2-(p-methoxyphenyl)-ethanol-1-d reported by Belleau and Burba. To substantiate this assignment the reduction of phenylacetaldehyde, 19, with the isobornyloxymagnesium bromide-1-d, 37, was carried out according to the procedure of Streitwieser and Wolfe (Equation 30).

The product, 35, was carefully purified by preparative gas chromatography to obtain an analytically pure sample. The nmr spectrum indicated 98% deuterium incorporation at C1. No scrambling had occurred. The sample was racemic, a result totally unexpected in view of the work of Belleau and Burba.
Phenylacetaldehyde was also reduced with lithium aluminum deuteride modified with quinine (see following section). This chiral reducing agent produced only racemic 2-phenylethanol-1-d. Thus far, the only route to chiral 2-phenylethanol-1-d, 35, is the reduction of optically active styrene oxide with borane-d₃ in the presence of added boron trifluoride etherate.
Asymmetric Synthesis of Styrene Oxide

During the course of the investigation of the stereochemical behavior of R-(+)-styrene oxide toward organometallic reagents, an investigation of the asymmetric synthesis of optically active styrene oxide was carried out. As mentioned earlier, styrene oxide has been prepared most often by the classical sequence of Eliel and Delmonte\(^1\) in which chiral mandelic acid is reduced to the diol, tosylated at the primary hydroxyl function, and closed to the epoxide with base. Other epoxides, with the exception of propylene oxide, are not easily accessible by this route because the precursor chiral \(\alpha\)-hydroxyacids must be synthesized and resolved.

Asymmetric epoxidation of suitable precursors is a potentially more general preparative procedure for obtaining chiral epoxides, but this approach has not been widely used because of the low optical purities (generally < 5%) obtained with the chiral reagents examined to date.*

The general route chosen for study in this work is shown in Equation 31. This approach involves the asymmetric reduction of an aryl or alkyl chloromethyl ketone, 68, with a chiral reducing reagent. The intermediate chlorohydrin obtained is converted to the epoxide by treatment with base.

*See pp 2-5.
This route seemed attractive for study because of the availability and variety of the necessary substrates and reagents. The synthesis of α-chloro ketones can be accomplished by several synthetic procedures. Also a number of chiral carbinolamines and monosaccharide derivatives with which lithium aluminum hydride can be modified are commercially available, or can be synthesized from readily available chiral compounds.

Červinka and his coworkers prepared a number of modified hydride reagents from lithium aluminum hydride and selected alkaloids. Some results of reductions of acetophenone with these reagents are given in Table 6. The best reagent for acetophenone reduction was the lithium aluminum hydride reagent modified with one equivalent of quinine. With this reagent, represented by 62, acetophenone was reduced to (+)-methylphenylcarbinol (48% ee of the R-enantiomer). The fact that the carbinolamine adducts of lithium

\[ \text{R} = \text{aryl or alkyl} \]

\[ \text{chiral} \]

\[\begin{align*}
\text{O} & \quad \text{R} \quad \text{C} \quad \text{CH}_2\text{Cl} \\
\text{1) LiAlH}_4\text{OR} & \quad \rightarrow \quad \text{R} \quad \text{C} \quad \text{CH}_2\text{Cl} \\
\text{2) H}_2\text{O}^+ & \quad \rightarrow \quad \text{R} \quad \text{C} \quad \text{CH}_2\text{Cl} \\
\end{align*}\]

*This structure is reasonable, but it has not been rigorously proven to be correct.
Table 6.
Reduction of Acetophenone with Alkaloid Modified LiAlH$_4$

\[
\text{Ph-C-CH}_3 + \text{LiAlH}_3(\text{OR}^*) \rightarrow \text{HO-C} \rightleftharpoons \text{H} + \text{H} \rightleftharpoons \text{C} \rightleftharpoons \text{OH} + \text{R}^*\text{OH}
\]

\[
\text{R}^*\text{OH} \quad \text{Methylphenylcarbinol Obtained} \quad \% \text{ ee} \quad \text{Conf.}
\]

<table>
<thead>
<tr>
<th>R*OH</th>
<th>Methylphenylcarbinol Obtained</th>
<th>% ee</th>
<th>Conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-Quinine</td>
<td></td>
<td>48%</td>
<td>R</td>
</tr>
<tr>
<td>(+)-Cinchonine</td>
<td></td>
<td>18%</td>
<td>S</td>
</tr>
<tr>
<td>(-)-Ephedrine</td>
<td></td>
<td>13%</td>
<td>R</td>
</tr>
<tr>
<td>(-)-N-ethylephedrine</td>
<td></td>
<td>25%</td>
<td>R</td>
</tr>
<tr>
<td>(-)-Quinidine</td>
<td></td>
<td>23%</td>
<td>S</td>
</tr>
<tr>
<td>(-)-Cinchonidine</td>
<td></td>
<td>12%</td>
<td>R</td>
</tr>
</tbody>
</table>
aluminum hydride give asymmetric reduction products indicates that these adducts, unlike some carbinol complexes, do not disproportionate to achiral lithium aluminum hydride before reduction takes place.

Asymmetric reduction has also been accomplished with chiral monosaccharide complexes of lithium aluminum hydride. Landor and coworkers\textsuperscript{51} found that lithium aluminum hydride modified with the dihydroxymonosaccharide 3-0-benzyl-1,2-cyclohexyldiene-α-D-glucofuranose, 70, was very efficient in reducing acetophenone with a relatively high degree of asymmetric induction (33\% ee). The reagent when further modified with one equivalent of ethanol, 71, reduced acetophenone to methylphenylcarbinol that was 71\% optically pure.

Some representative data for reductions of methyl ketone substrates are given in Table 7. In every example studied by Landor, the singly modified reagent, 70, gives the product carbinol of the S configuration, whereas reductions with the doubly modified reagent, 71, gives products of the R configuration. Landor has advanced a transition state model to account for these results.\textsuperscript{51c} It is based upon examination of molecular models of the cyclic reducing reagent, and involves choosing a preferred conformation for the complex 70 (Equation 32a). It was claimed that examination of molecular models suggests in this conformation \( \text{H}_1 \) is less
Table 7.

Reduction of Methyl Ketones with Monosaccharide Modified LiAlH$_4$

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Reagent 70</th>
<th>% ee of product</th>
<th>Conf. of product</th>
<th>Reagent 71</th>
<th>% ee of product</th>
<th>Conf. of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i$-Bu</td>
<td>30</td>
<td>S</td>
<td>17</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t$-Bu</td>
<td>4</td>
<td>S</td>
<td>18</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>33</td>
<td>S</td>
<td>71</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Naphthyl</td>
<td>29</td>
<td>S</td>
<td>40</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Me_2C=CH$</td>
<td>30</td>
<td>S</td>
<td>31</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>--</td>
<td>-</td>
<td>45</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$-Bu</td>
<td>12</td>
<td>S</td>
<td>13</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neopentyl</td>
<td>19</td>
<td>S</td>
<td>4</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$-Hexyl</td>
<td>12</td>
<td>S</td>
<td>25</td>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
shielded than \( H_2 \), and should therefore be the more accessible hydride for reduction. However, inspection of models suggests to the present author that removal of \( H_1 \) by addition of one equivalent of ethanol does not alter the steric requirements of the reagent to the extent that preferential addition of the hydride should now occur from the opposite face of the carbonyl substrate (Equation 32b).

\[
\begin{align*}
\text{(32a)} & \\
\begin{array}{c}
\text{H} \\
\text{Ph}
\end{array} & \text{Ph} \\
\text{H} & \text{Me} \\
\text{H} & \text{O} \\
\text{C} & \text{Ph} \\
\text{HO} & \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{R-(+)-75}
\end{align*}
\]

\[
\begin{align*}
\text{(32b)} & \\
\begin{array}{c}
\text{H} \\
\text{Ph}
\end{array} & \text{Ph} \\
\text{H} & \text{Me} \\
\text{HO} & \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{S-(--)-75}
\end{align*}
\]
Although the data (Table 7) do show a high degree of regularity for the substrates studied thus far, the model proposed by Landor is highly speculative, albeit successful, particularly in view of the fact that the structure of the reagent has not been established.

Reduction of Phenacyl Chloride with LiAlH₄ Modified with 3-0-benzyl-1,2-cyclohexyldiene-α-D-glucofuranose.

As a starting point for this investigation the reduction of phenacyl chloride, 72, with lithium aluminum hydride modified according to the procedures of Cervinka and Landor appeared most promising. However, the reduction of 72 with 3-0-benzyl-1,2-cyclohexyldiene-α-D-glucofuranose, 70, (Equation 33) did not go to completion, and gave a complex mixture of products. Styrene oxide, 4, was the minor product

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_2\text{Cl} \\
\frac{(1) \ 70}{(2) + \text{H}_3\text{O}^-} & \quad \frac{(3) - \text{OH}}{72} + \text{H}^- \quad \text{CH}_2 \quad \text{PhCh(OH)CH}_3 \\
\text{Ph} & \\
\text{72} & \quad \frac{4}{25:75} \quad \text{75} \\
\text{+ sugar}
\end{align*}
\]

and the undesired 1-phenylethanol, 75, presumably formed by reduction of the carbonyl group and hydrogenolysis at the carbon-chlorine bond*, was the major product. The products

*The origin of this by-product is more fully discussed on p. 63.
of interest were not easily separable from the sugar derivative.

Besides giving a poor yield of the desired product, 4, the reagent is also unattractive because of difficulties encountered during its synthesis (Figure 11). The preparation of the dicyclohexylidene adduct of dextrose, 73, was readily accomplished. If the reaction was carried out with slow addition of the acid catalyst at 0°, decomposition of the sugar was diminished. The first difficulty arose with the benzylation procedure, (11b). A competing reaction was the formation of dibenzylether (Equation 34), which could

$$\text{PhCH}_2\text{Cl} + \text{NaOH} \rightarrow \text{PhCH}_2\text{OH} + \text{NaCl} \xrightarrow{\text{NaOH}} \text{PhCH}_2\text{O}^-\text{Na}^+ + \text{H}_2\text{O}$$

$$\text{NaCl} + \text{Ph-CH}_2\text{-O-CH}_2\text{-Ph} \leftarrow \text{PhCH}_2\text{Cl}$$

not be removed from the desired benzylated derivative, 74, and was carried along in the synthesis. The hydrolysis step, (11c), also presented a problem in that the hydrolysis was not 100% selective for the terminal ketal. Some tetra-ol was produced, as well as unhydrolyzed 74, and these undesired by-products could not be removed. The product mixture was isolated as a heavy viscous liquid.
Figure 11.

Synthesis of 3-O-benzyl-1,2-cyclohexylidene-α-D-glucofuranose

(11a) $\text{CHO}$

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{CH}_2\text{OH} & \\
\end{align*}
\]

Dextrose

(11b) $73 + \text{PhCH}_2\text{Cl} \xrightarrow{\text{NaOH}} 74$

(11c) $74 \xrightarrow{75\% \text{HOAc}} 70$
Taking these synthetic difficulties into consideration, along with the undesirable product distribution from the reduction, and the isolation problems, this particular monosaccharide modified lithium aluminum hydride reagent does not appear to be of great practical utility.

Reduction of Phenacyl Chloride with LiAlH₄ Modified With Quinine.

Phenylacyl chloride was reduced according to the procedure of Červinka⁵⁰ (Equation 35) for the asymmetric

\[
\ce{\text{O} \quad \text{PhCCH₂Cl} \xrightarrow{\text{(1) LiAlH₃OR*}} \text{H} \quad \begin{array}{c}
\text{CH}_₂ \\
\text{Ph}
\end{array} + \text{Ph} \quad \begin{array}{c}
\text{CH}_3 \\
\text{OH}
\end{array}}
\]

\[
\text{R = Quinine} \quad \text{S-(-)-4} \quad \text{R-(+)-75}
\]

reduction of acetophenone. The reaction was carried out under a variety of conditions. The data summarized in Table 8 show that the quinine modified lithium aluminum hydride reagent, 76, reduced phenacyl chloride with high asymmetric bias.

In experiment 8a, styrene oxide of 84% optical purity was obtained. Considering the fact that optically active styrene oxide when synthesized from optically pure mandelic acid by the classical procedure of Eliel and Delmonic¹ was
Table 8.

Reductions of Phenacyl Chloride with LiAlH₄
Singly Modified with Quinine

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>LiAlH₃OQ (mmol)</th>
<th>Conc.** (m)</th>
<th>% Yield</th>
<th>% ee</th>
<th>Conf.</th>
<th>% Yield</th>
<th>% ee</th>
<th>Conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>44</td>
<td>0.10</td>
<td>28</td>
<td>84</td>
<td>S</td>
<td>39</td>
<td>5</td>
<td>R</td>
</tr>
<tr>
<td>8b</td>
<td>264</td>
<td>0.15</td>
<td>28</td>
<td>74</td>
<td>S</td>
<td>40</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>8c</td>
<td>500</td>
<td>0.25</td>
<td>20</td>
<td>61</td>
<td>S</td>
<td>38</td>
<td>23</td>
<td>R</td>
</tr>
<tr>
<td>8d*</td>
<td>22</td>
<td>~0.05</td>
<td>4</td>
<td>--</td>
<td>-</td>
<td>87</td>
<td>19</td>
<td>R</td>
</tr>
</tbody>
</table>

* Inverse addition of 76 to phenacyl chloride in this experiment.

** As a suspension in ether.

*** The reaction mixture was worked up with KOH prior to glpc analysis per 8a. In 8b, 8c, and 8d, glpc analysis was carried out on product mixture obtained without base work up.
of essentially the same optical purity (approximately 85%) the degree of asymmetric induction observed is exceptional.

In the reduction of phenacyl chloride with lithium aluminum hydride modified with a molar equivalent of quinine, chiral 1-phenylethanol, 75, is produced. There are several ways in which the carbinol could be formed; a few of the more plausible are shown in Figure 12. If (a) were the exclusive pathway the optical purity of the methylphenylcarbinol by-product should be the same as that of the styrene oxide, since these products arise from a common intermediate chlorohydrin. Furthermore the configurations of the oxide and carbinol should be related since in neither case is there any bond breaking at the asymmetric center subsequent to the formation of the chlorohydrin. In fact, the configuration corresponds, but the optical purity is lower than that of the styrene oxide (Table 8).
Figure 12.
Mechanisms of Carbinol Formation

(a) \( \text{PhCCH}_2\text{Cl} \) reduction \( \rightarrow \) \( \text{Ph}_\text{C} \equiv \text{CH}_2\text{Cl} \) hydrogenolysis \( \rightarrow \) \( \text{Ph}_\text{C} \equiv \text{CH}_3 \) R-(+)-75

(b) \( \text{PhCCH}_2\text{Cl} \) hydrogenolysis \( \rightarrow \) \( \text{PhCCH}_3 \) reduction \( \rightarrow \) \( \text{Ph}_\text{C} \equiv \text{CH}_3 \) R-(+)-75

(c) \( \text{PhCCH}_2\text{Cl} \) (1) reduction \( \rightarrow \) \( \text{Ph} \equiv \text{C} \leftrightarrow \text{CH}_2 \) terminal hydride ring opening \( \rightarrow \) \( \text{Ph}_\text{C} \equiv \text{CH}_3 \) R-(+)-75

S-(−)-4
If (b) were the exclusive pathway the configuration and optical purity of the methylphenylcarbinol should correspond to that observed for the reduction of acetophenone with reagent 76 (Table 6, first entry). In fact, the configuration corresponds, but the optical purity ranges from about 10 to 50% of that obtained in the acetophenone reduction.

If (c) were the exclusive pathway the epoxide should have the R configuration and, as in case (a), its optical purity should be the same as that of the styrene oxide. In fact, the configuration is R, but the optical purity is much lower than that of the oxide.

Therefore, all of the routes to carbinol by-product outlined in Figure 12 rationalize the configuration observed, but none of them account for the low optical purity. A tentative explanation is that the methylphenylcarbinol undergoes partial racemization via an MPV reduction route involving the potassium salt during the ring closure step. Alternatively, the carbinol could be produced by a completely different chiral reagent, i.e., the lithium aluminum hydride-quinine-alkoxy adduct. However, a full understanding of this facet of the reaction must await the results of future experiments.
The singly modified lithium aluminum hydride-quinine reagent is easy to prepare and use. In a typical reaction a 0.1 molar suspension of lithium aluminum hydride in ether is prepared and a molar equivalent of anhydrous quinine is added. Phenacyl chloride dissolved in anhydrous ether is added, and the resulting suspension is stirred at reflux for several hours. The reaction is terminated by the slow addition of dilute hydrochloric acid, and the organic products are isolated as an ether solution (see experimental for details). The chlorohydrin is ring closed to styrene oxide with methanolic KOH. The oxide obtained after one distillation through a short path apparatus contained about 25-30% methylphenylcarbinol as an impurity. Fractional distillation through a good fractionating column can separate styrene oxide and methylphenylcarbinol, but in this work the oxide was purified by preparative glpc. Oxide purified in this way always contained from 8-12% phenylacetaldehyde formed by thermal rearrangement of the oxide.

The data in Table 8 suggest that the reagent concentration is a critical variable. Asymmetric induction appears to increase as the reagent concentration decreases. More data are necessary before a definitive conclusion on this matter can be reached.
The lithium aluminum hydride reagent, 76 modified with one equivalent of quinine has three active hydrogens (or incipient hydrides) remaining. To determine the effect of successively replacing these active hydrogens with an achiral alkoxy group, reductions were carried out with 76 and one or two equivalents of anhydrous ethanol (Table 9).

Phenacyl chloride was reduced on a forty-four millimole scale with reagent 76 in the presence of one equivalent of added ethanol, and treated with base to give the optically active styrene oxide (Equation 36) in 70% yield and 64% excess of the S-enantiomer.

\[
\text{(1) 76 + EtOH} \\
\text{(3) } \overset{+}{\text{H}_3\text{O}} \\
\text{(4) } \overset{\text{OH}}{\text{PhCH(OH)CH}_3} \\
\text{Ph'CH}_2\text{Cl} \rightarrow \text{C} = \text{CH} + \text{PhCH(OH)CH}_3 \quad (36)
\]

There was a marked effect of added ethanol on the product distribution. The addition of one equivalent of ethanol gives a reagent which is presumed to have structure 78. This reagent causes much less hydrogenolysis of the carbon-chlorine bond than was observed with reagent 76, and after ring closure, styrene oxide is the major product.
Table 9.

Lithium Aluminum Hydride Modified with Quinine and Absolute Ethanol*

<table>
<thead>
<tr>
<th>LiAlH₄ (mmol)</th>
<th>Quinine (mmol)</th>
<th>EtOH (mmol)</th>
<th>CH₂Cl₂ Oxide</th>
<th>Alcohol</th>
<th>Chlorohydrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 44</td>
<td>44</td>
<td>--</td>
<td>2</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>(b) 22</td>
<td>22</td>
<td>22</td>
<td>28</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>(c) 22</td>
<td>22</td>
<td>44</td>
<td>94</td>
<td>2</td>
<td>--</td>
</tr>
</tbody>
</table>

*Product analysis was by glpc; no products were isolated in pure form.
Modification of lithium aluminum hydride with one equivalent of quinine and two equivalents of ethanol gives a reagent presumed to have structure 79, with a single hydrogen remaining. Reagent 79 does not reduce phenacyl chloride to the chlorohydrin nor does it cause hydrogenolysis of the carbon-chlorine bond, and the starting material was recovered.

The reduction of phenacyl chloride with 78 makes the preparation of styrene oxide having a reasonably high optical purity a relatively simple one day operation; a considerable improvement over the stereoselective procedure in this respect. Also, the optically active oxide was recovered 90% pure (10% alcohol as the only impurity) by distillation at 0.3 mm on a short path distillation apparatus. With more sophisticated fractional distillation equipment styrene oxide and methylphenylcarbinol can be more efficiently separated.

Lithium aluminum hydride was also modified with two equivalents of quinine to determine the effect of having two chiral moieties present (Equation 37). Reduction of phenacyl
chloride with the doubly modified reducing agent, 77, did not change the product distribution, and had little effect on the degree of asymmetric synthesis observed.

In order to compare the quinine-ethanol-LAH reagent, 78, with the quinine-LAH reagent of Červinka, 78 was used to reduce acetophenone (Equation 38).

It was found that 78 reduced acetophenone to (+)-1-phenylethanol (49% ee of the R-enantiomer). This is in excellent agreement with the results reported by Červinka for the reduction of acetophenone with 76 which produced (+)-1-phenylethanol (48% ee of the R-enantiomer).
From the data obtained for reductions with the various modified reagents examined (76-79) it is evident that after the introduction of one chiral quinine modifier, the asymmetric induction characteristics of the reagent are not appreciably altered by introduction of a second chiral quinine or achiral alcohol modifier. However, a marked effect on the reduction specificity of the reagent is observed in that addition of a second equivalent of alcohol causes a change in product distribution to favor the formation of chlorohydrin.

Optically active styrene oxide was also prepared by reduction of phenacyl chloride with cinchonine-ethanol-LAH reagent, 81 (Equation 39). The product distribution was the same as with the analogous quinine-ethanol-LAH reagent 78, but a lower asymmetric bias is observed and the enantiomeric oxide is produced. Červinka observed similar behavior for acetophenone reductions with quinine and cinchonine-LAH reagents such as 76.
These data show that the stereochemistry at the carbinol carbon exerts a considerable amount of control over the stereoselectivity of the reduction. Cinchonine and quinine have opposite stereoformulas with respect to the secondary alcohol position and it is seen that reagents prepared from these alkaloids give enantiomeric reduction products. However, since the two reagents do not give the same degree of induction (which they should if only the configuration at the secondary alcohol is effective) the total chirality and/or structure of the reagents also plays a role in the asymmetric induction mechanism.

Reductions of Aldehydes with Modified LiAlD$_4$

To test the applicability of reagent (78) for the asymmetric reduction of aldehydes, the reagent was prepared from lithium aluminum deuteride, quinine and ethanol (1:1:1 molar ratios) and allowed to react with benzaldehyde and phenylacetaldehyde. The data obtained are summarized in Table 10.
Table 10.
Reduction of Aldehydes with Quinine/Ethanol Modified LiAlD₄

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>% Yield</th>
<th>Alcohol</th>
<th>Optical Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) PhCH</td>
<td>70%</td>
<td>S- (+)</td>
<td>22%</td>
</tr>
<tr>
<td>(b) PhCH₂CH</td>
<td>38%</td>
<td>----</td>
<td>racemic</td>
</tr>
</tbody>
</table>

The reduction of benzaldehyde produced a 70% yield of (+)-benzyl alcohol-1-d, 82, (22% ee of the S-enantiomer). Benzylic alcohol-1-d has been prepared via fermenting yeast reduction of benzaldehyde-1-d. The maximum rotation for the alcohol was calculated to be \([\alpha]_D^{24} +1.58^\circ\). The configuration of the alcohol has been assigned by Streitwieser. 47

Optically active benzyl alcohol-1-d has also been prepared by reduction of benzaldehyde-1-d with several chiral reagents (Table 11). 53, 54 The amounts of asymmetric induction range from low of 10.4% in the case of (-)-isobornyloxyaluminum dichloride to a maximum of 64.5% in the case of (-)-bornyloxymagnesium bromide.

The reduction of phenylacetaldehyde produced racemic 2-phenylethanol-1-d. This result was unexpected in view of the preceeding asymmetric reduction of benzaldehyde by the same reagent. Careful examination of the nmr spectrum showed
### Table 11.
Asymmetric Synthesis of Benzylalcohol-l-d

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Aldehyde</th>
<th>[(\alpha)]_D \text{ obs}</th>
<th>Optical Purity</th>
<th>Conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-Isobornyloxy-aluminum dichloride</td>
<td>PhCDO</td>
<td>-0.165</td>
<td>10.4</td>
<td>R</td>
</tr>
<tr>
<td>(-)-(\alpha)-d-Isobornyloxy-aluminum dichloride</td>
<td>PhCHO</td>
<td>+0.281</td>
<td>17.8</td>
<td>S</td>
</tr>
<tr>
<td>(-)-Bornyloxy-aluminum dichloride</td>
<td>PhCDO</td>
<td>+0.517</td>
<td>32.7</td>
<td>S</td>
</tr>
<tr>
<td>(-)-Isobornyloxy-magnesium bromide</td>
<td>PhCDO</td>
<td>-0.98</td>
<td>62.5</td>
<td>R</td>
</tr>
<tr>
<td>(-)-(\alpha)-d-Isobornyloxy-magnesium bromide</td>
<td>PhCHO</td>
<td>+1.007</td>
<td>64.1</td>
<td>S</td>
</tr>
<tr>
<td>(-)-Bornyloxy-magnesium bromide</td>
<td>PhCDO</td>
<td>-1.019</td>
<td>64.5</td>
<td>R</td>
</tr>
<tr>
<td>(+)-2-Methyl-1-butyl-magnesium chloride</td>
<td>PhCDO</td>
<td>+0.29</td>
<td>18.0</td>
<td>S</td>
</tr>
<tr>
<td>Di-3-pinanylborane-d_1</td>
<td>PhCHO*</td>
<td>-0.10</td>
<td>6.0</td>
<td>R</td>
</tr>
</tbody>
</table>

98+% deuterium incorporation at the primary carbon. In the absence of deuterium scrambling, it can only be concluded that the reduction of phenylacetaldehyde with reagent 78 (and also with isobornylloxymagnesium bromide-1-d) (see page 50) proceeds with no asymmetric bias. Thus far, in the experience of the present author, it has been possible to obtain chiral 2-phenylethanol-1-d only by reaction of chiral styrene oxide with \(\text{BD}_3/\text{BF}_3\cdot\text{Et}_2\text{O}\) (Equation 18). A reaction that remains to be carried out is the reduction of phenylacetaldehyde-1-d with actively fermenting yeast according to the procedure of Mosher.\(^{52}\)

The data obtained in this investigation have only touched the surface of a potentially fruitful area of research. The solvent effects on the asymmetric hydride sources examined should be investigated to determine if even higher degrees of asymmetric induction can be obtained. There are also many other chiral carbinolamines that should be examined. Also it should be determined if the reagents can be employed to prepare internal epoxides. The applicability of these reagents to other substrates such as azomethines should also be investigated. The above areas of research are just a few of those that can be envisaged for these effective asymmetric hydride sources.
EXPERIMENTAL

GENERAL

METHODS

Gas Liquid Partition Chromatography (glpc). All quantitative analyses were carried out using a Varian Model 90P gas chromatograph. The recorder was equipped with a Disc integrater. Analyses and preparative separations were carried out on the following columns:

Column A: 10' x 1/4" 20% Carbowax 20M on Chromosorb W, 60/80 mesh;

Column B: 10' x 1/4" 5% STAP on Chromosorb G, A/W, DMCS, 60/80 mesh;

Column C: 3' x 1/8" 20% Silicone GE XE-60 on Chromosorb W, A/W, DMCS, 60/80 mesh;

Column D: 5' x 1/4" 20% Silicone SE-30 on Chromosorb W, 60/80 mesh.

Retention times (R.T.) are reported relative to the time of injection.

Infrared Absorption Spectra (ir). All ir spectra were obtained using a Perkin-Elmer Model 337 grating spectrophotometer. The spectra of liquids were obtained as films between salt plates. The spectra of solids were obtained as KBr pellets.
Mass Spectra (ms). All mass spectra were taken on a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

Nuclear Magnetic Resonance Spectra (nmr). All nmr spectra were determined using a Varian Model A-60 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to tetramethyldisilane.

Optical Rotation Data. Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005°, equipped with a mercury vapor light source and filtered to give readings at 578, 546, 435, 405, and 365 nm. Rotations are reported at the sodium-D line (589 nm), and were obtained from the values at 578 and 546 nm using the Drude equation.

\[ \alpha_D = \left[ \frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} \right] \frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} + 1.3727 \]

Melting Points. All melting points were taken on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected.

Compounds. Unless otherwise noted, compounds were purchased from commercial sources, and were used as received.

Dry Solvents. Diethyl ether (Fisher Anhydrous Ether) was dried over sodium wire. Tetrahydrofuran (THF) was re-
fluxed over and distilled from calcium hydride. Benzene was
dried by distillation (80°). Water was removed as an azeo-
tropic forerun. Pyridine was dried by refluxing over, and
distillation from, potassium hydroxide pellets. The distilled
pyridine was stored over 4-A molecular sieves.

Reactions. All reactions requiring anhydrous condi-
tions were run in a dry nitrogen atmosphere in oven or flame
dried glassware.

Preparation of Grignard and Dialkylmagnesium Reagents.
The Grignard reagents were prepared in the usual manner from
the corresponding alkyl halide and doubly sublimed magnesium
turnings. The dialkylmagnesium reagents were prepared by
the addition of anhydrous dioxane to the ethereal Grignard
reagent according to the method of Whitesides and Roberts.25
The dialkylmagnesium reagents were prepared free of MgX₂·dioxane
precipitate by filtration under dry N₂, and were stored under
N₂ at 0°. In the case of di-t-butylmagnesium, the precipitate
could not be filtered, and this reagent was prepared free of
precipitate by centrifugation. The Grignard reagents and di-
alkylmagnesium reagents were titrated according to the proce-
dure described by Watson and Eastham.36

R-(-)-2-Phenyl-1,2-Ethanediol (2). R-(-)-mandelic
acid (100 g, 0.66 m, [α]_
D
^{26}=-149.3 (c 3.65, H₂O) in dry
ether/THF (500 ml, 4:1), was added to a suspension of LiAlH₄
(38 g, 1 m) in dry ether (1500 ml) over a 5 hour period.
After addition was completed the reaction mixture was heated at reflux for 4 hours. The solution was then hydrolyzed with 500 ml of 10% $H_2SO_4$. The ether layer was decanted and combined with 5 x 500 ml ether extracts of the aqueous phase, concentrated to 800 ml, washed with saturated NaHCO$_3$, and dried (MgSO$_4$). Concentration gave 86 g of crude product. The product was recrystallized from acetone/hexane (1:3) to give 63 g (69%) of diol 2: mp 65.5-65.5°, $\left[\alpha\right]_{D}^{25} -40.5$ (c 2.0, 95% ethanol), 99.8% ee based on $\left[\alpha\right]_{D}^{25}$ (max) -40.6.$^\circ $  

R-(-)-1-Brosyloxy-2-Phenylethanediol (3). A solution of p-bromobenzenesulfonyl chloride (192 g, 0.75 m) in dry pyridine (400 ml) was added over a four hour period to a solution of R-(-)-2-phenyl-1,2-ethanediol, 2 (103.7 g, 0.75 m) in dry ether (1 liter) and dry pyridine (100 ml). The temperature was maintained below -5° during the addition. After addition was completed the solution was stirred an additional 14 hours, the temperature having risen slowly to 16°. The solution was poured into 1500 g of ice water containing 400 ml of concentrated HCl. The ether layer was decanted and combined with four 500 ml ether extracts of the aqueous phase. The combined ether solution was washed successively with 10% HCl and with water. The ethereal extract was dried (MgSO$_4$) and concentrated to give 250 g of a viscous oil. The oil was dissolved in benzene (400 ml). Petroleum
ether (30-60°) was added until the solution became cloudy. The solution became clear when it was heated. The brosylate crystallized when the solution was cooled yielding 138 g of product. The mother liquors were concentrated and second and third crops of crystals were collected. A total of 193 g (72%) of brosylate, 3, was obtained.

R-(+)-Styrene Oxide (4). A solution of potassium hydroxide (10 g, 0.178 m) in dry methanol (100 ml) was added slowly over a two hour period to a stirred solution of R-(−)-1-brosyloxy-2-phenyl-1,2-ethanediol, 3, (42.7 g, 0.132 m) in dry ether (400 ml). The reaction temperature was maintained at -16° during the addition. The solution was stirred an additional four hours at -16° and then four hours at room temperature. After cold water (400 ml) was added the ether layer was separated and combined with three 200 ml ether extracts of the aqueous phase. The combined ethereal solutions were washed with cold water, dried (MgSO₄) and concentrated to yield 15 ml of an oil. The oil was distilled at reduced pressure to give 13.5 g (80%) of R-(+)-styrene oxide, 4: bp 30-36°/0.2 mm, [α]D²⁵ +28.6, neat (84%) ee²⁵. The nmr spectrum (no. 8225) was identical to that obtained from an authentic sample of racemic styrene oxide.

Reaction of Diisopropylmagnesium with R-(+)-Styrene Oxide-4 in the Presence of MgBr₂-Dioxane.²⁵ Diisopropyl-
magnesium was prepared by the addition of dry dioxane (2.19 g, 25 mmol) to a stirred solution of isopropylmagnesium bromide (29 ml of a 0.86 molar solution in ether) over a 1 1/2 hr period. The precipitated magnesium bromide was not filtered. The suspension was stirred 8 hrs at room temperature and was then allowed to stand for 16 hrs. R-(+) -4 (2.0 g, 16.6 mmol, [\(\alpha\])\(_D\)\(^{25}\) +28.6°, neat 84% ee) in dry ether (10 ml) was added to the stirred diisopropylmagnesium-MgBr\(_2\)·dioxinate mixture. The reaction mixture was heated at reflux for 2 hrs. Saturated, aqueous NH\(_4\)Cl was added until the solid materials adhered to the side of the flask. The ether layer was decanted, dried (MgSO\(_4\)) and concentrated to give 2.72 g of crude product which was distilled to give 1.72 g of product, bp 68-75° (0.3 mm). A glpc analysis (Column A, 200°, He flow rate 160 ml/min) showed the product to be a mixture of 65% 3-methyl-2-phenyl-1-butanol (R.T. = 20.4°), 30% 3-methyl-1-phenyl-2-butanol (R.T. = 15.4°) and 5% unidentified material. Purification by preparative scale glpc gave 99+% pure samples of (+)-3-methyl-2-phenyl-1-butanol: [\(\alpha\])\(_D\)\(^{26}\) +6.15°, neat (53% ee of the S isomer based upon [\(\alpha\])\(_D\)\(^{25}\) +11.6)\(^{56}\), nmr (no. 8310): 7.24 (s, 5H), 3.78 (d, 2H, J = 6 Hz), 2.48 (q, 1H, J = Hz), 1.90 (m, 1H), 0.98 (d, 3H, J = 6 Hz), and 0.69 (d, 3H, J = 6 Hz); and racemic 3-methyl-1-phenyl-2-butanol. The nmr spectrum of the racemic 3-methyl-2-phenyl-
1-butanol (no. 8309) was identical to that obtained from an authentic sample prepared from phenylacetaldehyde and isopropylmagnesium bromide (nmr no. 8275).

Reaction of R-(+)-Styrene Oxide-4 with Diisobutylmagnesium in the Presence of MgBr₂·Dioxane. Diisobutylmagnesium was prepared by the addition of dry dioxane (2.92 g, 33.2 mmol) to isobutylmagnesium bromide (50 ml of a 0.65 m ether solution, 33.2 mmol) over 10 minutes with stirring. The suspension was stirred 16 hours at room temperature. R-(+)-4 (2.0 g, 16.6 mmol, 84% ee) in dry ether (20 ml of solution) was added at a rate that gave a gentle reflux. After addition was complete, the solution was stirred 2 hours at room temperature, and then 1/2 hour at reflux. Saturated aqueous NH₄Cl solution (~15 ml) was added to obtain a granular precipitate. The ethereal material was decanted and combined with a 50 ml ether extract of the precipitate, washed with cold water and dried (MgSO₄). A glpc analysis (Column A, 200°, He flow rate 150 ml/min) showed the product to be a mixture of 66% 3,3-dimethyl-2-phenyl-1-butanol (R.T. = 19.8 min), 29% 4-methyl-1-phenyl-2-pentanol (R.T. = 15.3 min) and 5% 2-phenylethanol (R.T. = 12.0 min). Purification by preparative scale glpc gave 99+% pure samples of (+)-3,3-dimethyl-2-phenyl-1-butanol: α_D +2.38, neat, [α]_D^{25} +4.25 (c 4.08, CHCl₃), nmr (no. 8330): 7.20 (s, 5H), 3.64 (d, 2H,
J = 6 Hz), 2.84 (m, 1H), 1.52 (m, 4H), 0.91 (d, 6H), mass spectrum (70 eV) m/e M+ 178; racemic 4-methyl-1-phenyl-2-pentanol: nmr (no. 8331): 7.24 (s, 5H), 3.81 (m, 1H), 2.67 (d of d, 2H), 1.84-1.20 (m, 4H), 0.97 (d, 3H, J = 6 Hz) and 0.95 (d, 3H, J = 6 Hz); and racemic 2-phenylethanol: nmr (no. 8332): 7.25 (s, 5H), 3.84 (t, 2H, J = 5 Hz), 2.86 (t, 2H, J = 5 Hz) and 1.62 (s, 1H). The nmr spectrum was identical to that of an authentic sample.

Reaction R-(+)-Styrene Oxide (4) with Di-t-butylmagnesium in the Presence of MgCl2·Dioxane. Di-t-butylmagnesium was prepared by the addition of dry dioxane (2.92 g, 33.2 mmol) to t-butylmagnesium chloride (79 ml of a 0.42 m ether solution, 33.2 mmol) and the resulting suspension was stirred 1/2 hour at room temperature. R-(+)-4 (2.0 g, 16.6 mmol, 84% ee) in dry ether (10 ml of solution) was added. The mixture was stirred 6 hrs at room temperature, hydrolyzed with saturated, aqueous NH4Cl solution, and worked up as before to give 2.77 g of crude product as an oil. A glpc analysis (Column A, 220°, He flow rate 200 ml/min) showed the product to be 79% 2-phenylethanol (R.T. = 5.7 min), 18% 3,3-dimethyl-2-phenyl-1-butanol (R.T. = 8.6 min) and 3% 3,3-dimethyl-2-phenyl-1-butanol (R.T. = 12.6 min). The last two products could not be isolated in sufficient quantities for rotation data to be obtained.
Reaction of R-(+)-Styrene Oxide (4) with Diethylmagnesium. R-(+)-4 (1.0 g, 8.3 mmol, 84% ee) in dry ether (15 ml of solution) was added to diethylmagnesium (13.3 ml of a 1.25 m solution in ether, 16.6 mmol). The solution was stirred at room temperature for 7 hrs, and was then hydrolyzed with saturated aqueous NH₄Cl solution. The ether layer was decanted, combined with a 50 ml ether extraction of the solid precipitate, dried (MgSO₄), and concentrated to give 1.04 g of an oil. A glpc analysis (Column A, 195°, He flow rate 150 ml/min) showed the product to be a mixture of 95% 2-phenyl-1-butanol (R.T. = 12 min) and 5% unidentified material. A small amount (~16%) of unreacted oxide was also present. The 2-phenyl-1-butanol was purified by preparative scale glpc (Column A) 99+% pure: [α]D²⁶ +10.0, neat, nmr (no. 8368): 7.18 (s, 5H), 3.60 (d, 2H, J = 6 Hz), 2.52 (m, 1H), 2.18 (s, 1H), 1.58 (m, 2H), and 0.80 (t, 3H, J = 6 Hz).

Reaction of R-(+)-Styrene Oxide (4) with Di-t-butylmagnesium. R-(+)-4 (2.0 g, 16.6 mmol, 89% ee) in dry ether (10 ml of solution) was added to di-t-butylmagnesium (98 ml of a 0.17 m ether solution, 16.6 mmol). The reaction was heated at reflux for 4 hrs, and hydrolyzed with saturated, aqueous NH₄Cl solution. The ether layer was decanted, combined with a 50 ml ether extraction of the precipitate, dried (MgSO₄), and concentrated to give 2.2 g of an oil.
A glpc analysis (Column C) showed the product to be a mixture of compounds, the major component (~70%) being 3,3-dimethyl-2-phenyl-1-butanol. The alcohol was obtained 98% pure by column chromatography on neutral silica (40 g) using 10% benzene in petroleum ether (30-60°) as eluent: (-)-3,3-dimethyl-2-phenyl-1-butanol, [α]_{D}^{26} -0.14 (c 0.48, CHCl₃), 5% ee of the S isomer based on [α]_{D}^{26} max of 16.9°; NMR (no. 9264): 7.09 (s, 5H), 3.75 (d, 2H, J = 6 Hz), 2.46 (t, 1H, J = 6 Hz) and 0.80 (s, 9H).

Reaction of R-(+)-Styrene Oxide (4) with Diethylmagnesium in the Presence of MgCl₂-Dioxane. Diethylmagnesium was prepared by the addition of dry dioxane (1.1 g, 12.5 mmol) to an ether solution of ethylmagnesium chloride (60 ml of a 0.48 m solution, 25 mmol). The resulting suspension was stirred for 1/2 hr at room temperature. R-(+)-4 (1.5 g, 12.5 mmol, 89% ee) was added slowly. The solution was stirred at room temperature for 45 min, and then was heated at reflux for 1 hr. The solution was hydrolyzed with saturated NH₄Cl solution, the ether layer decanted, dried (MgSO₄), and concentrated to give 1.6 g of product. A glpc analysis (Column D, 128°, He flow rate 60 ml/min) showed the product to be 97% 2-phenyl-1-butanol (R.T. = 21.2 min) and 3% 1-phenyl-2-butanol (R.T. = 18.6 min). A 99+% pure sample of (+)-2-phenyl-1-butanol was obtained by preparative glpc: [α]_{D}^{26}
$+11.6^\circ$, neat (68% ee based on $\alpha_D$ max of $16.9^\circ$)$^{57}$, nmr (no. 9710): 7.27 (s, 5H), 3.75 (d, 2H, $J = 7$ Hz), 2.66 (m, 1H), 1.67 (m, 2H), 1.68 (s, 1H) and 0.83 (t, 3H, $J = 7$ Hz).

**Reaction of R-$(+)$-Styrene Oxide (4) with Diethylmagnesium in the Presence of MgI$_2$·Dioxane.** The reaction was carried out exactly as described for the reaction of R-$(+)$-4 with Et$_2$Mg in the presence of MgCl$_2$·dioxane, to give 1.14 g of product. A glpc analysis (Column D, same conditions) showed the product to be a mixture of 60% 2-phenyl-1-butanol and 40% 1-phenyl-3-butanol. A 99+% pure sample of $(+)$-2-phenyl-1-butanol was obtained by preparative glpc: $[\alpha]_D^{26}$ $+10.70^\circ$ ($c$ 0.0254, ethanol), 17% ee of the S isomer based on $[\alpha]_D^{25}$ max $51.6^\circ$ ($c$ 3.98, ethanol)$^{57}$. The nmr (no. 9711) was identical to that of an authentic sample.

**Reaction of R-$(+)$-Styrene Oxide (4) with BD$_3$ Generated in situ in THF.** Deuteroborane was prepared by the addition of BF$_3$·Et$_2$O (4.25 g, 30.0 mmol) in dry THF (10 ml) to lithium aluminum deuteride (1.05 g, 25 mmol) in dry THF (40 ml). The resulting suspension was stirred 1/2 hour at room temperature and then cooled to $0^\circ$. R-$(+)$-4 (2.0 g, 16.5 mmol, 90% ee) in dry THF (20 ml of solution) was added slowly, and the reaction mixture was stirred 1 hr at $0^\circ$ and an additional 4 hrs at room temperature. The reaction was hydrolyzed by the slow addition of water (5 ml), and saturated, aqueous
NaCl solution was added (100 ml). The organic phase was separated, combined with three ether extractions (50 ml) of the aqueous phase, dried (MgSO₄), and concentrated to give 2.29 g of product. Methanol was added (5 ml) and the solution was distilled giving 1.32 g of product, bp 55-65° (0.4 mm). A glpc analysis (Column A, 150°, He flow rate of 30 ml/min) showed the product to be a mixture of 64% 1-phenylethanol (R.T. = 12.5 min) and 2-phenylethanol (R.T. = 18.4 min). The two components were isolated 99+% pure by preparative scale glpc to give: S-(-)-1-phenylethanol-1-d, [α]D²⁵⁻38.3°, neat (89% ee based on [α]D²⁵ max of 43.7°)⁵⁸, nmr (no. 9745): 6.94 (s, 5H), 4.64 (d, 1H, J = 3 Hz), 4.28 (t of d, 1H, J = 3 Hz and J = 6.5 Hz) and 1.01 (d, 2H, J = 6.5 Hz); mass spectrum: 99% d₁, and S-(-)-2-phenylethanol-2-d, [α]D²⁵⁻1.22°, neat, (rotation uncorrected for d₀), nmr (no. 9749): 6.59 (s, 5H), 4.08 (s, 1H), 3.12 (d, 2H, J = 7.5 Hz) and 2.15 (t, 1H, J = 7.5 Hz), mass spectrum: 92% d₁.

Reaction of R-(+)-Styrene Oxide (4) with BD₃/BF₃·Et₂O. Borane-d₃ was prepared according to the procedure of Brown and Zweifel.⁵⁹ Boron trifluoride etherate (7.09 g, 50 mmol) was added to a suspension of LiAlD₄ (1.05 g, 25 mmol) in dry ether (50 ml). With a stream of dry N₂ the borane-d₃ was swept into a second flask containing dry THF (65 ml). BF₃·Et₂O (3.17 g, 20 mmol) was added to the BD₃/THF solution,
and the solution was cooled to 0°. R-(+)-4 (2.4 g, 20 mmol; 78% ee) in dry ether (10 ml of solution) was added slowly. The solution was stirred at 0° for 1/2 hr and then an additional hour at room temperature. The reaction mixture was hydrolyzed by the slow addition of water (5 ml). Hydrochloric acid (10 ml, 10%) was added and the solution was stirred for 15 min at room temperature. The solution was treated with saturated NaCl solution (50 ml), the organic layer was separated and combined with three 50 ml ether extractions of the aqueous phase, washed with saturated NaCl, saturated NaCHO₂, ether and dried (MgSO₄). Concentration gave 2.58 g of product. A glpc analysis (Column A, 150°, He flow 30 ml/min) showed the product to be ~95% 2-phenylethanol. Distillation gave 1.03 g (bp 65-68°/0.3 mm) of 2-phenylethanol-1-d: [α]_

D

25

^D

-0.35° neat, nmr (no. 9802): 6.78 (s, 5H), 4.24 (s, 1H), 3.29 (t, 1H, J = 7 Hz) and 2.35 (d, 2H, J = 7 Hz). The pot residue (1.5 g) was also 2-phenylethanol.

Preparation of R-(+)-Styrene Oxide-2,2-d₂. The labeled epoxide was prepared from R-(−)-mandelic acid (25.8 g, 0.17 m) in the same manner as the perhydroxide but using LiAlD₄. A total of 3.0 g (15%) of R-(+)-4-2,2-d₂, bp 40° (0.3 mm) was obtained: [α]_

D

25

[^D] +24.1° neat (71% ee), nmr (no. 10682): 6.92 (s, 5H) and 3.42 (s, 1H).
Reaction of R-(+)-Styrene Oxide-2,2-d$_2$ with BD$_3$/BF$_3$·Et$_2$O. The reaction was carried out on a 25 mmol scale exactly as in the case of the perhydrooxide to give 1.0 g of product. A glpc analysis (Column A, 180°, flow rate 60 ml/min) showed the product to be a mixture of 85% 2-phenylethanol (R.T. = 5.3 min), 3% 1-phenylethanol (R.T. = 7.1 min) and 13% unreacted oxide (R.T. = 5.3 min). The major product 2-phenylethanol-1,1,2-d$_3$ was obtained 98+% pure by preparative glpc (2% 1-phenylethanol impurity): racemic, nmr (no. 10856): 7.17 (s, 5H), 3.10 (s, 1H), and 2.70 (s, 1H).

Attempted Preparation of Phenylacetaldehyde-1-d.

(1) The procedure of Seebach, Erickson and Singy was used. Dry HCl was bubbled through a solution of phenylacetaldehyde (12.0 g, 0.10 mol) and 1,3-dithiaproppane (14.2 g, 0.12 mol) in chloroform (200 ml) until the solution was saturated (~5 min). The exothermic reaction was moderated by external cooling with an ice bath. The solution was allowed to stand 1/2 hr, and was successively washed with water, 10% NaOH, and water again, before it was suction filtered through anhydrous Na$_2$SO$_3$ and concentrated to give 13.0 g of clear oil. The nmr spectrum (no. 9805) showed: 7.23 (s, 5H), 4.18 (t, 1H, J = 7 Hz), 2.99 (d, 2H, J = 7 Hz), 2.74 (t, 4H, J = 7 Hz) and 1.90 (m, 2H), and is consistent with the desired product.
The thioacetal was used without further purification.

The 1,3-dithia acetal (13.0 g, 62 mmol) in dry THF (150 ml) was allowed to react with n-butyl lithium (75 mmol) at -60°C. D$_2$O (10 ml, 99.9% d$_2$) was added, and the reaction mixture was allowed to warm to room temperature, then concentrated HCl (5 ml) was added. The solution was concentrated to 20 ml and the resulting residue was extracted with CH$_2$Cl$_2$/pentane (50:50), washed with NaHCO$_3$, saturated NaCl and dried (K$_2$CO$_3$). Filtration and concentration yielded 11.0 g (85%) of product. The nmr spectrum (no. 9810) indicated 30% deuterium incorporation at the C$_1$ position, and 70% deuterium incorporation at the benzylic position. The product was recycled, and showed no appreciable gain in deuterium incorporation at the C$_1$ position.

(2) Application of the method of Walborsky, Morrison and Niznik via the addition of phenylmagnesium bromide to 1,1,4,4-tetramethylbutylisocyanide followed by D$_2$O addition gave the imine addition product in only 25% yield. The nmr spectrum (no. 10860) showed only 50% dueterium incorporation at the C$_1$ position.

(3) A variation of the method of Walborsky and Niznik which involves the addition of phenyllithium to the isocyanide was not successful. Benzyllithium could not be generated successfully according to the procedure of
Gilman and McNich, and a nearly quantitative recovery of benzyl methyl ether was realized.

**Preparation of 1,2:5,6-di-O-Cyclohexylidene-α-D-Glucofuranose.** Concentrated $H_2SO_4$ (6.5 ml) was added slowly with stirring to a solution of D-glucose (45 g, 0.25 mole) in cyclohexane (100 ml, 1 mole) at 0°. The solution was stirred 4 hrs at 0° during which time it solidified. Heptane (500 ml) was added, and the reaction mixture was heated until the solid material dissolved. The hot solution was filtered, allowed to cool, and refrigerated. The product was allowed to crystallize overnight. It was filtered and recrystallized from n-heptane (20 ml/g) to give 52 g (61%) of product furanose: mp 131-133°, $[\alpha]_D^{26}$ -2.79° (c 18.05, ethanol).

**Preparation of 3-O-Benzyl-1,2:5,6-di-O-Cyclohexylidene-α-D-Glucofuranose.** Potassium hydroxide (30 g, 0.54 mole) was added with stirring to a suspension of 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (12.8 g, 37 mmol) in benzyl chloride (40 g, 0.317 mole). The mixture was heated at 150° for four hrs. After cooling, water (300 ml) was added and the aqueous material was extracted with CHCl$_3$ (300 ml). The organic material was washed with saturated NaCl solution and dried (MgSO$_4$). The solvent and excess benzyl chloride were removed by distillation at reduced pressure.
(0.2 mm) to leave 20 ml of a clear yellow viscous oil. The nmr spectrum (no. 10525) indicated a mixture of desired product and dibenzyl ether (70:30). This material was carried on to the hydrolysis step without further purification.

**Preparation of 3-O-Benzyl-1,2-0-Cyclohexylidene-α-D-Glucofuranose.**

3-O-Benzyl-1,2:5,6-di-0-cyclohexylidene-α-D-glucofuranose (~20 g) was dissolved in 75% acetic acid (80 ml) and heated with stirring at 65° for 2 hrs. The excess acid was removed at reduced pressure. The resulting oil was dissolved in CHCl₃, washed with dilute NaHCO₃, water, and dried CaCl₂. Filtration and concentration gave 12.0 g of a yellow oil. The nmr spectrum (no. 10274) indicated that the product was a mixture of the desired product and dibenzyl ether (70:30).

**Reaction of Phenacyl Chloride with LiAlH₄ Modified with 3-O-Benzyl-1,2,0-Cyclohexylidene-α-D-Glucofuranose.**

The reduction was carried out exactly as described by Landor for the reduction of acetophenone, to yield, after treatment with base, 5 g of a viscous oil. A glpc analysis (Column A, 180°, flow rate 60 ml/min) indicated a complex product mixture, from which it was not feasible to separate the desired products.
Reaction of Phenacyl Chloride with LiAlH₄ Modified with Quinine. (-)-Quinine (14.2 g, 44 mmol) in dry ether (50 ml) was added to a suspension of LiAlH₄ (1.68 g, 44 mmol) in dry ether (50 ml). The suspension was stirred 30 mins and then heated at reflux. Phenacyl chloride (6.20 g, 40 mmol) dissolved in dry ether (10 ml of solution) was added over 10 mins. The reaction mixture was maintained at reflux for 4 hrs, allowed to cool, hydrolyzed with water (15 ml), treated with 10% HCl (40 ml), and the ether layer separated and combined with three 50 ml ether extractions of the organic phase. The ether solution was cooled to 0°, and methanolic KOH (1.7 g, 30 mmol in 10 ml) was added. The solution was allowed to stir 1 hr at room temperature, water (100 ml) was added, the ether layer was separated and combined with three 50 ml ether extractions of the aqueous phase. The combined ethereal material was washed with 10% HCl, NaHCO₃, and dried (MgSO₄). Concentration gave 3.60 g of product. A glpc analysis (Column A, 175°, He flow rate 40 ml/min) showed the product to be 62% 1-phenylethanol (R.T. = 5.2 min) and 38% styrene oxide (R.T. = 2.1 min). The product was distilled to give 3.0 g (bp 33-37°/0.1 mm) of clear colorless liquid, which was a 60:40 mixture of alcohol and oxide. The products were isolated by preparative glpc to give S-(-)-styrene oxide (12% phenylacetaldehyde by nmr): [α]₂⁵°D = -25.2° neat
(84% ee), nmr (no. 10098), and R-(+)-1-phenylethanol (99+% pure glpc): $[\alpha]_D^{25} +1.97^\circ$ neat (4.5% ee), nmr (no. 10099). The nmr spectra of the products were identical to those of authentic samples.

**Effect of Added Phenylacetaldehyde on the Rotation of Optically Active Styrene Oxide.** To determine the effect of phenylacetaldehyde impurity on the rotation of the optically active oxide samples obtained by preparative glpc, a sample of R-(+)-4 was prepared by preparative glpc. The sample which exhibited $[\alpha]_D^{26} +8.6^\circ$ neat was found to contain 12.5% phenylacetaldehyde from analysis of the nmr spectrum (no. 10258). The corrected rotation of the sample would be $[\alpha]_D^{26} +9.8^\circ$ which corresponds to an optical purity of 29.4%. This sample was then diluted with a few drops of phenylacetaldehyde. The new sample exhibited a rotation of $[\alpha]_D^{26} +7.22^\circ$ neat. An nmr spectrum (no. 10260) taken of this sample indicated 24.5% phenylacetaldehyde. The adjusted rotation would then be $[\alpha]_D^{26} +9.6^\circ$ which corresponds to an optical purity of 29.1%. The presence of phenylacetaldehyde has little effect on the observed rotation of optically active styrene oxide. In the preceding experimental procedure, and all following, the $[\alpha]_D$ reported are calculated from $\alpha_D$ observed. The % enantiomeric excess has been corrected for product purity as established by nmr or glpc.
Large Scale Reduction of Phenacyl Chloride with LAH-Quinine. Quinine (100 g, 0.264 m) was added to a suspension of LiAlH$_4$ (10 g, 0.264 mol) in dry ether (1500 ml). The suspension was maintained at reflux for 1 hr and phenacyl chloride (32 g, 0.264 mol) in dry ether (200 ml of solution) was added over a two hr period. The reaction was maintained at reflux for 4 hrs, and worked up as before to give 22.1 g of product. A glpc analysis showed the product to be 42% styrene oxide and 58% 1-phenylethanol. Preparative glpc gave S-(-)-styrene oxide (9% phenylacetaldehyde by nmr): $[\alpha]_D^{25} -17.1^\circ$ neat (74% ee). The nmr spectrum (no. 10155) was identical to that of an authentic sample.

Repeated Large Scale Reduction of Phenacyl Chloride with LAH-Quinine. The reaction was carried out as described above on a 0.5 scale (0.25 molar suspension in ether) to yield 45.0 g of product. A glpc analysis indicated the product to be a 25:75 mixture of oxide and alcohol. The products were distilled at reduced pressure through a 10 cm Vigreaux column. Preparative glpc gave S-(-)-styrene oxide (30% phenylacetaldehyde by nmr): $[\alpha]_D^{26} -14.7^\circ$ neat (61% ee), nmr spectrum (no. 11124) and R-(+)-1-phenylethanol (99+% pure): $[\alpha]_D^{24} +10.0^\circ$ neat (23% ee).
Reaction of Phenacyl Chloride with LAH·Quinine: Inverse Addition. Quinine (9.95 g, 30 mmol) was added to a suspension of LiAlH₄ (0.84 g, 22 mmol) in dry ether (200 ml). The solution was heated at reflux for 1 hr and then allowed to cool to room temperature. The suspension was pumped with dry N₂ into a second flask containing phenacyl chloride (3.1 g, 22 mmol) in dry ether (50 ml of solution). Additional dry ether (200 ml) was added to the LAH·quinine flask to flush the remaining LAH·quinine into the reaction flask. Work up in the usual manner gave 2.4 g of product. A glpc analysis indicated the product to be a mixture of 96% 1-phenylethanol and 4% styrene oxide. The nmr (no. 10213) of the alcohol was identical to that from an authentic sample. Rotation data was obtained on the unpurified product mixture. R-(+)
1-phenylethanol: [α]_{D}^{25} +7.95° neat (18.5% ee, minimum value).
Reaction of Phenacyl Chloride with LiAlH₄ Modified with Quinine and One Equivalent of Ethanol. Quinine (11 mmol) was added to a suspension of LiAlH₄ (11 mmol) in dry ether (100 ml). The resulting suspension was heated at reflux for 1/2 hr and allowed to cool to room temperature. Anhydrous ethanol (11 mmol) in dry ether (10 ml of solution) was added, and the resulting suspension was stirred 1 hr at reflux. Phenacyl chloride (11 mmol) in dry ether (10 ml of solution) was added and the reaction was heated at reflux for 4 hrs. Work up in the usual manner, omitting treatment with methanolic KOH, gave 1.0 g of product. A glpc analysis (Column A, 205°, He flow rate 20 ml/min) showed the product to be a mixture of 9% styrene oxide (R.T. = 2.6 min), 47% 1-phenylethanol (R.T. = 3.3 min), 28% phenacyl chloride (R.T. = 7.6 min) and 59% 2-chloro-1-phenylethanol (R.T. = 9.8 min). The products were not isolated, but identified by comparative glpc retention times.

Reaction of Phenacyl Chloride with LiAlH₄ Modified with Quinine and Two Equivalents of Ethanol. The reaction was carried out exactly as described above on an 11 mmol scale (Quinine and LAH). In the reaction 22 mmol of anhydrous ethanol was added. Work up, omitting treatment with methanolic KOH, gave 1.6 g of product. A glpc analysis (Column A, same conditions) showed the product to be 6%
styrene oxide, 7% 1-phenylethanol, 3% 2-chloro-1-phenylethanol and 84% phenacyl chloride. The starting material was recovered by recrystallization from pentane.

Repeated Reaction of Phenacyl Chloride with LiAlH$_4$ Modified with Quinine and One Equivalent of Ethanol. The reaction was carried out on a 20 mmol scale exactly as described previously. Treatment of the reaction solution with methanolic KOH and work up as usual gave 3.0 g of a yellow oil. The oil was distilled to give 1.0 g of product, bp 33-40° (0.3 mm). A glpc analysis (Column B, 180°, He flow rate 50 ml/min) showed the distillate to be a mixture of 92% styrene oxide (R.T. = 8.2 min) and 8% 1-phenylethanol (R.T. = 14.0 min). A glpc analysis of the original product mixture showed the product to be 75% oxide and 25% alcohol. The rotation of the oxide obtained from the distillate without removal of the alcohol by preparative glpc was $\Delta [\alpha]_{D}^{26} -20.0$ neat (64% ee, minimum value). The nmr (no. 10216) was identical in all respects to that of an authentic sample, and also showed the presence of 8% (+)-l-phenylethanol. The rotation is corrected only for % purity and is not corrected for the presence of the optically active l-phenylethanol.
Reaction of Phenacyl Chloride with LiAlH₄ Modified with Two Equivalents of Quinine. Quinine (12.2 g, 40 mmol) was added to a suspension of LiAlH₄ (0.76 g, 20 mmol) in dry ether (200 ml). The resulting suspension was stirred at reflux 1 hr and phenacyl chloride (3.08 g, 20 mmol) in dry ether (50 ml of solution) was added. The reaction mixture was heated at reflux for 6 hrs and worked up in the usual manner to give 3.0 g of oil. The oil was distilled to give 1.42 g of product, bp 33-40° (0.3 mm). A glpc analysis (Column B, same conditions) showed the distillate to be 92% styrene oxide and 8% 1-phenylethanol. Preparative glpc gave S-(-)-styrene oxide (13% phenylacetaldehyde by nmr): [α]D -18.9° neat (55% ee). The nmr spectrum (no. 10218) was identical to that of an authentic sample.

Reaction of Acetophenone with LiAlH₄ Modified with Quinine and Ethanol. Quinine (6.4 g, 20 mmol) was added to a suspension of LiAlH₄ (0.76 g, 20 mmol) in dry ether (100 ml). The suspension was stirred at room temperature for 1/2 hr, and then anhydrous ethanol (0.92 g, 20 mmol) in dry ether (5 ml of solution) was added. The resulting suspension was stirred for 1/2 hr at reflux and then acetophenone (2.4 g, 20 mmol) in dry ether (10 ml of solution) was added. The reaction mixture was stirred at reflux for 6 hrs. Work up in the usual manner gave 1.64 g of product (67%), bp 45°
The sample was 100% pure (glpc and nmr). R-(+)-1-phenylethanol: $[\alpha]_{D}^{25} = +21.7^\circ$ neat (49% ee). The nmr spectrum (no. 10269) was identical to that of an authentic sample.

**Reaction of Phenacyl Chloride with LiAlH$_4$ Modified with Cinchonine and Ethanol.** The reaction was run on a 20 mmol scale as described before. Work up with methanolic KOH gave 3.0 g of product shown by glpc (Column B, 220°, He flow rate 50 ml/min) to be a mixture of 75% styrene oxide, 25% 1-phenylethanol. Preparative glpc gave R-(+)-styrene oxide (12.5% phenylacetaldehyde by nmr): $[\alpha]_{D}^{25} = +7.22$ neat (28% ee), nmr (no. 10258), and S-(-)-1-phenylethanol: $[\alpha]_{D}^{26} = -11.1^\circ$ (c 2.6, ethanol), 25% ee, nmr (no. 10259). The nmr spectra were identical to those of authentic samples.

**Reduction of Benzaldehyde with LiAlD$_4$ Modified with Quinine and One Equivalent Ethanol.** Quinine (6.4 g, 20 mmol) was added to a suspension of LiAlD$_4$ (0.84 g, 20 mmol) in dry ether (100 ml). The resulting suspension was stirred at reflux for 1/2 hr, dry ethanol (0.92 g, 20 mmol) was added, and the suspension heated at reflux for 1/2 hr. Benzaldehyde (2.12 g, 20 mmol, freshly distilled) in dry ether (10 ml of solution) was added, and the reaction was heated at reflux for 4 hrs. Work up in the usual manner gave 1.2 g of crude, undistilled product. A glpc (Column B, 180°, He flow 40
ml/min) indicated 96% benzylic alcohol and 4% unidentified materials. Preparative glpc gave S-(+)-benzyl alcohol-l-d: $\left[\alpha\right]_D^{26} +0.34^\circ$ neat (22% ee based on $\left[\alpha\right]_D^{\max} 1.58^\circ$)\textsuperscript{52}, nmr (no. 11107): 6.60 (s, 5H), 4.65 (s, 1H) and 3.80 (s, 1H).

Reduction of Phenylacetaldehyde with LiAlD\textsubscript{4} Modified with Quinine and Ethanol. Phenylacetaldehyde was reduced on a 20 mmol scale in the same manner as was benzaldehyde, to give 2.4 g of crude undistilled product. A glpc analysis (Column B, 210°, flow rate 50 ml/min) showed the product to be a mixture of 62% phenylacetaldehyde (R.T. = 5.4 min) and 38% 2-phenylethanol (R.T. = 9.2 min). Preparative glpc gave racemic 2-phenylethanol-l-d: nmr (no. 11151): 7.36 (s, 5H), 3.70 (t, 1H, J = 7 Hz), 3.17 (s, 1H) and 2.24 (d, 2H, J = 7 Hz).

Reduction of Phenylacetaldehyde with Isobornylloxy-magnesium Bromide-l-d.\textsuperscript{47b} The deuterated isoborneol was prepared in 97% yield from the reduction of d-camphor (40 g, 292 mmol, $\left[\alpha\right]_D^{26} +44.2^\circ$, c 12.5, ethanol, 100% ee) with LiAlD\textsubscript{4} (5.04 g, 120 mmol). The ir spectrum showed no carbonyl absorption band. Isoborneol-l-d (39.0 g, 280 mmol) in dry ether (100 ml) was added to ethylmagnesium bromide (250 mmol) in ether (400 ml). Benzene (300 ml) was added, and the solvent was distilled until the distillate temperature reached 75°. After cooling the reaction mixture to room temperature,
freshly distilled phenylacetaldehyde (bp 83°/10 mm) in ether (25 ml of solution) was added, and the resulting mixture was stirred for 6 hrs at room temperature. The benzene was removed under reduced pressure on a rotovaporator, water (200 ml) was added, and the product was heated at reflux. The isoborneol, borneol and camphor adhered to the reflux condenser coils, and were removed by periodic replacement with a clean condenser. After 8 hrs no more solids adhered to the condenser coils. The aqueous phase was extracted with ether (3x100) and the combined ethereal material was dried (MgSO₄). Concentration gave 13.0 g of product which still smelled of camphor. A small portion was distilled to give 3 g of distillate (bp 75°/10 mm). This product also smelled of camphor. Preparative glpc gave racemic 2-phenylethanol (99+% pure): nmr (no. 10370): 6.68 (s, 5H), 4.24 (s, 1H), 3.20 (t, 1H, J = 7 Hz) and 2.29 (d, 2H, J = 7 Hz). The spectrum was identical to that of the sample obtained from reaction of R-(+)-4 with BD₃/BF₃·Et₂O.
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