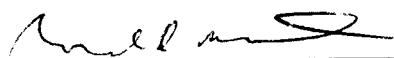


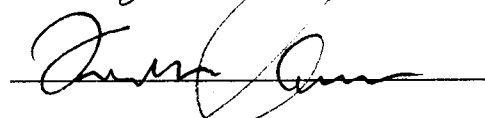
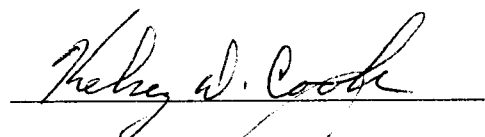
To the Graduate Council:

I am submitting herewith a dissertation written by Mitchell Allison Rhea entitled "The Stereochemistry of the S_N2' Reaction Between (S)-(+)-3-Chloro-1-butene-Z-1-d and Methylamine." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in chemistry.



R. M. Magid, Major Professor

We have read this dissertation
and recommend its acceptance:



Accepted for the Council:



Vice Provost
and Dean of the Graduate School

THE STEREOCHEMISTRY OF THE S_N2' REACTION BETWEEN
(*S*)-(+)-3-CHLORO-1-BUTENE-*Z*-1-*d* AND METHYLAMINE

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Mitchell Allison Rhea

December 1990

DEDICATION

This dissertation is dedicated to Dr. Benjamin H. Gross. His influence, wisdom, concern, and scores of other enviable characteristics have had a profound influence on me.

ACKNOWLEDGEMENTS

The magnitude of the tome that would be required to properly acknowledge everyone that has left a lasting impression on me or offered an encouraging word and support, in both good times and bad, during my time as a graduate student, would dwarf the dissertation itself. This is the fundamental reason that the task would be neither realistic nor possible. A second, but no less important reason, is that many of the specific details of these moments have faded with the years, but the encounters and words were much needed and appreciated in their time.

Nevertheless, there are those who must be expressly mentioned. I would like to express my love and appreciation for my parents, whose years of patience, understanding, and encouragement (and financial support!) have made much of this possible. Next, grateful appreciation and sincere admiration must go to Dr. Ronald M. Magid for his proficiency, counsel, standards, and incredible patience. Without my peers to rely on, the entire task would have been nearly impossible; but particular thanks go to Richard Boothe, Terry Sumpter, Eddie Brown, Chris Coholic, Jeff Gee, and Randall Hinton. Not to be overlooked are the departmental secretaries, and specifically Carol Moulton and the late Agnes Scott, whose patience and assistance cannot be forgotten, along with the staffs of the various departmental shops. The financial assistance given to me by the Chemistry Department has also been greatly appreciated.

ABSTRACT

Allylic compounds are known to undergo substitution reactions and some are thought to proceed by an S_N2' mechanism, that is, with rearrangement of the allylic system. While the general reaction mechanism itself has enjoyed much conjecture, the stereochemical considerations of the mechanism have received far less attention.

The reaction between (*S*)-(+)-3-chloro-1-buten-*Z*-1-*d* and monomethylamine was shown to proceed with *syn* stereoselectivity to produce a mixture of optically active amines. In order to have meaningful comparisons with analogous, saturated, optically active, reference compounds, it was necessary to reduce this initial mixture with diimide. A reference compound of known optical purity and absolute configuration was then synthesized and its optical rotations were corrected by comparison with the rotations of the alcohol from which it was made in order to obtain its $[\alpha]_{\max}$. After correcting for the deuterium content, the relative amounts of *E* and *Z* isomer in the initial S_N2' mixture, and the optical activity of the allylic substrate, the rotations of the reduced S_N2' mixture were compared with those of the reference compound. These comparisons led to the conclusion that the mechanism was proceeding with *syn* stereoselectivity by 75:25; that is, the nucleophile was approaching the allylic system from the same side as the leaving group was departing.

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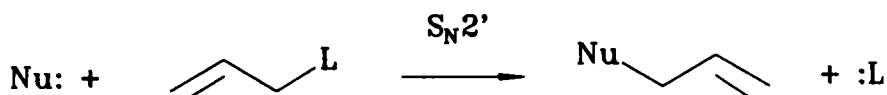
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CHAPTER I

INTRODUCTION

The notion of an S_N2' mechanistic pathway was first suggested some five decades ago.¹ The process is a bimolecular nucleophilic substitution pathway, but it differs from the "conventional" bimolecular nucleophilic substitution pathway in that it occurs with a rearrangement of an allylic system associated with the leaving group, L (Equation 1). Note that in the following equation, the nucleophile and the leaving group can be either neutral or charged; that is, the charge on the nucleophile increases by 1 as the reaction proceeds, while the charge on the leaving group decreases by 1.

Equation 1



The general considerations of the reactions of these allylic substrates and various nucleophiles have been studied at some length. The specific areas of the stereo- and the regiochemical aspects have received for less attention. The stereoelectronic preference of the S_N2' reaction should be possible to ascertain by the use of optically active, deuterium-labeled acyclic substrates which are free of any conformational or steric constraints.

A detailed understanding of how bonds are made and broken in a reaction is of fundamental importance to mechanistic and synthetic chemists,² especially when the S_N2' reaction is frequently used in synthetic schemes.

This work is an attempt to determine if there is any stereoelectronic preference inherent in the S_N2' reaction between (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* and monomethylamine.

CHAPTER II

A BRIEF LOOK AT THE HISTORY OF THE S_N2' REACTION

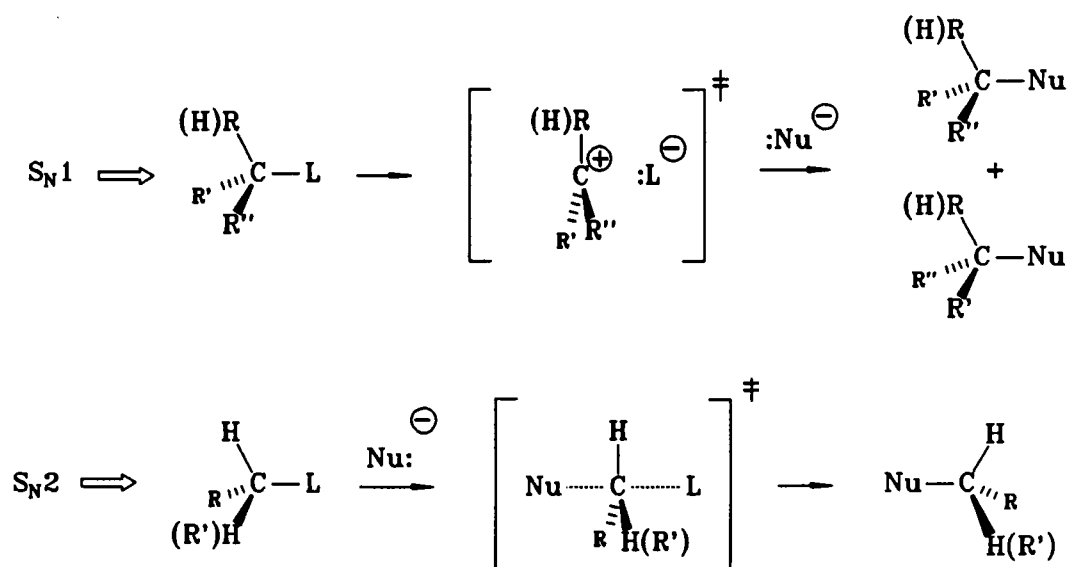
A. General Considerations

The reader will no doubt be able to recall substitution reactions from his or her earliest experiences with organic chemistry. Of the many various types of substitution reactions, the only ones pertinent to the discussion at hand are those for aliphatic substrates. To further narrow the scope somewhat, within this particular class of reactions only the unimolecular and the bimolecular nucleophilic substitution reactions will be discussed. These reactions were known in the 1920s,³ but the first mechanistic details were proposed by Hughes and Ingold in the early 1930s.⁴ The unimolecular mechanism, designated by S_N1 , would be expected to operate for tertiary (3°) and sterically crowded secondary (2°) carbon centers. The bimolecular pathway, designated as S_N2 , would be followed in the cases of primary (1°) and less sterically hindered secondary sites (Equation 2).

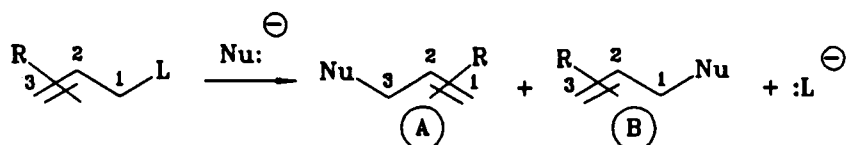
When one of the alkyl groups, R, happens to be an vinylic system, some rather interesting results can occur. It should be noted that there are other factors involved than merely the structure of the substrate that exert an influence on the outcome of these reactions and that these factors will be addressed later.

While doing solvolysis studies using allyl substrates, an isomeric mixture of products was discovered (Equation 3).³

Equation 2

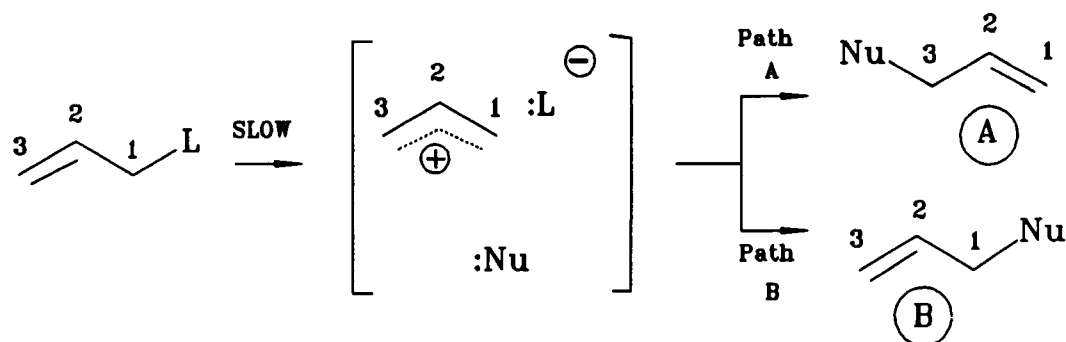


Equation 3

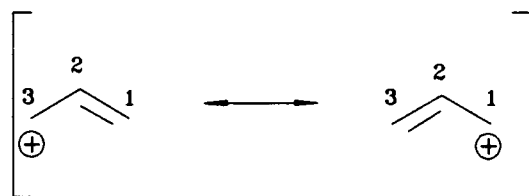


It wasn't until the mid-1930's that a mechanism was proposed to explain these results.⁴ Since the reaction conditions were such as to encourage solvolysis of the substrate, the mechanism was designated as a unimolecular, aliphatic, nucleophilic substitution that included a rearrangement of the allylic system to give rise to product A (Equation 4), hence the designation of $\text{S}_{\text{N}}1'$ where the prime indicates the allylic rearrangement. The first step of the mechanism, which is the rate-determining step as well, is the departure of the leaving group, L, to form an allylic cation (Equation 4). Since the allylic cation is a resonance hybrid of two contributing resonance structures (Equation 5), most of the carbocation character is focused on

Equation 4



Equation 5



the terminal carbon atoms. Because of this, a nucleophile, Nu, can attack the allylic system by either of two routes. Path A attaches the nucleophile to carbon-3 (or the γ -carbon), while Path B gives the 1-substituted (or the α -substituted) product. This mechanism became well-established and widely accepted.

But is this the only mechanism that could explain the formation of the rearranged product? A few years later, in 1937 and 1938, the idea of another mechanistic pathway came to the forefront in an attempt to explain the isomeric product mixture that is sometimes obtained with allylic substrates. Three chemists, Bergmann,⁵ Hughes,⁶ and Winstein,⁷ independently offered a concerted mechanism called S_N2' . However, just as the stepwise S_N1 and the concerted S_N2 mechanisms differ only in timing, so, too, do the S_N1' and the S_N2' .¹ Thus the notion of the S_N2' mechanism was born. The proposed mechanism requires that the

nucleophile, Nu:, attack at carbon-3 (the γ -carbon) in the allylic system, along with a shift of the π -electrons and departure of the leaving group, L, occurring in a concerted fashion (Equation 6).

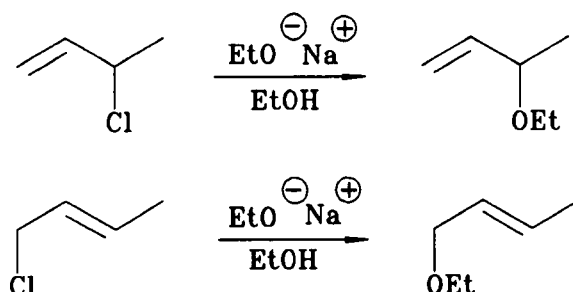
Equation 6



Immediately, several research groups set about the task of providing a *bona fide* example of a reaction that followed the newly proposed pathway. One of the first reported attempts at providing such an example came in 1941 by Catchpole and Hughes.⁸

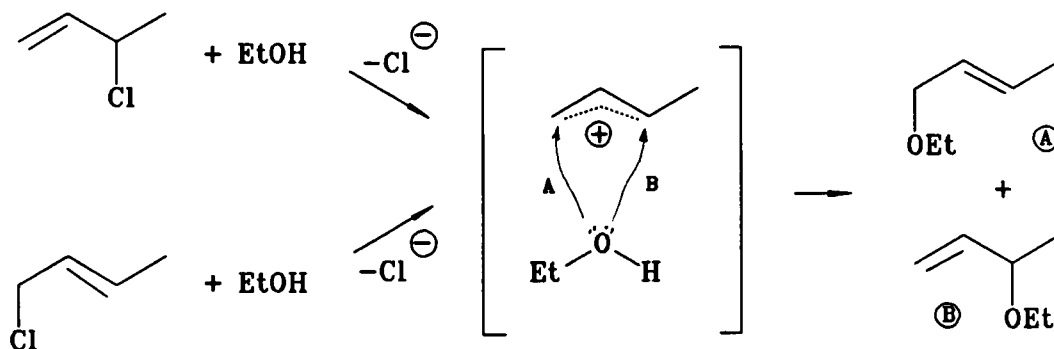
Their efforts focused on two types of reactions. The first reaction employed conditions favorable to the bimolecular-type reactions using equal concentrations of 3-chloro-1-butene (α -methylallyl chloride) or 1-chloro-2-butene (crotyl chloride) as the substrate with sodium ethoxide as the nucleophile. In each case, only the unrearranged product from the $\text{S}_{\text{N}}2$ reaction on each substrate was isolated (Equation 7).

Equation 7



The other reaction used the same chloride substrates, but under conditions favorable to the solvolysis mechanism; that is, the ethoxide was used in very low concentration in ethanol. Regardless of which allylic chloride was used, the same isomeric mixture of the unrearranged and rearranged products was obtained (Equation 8).

Equation 8



Isolation of a similar product mixture indicates that a common reaction intermediate is being formed during the course of the reaction, and that intermediate, in this case, is probably the allylic cation. Unfortunately, the bimolecular substitution reaction produced no evidence of the formation of any rearranged product. Both of these bits

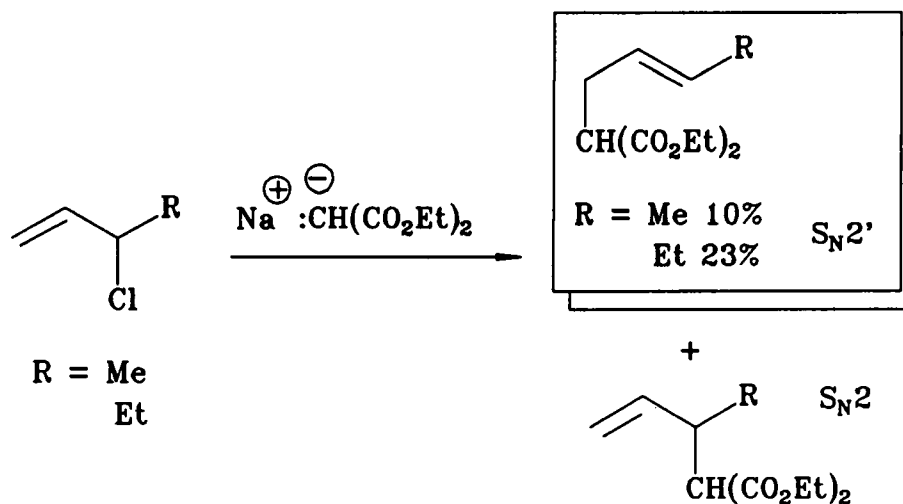
of information only served as further testimony for the S_N1 , S_N1' , and S_N2 mechanisms. The search went on.

A year later, in 1942, hoping to detect something that Hughes had missed, Young and his co-workers reinvestigated Hughes' work with the same allylic chlorides.⁹ The results were the same; that is, the reaction favoring the bimolecular pathway produced no rearranged products while the other yielded the same isomeric mixture. They too concluded that only the cases for S_N2 and S_N1' were strengthened.

The year was 1948 and it brought with it a pronouncement by Hughes and co-workers that their work had shown that "although the simple substitution mechanism, S_N2 , can readily be observed, the substitution with rearrangement, S_N2' , apparently cannot be realized."¹⁰ They reasoned that the presence of the π -electron cloud apparently protects the terminal olefinic carbon nucleus from attack by the nucleophile, even though from a steric standpoint, attack at this position (the γ -carbon) would be preferred over attack at carbon-1 (the α -carbon).

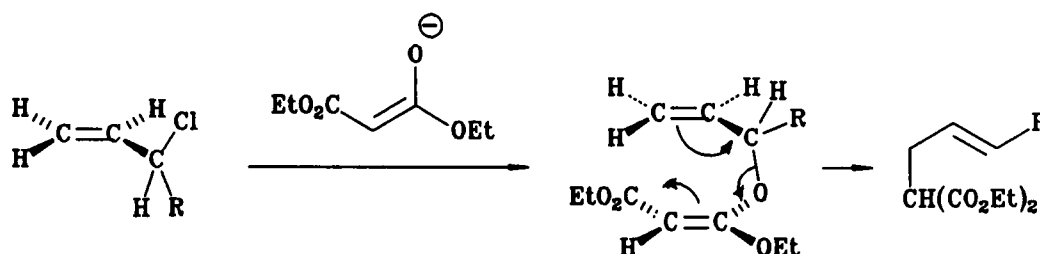
As is often the case after a definitive statement such as Hughes' appears, some event comes along to disprove it. Just one year later in 1949, an apparent example of the S_N2' reaction was discovered by Young *et al.*¹¹ They found that 3-chloro-1-butene (α -methylallyl chloride) and 3-chloro-1-pentene (α -ethylallyl chloride) produced small, although isolable, amounts of the corresponding rearranged products (10% and 23%, respectively) using sodium diethyl malonate as the nucleophile (Equation 9). But not everybody was convinced that the rearranged product of this reaction arose by way of an S_N2' mechanism. Dewar suggested that the same product could be obtained by the *O*-alkylation followed by Claisen rearrangement

Equation 9



(Equation 10).¹² Dewar's claim was contested but not refuted at the time.

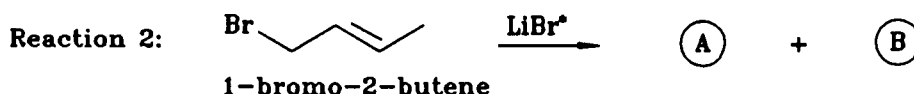
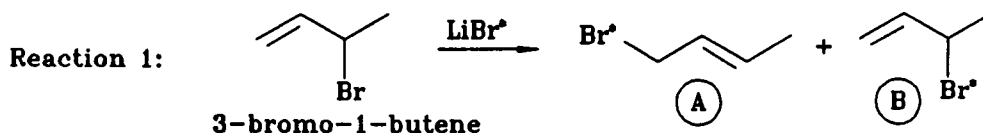
Equation 10



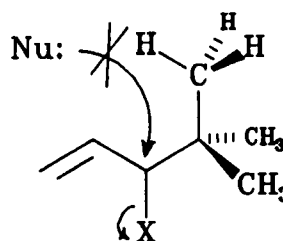
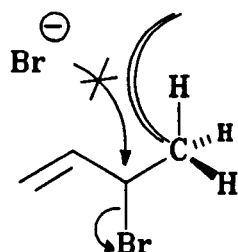
In 1951, Hughes offered an explanation as to its elusive nature. It wasn't that the $\text{S}_{\text{N}}2'$ pathway did not exist, but that when it had to compete with the simple $\text{S}_{\text{N}}2$ mechanism, the much slower $\text{S}_{\text{N}}2'$ route only appeared to be non-existent. To prove his point, he devised an experiment which used a radioisotope of bromide as the nucleophile and 3-bromo-1-butene (α -methylallyl bromide) and 1-bromo-2-butene (crotyl bromide) as the halide substrates. With this combination of reactants, simple $\text{S}_{\text{N}}2$ reactions would be detected by recovery of radio-labeled unrearranged allylic

halide. Any S_N2' reactions could be detected by the incorporation of the labeled bromine concurrent with production of rearranged material¹³ (Equation 11).

Equation 11



The results of this experiment showed that the S_N2' pathway does indeed exist, but that, as predicted, it is definitely much slower than its S_N2 counterpart. England and Hughes found that the 3-bromo-1-butene underwent the S_N2 process some 60 times faster than it underwent the S_N2' process. In the case of the 1-bromo-2-butene, they found that the S_N2 pathway was being followed some 28000 times more often than the S_N2' route. They also suggested that the decrease in the observed rates of reaction, that is, from 28,000 to 60 times the rate of the S_N2' reaction, was not due

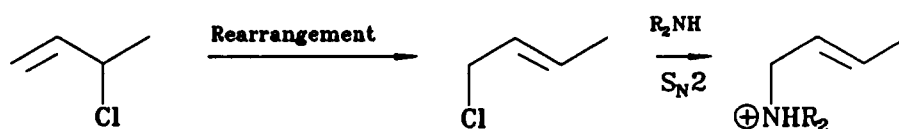


to any difference in the rate of the S_N2' process, but instead could be attributed to the steric effect imposed by the methyl group at carbon-3 in the case of 3-bromo-1-butene. A similar idea was expressed earlier by Catchpole¹⁰ and co-workers when trying to force S_N2' conditions by substituting a *tert*-butyl group on the α -carbon.

That same year, Young and coworkers found that the reaction between 3-chloro-1-butene and diethylamine gave essentially only the rearranged product.¹⁴ But was this reaction following the S_N2' pathway? Before they could answer this, three facts had to be established:

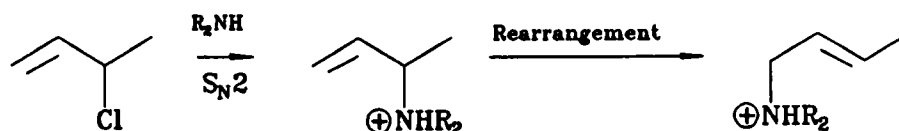
- 1.) Under the reaction conditions, the starting allylic chloride did not rearrange to the isomeric 1-chloro-2-butene ($\text{CH}_3\text{-CH=CH-CH}_2\text{-Cl}$) followed by attack of diethylamine in simple S_N2 fashion.

Figure 2



- 2.) If there was no prior rearrangement occurring (as in Part 1.) then there was no rearrangement of an initially formed S_N2 product under the reaction conditions to give the apparent S_N2' product.

Figure 3



- 3.) The formation of the rearranged product followed second order kinetics.

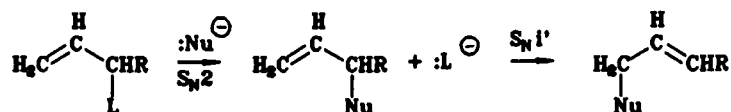
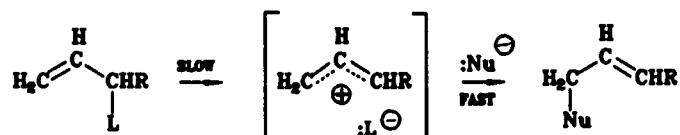
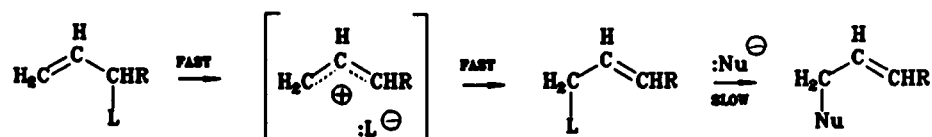
$$\text{rate} = k [\text{alkyl halide}][\text{R}_2\text{NH}]$$

Indeed, each of these conditions was shown to be the case in the reaction.

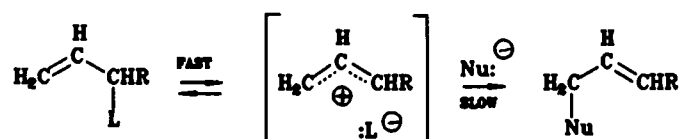
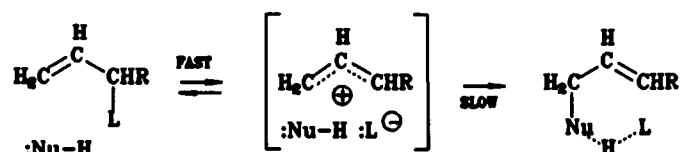
Bordwell¹⁵ has expressed considerable doubts about the concertedness of several reactions that are considered to be concerted; one of these is the $\text{S}_{\text{N}}2'$ reaction. Bordwell has stated that despite its logical and aesthetic appeal, this concerted mechanism has had little evidence in support of it. He has proposed five other possible mechanistic pathways (see Scheme 1) which could explain the formation of the rearranged product.

Before the $\text{S}_{\text{N}}2'$ reaction can be classified as a concerted process, there has to be some evidence to eliminate other possible pathways to the observed rearranged product. Path A, suggested by Dewar,¹² de la Mare,¹⁶ and Ingold,¹⁷ has been invoked on two occasions to explain the formation of the rearranged product. According to Bordwell,¹⁵ one should be able to rule out Path B given that the reaction is observed to have second-order kinetics; however, the experimental error when measuring rates of reactions is sometimes large enough in kinetic investigations to allow for 10-20% of the rearranged product to be formed by this pathway without indicating the bimolecular nature of the mechanism (recall the alleged first reported evidence by Young and his co-workers). Path C could be ruled out if it could be shown that the starting allylic substrate was not first rearranging under the reaction conditions; however, if the $\text{S}_{\text{N}}2$ part of this combination occurs much faster than the initial rearrangement, rearranged substrate would never be detected. Paths D and

Scheme 1

Path A: S_N2-S_N1' Path B: S_N1 Path C: $S_N1'-S_N2$ 

Path D: Attack of Nu: in the rate-limiting step

Path E: An S_N1' -like process

E are two other possible variations that also give the rearranged product but cannot be ruled out.

Also according to Bordwell,¹⁵ one cannot ignore the "strong tendency" of allylic halides to undergo carbocation-type reactions. By placing electron-withdrawing substituents on the allylic halide, this tendency can be lessened; furthermore, the carbon-carbon double bond would be more susceptible to attack by a nucleophile.

The following three examples were explored. The electron-withdrawing sulfonyl group should facilitate S_N2' reactions while discouraging S_N1 reactions. The results showed that neither epimer of compound A underwent reaction with either piperidine or triethylammonium thiophenoxide.¹⁸ For compound B, it was expected that this analog of 3-chloro-1-butene (which yielded the rearranged product almost exclusively when the nucleophile used was diethylamine) would be even more reactive in the S_N2' sense because one of the terminal olefinic hydrogens has been replaced by a sulfonyl group. It turned out the only reaction, even with sodium methoxide in methanol, was the tautomerization of the allylic chloride ($\text{PhSO}_2\text{CH}=\text{CHCHClCH}_3 \rightleftharpoons \text{PhSO}_2\text{CH}_2\text{CH}=\text{CCH}_3\text{Cl}$). Greater success in forcing S_N2' reactions was seen with compounds such as C. Bordwell concedes that it would be difficult to say that the reactions were not going by an S_N2' process, but is quick to add that there seems to be no unambiguous examples of a reaction following an S_N2' mechanistic pathway. Since the product resulting from each of the previous examples of alkyl halides can be explained by other routes, he concludes that the concerted S_N2' reaction may well be a "myth."

Sneen also said that the mechanism was not concerted; he favored a pathway involving ion-pairs that were presumably intimate.¹⁹ He did go on to define exactly what he means by the term "ion-pair." He suggests that the intermediate is not a pair of point charges, but instead a compound containing "extended covalent bonds with considerable ionic character."

McLennan²⁰ defended the traditional viewpoint of a concerted mechanism, albeit one where the bonds become very polarized with the approach of the nucleophile.

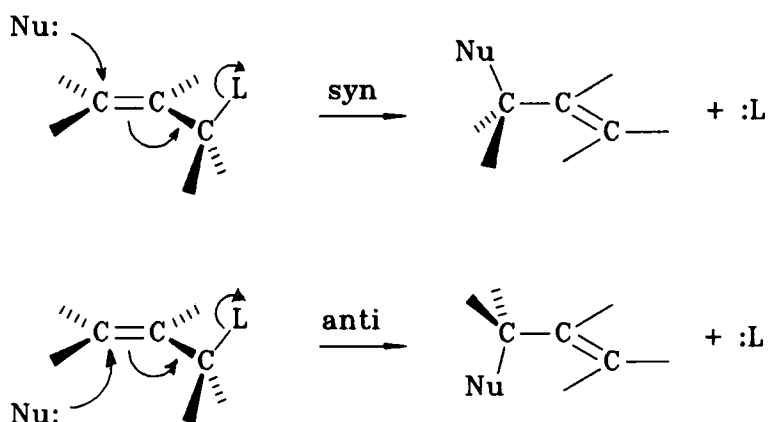
B. The Mechanism in Three Dimensions

1. In Theory

Once it was shown that a reaction presumably followed an S_N2' pathway, the task of delving further into the mechanism, specifically the stereochemistry, could commence.

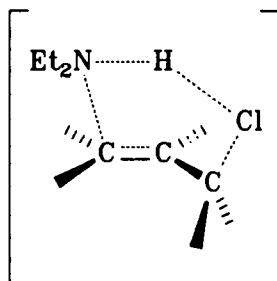
The sp^3 hybridized orbital of the carbon which bears the leaving group will eventually become one of the p-orbitals of the new carbon-carbon double bond. In order for overlap between the orbitals to occur, which is required for the rearrangement of the double bond to take place, the adjacent p-orbital and the sp^3 orbital between the carbon and leaving group must lie in the same plane.

Equation 12



With this in mind then, there are two possible ways in which the nucleophile can approach the allylic substrate (Equation 12). If the nucleophile, Nu:, attacks the substrate from the same side as that from which the leaving group, L, departs, it bears the designation of *syn*-attack. On the other hand, *anti*-attack is used to describe the approach of the nucleophile from the opposite side of the leaving group.

There are proponents for both modes of attack. The first proposal of which, if either, mode of attack might be preferred was qualitatively suggested by Winstein.⁷ He submitted that the nucleophile would be expected to enter on the same side as the leaving group (*syn*-attack).⁹ This particular orientation would provide a high



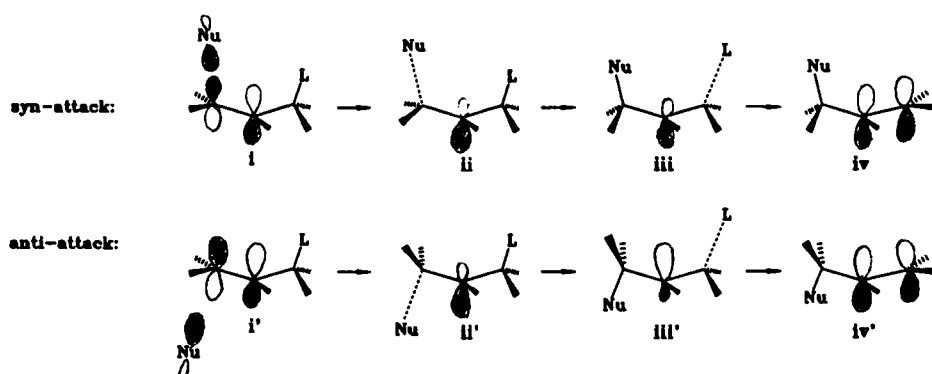
degree of electron density to the back side of the carbon to leaving group bond in order to facilitate its departure in a process reminiscent of a simple S_N2 reaction (Equation 2, p. 3). This arrangement would also facilitate the formation of the new carbon-carbon double bond by providing that the sp^3 orbital that will undergo rehybridization and become one of the p-orbitals of the double bond be in the proper orientation for the necessary overlap to occur. In addition to these orbital considerations, the formation of the S_N2' product was rationalized by suggesting the possibility that hydrogen bonding could be taking place in the transition state. This could only occur if *syn*-attack were followed. However, the fact that rearranged substitution product was obtained by Young²¹ using trimethylamine as the nucleophile has created some doubt as to whether the hydrogen bonding in the transition state was a requisite.

With so many atoms undergoing rehybridization in the transition state, there was the opportunity to observe diverse kinetic isotope effects. If hydrogen bonding were occurring in the transition state, a positive kinetic isotope effect would be observed if the amine nucleophile bore an amino deuterium rather than a proton. Dittmer and Marcantonio²² observed no such effect using 3-chloro-1-butene as the substrate with either Et_2N-D or $Ph(CH_3)N-D$ as the nucleophile. On the other hand, Fry²³ did find a positive effect when labeling the chlorine with ^{37}Cl , as well as when each of the three carbons of the allylic system was labeled with ^{14}C . These results indicated that the reaction was concerted, but that hydrogen bonding in the transition state might or might not be occurring.

Winstein suggested that neutral nucleophiles would form a partial positive charge and therefore help to stabilize the partial negative charge that would form on the leaving group. On the other hand, he suggested that negatively charged nucleophiles would have a destabilizing effect on the transition state due to the electrostatic repulsions between the negative charge on the nucleophile and the developing negative charge on the leaving group. This proposal could also explain why only S_N2 products were seen in the reaction of acetate ion or ethoxide ion with 3-chloro-1-butene (Equation 7, p. 7). In the case where the diethylmalonate ion was the nucleophile (Equation 9, p. 8), there was competition of the S_N2 and S_N2' mechanisms, with the S_N2 route predominating. All of the uncharged nucleophiles, including triethylamine and di- and trimethylamine, reported by Young gave almost exclusively the rearranged product from the S_N2' pathway.²¹

A more quantitative approach was used by Drenth²⁴ in which simple Hückel molecular orbital calculations were applied to allylic systems and he concluded that the reaction should follow a concerted pathway and undergo *syn*-attack by the nucleophile. This method was followed in 1975 by Fukui²⁵ and he used molecular orbital arguments to propose that the addition should favor the *syn*-approach. He argued that the LUMO of the allyl chloride is concentrated in the *syn* direction more than in the *anti* direction. Most arguments favoring *syn*-attack involve some sort of orbital symmetry considerations. Epiotis *et al.* were also in agreement with the *syn*-attack of neutral nucleophiles using molecular orbital arguments to substantiate their claim.²⁶

More recently, Houk and co-workers²⁷ predicted the same outcome by employing *ab initio* calculations. Stohrer²⁸ also used *ab initio* calculations but also included semiempirical calculations to support the case for *syn*-attack. A graphical representation can be used to summarize the molecular orbital considerations in arguing for *syn*-attack. It may not make sense at first why the nucleophile, Nu, would



attack an anti-bonding orbital vs. a bonding orbital (as in *i* and *i'*), but it will probably do so since the anti-bonding orbital is empty while the bonding orbital is filled. The middle carbon does not participate directly in the reaction, but it does develop some negative charge and undergoes rehybridization in the direction of being sp^3 hybridized as the reaction proceeds. The more negative charge it develops, the more its orbital resembles that of an sp^3 hybridized carbanion. In the *syn* reaction, the bigger orbital lobe on C-2 remains on the same side of the molecule throughout the reaction. In the *anti* reaction, the bigger orbital lobe on C-2 must change sides during the reaction. The barrier to this inversion increases with greater accumulation of negative charge at C-2 in the transition state. If bond-breaking of the leaving group, L, lags behind the bond-making of the nucleophile, Nu, greater negative charge

should develop on C-2 in the transition state. This means that a difficultly cleavable leaving group should favor *syn*-attack, while an easily cleavable leaving group should favor *anti*-attack.

Dewar cites the lack of evidence for the reaction being synchronous. He employed MNDO calculations using 3-chloropropene as the model substrate and chloride ion as the nucleophile.^{29,30} Reasoning that MNDO calculations are satisfactory in describing aliphatic substitutions in general, there is little reason for him to doubt the validity of the calculations on the allylic system. His calculations lead to a prediction of a stepwise mechanism.

In 1985, Bach and Wolber³¹ found "no theoretical justification for *syn*-attack" in the S_N2' mechanism to be preferred over *anti*-attack. Their claim was based on 4-31G optimizations. In fact, they suggested that both modes of attack were possible, and that the calculations indicated the *anti*-orientation was slightly preferred. They also suggested that the observed preference of *syn*- over *anti*-attack was probably due to secondary bonding interactions. For example, for hydrogen bonding to occur in the transition state in the reaction of an allyl chloride and a primary or secondary amine, if it occurs, is required that the mechanism proceed in a *syn* fashion.

By analyzing the S_N2' transition state using Woodward-Hoffmann rules, Anh³² concluded that a concerted reaction that was fully synchronous would proceed by *anti*-attack of the nucleophile. On the other hand, he proposed that *syn*-attack should be favored for a concerted reaction where bond-breaking was advanced

relative to attack by the nucleophile. Houk disagreed and said Anh used incorrect molecular orbitals in his analysis.

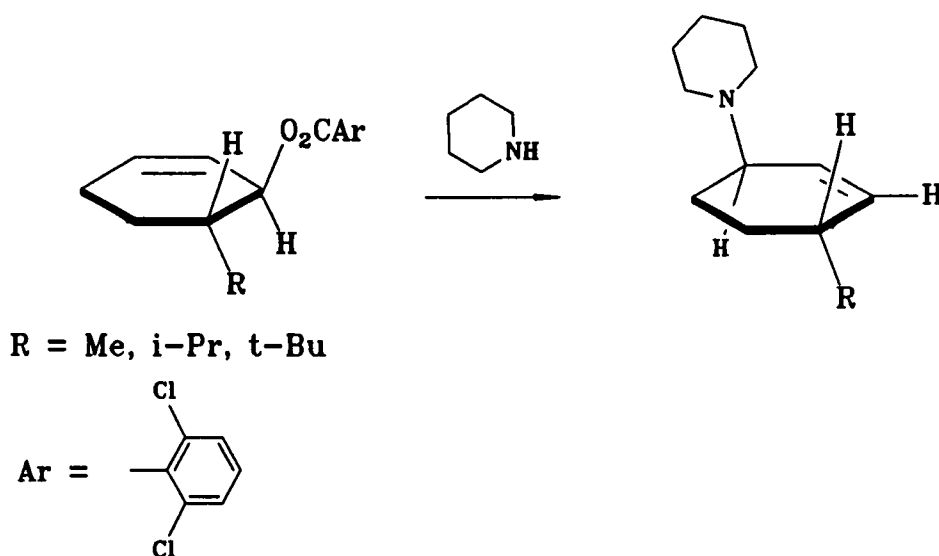
Wintner³³ used the τ bond model to predict that the leaving should depart from the same side as the nucleophile enters (*syn*).

The list could go on, but the point is that there are two camps on the subject with a few campers scattered in the middle. One camp espouses the idea that the mechanism proceeds with *syn*-attack, while the other one supports the idea that the mechanism follows an *anti*-attack route.

2. How the Theory Holds Experimentally

All of the theory in the world is of little use unless there is experimental evidence to test it. The first attempt to experimentally examine the stereochemistry of the S_N2' reaction was by Stork and White^{34,35} using ester derivatives of *trans*-

Equation 13

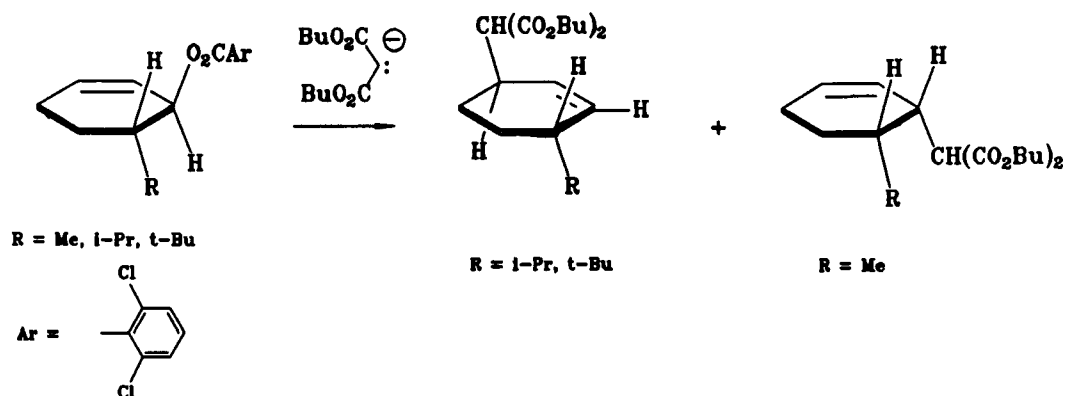


6-alkyl-2-cyclohexen-1-ols (Equation 13). There were two reasons for choosing this cyclohexenyl system:

1. The R group was to deter any S_N2 reaction that might occur, and it would serve as a marker to establish the regio- and stereochemistry of the nucleophilic attack.
2. This system also allowed them to rule out the possibility of an initial slow S_N2 reaction followed by a fast rearrangement to the apparent S_N2' product since any rearrangement would necessarily favor the *cis*-product.

Their results with piperidine (Equation 13) and malonic ester anion (Equation 14) as the nucleophiles, showed that in each case the reaction was following second order kinetics and that rearrangement of the double bond was indeed taking place, making this an S_N2' reaction; in addition, the rearranged products were shown to have arisen from *syn*-attack. In only one case, where malonic ester anion was the nucleophile and the R group was methyl was any S_N2 product observed. The authors speculated that the reluctance of the negatively charged nucleophile to approach the electron-rich π -cloud of the carbon-carbon double bond was greater than any steric complications imposed by the methyl group. On the other hand, when the R group was changed to a bulkier isopropyl (*i*-Pr) or *tert*-butyl (*t*-Bu) group, the steric problems introduced were now greater than the anion's aversion to attack the double bond, thus resulting in the rearranged products.

Equation 14



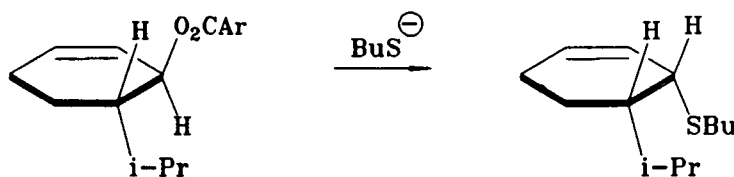
While probably not a major consideration in the design of the experiment, the authors did point out that the result from the reaction of the unsaturated cyclic ester with malonate anion as the nucleophile could be used to demonstrate that the mechanism proposed earlier by Dewar^{11, 12} to explain the rearranged product was not occurring. Recall that he had suggested that a slow *O*-alkylation in an $\text{S}_{\text{N}}2$ reaction followed by a fast Claisen-type rearrangement of the intermediate was another possible route to the rearranged product (see Equation 10, p. 9); this would, of necessity, give the epimer of the observed product.

Because this was the first experiment to attempt to demonstrate a preference for *syn*-attack and because of the availability of better analytical processes some years later, Stork and Kreft³⁶ thought it worthwhile to reinvestigate. So in 1977, they used the same cyclohexenyl system where the alkyl group, R , was isopropyl and the nucleophile was piperidine. Under the same conditions as before, they obtained a 71:29 mixture of *syn:anti* products (vs. 100% *syn*-attack in the previous study). The analytical techniques hadn't improved that much, so the researchers were skeptical.

It was discovered that longer reaction times gave increasing amounts of the *anti* product. This observation led the researchers to look at the unreacted cyclohexenyl ester for possible rearrangement prior to attack by the nucleophile. Indeed, they found that some 20% of it had rearranged. The next step was to run a similar reaction but stop it before it went to completion. They got a 91:9 mixture of *syn*- to *anti*-attack. With this ratio more in line with their earlier results, they concluded that the so-called *anti* product was actually the result of an S_N2 reaction on the rearranged substrate.

In order to begin with a more stable substrate, Stork and Kreft³⁶ repeated the experiment with a similar *trans*-compound, but instead of 2,6-dichlorobenzoate as the leaving group, 2,4,6-trimethylbenzoate (mesitoate) was used. Since this was a poorer leaving group, rearrangement should have been less of a problem. The researchers subjected the ester to reflux at 130 °C for 24 h and found no rearranged ester. The same held true when the experiment run in the presence of nucleophiles; that is, the recovered starting ester showed no sign of rearrangement. This wasn't the case, however, when butyl thiolate was used as the nucleophile (Equation 15). In refluxing

Equation 15



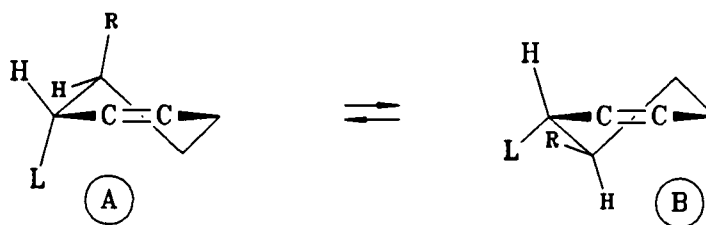
butanol, 68.5% of the product mixture was the result of an S_N2 process while the

other 31.5% was a mixture of *syn*- and *anti*-attack product from the S_N2' pathway in a 9 to 1 ratio, respectively. When hexamethylphosphoramide (HMPA) was substituted as the solvent, again the *syn*-attack product was favored over the *anti*-addition product but now only by a little more than 2 to 1. When the *cis*-mesitoate was refluxed in butanol, a 1:1 mixture of $S_N2:S_N2'$ products was obtained. The product mixture in the S_N2' portion was about 1:2 but now favoring *anti*-attack.

Dobbie and Overton³⁷ repeated Stork and White's work using the same 2,6-dichlorobenzoyl ester with piperidine acting as the nucleophile. Not surprisingly, their results agreed with those of Stork and Kreft. Further, they reasoned that all of the S_N2' product formed was from *syn*-attack and that any *anti* S_N2' product was coming from rearrangement of the ester prior to attack by the nucleophile in an S_N2 fashion.

The results of the experiments by Stork and Kreft and by Dobbie and Overton showed that *syn*-attack was favored over *anti* in most instances, but there are two possible factors which could influence the outcome of the reaction: (1) an inherent S_N2' preference, and (2) a conformational preference. A closer look at the cyclohexenyl ester is necessary. The cyclohexene ring itself exists as an equilibrating

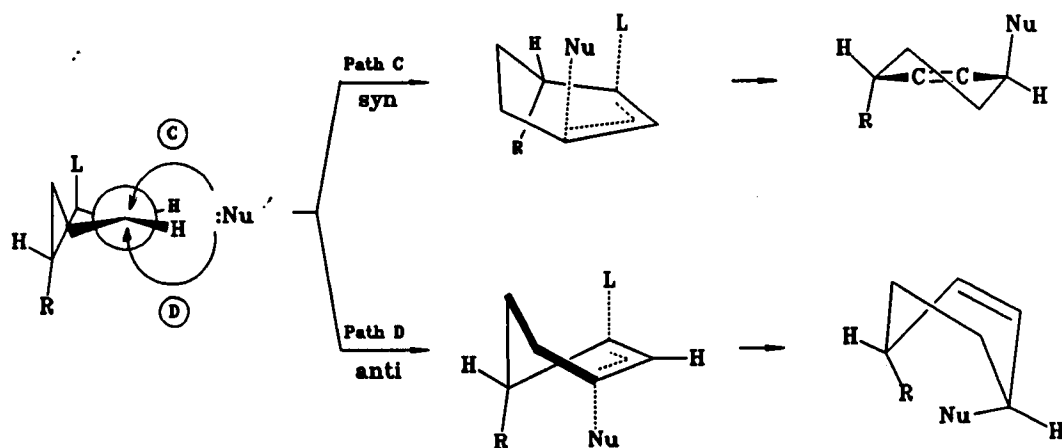
Equation 16



mixture of half-chair conformers. In conformation A, the σ -bond between the leaving group, L, and the carbon is almost in the same plane as the p-orbitals of the double bond. Rearrangement of the π -system requires that the adjacent p-orbital and the σ -bond between the carbon and the leaving group lie in the same plane in order for favorable overlap to occur during rehybridization and formation of a new π -bond. Therefore, conformation A would be predicted to be the reactive species. It turns out that conformers A and B are very close in energy, so there will be about an equal mixture at equilibrium, but according to the Curtin-Hammett principle, this will have no bearing on the outcome of the reaction.³⁸

If conformer A is the reactive species, then there are, in principle, two possible modes of attack by the nucleophile: from above the ring (*anti*-attack) or from below the ring (*syn*-attack). If the nucleophile proceeds to attack the double bond in an *anti* fashion, the resulting product will be in a boat conformation. If *syn*-attack is

Equation 17

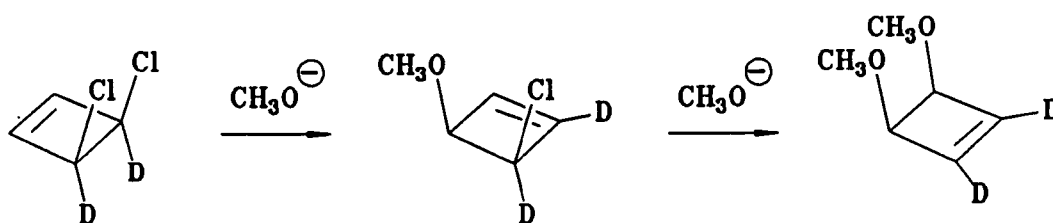


followed, the new product is in another half-chair conformation. Since the transition

states leading to each of these products will somewhat resemble the products, one would expect the path leading to the more stable half-chair conformation to be followed more than the route to the less stable boat conformation; that is to say, *syn*-attack would be preferred over *anti*-attack. These arguments were proposed in 1978 by Toromanoff.^{39,40} In a series of papers, he used a similar torsional angle study to conclude that *syn*-attack should be favored over *anti*. So it may be that even though the results by Störk and White^{34,35} (page 22) are regarded as the first evidence of *syn*-attack preference, it could be that the cyclohexenyl ring system has a built-in conformational bias favoring such an attack.

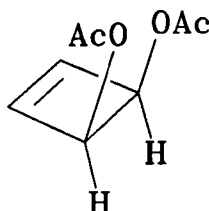
A less conformationally biased cyclobutenyl ring system was explored by Kirmse *et al.*⁴¹ By following the reaction of methoxide ion on *cis*-3,4-dichlorocyclobutene-3,4-*d*₂ with NMR, they were able to tell that the product was formed by two

Equation 18



successive S_N2' displacements and that the methoxide was attacking in a *syn* fashion in each case. If steric effects alone were controlling the addition, as Toromanoff^{39,40} had suggested, one would have expected *anti*-attack to occur.

Houk and co-workers⁴² obtained anomalous results in a 1,3-dipolar addition reaction using a similar cyclobutenyl system. They determined that the sp_2 carbons



were probably not planar by performing STO-3G calculations on *cis*-3,4-difluorocyclobutane. They found these carbons to actually be pyramidal with the hydrogens directed away from the fluorines (Equation 19); however, this conformation is

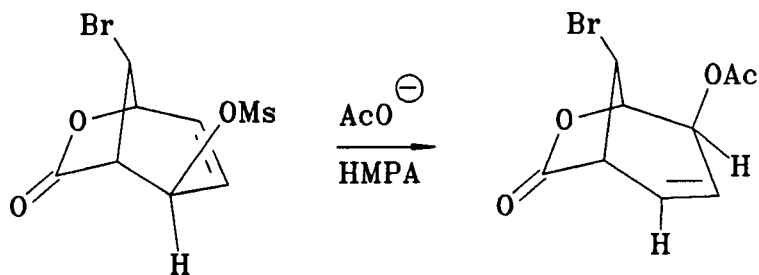
Equation 19



avored by only 1 kcal/mol over the other pyramidal conformation (that is, with the hydrogens directed slightly toward the fluorines). A similar scenario might explain Kirmse's (page 28) observations. If the olefinic carbons (Equation 18) were also somewhat pyramidalized, with the more stable conformation having the hydrogen atoms directed away from the chlorine atoms, this could sterically hinder *anti*-attack leading to a preference for *syn*-attack due to conformational bias.

Ikota and Ganem⁴³ observed allylic rearrangement in the following bicyclic mesylate (Equation 20). They showed that the reaction was following second order

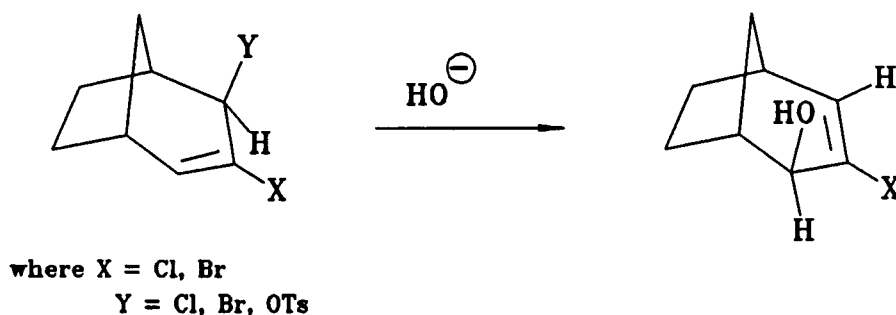
Equation 20



kinetics and that the starting bicyclic compound was stable toward rearrangement under the reaction conditions. Only the *syn*-attack product was observed.

Maskill and Wilson⁴⁴ reported similar results on an analogous compound (Equation 21). Their results might be explained as being an artifact of less steric

Equation 21

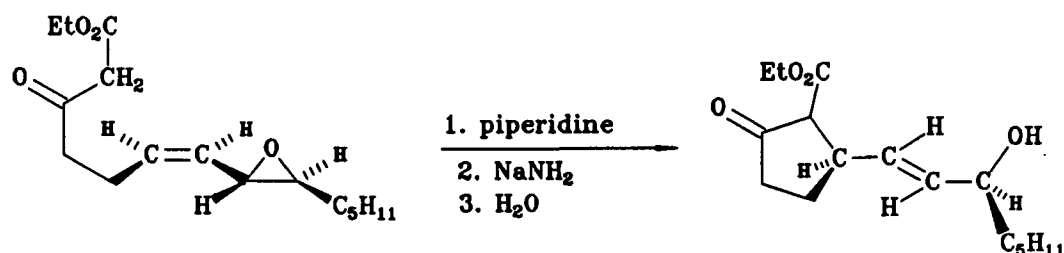


crowding when the nucleophile approached the *exo*- rather than the *endo*-face of the bicyclic system.

Studies of intramolecular $\text{S}_{\text{N}}2'$ reactions have led to no clear-cut preference for either *syn*- or *anti*-attack. Indeed, it appears that by building in conformational restraints, either mode of attack can be favored. An early example of an intramolecular

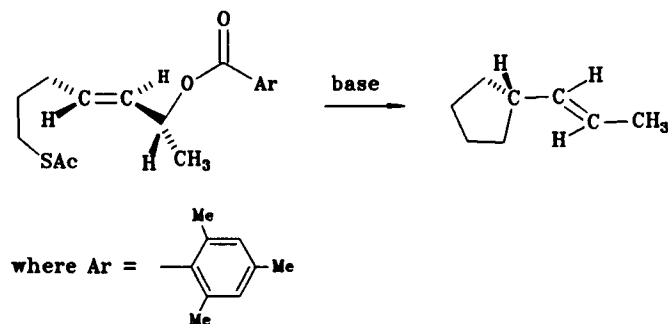
reaction was provided by Martel *et al.*^{45,46} (Equation 21, Equation 22). The *syn*-attack product was observed exclusively.

Equation 22



Stork and Kreft³⁶ used a similar substrate but with a thiolate ion as the nucleophile (Equation 23). By starting with the optically pure mesitoate, they were

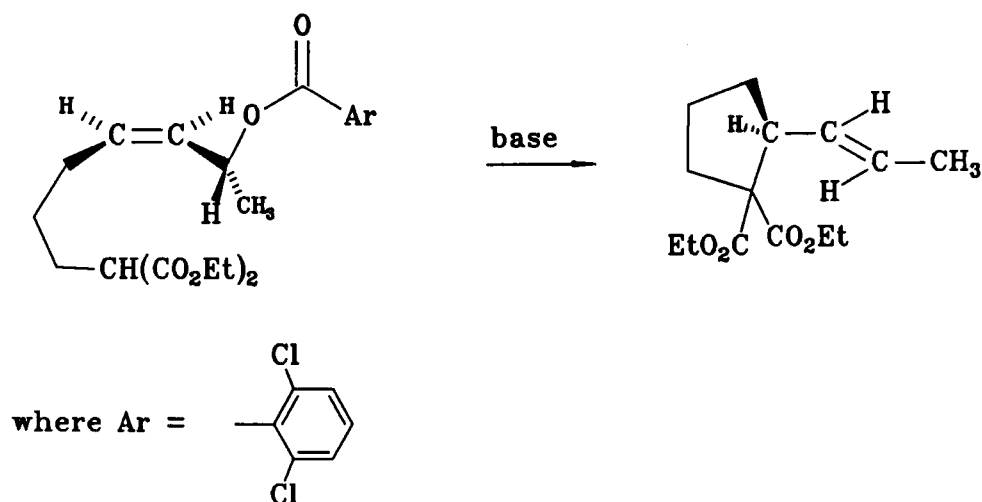
Equation 23



able to distinguish between *syn*- and *anti*-attack by measuring the relative amounts of the *E*- and *Z*-isomers, respectively, and the stereochemistry at the stereogenic carbon. The results indicated *anti*-attack of the thiolate almost exclusively.

This was a puzzling development since these reactions used similar substrates with different but negatively charged nucleophiles. Stork and Schoofs⁴⁷ tried to

Equation 24

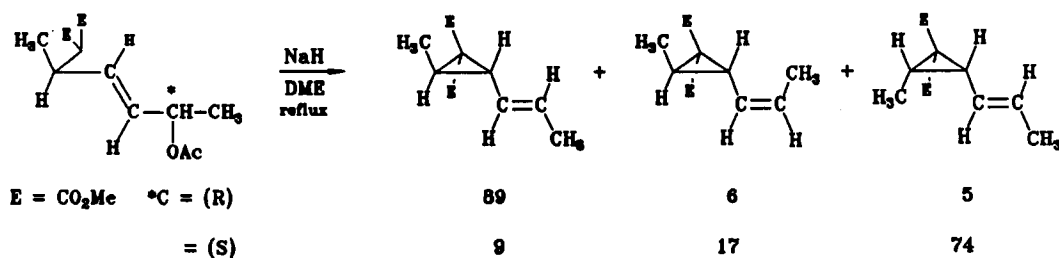


explain these anomalous results by employing bits and pieces of the molecules from each experiment, that is, a nucleophile similar to that used by Martel *et al.* and a leaving group analogous to that used by Stork and Kreft (Equation 24). Stork and Schoofs observed *anti*-attack in the cyclization. From this, they concluded that the preference for *syn*-attack in the Martel case must be due to the different leaving group. Moreover, Stork suggested that the preference for *syn*-addition in the Martel case could be a result of chelation between the epoxide oxygen and the counterion of the nucleophile.

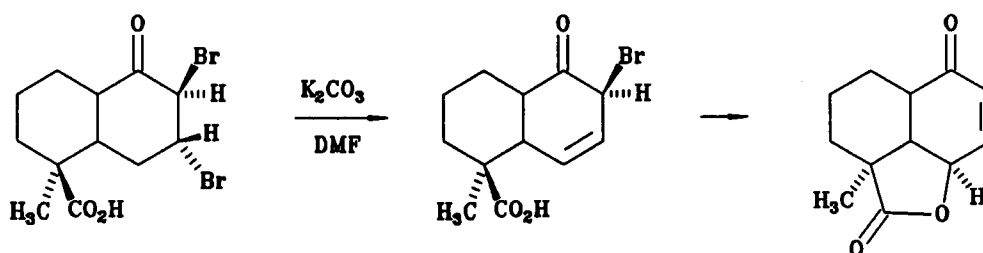
Bäckvall and co-workers⁴⁸ also examined an intramolecular case on a similar system (Equation 25). As seen by the relative amounts of each of the three products isolated from the reaction, there is a strong tendency for *syn*-attack (compare this with the results of Martel *et al.* and Stork and Kreft, p. 31).

A couple of other examples will illustrate how *syn*- or *anti*-attack can be forced on a reaction. Consider the formation of a lactone by intramolecular S_N2'

Equation 25



Equation 26



cyclizations: in the first example, Welch and co-workers⁴⁹ formed the lactone by *syn*-attack of the carboxylate ion (Equation 26), whereas Schomburg and Landry⁵⁰ also formed a lactone by *anti*-attack $\text{S}_{\text{N}}2'$ cyclization (Equation 27).

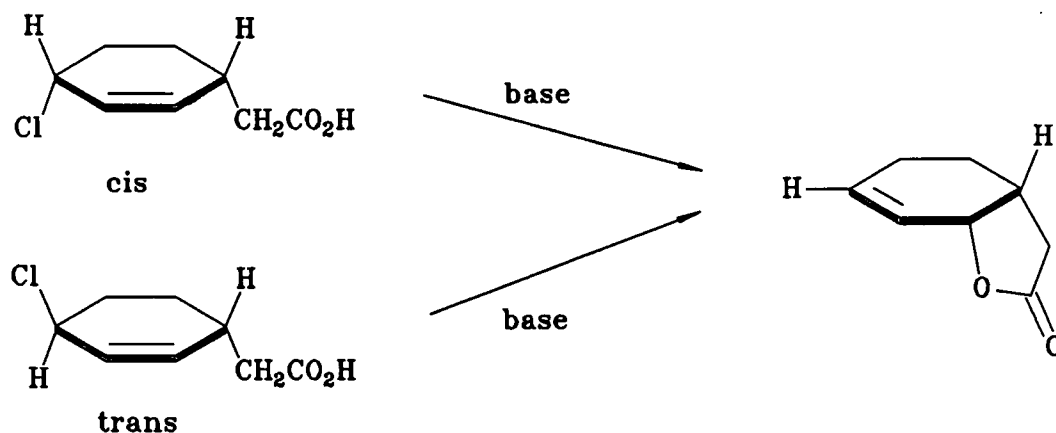
Equation 27



So what is the preference of the intramolecular reaction where there is truly an equally likely chance of either *syn*- or *anti*-attack? Chiche and co-workers⁵¹ examined the following reactions (Equation 28). Since the *cis*-isomer cyclizes by *syn*-

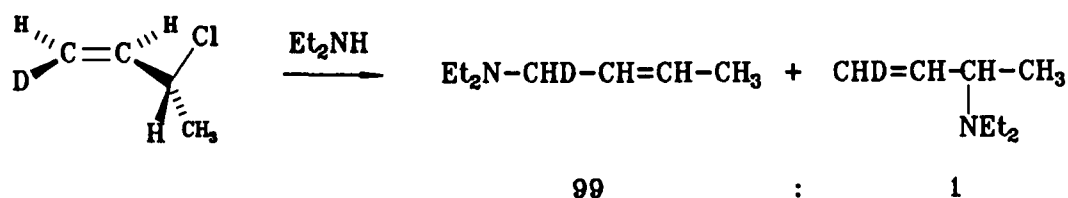
attack and the *trans*-isomer by *anti*-attack to give the same product, the researchers could measure the relative rates for each of the isomers. They found that, in base, the *cis*-isomer underwent cyclization (*via syn*-attack) some 250 times faster than the *trans*-isomer (*via anti*-attack).

Equation 28



Can this seemingly general bias found in most cyclic substrates somehow be avoided and yet be able to determine the stereochemistry of the reaction? The obvious answer is to study intermolecular reactions on acyclic substrates. Magid and

Equation 29



Fruchey⁵² chose to explore the reaction of deuterium-labeled optically active 3-chloro-1-butene (α -methylallyl chloride) with diethylamine (Equation 29). This reaction had been shown earlier by Young *et al.* to follow second order kinetics and the substrate was stable toward rearrangement under the reaction conditions. Therefore any rearranged product was attributed to the S_N2' process. In fact, the resulting product mixture was found to favor the S_N2' product over the S_N2 product by 99 to 1.

Scheme 2 shows the possible ways in which the nucleophile, Et_2NH , can attack the allylic substrate (illustrated, arbitrarily with the *R*-enantiomer). Since there is free rotation about the carbon-carbon single bond, there are two possible orientations in which the σ -bond to the leaving group and the adjacent p-orbital of the π -bond can lie in the same plane (recall that this is a requirement for the concerted S_N2' process, p. 15); that is, the chlorine can lie above the plane of the double bond or below the plane. If the reaction does in fact proceed by *syn*-attack, then a mixture of the (*R*)-*E* and (*S*)-*Z* products will be obtained. Conversely, if *anti*-attack is the mode of choice, a mixture of (*S*)-*E* and (*R*)-*Z* products will result. Whichever the case may be, the product mixture was found to be a 95:5 mixture of *E*- and *Z*-isomers. If it is assumed that the reaction is stereospecific, this ratio would also correspond to the relative amounts of (*R*) and (*S*) isomers produced. That is, if *syn*-attack is followed, then the product mixture will consist of 95% of the (*R*)- and 5% of the (*S*)-isomer.

The optical rotations of the analogous saturated amines were known, so the reaction products were reduced with diimide. The rotation of the reduced mixture

rotation data, with 96% stereoselectivity. Other secondary amines, dimethylamine and piperidine, gave 95% *syn* and 99% *syn*, respectively. It should be noted that corrections such as optical purity of the starting allylic chloride, *etc.*, are included in these data.

In 1978, Oritani and Overton⁵³ used a similar allylic substrate except 2,6-dichlorobenzoate was the leaving group rather than chloride. In addition, they used an optically pure primary amine, (*S*)-(-)-1-phenylethylamine (α -methylbenzylamine), as the nucleophile. While the results of this study agreed that *syn*-attack was preferred, as with the secondary amines used by Magid and Fruchey⁵², the researchers found that it was only the case 60% of the time. They attributed this lower selectivity to the decreased ability of the ester to form hydrogen bonds with the amine hydrogen in the transition state. Other explanations have mentioned the polarity differences between the primary and secondary amines used in the two studies,⁵⁴ as well as differences in the leaving groups.

More recently, Georgoulis and Ville⁵⁵ found that ethanolysis of (*R*)-(-)-3-chloro-1-butene-*Z*-1-*d* and (*R*)-(-)-3-chloro-1-butene-*Z*-1,2-*d*₂ resulted in a 94% preference of *syn*-attack over *anti*-attack. However, it must be noted that the nature of the reaction increasingly favors the rearrangement of the starting allylic substrate prior to attack by the nucleophile.

C. The Problem at Hand

As discussed previously, there is usually some built-in conformational bias in cyclic systems favoring one or the other of the possible modes of attack, making them

unsuitable as substrates when looking for a stereoelectronic preference of attack. Also as stated earlier, an obvious solution to this dilemma is to use acyclic substrates such as those used by Magid and Fruchey⁵² and Oritani and Overton⁵³. The absence of the rigid conformational constraints should allow for a more precise appraisal of the preferred mode of attack.

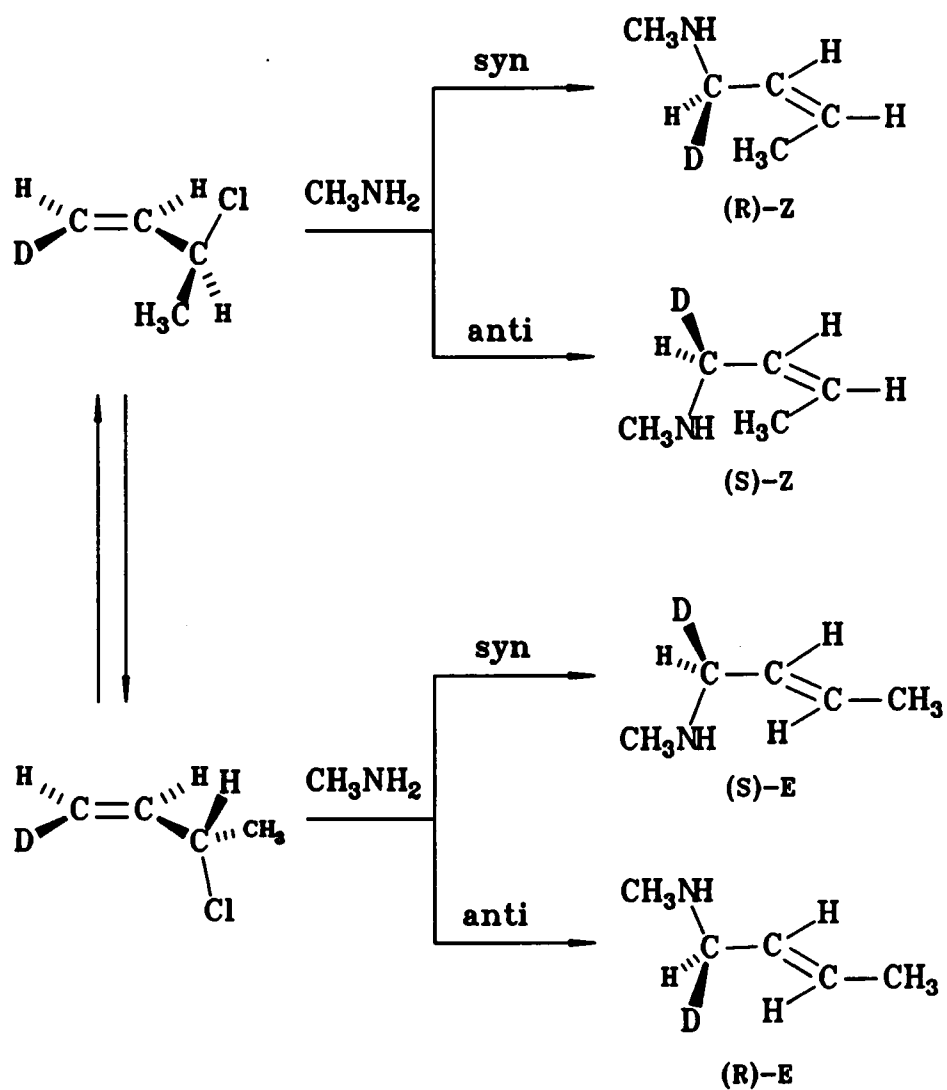
The purpose of this work was to study the stereochemistry of attack using the same substrate used by Magid and Fruchey, with a primary amine, monomethylamine, similar to the Oritani and Overton⁵³ case. Since the substrate has been shown to be stable toward rearrangements under more severe reaction conditions, it was assumed to be stable here as well. As second order kinetics were observed in the cases of other primary and secondary amines in reaction with similar substrates, it was assumed that the reaction in this study is following second order kinetics as well.

In order for the polarimetry data to be meaningful, it was necessary to synthesize reference compounds of known optical purity and absolute configuration by independent routes. Since it would have been difficult to synthesize the unsaturated compounds, the corresponding saturated amines were made. In turn, this required that the product mixtures of the reaction in question also be reduced for comparison purposes.

Just as in the prior cases, the allylic chloride can achieve two possible conformations in which favorable overlap of the necessary orbitals can occur before rearrangement can take place. As shown below (Equation 30), attack of the nucleophile, CH_3NH_2 , on the (*S*)-(+)-chloride can lead to four possible stereo-

isomers. *Syn* attack would produce a mixture of (*R*)-*Z* and (*S*)-*E* isomers and *anti* attack would produce a mixture of (*S*)-*Z* and (*R*)-*E* isomers.

Equation 30

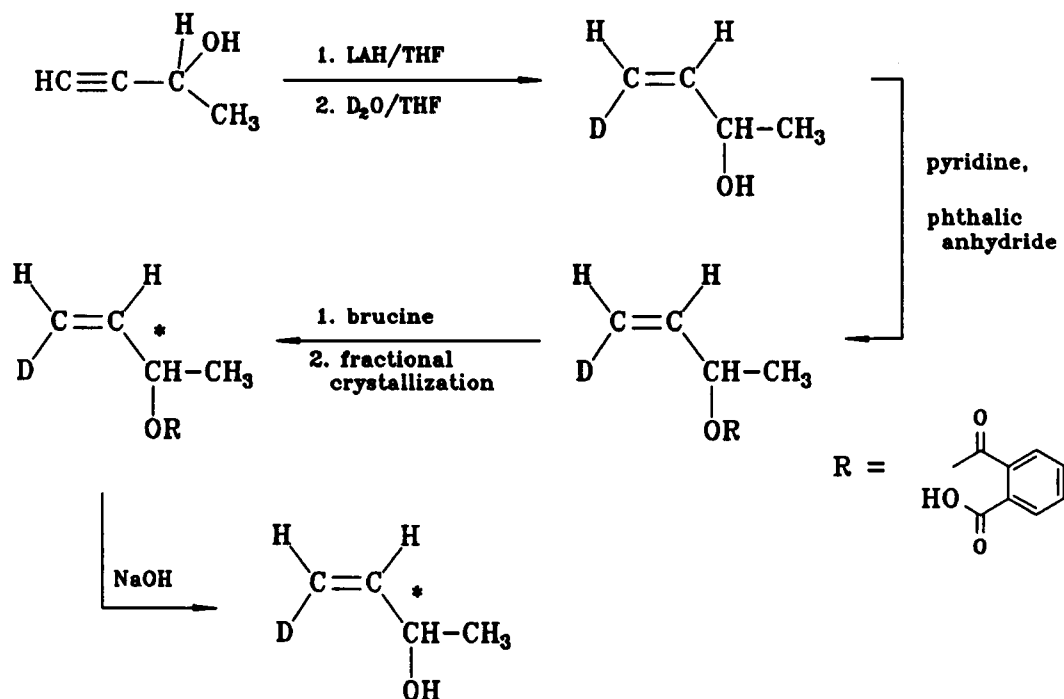


CHAPTER III

RESULTS AND DISCUSSION

Since the reaction of interest was between an optically active deuterium-labeled allylic chloride and monomethylamine, the first order of business was to prepare this substrate. This chloride had been synthesized earlier by Magid and Nieh⁵⁶ and the procedure was modified by Magid and Fruchey⁵². They began by reducing a racemic mixture of 3-buten-2-ol with lithium aluminum hydride (LAH) and quenching the reaction with deuterium oxide (D_2O), in order to place the deuterium label in the desired *Z*-configuration in the alkene (Equation 31). The racemic allylic alcohol was then allowed to react with phthalic anhydride followed by brucine to yield the brucine salt of the phthalate half-ester, half-acid. Fractional crystallization of this salt, followed by hydrolysis of the ester gave the deuterium-labeled optically active alcohol. Although the alcohol obtained by this method was, in fact, optically active, a large quantity of the deuterium-labeled allylic substrate was wasted. In principle, the best yield of either enantiomer of the optically active alcohol would be 50%. In practice however, the fractional crystallization of the brucine salt yielded several batches of varying optical purity. Only those fractions with the highest optical purity were utilized in order to achieve the highest possible rotations (thereby minimizing the experimental errors associated with the accuracy, sensitivity, and reproducibility of the polarimeter). The result was that substantially less than 50% of the desired optically active alcohol was available for making the allylic chloride.

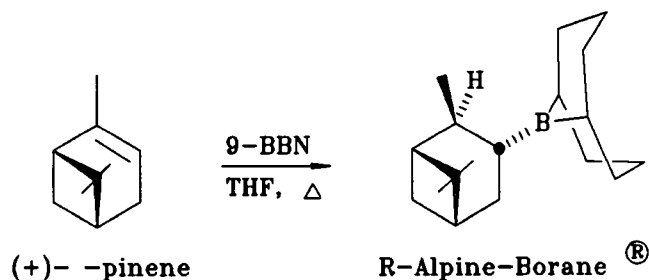
Equation 31



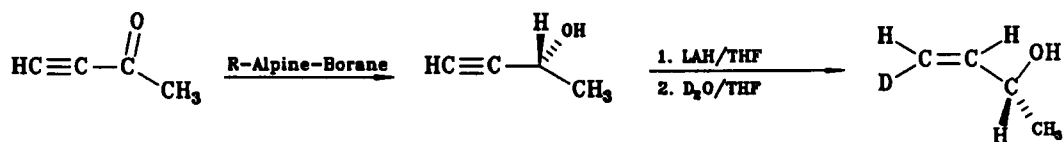
Because of this problem, another route to the deuterium-labeled optically active alcohol was sought, preferably one in which the fractional crystallization of the highly toxic brucine salt could be avoided. The development of asymmetric reducing agents, makes possible to create the optically active propargylic alcohol by reducing 3-butyne-2-one.⁵⁷ Out of several possibilities, the agent of choice was *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, which is available commercially as a 0.5 *M* solution in tetrahydrofuran from Aldrich Chemical Company and is given the trade name *R*- or *S*-Alpine-Borane[•], which is derived from either (+)- or (-)- α -pinene, respectively (Equation 32).

By using *R*-Alpine-Borane[•], an acetylenic ketone can be asymmetrically reduced in such a way as to give an optically active alkynyl alcohol⁵⁷ (Equation 33).

Equation 32

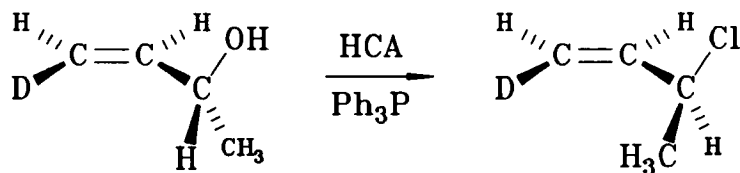


Equation 33



With the stereocenter now in place, the next step was to reduce the carbon-carbon triple bond. Use of the same procedure as before, that is, reduction of the triple bond with lithium aluminum hydride (LAH) followed by quenching with deuterium oxide (D_2O), gave the *Z*-isomer of the deuterium-labeled alcohol. All that

Equation 34



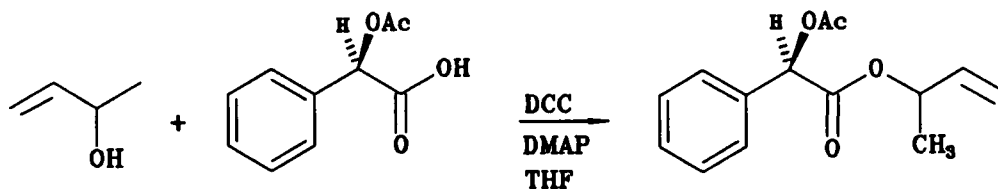
was left then was to convert this alcohol into the chloride using hexachloroacetone and triphenylphosphine (Equation 34). Although this last reaction occurs at the stereogenic carbon, it had been shown by Magid and Fruchey⁵² that it proceeded by

an S_N2 mechanism and results in 100% inversion of configuration at the stereocenter. Thus no optical activity was lost.

Following this series of reactions, then, the ketone was reduced to give (*R*)-(+)-3-butyne-2-ol⁵⁷ (85.5% yield; 58.5% optically pure). In turn, the triple bond was reduced to give (*R*)-(-)-3-buten-2-ol-*Z*-4-*d*,^{58,59} (33.3% yield; 66.3% optically pure) which was subsequently converted into (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d*,⁶⁰ (53.2% yield; 64.3% optical purity). It should be noted that this series of reactions was repeated several times, and that the stated yields and optical purities are typical numbers.

A slight discrepancy in the optical rotation data of the compounds above needs to be addressed. One would expect, not unreasonably, that the optically active 3-buten-2-ol would have the same optical purity as the acetylenic alcohol from which it came. Note that the enantiomeric excess of the butenol is 66.3%, while the butynol from which it was made is 58.5% optically pure. This is not to imply that optical activity is being created from optically inactive reagents, so certainly, one or the other or maybe both of the values must be incorrect. As a check, Fragale⁶¹ attempted

Equation 35

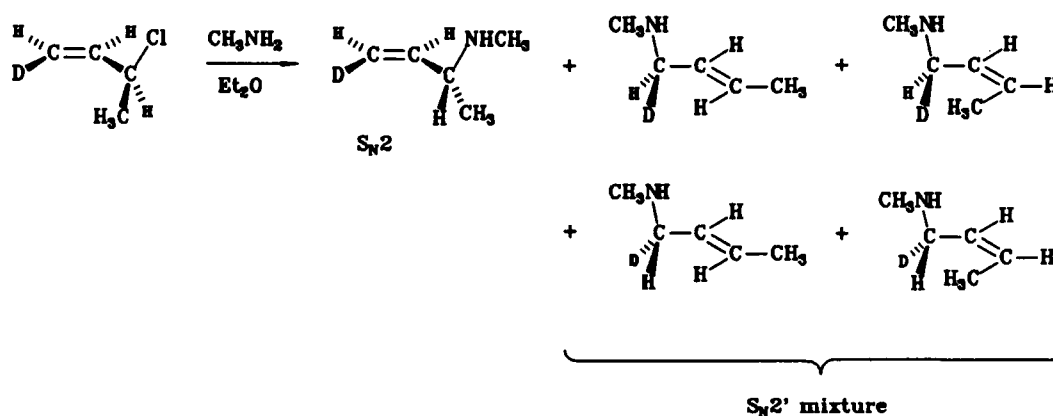


to make a Mosher-type derivative from a racemic mixture of each of the unsaturated alcohols with (*R*)-(-)- α -(acetoxy)phenylacetic acid ((*R*)-(-)-*O*-acetylmandelic acid). This is illustrated with 3-buten-2-ol (Equation 35). This should produce an equal mixture of diastereomers in which some of the protons will be in different environments, thus giving them different chemical shifts in the NMR spectrum. Integration of the appropriate regions of the NMR spectrum should confirm a 50:50 mixture of the diastereomers. Subsequent reactions using the optically active analogs of these racemates with the same optically active carboxylic acid should yield differing amounts of the diastereomers and whose relative integrals should correspond to the enantiomeric excess of the alcohols from which they were made. From this, a more precise $[\alpha]_{\max}$ should be obtained. The reaction of ($\pm$)-3-butyn-2-ol with (*R*)-(-)- α -(acetoxy)phenylacetic acid produced an unequal mixture of diastereomers according to the NMR integral, even though the polarimetry data indicated that the starting alcohol was in fact a racemic mixture. Nevertheless, an attempt was made to make the same ester derivative using an optically active sample of 3-butyn-2-ol. The polarimetry data for this compound indicated that it was 58.5% optically pure, but the NMR integration data could never be reconciled anywhere close to this value, so the attempt was abandoned. Better success was had in the reaction of ($\pm$)-3-buten-2-ol with the same optically active acid. In this case, the NMR integrations agreed with the polarimeter; both sources confirmed that it was a 50:50 mixture. The experiment was repeated with (*R*)-(-)-3-buten-2-ol-*Z*-4-*d*. The polarimetry data found this compound to be 66.3% optically pure. The NMR integration showed approxi-

mately an 85:15 ratio of the diastereomers were present. This corresponds to about a 70% enantiomeric excess of the (*R*)-isomer, certainly within experimental error and instrumental reliability and precision to the 66.3% enantiomeric excess obtained from the polarimeter values. This means that there is probably a discrepancy in the $[\alpha]_{\max}$ of the acetylenic alcohol, but this is of little consequence to the reaction at hand.

With the synthesis of the optically active deuterium-labeled allylic chloride completed, the next step was the reaction of interest, that is, the reaction between (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* and monomethylamine (Equation 36).

Equation 36



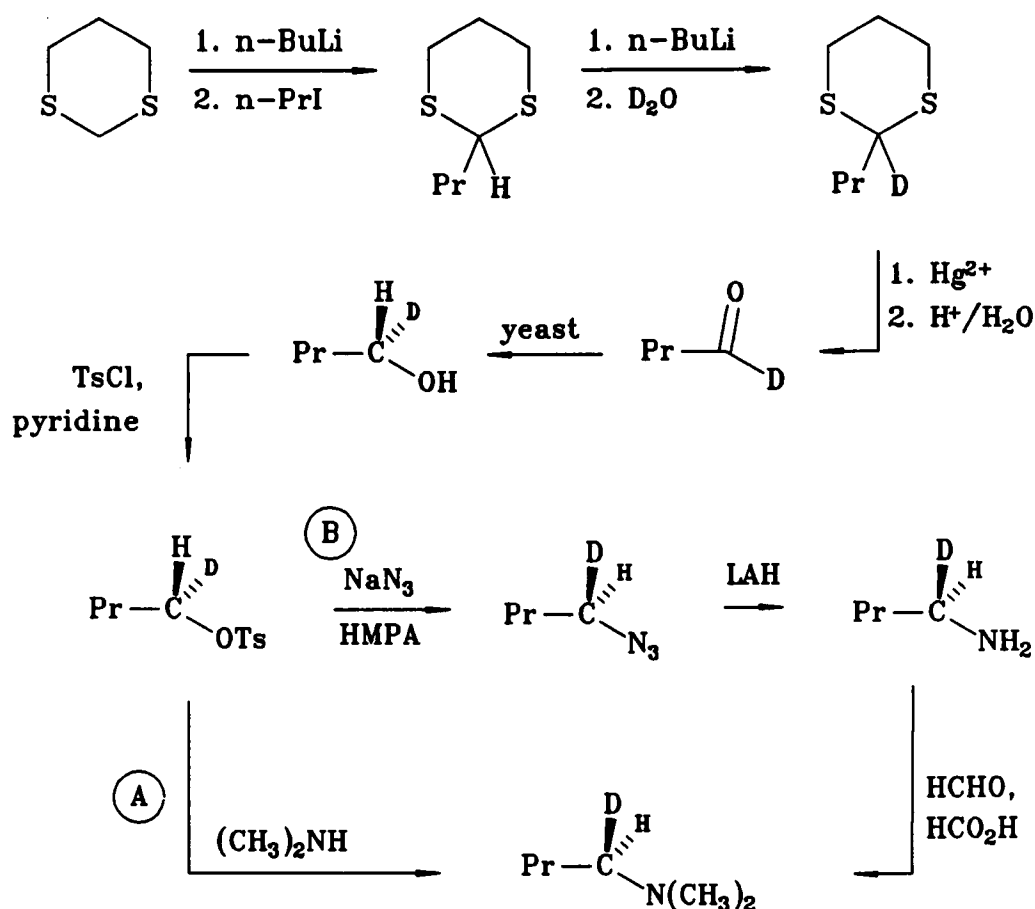
This reaction, using ($\pm$)-3-chloro-1-butene, produced a 55:45 mixture of $\text{S}_{\text{N}}2$: $\text{S}_{\text{N}}2'$ products. The $\text{S}_{\text{N}}2'$ product mixture consisted of *E*- and *Z*-stereoisomers in a ratio 95:5. Two assumptions were made concerning this reaction: (1) the $\text{S}_{\text{N}}2$ product was formed with 100% inversion of configuration at the stereogenic center and (2) that the $\text{S}_{\text{N}}2'$ product mixture contained all four possible stereoisomers resulting from both *syn*- and *anti*-attack of monomethylamine on the allylic chloride.

Separation of the unrearranged product from the rearranged product mixture was possible by preparative gas chromatography. The unrearranged product had the following optical rotations: $[\alpha]_D^{25} -5.733^\circ$, $[\alpha]_{578}^{25} -6.260^\circ$, $[\alpha]_{546}^{25} -7.667^\circ$, $[\alpha]_{436}^{25} -19.853^\circ$, and $[\alpha]_{365}^{25} -45.067^\circ$ ($\ell = 0.1$, neat). The configuration at the stereocenter should be (*R*) since the rotation of commercially available (*R*)-*sec*-butylamine (Aldrich) also has a negative rotation. The rotation data for the commercial sample were as follows: $[\alpha]_D^{19.6} -7.82^\circ$, $[\alpha]_{578}^{19.6} -8.14^\circ$, $[\alpha]_{546}^{19.6} -9.17^\circ$, $[\alpha]_{436}^{19.6} -14.81^\circ$, and $[\alpha]_{365}^{19.6} -21.31^\circ$ ($\ell = 0.1$, neat). In addition, the *N,N*-dimethyl product from the Eschweiler-Clarke reaction of this optically active amine also had a negative rotation. The rotation data for this product are as follows: $[\alpha]_D^{22} -20.2^\circ$, $[\alpha]_{578}^{25} -21.0^\circ$, $[\alpha]_{546}^{22} -23.8^\circ$, $[\alpha]_{436}^{22} -37.0^\circ$, and $[\alpha]_{365}^{22} -50.8^\circ$. This means that the majority of the substitutions taking place at the stereocenter was, in fact, S_N2 .

As stated earlier, the information gleaned from the polarimetry data on such a mixture would not be very meaningful unless there was also polarimetry data on these compounds where the optical purity and the absolute configuration were known. With this in mind and the experimental reaction mixture in hand, the next thing that had to be done was the preparation of the reference compounds.

Magid and Fruchey had earlier published a preparation of the saturated analog (Scheme 3). 1-Propyl iodide was allowed to react with the anion of 1,3-dithiane, produced from reaction with *n*-butyllithium. This propyl dithiane was again treated with *n*-butyllithium and the reaction quenched with deuterium oxide to give the deuteriated analog. Hydrolysis of the heterocyclic ring with mercuric chloride

Scheme 3

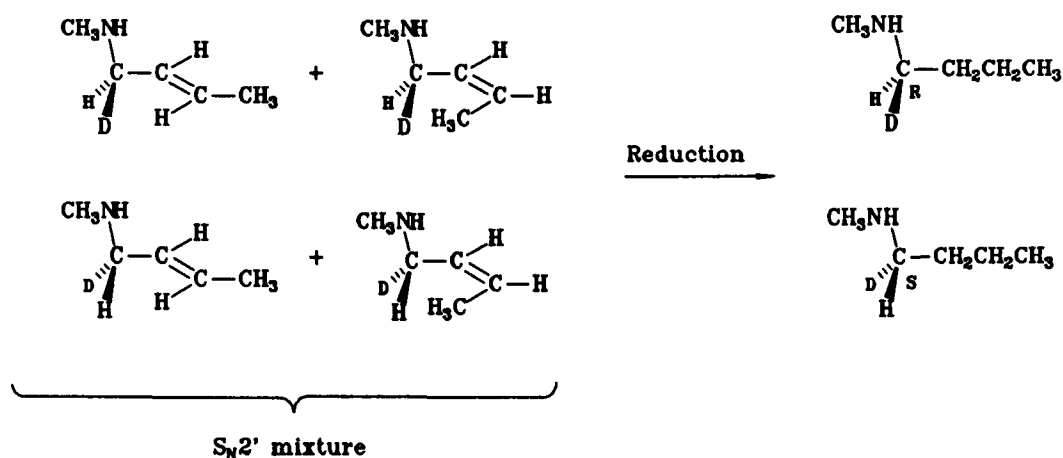


gave butanal-1- d , which underwent a yeast reduction to give optically active butanol-1- d which was treated with tosyl chloride in pyridine to yield butyl-1- d tosylate. The idea was that optically active deuterium labeled butyl-1- d tosylate would undergo an $\text{S}_{\text{N}}2$ reaction with the nucleophile, $(\text{CH}_3)_2\text{NH}$ (Path A, Scheme 3)). As a check, they allowed the same tosylate to react with sodium azide in hexamethylphosphoramide (Path B, Scheme 3), a much better and smaller nucleophile than the secondary amine, which should certainly give 100% inversion of configuration and optical purity at the reaction center. The product from this route was reduced with lithium

aluminum hydride, then *N*-methylated using the Eschweiler-Clarke procedure. Since neither the reduction nor the methylation takes place at the stereocenter, the *N,N*-dimethyl amine should have the same configuration at the stereocenter as the azide (or the opposite configuration of the starting tosylate). In fact, the amines produced by the independent routes had identical optical rotations.

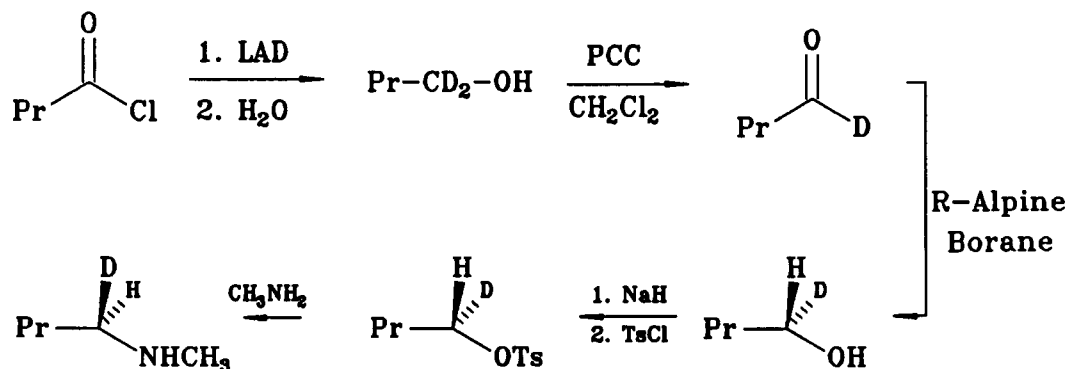
Since an unsaturated reference compound would be very difficult to synthesize, a similar plan was followed leaving only reduction of the S_N2' reaction mixture (Equation 37) in order to compare the results.

Equation 37



In this study, it will be assumed that a reaction between monomethylamine and a similar butyl-1-*d* tosylate will also undergo an S_N2 reaction in the same way as the *N,N*-dimethylamine did earlier (Scheme 3). However, again, the availability of asymmetric reducing agents provided an alternate route to the optically active butyl-1-*d* tosylate.

Equation 38



Butyryl chloride was reduced with lithium aluminum deuteride (LAD) followed by quenching with H_2O to give butanol-1,1- d_2 . It should be noted that dideuterio-butyl butyrate was also produced in the reaction. However, it was possible to hydrolyze the ester to release additional deuteriated alcohol for use. This alcohol was oxidized with pyridinium chlorochromate to yield the deuterio aldehyde. Several other oxidizing agents were tried, such as potassium dichromate/ H_2SO_4 , with less than promising results. This particular step is the one disadvantage to the whole process. Although butyryl chloride is inexpensive, the lithium aluminium deuteride used to reduce the acyl chloride is relatively expensive; in addition, one wastes one of the deuteriums in the next step. To compound the problem, the oxidation step didn't give the yields hoped for considering the cost of the reaction. Just as in the case of the preparation of the deuterium-labeled optically active allylic alcohol, *R*-Alpine-Borane[•] was used rather than a messy yeast reduction to reduce the carbonyl compound. At this point, care had to be taken to ensure that all of the liberated (1*R*)-(+)- α -pinene was removed from the alcohol as this was the last compound of

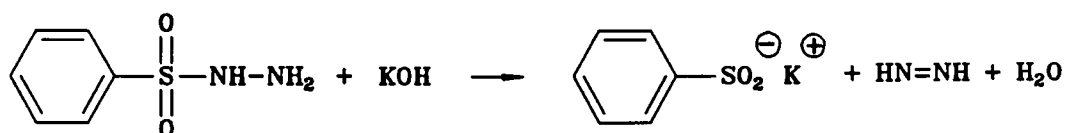
the sequence for which there were any optical rotation data and absolute configuration information. That is, from that point on, it had to be assumed that no optical activity was being lost in making the tosylate and that the reaction of methylamine with the tosylate was a true S_N2 process with 100% inversion of configuration at the reacting center. Table 1 contains the polarimetry data for (*R*)-*N*-methyl-1-butanamine-1-*d*.

Table 1. Polarimetry data for (<i>R</i>)- <i>N</i> -methyl-1-butanamine-1- <i>d</i> ($\ell = 0.1$, neat)		
Wavelength (λ , in nm)	$[\alpha]^{25}$	$[\alpha]_{\max}^{25}$
589	+1.67°	+2.64°
578	+1.74	+2.74
546	+2.01	+3.18
436	+3.61	+5.70
365	+5.86	+9.26

The values for $[\alpha]_{\max}$ for the butyl-1-*d* tosylate were corrected for the fact that the butanol-1-*d* was only 63.3% optically pure.⁶²

With the reference compound in hand, it was then necessary to reduce the carbon-carbon double bonds of the compounds in the S_N2' mixture giving a mixture of (*R*)- and (*S*)-*N*-methyl-1-butanamine-1-*d*. The most common method of hydrogenating a carbon-carbon double bond is catalytic hydrogenation.⁶³ However, this method won't work very well in this case since exchange of hydrogens can take place at the surface of the catalyst. For symmetrical double bonds, a likely candidate is diimide. There are two ways in which to generate diimide *in situ*. The first is by treatment of potassium azodicarboxylate (KOOC-N=N-COOK) in acid.⁶⁴ This method is unlikely to succeed here because of the acidic media in which the reaction must be run could change the reactivity of the allylic amine. The second, and more promising, method turned out to be the method of choice. Here diimide was produced by the base catalysis of *p*-toluenesulfonhydrazide (Equation 39). The

Equation 39



diimide then reduces the carbon-carbon double bond (Equation 40).

Equation 40



Before any meaningful comparisons can be made between the rotations of this reduced mixture of (*R*) and (*S*) amines and those of the reference compound, some corrections must be made on the observed rotations of the mixture. This mixture of amines could not be any more optically pure than the starting allylic chloride (64.3%). The next correction to be made was concerned with the deuterium content and the orientation of the label in the allylic chloride. Since the *Z*-isomer leads to one enantiomer in the S_N2' reaction, while the *E*-isomer leads to the opposite enantiomer, the relative amounts of each of these configurations about the carbon-carbon double bond must be accounted for. The integration of the appropriate regions of the ^1H -NMR spectrum of (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* spectrum indicated that the chloride was 95.7% *Z*-deuteriated, 3.6% non-deuteriated, and 0.7% *E*-deuteriated. Therefore, the maximum optical purity due to the presence of the wrong isomer was 95.0% (95.7-0.7). The last correction was for the relative amounts of *E* and *Z* compounds present in the S_N2' reaction mixture. The *Z*-isomer would give one enantiomer, while the *E*-isomer would give the opposite enantiomer upon reduction of the double bond. The ratio was obtained by integration of the ^{13}C -NMR spectrum of the mixture over the appropriate regions and was determined to be 89.5:10.5 with the *E*-isomer predominating over the *Z*-isomer. Table 2 contains the raw data obtained for the observed rotation, α ; the corrected values for the observed rotation, $\alpha_{\text{corrected}}$; the specific rotation calculated using the corrected observed rotation; and the optical purity when compared to the reference compound.

Table 2. Optical purity of the reduced S_N2' mixture at various wavelengths ($l = 0.01$, neat).				
Wavelength (λ , in nm)	Observed rotation, α	Corrected observed rotation, $\alpha_{\text{corrected}}$	Specific rotation, [α]	Optical purity
589	-0.004°	-0.008°	-1.07°	40.5%
578	-0.004	-0.008	-1.07	39.1
546	-0.006	-0.012	-1.63	51.2
436	-0.010	-0.021	-2.85	50.0
365	-0.016	-0.033	-4.48	48.4

Based on these data, one can determine the stereoselectivity of the S_N2' reaction between (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* and monomethylamine. The reference compound has absolute configuration of (*R*) and a positive optical rotation. This means that the major component of the mixture must be the (*S*)-enantiomer. The second piece of evidence is that the S_N2' mixture contains an 89.5: 10.5 mixture of *E* and *Z* isomers, respectively. It follows then that the majority of compounds in the mixture has an (*S*) configuration at the stereogenic carbon and an *E* configuration of the double bond revealing a preference for *syn* stereoselectivity. Once *syn* selectivity was established, the optical purity information given in Table 2 (page ?) offered some insight as to the degree of this stereoselectivity. Since the last two entries have a greater number of significant figures, only they will be used in the determination of the amount of preference. For example, in the last entry (wavelength = 365 nm) a calculated optical purity of

48.4% is given for the reduced S_N2' mixture of (*R*) and (*S*) enantiomers. It is shown that the major component of the mixture is the (*S*)-isomer and that the enantiomers are present in an 74.2:25.8 ratio. This ratio also represents the preference of *syn*-attack over *anti*-attack. Table 3 (page 55) contains the results of similar calculation at the other wavelenth.

It should be noted that only the last two entries may be precise as these wavelength had the greater number of significant figures in the observed rotation used in the calculations of these numbers. An average of these two number gives a preference of *syn*-attack of 74.6% to 25.4% for *anti*-attack. This study has shown that the reaction between (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* and mono-methylamine proceeds with *syn* stereoselectivity, but it does not try to settle the doubts about concertedness expressed by Bordwell. These results are in agreement with the majority of the theoretical predictions, as well as most of the experimental evidence when using substrates free of conformational bias or steric constraints. Therefore, it can be concluded that the *syn* stereoselectivity observed in this reaction is attributable to the stereoelectronic preference inherent to the S_N2' reaction itself.

Other results from Magid's research laboratory have addressed similar problems. Bass⁶⁵ used the same allylic chloride as used in this study, but employed trimethylamine as the nucleophile. He obtained a mixture of rearranged and unrearranged products, which indicates that hydrogen bonding in the transition state is not a requirement for the rearrangement. Unfortunately, he was

unable to separate the two components of the mixture, so it was not possible to determine with certainty whether the attack was *syn* or *anti*. The present study used the same allylic substrate ((*S*)-(+)-3-chloro-1-butene-*Z*-1-*d*) as Bass and a primary amine (in this case CH₃NH₂) as the nucleophile as in the Oritani and Overton work⁵³, while Hinton⁶⁶ used the same allylic substrate as Oritani and Overton (3-buten-2-yl-*Z*-4-*d* 2,6-dichlorobenzoate) with a secondary amine (piperidine). The reaction with piperidine yielded only the rearranged product, but with nonsensical results. Hinton calculated that the reaction proceeded with 135 - 141% *syn* stereoselectivity.

Table 3. Summary of calculations of stereoselectivity based on the optical purity at various wavelengths.			
Wavelength (λ , in nm)	Optical purity ^a	% <i>syn</i> -attack	% <i>anti</i> -attack
589	40.5%	70.3	29.7
578	39.1	69.6	30.4
546	51.2	75.6	24.4
436	50.0	75.0	25.0
365	48.4	74.2	25.8

^aThe optical purities are reproduced here from Table 2 for convenience.

CHAPTER IV

EXPERIMENTAL

A. General Methods

All glassware and equipment used in the following experiments involving air-sensitive compounds were oven-dried for at least 4 h at a temperature of at least 140 °C prior to use. The apparatus was then assembled, while still hot, into the required set-up. Any remaining openings were capped with rubber septa and the apparatus was allowed to cool to room temperature while flushing with dry argon. An oil bubbler was used to ensure that either a positive pressure or flow of dry argon was constantly maintained throughout the system. Air-sensitive reagents were transferred into the reaction vessel using either a cannula or a syringe. Any volume measurements required when using air-sensitive reagents were done with either a syringe or an inert-atmosphere graduated cylinder.

Routine nuclear magnetic resonance (NMR) spectra were obtained on a JEOL FX-90Q spectrometer (90 MHz). High-resolution spectra were acquired on a Nicolet NT200 spectrometer (200 MHz). Tetramethylsilane (TMS) was used as an internal reference when deuteriated organic solvents were employed. 3-(Trimethylsilyl)-propanesulfonic acid, sodium salt (DSS) was used as the internal reference or TMS as the external reference when deuterium oxide (D_2O) was required as the solvent.

All optical rotation measurements were carried out on a Perkin-Elmer Model 241 spectrophotometer under the conditions stated in the descriptive schemes of the reactions. An analogous racemic compound was used as a blank in obtaining the observed rotation of the optically active compounds. Analytical scale separations were done on a Hewlett-Packard Model 5750 gas chromatograph. Helium was used as the carrier gas at a typical flowrate of approximately 75 mL/min unless otherwise indicated. The columns were constructed of $\frac{1}{8}$ in. (outer diameter) stainless steel tubing with a stationary phase coated on 80-100 mesh Chromosorb W as the solid support. The analytical scale columns used were as follows:

Column AA - 10 ft, 20% Carbowax 20 M;

Column AB - 10 ft, 10% SE-30;

Column AC - 20 ft, 30% SE-30.

Preparative scale separations were achieved on a Varian Aerograph Model 920 gas chromatograph. As in the case of the analytical gas chromatography, helium gas was again used as the carrier gas at a typical flowrate of approximately 60 mL/min. The columns were constructed from $\frac{3}{8}$ in. (outer diameter) aluminum tubing with the stationary phase coated onto 45-60 mesh Chromosorb W as the solid support. The columns used for preparative scale separations were as follows:

Column PA - 10 ft, 20% Carbowax 20 M;

Column PB - 10 ft, 30% Carbowax 20 M on 80-100 mesh DMCS;

Column PC - 10 ft, 20% Carbowax 20 M, 5% potassium hydroxide;

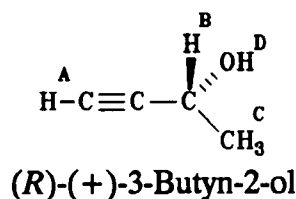
Column PD - 10 ft, 15% β,β' -Oxydipropionitrile;

Column PE - 8 ft, 10% SE-30;

Column PF - 10 ft, 30% SE-30, 5% potassium hydroxide.

B. Preparative procedures and reactions

1. Preparation of (*R*)-(+)-3-Butyn-2-ol



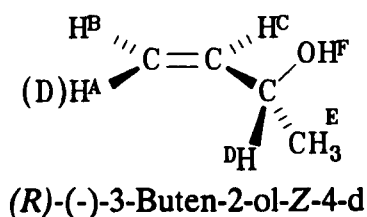
A 2-L three-necked round-bottomed flask, a 250-mL pressure-equalizing addition funnel, a Claisen stillhead, a condenser, a vacuum adapter, a 1-L round-bottomed receiving flask with a side-arm inlet, and a magnetic stirring bar were oven-dried, and assembled into a simple distillation apparatus while still hot. The remaining openings were capped with rubber septa and the system was allowed to cool to ambient temperature while being flushed with dry argon.

B-Isopinocampheyl-9-borabicyclo[3.3.1]nonane (800 mL, 0.4 mol; 0.5 *M* in tetrahydrofuran) (*R*-Alpine-Borane[®]; Aldrich) was transferred to the 2-L flask *via* a stainless steel cannula. A water bath (75-80 °C) was placed around the flask and the tetrahydrofuran was then removed by simple distillation at ambient pressure, while still under an argon atmosphere. The addition funnel was charged with 3-butyn-2-one (27.2 g, 0.400 mol) (Farchan Chemical Company). A water bath (ambient temperature) was placed around the flask and the ketone was added

dropwise to the stirred solution. The pale yellow solution was allowed to stir at ambient temperature for a period of 5 days. During this time, the solution turned a dark amber color as the reaction proceeded. The solution was then cooled in an ice/water bath for 30 min before freshly distilled benzaldehyde (20.5 mL, 0.2 mol) (Mallinckrodt) was added dropwise to the cold, stirred borane solution. The ice/water bath was removed and the solution stirred at ambient temperature for a period of 2 h. The liberated α -pinene was then removed by vacuum distillation. A water bath (30-40 °C) was used to warm the solution as the pressure was slowly reduced to about 2 mm Hg in small increments using a manostat. The distillation was continued until the bubbling in the distilling flask had all but stopped. The system was brought back to atmospheric pressure, but the argon atmosphere was maintained. The solution was cooled to 0 °C by means of an ice/water bath, and anhydrous ether (250 mL) (Mallinckrodt) was transferred via a cannula. This was followed by the dropwise addition of ethanolamine (35 mL, 0.58 mol) (Mallinckrodt) to the cold, stirred solution. At this point, a yellow borane-complex precipitated in the orange supernatant liquid and the mixture was allowed to stir 18 h at ambient temperature before the solid was removed by vacuum filtration. The filter cake was rinsed several times with ether until essentially all of the yellow color had been removed. The filtrate was dried over anhydrous magnesium sulfate. The drying agent was removed by gravity filtration and the filter cake was rinsed with a small amount of anhydrous ether. The solution was concentrated fractional distillation of the ether employing a 30 in. Vigreux column at reduced pressure with the receiving

flask being well cooled in a dry ice/acetone bath. After much of the ether appeared to have been removed, the remaining liquid was transferred to smaller scale glassware for the fractional distillation of the alcohol at reduced pressure. The distillate containing the alcohol was further purified by preparative gas chromatography using column PA; 14.2 g (0.204 mol, 51.0%) of (*R*)-(+)-3-butyne-2-ol was obtained; $[\alpha]_D^{24} +28.00^\circ$ (neat, $\ell = 1$), optical purity 58.5% (lit. value^{67,70} $[\alpha]_{\max} = +52^\circ$); ^1H -NMR (CDCl_3) δ 1.47 (d, 3H, $J_{\text{BC}} = 6.62$ Hz, H_C), 2.47 (d, 1H, $J_{\text{AB}} = 2.10$ Hz, H_A), 2.70 (br s, 1H, H_D), 4.54 (dq, 1H, $J_{\text{AB}} = 2.10$ Hz, $J_{\text{BC}} = 6.62$ Hz, H_B).

2. Preparation of (*R*)-(-)-3-Buten-2-ol-Z-4-d



A 2-L three-necked round-bottomed flask, a 250-mL pressure-equalizing addition funnel, and a 1.5 in magnetic stirring bar were assembled.

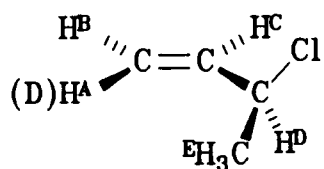
The flask was charged with (*R*)-(+)-3-butyne-2-ol (14.2 g, 0.20 mol; optical purity 58.5%) along with dry tetrahydrofuran (500 mL; freshly distilled from sodium/benzophenone ketyl) (Mallinckrodt). Then lithium aluminum hydride (250 mL, 0.25 mol) (1.0 *M* in tetrahydrofuran) (Aldrich) (LAH) was added dropwise to the stirred alcohol/tetrahydrofuran solution which was being cooled in an ice/water bath. After the addition was complete, the solution was allowed to warm to ambient temperature and stand under an atmosphere of argon for a period of 15 h before the

dropwise addition of deuterium oxide (18 mL, 0.91 mol) (Aldrich) (D_2O) dissolved in dry tetrahydrofuran (150 mL; freshly distilled from sodium/ benzophenone ketyl) (Mallinckrodt) dropwise to the stirred alcohol/hydride complex which was again being cooled in an ice/water bath.

After stirring for about 2 h, the system was opened to the atmosphere. The greyish-white solid was removed by vacuum filtration. The filter cake was rinsed with tetrahydrofuran (2 x 50 mL) and the filtrate was dried over anhydrous magnesium sulfate (Fischer Scientific). The drying agent was removed by gravity filtration and rinsed with dry tetrahydrofuran. The alcohol was initially purified by fractional distilled and then further purified by preparative gas chromatography using column PA; 4.693 g (0.0643 mol, 32.15%) of (*R*)-(-)-3-Buten-2-ol-*Z*-4-*d* was obtained; $[\alpha]_D^{19.5} -22.309^\circ$ (neat, $\ell = 1$) (lit. value^{68,69,70} $[\alpha]_{\max} = 33.7^\circ$). Therefore the optical purity is 66.2%. ^1H -NMR ($CDCl_3$) non-deuteriated compound: δ 1.28 (d, 3H, $J_{DE} = 6.42$ Hz, H_E), 1.64 (s, 1H, H_E), 4.31 (m, 1H, H_D), 5.07 (dd, 1H, $J_{AC} = 10.36$ Hz, $J_{AD} = 1.34$ Hz, $J_{AB} = 1.38$ Hz, H_B), 5.21 (ddd, 1H, $J_{AB} = 1.38$ Hz, H_A), 5.92 (ddd, 1H, $J_{AC} = 17.22$ Hz, $J_{BC} = 10.36$ Hz, $J_{CD} = 5.78$ Hz, H_C); deuteriated compound: δ 1.27 (d, 3H, $J_{DE} = 6.42$ Hz, H_E), 2.10 (s, 1H, H_F), 4.30 (dp, 1H, H_D), 5.04 (dd, 1H, $J_{BC} = 10.42$ Hz, $J_{BD} = 1.21$ Hz, H_B), 5.90 (m, 1H, $J_{BC} = 10.42$ Hz, $J_{CD} = 5.75$ Hz, H_C).

3. Preparation of (*S*)-(+)-3-Chloro-1-butene-*Z*-1-*d*

A 250-mL three-necked round-bottomed flask, a stillhead, a condenser, a vacuum adapter, and a 10-mL conical receiving flask were assembled into a simple



(*S*)-(+)-3-Chloro-1-butene-*Z*-1-*d*

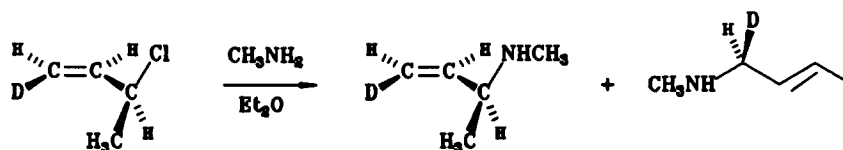
distillation apparatus. Rubber septa were used to cap the two remaining necks of the flask and a thermometer was inserted through a small hole in one of the septa. The receiving flask was immersed in a dry ice/acetone bath and dry ice was packed up around the vacuum adapter as high as possible.

The distillation flask was charged with (*R*)-(-)-3-buten-2-ol-*Z*-4-*d* (3.9 g, 0.053 mol, 66.2% optically pure) and hexachloroacetone (37 mL, 0.240 mol) (Aldrich). The bulb of the thermometer, which had been inserted through the septum, was submerged in the stirred liquid. The solution was cooled to 0 °C by means of an ice/salt/water bath before adding triphenylphosphine (21.0 g, 0.080 mol) (Aldrich) in small portions by rapidly removing and replacing the rubber septum. By adjusting the rates and amounts of these additions, the temperature of the mixture was kept as close to 0 °C as possible and never allowed to go above 5 °C.

The ice/salt/water bath was removed, the rubber septa were replaced with ground glass stoppers, and the pale yellow solution was allowed to stir at room temperature for about 1 hr. The chloride was then flash distilled using a warm water bath at about 40 °C and a pressure of 5 - 6 mm Hg. The distillate was further purified using column PE; 2.213 g (0.024 mol, 45.6%) of (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* was obtained; $[\alpha]_D^{25} +39.151^\circ$ (neat, $\ell = 0.1$) (lit. value⁷¹ $[\alpha]_{\max}^{25} +61.1^\circ$, neat). Therefore the optical purity is 64.1%. ¹H-NMR (CDCl₃) non-deuteriated compound:

δ 1.60 (d, 3H, $J_{CD} = 6.64$ Hz, H_E), 4.52 (m, 1H, H_D), 5.10 (qd, 1H, $J_{BC} = 10.12$ Hz, $J_{BD} = 0.93$ Hz, $J_{AB} = 0.92$ Hz, H_B), 5.25 (qd, 1H, $J_{AC} = 16.96$ Hz, $J_{AD} = 1.05$ Hz, $J_{AB} = 0.92$ Hz, H_A), 5.95 (qd, 1H, $J_{BC} = 10.09$ Hz, $J_{AC} = 16.96$ Hz, $J_{CD} = 7.37$ Hz, H_C); deuteriated compound: δ 1.60 (d, 3H, $J_{CD} = 6.65$ Hz, H_E), 4.53 (ddq, 1H, $J_{AC} = 7.38$ Hz, $J_{CD} = 6.65$ Hz, $J_{BC} = 0.81$ Hz, H_D), 5.11 (dd, 1H, $J_{AB} = 10.16$ Hz, $J_{AC} = 0.81$ Hz, H_B), 5.95 (ddt, 1H, $J_{BC} = 10.16$ Hz, $J_{CD} = 7.38$ Hz, $J_{AC} = 2.59$ Hz, H_C).

4. Reaction of (*S*)-(+)-3-Chloro-1-butene-*Z*-1-*d* with monomethylamine

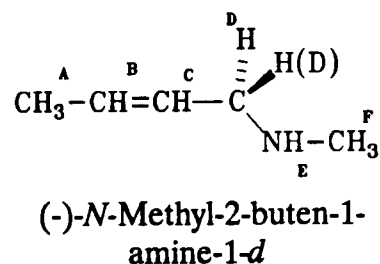


A 100-mL thick-walled pressure tube (Ace Glass Company) was fitted with a magnetic stirring bar and capped with a rubber septum. The pressure tube was cooled to 0 °C using an ice/water bath while flushing with dry argon. It was allowed to cool for a period of 30 min before adding anhydrous diethyl ether (15 mL) (Mallinckrodt) along with (*S*)-(+)-3-chloro-1-butene-*Z*-1-*d* (0.019 mol, 1.758 g, approximately 2 mL; optical purity 64.1%). This was accomplished by rapidly removing and replacing the septum. Monomethylamine (0.019 mol, 6 g, 9 mL; approximate values) (Matheson Gas Company) was added to the pressure tube using a cold graduated cylinder. The tube was sealed with a #15 Ace-thred[®] cap and allowed to warm slowly to ambient temperature behind a Plexiglas[®] shield. During the period of 5 days for which the solution was stirred, two layers formed.

The pressure tube was returned to an ice/water bath for a period of 30 min prior to uncapping. Once opened, the contents of the pressure tube were transferred to a small round-bottomed flask which was fitted with a water-cooled reflux condenser and also cooled in an ice/water bath. A portion (4 mL) of a potassium hydroxide (0.072 mol, 4.0 g) (KOH) (Mallinckrodt) solution, dissolved in distilled water (8 mL), was slowly dropwise through the condenser to the cold ether/amine solution. The resulting layers were separated and the aqueous layer was returned to the round-bottomed flask. The remaining portion (4 mL) of the aqueous potassium hydroxide solution was added to this aqueous layer forming yet another organic layer. The basic aqueous layer was then subjected to continuous extraction with ether (Mallinckrodt) for 12 h. The organic layers were combined and dried over anhydrous potassium carbonate (K_2CO_3) (Mallinckrodt). The majority of the ether was then slowly distilled from the amine by fractional distillation through a Vigreux column. The amine mixture was further purified using column PC; 0.737 g (8.57 mmol) of (-)-*N*-methyl-2-buten-1-amine-1-*d* (a mixture of *E*- and *Z*-isomers) was obtained; $[\alpha]_D^{25} -0.72^\circ$, $[\alpha]_{578}^{25} -0.75^\circ$, $[\alpha]_{546}^{25} -0.85^\circ$, $[\alpha]_{436}^{25} -1.68^\circ$ (neat, $\ell = 0.1$) along with 0.87 g (10.12 mmol) of (-)-*N*-methyl-3-buten-2-amine-*Z*-4-*d*; $[\alpha]_D^{25} -5.733$, $[\alpha]_{578}^{25} -6.160$, $[\alpha]_{546}^{25} -7.667$, $[\alpha]_{436}^{25} -9.853$, $[\alpha]_{365}^{25} -15.067$ (neat, $\ell = 0.1$).

^1H -NMR ($CDCl_3$) non-deuteriated compound:

δ 1.69 (m, 3H, H_A), 2.13 (br s, 1H, H_E), 2.40 (s, 3H, H_F), 3.13 (dd, 2H, $J_{CD} = 5.27$ Hz, $J_{BD} = 1.19$ Hz, H_D), 5.6 (m, 2H, $H_{B,C}$); deuteriated compound: δ



1.68 (dd, 3H, H_D), 1.81 (br s, 1H, H_E), 2.40 (s, 3H, H_F),
3.10 (m, 1H, H_D), 5.6 (m, 2H, $H_{B,C}$). (-)-*N*-methyl-3-

buten-2-amine-*Z*-4-*d*: non-deuteriated compound: δ

1.15 (d, 3H, $J_{DE} = 6.47$ Hz, H_E), 1.31 (br s, 1H, H_F),

2.37 (s, 3H, H_G), 3.05 (dq, 1H, H_D), 5.05 (ddd, 1H,

$J_{BC} = 10.09$ Hz, $J_{BD} = 0.73$ Hz, $J_{AB} = 1.82$ Hz, H_B), 5.10 (ddd, 1H, $J_{AC} = 17.2$ Hz,

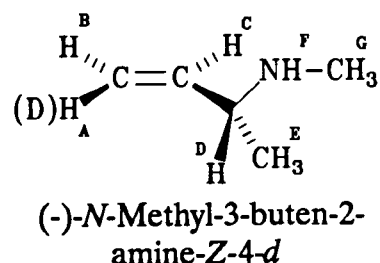
$J_{AB} = 1.84$ Hz, $J_{AD} = 0.94$ Hz, H_A), 5.66 (ddd, 1H, $J_{AC} = 17.2$ Hz, $J_{BC} = 10.09$ Hz,

$J_{CD} = 7.55$ Hz, H_C); deuteriated compound: δ 1.15 (d, 3H, $J_{DE} = 6.47$ Hz, H_E),

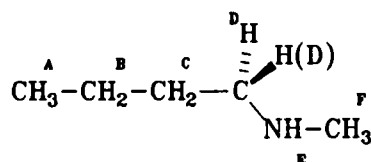
1.43 (br s, 1H, H_F), 2.37 (s, 3H, H_G), 3.05 (br p, 1H, H_D), 5.04 (dd, 1H, $J_{BC} = 10.23$

Hz, $J_{BD} = 0.62$ Hz, H_B), 5.65 (ddt, 1H, $J_{BC} = 10.23$ Hz, $J_{CD} = 7.59$ Hz, $J_{AC} = 2.55$

Hz, H_C).



5. Diimide reduction of (*S*)-(-)-*N*-Methyl-2-buten-1-amine-1-*d*



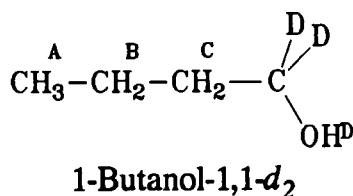
A 250-mL round-bottomed flask was fitted with a spiral condenser and equipped with a magnetic stirring bar.

An solution of potassium hydroxide (18.5 g, 330.4 mmol) (KOH) (Mallinckrodt) in distilled water (25 mL) was added (half of the volume was added initially). Then *p*-toluenesulfonhydrazide (30.7 g, 165.2 mmol) (PTSH) (Aldrich) was added in small portions to the stirred KOH solution and the solid allowed to dissolve between additions. This was followed by the dropwise addition of *N*-methyl-2-buten-1-amine-1-

d (0.61 g, 7.09 mmol) using a pipet. The flask was rinsed with the remaining KOH solution and the washings added to the reaction flask. The dark yellow/brown solution was then heated to reflux for 8 h. The solution was allowed to stand overnight. An additional 25 mL of water was added and the reflux was continued for another 8 h.

The cooled solution was extracted with ether (4 x 40 mL) and the combined ether extracts were first dried over anhydrous potassium carbonate then over anhydrous magnesium sulfate. Most of the ether was removed by slow fractional distillation and the pot residue further purified by preparative gas chromatography using column PC; 0.182 g (2.07 mmol) of (*R*)-(-)-*N*-methyl-1-butanamine-1-*d* was obtained; $[\alpha]_{436}^{25} -1.36^\circ$, $[\alpha]_{365}^{25} -2.038^\circ$ ($\ell = 0.01$, neat); optical purity 66.4%. ^1H -NMR (CDCl_3) non-deuteriated compound: δ 0.92 (t, 3H, $J_{AB} = 7.08$ Hz, H_A), 1.17 (br s, 1H, H_E), 1.4 (m, 4H, $\text{H}_{B,C}$), 2.43 (s, 3H, H_F), 2.56 (t, 2H, $J_{CD} = 6.98$ Hz, H_D); deuteriated compound: δ 0.92 (t, 3H, t, $J_{AB} = 7.1$ Hz, H_A), 1.37 (m, 4H, $\text{H}_{B,C}$), 1.65 (br s, 1H, H_E), 2.43 (s, 3H, H_F), 2.55 (tt, 1H, $J_{CD} = \text{ca. } 7.0$ Hz, $J_{\text{Ddeuterium}} = \text{ca. } 1.6$ Hz, H_D).

6. Preparation of 1-Butanol-1,1- d_2 ⁷²

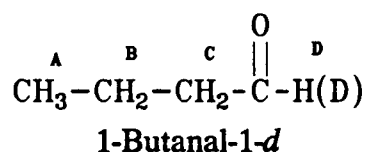


A 500-mL round-bottomed flask was charged with dry diethyl ether (200 mL; freshly distilled from sodium/benzophenone ketyl) (Mallinckrodt). Lithium aluminum deuteride (5.00 g, 0.119 mol) (Aldrich) was slowly added to the dry ether with stirring.

The addition funnel was charged with butyryl chloride (15.45 mL, 0.148 mol) (Aldrich) which had been dissolved in dry ether for a total volume of 50 mL. The flask was cooled in an ice/water bath prior to the dropwise addition of the butyryl chloride/ether solution.

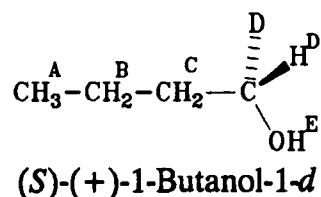
After warming to ambient temperature, the milky-white solution was stirred for a period of 2 h. The flask was returned to the ice/water bath for 30 min before adding aqueous concentrated KOH solution (about 15 mL) dropwise to the stirred solution. The white solids were collected by vacuum filtration and washed with ether. There was a small aqueous layer formed which was separated before drying the ether layer over anhydrous potassium carbonate (K_2CO_3). The ether was removed by fractional distillation through a vacuum-jacketed Vigreux column followed by distillation of the dideuterio-alcohol through the Vigreux column at reduced pressure into an ice cooled receiving flask; 10.32 g (0.14 mol) of 1-butanol-1,1- d_2 was obtained. ^1H -NMR ($CDCl_3$) non-deuteriated compound: δ 0.93 (t, 3H, $J_{AB} = 7.16$ Hz, H_A), 1.4 (m, 2H, $J_{AB} = 7.16$ Hz, H_B), 1.5 (m, 2H, H_C), 1.84 (s, 1H, H_E), 3.64 (t, 2H, $J_{CD} = 6.48$ Hz, H_D); deuteriated compound: δ 0.93 (t, 3H, $J_{AB} = 7.15$ Hz, H_A), 1.4 (m, 2H, $J_{AB} = 7.15$ Hz, H_B), 1.5 (m, 2H, H_C), 2.58 (s, 1H, H_D).

7. Preparation of 1-Butanal-1- d



A 250-mL three-necked round-bottomed flask, a 50-mL pressure-equalizing addition funnel, a Claisen adapter, a stillhead, a condenser, a vacuum adapter, and a 100-mL round-bottomed receiving flask were assembled into a simple distillation apparatus. The flask was charged with 1-butanol-1,1- d_2 (11.816 g, 0.155 mol) and distilled water (13 mL). A solution of chromic acid, made by dissolving potassium dichromate (15,288 g, 0.052 mol) in water (95 mL) followed by the slow addition of concentrated sulfuric acid (12 mL, 0.208 mol), was added dropwise to a warmed alcohol/water solution. The butanal was steam-distilled from the aqueous reaction mixture. The aqueous layer of the distillate was saturated with sodium chloride and the layers were separated; 4.7 g (0.064 mol) of 1-butanol-1- d was obtained. $^1\text{H-NMR}$ (CDCl_3): non-deuteriated compound: δ 0.97 (t, 3H, $J_{AB} = 7.40$ Hz, H_A), 1.67 (doublet of sextets, 2H, $J_{AB} = 7.40$ Hz, $J_{BC} = 7.25$ Hz, $J_{BD} = 0.5$ Hz, H_B), 2.42 (dt, 2H, $J_{BC} = 7.25$ Hz, $J_{CD} = 1.83$ Hz, H_C), 9.77 (t, 1H, $J_{CD} = 1.83$ Hz, H_D); deuteriated compound: δ 0.96 (t, 3H, $J_{AB} = 7.41$ Hz, H_A), 1.66 (sextet, 2H, $J_{AB} = 7.41$ Hz, $J_{BC} = 7.33$ Hz, H_B), 2.41 (t, 2H, $J_{BC} = 7.22$ Hz, H_C).

8. Preparation of (*S*)-(+)-1-Butanol-1- d



A 250-mL, three-necked, round-bottomed flask, a 50-mL, pressure-equalizing addition funnel, a Claisen adapter/stillhead, a condenser, a vacuum adapter, a 100-mL round-bottomed receiving flask, and a magnetic stirring bar were oven-dried and

assembled into a simple distillation apparatus while still hot. The remaining openings were capped with rubber septa and the apparatus was allowed to cool to room temperature while flushing with dry argon.

An inert-atmosphere graduated cylinder (which had also been oven-dried and cooled under argon) was used to transfer *R*-Alpine-Borane[®] (120 mL, 0.06 mol; 0.5 *M* in THF) (Aldrich). The THF was removed by distillation at atmospheric pressure under an argon atmosphere. After the removal of the THF, the flask was cooled in an ice/water bath before adding butyraldehyde-1-*d* (4.00 g, 0.055 mol) dropwise to the borane complex. This solution was allowed to stir for a period of 16 hrs.

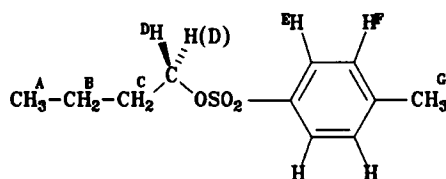
The solution was again cooled in an ice/water bath before the dropwise addition of freshly distilled benzaldehyde (4.6 mL, 0.045 mol) (Mallinckrodt). The ice/water bath was removed, the solution was allowed to warm to room temperature, and stirred for 2 h. The liberated α -pinene was removed by distillation at reduced pressure. A warm water bath was maintained at about 40 °C and the pressure was slowly lowered to a final pressure of 1.5 mm Hg. Upon completion of the distillation, the apparatus was returned to ambient pressure but still under an argon atmosphere.

The flask was returned to the ice/water bath. Anhydrous diethyl ether (50 mL) (Mallinckrodt) was added to the yellow solution via syringe prior to the dropwise addition of 2-aminoethanol (0.12 mol, 7.33 g, 7.2 mL) (EM Science). A yellow solid immediately precipitated.

The yellow solid was removed by vacuum filtration, the filter cake was washed with ether (50 mL), and the filtrate dried over anhydrous K₂CO₃ (Mallinckrodt). The

ether was removed by fractional distillation through a vacuum-jacketed Vigreux column. The alcohol was distilled at reduced pressure (aspirator) into an ice cooled receiving flask; 2.13 g (0.030 mol, 73.7%) of (*S*)-(+)-1-butanol-1-*d* was obtained; $[\alpha]_D^{27.5} +0.460^\circ$ (neat, $\ell = 0.1$) (lit. value⁷³ $[\alpha]_D^{27.5}(\text{max}) = +0.471^\circ$, neat). Therefore the optical purity of the alcohol is 97.7%. It should be noted that the commercial *R*-Alpine-Borane[•] was 98% enantiomerically pure. ¹H-NMR (CDCl₃) non-deuteriated compound: δ 0.93 (t, 3H, $J_{AB} = 7.16$ Hz, H_A), 1.4 (m, 2H, $J_{AB} = 7.16$ Hz, H_B), 1.5 (m, 2H, H_C), 1.84 (s, 1H, H_E), 3.64 (t, 2H, $J_{CD} = 6.48$ Hz, H_D); deuteriated compound: δ 0.93 (t, 3H, $J_{AB} = 7.17$ Hz, H_A), 1.4 (m, 2H, $J_{AB} = 7.17$ Hz, H_B), 1.5 (m, 2H, H_C), 2.11 (br s, 1H, H_E), 3.56 (tt, 1H, $J_{CD} = 6.53$ Hz, $J_{\text{Ddeuterium}} = 1.44$ Hz, H_D).

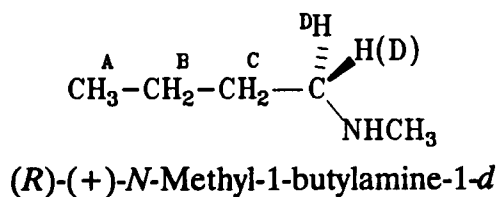
9. (*S*)-(-)-1-Butyl-1-*d* tosylate



(*S*)-(-)-1-butyl tosylate-1-*d* was obtained from Randall Hinton⁶⁸ and distilled at reduced pressure (143°/2 mm Hg) before use; $[\alpha]_D^{25} -0.196^\circ$, $[\alpha]_{578}^{25} -0.205^\circ$, $[\alpha]_{546}^{25} -0.235^\circ$, $[\alpha]_{436}^{25} -0.416^\circ$ (neat, $\ell = 0.1$). ¹H-NMR (CDCl₃) non-deuteriated compound: δ 0.86 (t, 3H, $J_{AB} = 7.28$ Hz, H_A), 1.33 (m, 2H, H_B), 1.63 (m, 2H, H_C), 2.45 (s, 3H, H_G), 4.03 (t, 2H, $J_{CD} = 6.42$ Hz, H_D), 7.34 (d, 2H, H_F), 7.80 (d, 2H, H_E); deuteriated compound: δ 0.850 (t, 3H, $J_{AB} = 7.23$ Hz, H_A), ca. 1.3 (m, 2H, H_B), ca. 1.6 (m, 2H, H_C), 2.44 (s, 3H, H_G), 4.01 (tt, 1H, $J_{CD} = 6.45$ Hz, $J_{\text{Ddeuterium}} = 1.10$

Hz, H_D), 7.34 (m, 2H, H_F), 7.79 (m, 2H, H_E); ¹³C-NMR (CDCl₃) non-deuteriated compound: δ 13.37 (H_A), 18.60 (H_B), 21.62 (H_C), 30.79 (H_G), 70.37 (H_D), 127.82 (H_F), 129.76 (H_E).

10. Preparation of (*R*)-(+)-*N*-Methyl-1-butan-1-amine-1-*d*



A pressure tube, cooled in an ice/water bath and flushed with dry argon, was charged with (*S*)-1-butyl-1-*d* tosylate (0.0133 mol, 3.0 g; optical purity 63.3% based on the optical purity of the alcohol from which it was made) (generously provided by Randall Hinton). A graduated cylinder, cooled in a dry ice/acetone bath, was used to transfer methylamine (*ca.* 0.12 mol, *ca.* 5.5 mL) (Aldrich) to the pressure tube. The tube was sealed, the contents allowed to warm slowly to room temperature and stirred for a period of 6 days behind a Plexiglas[®] shield.

The pressure tube was returned to an ice/water bath for 30 min prior to opening. The excess methylamine was allowed to boil off by placing the tube in a room temperature water bath. Once most of the methylamine was gone, the tube was again returned to the ice/water bath. A solution of 10 *N* sodium hydroxide (NaOH) (0.019 mol, 19 mL) (Mallinckrodt) along with ether (19 mL) was added to the tube. The layers were separated and the aqueous layer was extracted with ether (4 x 20 mL). The combined ether extracts were first dried over anhydrous potassium carbonate, followed by drying over 3Å molecular sieves. Most of the ether was then

removed by fractional distillation and the pot residue was further purified by preparative gas chromatography using column PC; 0.432 g (1.9 mmol) of (*R*)-(+)-*N*-methyl-1-butylamine-1-*d* was obtained; $[\alpha]_D^{25} + 1.67^\circ$, $[\alpha]_{578}^{25} + 1.74^\circ$, $[\alpha]_{546}^{25} + 2.01^\circ$, $[\alpha]_{436}^{25} + 3.61^\circ$, $[\alpha]_{365}^{25} + 5.86^\circ$ (neat, $\ell = 0.1$) (the alcohol used to make the tosylate was 63.3% optically pure; therefore $[\alpha]_{\max} = + 2.64^\circ$ at 589 nm, $[\alpha]_{\max} = + 2.74^\circ$ at 578 nm, $[\alpha]_{\max} = + 3.18^\circ$ at 546 nm, $[\alpha]_{\max} = + 5.70^\circ$ at 436 nm, $[\alpha]_{\max} = + 9.26^\circ$ at 365 nm, neat). Therefore the amine is also considered to be 63.3% optically pure. $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (t, 3H, t, $J_{AB} = 7.1$ Hz, H_A), 1.37 (m, 4H, $\text{H}_{B,C}$), 1.65 (br s, 1H, H_E), 2.43 (s, 3H, H_F), 2.55 (tt, 1H, H_D).

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