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**PART I ASYMMETRIC REDUCTION OF KETONES WITH THE
GRIGNARD REAGENT FROM
R-1-BROMO-2-PHENYLETHANE-1,1,2-DEUTERIUM(3) PART II
ELECTROPHILICALLY ASSISTED NUCLEOPHILIC OPENING OF
OPTICALLY ACTIVE STYRENE-OXIDE**

JOSEPH EDWARD TOMASZEWSKI

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PART I. ASYMMETRIC REDUCTION OF KETONES
WITH THE GRIGNARD REAGENT FROM
R-1-BROMO-2-PHENYLETHANE-1,1,2-d₃

PART II. ELECTROPHILICALLY ASSISTED
NUCLEOPHILIC OPENING OF
OPTICALLY ACTIVE STYRENE OXIDE

by

JOSEPH EDWARD TOMASZEWSKI

B. S., University of Scranton, 1965

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

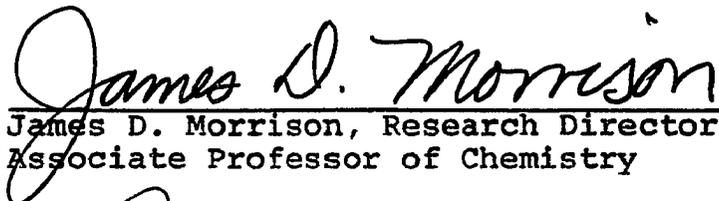
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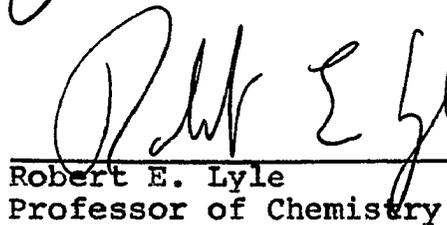
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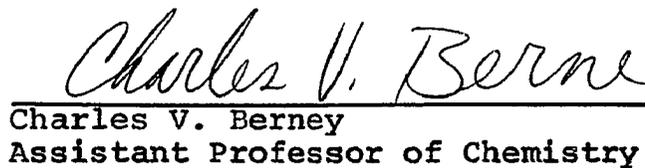
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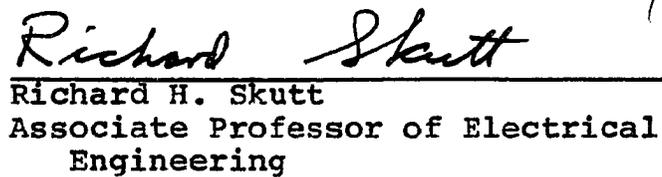
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ABSTRACT

PART I. ASYMMETRIC REDUCTION OF KETONES
WITH THE GRIGNARD REAGENT FROM
R-1-BROMO-2-PHENYLETHANE-1,1,2-d₃

PART II. ELECTROPHILICALLY ASSISTED
NUCLEOPHILIC OPENING OF
OPTICALLY ACTIVE STYRENE OXIDE

by

JOSEPH EDWARD TOMASZEWSKI

Part I. The preparation of the Grignard reagent from R-1-bromo-2-phenylethane-1,1,2-d₃ and its reaction with phenyl *t*-butyl and phenyl trifluoromethyl ketones is discussed. The optically active alcohol products produced in each reaction were analyzed as diastereomeric esters of (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride by 100 MHz NMR spectroscopy. In the case of the reduction of phenyl *t*-butyl ketone, unlabeled and labeled phenyl-*t*-butylcarbinol (48.6%) was produced with a 6.7% ee (enantiomeric excess) of the S-(-) isomer. The stereoselectivities of H and D transfer were almost the same, i.e., 13.5% ee of the S isomer for H transfer and 13.3% ee of the R isomer for D transfer. However, in the reduction of phenyl trifluoromethyl ketone, unlabeled and labeled phenyltrifluoromethylcarbinol (75.5%) was produced with a 6.5% ee of the R-(-) isomer. The stereoselectivities of H and D transfer

differed by 6.3% with D transfer being more stereoselective, i.e., 29.6% ee of the R isomer for H transfer and a 35.9% ee of the S isomer for D transfer. Hydrolysis of the Grignard reagent produced S-(+)-1-phenylethane-1,2,2-d₃, which exhibited a rotation ($[\alpha]_D^{22}$) of +1.04°. Maximum rotations were calculated for 1-phenylethane-1,2,2-d₃ and 2-phenylethanol-1,1,2-d₃.

Part II. The preparation of R-(+)-styrene oxide and its reaction with the AlD₃/Et₂O, AlD₃/THF, B₂D₆/BF₃·OEt₂ and Et₂Mg/MgBr₂·dioxanate reagents is discussed. When styrene oxide was reacted with the AlD₃/Et₂O reagent, S-(-)-1-phenylethanol-2-d and S-(-)-2-phenylethanol-2-d were produced in 34% and 62% yields, respectively. Reaction with the AlD₃/THF reagent produced S-(-)-1-phenylethanol-2-d and S-(-)-2-phenylethanol-2-d in 66% and 22% yields, respectively. The reaction with the B₂D₆/BF₃·OEt₂ reagent produced S-(-)-2-phenylethanol-1-d of 11-14% ee in a 72% yield (the configuration and the % ee are only tentatively assigned). Finally, the reaction with Et₂Mg/MgBr₂·dioxanate produced (-)-1-phenyl-2-butanol of very low optical purity and S-(+)-2-phenyl-1-butanol of 44% ee in 30% and 50% yields, respectively. Mechanisms have been postulated for all of these reactions. Styrene oxide was also prepared by an asymmetric reduction reaction. When the Grignard reagent from R-(-)-1-chloro-2-phenylbutane was allowed to react with α-chloroacetophenone, S-(-)-styrene oxide of 14% ee was produced in a 39% yield after hydrolysis with KOH.

PART I
INTRODUCTION

The reduction of carbonyl compounds with Grignard reagents has been extensively studied in the past.¹ The reduction reaction was discovered by Grignard² in his original study of the reaction; and Conant and Blatt³ later observed that reduction readily took place with sterically hindered ketones. While Grignard reagents also add to carbonyl compounds, this treatise will only be concerned with the reduction reaction (Figure 1).

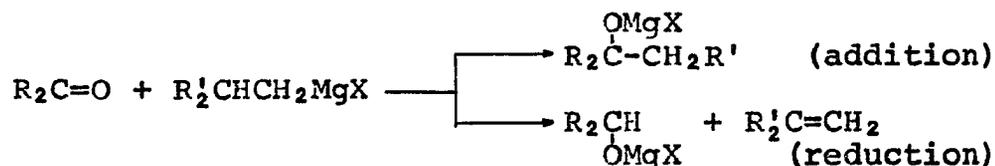


Figure 1. Reduction and addition reactions of carbonyl compounds with Grignard reagents.

Little was known about the mechanism of the reduction reaction until 1942, when Whitmore and George⁴ proposed their now famous mechanism (Figure 2). The principal supporting evidence for this mechanism was the observation that a correlation existed between the extent of reduction and the availability of β -hydrogens in the Grignard reagent (the neopentyl Grignard reagent with no β -hydrogens gave no reduction with diisopropyl ketone, while the *t*-butyl

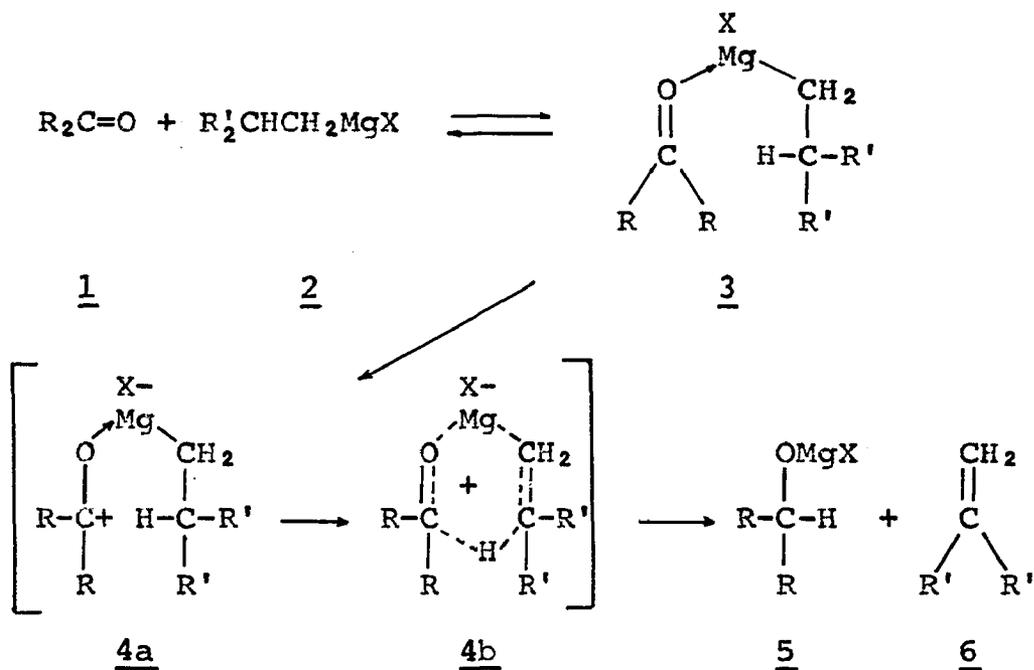


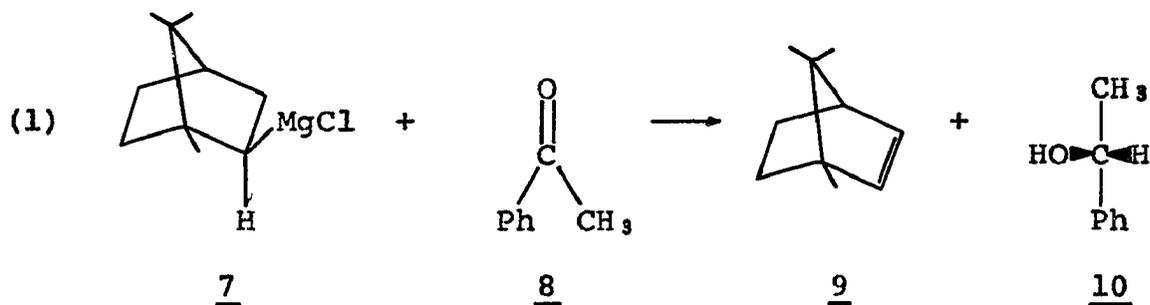
Figure 2. Whitmore mechanism for Grignard reductions.

Grignard reagent, with nine β -hydrogens, gave 95% reduction.) The mechanism depicts the reaction as the reversible formation of complex 3, which then proceeds to transfer a β -hydrogen directly from the reagent to the substrate.

The fact that the β -hydrogen is the one that is transferred has been proven by the deuterium labelling experiments of Dunn and Warkentin.⁵ When benzophenone was allowed to react with the β -deuteroisobutyl Grignard reagent, the product (benzhydrol) contained deuterium. However, when benzophenone was reduced with the α - and γ -deutero Grignard reagents, the benzhydrol obtained did not contain any deuterium.

The first observation of an asymmetric Grignard reduction was made by Vavon and coworkers⁶ in the reaction of acetophenone (8) with the reagent (7) prepared from

"pinene hydrochloride" to give R-(+)-methylphenylcarbinol (10, 30% ee).



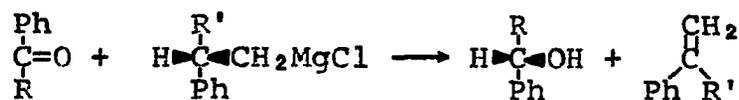
The reagent consists of a mixture of the bornyl- and isobornyl-magnesium chlorides, and it was presumed that only the *exo*-isobornyl species (7) is the active reducing agent. However, recent work in these laboratories has cast some doubt on the validity of this assumption.⁷ Vavon and Angelo⁸ extended this reaction to a series of alkyl phenyl ketones but made no attempt to interpret the results other than to say that a relationship existed between the extent of asymmetric reduction and the steric hindrance of the ketone.

Since this first example of an asymmetric Grignard reduction, Mosher and coworkers⁹⁻²³ have expanded the reaction substantially and have contributed much to a more complete understanding of the mechanism. A brief summary of this work is given in Table 1.

In the form of a general model, the reaction can be visualized as shown in Figure 3.

It is presumed that reduction mode 13a will be favored over 13b because of the lower energy steric

TABLE 1

ASYMMETRIC REDUCTION OF ALKYL PHENYL
KETONES BY GRIGNARD REAGENTS^a

Per Cent Asymmetric Synthesis

R	R'=Me	Et	<i>i</i> -Pr ^d
Me	38 ^b	47 ^c	---
Et	38 ^b	52 ^c	66
<i>i</i> -Pr	59 ^b	82 ^c	80
<i>t</i> -Bu	[22] ^{b, f}	16 ^c	91
CF ₃	47 ^e	38 ^e	22

- (a) In some experiments the enantiomeric reagent was employed and the enantiomeric carbinol was formed from that shown in the equations.
 (b) See reference 12.
 (c) See reference 11.
 (d) See reference 19.
 (e) See reference 21.
 (f) Product has configuration opposite to that shown.

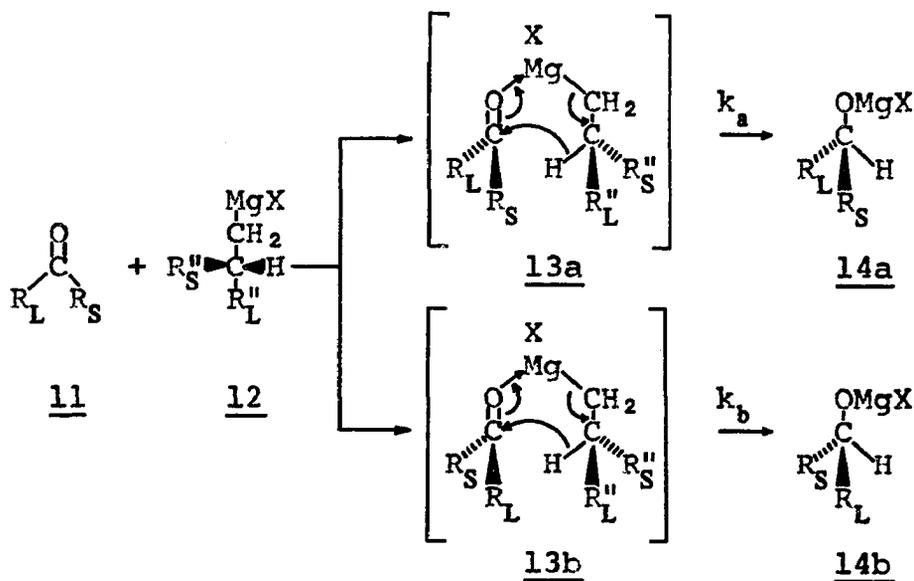


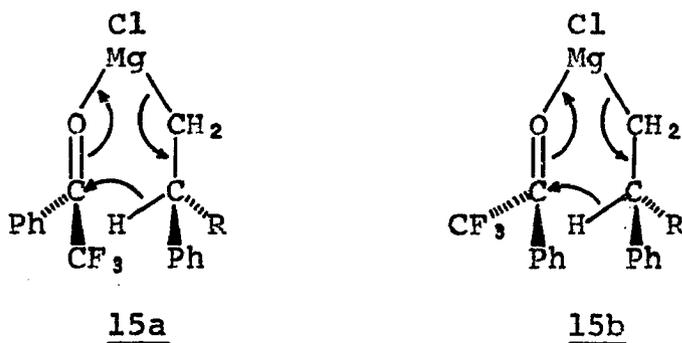
Figure 3. Competing modes of reduction in the asymmetric reduction reaction.

interactions involved. In 13a, a better fit of the two pairs of interfering groups is possible than in 13b, i.e., $(R_S \text{ vs } R_L'') + (R_L \text{ vs } R_S'')$ is favored over $(R_S \text{ vs } R_S'') + (R_L \text{ vs } R_L'')$. Thus, isomer 14a will be produced in excess. This model has been extremely successful in predicting the stereochemistry of the reaction and there are very few exceptions to it.²⁴ One exception is the reduction of phenyl *t*-butyl ketone by the Grignard reagent from S-(+)-1-chloro-2-phenylpropane which gives predominantly the enantiomer opposite to that predicted on the basis of the above model, assuming *t*-butyl is smaller than phenyl.¹² This result serves as a warning that there are limitations to the use of this asymmetric synthesis for the determination of absolute configurations.

Another apparent exception is the asymmetric reduction of phenyl trifluoromethyl ketone by the Grignard reagent from S-(+)-1-chloro-2-methylbutane. From van der Waals radii,²⁵ rotational barriers in substituted ethanes,²⁶ conformational energy barriers,²⁷ and u.v. spectral measurements,²⁸ one must conclude that the trifluoromethyl group has a smaller steric bulk than phenyl (and also *t*-butyl). Thus, one would predict, on steric grounds alone, that 13a (where: $R_L = \text{Ph}$, $R_S = \text{CF}_3$, $R_L'' = \text{Et}$ and $R_S'' = \text{Me}$) is the preferred mode of reduction, and that enantiomer 14a (where: $R_L = \text{Ph}$, $R_S = \text{CF}_3$) should be obtained. Contrary to this prediction, a 22% asymmetric synthesis of the opposite enantiomer (14b) was obtained.²¹ This is a clear

exception to the "best steric fit" picture of this reaction; and there seems to be no highly satisfactory way of rationalizing this observation.

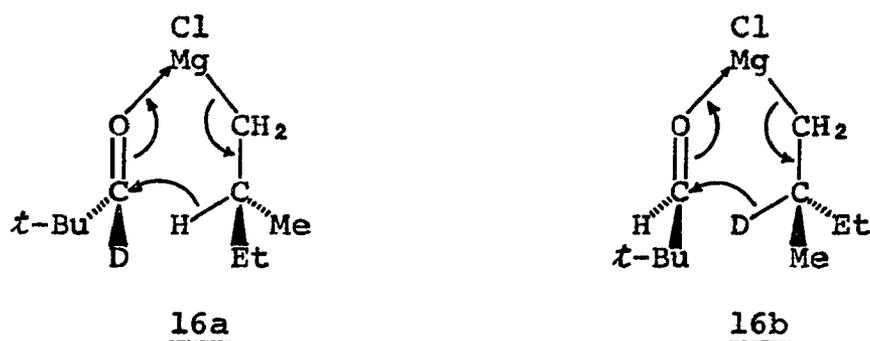
The fact that electronic factors are important in certain cases is illustrated by the reduction of phenyl trifluoromethyl ketone by a Grignard reagent possessing a phenyl group in the *beta* position. Again, steric considerations alone predict that 15a should be preferred, but the results show that this is not the case and that a presumed electronic repulsion between trifluoromethyl and phenyl is the overriding consideration which determines that the lower energy mode of reduction is that represented by 15b, in which the phenyl groups are forced to be cisoid in the transition state.



While this part of the thesis is concerned with the asymmetric Grignard reduction reaction it is equally concerned with a comparison of the transfer of H *versus* the transfer of D from the Grignard reagent to the carbonyl compound.

A related study of this kind was carried out by Mosher and coworkers^{14, 18, 23} in the preparation of optically

active 1-deutero-primary alcohols. A synthesis of this kind can be achieved in one of two ways: (1) by transferring hydrogen to a deuterioaldehyde, or (2) by transferring deuterium to an isotopically normal aldehyde. Models for the comparable preferred modes of reductions for the formation of neopentyl-1-d alcohol, utilizing enantiomeric labeled and unlabeled 2-methylbutyl Grignard reagents are shown below.



While these modes of reduction are very closely related, they are not identical or enantiomeric. In 16a, a C-H bond is being broken and reformed. In 16b, a C-D bond is being broken and reformed. The other difference is that in 16a, ethyl and deuterium are cisoid while in 16b, ethyl and hydrogen are cisoid. The observation by Dunn and Warkentin⁵ of an isotope effect (k_H/k_D) of 2.3 indicates that the transfer of deuterium will be appreciably slower than that of hydrogen in such reactions.

It was believed that the stereoselectivities of these two modes of reductions (16a and 16b) should be about the same. However, it was observed that while hydrogen

transfer gave 12% asymmetric reduction, the comparable deuterium transfer gave 36% asymmetric reduction.²⁹ Since these experiments were done before gas chromatographic purification techniques were available, and because the rotation of the product was very small, the study should be repeated. If these results are correct, an interesting rationalization seems to be one based on the tunneling effect.²⁹ Since hydrogen has a longer de Broglie wavelength, it can be transferred from reagent to substrate without going over the energy barrier. Therefore, the transfer of hydrogen could take place between the carbon atoms of the Grignard reagent and the aldehyde when they are appreciably farther apart than in the case of deuterium transfer which shows less tunneling.

Thus, the steric interactions would be accentuated in the transfer of deuterium *versus* hydrogen because of the necessity for the carbon atoms to be closer together in the former case and this would contribute to crowding in the transition state.

When Morrison and Mosher³⁰ reduced phenyl *t*-butyl ketone with the Grignard reagent from S-(+)-1-chloro-2-phenylbutane-2-d, the amount of asymmetric synthesis was the same (within experimental error) as that for the analogous reduction with the non-deuterated Grignard reagent (15% *versus* 16%). They found the same to be true for the reduction of phenyl ethyl ketone with the same Grignard reagents (54% for hydrogen transfer and 55% for deuterium).

While these reactions are not exactly comparable to the reduction of trimethylacetaldehyde represented by 16a and 16b, they do suggest that the important factor is the difference in the "steric size" of H vs D and not an intrinsic difference in the stereoselectivity of H vs D transfer.

Statement of the Problem

Thus, it was the objective of this research to combine these factors into one system, i.e. a Grignard reagent that can transfer either H or D. In principle, with this kind of system, only one experiment is necessary to determine the stereoselectivity of H vs D transfer. However, in practice, a new analytical method had to be developed in order to carry out this study. The overall technique employed is a form of optical-isotopic double labeling and this investigation represents the first use of this method to study the relative energies of closely related competing transition states for ketone reduction. The reducing system ultimately chosen for this investigation was the Grignard reagent from R-1-bromo-2-phenylethane-1,1,2-d₃. Its synthesis and the results of its reactions with phenyl *t*-butyl ketone and phenyl trifluormethyl ketone are discussed in the following section.

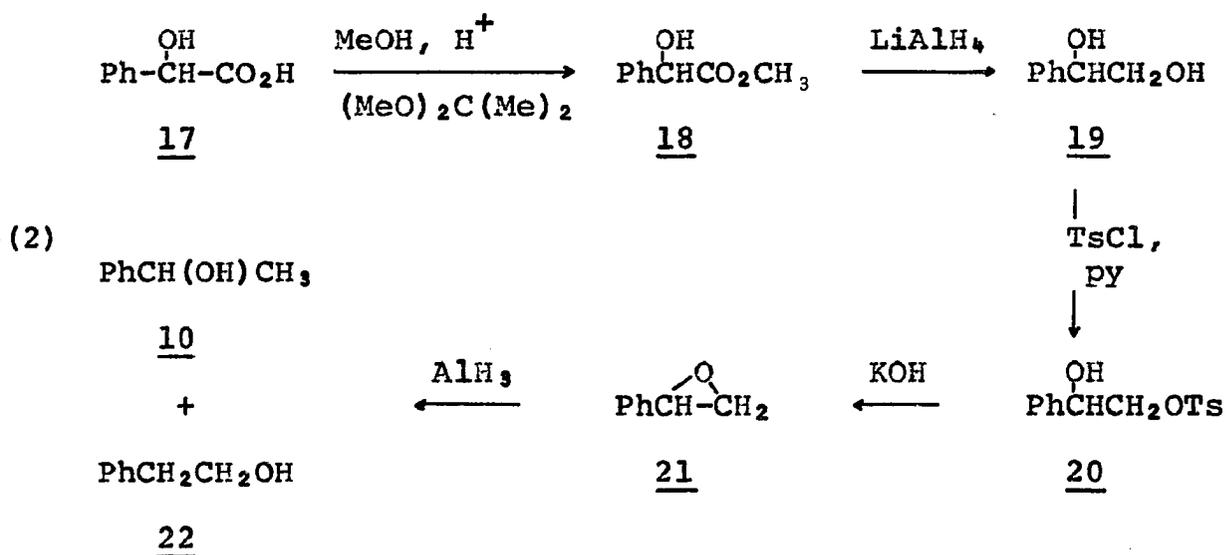
RESULTS AND DISCUSSION

The Preparation of the Grignard Reagent

The development of a suitable synthesis of the Grignard reagent from chiral 1-bromo-2-phenylethane-1,1,2-d₃ proved to be a problem in itself. The synthetic routes that were initially attempted will be discussed first to illustrate the problems that were encountered.

The synthetic route attempted first was similar to the final route chosen in that the starting material in each was chiral mandelic acid. Mandelic acid (17) was chosen as the starting material because it could be easily resolved;³¹ later in the investigation optically active mandelic acid of high optical purity became commercially available. The resolved mandelic acid was converted to the methyl ester (18) by the action of methanol, hydrochloric acid and 2,2-dimethoxypropane according to the general procedure of Lorette and Brown.³² The 2,2-dimethoxypropane acts as a water scavenger thus allowing the esterification to go to completion in a short period of time. The ester was then reduced with lithium aluminum hydride to give 1-phenyl-1,2-ethanediol (19).³³ Conversion of the diol to the monotosylate (20) and ring closure to styrene oxide (21) was accomplished by a slight modification of the

procedure of Eliel and Delmonte.³⁴ At first, it was felt that the synthesis of the desired chiral halide could be achieved through an alane reduction of styrene oxide (see Reaction Sequence 2). However, when styrene oxide was reduced with the $\text{AlH}_3/\text{Et}_2\text{O}$ reagent according to the procedure of Rerick and Eliel,³⁵ the products obtained were shown to be 2-phenylethanol (22) and 1-phenylethanol (10) in 58% and 42% yields, respectively. This reduction was carried



out under a number of different conditions, and it was found that the product ratio remained essentially the same; it was not possible to increase the relative yield of 22. Since a large scale preparative gas chromatographic separation was found to be extremely difficult and time consuming for this mixture, this synthetic route was abandoned.

The next synthetic scheme that was attempted involved the preparation of α -deuteromandelic acid. The incorporation of deuterium was attempted by several different methods. The first of these was a deuterium-hydrogen

exchange on methyl mandelate. When methyl mandelate in a carbon tetrachloride solution was treated with potassium *t*-butoxide and deuterium oxide for one-half hour at room temperature, the resulting mandelic acid was found to contain no deuterium. The reaction of methyl mandelate with sodium methoxide in methanol- $O-d$ solution again produced no deuterium incorporation in the resulting mandelic acid. The third exchange reaction involved treating methyl mandelate with a solution prepared by dissolving sodium in methanol- $O-d$. This time, there was some deuterium incorporation in the resulting mandelic acid, but it was less than 10%.

The next synthetic route attempted involved the reduction of phenylglyoxylic acid to mandelic acid. When phenylglyoxylic acid was treated with sodium amalgam in a weakly alkaline aqueous solution,³⁶ mandelic acid was produced in only 31% yield. The hydrogenation of phenylglyoxylic acid with a Pt/C catalyst in a methanolic sodium hydroxide solution produced mandelic acid in a 90% yield. However, when deuterium gas was used under the same conditions, the recovered mandelic acid contained no deuterium. This seemed to indicate that the solvent was participating in the hydrogenation in some manner. When methanol- $O-d$ was used in the reduction, the resulting mandelic acid contained approximately 80% deuterium. After numerous other attempts to effect the exchange and reduction reactions, these experiments were finally abandoned due to

low yields, low deuterium incorporation and the excessive cost that would be involved in large-scale preparations.

The synthetic route finally chosen is illustrated in Figure 4. S-(+)-Mandelic acid (17) was converted to

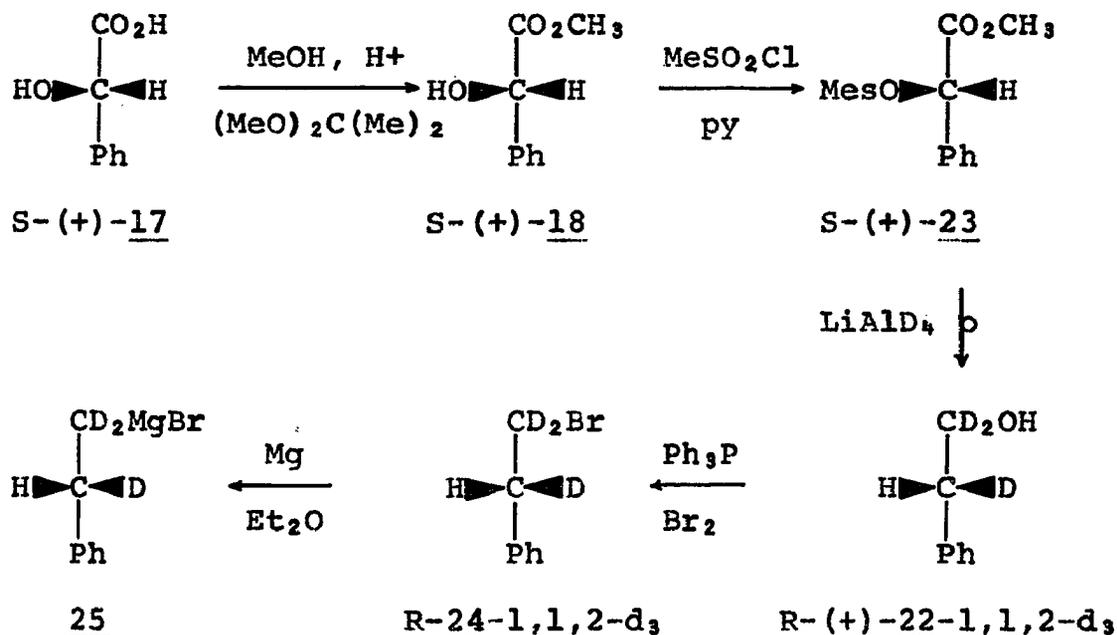


Figure 4. Preparation of the Grignard reagent 25.

the methyl ester (18) according to the general procedure of Lorette and Brown³² in a 96% yield. The ester was converted to S-(+)-methyl-O-mesyl mandelate (23) in a 70% yield by treatment with methanesulfonyl chloride in a pyridine solution at -5°C. Reduction of the mesylate with lithium aluminum deuteride produced R-(-)-2-phenylethanol-1,1,2-d₃ (22) in a 64% yield. That the reduction did proceed as was expected³⁷ has been supported independently by Green and coworkers.³⁸ Starting with R-(-)-mandelic acid (R-17), these workers prepared S-(+)-2-phenylethanol-2-d (S-22) by a similar sequence of reactions (see Figure 5).

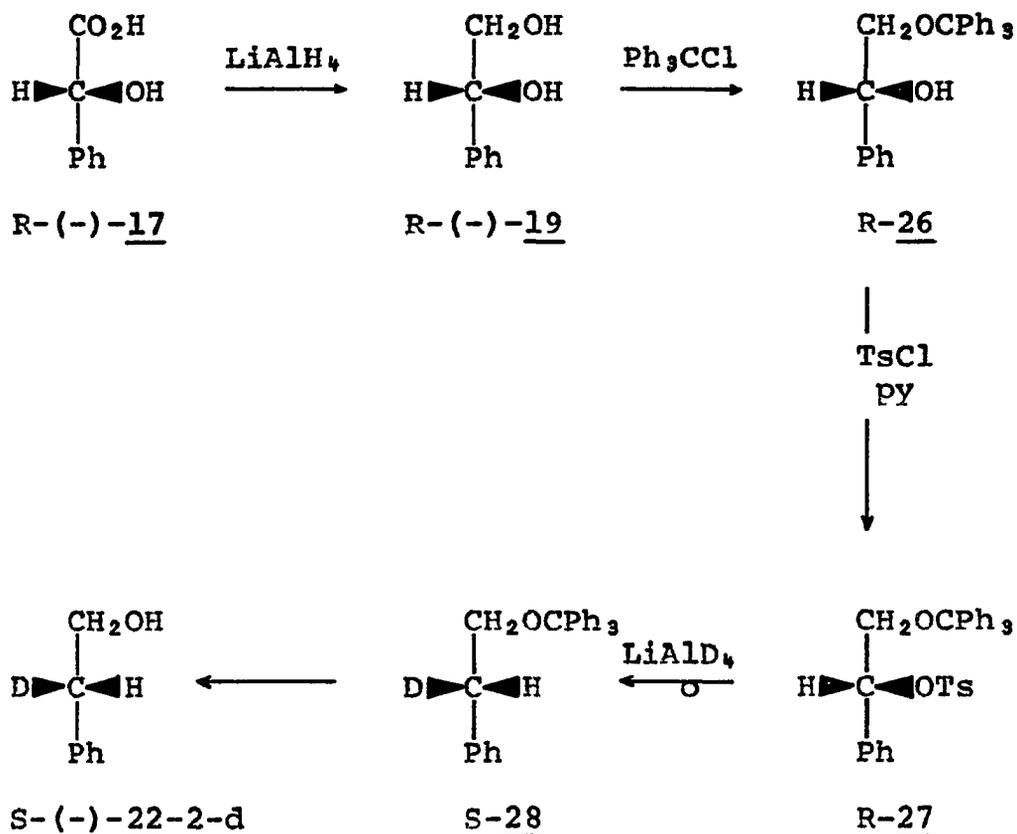


Figure 5. Green scheme for the preparation of S-(-)-2-phenylethanol-2-d.³⁸

When 22 was initially prepared, it was believed by both this author and Green that the rotation should be the opposite of that reported by DePuy and coworkers³⁹ (see Figure 6). However, it wasn't until after this work was completed that the conflict was resolved. When analyzed by glpc, the sample of 22 ($[\alpha]_D -1.36^\circ$) appeared to be pure; however, purification of 22 by preparative glpc gave a sample of 2-phenylethanol-1,1,2-d₃ (R-22-1,1,2-d₃) which exhibited a rotation of $+1.06^\circ$. A second purification by preparative glpc gave a sample of R-22-1,2,2-d₃, which exhibited the same rotation. Thus, it seems that there was

a contaminant present of high optical rotatory power which was not observed by glpc analysis of the sample. This result, i.e., a (+) rotation, agrees with that predicted by Brewster's rules.*

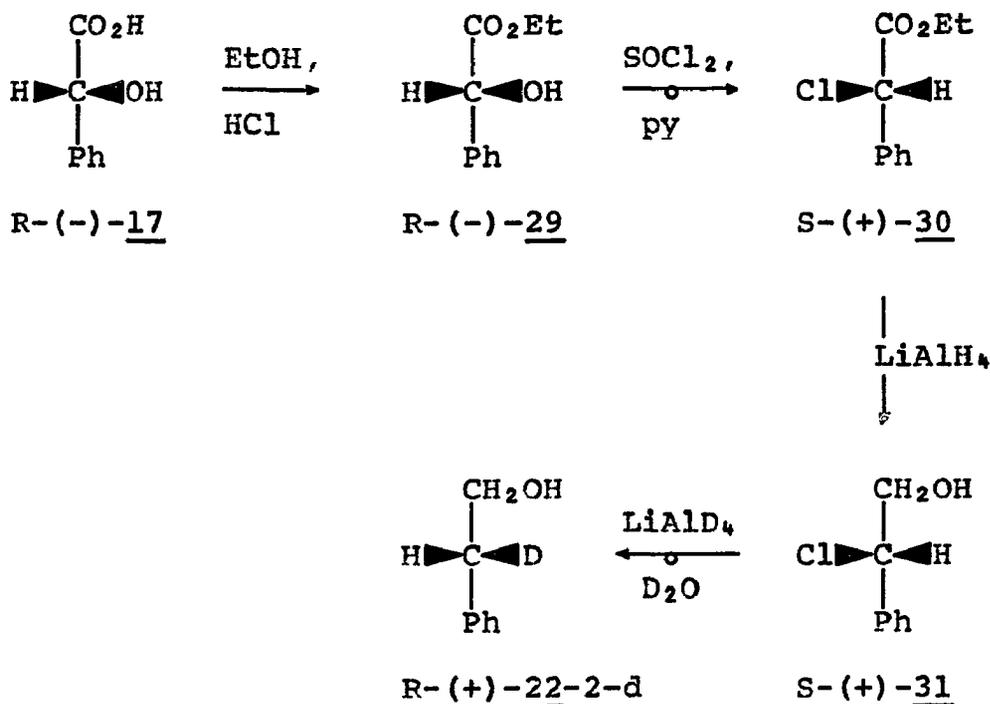
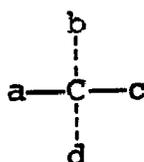


Figure 6. DePuy scheme^{39, 40} for the preparation of optically active 2-phenylethanol-2-d.

A side product in the reduction of methyl-O-mesyl mandelate (23) was 1-phenylethanol (10). Its formation

*Brewster's rule (see reference 48) states that a compound with the configuration shown below will have a dextrorotatory rotation if the polarizabilities of the attached groups decrease in the order $a > b > c > d$.



can be accounted for in the following manner (see Figure 7). The ester group is first reduced by lithium aluminum deuteride to give the alkoxide (32) which then displaces the mesylate group with inversion³⁴ to give the epoxide (21).

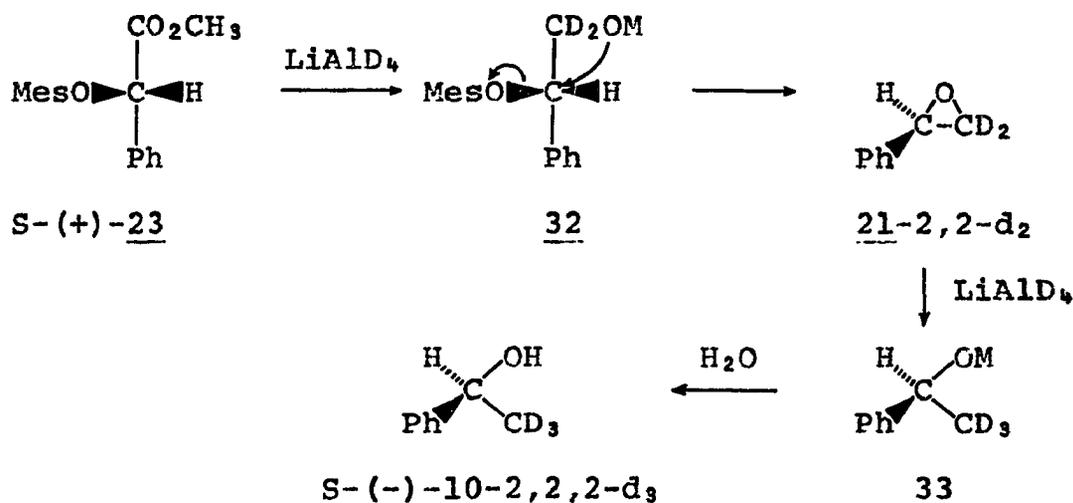


Figure 7. Formation of 1-phenylethanol from reduction of S-(+)-23.

The epoxide then undergoes reduction to give S-(-)-1-phenylethanol-2,2,2-d₃ (10). The evidence for this chain of events is as follows: (1) traces of styrene oxide were found in the product mixture when analyzed by glpc; and (2) the rotation of 22 was more levorotatory when there was more of 10 present in the sample, and decreased as the percentage of 10 in the sample decreased. This indicates that the 1-phenylethanol (10) had the S-(-) configuration.

The preparation of R-1-bromo-2-phenylethane-1,1,2-d₃ (24) was accomplished in a 46% yield according to the general procedure of Wiley and coworkers⁴² with

triphenylphosphine and bromine. The bromide (24) was then subjected to solvolysis in methanol in an attempt to remove the 1-bromo-1-phenylethane from the 1-bromo-2-phenylethane-1,1,2-d₃ (24).⁴³ Column chromatography of the solvolysis mixture gave a sample of 24 that was only 90% pure--the remaining 10% consisted of 4.5% 1-bromo-1-phenylethane-2,2,2-d₃ and 5.5% styrene plus ethylbenzene. No further purification was attempted and the bromide of this purity was used to prepare the Grignard reagent (25) in the usual manner from triply-sublimed magnesium turnings (86% yield by acid-base titration).

The deuterium content of both the alcohol (22) and the bromide (24) was determined by mass spectroscopy (for a detailed description of the deuterium content calculation see Appendix I). The results are summarized in Table 2.

TABLE 2

DEUTERIUM ANALYSIS OF R-(+)-2-PHENYL-ETHANOL-1,1,2-d₃ (22) AND R-1-BROMO-2-PHENYLETHANE-1,1,2-d₃ (24) BY MASS SPECTROSCOPY

Compound	%d ₂	%d ₃	%d ₄
22	5.6	92.0	2.2
24	6.7	93.2	---

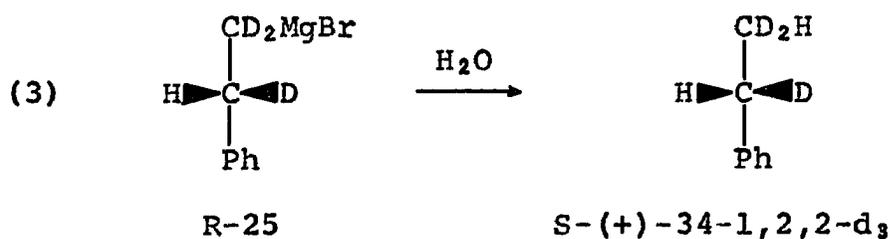
Using these values (i.e., assuming that only d₃ bromide contributes to the optical activity) together with the optical purity of the methyl mandelate used in the

synthesis (96%) and assuming no racemization in the reaction sequence 17 thru 24, the maximum enantiomeric purity of the bromide can be estimated to be 93.5%. However, Helmkamp and Rickborn^{37a} have shown that the reduction of a secondary mesylate proceeds with about 20% racemization. Therefore, the maximum optical purity of 22 and hence of 24 is probably about 75%. However, the optical purity of the bromide used to prepare the Grignard reagent is not crucial for the discussion of the Grignard reductions. To the extent that it is enantiomerically impure, the enantiomeric purity of reduction products simply will be lower than would be the case with an enantiomerically pure Grignard reagent. No corrections will be made for the estimated enantiomeric purity of the Grignard reagent in considering the amount of asymmetry induced in the reduction reactions.

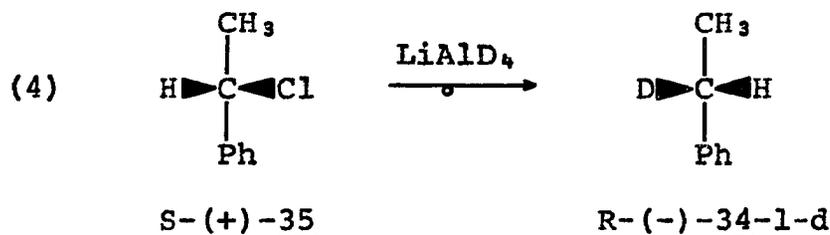
Reactions of the Grignard Reagent from

R-1-bromo-2-phenylethane-1,1,2-d₃

An aliquot of the Grignard reagent (25) was hydrolyzed with water to obtain a sample of the hydrocarbon (Equation 3). The 1-phenylethane-1,2,2-d₃ (34) that was isolated had a rotation ($[\alpha]_D^{22}$) of +1.04°. The configuration of (-)-1-phenylethane-1-d from the LiAlD₄ reduction



of S-(+)-1-chloro-1-phenylethane (35) has been unambiguously demonstrated to be R by Streitwieser and coworkers.⁴⁴ Therefore, the configuration of 34 is almost certainly S, which is consistent with the configurations of its mandelic acid precursor and the presumed stereochemistries of the linkage reactions. Streitwieser calculated the maximum rotation of 1-phenylethane-1-d to be 0.76° based on a maximum rotation of 116° for the precursor chloride. This same reduction (Equation 4) has also been carried



out by Eliel,⁴⁵ Dauben and McCoy⁴⁶ and Streitwieser and Reif.⁴⁷ The maximum rotation of 1-chloro-1-phenylethane (35) has been calculated to be 125.4° by Eliel.⁴⁸ Therefore, assuming no racemization in the lithium aluminum deuteride reduction of 35, the published estimates of the maximum rotation of 1-phenylethane-1-d vary from 0.71 to 1.00° with most estimates in the range 0.7-0.8°.

Mosher and coworkers¹⁵ have shown that the lithium aluminum deuteride reduction of R-(+)-1-chloro-1-phenylbutane, prepared by chlorination of S-(-)-1-phenyl-1-butanol with POCl₃/pyridine, proceeded with appreciable racemization. It was assumed that there was about 20% racemization in the chlorination and about 50% in the

reduction. The S-(+)-1-phenylbutane-1-d recovered from this reduction had a rotation of $+0.84^\circ$ and this is less than half of the maximum rotation of 2.2° calculated by Verbit.⁴⁹ Since Mosher and coworkers used the same reactions in their synthesis that Eliel⁴⁵ used in the preparation of 1-phenylethane-1-d, the maximum calculated rotation for 1-phenylethane-1-d (about 0.8°) may be too low by a factor of 2.6. If this is true, which seems very likely, then the maximum rotation of 1-phenylethane-1-d should be about 2.1° . Therefore, since the rotation of the 1-phenylethane-1,2,2-d₃ (34) obtained in this investigation was 1.04° , its optical purity, and consequently the optical purity of R-(+)-2-phenylethanol-1,1,2-d₃ (22) and R-1-bromo-2-phenylethane-1,1,2-d₃ (24), should be approximately 49.5% (assuming that the deuterium atoms in the CD₂H group do not appreciably affect the rotation). This would correspond to approximately 44% racemization in the lithium aluminum deuteride reduction of methyl-O-mesyl mandelate (23), a figure that is in line with that expected by extrapolation from similar reactions. Using this value of 49.5% ee for R-(+)-2-phenylethanol-1,1,2-d₃, its maximum rotation can be calculated to be approximately 2.14 (see Table 3).

The reaction of the Grignard reagent (25) prepared from R-1-bromo-2-phenylethane-1,1,2-d₃ with phenyl *t*-butyl ketone (36) produced 48.6% phenyl-*t*-butylcarbinol (37), which contained 25-30% deuterium at the carbinol

the R isomer of labeled plus unlabeled phenyltrifluoromethylcarbinol (39) was produced in 7.1% ee.⁵⁰

TABLE 4

REDUCTION PRODUCTS FROM THE REACTION OF THE GRIGNARD REAGENT 25 WITH PHENYL *t*-BUTYL AND PHENYL TRIFLUOROMETHYL KETONES

	Partially Labeled Alcohols	
	<u>37</u>	<u>39</u>
Actual Yield (%)	48.6	75.5
$[\alpha]_D^{23}$	-2.79	-2.26
% ee	7.66 ^a	7.1 ^b
Configuration	S ^a	R ^b
% d (NMR)	30	40
% d (Mass Spec.) ^c	24.8	36.2

- (a) See reference 8 for the maximum rotation and configurational assignment.
 (b) See reference 50 for the maximum rotation and configurational assignment.
 (c) See Appendix I.

Prior consideration of the competing modes of reduction shown in Figures 8 and 9 led to the *a priori* conclusion that 40b and 41b should be the favored ones for hydrogen transfer and that 40d and 41d should be the favored ones for deuterium transfer on the basis of steric interactions alone. This conclusion is based on the fact that phenyl has been shown to have a greater steric requirement than both *t*-butyl and trifluoromethyl.²⁵⁻²⁸ However, contrary to predictions based on steric size, it has been shown for a number of asymmetric reductions¹⁹⁻²² that phenyl and trifluoromethyl groups prefer to be transoid to one another, apparently because of strong electronic interactions. Therefore, by analogy to these closely

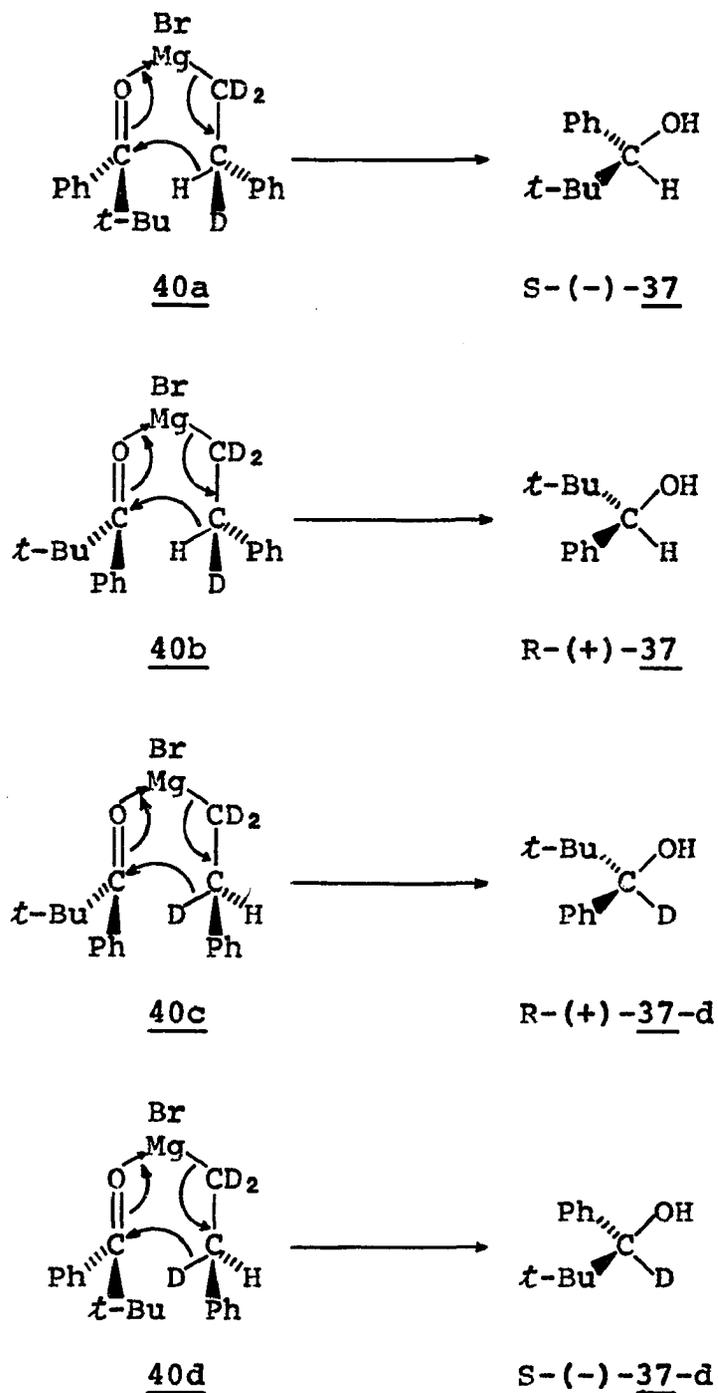


Figure 8. Competing modes of reduction of phenyl *t*-butyl ketone by the Grignard reagent from *R*-(-)-1-bromo-2-phenylethane-1,1,2- d_3 .

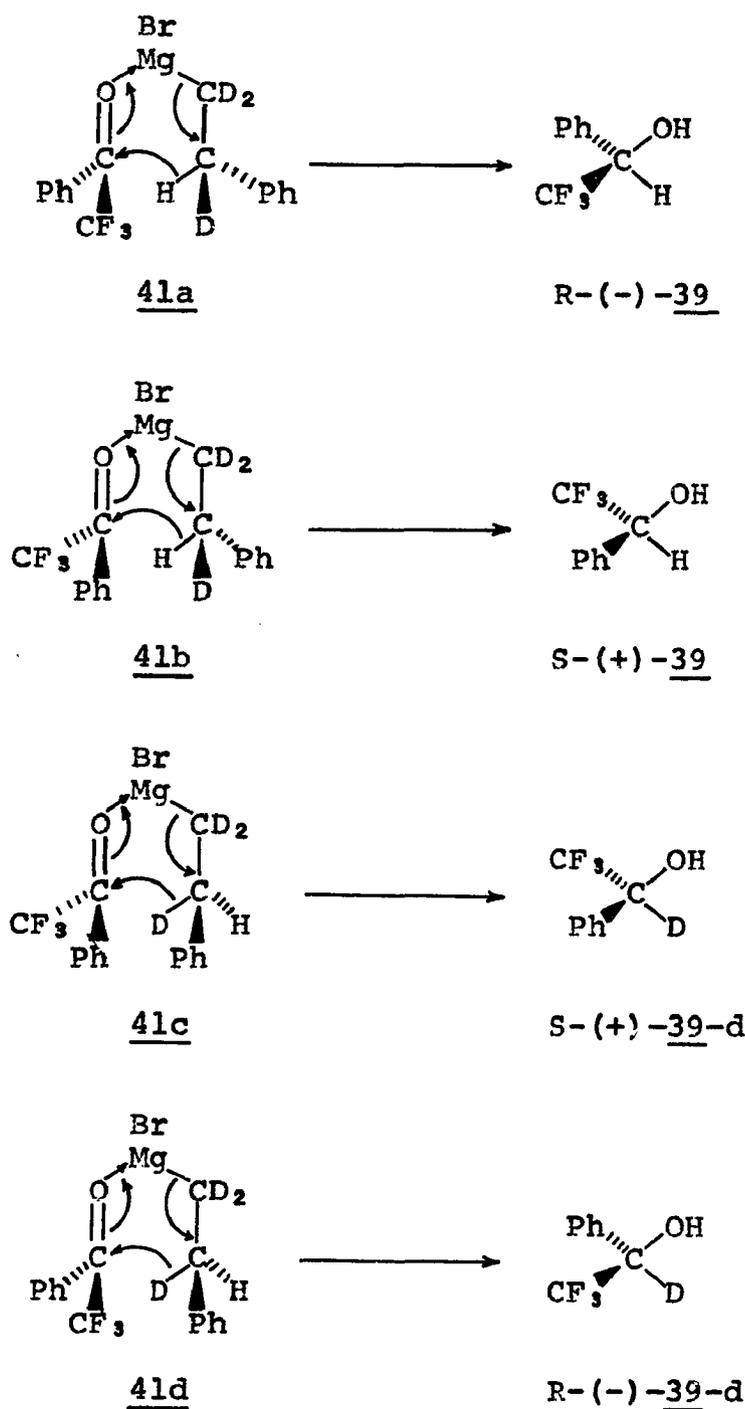


Figure 9. Competing modes of reduction of phenyl trifluoromethyl ketone with the Grignard reagent from R-(-)-1-bromo-2-phenylethane-1,1,2-d₃.

related reductions, the reduction modes illustrated by 41a and 41c should be the favored ones for hydrogen and deuterium transfer, respectively, and not 41b and 41d.

While the results in Table 4 do suggest the overall stereospecificity of the reactions (neglecting rotation isotope effects) and the approximate deuterium content, they do not reveal the stereoselectivity of hydrogen vs deuterium transfer. For example, in the case of the reduction of phenyl *t*-butyl ketone the following limits are obtained: (1) the contribution of 40a must be between 27 and 54% while that of 40b must be between 19 and 46%; (2) the contributions of 40c and 40d must be between 0 and 27%. Thus, one cannot make an accurate estimate of the relative contributions of the reduction modes for this reaction. The same holds true for the phenyltrifluoromethyl ketone reduction. Therefore, it was necessary to find a method of accurately determining the amount of each product formed in these reactions before any meaningful discussion of the results could be attempted.

Initially, it was thought that a classical resolution might be carried out on the half-phthalates of the carbinols.^{50, 51} However, due to the difficulty of working with very small quantities and the necessity that complete recovery of each enantiomer must be obtained for a strictly valid result (i.e., to avoid isotope fractionation), this method was abandoned in favor of an NMR method. Mosher and coworkers⁵² had developed a NMR method for the determina-

tion of the enantiomeric purity of secondary alcohols and certain amines. It was felt that this technique might also be applied in the present study.

To be successful in this case, this absolute method would require the complete reaction of each of the carbinol mixtures 37 and 39 with (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (MTPA, 42, probably of the R configuration) to produce a mixture of diastereomeric MTPA esters 43a, b, c and d (Scheme 7); and the analysis of this mixture for diastereomeric and isotopic composition. Such a double analysis had not been attempted previously. The reliability of this technique for the enantiomeric analysis of unlabeled compounds can be seen from the following results reported by Mosher and coworkers.⁵² A sample of (+)-phenyltrifluoromethylcarbinol of 45.2% ee as indicated by its rotation was determined to have a 44.9% ee by the NMR analysis of the MTPA esters; and (+)- α -phenylethylamine, 42.2% ee by rotation, was shown to have a 42.4% ee by NMR analysis of the diastereomeric MTPA amides. Since the initial development of this procedure, numerous refinements have reduced the amount of error considerably.

The results from the NMR analysis of the diastereomeric and partially labeled MTPA esters of alcohol mixtures 37 and 39 are given in Table 5. A complete discussion of the application of the technique used to obtain these results is given in Appendix II along with the chemical shifts of the various groups on the MTPA esters.

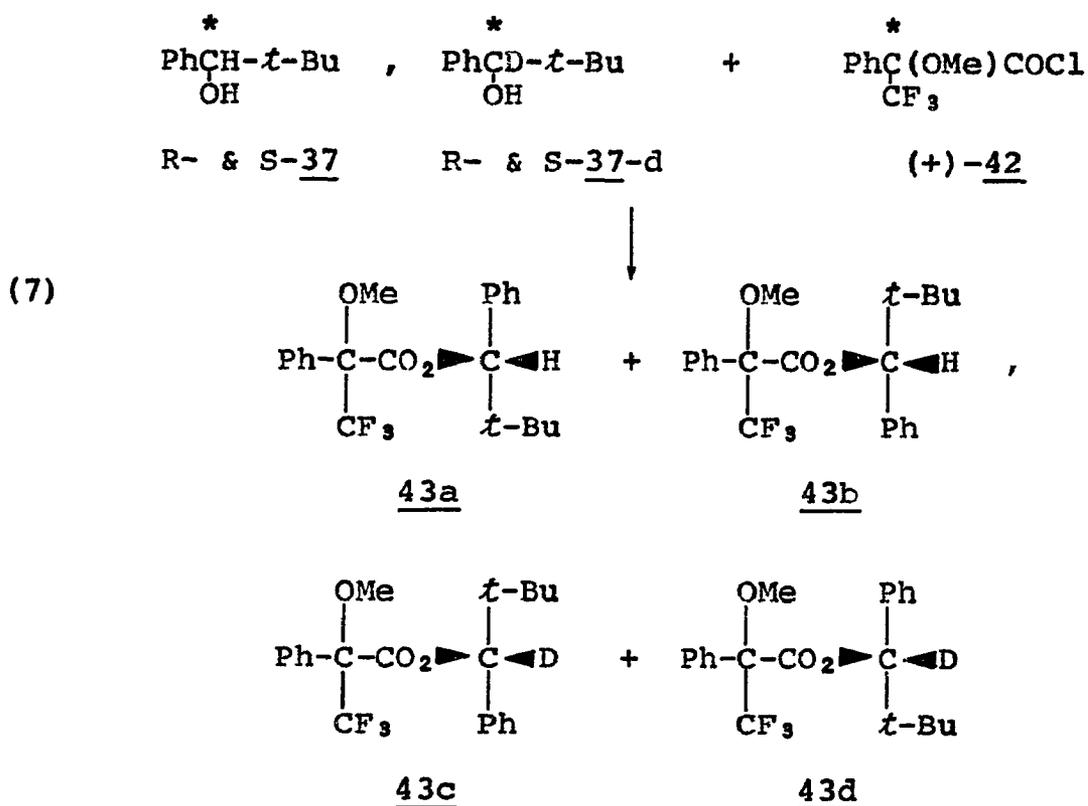


TABLE 5

NMR ANALYSIS OF THE MTPA ESTERS OF
 PHENYL-*t*-BUTYLCARBINOL (37) AND
 PHENYLTRIFLUOROMETHYLCARBINOL (39)^{a, b}

	<u>37</u>	<u>39</u>
Net % ee ^c	6.7 (S)	6.5 (R)
H % ee	13.5 (S)	29.6 (R)
D % ee	13.3 (R)	35.9 (S)
% deuterium _d	27.0	35.0
% deuterium ^m	26.8 ± 0.25	35.3 ± 0.1

- (a) This analysis was performed at Stanford University on a Varian HA-100 NMR Spectrometer.
 (b) Maximum error is ±1%.
 (c) The % ee from the rotations were 7.66% and 7.1% respectively.
 (d) From combustion analysis performed by Josef Nemeth, Urbana, Illinois.

From the table it can be seen that the net % ee of the phenyl-*t*-butylcarbinol (i.e., the percent excess of labeled plus unlabeled S-37) was 6.7% as compared to a value of 7.66% calculated from the specific rotation. For phenyl-trifluoromethylcarbinol these values were 6.5% and 7.1%. This is a perfect example of the phenomenon observed by Horeau,⁵³ who showed that the optical purity and the enantiomeric purity of a chiral substance are not necessarily equivalent as was previously thought to be the case. Therefore, the optical rotation cannot always be used as a precise measurement of the enantiomeric purity of a chiral substance, although in many cases it is probably accurate within experimental error.

An analysis of the results given in Table 5 shows that the overall isotope effect (k_H/k_D) for the reaction with phenyl *t*-butyl ketone was 2.7, which is comparable to the value of 2.3 observed by Dunn and Warkentin⁵ for the reduction of benzophenone with the β -deuteroisobutyl Grignard reagent. The overall k_H/k_D for the reaction with phenyl trifluoromethyl ketone was 1.85, which is almost the same as the value of 1.94 observed by Ridgway⁵⁴ for the reduction of the same ketone with a γ -asymmetric Grignard reagent.

The values in Table 5 also show that the stereoselectivity of H vs D transfer was the same in the reduction of phenyl *t*-butyl ketone (13.5% vs 13.3%), but differed by 6.3% in the reduction of phenyl trifluoromethyl ketone (29.6% vs 35.9%). This difference in behavior will be discussed later.

By using the values from the NMR analyses, it was possible to estimate quantitatively the percentage of each enantiomer being produced by the competing modes of reduction that were illustrated in Figures 8 and 9. The results of these calculations are shown in Figures 10 and 11. The competing modes of reduction are shown in an abbreviated form in these figures with the groups on the left side of the vertical line being those on the ketone and those on the right the groups on the asymmetric carbon of the Grignard reagent.

Ketone		Grignard Reagent		
$\begin{array}{c c} \text{Ph} & \text{Ph} \\ \hline t\text{-Bu} & \text{D} \end{array}$			$\xrightarrow{41.4\%}$	S-(-)- <u>37</u>
<u>40a</u>				
$\begin{array}{c c} t\text{-Bu} & \text{Ph} \\ \hline \text{Ph} & \text{D} \end{array}$			$\xrightarrow{31.6\%}$	R-(+)- <u>37</u>
<u>40b</u>				
$\begin{array}{c c} t\text{-Bu} & \text{H} \\ \hline \text{Ph} & \text{Ph} \end{array}$			$\xrightarrow{15.3\%}$	R-(+)- <u>37-d</u>
<u>40c</u>				
$\begin{array}{c c} \text{Ph} & \text{H} \\ \hline t\text{-Bu} & \text{Ph} \end{array}$			$\xrightarrow{11.7\%}$	S-(-)- <u>37-d</u>
<u>40d</u>				

Figure 10. Quantitative estimate of the contributions of the competing modes of reduction shown in Figure 8.

Ketone | Grignard Reagent

$\begin{array}{c c} \text{Ph} & \text{Ph} \\ \hline \text{CF}_3 & \text{D} \end{array}$ <p><u>41a</u></p>	42.1% \longrightarrow	R-(-)- <u>39</u>
$\begin{array}{c c} \text{CF}_3 & \text{Ph} \\ \hline \text{Ph} & \text{D} \end{array}$ <p><u>41b</u></p>	22.9% \longrightarrow	S-(+)- <u>39</u>
$\begin{array}{c c} \text{CF}_3 & \text{H} \\ \hline \text{Ph} & \text{Ph} \end{array}$ <p><u>41c</u></p>	23.8% \longrightarrow	S-(+)- <u>39-d</u>
$\begin{array}{c c} \text{Ph} & \text{H} \\ \hline \text{CF}_3 & \text{Ph} \end{array}$ <p><u>41d</u></p>	11.2% \longrightarrow	R-(-)- <u>39-d</u>

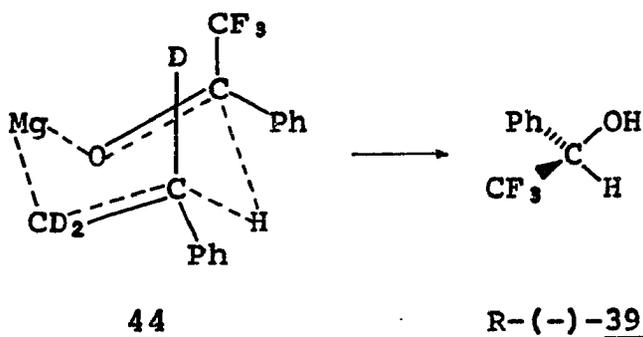
Figure 11. Quantitative estimate of the contributions of the competing modes of reduction shown in Figure 9.

From Figure 10 it can be seen that both hydrogen and deuterium transfer are favored when the phenyl groups are cisoid to one another (as in 40a and 40c) by a factor of 1.3 over the reduction modes (40b and 40d) in which the phenyl groups are transoid to one another.

This result is an obvious deviation from the accepted picture of the asymmetric Grignard reduction. The only precedent for this type of behavior, i.e., a Grignard reduction in which the phenyl groups prefer to be cisoid to one another and not transoid as would be predicted on

the basis of steric interactions, was that observed by Aaron¹² in the reduction of phenyl *t*-butyl ketone with the Grignard reagent from S-(+)-1-chloro-2-phenylpropane. In this case, the favored transition state was that in which the two phenyl groups were cisoid to one another. The fact that this phenomenon has only occurred in the reduction of phenyl *t*-butyl ketone with a Grignard reagent containing a phenyl group and either a methyl, hydrogen or deuterium on the asymmetric carbon suggests that some subtle effect causes a deviation from the norm when the small group reaches a certain "critical" size.

From Figure 11 it can be seen that both hydrogen and deuterium transfer are favored when the phenyl groups are cisoid (41a and 41c) in the reduction of phenyl trifluoromethyl ketone as was shown to be the case in the reduction of phenyl *t*-butyl ketone. This typical deviation of the stereochemistry of phenyl trifluoromethyl ketone Grignard reductions from the "steric size" model has already been rationalized in terms of the electronic repulsion between phenyl and the trifluoromethyl group. It has also been suggested that the transition states for the reduction of trifluoromethyl ketones may deviate sufficiently from a planar situation to one with cyclohexane-like character such as that represented by 44.²⁴ The conformation of lowest energy in this case is assumed to be that in which the two phenyl groups are situated in the equatorial or pseudoequatorial positions. This conformation would predict



the major product observed in this case and in many others. A deviation from planarity might also be the explanation for the results observed for phenyl *t*-butyl ketone in this investigation and in that of Aaron.¹²

To facilitate the discussion of the results given in Table 5 and shown in Figures 10 and 11, the free energy differences ($-\Delta\Delta G^\ddagger$) between the competing modes of reduction were calculated (see Table 6), and are illustrated diagrammatically in Figure 12. While nine energy differences for each reaction are listed in Table 6, only a few will be discussed at this time.

TABLE 6

CALCULATED FREE ENERGY DIFFERENCES BETWEEN
THE COMPETING MODES OF REDUCTION FOR PHENYL
t-BUTYL (40) AND PHENYL TRIFLUOROMETHYL KETONES (41)

No.	Competing Modes of Reduction	$-\Delta\Delta G^\ddagger$ (<u>40</u>)	$-\Delta\Delta G^\ddagger$ (<u>41</u>)
1	$\frac{a}{b}$	161 cal.	365 cal.
2	$\frac{c}{d}$	157	452
3	$\frac{a}{a} + \frac{b}{c} + \frac{d}{d}$	595	370
4	$\frac{a}{a} + \frac{d}{b} + \frac{c}{c}$	72	78
5	$\frac{a}{a} + \frac{c}{b} + \frac{d}{d}$	163	395
6	$\frac{a}{c}$	596	342
7	$\frac{b}{d}$	595	429
8	$\frac{a}{d}$	757	794
9	$\frac{b}{c}$	435	-23

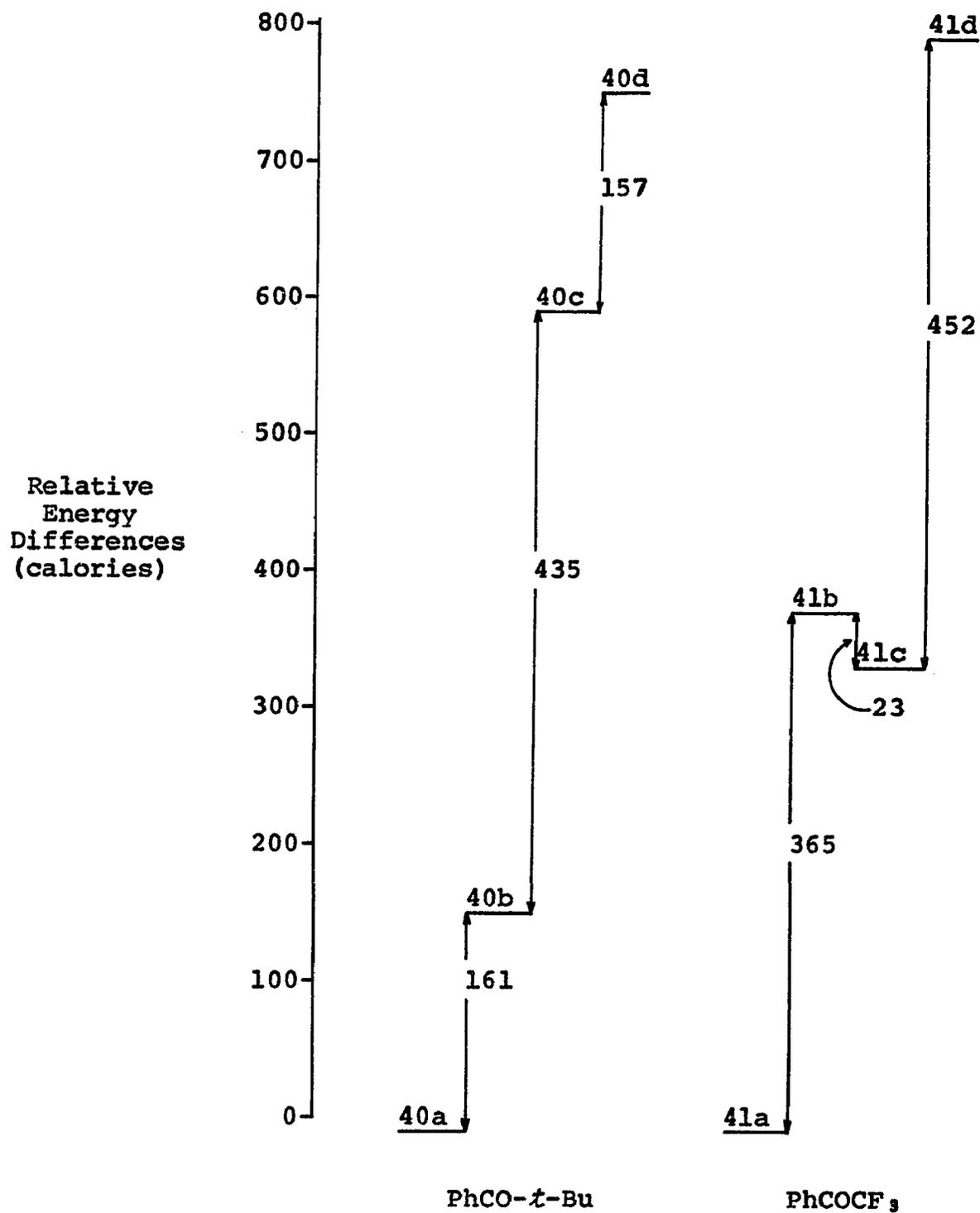


Figure 12. A plot of the relative energy differences for the competing modes of reduction for phenyl *t*-butyl and phenyl trifluoromethyl ketones.

For the reduction of phenyl *t*-butyl ketone, it can be seen that the energy differences ($-\Delta\Delta G^\ddagger$) between the pair of diastereomeric reduction modes for each reaction (i.e., for hydrogen and deuterium transfer) is very small and that the energy difference is nearly the same for both sets; i.e., 40a is favored over 40b by 161 calories and 40c over 40d by 157 calories. In other words, the stereoselectivity of hydrogen and deuterium transfer are nearly the same as was indicated by the results from the NMR analysis of the diastereomeric MTPA esters (13.5% ee vs 13.3% ee). This seems to indicate that there is very little energy difference between the interactions *t*-Bu vs D and *t*-Bu vs H as well as those for Ph vs H and Ph vs D.

For the reduction of phenyl trifluoromethyl ketone, it can be seen that the stereoselectivity of deuterium transfer was greater than that for hydrogen transfer; i.e., 41c was favored over 41d by 452 calories whereas 41a was favored over 41b by only 365 calories. This difference of 87 calories accounts for the observed 6.3% difference in the stereoselectivities of deuterium and hydrogen transfer (35.9% ee vs 29.6% ee respectively). However, these results do not directly indicate why there should be a difference in the stereoselectivity of deuterium vs hydrogen transfer for phenyl trifluoromethyl ketone but not for phenyl *t*-butyl ketone.

It was previously stated that the results of Mosher and coworkers^{2,3} for the reduction of labeled and unlabeled

trimethylacetaldehyde with enantiomeric unlabeled and labeled 2-methylbutyl Grignard reagents (see 16a and 16b), i.e., 12% asymmetric reduction for hydrogen transfer and 36% for deuterium transfer, might be rationalized in terms of the tunneling effect. When Morrison and Mosher³⁰ reduced phenyl *t*-butyl and phenyl ethyl ketones with the labeled and unlabeled Grignard reagent from S-(+)-1-chloro-2-phenylbutane they observed no significant difference in the amount of asymmetric reduction for H and D transfer. These results seemed to indicate that the important factor in these reactions may be a non-bonded isotopic disparity and not the tunneling effect.

The present experiments were designed to take all of these factors into consideration in one experiment, i.e., both hydrogen and deuterium transfer as well as hydrogen and deuterium compression. The advantage of this is that all of these events are taking place simultaneously under the same set of conditions. Thus, there are no external factors, such as time, temperature and work-up procedures, that have to be taken into account in the discussion of the results.

In the case of the reduction of phenyl *t*-butyl ketone there was no isotope effect on the stereoselectivity of H and D transfer even though both kinds of isotopic disparity mentioned above were present. This was also observed for phenyl *t*-butyl ketone when it was reduced with a chiral 3-phenylbutyl Grignard reagent stereospecific-

cally deuterated at the two position.⁵⁴ A moderate difference was observed for the reduction of phenyl trifluoromethyl ketone with this reagent as in this work; but a very large effect (% ee D transfer/% ee H transfer =8.5) was observed with phenyl isopropyl ketone. Thus, it seems that phenyl *t*-butyl ketone is probably insensitive to the factors responsible for this effect. All of this data seems to suggest that this "isotope steric size" factor is only felt in those reactions in which there are rather large energy differences (due to steric and/or electronic interactions) between the competing diastereomeric transition states.

From Figure 13, which is a plot of the percent asymmetric reduction of phenyl *t*-butyl and phenyl trifluoromethyl ketones *versus* increasing size of the other interacting group (R_2) on the Grignard reagent $\text{PhCR}_1\text{R}_2\text{CH}_2\text{MgX}$ of the *S* configuration, it can be seen that in each case there appears to be an increase in stereoselectivity (increase of %R for $\text{PhCO-}t\text{-Bu}$ and of %S for PhCOCF_3) as the "size" of R_2 increases up to methyl and then a decrease from ethyl to isopropyl (R_1 is the group being transferred). An observation such as this indicates that there may be a "critical total bulk" factor for transition states with lower stereoselectivity observed on either side of an optimum array of groups. In a low total bulk situation (e.g., A and B), steric compression is readily relieved; whereas in higher total bulk situations (e.g., D and E),

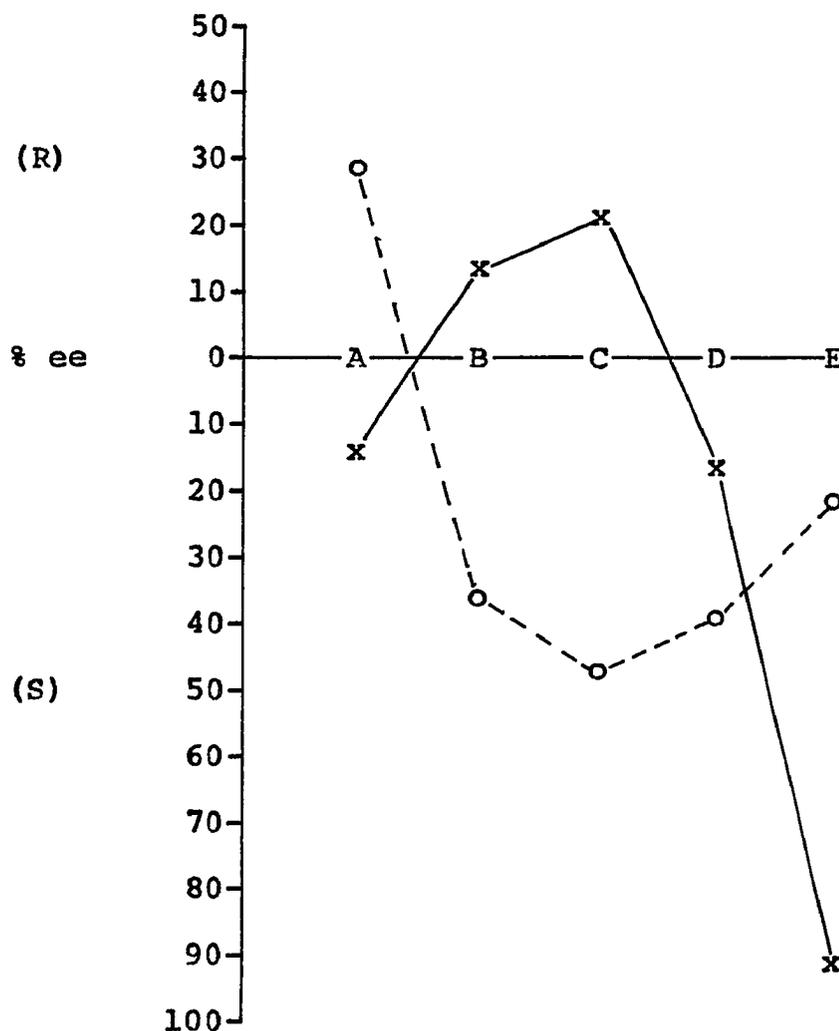


Figure 13. A plot of percent asymmetric reduction of phenyl *t*-butyl (x—x) and phenyl trifluoromethyl (o--o) ketones *versus* increasing size of the R₂ group on the Grignard reagent PhCR₁R₂CH₂MgX of S configuration where:

A	R ₁ = H,	R ₂ = D
B	D,	H
C	H,	Me
D	H,	Et
E	H,	<i>i</i> -Pr

The group R₁ is the one being transferred, while R₂ and Ph are the groups on the Grignard reagent interacting with the groups on the ketone.

discrimination between the diastereomeric transition states fades as R_2 approaches the size of its companion phenyl group. At some optimum bulk, these factors balance; in this series that point is reached with the 2-phenylpropyl Grignard reagent ($R_2 = \text{Me}$).

Thus, it seems that these results, i.e., a greater stereoselectivity for deuterium transfer, may be due to an isotopic size disparity between hydrogen and deuterium and not to an intrinsic difference in the stereoselectivity of hydrogen deuterium transfer. However, it is not possible to pin-point the origin of this effect at this time; and further work must be done in this area before the exact nature of this effect can be determined.

While the experiments that have been described in this thesis, i.e., the reduction of phenyl *t*-butyl and phenyl trifluoromethyl ketones with the Grignard reagent from R-1-bromo-2-phenylethane-1,1,2- d_3 , do not directly reveal the nature of the isotope effect on stereoselectivity, they do establish another example of the effect and an exception to it. The design of these experiments is novel and the techniques involved, especially the method of analysis, will be useful in future studies.

EXPERIMENTAL

Analyses: All carbon and hydrogen analyses were performed on an F & M Carbon, Hydrogen, Nitrogen Analyzer, Model 185.

Gas-Liquid Phase Chromatography: All quantitative analyses were carried out on a Perkin-Elmer Vapor Fractometer, Model 154 equipped with a Disc integrator. No corrections were made for differences in thermal conductivity. Preparative scale runs were carried out on an Aerograph Autoprep, Model A-700. Retention times (R.T.) are given for all of the principal products.

Unless otherwise noted all quantitative analyses were carried out under the following conditions: 1m x 6mm 20% Carbowax 20M on Chromosorb W-AW/DMCS column, 175°, 10psi; all preparative separations were carried out on a 10' x 1/4" 10% Carbowax 20M on 60/80 Chromosorb W column.

Infra-Red: All IR spectra were taken on a Perkin-Elmer Infracord Spectrometer using the 1601 and 1181 cm^{-1} bands of polystyrene as reference points. The spectra of solids were taken as mulls and those of liquids as a smear between salt plates.

Mass Spectra: All mass spectra were taken on a Hitachi Perkin-Elmer RMU-6E Mass Spectrometer.

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

NMR: All NMR spectra were run on a Varian Model A-60 NMR Spectrometer. The chemical shifts are given in parts per million (ppm) relative to a tetramethylsilane standard (the standard was used internally with solutions and externally with neat liquids).

Optical Rotations: All rotations were run on a Zeiss Photoelectric Precision Polarimeter 0.005°. Rotations at the sodium-D line (589 nm) were calculated from the following equation:

$$\alpha_D = \left(\frac{\frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}}}{\frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} + 1.3727} \right) \alpha_{546}$$

General: All boiling points are uncorrected. The dry ether used in most of the reactions was Fisher Anhydrous Ethyl Ether (E-138) which was stored over sodium wire. Reactions requiring anhydrous conditions were run in a dry nitrogen atmosphere in oven-dried glassware. Dilute solutions of sulfuric and hydrochloric acids are described in terms of the volume per cent of concentrated acid used to prepare the dilute solution. The lithium aluminum deuteride used was 98% d₄. When IR and NMR spectra are

listed, they will be reported as follows: IR(9966) or NMR(5646). The numbers in parentheses correspond to the spectrum number. The numbers that follow glpc analyses are coded from the research notebook, e.g. II-58-1 means Book II, page 58, glpc analysis number one.

Phenyl *t*-Butyl Ketone (36):²⁴ An ether solution (480ml) of *t*-butylmagnesium chloride, prepared in the usual manner from *t*-butyl chloride⁵⁵ (75.0g, 0.865mol) and magnesium turnings (19.3g, 0.865g-atm) was added dropwise to a solution of benzonitrile (44.0g, 0.425m) and cuprous chloride (1g) in 100ml of dry ether. The reaction mixture was heated under reflux for two hours and then 500ml of 10% HCl was added. The mixture was heated under reflux for one hour to complete hydrolysis. The organic layer was separated, combined with several ether extracts and washed with water. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. Distillation of the residue gave 52.3g of product, b.p. (0.4mm) 51-56°, 93% pure by glpc (II-25, R.T. of ketone 4'55"). The ketone, 48.6g (70.6%), was obtained by redistillation and characterized by IR(9966).

Phenyl Trifluoromethyl Ketone (38):⁵⁶ A solution of phenylmagnesium bromide was prepared in the usual manner from magnesium turnings (49g, 2g-atm) and bromobenzene (320g, 2mol) in 400ml of dry ether. A solution of trifluoroacetic acid (90g, 0.79mol) in 200ml dry ether was added dropwise with caution to maintain a gentle reflux. The reaction mixture was allowed to stand overnight at room temperature and then was heated under reflux for two hours. It was then cooled to room temperature and hydrolyzed with 600ml of 50% (v/v) HCl. The organic layer was separated and combined with

three ether extracts. The ether solution was washed once with saturated aqueous sodium bicarbonate and twice with water, it was then dried (MgSO_4) and the ether was removed under reduced pressure. Distillation of the residue at aspirator pressure gave two fractions:

Fraction	b.p.	Wt(g)	% Ketone*
1	62°	4.7	94.6
2	62-66°	93.5	99+

*Glc (II-12, 10' x 1/4" Silicon SE-30 on 60/80 Chromosorb W, 120°, 60ml/min, R.T. of ketone, 4'50").

The yield was 71.7%. The ketone was characterized by IR(11007).

S-(+)-Methyl Mandelate (18):³²A stirred solution of S-(+)-mandelic acid (100g, 0.658mol, Aldrich Chemical Company, Incorporated; $[\alpha]_D^{30}$ +147.38, (578) +154.61, (546) +177.55 $\pm 0.005^\circ$ (l 1.0, c 2.005, water; 94.1% ee⁵⁷), dry methanol (21.1g, 0.658mol), 2,2-dimethoxypropane (66.5g, 0.658mol) and concentrated hydrochloric acid (7ml, 0.1647mol) was heated at 45°C for four hours. The reaction mixture was allowed to stand overnight at room temperature, then all volatile materials were removed at reduced pressure. The residue (108g) was recrystallized from 300ml benzene/30-60° pet. ether (1:2) to give 104.9g (96%) of pure ester as shown by TLC; m.p. 55.8°C, $[\alpha]_D^{22}$ +171.44, (578) +179.90, (546) +207.35 $\pm 0.005^\circ$ (l 1.0, c 2.04, chloroform), 96.85%

ee based on $[\alpha]_D$ (max) $+176^\circ$.³³

NMR(5646): 6.82(S,5H), 4.73(S,1H), 3.60(S,1H), 3.38(S,3H).

S-(+)-Methyl-O-Mesyl Mandelate (23): S-(+)-methyl mandelate (104.9g, 0.63mol) was dissolved in 250ml of dry pyridine and cooled to -5°C in an ice-salt bath. Methanesulfonyl chloride (80.18g, 0.70mol) was added dropwise (2.5 hours) so that the temperature did not exceed 0°C . The reaction mixture was stirred for one hour at -5°C and then poured into a cold, stirred solution of 5% sulfuric acid (800ml). The precipitated mesylate was collected by filtration and air dried. Recrystallization from acetone/water gave 106g (69.5%) of pure mesylate, m.p. $115-115.5^\circ\text{C}$, $[\alpha]_D^{25} +108.71$, (578) $+114.24$, (546) $+132.28 \pm 0.005^\circ$ (l 1.0, c 1.58, chloroform).

NMR(5682): 7.44(S,5H), 5.95(S,1H), 3.77(S,3H), 3.07(S,3H).

C&H Analysis (II-19): calc; C-49.17, H-4.95.

found; C-49.10, H-5.20.

R-(-)-2-Phenylethanol-1,1,2-d₃ (22): To a stirred suspension of lithium aluminum deuteride (18.03g, 0.43mol) in 600ml of dry ether, a solution of S-(+)-methyl-O-mesyl mandelate (105g, 0.43mol in 950ml of dry THF) was added dropwise to maintain a gentle reflux. The reaction mixture was heated under reflux for 2.5 hours, allowed to cool to room temperature, and then hydrolyzed with 750ml of 10% HCl. The organic layer was combined with several ether extracts, washed with water and dried (MgSO_4). After

removal of the ether the residue was distilled to give
36.07g of product:

Fraction	b.p. (0.6mm)	Wt (g)	%PhCH(OH)CH ₂ D*	%PhCHDCD ₂ OH*
1	74°	0.20	30.8	66.4
2	74-75°	10.21	8.7	91.3
3	"	6.50	5.9	94.1
4	"	14.08	1.5	98.5
5	"	2.70	---	97.4
6	"	2.38	---	97.5

*GlpC analysis (II-20 R.T. 1-phenylethanol, 5'10",
2-phenylethanol, 8'55").

The yield of 2-phenylethanol-1,1,2-d₃ was 34.4g
(64%), α_D^{20} -1.39, (578) -1.45, (546) -1.63 \pm 0.005° (l 1.0,
neat, fraction 4).

NMR(5724,7339): 6.93(S,5H), 3.90(S,1H), 2.50(S,0.94H).

Mass Spectrum (II-20): 5.6% d₂, 92.0% d₃, 2.2% d₄.

R-1-Bromo-2-phenylethane-1,1,2-d₃ (24):⁴² To a stirred
solution of R-(-)-2-phenylethanol-1,1,2-d₃ (25.14g, 0.2008mol;
96.4% pure) and triphenylphosphine (52.67g, 0.2008mol)
in 175ml of dry DMF, bromine was slowly added (keeping
the temperature below 55°C) until a yellow color persisted.
The reaction mixture was stirred for one hour at room tem-
perature and then all volatile materials were removed at
reduced pressure. The residue was poured into water and
the separated bromide was taken up in ether. The ether
solution was dried (MgSO₄) and the ether was removed at
reduced pressure. Distillation of the residue gave 18.05g
of product, b.p. (0.4mm) 44-46°, 93.6% pure by glpc

(II-21-1), α_D^{21} -2.34, (578) -2.44, (546) -2.79 $\pm 0.005^\circ$
 (ℓ 1.0, neat; 96.2% 1-bromo-2-phenylethane, 0.76% 1-bromo-
 1-phenylethane and 3.04% styrene).

NMR(7338): 6.87(M,5H), 2.60 (S,0.94H).

Solvolysis to Remove 1-bromo-1-phenylethane:⁴³ The mixture of bromides was heated under reflux with 50ml of absolute methanol for 24 hours. The methanol was removed and the residue was distilled to give 15.1g, b.p. (0.4mm) 47-8°, of product which was shown to be 91.2% 1-bromo-2-phenylethane by glpc (II-22-1). Column Chromatography (18" x 3/4" Fisher A-950 Neutral Alumina Column of Brockman activity 1, 80/200 mesh; eluted with ether) was used to purify the bromide. The ether was removed and the product was redistilled to give 11.3g, b.p. (0.55mm) 53-5°, 90% 1-bromo-2-phenylethane-1,1,2-d₃, 4.56% 1-bromo-1-phenylethane-2,2,2-d₃ and 5.44% styrene plus ethylbenzene as shown by glpc analysis (II-22-2). Although the rotation of the bromide sample was (-), this may not correspond to the rotation of the R bromide since the sample was not purified by glpc. Mass Spectrum (II-22): 6.7% d₂, 93.2% d₃.

Grignard Reagent from R-1-bromo-2-phenylethane-

1,1,2-d₃ (25): The Grignard reagent was prepared from triply-sublimed magnesium (1.400g, 0.0576g-atm) and a mixture of the bromides (10.16g 1-bromo-2-phenylethane-1,1,2-d₃ and 0.52 1-bromo-1-phenylethane-2,2,2-d₃, 0.0569mol) in 65ml of dry ether in the usual manner. The

Grignard solution was stirred for 2 hours at room temperature and used immediately in the following reactions. Acid-base titration showed the solution to be 0.678M (82.5% yield).

S-(+)-1-phenylethane-1,2,2-d₃ (34): A 10ml aliquot of the Grignard reagent 25 was hydrolyzed with 25ml of water. The organic layer was separated and combined with several ether extracts. The ether solution was washed with water and dried (MgSO₄). The ether was removed and the residue was distilled to give 0.58g of impure hydrocarbon, b.p. (≈1atm) 134-6°. One preparative glpc separation (100°, 60ml/min) gave pure ethylbenzene as shown by glpc analysis (II-23, 100°, 5psi, R.T. of 1-phenylethane, 5'10"), $[\alpha]_D^{22} +1.04$, (578) +1.09, (546) +1.26 ±0.05° (ℓ 0.1, neat).

Reactions of the Grignard Reagent from

R-1-bromo-2-phenylethane-1,1,2-d₃

Phenyl *t*-Butyl Ketone: To a 40ml aliquot of the Grignard reagent 25 (0.027mol), a solution of phenyl *t*-butyl ketone (4.4g, 0.027mol) in 30ml of dry ether was added dropwise to maintain a gentle reflux. The reaction mixture was heated under reflux for 1.5 hours, allowed to cool to room temperature and hydrolyzed with 50ml of 10% HCl. The organic layer was separated and combined with several ether extracts of the aqueous layer. The ether solution was washed with 5% aqueous sodium bicarbonate solution and water, dried

(MgSO₄) and the ether removed under reduced pressure. Distillation of the residue gave 3.5g of product.

Fraction	b.p. (0.4mm)	Wt(g)	% Alc*
1	33°	0.10	---
2	57-9	2.45	50.4
3	59-76	0.05	---
4	76	0.90	98.7

*% phenyl-*t*-butylcarbinol by glpc (II-25, R.T. 10'10")

The yield of phenyl-*t*-butyl carbinol was 2.17g (48.6%), $[\alpha]_D^{23}$ -2.79, (578) -2.94, (546) -3.44 \pm 0.005° (l 1.0, c 10.02, ether), 7.66% ee S-(-) based on $[\alpha]_{578}$ 38.4°.⁸

NMR(5837): 6.91(S,5H), 3.91(S,0.7H), 3.20(S,1H), 0.60(S,9H).

Mass Spectrum (II-25): 76.1% d₀, 23.8% d₁.

Phenyl trifluoromethyl Ketone: A 20ml aliquot of the Grignard reagent 25 (0.0135mol) was allowed to react with a solution of phenyl trifluoromethyl ketone, (2.34g, 0.0135 mol) in 20ml of dry ether in the manner described for phenyl *t*-butyl ketone.

Fraction	b.p. (11mm)	Wt(g)	% Alc*
1	27°C	0.66	75.22
2	77.5-78.5	1.00	92.32
3	"	0.95	97.75

*% phenyltrifluoromethylcarbinol by glpc (II-24, R.T. 10'36").

The total yield of alcohol was 1.79g (75.5%). The alcohol was purified by one preparative glpc separation (185°,

85ml/min) and shown to be 99.4% pure by glpc analysis (II-24-2); $[\alpha]_D^{23}$ -2.26, (578) -2.36, (546) -2.68 $\pm 0.01^\circ$ (l 0.5, neat), 7.1% ee R-(-) based on $[\alpha]_D$ (max) 31.85° .⁵⁰
NMR (5836): 7.28(S,5H), 4.69(Q,0.6H), 3.92 (S,1H).
Mass Spectrum (II-24): 63.8% d_0 , 36.2% d_1 .

Purification of R-2-phenylethanol-1,1,2- d_3 (22): Purification of 22 by preparative glpc gave a sample of the alcohol which exhibited the following rotation, $[\alpha]_D^{26}$ +1.064, (578) 1.319, (546) 2.468 $\pm 0.025^\circ$ (l 0.2, neat). A second purification gave a sample of 22 which exhibited the same rotation. Analysis of glpc showed the sample to be 99+% pure. The compound that had previously contaminated the alcohol was collected, but was of insufficient size for identification.

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APPENDIX I

Determination of Deuterium Content

by Mass Spectroscopy

The method used for the calculation of the deuterium content of the reaction products is from K. Biemann, "Mass Spectrometry Organic Chemical Applications," McGraw-Hill Book Company, Incorporated, New York, 1962, pp. 204-227.

The first step is to determine the amount of electron energy (eV) needed to give a reasonably intense parent peak (M), but which does not give a M-1 peak when the compound to be studied is only one mass unit higher than the non-deuterated compound. For all of the compounds studied in this work, 10eV was found to give optimum results.

The next step is to run the spectrum of the non-deuterated compound and determine the ratio of the M+1, M+2, etc. to the parent peak. This is done as follows (the example given will be for 2-phenylethanol and 2-phenylethanol-2-d, II-58-2):

For PhCH ₂ CH ₂ OH:	M	, 122 = 104 units	
	M+1,	123 = 8 units	(A)
	M+2,	124 = 7 units	

Therefore, setting the M peak at 1.00, the M+1 = 0.077 and M+2 = 0.0096.

To calculate the amount of deuterium in II-58-2, the peak heights of the M, M+1, M+2 fragments are measured (arbitrary units).

$$\begin{aligned} M, 122 &= 6 \text{ units} \\ M+1, 123 &= 214 \text{ units} \\ M+2, 124 &= 20 \text{ units} \end{aligned} \quad (\text{B})$$

The entire peak at mass 122 (6.0) is due to unlabeled species.

To compute the contribution of the unlabeled species to M, M+1, and M+2, multiply the peak height at M with the abundance of M, M+1, and M+2 in the standard.

$$\begin{aligned} 6 \times 1.00 &= 6.00 \\ 6 \times 0.077 &= 0.46 \\ 6 \times 0.0096 &= 0.06 \end{aligned} \quad (\text{C})$$

Subtract C from B:

$$\begin{array}{r} 6 \\ -6 \\ \hline 0 \end{array} \quad \begin{array}{r} 214.00 \\ -0.46 \\ \hline 213.54 \end{array} \quad \begin{array}{r} 20.00 \\ -0.06 \\ \hline 19.94 \end{array} \quad (\text{D})$$

The peak height due to singly labeled species is 213.54 units. Compute its contribution to M+1 and M+2.

$$\begin{aligned} 213.54 \times 1.00 &= 213.54 \\ 213.54 \times 0.077 &= 16.44 \end{aligned} \quad (\text{E})$$

Subtract E from D:

$$\begin{array}{r} 213.54 \\ -213.54 \\ \hline 0 \end{array} \quad \begin{array}{r} 19.94 \\ -16.44 \\ \hline 3.50 \end{array} \quad (\text{F})$$

The peak height due to doubly labeled species is 3.5 units.

Since there are no species containing more than two deuterium atoms, the sum of the corrected species is:

$$6.0 + 213.54 + 3.5 = 223.04$$

The distribution in mole % is:

$$(6.0/223.04) (100) = 2.7\% d_0$$

$$(213.54/223.04) (100) = 95.7\% d_1$$

$$(3.5/223.04) (100) = 1.5\% d_2$$

APPENDIX II

CHEMICAL SHIFTS OF THE DIASTEREOMERIC MTPA
ESTERS OF PHENYL-*t*-BUTYLCARBINOL (37) AND
PHENYLTRIFLUOROMETHYLCARBINOL (39)^a

Compound	CF ₃ ^b	OCH ₃	H	Other
R-(+)- <u>37</u>	670	206	345.5	53 (<i>t</i> -Bu)
S-(-)- <u>37</u>	623	210	337.5	56 (<i>t</i> -Bu)
S-(+)- <u>39</u>	551	208	381.2	1106 (CF ₃) ^c
R-(-)- <u>39</u>	501	216	376.8	1086 (CF ₃) ^c

- (a) Chemical shifts are expressed in Hz downfield from TMS or TFA.
 (b) Trifluoromethyl group on MTPA.
 (c) Trifluoromethyl group on the alcohol.

The results obtained from the analysis of the diastereomeric MTPA esters of the partially labeled carbinols 37 and 39 were determined as follows:

1. For phenyl-*t*-butylcarbinol (37):
 - a) The net % ee and the % D were determined from numerous integrations of the diastereomeric carbinol proton signals.
 - b) The % H ee was determined from numerous integrations of the diastereomeric MTPA trifluoromethyl group signals.
 - c) The % D ee was calculated from the results of the above measurements.

2. For phenyltrifluoromethylcarbinol (39):

All of the results were determined from numerous planimeter measurements of four different scans of the diastereomeric carbinol trifluoromethyl group signals. A reproduction of one of the actual NMR spectra is shown in the following figure.

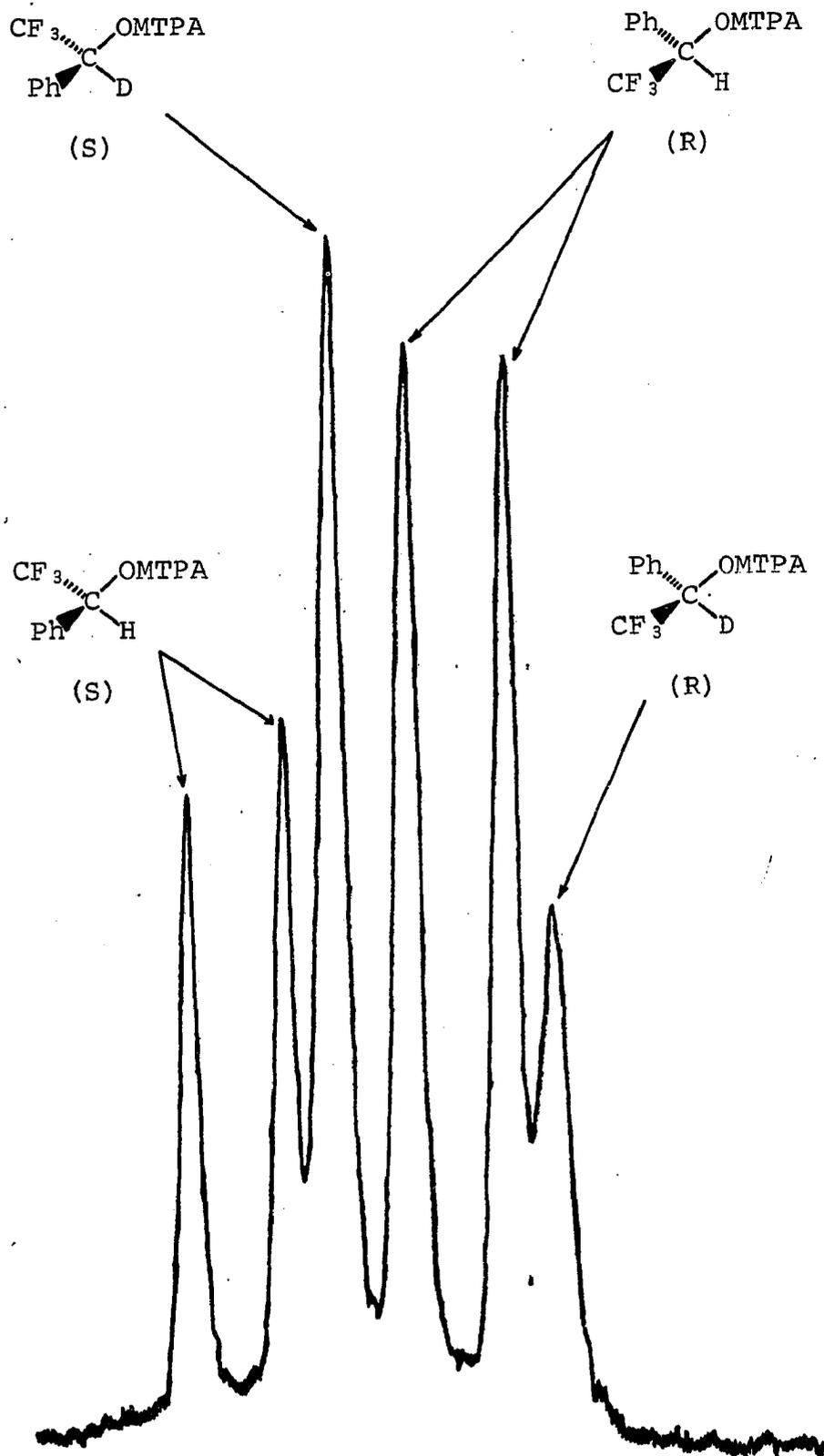


Figure 14. NMR spectrum of the diastereomeric carbinol trifluoromethyl groups.

PART II. ELECTROPHILICALLY ASSISTED
NUCLEOPHILIC OPENING OF
OPTICALLY ACTIVE STYRENE OXIDE

INTRODUCTION

Synthesis of Optically Active Styrene Oxide

The first synthesis of optically active styrene oxide (4) was reported by Eliel and Delmonte¹ in 1956. It involved the reaction of 1-phenyl-1,2-ethanediol (2) with p-toluenesulfonyl chloride to give the monotosylate (3), which was converted to the epoxide (4) in a 42% yield by reaction with base (Figure 1).

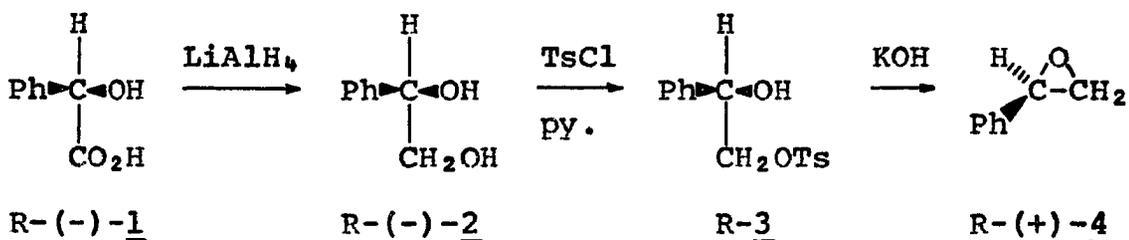
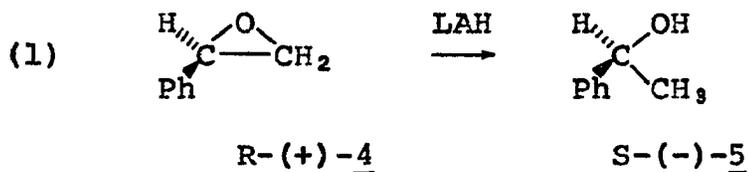


Figure 1. Preparation of R-(+)-styrene oxide.

The optical purity of the epoxide was determined by lithium aluminum hydride reduction to 1-phenylethanol (5).



From the signs and magnitudes of the rotations of the mandelic acid used and 1-phenylethanol obtained,

ElieI and Delmonte¹ calculated that the reaction sequence shown in Figure 1 involved at least 85% retention of configuration (i.e., at most 15% racemization). The maximum rotation of styrene oxide was calculated to be 33° (neat). The reason for the loss of optical purity was not determined; several possibilities can be envisaged: (1) one or more of the steps in the synthesis may have been less than 100% stereospecific; (2) one of the intermediates, or styrene oxide, may have partially racemized; or (3) a small amount of secondary tosylate [PhCH(OTs)CH₂OH] may have been formed; if so, it would have been converted to epoxide with inversion of configuration at the asymmetric carbon.

In 1962, Berti and coworkers² synthesized R-(+)-styrene oxide by a slight modification of the method used by ElieI and Delmonte. Using sodium methoxide instead of potassium hydroxide in the cyclization step, the yield was improved by about 14% and the rotation of the styrene oxide, i.e. $[\alpha]_D + 34.2^\circ$ (neat), was the highest yet reported. It was stated that the optical purity of the epoxide must be greater than 90%.

Another modification of ElieI and Delmonte's work, in which the monobrosylate was used instead of the monotosylate, was introduced by Tömösközi.³ The basic advantage of this method is that the brosylate is more stable than the tosylate and can be readily purified by recrystalliza-

tion. The end result is a substantial enhancement of the yield to about 80%.

In 1966, after preparing S-(-)-styrene oxide according to Eliel and Delmonte's procedure, Pasto and coworkers⁴ reported that $[\alpha]_D$ (max) for styrene oxide should be 34.2°.

Optically active styrene oxide has also been prepared by asymmetric induction reactions.^{5, 6, 9} Henbest and coworkers⁵ obtained S-(-)-styrene oxide (2.0-4.4% ee) through the action of (+)-monopercamphoric acid on styrene in a variety of solvents. The model used to predict the course of the reaction is depicted as follows.

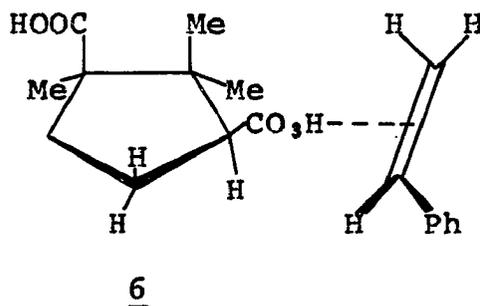


Figure 2. Henbest model for asymmetric epoxidation with 1S-(+)-monopercamphoric acid (6).

The hydrogen on the asymmetric α -carbon and the carbonyl group of the peracid are eclipsed and the largest groups on the α -carbon [$-\text{C}(\text{CH}_3)_2$] and the alkene (R) are on opposite sides of the plane of the model as shown above.

Montanari and coworkers⁶ also prepared optically active styrene oxide by this same method. Using several different peracids, optically active styrene oxide was obtained (1.5-4.6% ee). The model used (Figure 3) for

predicting the absolute configuration of the epoxide is analogous to that proposed⁸ for the asymmetric oxidation of sulfides to sulfoxides with peracid. However, the authors warn that in the epoxidation of other olefins, stereoelectronic factors may change the mechanism. The

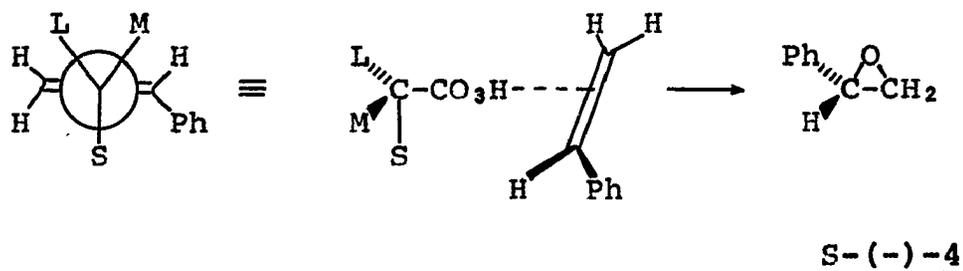
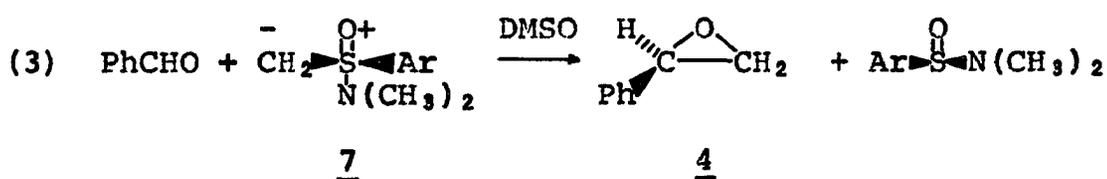


Figure 3. Montanari model for asymmetric epoxidation.

model depicted in Figure 3 does not necessarily mean that asymmetric induction is due to direct steric interactions between the groups S, M and L of the peroxyacid and those of the alkene. In fact, it is likely that in these oxidations asymmetric induction is transmitted through a solvent shell.^{5, 7} This hypothesis is supported by the activation parameters for both the epoxidation of alkenes⁵ and the oxidation of sulfides to sulfoxides⁸ measured in various solvents.

Johnson and Schroeck⁹ prepared optically active styrene oxide through the reaction of benzaldehyde with an optically active oxo-sulfonium methylide (7).

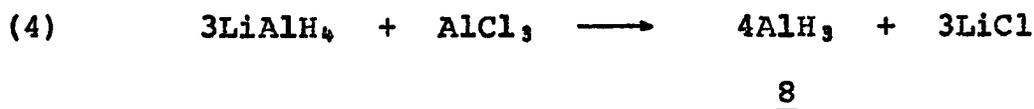


The optical purity of 4 was reported to be 5%. (However, this was based on $[\alpha]_D$ (max) $+31^\circ$, which is not the maximum rotation of styrene oxide).

The Reaction of Epoxides with Mixed Hydride Reagents

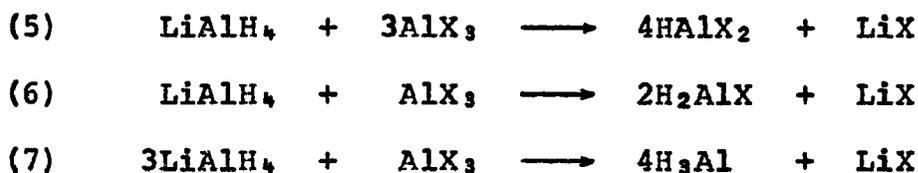
The reaction of styrene oxide (and other epoxides) with mixed hydride reagents (those hydrides prepared from 3:1, 1:1, 1:3, and 1:4 molar ratios of LiAlH_4 and AlCl_3) has received much attention.¹⁰⁻¹²

In 1947, Schlesinger and coworkers¹³ found that aluminum hydride, also called alane, (8) was formed when lithium aluminum hydride and aluminum chloride were mixed in a 3:1 molar ratio in ether. This reaction was also



observed by Wiberg and coworkers.¹⁴ It was noted, that the alane ether solution is not stable and that the alane precipitates out of solution as a polymer within minutes after mixing the reagents.

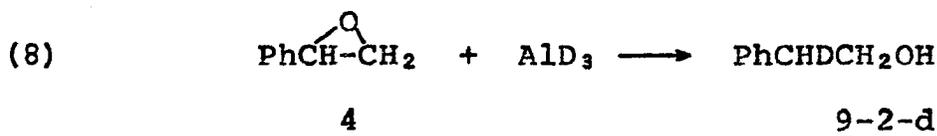
In 1966, Ashby and Prather¹⁵ studied the composition of the "mixed hydride" reagents in diethyl ether solution. The study showed that the reduction of aluminum halide to aluminum hydride by lithium aluminum hydride proceeds stepwise by way of the intermediate hydridoaluminum halides. By controlling the stoichiometry, these intermediates could be prepared (Equations 5-7) and isolated



as amine complexes. The composition of each amine complex was determined by elemental analysis.

Eliel and Delmonte^{16, 17} have shown that the direction of ring opening of styrene oxide by mixed hydride is dependent upon the ratio of $\text{LiAlH}_4/\text{AlCl}_3$ used. Their results are summarized in Table 1. As can be seen from the table, the use of a large excess of aluminum chloride reverses the direction of ring opening. This was interpreted at the time to mean that the 1:4 mixed hydride reduction proceeded through phenylacetaldehyde formed by a hydride shift.

The first example of the reduction of styrene oxide with the $\text{AlD}_3/\text{Et}_2\text{O}$ reagent ($3\text{LiAlD}_4/1\text{AlCl}_3$)* was reported by Eliel.¹⁸ However, the only data given was that which is illustrated in equation 8.



*When the term alane is used in this thesis, it is intended to signify the reagent prepared from $\text{LiAlH}_4/\text{AlCl}_3$ in a 3:1 molar ratio.

TABLE 1
REDUCTION OF STYRENE OXIDE WITH
"MIXED HYDRIDE" REAGENTS

$$\text{PhCH}-\text{CH}_2 \xrightarrow{\text{O}} \text{PhCH}(\text{OH})\text{CH}_3 + \text{PhCH}_2\text{CH}_2\text{OH}$$

4
5
9

LiAlH ₄ :AlCl ₃	% <u>5</u>	% <u>9</u>
1:0	90-95	5-10
1:1	16	84
1:4 ^a	2-5 ^b	95-98 ^c
1:4 ^a	2 ^b	94.6 ^c

(a) LiAlD₄
 (b) PhCH(OH)CH₂D
 (c) PhCH₂CHDOH

TABLE 2
REDUCTION OF EPOXIDES WITH
"MIXED HYDRIDE" REAGENTS

$$\text{R}_2\text{C}-\text{CHR}' \xrightarrow{\text{O}} \text{R}_2\text{CHCH}(\text{OH})\text{R}' + \text{R}_2\text{R}'\text{CCH}_2\text{OH}$$

10a
11
12

b
11
12

R = R' = Ph
R' = *t*-Bu,
R = Me

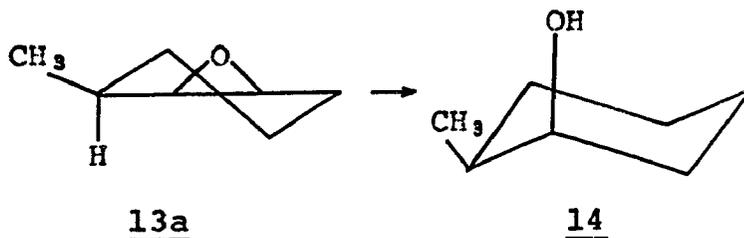
Epoxide	LiAlH ₄ /AlCl ₃	% <u>11</u>	% <u>12</u>
<u>10a</u>	3/1	100 ^b	0
<u>10a</u>	3/1 ^a	100 ^b	0
<u>10a</u>	1/4	0	67
<u>10b</u>	LiAlH ₄	100	0
<u>10b</u>	3/1	mainly	
<u>10b</u>	4/1		mainly

(a) LiAlD₄
 (b) Ph₂CDCH(OH)Ph

Rerick and Eliel¹⁹ have done a more extensive study on the direction of ring opening of epoxides with mixed hydride reagents and their results are summarized in Table 2. An excess of AlCl_3 not only reverses the direction of ring opening, but also causes migration of a phenyl group (10a) or a *t*-butyl group (10b).

Rickborn and Quartucci²⁰ observed that the reduction of *trans*-4-*t*-butylcyclohexene oxide with alane was slightly more stereospecific than the corresponding reduction with lithium aluminum hydride. Reduction with alane gave >99% of the *trans*-3-*t*-butylcyclohexanol while lithium aluminum hydride gave 90% of the same product plus 10% of the isomer.

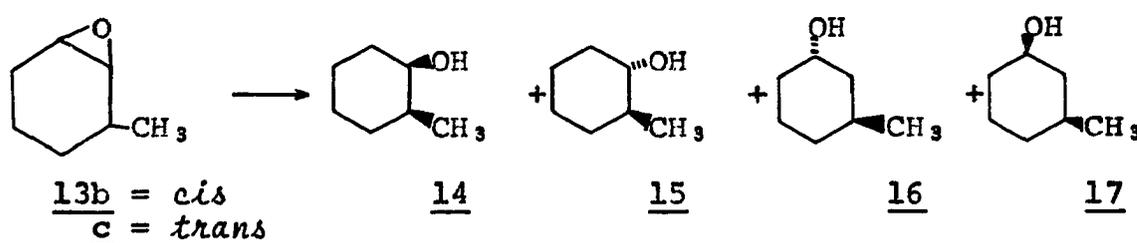
Rickborn and Lamke²¹ shed more light on the subject by doing a more extensive study of 3-methylcyclohexene oxide with the same reagents (see Table 3). It can be seen that while lithium aluminum hydride proceeds mainly with retention of configuration (*cis*-epoxide to *cis*-alcohol and *trans*-epoxide to *trans*-alcohol), it also gives some inverted product. Reduction with alane appears to be completely stereospecific in that only *cis*-alcohol is formed from *cis*-epoxide and *trans*-alcohol from *trans*-epoxide.



The major reduction pathway thus appears to involve diaxial opening presumably through a more stable quasi-equatorial methyl half-chair conformer (13a).

TABLE 3

REDUCTION OF 3-METHYLCYCLOHEXENE OXIDE
WITH HYDRIDE REAGENTS



Epoxide	Hydride	<u>14</u>	<u>15</u>	<u>16</u>	<u>17</u>
<u>13b</u>	LiAlH ₄	89	9	--	2
<u>13c</u>	"	--	30	61	9
<u>13b</u>	AlH ₃	94	--	--	6
<u>13c</u>	"	--	32	68	--

The results of previous workers may be rationalized by the following mechanistic picture which is an adaptation of that proposed by Ashby and Prather.¹⁵ The reduction of triphenylethylene oxide with mixed hydride (LiAlH₄/AlCl₃, 1:4)¹⁹ probably involves electrophilic attack by HAlCl₂ (18) at the oxygen atom of the epoxide. The resulting adduct (19) has an Al-H bond from which hydride attack on the ring carbons can occur via a four-center transition state (20). The hydride could attack the secondary epoxide carbon atom as well as the tertiary position (illustrated by 20) to produce 1,1,2-triphenylethanol. When the attack-

differentiate between these possibilities for styrene oxide is to study the reduction of the optically active species.

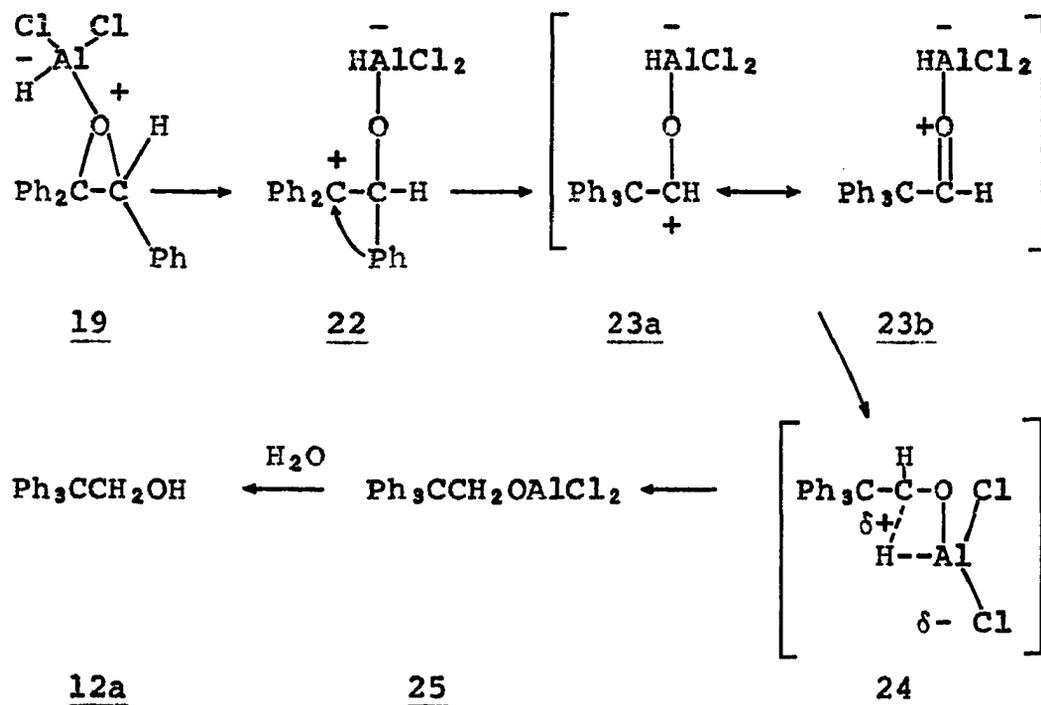
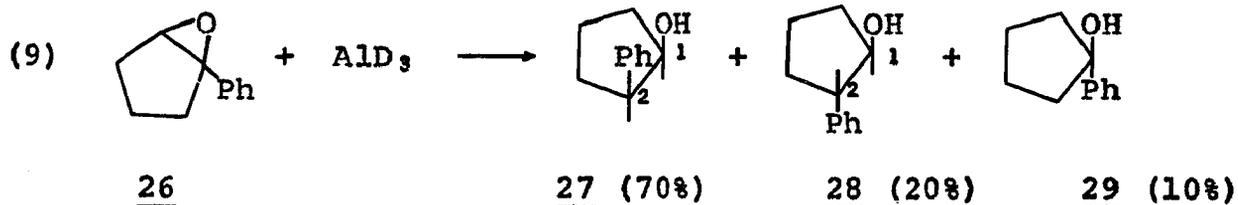


Figure 5. Complex formation followed by phenyl migration and hydride transfer.

Reduction of 1-phenylcyclopentene oxide (26) with alane (8) occurs with overall *trans* stereochemistry.^{22, 23}



It was demonstrated by reduction with trideuteroalane that the reaction probably proceeded by an intermolecular process. Compound 27 was formed in an 80% yield with >0.8 deuterium at C₂ and <0.2 deuterium at C₁. The intermolecular attack

(Figure 6) observed is expected to predominate only when excess alane is present.

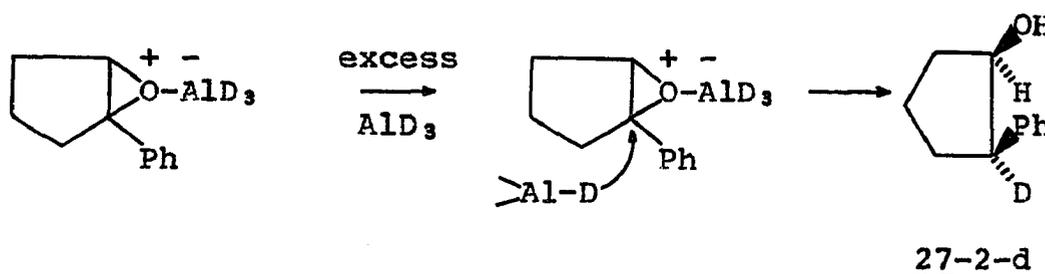


Figure 6. Intermolecular attack of alane.

Inverse addition of insufficient alane gives products whose structures imply that under these conditions substantial rearrangement *via* a 1,2-hydride shift takes place (Figure 7). Alkoxyaluminum hydrides have been shown to be comparable to alane in terms of their Lewis acidity; but they are less reactive hydride sources, thus allowing the rearrangement pathway to become competitive.

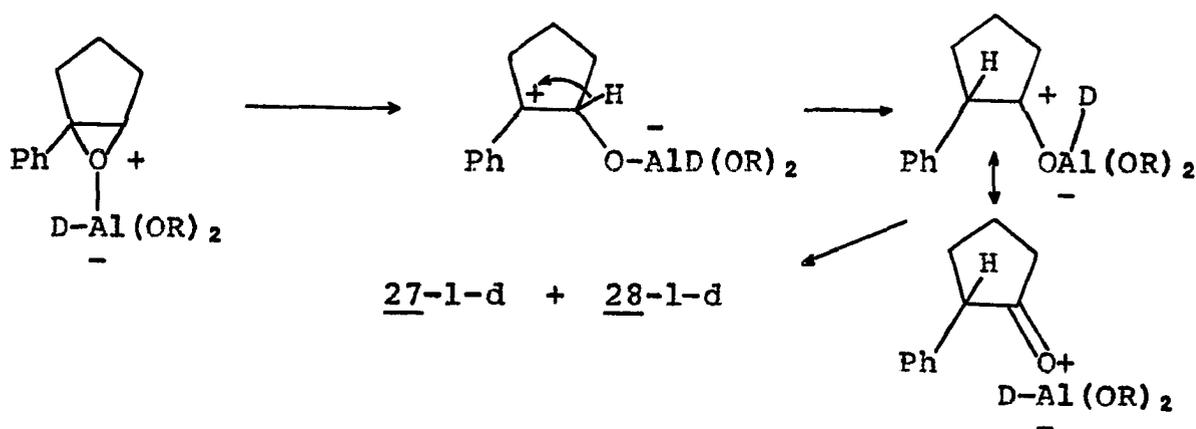


Figure 7. Complex formation followed by hydride migration.

A third pathway for reduction is *via* an intramolecular mechanism (Figure 4),¹⁵ which leads to 28-2-d.

However, this product (28-2-d) is only a minor one for the range of conditions studied by Lansbury and Pattison.²³ The authors make the comment that this may be a consequence of the substantial bond angle and torsional strain inherent in the cyclopentene oxide system. This strain may cause 26 to undergo Lewis acid catalyzed ring opening more readily than styrene oxide or even 1-phenylcyclohexene oxide, hence, facilitating rearrangement.

When 1-phenylcyclopentene oxide (26) was reduced with AlD_3 in THF, prepared by Brown's method,* the results were similar, but not identical to those obtained with "mixed hydride" in ether (solutions of the latter reagent contain lithium chloride). The use of an alane/THF reagent which was virtually free of lithium sulfate gave 27 exclusively. Thus, it seems that lithium salts play an important role in some alane reductions.

The reduction of styrene oxide with alane/THF gave 73% 1-phenylethanol and 27% 2-phenylethanol.²⁵ The reduction of other epoxides with this reagent is summarized in Table 4.

*The Brown method²⁴ for the preparation of alane is to treat a clear, standardized solution of lithium aluminum hydride with the theoretical quantity of 100% sulfuric acid. The precipitated lithium sulfate is then filtered to give a clear alane/THF reagent. The reaction is shown in equation 10.



TABLE 4
 REDUCTION OF EPOXIDES WITH
 ALANE/THF REAGENT AND LiAlH_4 ²⁵

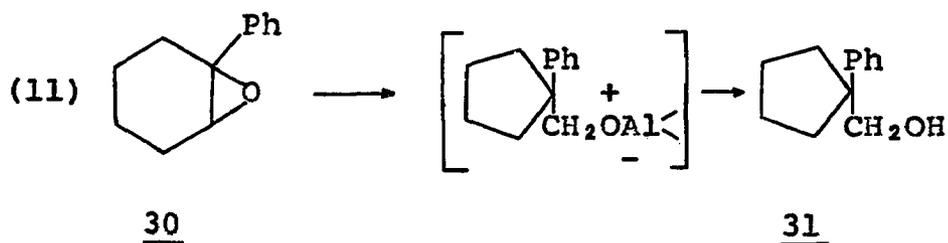
Epoxide	Hydride	Product
1-phenyl-cyclohexene oxide	LiAlH_4	100% 1-phenylcyclohexanol
	AlH_3	64% 1- and 36% <i>cis</i> -2-phenylcyclohexanol
1-phenyl-cyclopentene oxide	LiAlH_4	87% 1- and 13% <i>cis</i> -2-phenylcyclopentanol
	AlH_3	9% 1- and 91% <i>cis</i> -2-cyclopentanol
Norbornene oxide	LiAlH_4	100% <i>exo</i> -2-norbornanol
	AlH_3 (25°)	69% <i>exo</i> -2- and 31% 7-norbornanol
	AlH_3 (65°)	51% <i>exo</i> -2-, 48% 7- and 1% <i>endo</i> -2-norbornanol

By comparing data from reductions of styrene oxide with mixed hydride reagents, Ashby and coworkers²⁶ made the following observations. (1) There is a significant solvent effect observed in going from diethyl ether to tetrahydrofuran. In a solvent such as THF, which increases the hydride donor ability of the mixed hydride reagent, it is found that direct reduction is the predominant mechanism. The results also indicate that for the most part direct reduction probably does not involve complexed hydride since this should result in the predominant formation of 2-phenylethanol. (2) The product ratios arising from the reductions with several alkoxyaluminum hydrides and aluminum hydride are similar, but there is a noticeable decrease in the percentage of 2-phenylethanol when proceed-

ing from AlH_3 to dimeric $\text{AlH}_2\text{O}-i\text{-Bu}$ to the more highly associated $\text{AlH}_2\text{O}-i\text{-Pr}$. The trend probably reflects the "size" of the reagent.

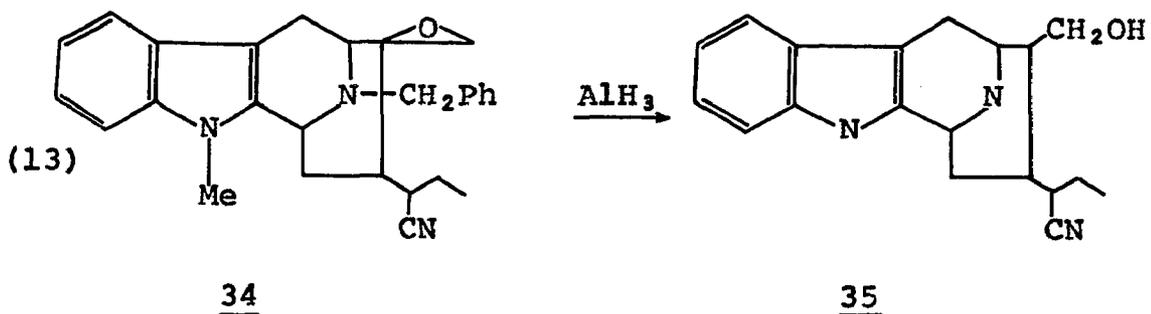
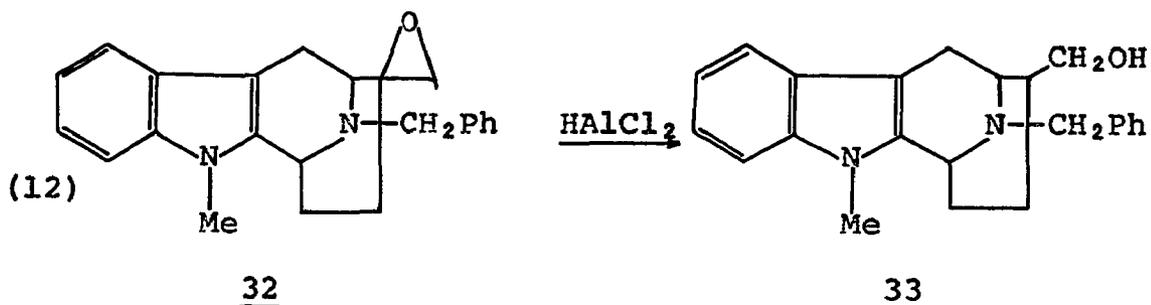
Ashby and Cooke²⁷ determined the effect of mixed hydride stoichiometry, the nature of the halogen in mixed hydride reagents and the solvating ligand on the product ratios of epoxide reductions and have drawn the following conclusions. (1) The use of $\text{LiAlH}_4:\text{AlCl}_3$ in the ratios of 1:3 and 1:4 appears to give the same product distribution. (2) The presence of LiCl in the reaction medium does not exert any dramatic effect on the product distribution suggesting that LiCl probably does not take part in the reaction by complexation with the epoxide. (3) When mixed hydride reagents are solvated by tetrahydrofuran, the resulting mixed hydride is a better hydride donor than when diethyl ether is used as the solvent. The results obtained with triethylamine indicate that it is very similar to diethyl ether in this respect.

Laurent and Villa²⁸ studied the reaction of 1-phenylcyclopentene oxide (26) and 1-phenylcyclohexene oxide (30) with the reagents from $\text{LiAlH}_4:\text{AlCl}_3$ in 1:4 and 1:3 ratios. The reaction of 1-phenylcyclohexene oxide with the 1:4 reagent produced striking results. The *cis*- and *trans*-2-phenylcyclohexanols were only minor products in the reaction. The major product of the reaction was 31, which results from carbonium ion formation followed by migration of a methylene group in the ring. Reduction



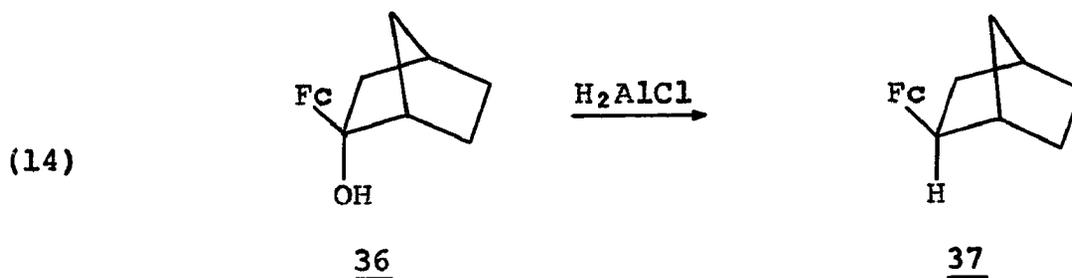
of 1-phenylcyclopentene oxide with the 1:4 and 1:3 reagents preferentially produced *trans*-2-phenylcyclopentanol, arising from carbonium ion formation and hydride migration.

Mashimo and Sato²⁹ have used the "mixed hydride" reagents (HALCl_2 and AlH_3) to prepare the intermediates 33 and 35 in their synthesis of isoajmaline, showing that the reagents have practical synthetic applications (Equations 12 and 13).

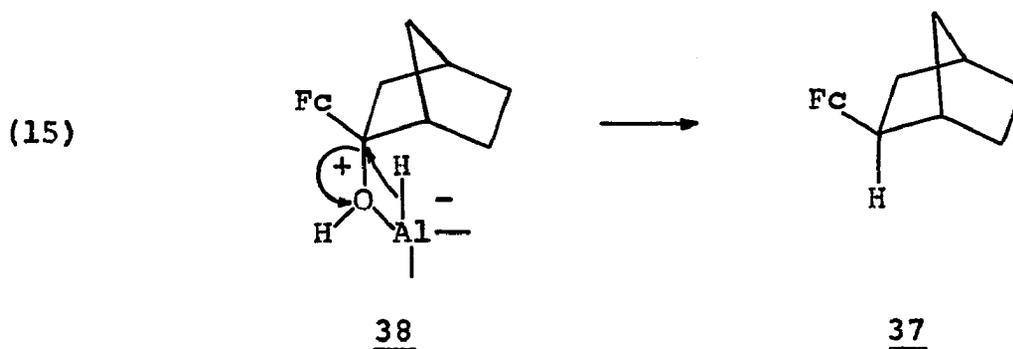


In a related study of the stereochemistry of the hydrogenolysis of C-O bonds with a mixed hydride reagent,

Habib and Watts³⁰ have shown that the reduction of 2-*exo*-(36) and 2-*endo*-ferrocenyl-2-norbornanol with dihydridoaluminum chloride proceeds with complete retention of configuration to give the 2-*exo*-(37) and 2-*endo*-ferrocenyl-norbornanes, respectively. To account for the stereospecificity of the reaction, Habib and Watts envision prior coordination of an oxygen to aluminum to give an intermediate



of the type (38), and concerted displacement by hydride through a four-center transition state to give the product (37) with retention of configuration.



The foregoing discussion shows that the mixed hydride opening of epoxides is a well-known reaction and the stereochemistry has been studied. Up to this time, however, no definitive work has been done with an acyclic epoxide in terms of the stereochemistry of the reaction with mixed hydrides.

Reaction of Epoxides with Borane

Compared to alane, diborane is a reducing agent with much stronger electrophilic or "acidic" properties.

The first report of the reaction of an epoxide with borane was by Stone and Emeleus.³¹ However, their interest was centered around the polymerization of epoxides. The reaction of ethylene oxide and propylene oxide with diborane produced diethoxyborane and diisopropoxyborane, respectively, plus large amounts of polymeric material of the general structure $H(CHRCH_2O)_nBH_2$, where R is hydrogen or methyl.

In 1960, Brown and Subba Rao³¹ reported the reduction of propylene and styrene oxides. The reduction of styrene oxide by the *in situ* generation of borane from sodium borohydride and boron trifluoride ethyl etherate produced a mixture of 2-phenylethanol (73%) and 1-phenylethanol (27%).

However, it wasn't until 1966 that a careful investigation of the reaction was conducted. Pastro and coworkers³³ reduced a number of different epoxides with borane- d_3 and determined the deuterium distribution in the products. The reaction was found to be very complex, as illustrated in Figure 8. Reduction of *cis*- and *trans*-2-butene oxides (39a) occurred without rearrangement and with complete inversion at the epoxide carbon atom undergoing attack. The initial reaction is believed to be the formation of a complex (40) of the epoxide and borane- d_3 . It does not

seem reasonable that the borane-d₃ portion could transfer deuteride in a concerted, intramolecular ring opening with inversion. Furthermore, it appears that borodeuteride is not involved since the product distribution reported by Brown and Subba Rao³¹ with BH₃/BH₄⁻ differs from that observed by Pasto and coworkers.³³

The source of deuteride does not seem to be very nucleophilic since both epoxide and tetrahydrofuran successfully compete with the source of deuteride for the epoxide-borane-d₃ complex (40) forming ether adducts. Thus, the most likely source of deuteride is either borane-d₃ or possibly another molecule of the complex 40.

The low nucleophilic character of the source of deuteride is such that carbonium ion intermediates can form in those cases where substituents are present which lead to stabilization of such ions. As indicated in Figure 8 the ionic intermediate (42) can undergo rearrangement by hydride migration (if styrene oxide is reduced) or hydride and phenyl migration (if *cis*- or *trans*-stilbene oxide is reduced). These migrations result in the formation of a borane-d₃ complex of the corresponding carbonyl compounds 44 and 46, which can undergo intramolecular reduction to give the 1-deutero alcohols. If intermediate (42) is attacked by deuteride, the resulting alcohol will have deuterium in the 2-position. The intermediacy of 42 seems very plausible because both *cis*- and *trans*-stilbene oxides give the same mixture of *erythro*- and *threo*-2-deutero-1,2-diphenylethanol (43b).

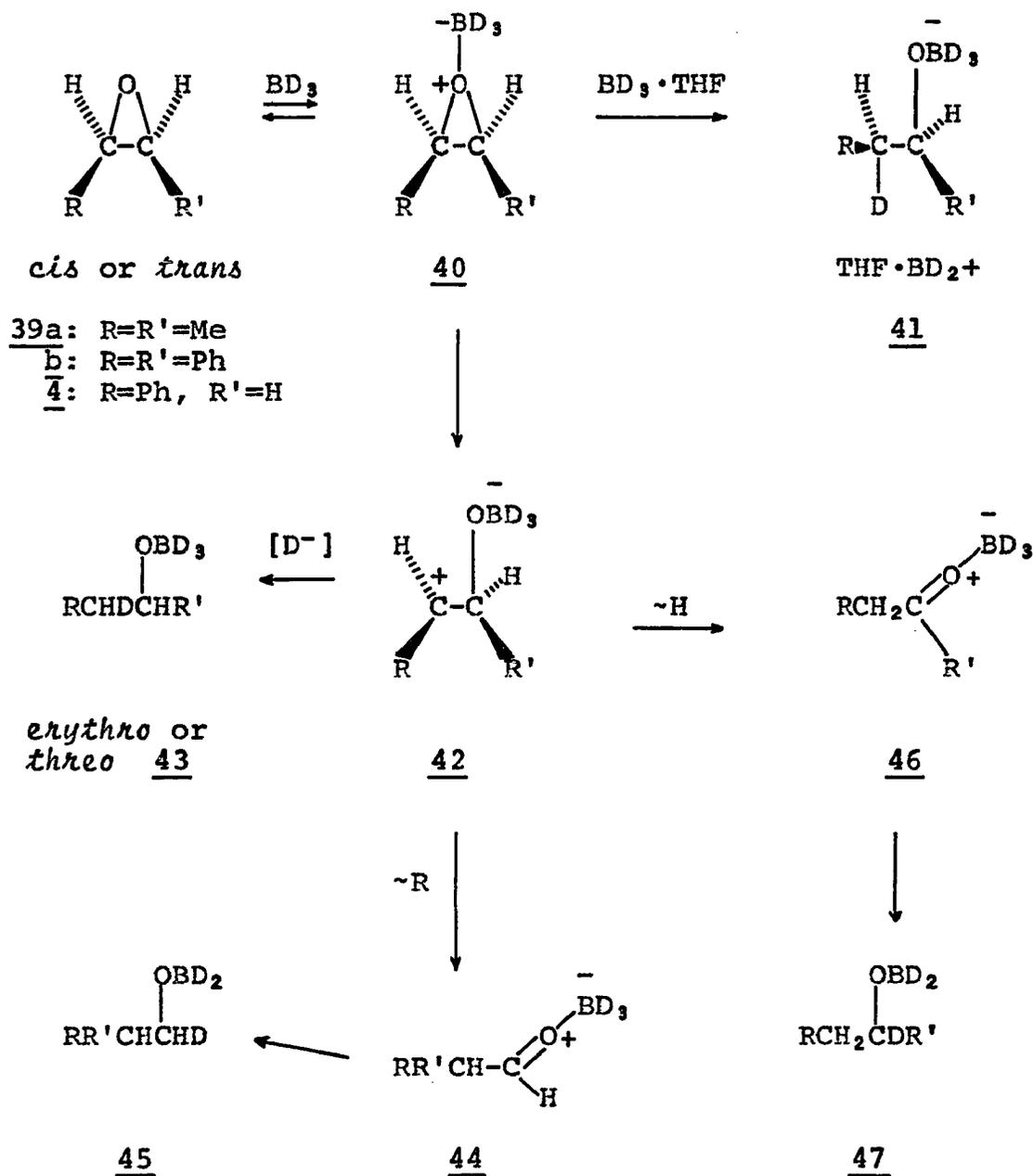


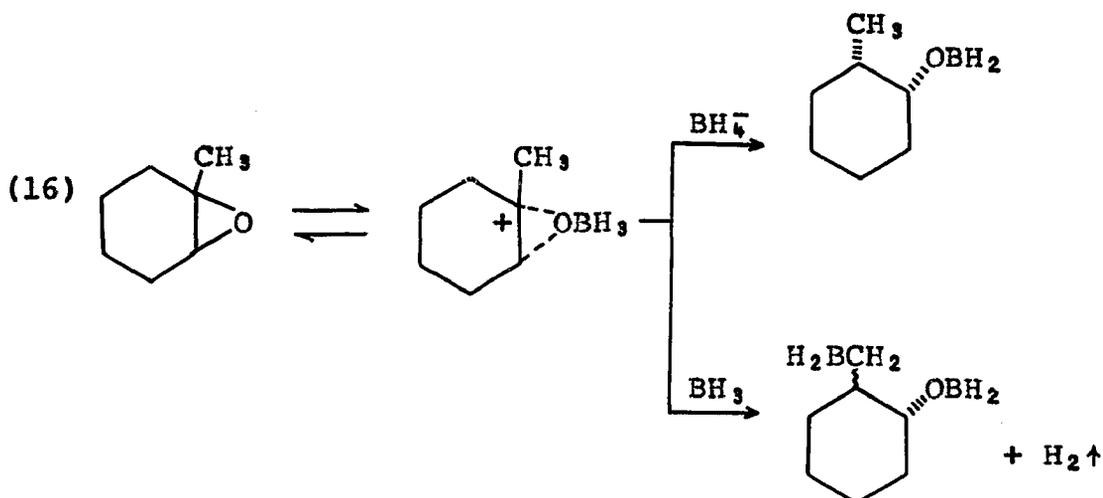
Figure 8. A mechanism for the reaction of an epoxide with deuteroborane (continued on next page).

Products 49 and 53 result from nucleophilic attack on the epoxide-borane-d₃ complex 40 by tetrahydrofuran and epoxide, to give intermediates 48 and 52, respectively. Nucleophilic attack by deuteride then yields the products 49 and 53. The formation of 50 and 51 is the result of similar reactions of 48.

Thus, the complexity of the borane-epoxide reaction is readily apparent.

In an attempt to increase the rate of reaction of borane with epoxides, Brown and Yoon³⁴ added some borohydride to the reaction. The result was a substantial enhancement of the rate as well as the yield of alcohol product, especially in the case of trisubstituted epoxides. The reaction is pictured as preliminary complexation of the epoxide with borane and then preferential attack by borohydride at the polarized tertiary position, with inversion, to form *cis*-2-methylcyclohexanol when 2-methylcyclohexene oxide is reduced. If no borohydride were present, then diborane apparently attacks electrophilically at the methyl group (Equation 16), with evolution of hydrogen.

The product distribution in the reduction of 2-methylcyclohexene oxide with diborane/borohydride is quite different from that obtained from reduction with $\text{AlH}_3 \cdot 2\text{AlCl}_3$. In the former case the only products were 1-methylcyclohexanol (24%) and *cis*-2-methyl-cyclohexanol (76%), whereas in the latter case four products are formed; 1-methylcyclo-



hexanol (10%), *cis*-2-methylcyclohexanol (19%), *trans*-2-methylcyclohexanol (11%) and (1-methyl)cyclopentylcarbinol (60%). These latter results parallel those of Laurent and Villa²⁸ for 1-phenylcyclohexene oxide.

In another modification of the reaction of an epoxide with borane, Brown and Yoon³⁵ added boron trifluoride as a catalyst. The introduction of boron trifluoride into the system produces ring opening of the epoxide to form the least substituted alcohol almost exclusively. A summary of these results is given in Table 5.

The reduction of 2-phenylcyclopentanone gave the same product ratio as did reduction of 1-phenylcyclopentene oxide under the same conditions.³⁵ Therefore, it seems probable, at least with this substrate, that the reaction involves a rearrangement of the epoxide to a carbonyl derivative under the influence of the boron trifluoride, followed by a rapid reduction of the carbonyl derivative.

All of these results make it clear that the reductive possibilities with diborane can be greatly modified

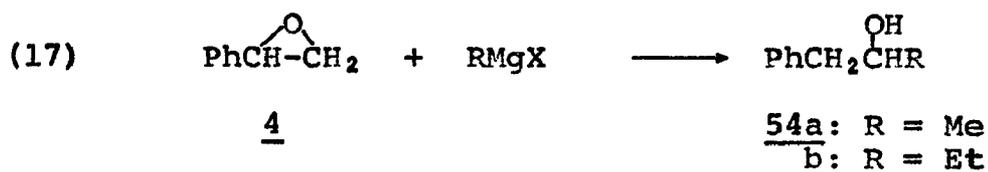
TABLE 5
REACTION OF EPOXIDES WITH $B_2H_6/BF_3 \cdot OEt_2$

Epoxide	Product	% Yield
styrene oxide	2-phenylethanol	98
α -methyl styrene oxide	2-phenylpropanol	100
<i>trans</i> - β -methyl styrene oxide	1-phenyl-2-propanol 2-phenylpropanol	(97) (3)
α -phenyl styrene oxide	2,2-diphenylethanol	95
1-phenyl cyclopentene oxide	<i>cis</i> -2-phenylcyclo- pentanol <i>trans</i> -2-phenylcyclo- pentanol	18 82

by using it in the presence of a nucleophilic component, such as lithium or sodium borohydride, or an electrophilic component, such as boron trifluoride.

The Reaction of Epoxides with
Grignard Reagents and R_2Mg

The first example of the reaction of a Grignard reagent with an epoxide was reported in 1908 by Tiffeneau and Forneau.³⁶ When styrene oxide was allowed to react with the Grignard reagents from methyl- and ethyl bromides, the products formed were 1-phenyl-2-propanol (54a) and 1-phenyl-2-butanol (54b) respectively. The fact that



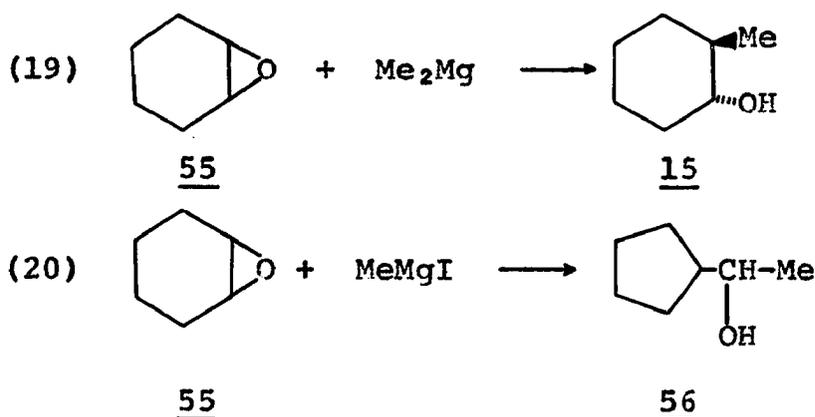
phenylacetaldehyde produced these same products when reacted with methyl- and ethylmagnesium bromides suggested that an aldehyde intermediate was the species being reduced. The formation of the aldehyde can be accounted for by ring opening of the epoxide to form a carbonium ion which then rearranges with hydride migration to form the aldehyde (cf. Figure 8, Pasto's mechanism for the reduction of styrene oxide with borane for a comparable reaction sequence).

In 1929, Schlenk and Schlenk³⁷ observed that the reaction of a Grignard reagent with dioxane resulted in the formation of a dialkylmagnesium reagent and a precipitate



of magnesium bromide-dioxanate. The reagent could be used with the precipitate present or the solution could be filtered to give a halide-free solution of dialkylmagnesium reagent. In 1950, Kullman³⁸ confirmed the earlier results of Noller and White³⁹ and showed that the addition of sufficient dioxane to an ethereal solution of ethylmagnesium bromide to effect complete precipitation of bromide leaves only 55-60% of the ethyl groups in solution in the form of diethylmagnesium. The diethylmagnesium content of the solution increases with time such that after 24 hours the percentage of ether-soluble ethyl groups reaches 70-75%. When the same amount of dioxane is added in three or four portions, with approximately 24 hours intervening between each addition, 93-97% of the ethyl groups are accounted for in the ethereal solution of diethylmagnesium.

The first example of the reaction of an epoxide with a dialkylmagnesium reagent was reported by Bartlett and Manly Berry in 1934.⁴⁰ When a filtered solution of dimethylmagnesium was allowed to react with cyclohexene oxide (55), the resulting product was *trans*-2-methylcyclo-

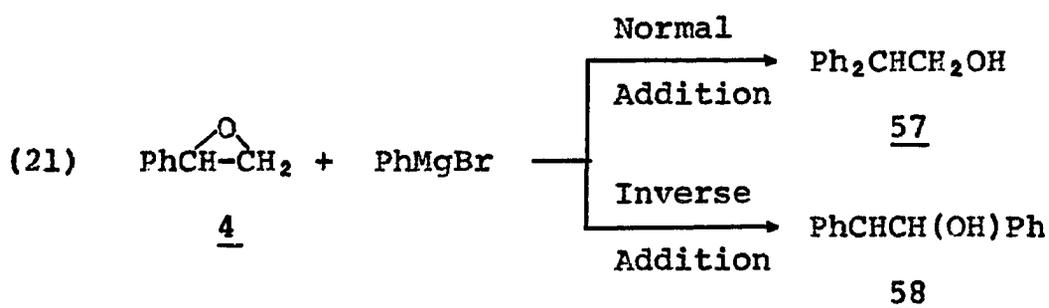


hexanol (15). The reaction with a filtered solution of diethylmagnesium produced *trans*-2-ethylcyclohexanol. However, when the same epoxide was treated with the Grignard reagent from methyl iodide, the reaction involved a ring contraction to form 56.

Norton and Hass confirmed these results in a study of acyclic, alkyl-substituted epoxides.⁴¹ When allowed to react with a filtered solution of diethylmagnesium, these epoxides formed the alcohol resulting from attack of an ethyl group at the least-hindered carbon atom of the epoxide, whereas the reaction with ethylmagnesium bromide produced an alcohol resulting from attack of an ethyl group on a carbonyl derivative formed after initial epoxide rearrangement.

The work of Cottle and Powell⁴² was consistent with these earlier studies. The only new entry was the reaction of 2,3-epoxybutane with the magnesium bromide-dioxanate precipitate from the ethyl Grignard reagent. The result was the same in this case as for the reaction with a filtered solution of diethylmagnesium, i.e., the product formed was 3-methyl-2-pentanol. This result confirmed the observations of Kullman³⁸ and Noller and White³⁹ that the magnesium bromide-dioxante precipitate contained some diethylmagnesium.

Kharasch and Clapp⁴³ noted a striking reversal in the direction of ring opening of styrene oxide with phenylmagnesium bromide when the order of addition of the reactants was reversed. When styrene oxide was added to phenylmagnesium bromide (normal addition), the product that was obtained (2,2-diphenylethanol, 57) resulted from displacement at the more-hindered carbon of the epoxide and none of 58 from addition to a carbonyl rearrangement



product as was observed by Tiffeneau and Forneau³⁶ with methyl- and ethylmagnesium bromides. However, 58 was obtained when the Grignard reagent was added to the styrene oxide (inverse addition).

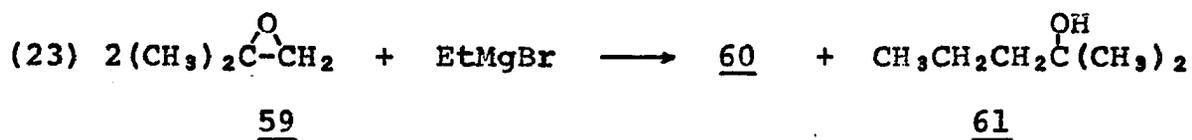
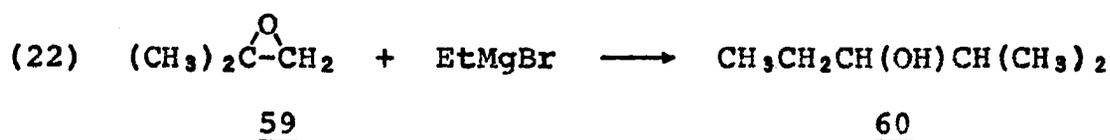
Golumbic and Cottle⁴⁴ obtained the same product (54a) as Tiffeneau and Forneau³⁶ from the reaction of styrene oxide with methylmagnesium iodide. The addition of magnesium iodide did not seem to have any effect on the course of the reaction other than to reduce the yield of 1-phenyl-2-propanol substantially. The reaction of propylene oxide with a filtered solution of dimethylmagnesium produced 2-butanol, resulting from attack at the least hindered carbon, whereas the same reagent with styrene oxide produced 2-phenyl-1-propanol, resulting from attack at the more-hindered epoxide carbon atom.

Whitesides and Roberts⁴⁵ observed that diisopropylmagnesium, magnesium bromide/dioxanate reacted with styrene oxide *via* attack at the more-hindered epoxide carbon to give the primary alcohol, 3-methyl-2-phenyl-1-butanol.

When Cottle and Hollyday⁴⁶ compared the reaction of ethylene oxide with *n*-butylmagnesium bromide and di-*n*-butylmagnesium, magnesium bromide-dioxanate, they found relatively little difference in the product distribution. Reaction with the former reagent produced 65% 1-hexanol and only 10% of 2-hexanol, the latter resulting from addition to acetaldehyde formed by a hydride shift. The formation of so little 2-hexanol is somewhat surprising in view of the fact that most of the earlier studies found that the rearranged product was the predominant one under similar conditions. When ethylene oxide was allowed to react with the latter reagent, 44% 1-hexanol was produced,

but 1.8% 2-hexanol was also found. This is the first report of rearrangement during the reaction of an epoxide with a dialkylmagnesium reagent.

Huston and Brault⁴⁷ discovered that with 59 and an ethyl Grignard reagent the product ratio is dependent upon the ratio of epoxide to Grignard reagent. When allowed to react in a 1:1 molar ratio, the rearranged product (60) was formed in a 42% yield. However, when a 2:1 molar ratio of epoxide:RMgX was used, almost equal amounts of the rearranged (60) and direct displacement (61) products were



formed (13.2% 60 and 17.9% 61). Both reactions were accompanied by substantial formation of 1-bromo-2-methyl-2-propanol. When a 1:2 molar ratio was used only the rearranged product (60) was formed. The reaction of equimolar amounts of epoxide and a filtered solution of diethylmagnesium led to the exclusive formation of the direct displacement product (61).

Freedman and Becker⁴⁸ have shown that 1,2-epoxybut-3-ene (62) reacted in the same manner as styrene oxide with diethylmagnesium (filtered) and ethylmagnesium bromide.

When allowed to react with diethylmagnesium, 2-vinylbutanol (63) was produced, presumably from the attack of a dimeric

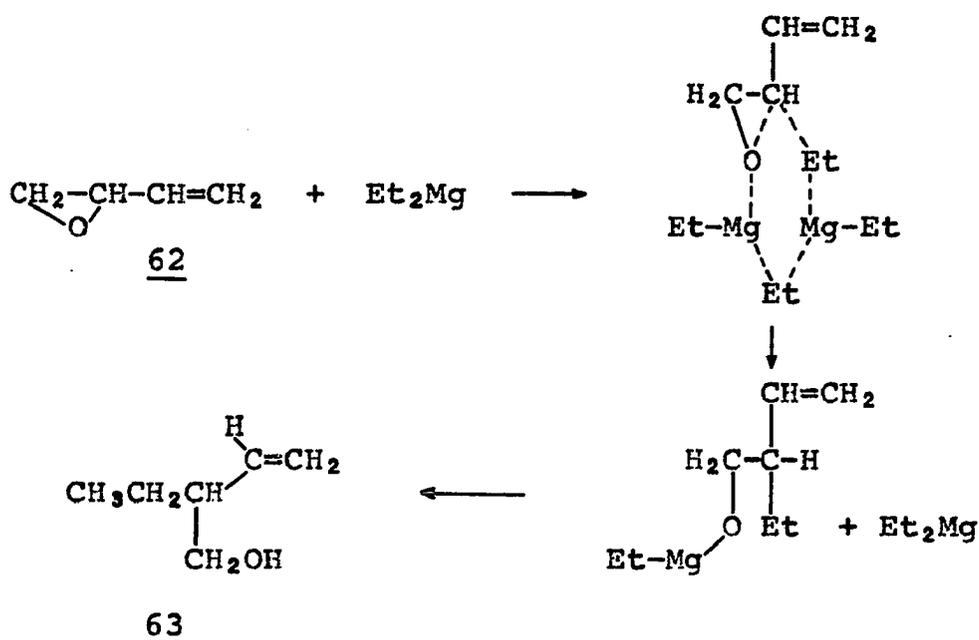


Figure 9. Mechanism of diethylmagnesium reaction with an epoxide.

diethylmagnesium species, which is coordinated to the epoxide, at the more-hindered epoxide carbon. As envisioned by Freedman and Becker (see Figure 9) this process would involve retention of configuration if an epoxide of known configuration were used in this reaction.

Schaap and Arens⁴⁹ reinvestigated the reaction of propylene oxide with various organomagnesium reagents and did a careful analysis of the reaction products. From this work the following conclusions may be drawn. The course of the reaction is dependent upon three factors: (1) the Lewis acidity of the magnesium in the Grignard complex; (2) the nucleophilicity of the reacting ligand; and (3) the basicity of the solvent.

The extent to which the ligands satisfy the electron demand of the magnesium determines the Lewis acidity of the Grignard reagent. The more electron-donating the ligand, the more it will reduce the acidity of the magnesium making it a weaker Lewis acid. With stronger Lewis acids, there can be more complete ring opening of the propylene oxide *via* a S_N1 -mechanism; whereas complexing with a moderately strong Lewis acid will only activate (polarize) the C-O bonds of the epoxide, thus making reaction possible through either a S_N2 - or S_N1 -mechanism. Therefore, the stronger the Lewis acidity, the more complete ring opening will be.

In general, the more nucleophilic the ligand, the more it will attack the least-substituted carbon atom; whereas a ligand of low nucleophilic reactivity will be less discriminating.

Results obtained in ether *vs* THF solvents reveal the role of solvent basicity. When THF was used as the solvent in place of ether, attack took place almost exclusively at the least-substituted carbon atom of the propylene oxide. This is attributed to the fact that THF is a better base than ether; and, therefore, will simultaneously increase ligand nucleophilicity and decrease the Lewis acidity of the magnesium complex.

The structure of the epoxide itself also plays an important role in the direction of ring opening. When the substituent in a mono-substituted epoxide is large, attack will take place mainly at the terminal carbon atom.

If the substituent is a (potential) electron-donating group, then attack will take place at the secondary carbon atom because the substituent can stabilize the incipient carbonium ion. Electron-withdrawing groups have the opposite effect.

Thus, it seems that the reaction of an epoxide with an organomagnesium reagent can proceed by two different mechanisms: (1) direct displacement at either the more- or least-hindered carbon atom of the epoxide; or (2) rearrangement to a carbonyl intermediate to which the Grignard reagent then adds. The course of the reaction depends upon the structure of the epoxide as well as the organomagnesium reagent.

Statement of the Problem

Even though a considerable amount of work has been done on all of the reactions discussed in this section, no definitive work has been done on the stereochemistry of the ring-opening of an optically active acyclic epoxide with these reagents, namely the $\text{AlH}_3/\text{Et}_2\text{O}$, AlH_3/THF , $\text{B}_2\text{H}_6/\text{BF}_3 \cdot \text{OEt}_2$ and $\text{R}_2\text{Mg}/\text{MgBr}_2 \cdot \text{dioxanate}$ reagents. Studies of Grignard reduction reactions in this laboratory led to an interest in these reactions as possible synthetically useful routes to Grignard reagent precursors of known absolute configuration. Thus, this exploratory investigation was initiated to determine their stereochemistry and synthetic utility. The substrate chosen for study was optically active styrene oxide because it is rather easily synthesized.

The synthesis of R-(+)-styrene oxide and the results of this preliminary study are discussed in the following section.

RESULTS AND DISCUSSION

The Preparation of Optically Active Styrene Oxide

The preparation of R-(+)-styrene oxide (4) was effected from R-(-)-mandelic acid (1) of 89% ee⁵⁰ (see Figure 10) in the following manner. The mandelic acid was converted to R-(-)-methyl mandelate (64) in 97% yield according to the general procedure of Lorette and Brown.⁵¹ Lithium aluminum hydride reduction of 64 produced R-(-)-1-phenyl-1,2-ethanediol (2) in 57% yield. Conversion of the diol to R-(-)-2-brosyloxy-1-phenylethanol (65) was effected by reaction with p-bromobenzenesulfonyl chloride in pyridine solution at 0°C in a 67% yield. Ring

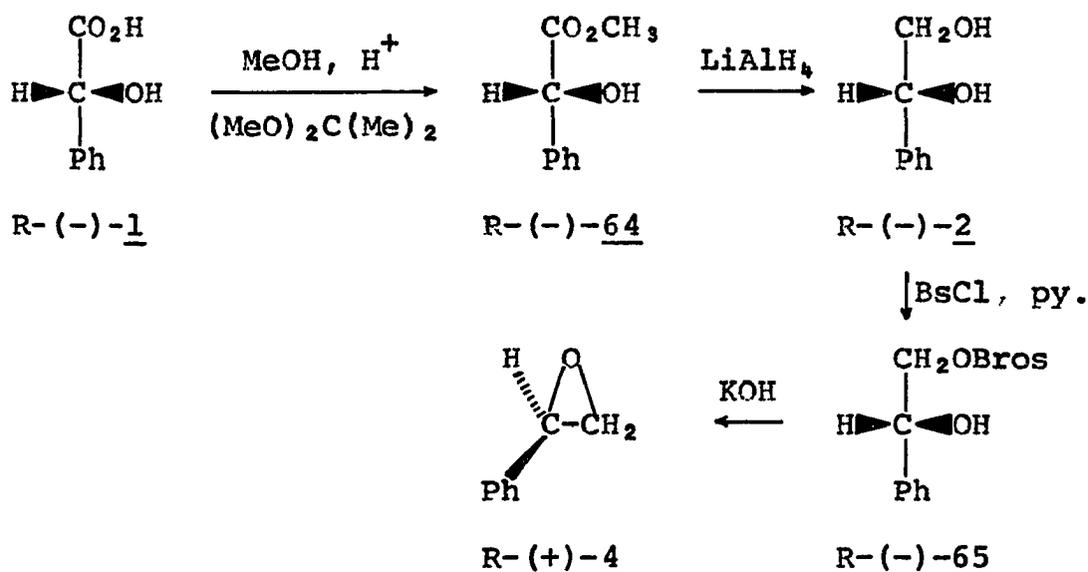
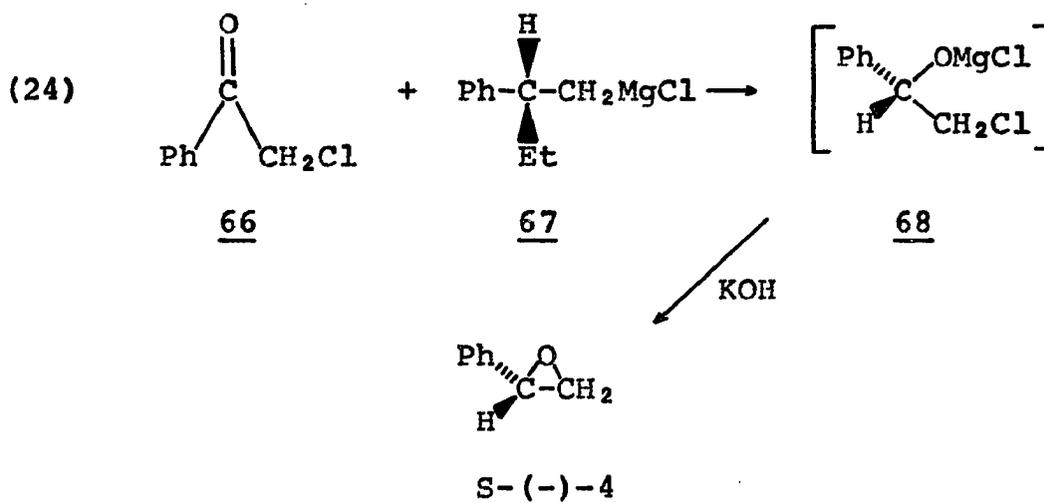


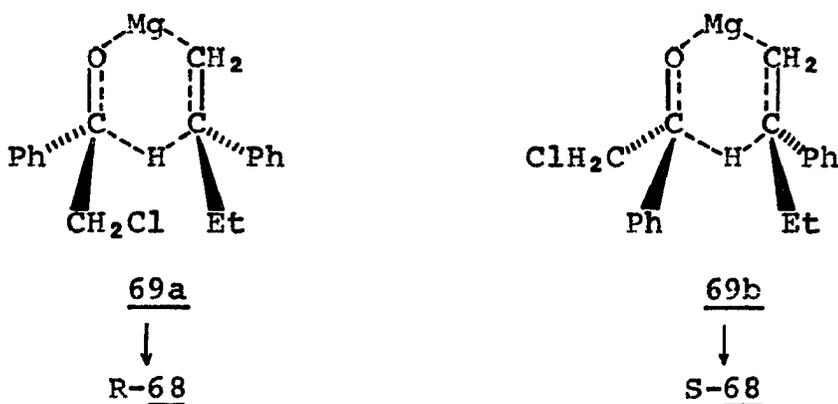
Figure 10. Preparation of R-(+)-styrene oxide.

closure to form the epoxide was accomplished by treating the brosylate with a methanolic solution of potassium hydroxide at -5°C .³ The yield of styrene oxide (4) in the final step was 76% (87% ee of the R configuration).² The overall yield of this reaction sequence was 25% based on mandelic acid. However, it has been found that this yield can be substantially increased using an improved method for recovery of the diol (2) from the lithium aluminum hydride reduction of 64. A trial reduction of racemic ester using the improved method gave an 85% yield of the diol as compared to the 57% obtained in the original sequence. This increases the possible overall yield to 42%.

A new synthesis of partially active styrene oxide was developed in this laboratory in the course of this investigation. The procedure involved the asymmetric reduction (Equation 24) of α -chloroacetophenone (66) with the Grignard reagent (67) prepared from R-(-)-1-chloro-2-phenylbutane to produce the chlorohydrin (68) as an intermediate. Ring closure was effected by working up of the reaction with a potassium hydroxide solution. Styrene oxide was recovered in a 39% yield and found to contain a 14% ee of the S configuration. Since the optical purity of the chloride used to prepare the Grignard reagent (67) was only 80% ee,⁵² the reaction gave 18% asymmetric induction after correcting for the optical purity of the chloride.



Consideration of the transition state models 69a and 69b for this reaction shows that, as might be expected on the basis of steric factors alone, the one favored was 69b in which the two phenyl groups are transoid to one another.⁵³



It was determined that it was best to isolate the chlorohydrin first so that the 2-phenylbutane and the 2-phenyl-1-butene from the Grignard reagent could be removed. The pure chlorohydrin was then treated with potassium hydroxide to effect ring closure. The yield of this two-step sequence was comparable to that of the

one-step (36% vs 39%), but the styrene oxide isolated by simple distillation from the two-step reaction was of higher chemical purity than that from the one-step (98% vs 50%).

When the reduction was attempted with α -bromoacetophenone, the yield of 2-bromo-1-phenylethanol was only about 5%, and no attempt was made to convert it to styrene oxide. The low yield of reduction in this case was due to the formation of large amounts of condensation by-products.

The Reaction of R-(+)-Styrene Oxide with Alane Reagents

The reaction of R-(+)-styrene oxide (4) with the $\text{AlD}_3/\text{Et}_2\text{O}$ reagent (prepared from LiAlD_4 and AlCl_3 in a 3:1 molar ratio in ether)¹³ and with the AlD_3/THF reagent (prepared from LiAlD_4 and D_2SO_4 in a 2:1 molar ratio in THF)²⁵ will be considered together. While constitutionally similar, these reagents are quite different from one another in terms of their reactivity toward epoxides. This difference will be shown in the following discussion.

When R-(+)-styrene oxide was allowed to react with the $\text{AlD}_3/\text{Et}_2\text{O}$ reagent in a 1:1 molar ratio according to the procedure of Eliel and Delmonte,¹⁶ the products obtained were 1-phenylethanol (5) and 2-phenylethanol (9) in 34.2% and 62.1% yield, respectively. The rotation

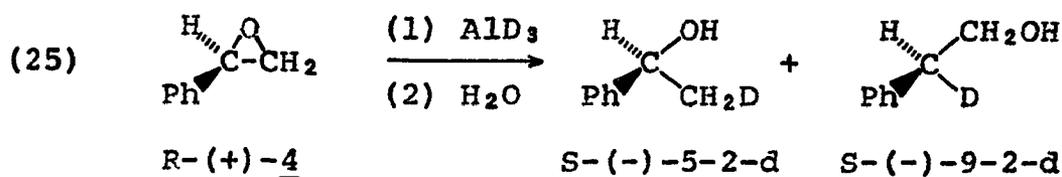
data (see Table 6) showed that 5 possessed the S configuration⁵⁴ and 9, the S configuration.⁵⁵ From the NMR data it can be seen that all of the deuterium in each case is at the C₂ position of the product (the C₂ position of 1-phenylethanol corresponds to the C₂ position in styrene oxide whereas the C₂ position of 2-phenylethanol corresponds to the C₁ position of styrene oxide). Since the LiAlD₄ that was used contained 98% d₄, a minimum of 2% d₀ should

TABLE 6
RESULTS OF THE REDUCTION OF R-(+)-STYRENE OXIDE^a
WITH THE AlD₃/Et₂O REAGENT

	PhCH(OH)CH ₂ D	PhCHDCH ₂ OH
Actual yield (%)	34.2	62.1
[α] _D	-41.1 _b	- 1.12
% ee	94.3 ^b	52.4 ^c
Configuration	S	S
NMR %d at C ₁	---	---
%d at C ₂	99	99
Mass Spec ^d %d ₀	3.3	2.7
%d ₁	96.6	95.7
%d ₂	---	1.5

- (a) The optical purity of the styrene oxide used was 87%.
 (b) See reference 56 for [α]_D (max).
 (c) See page 21 of Part I for the calculated maximum rotation.
 (d) See Appendix I of Part I.

be observed in each product (if all of the deuteride was consumed in the reaction); and the above results are in fair agreement with this value. Therefore, the products from this reaction are S-(-)-1-phenylethanol-2-d (5) and S-(-)-2-phenylethanol-2-d (9) as illustrated in equation 25.



The reaction of R-(+)-styrene oxide (4) with the AlD₃/THF reagent in a 1:1 molar ratio according to the procedure of Yoon and Brown²⁵ produced the same products but in substantially different yields (65.9% 1-phenylethanol and 21.9% 2-phenylethanol). Again the rotation data (see Table 7) indicated that the configurations of 5 and 9 were both S, and the NMR data showed that all of the deuterium was at the C₂ position in each product.

TABLE 7

RESULTS OF THE REDUCTION OF R-(+)-STYRENE OXIDE^a
WITH THE AlD₃/THF REAGENT

	PhCH(OH)CH ₂ D	PhCHDCH ₂ OH
Actual Yield (%)	65.9	21.9
[α] _D	-42.2	- 1.86
% ee	96.9 ^b	87 ^c
Configuration	S	S
NMR %d at C ₁	---	---
%d at C ₂	99	99
Mass Spec ^d %d ₀	3.3	2.1
%d ₁	96.6	95.5
%d ₂	---	2.3

- (a) The optical purity of the styrene oxide used was 87%.
- (b) See reference 56 for [α]_D (max).
- (c) See page 21 of Part I for the calculated maximum rotation.
- (d) See Appendix I of Part I.

These results indicate that, with both of the alane reagents, the reduction of styrene oxide to give the secondary alcohol (1-phenylethanol) took place *via* deuteride attack at C₂ with no change of configuration at C₁. The 2-phenylethanol-2-d was formed with deuterium replacing oxygen with inversion of configuration.

The results with styrene oxide confirm the observations of Lansbury and coworkers^{22, 23} with 1-phenylcyclopentene oxide (26). When 26 was allowed to react with the AlD₃/Et₂O reagent, the reaction proceeded with about 70% inversion; whereas, the reaction with the AlD₃/THF reagent proceeded with 98% inversion. In comparison, the reaction of styrene oxide with these reagents produced almost the same results, i.e., 60% inversion with the former reagent and 100% with the latter. The only difference between the reactions of these reagents with the two epoxides was that the reduction of 1-phenylcyclopentene oxide was accompanied by substantial rearrangement and styrene oxide with none.

The mechanism of the styrene oxide-alane reaction seems to involve the initial formation of an alane-epoxide complex (70) followed by either inter- or intramolecular hydride transfer (see Figure 11). In the case of the formation of 1-phenylethanol (5), the reaction could proceed by either pathway 71a or 71b and still give the same product, i.e., S-(-)-1-phenylethanol-2-d [S-(-)-5-2-d]. However,

because the optical purity of 5, obtained in both reactions, was slightly higher than that of the styrene oxide used (cf. 94.3% ee of 1-phenylethanol-2-d from the $\text{AlD}_3/\text{Et}_2\text{O}$ reaction and 96.9% ee from the AlD_3/THF reaction with the optical purity of the styrene oxide used, i.e., 87% ee), it seems that one enantiomer of the epoxide (i.e., the R isomer) is reacting preferentially with alane by way of the intramolecular pathway 71b, or that the reducing agent is another molecule of the alane-epoxide complex (70), and it is asymmetrically reducing the epoxide by way of the intermolecular pathway 71a. Not only is there no precedent for the former explanation, i.e., a preferential reaction of one enantiomer over the other with an achiral reagent, but it is disallowed on the basis of symmetry arguments. Therefore, it seems that the only reasonable explanation is that the reaction is proceeding by pathway 71a. Since the optical purity of the S-(-)-1-phenylethanol-2-d obtained in each reaction was almost the same (94.3% ee and 96.9% ee), the differences in the reagents did not seem to significantly affect the degree of optical enrichment.

The formation of the 2-phenylethanol could also take place by two possible pathways (73a and 73b). However, the predominant pathway is the intermolecular reduction illustrated by 73a to give inversion of configuration. A comparison of the yields and optical rotations of the S-(-)-2-phenylethanol-2-d obtained in each reduction (cf.

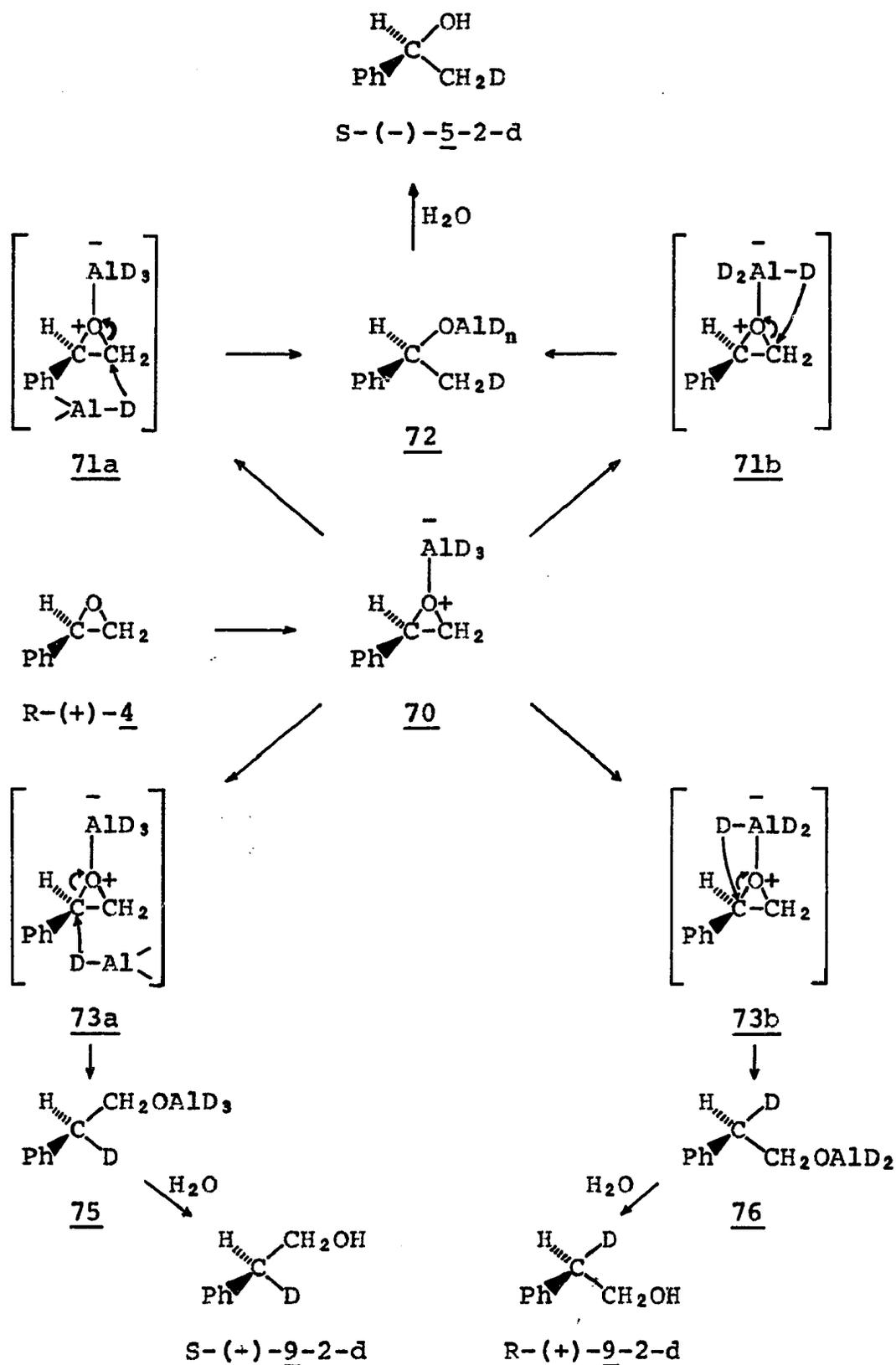
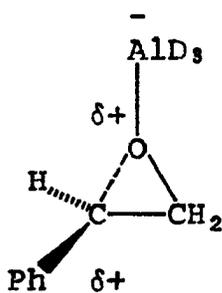


Figure 11. Mechanisms for the reaction of R-(+)-styrene oxide with AlD₃.

data in Tables 6 and 7) shows a distinct difference in the stereochemical behavior of the two reagents used. The 2-phenylethanol obtained from the reduction of styrene oxide with the $\text{AlD}_3/\text{Et}_2\text{O}$ reagent is of much lower optical purity than that obtained from the reduction with the AlD_3/THF reagent. Due to the higher basicity of the THF as compared to ethyl ether, the nucleophilicity of the hydride ligands will be increased as the Lewis acidity of the aluminum in complex (70) decreases.^{26, 49} Thus, epoxide activation (C-O bond polarization) is poor in THF and C-O bond breaking and C-D bond formation should take place in a concerted fashion. This phenomenon also accounts for the higher yield of the secondary alcohol (1-phenylethanol). In ethyl ether, epoxide activation will be more pronounced and C-O bond polarization should take place between the secondary epoxide carbon and the oxygen as illustrated in 77 because the phenyl group



77

would stabilize this incipient carbonium ion. Thus, hydride attack should take place predominantly at the secondary carbon (73a) to give 2-phenylethanol. The formation of

this more open carbonium ion would also account for the lower optical purity of the S-(-)-2-phenylethanol-2-d formed in the $\text{AlD}_3/\text{Et}_2\text{O}$ reaction.

The presence of the salts LiCl and Li_2SO_4 in these reactions did not seem to exert any influence on the product yields, e.g., the yields of 5 and 9 in the AlD_3/THF reaction (with Li_2SO_4 present) are essentially the same as those reported by Brown²⁵ with the salt free reagent. This is consistent with the observation by Ashby and Cooke²⁷ that the presence of lithium chloride does not exert any dramatic effect on the product distribution suggesting that lithium chloride does not take part in the reaction by complexation with the epoxide. However, Lansbury and coworkers²³ state that the salt (Li_2SO_4) does make a difference in the product distribution with 2-phenylcyclopentene oxide. The bicyclic epoxide may be a special case; and furthermore, since the reactions were not run under exactly the same conditions (the ratio of epoxide to alane was 2:1 in the reaction with some Li_2SO_4 present and greater than 2:1 in the salt-free reaction) the important variable cannot be identified with certainty at this time. If there was a salt effect, it was not very dramatic; the reagent with Li_2SO_4 present gave 89% *cis*- and 6% *trans*-2-phenylcyclopentanol, whereas the salt-free reagent gave only the *cis* isomer. Thus, it seems doubtful that the presence of a lithium salt exerts any dramatic influence on the course of the reaction.

The above work has shown that the reduction of an optically active epoxide with alane does produce optically active products. More specifically, under the conditions specified the reduction of R-(+)-styrene oxide with AlD_3 proceeds with no change of configuration (probably through an intermolecular mechanism) to give S-(-)-1-phenylethanol-2-d, and with inversion of configuration (probably by way of an intermolecular mechanism) to give S-(-)-2-phenylethanol-2-d in both ethyl ether and THF solvents. While these results are definitive in themselves, much work remains to be done in order to complete the picture of the reaction. Specifically, the following points deserve attention: the preparation of AlD_3 from $\text{LiAlD}_4/\text{AlCl}_3$ (3:1) in THF and from $\text{LiAlD}_4/\text{D}_2\text{SO}_4$ (2:1) in ether to determine the effect of the solvent; the control of the temperature and time of reaction so that meaningful studies of other variables (e.g., concentration) may be accomplished, and a valid comparison of reagents prepared in different ways may be obtained; and naturally, the application of this work to other systems to test the generality of the above results.

The Reaction of R-(+)-Styrene Oxide with
the $\text{B}_2\text{D}_6/\text{BF}_3 \cdot \text{OEt}_2$ Reagent

The reaction of R-(+)-styrene oxide (4) with the $\text{B}_2\text{D}_6/\text{BF}_3 \cdot \text{OEt}_2$ reagent according to the procedure of Brown and Yoon³⁵ gave 71.8% of 2-phenylethanol, which was shown

to be predominantly the levorotatory isomer of 2-phenylethanol-1-d (9) (Table 8).

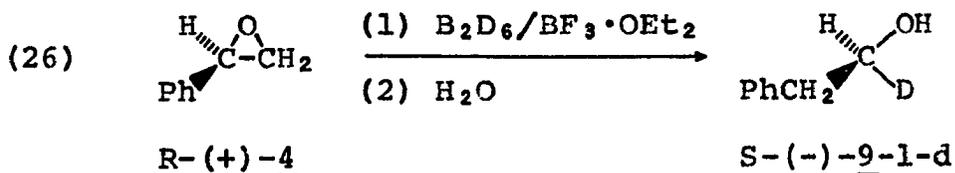


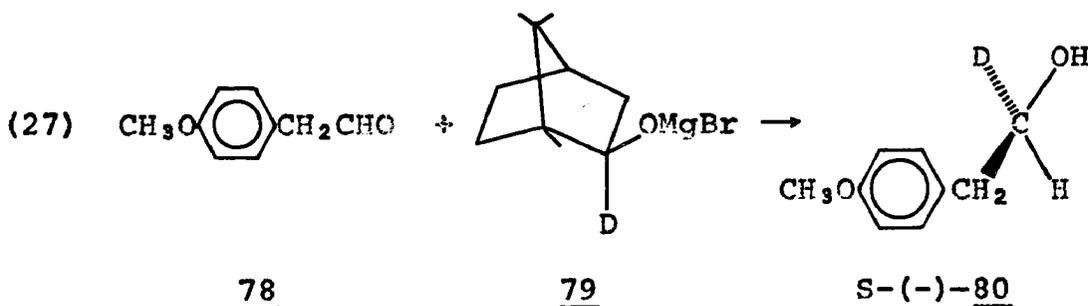
TABLE 8

RESULTS OF THE REACTION OF R-(+)-STYRENE OXIDE WITH THE B₂D₆/BF₃·OEt₂ REAGENT

Actual Yield (%)	71.8
α_D	-0.415
NMR %d at C ₁	99
%d at C ₂	---
Mass Spec ^a %d ₀	2.2
%d ₁	96.5
%d ₂	1.3

(a) See Appendix I of Part I.

The configuration of (-)-2-phenylethanol-1-d has been tentatively assigned by reference to a related configurational assignment for 2-(*p*-methoxyphenyl)-ethanol-1-d (80). Belleau and Burba⁵⁸ have shown that the reduction of (*p*-methoxyphenyl)acetaldehyde (78) with the magnesium alkoxide of *exo*-isoborneol-1-d (79) proceeded to give (-)-2-(*p*-methoxyphenyl)-ethanol-1-d (80). Assuming that



this asymmetric reduction obeys the stereocorrelation model for reductions with isobornyloxymagnesium bromide, (-)-80 is assigned the S configuration. Further assuming that the *p*-methoxyl group does not significantly affect the sign of the rotation, then the configuration of (-)-2-phenylethanol-1-d should also be S. The latter assumption appears to be reasonable and is based on the following observations: (1) Mosher and coworkers⁵⁹ have shown that the sign of the rotation of S-(+)-2-phenylbutanoic acid and its derivatives is unaffected by the substitution of a methoxy group in the *para* position; and (2) Eliel⁶⁰ has also shown that substitution of an acetyl group in R-(-)-1-phenylethane-1-d did not affect the sign of the rotation. Assuming the configurational assignment is correct, attack by deuteride would have to take place with inversion of configuration as shown in step d of Figure 12 to produce S-(-)-2-phenylethanol-1-d.

Since it has been shown in related cases that the *p*-methoxy group affects neither the sign nor appreciably affects the magnitude of the rotation, the maximum rotation of 2-phenylethanol-1-d should be of the same order of magnitude as that of the *p*-methoxy compound (80). It was stated⁵⁸ that the optical purity of 80, which exhibited a rotation of 1.44°, was about 40-50%. Therefore, the S-(-)-2-phenylethanol-1-d produced in this investigation is probably about 11-14% optically pure, which means that

the reaction of R-(+)-styrene oxide with BD_3/BF_3 proceeded with about 13-16% transfer of chirality.

One mechanism for the reaction can be envisioned as an initial complexation of styrene oxide by boron trifluoride followed by essentially complete ring opening to form the secondary carbonium ion (82) due to the strong Lewis acid character of the boron trifluoride. The secondary carbonium ion will be formed in preference to the primary one due to resonance stabilization by the phenyl group. Ring opening will be accompanied by rotation about the $\text{C}_1\text{-C}_2$ bond. Viewing the process along the $\text{C}_1\text{-C}_2$ axis and remote from C_2 , the favored direction of rotation is seen as clockwise with the complexed oxygen moving past hydrogen, rather than counterclockwise past phenyl. The rotation positions H_R in an orientation more favorable for migration than is H_S . A preferential H_R hydride shift generates 84 in resonance with 85. Reduction by borane- d_3 would give 2-phenylethanol-1-d after hydrolysis (See Figure 12).

Yoon and Brown²⁵ originally postulated the rearrangement to a carbonyl intermediate after showing that the reduction of 2-phenylcyclopentanone gave the same product ratio as 1-phenylcyclopentene oxide when reduced under the same conditions. Pasto and coworkers³³ have also postulated the intermediacy of a carbonyl compound in the reduction of an epoxide with borane- d_3 (cf. Figure 8). However, an intermediate with the characteristics of 84 or

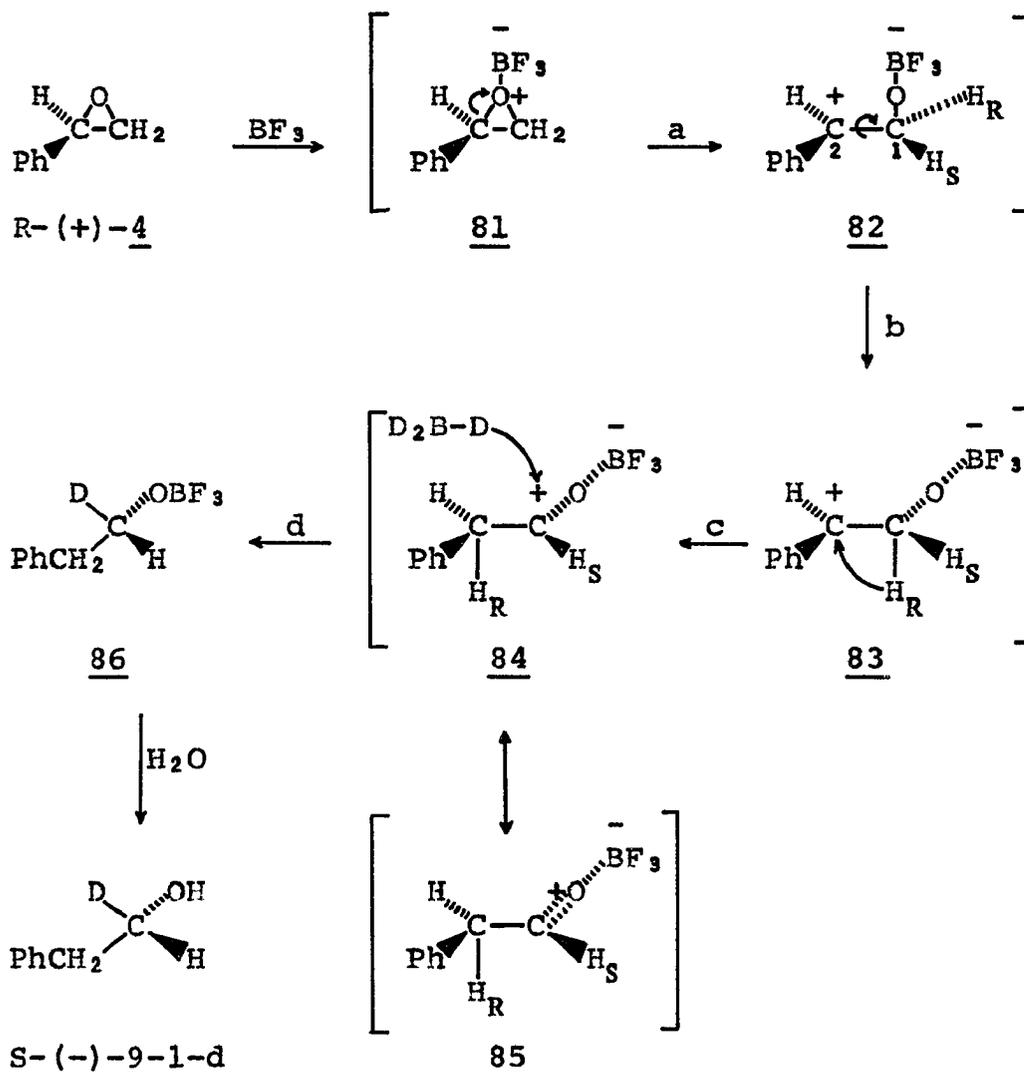


Figure 12. A mechanism for the reaction of R-(+)-styrene oxide with the B₂D₆/BF₃·OEt₂ reagent.

85 seems rather unlikely in view of the optical activity of the S-(-)-9-1-d produced in this reaction. If the mechanism shown in Figure 12 is a good approximation of the actual chain of events, then there must be a high degree of concertedness to the steps **a** through **d**. The chiral influence of the asymmetric carbon in R-(+)-4 appears to exert a considerable measure of control over the process.

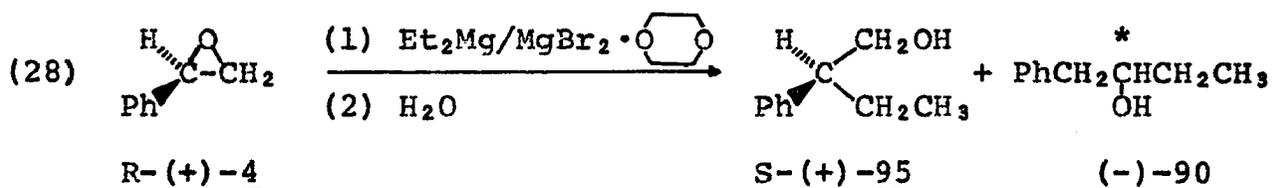
Hydrogen participation in the ring opening step

is not without analogy. Tichý and coworkers⁵⁷ recently proposed a similar kind of participation in the solvolysis of 2-alkylcyclohexyl tosylates.

The only other possible explanation for the formation of chiral product is that the deuteride source is chiral. For example, one might hypothesize that BD_3 is utilized as a complex with R-(+)-4, rather than as free borane. This possibility cannot be excluded at the present time and further experiments are needed to clarify this point.

The Reaction of R-(+)-Styrene Oxide with
Diethylmagnesium/Magnesium Bromide Dioxanate

The reaction of R-(+)-styrene oxide (4) with diethylmagnesium/magnesium bromide dioxanate according to the procedure of Whitesides and Roberts⁴⁵ produced 30% of 1-phenyl-2-butanol (90) and 50.2% of 2-phenyl-1-butanol (95).



The products obtained were shown to be the levorotatory isomer of 90 and the dextrorotatory isomer of 95; the latter contained a 43.9% ee⁵² of the S isomer (Table 9).

The reaction probably involves (see Figure 13) the initial formation of a magnesium-epoxide complex (87). The formation of 1-phenyl-2-butanol (90) can be explained

TABLE 9

RESULTS OF THE REACTION OF R-(+)-STYRENE^a
OXIDE WITH Et₂Mg/MgBr₂·DIOXANATE

	PhCH ₂ CH(OH)Et	PhCH(Et)CH ₂ OH
Actual Yield (%)	30	50.2
α _D	-0.31	+7.44
% ee	---	43.9
Configuration	---	S

(a) The optical purity of the styrene oxide used was 87%.

by the addition of an ethyl group to the aldehyde intermediate (88) formed as a result of ring opening and hydride migration. The fact that this alcohol exhibited a very small rotation seems to indicate that the rearrangement and subsequent addition are not taking place in a highly concerted fashion as might be the case in the borane-d₃/boron trifluoride etherate reduction (see previous section).

Since the 2-phenyl-1-butanol (95) formed in this reaction had predominantly the S configuration, the principal mode of reaction is thought to be one of inversion through an intermolecular pathway as illustrated in 92. The fact that the optical purity of the 2-phenyl-1-butanol was only about half that of the styrene oxide (43.9% ee vs 87.1% ee) suggests that there is considerable carbonium ion character at the secondary epoxide carbon or that the reaction also proceeded partially by an intramolecular pathway (91) with retention of configuration. No definitive statement can be made at this time as to which is the predominant mode of reaction. If the racemization is due to a competitive

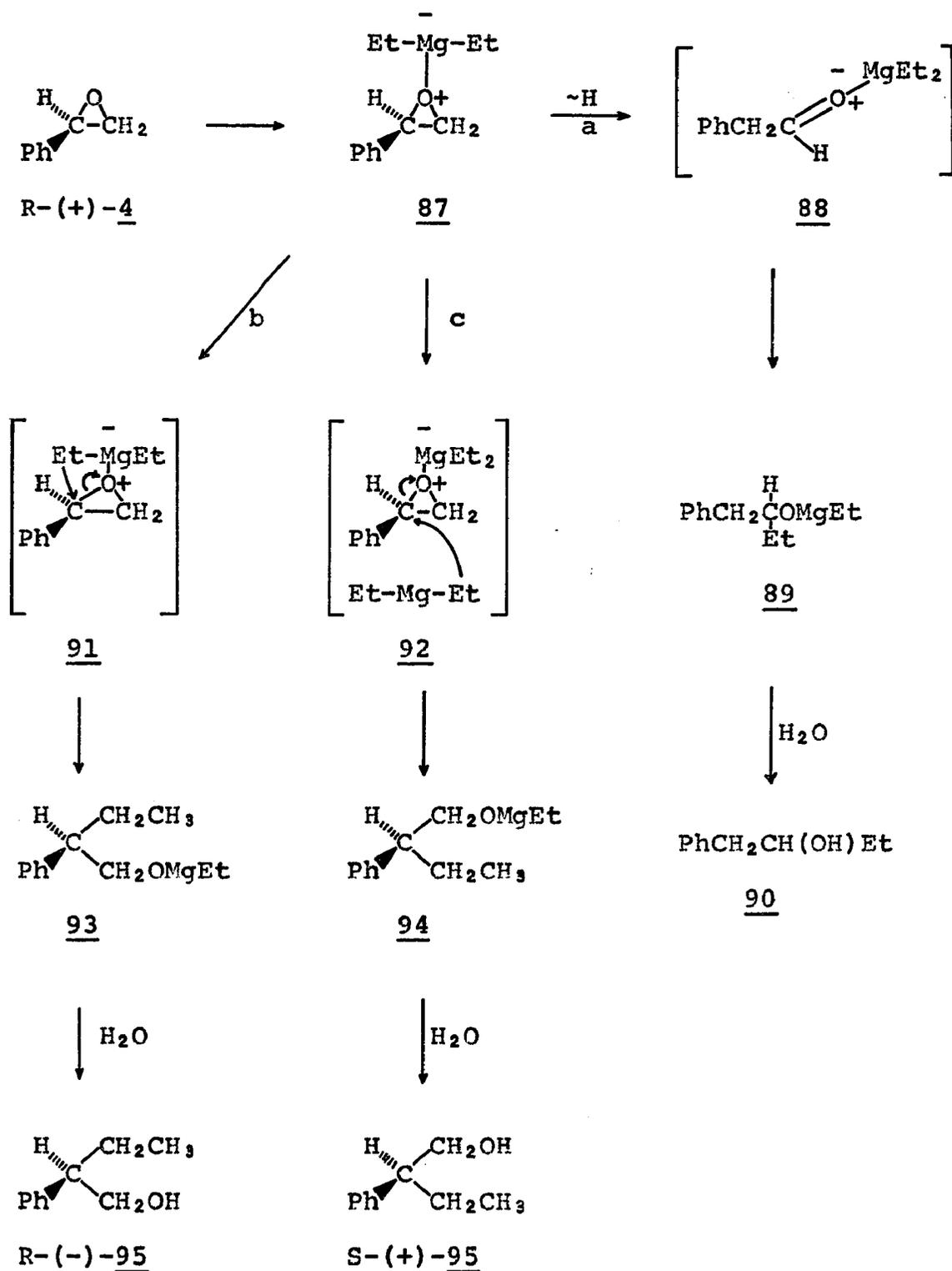


Figure 13. Mechanisms for the reaction of R-(+)-styrene oxide with $\text{Et}_2\text{Mg}/\text{MgBr}_2 \cdot \text{dioxanate}$.

intramolecular pathway (91), then the optical purity of the 2-phenyl-1-butanol formed from the reaction of chiral styrene oxide with a large excess of the Grignard dioxane might be expected to be more nearly the same as that of the styrene oxide used. However, if the racemization is due primarily to non-concerted ring opening, then the optical purity of the 2-phenyl-1-butanol would not be increased significantly from that observed with an equimolar amount of reagent.

The fact that the exploratory work discussed in this section has posed a number of new questions about the electrophilically assisted ring opening reactions of epoxides illustrates the complex nature of such reactions and implies that they will continue to be of interest to the organic chemist for some time to come. Even though this investigation has not given a definitive picture of all the mechanistic details involved, it must be remembered that the original objective was to determine if these reactions proceeded to give optically active products. This question has been answered in the affirmative; in fact, optically active products were obtained from all of the reactions studied.

EXPERIMENTAL

General: All statements on pp. 39 to 41 of the Experimental Section of Part I are the same for Part II except that the preparative GLPC conditions are different. In this section the conditions were: 10' x 1/4" 20% Carbowax 20M on Chromosorb W-HP Column, 180°, 120ml/min.

R-(-)-Methyl Mandelate (64):⁵¹ The ester was prepared exactly as directed on p. 43 from R-(-)-mandelic acid, $[\alpha]_D -139.09$, (578) -145.90 , (546) $-167.27 \pm 0.01^\circ$ (l 0.5, c 2.2, water), 88.8% ee.⁵⁰ The yield of ester was 105.4g (96.5%), m.p. 54° , $[\alpha]_D^{27} -164.45$, (578) -177.71 , (546) $-198.26 \pm 0.01^\circ$ (l 0.5, c 1.84, chloroform), 93.4% ee.⁶¹ NMR(6942): 6.82(S,5H), 4.73(S,1H), 3.60(S,1H), 3.38(S,3H).

R-(-)-1-Phenyl-1,2-Ethanediol (2):³ To a stirred suspension of lithium aluminum hydride (17.5g, 0.46mol) in 500ml of dry ether, a solution of R-(-)-methyl mandelate (100g, 0.6mol) in 1l of dry ether was added dropwise to maintain a gentle reflux (3.5 hours). The mixture was heated under reflux for 1.5 hours, allowed to cool to room temperature and then hydrolyzed with 750ml of 10% sulfuric acid. The organic layer was separated from the aqueous layer and combined with several ether extracts of the aqueous layer. The ether solution was washed with cold 5% sodium hydroxide solution and dried ($MgSO_4$). The ether was removed at reduced pressure; the crude diol was recrystallized from benzene/30-60° pet ether (3:2) to give 47.4g (57.2%) of diol, m.p. $65-65.5^\circ C$; $[\alpha]_D^{22} -35.7$, (578) -37.07 , (546) $-41.37 \pm 0.01^\circ$ (l 0.5, c 3.48, 95% EtOH), 87.9% ee based on $[\alpha]_D$ (max) 40.6° .⁶² NMR(7141): 7.25(S,5H), 4.72(t,1H), 4.25(S,2H), 3.60(d,2H).

R-(-)-2-Brosyloxy-1-Phenylethanol (65):³ To a stirred solution of p-bromobenzenesulfonyl chloride (83.2g, 0.325mol) in 250ml of dry pyridine at $-5^\circ C$, a solution of R-(-)-

1-phenyl-1,2-ethanediol (45.0g, 0.325mol in 250ml of dry pyridine) was added dropwise so that the temperature did not exceed 0°C. The mixture was placed in the refrigerator (5°C) for 72 hours and then allowed to stand at room temperature for 1.5 hours. The mixture was then poured into ice-cold, dilute hydrochloric acid (1200g ice + 200ml conc. HCl); and the gummy solid which deposited was taken up in ether. The ether extracts were washed with dilute HCl and water and then dried (MgSO₄). Removal of the ether left a viscous oil which was dissolved in 270ml of benzene/30-60° pet ether (1.25:1) and placed in a refrigerator. The crystals that deposited were filtered, washed with 30-60° pet ether and air dried. The yield of brosylate was 77.9g (67%), m.p. 70-71°; $[\alpha]_D^{22}$ -32.02, (578) -33.59, (546) -38.61 ± 0.01° (l 0.5, c2.59, 95% EtOH).
NMR(7190): 7.35(s,4H), 7.16(s,5H), 4.81(m,1H), 3.92(t,2H), 3.34(s,1H).

R-(+)-Styrene Oxide (4):³ The brosylate (76.5g, 0.214mol) was dissolved in 400ml of dry ether, cooled to -5°C and treated with a solution of potassium hydroxide (16.0g, 0.287mol) in 160ml of dry methanol) in a dropwise manner so that the temperature did not exceed 0°C. After addition, 750ml of cold water was added to the reaction mixture and the aqueous layer was extracted with ether. The combined ether extracts were washed with water and dried (MgSO₄).

The ether was removed at reduced pressure and the residue was distilled.

Fraction	b.p. (6.5mm)	Wt(g)	% epoxide*
1	67°	0.25	98.6
2	67-69	18.30	98.3
3	70-95	1.30	76.9
4	95-100	1.40	23.8

Fractions 1-3 were combined and redistilled to purify the epoxide further.

Fraction	b.p. (17mm)	Wt(g)	% epoxide*
1	83-86°	16.0	99+
2	87	1.5	94.9
3	88	1.2	89.3
4	88-111	2.2	45.4

*Glpc (II-55, 1m x 6mm Silicon GE XE-60 nitrile gum on Chromosorb W, 125°, 5psi; R.T. of epoxide 3'10"). The other component was 1-phenylethanol.

The yield of epoxide was 19.55g (76%); $[\alpha]_D^{28} +29.8$, (578) $+31.2$, (546) $+35.5 \pm 0.01^\circ$ (20.5, neat), 87.1% ee based on $[\alpha]_D +34.2^\circ$.²

Reactions of R-(+)-Styrene Oxide

Reaction with AlD_3/Et_2O Reagent:¹⁶ To a cold, stirred solution of anhydrous aluminum chloride (1.067g, 0.008mol) in 40ml of dry ether, lithium aluminum deuteride (1.05g, 0.025mol) and 25ml of dry ether were added. The mixture was stirred for 45 minutes at room temperature and then a solution of R-(+)-styrene oxide (4.00g, 0.0234mol) in 25ml of dry ether was added dropwise to maintain a gentle

reflux. The mixture was heated under reflux for two hours, allowed to cool to room temperature and then 10ml of water and 25ml of 10% sulfuric acid were added. The organic layer was separated and combined with several ether extracts of the aqueous layer. The ether solution was dried (MgSO_4) and then the ether was removed. Distillation of the residue gave 3.95g (96.4%) of product, b.p. (0.3mm) 55-57°. Glpc analysis (II-58-1) showed the sample to be 35.5% 1-phenylethanol (R.T. 3'25") and 64.5% 2-phenylethanol (R.T. 5') corresponding to yields of 34.2% and 62.2%, respectively. Two preparative scale glpc separations gave samples that were 99+% pure (II-58-2):

1-Phenylethanol-2-d, $[\alpha]_D^{30}$ -41.1, (578) -43.0, (546) -48.95 \pm 0.025° (l 0.2, neat), 94.3% ee S-(-) based on $[\alpha]_D$ (max) 43.6°. ⁵⁶
 NMR(7261): 6.79(S,5H), 4.51(S,1H), 4.25(t,1H), 0.88(d,2H).
 Mass Spectrum (II-58-1): 3.3% d_0 , 96.6% d_1 .

2-Phenylethanol-2-d, α_D^{30} -1.15, (578) -1.21, (546) -1.40 \pm 0.01° (l 0.5, neat), S configuration.
 NMR(7240): 6.72(S,5H), 4.37(S,1H), 3.28(d,2H), 2.34(t,1H).
 Mass Spectrum (II-58-2): 2.7% d_0 , 95.7% d_1 , 1.5% d_2 .

Reaction with AlD_3 /THF Reagent: ²⁵ To a stirred suspension of lithium aluminum deuteride (1.05g, 0.025mol) in 25ml of dry THF, dideuterosulfuric acid (1.26g, 0.0125mol, Dia-prep Incorporated, 99.5%D) was added dropwise with caution. The mixture was stirred for forty-five minutes at room

temperature and then a solution of R-(+)-styrene oxide (4.00g, 0.0234mol) in 25ml of dry THF was added dropwise to maintain a gentle reflux. The reaction mixture was stirred for one hour at room temperature and then hydrolyzed with a 1:1 mixture of THF/water. The aqueous layer was saturated with potassium carbonate and the organic layer was then separated from it. The ether extracts of the aqueous layer were combined with the organic layer and dried (MgSO₄). The ether was removed at reduced pressure and the residue was distilled to give 3.6g (87.8%) of product b.p. (0.25mm) 49-51°. Glpc analysis (II-57-1) showed the product to be 75% 1-phenylethanol (R.T. 3'25") and 25% 2-phenylethanol (R.T. 5') corresponding to yields of 65.9% and 21.9%, respectively. Purification by two preparative scale glpc separations gave samples that were 99+% pure (II-57-2):

1-Phenylethanol-2-d, $[\alpha]_D^{25}$ -42.2, (578) -44.2, (546) -50.45 \pm 0.01° (ℓ 0.5, neat), 96.9% ee S-(-).⁵⁶
 NMR(7269): 6.75(s,5H), 4.44(s,1H), 4.25(t,1H), 0.80(d,2H).
 Mass Spectrum (II-57-1): 3.3% d_0 , 96.6% d_1 .

2-Phenylethanol-2-d, α_D^{24} -1.90, (578) -2.00, (546) -2.35 \pm 0.05° (ℓ 0.1, neat), S configuration.
 NMR(7268): 6.66(s,5H), 4.29(s,1H), 3.23(d,2H), 2.25(t,1H).
 Mass Spectrum (II-57-2): 2.1% d_0 , 95.5% d_1 , 2.3% d_2 .

Reaction with B₂D₆/BF₃·OEt₂ Reagent:³⁵ Deuteroborane was prepared according to the method of Brown and Zweifel⁶³

from lithium aluminum deuteride 1.05g, 0.025mol) and boron trifluoride etherate (7.09g, 0.05mol) in 35ml of dry ether, and flushed into a separate flask containing 50ml of dry THF. Boron trifluoride etherate 3.17g, 0.02mol) was added to the deuteroborane/THF solution and the solution was cooled to 0°C. A cold solution of R-(+)-styrene oxide (2.4g, 0.02mol in 20ml of dry THF) was added dropwise and then the solution was stirred for one-half hour at 0°C. The solution was allowed to warm to room temperature and was then hydrolyzed with 25ml of water. The aqueous phase was saturated with potassium carbonate, and the organic layer was separated from it. The organic layer was combined with the ether extracts of the aqueous layer and dried (MgSO₄). The ether was removed at reduced pressure and then 5ml of methanol was added to the residue. The methanol solution was distilled to give 1.8g of product, b.p. (0.25mm) 49-50°, 97.3% pure by glpc (II-59-1, R.T. 5"). Purification by one preparative scale glpc separation gave a sample that was 99+% pure glpc (II-59-2). The yield of 2-phenylethanol-1-d was 71.8%, α_D^{29} -0.415, (578) -0.475, (546) -0.525 \pm 0.025° (l 0.2, neat).

NMR(7230): 6.76(s,5H), 4.19(s,1H), 3.22(t,1H), 2.31(d,2H).

Mass Spectrum (II-59): 2.2%d₀, 96.5%d₁, 1.3%d₂.

Reaction with Diethylmagnesium/Magnesium bromide dioxanate:⁴⁵

Diethylmagnesium was prepared by the addition of dry dioxane (2.35g, 0.0233mol) to a solution of ethylmagnesium bromide

(22.8ml of 1.02M solution, 0.023mol). The precipitated magnesium bromide dioxanate was not filtered off. The reaction mixture was stirred for ten minutes and then R-(+)-styrene oxide (2.00g, 0.0166mol) was added dropwise to maintain a gentle reflux. The reaction mixture was then stirred for four hours at room temperature, heated under reflux for one hour; and a saturated aqueous ammonium chloride solution was added until the solids conglomerated on the sides of the flask. The ether was decanted off and dried ($MgSO_4$). Removal of the ether and distillation of the residue gave 2.1g of product, b.p. (0.3mm) 65-68°. Glpc analysis (II-56-1) showed the product to be a mixture of 35.9% 1-phenyl-2-butanol R.T. 4'45") and 60.6% 2-phenyl-1-butanol (R.T. 6'20") corresponding to yields of 30% and 50.2%, respectively. Purification by two preparative scale glpc separations gave samples that were 99+% pure (II-56-2):

1-Phenyl-2-butanol, α_D^{25} -0.31, (578) -0.325, (546) -0.375 \pm 0.025° (ℓ 0.2, neat).

NMR(7289): 7.15(s,5H), 3.62(m,1H), 2.60 and 2.55(d,d,3H), 1.42(q,2H), 0.95(t,3H).

IR(12073): 3425(s), 2915(s), 1601(m), 1475(s), 1425(s), 1100(m), 1000(m), 960(s), 820(w), 720(s), 670(s).

C & H Analysis (II-56-1): calc; C-79.95, H-9.39.

found; C-80.25, H-9.34.

Mass Spectrum (II-56-1): m/e 150 (M).

2-Phenyl-1-butanol, $\alpha_D^{28} +7.44$, (578) $+7.75$, (546) $+8.775 \pm 0.025^\circ$, (l 0.2, neat), 43.9% of S-(+) ee based on $\alpha_D -16.5^\circ$ (97.3% ee).⁵²
 NMR(7288): 6.81(S,5H), 3.92(S,1H), 3.26(d,2H), 2.27(m,1H),
 1.28(m,2H), 0.47(t,3H).

S-(-)-Styrene Oxide (S-4): A solution of α -chloroaceto-phenone (15.46g, 0.1mol in 150ml of dry ether) was added dropwise (1.5 hours) to a stirred solution of the Grignard reagent (173ml of 0.58M solution, 0.1mol) prepared from R-(-)-1-chloro-2-phenylbutane of 80% ee according to the procedure of Birtwistle and coworkers.⁵² The reaction mixture was stirred for four hours at room temperature, cooled to 0°C, and treated with a methanolic solution (175ml) of potassium hydroxide (16.83g, 0.3mol) in a dropwise manner so that the temperature did not exceed 5°C. After addition, 200ml of cold water was added to the reaction mixture. The mixture was filtered, and the aqueous layer was extracted with ether. The combined ether extracts were washed once with 5% H₂SO₄, twice with 5% NaOH and twice with water and then dried (MgSO₄). The ether was removed at reduced pressure, and the residue was distilled at aspirator pressure to give 13.05g of product, b.p. 62-77°, 38.5% pure by glpc (II-45-1, 1m x 6mm Silicon GE XE-60 nitrile gum on Chromosorb W, 125°, 5psi; R.T. of epoxide 3'10") corresponding to a yield of 39%. Purification by two preparative scale glpc separations gave a 99+% pure (glpc II-45-2) sample of styrene oxide, $[\alpha]_D^{25} -4.81$, (578) -5.02 , (546) $-5.79 \pm 0.01^\circ$ (l 0.5, neat), 13.9% ee S-(-).²

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