To the Graduate Council:

I am submitting herewith a thesis written by Tim Joseph Reed entitled "Synthesis of Oxygen-17 Enriched Alcohols Via the Oxidation of Organoborane Intermediates." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

George W. Kabalka

George W. Kabalka, Major Professor

We have read this thesis
and recommend its acceptance:

William E. Bull

Charles A. Lane

Accepted for the Council:

Lewis Minkel

The Graduate School

SYNTHESIS OF OXYGEN-17 ENRICHED ALCOHOLS VIA THE OXIDATION OF ORGANOBORANE INTERMEDIATES

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Tim Joseph Reed

December 1983

DEDICATION

This work is dedicated to my best friend and loving wife, Renee, whose unconditional love, prayerful support, encouragement, and companionship are greatly appreciated and treasured.

ACKNOWLEDGMENTS

The author extends his deepest appreciation and gratitude to his parents (Al and Helen) and sister (Sherrie) for their love, continual encouragement, and steadfast support through prayer. Heartfelt appreciation is also extended to the author's godparents (Euel and Wanda Whitaker) and father and mother-in-law (Gene and Beverly Kinney) for their continual love, support, and prayers.

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Although many people have graciously influenced the author's personal and academic life, the ultimate glory, honor, and praise belongs only to Jesus Christ, Lord and Savior.

> Shout joyfully to the Lord, all the earth. Serve the Lord with gladness; come before Him with joyful singing. Know that the Lord Himself is God; it is He who has made us, and not we ourselves; we are His people and the sheep of His pasture. Enter His gates with thanksgiving, and His courts with praise. Give thanks to Him; bless His name. For the Lord is good; His lovingkindness is everlasting and His faithfulness to all generations.
>
> Psalm 100

ABSTRACT

Oxygen-17 enriched alcohols are conveniently synthesized via the reaction of trialkylboranes with a limited quantity of oxygen-17 enriched molecular oxygen. Functional substituents, present in reactant alkenes, are unaffected by this hydroboration-oxidation method.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

A. General Introduction

Alcohols, isotopically enriched with stable oxygen-17, play an increasingly important role in medical, chemical, and biological research.[1] Stable oxygen-18[1] and radioactive oxygen-15[2] have also been used as isotopic labels. The increased interest in the area of oxygen isotope incorporation is primarily due to improved methods of analysis [multinuclear fourier transform (FT) nuclear magnetic resonance (NMR) for oxygen-17; mass spectrometry for oxygen-18; positron emission tomography for oxygen-15] and greateravailability of the isotopes.[1]

The development of new methods for isotope incorporation into molecules is essential if their use is to be maximized. It has been reported that isotopes of carbon,[3,4] iodine,[5] bromine,[6] and nitrogen[7] have been conveniently incorporated into a variety of molecules via organoborane chemistry.

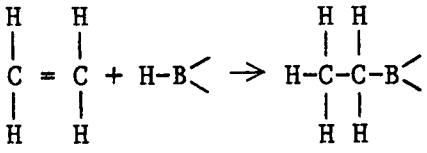
In the years since 1939, when Brown, Schlesinger and Burg reported that diborane (B_2H_6) reduced the carbonyl group of aldehydes and ketones, organoborane chemistry has expanded into one of the most useful tools available in synthetic organic chemistry.[8] Two aspects contributing to the utility of organoboranes are their availability and their wide range of reactivity. Many important classes of organic compounds are easily prepared via the conversion of organoborane

intermediates;[9] these include alcohols, aldehydes, ketones, carboxylic acids and their derivatives, nitriles, amines, alkenes, dienes and alkyl halides.[9] Carbon-carbon bond formation and the construction of carbocyclic compounds are also readily achieved through reactions involving organoboranes.[10]

The number of organoborane oxidation reactions have increased in importance as organoborane chemistry has expanded. In this chapter, the hydroboration reaction and various oxidation reactions will be reviewed.

B. The Hydroboration Reaction

The hydroboration of olefins, first reported by Brown and Rao in 1956,[8] is extremely useful in organic chemistry (Equation 1).[10] The



(1)

reaction of organic compounds containing multiple bonds with a standardized borane-tetrahydrofuran solution (BH_3:THF) is the method of choice for the production of most organoboranes (Equation 2).[10]

$$3RCH = CH_2 + H_3B{:}THF \longrightarrow (RCH_2CH_2)_3B + THF \qquad (2)$$

Another hydroborating agent which is used in the synthesis of organoboranes is the borane-dimethylsulfide complex [$BH_3{:}(CH_3)_2S$].[10] Although this complex is more stable than the BH_3:THF complex, and a variety of solvents (ethereal and hydrocarbon) may be used, the

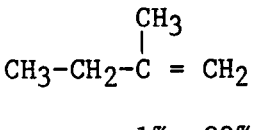
presence of dimethylsulfide during and after the reaction is a disadvantage to its use.[10]

A vast majority of unsaturated molecules are successfully hydroborated to the corresponding organoboranes. For example, alkenes containing two, three, and four alkyl substituents about the double bond will undergo hydroboration.[10] Trialkylboranes are readily formed from alkenes containing unhindered double bonds. However in the case of more hindered double bonds, the reaction may cease at the dialkylborane stage (as in the hydroboration of trimethylethylene to yield disiamylborane) or even the monoalkylborane stage (as in the hydroboration of tetramethylethylene to yield thexylborane).[10]

The regiochemistry of hydroboration has been extensively investigated by examining the alcohols obtained after oxidation of the product organoboranes. In the case of simple alkenes, 93-94% of the boron atoms are placed at the terminal carbon and 6-7% at the non-terminal carbon.[11] Thus, the hydroboration of simple olefins results in the predominate formation of the anti-Markovnikov product.[10]

Alkyl branching on non-olefinic carbons does not substantially affect the regiospecificity of hydroboration. For disubstituted internal olefins, R-CH=CH-R' (2-pentene and 2-hexene), the boron atom is directed, in approximately equal amounts, to the second and third

carbon atoms.[11] However, alkyl substituents on the non-terminal olefinic carbon increase the percentage of boron attached to the terminal carbons, as with 2-methyl-1-butene (I) and 2-methylstyrene (II).[11] Internal olefins exhibit much the same characteristics. The boron atom is predominately directed to the carbon with the least alkyl branching, as with 2-methyl-2-butene (III).[11]



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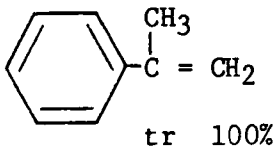

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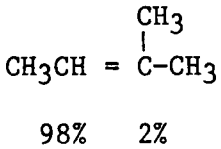

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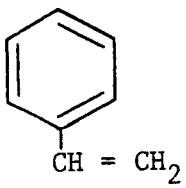
Aryl groups cause increased placement of the boron atom on the non-terminal carbon. Substituents on the benzene ring further influence the boron placement.[11]



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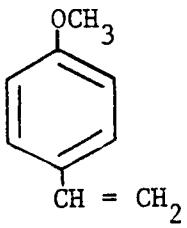

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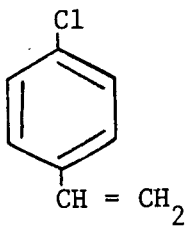

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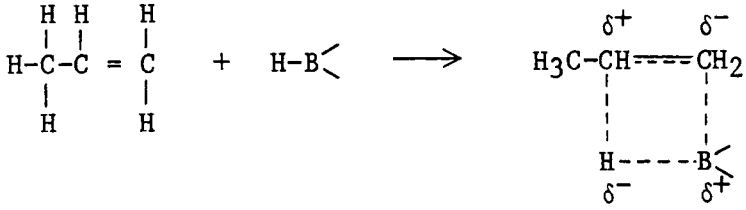
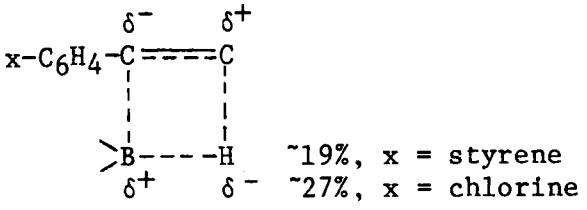
A four-centered transition state is accepted for the addition of the boron-hydrogen bond to carbon-carbon multiple bonds (Equation 3).[11]



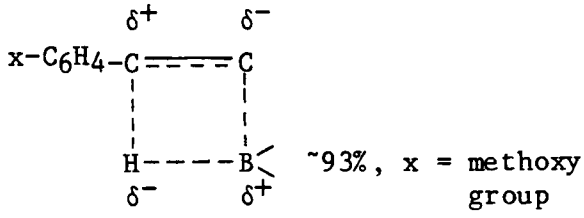
(3)

In the case of styrene, electron withdrawing substituents favor the placement of an increased percentage of the boron on the non-terminal carbon (Equation 4),[11] whereas, powerful electron



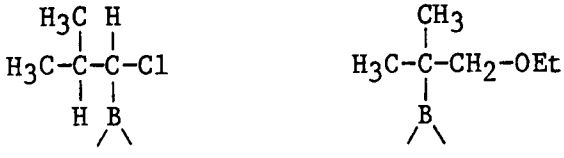
(4)

donating substituents lead to an increased percentage of the boron at the terminal carbon (Equation 5).[11]

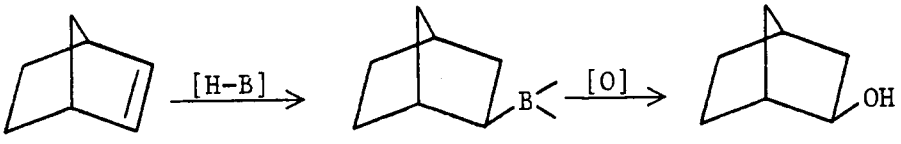


(5)

Other substituents also affect the direction of hydroboration. For example, the powerful electron attracting ability of chlorine causes increased placement of the boron atom on the terminal carbons.[10] The opposite effect is exhibited by the electron donating ethoxy group.[10]

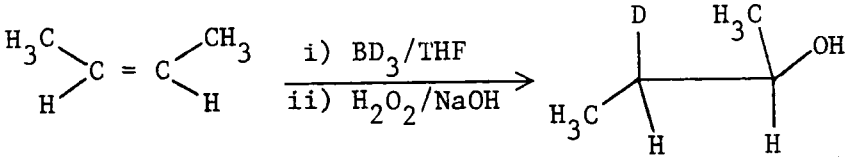


The oxidation of organoboranes with alkaline hydrogen peroxide to form the corresponding alcohols has provided much information about the stereochemistry of the hydroboration reaction. The oxidation of tri-(1-methylcyclopentyl)borane and tri-(1-methylcyclohexyl)borane forms trans-2-methylcyclopentanol and trans-2-methylcyclohexanol, respectively.[12] These products show that oxidation proceeds with retention of configuration.[12] This conclusion is further supported by studies performed on norbornene and acyclic alkenes. The hydroboration of norbornene followed by oxidation yields exo-norborneol exclusively (Equation 6).[12] Kabalka and coworkers have reported that



(6)

the reaction of both cis- and trans-2-butene with borane-d_3, followed by oxidation, produce erythro- and threo-2-butanol-3-d, respectively (Equations 7 and 8).[13]



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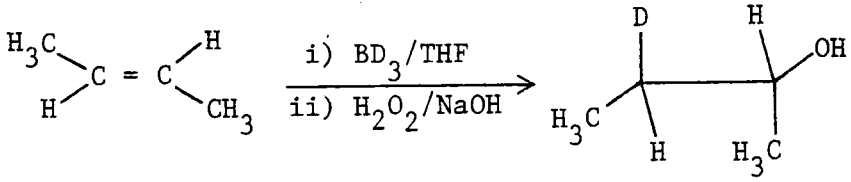
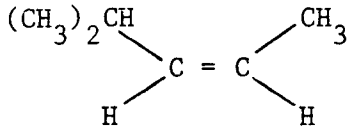


(8)

The hydroboration of (E)- and (Z)-1-hexene,2-d_2 with dialkylboranes form threo- and erythro-(1,2-dideuteriohexyl)dialkylboranes, respectively.[14] In addition, hydroboration of (E)- and (Z)-1-hexene-1-d with di(2-deuteriocyclohexyl)borane-B-d produces erythro- and threo-(1,2 dideuteriohexyl)di(deuteriocyclohexyl) borane, respectively.[14] These results are consistent with a stereospecific cis addition of the boron-hydrogen bond to the carbon-carbon multiple bond, from the least hindered side, with retention of configuration in the oxidation stage.[12]

One key advantage of the hydroboration reaction is that a wide range of functionalities can be tolerated, thus providing organoboranes containing such groups.[10] Groups such as halogens, alkoxy groups and nitriles are unaffected by hydroboration.[3] Also, esters, such as methyl-10-undecenoate and compounds containing sulfur, such as 3-p-tolylthio-2-methylpropene, can be successfully hydroborated. Unsaturated molecules containing the carbonyl group must first be derivitized to the corresponding acetals, ketals or esters before hydroboration.[10] This normally prevents the reduction of the carbonyl group.

The hydroboration of unsaturated molecules with BH_3:THF presents problems due to the low steric requirements and low selectivity of this reagent.[10] For example, the hydroboration of 2-methyl-3-pentene(IV) and allyl chloride(V) with BH_3:THF, shows little selectivity. These problems are overcome by using hydroborating reagents which are



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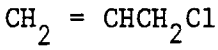
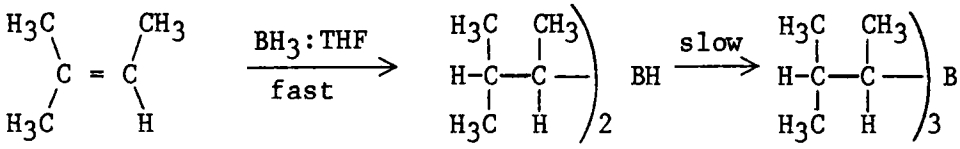


50% 50%
(V)

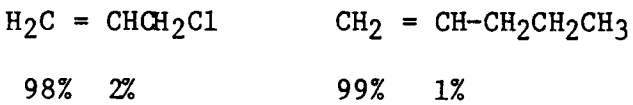
sterically more hindered than and electronically different from BH_3:THF.[10]

Disiamylborane, a monofunctional hydroborating reagent, is prepared by reacting BH_3:THF with 2-methyl-2-butene (Equation 9).[10] This reagent



(9)

exhibits enhanced selectivity compared to BH_3:THF.



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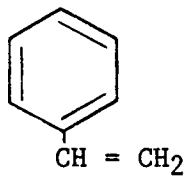

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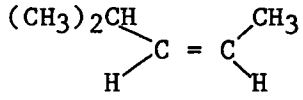

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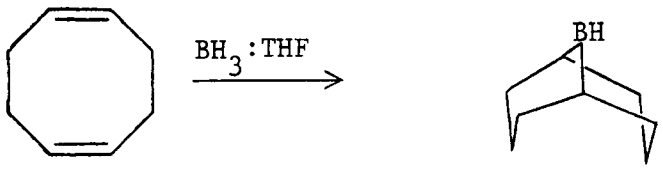
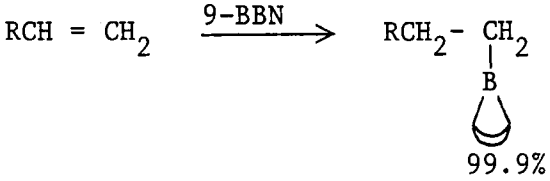
The reaction of 1,5-cyclooctadiene with BH_3:THF produces 9-borabicyclo [3.3.1] nonane (9-BBN), another monofunctional hydroborating reagent (Equation 10).[3] This reagent is thermally stable



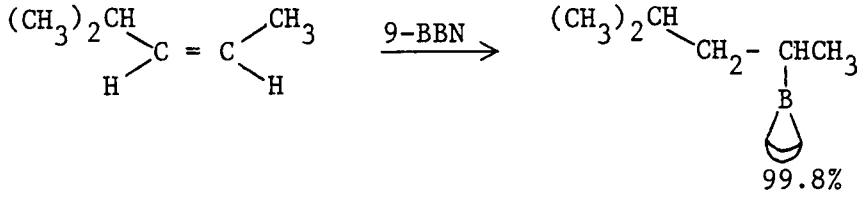
(10)

and exhibits some stability in air.[10] Hydroboration of olefins with 9-BBN exhibits remarkable regioselectivity.[10] Terminal olefins react to place 99.9% of the boron atoms at the terminal position (Equation 11).[10]



(11)

Internal olefins also react with 9-BBN (Equation 10). Enhanced regioselectivity is exhibited, as in cis-4-methyl-2-pentene (Equation 12):[10]



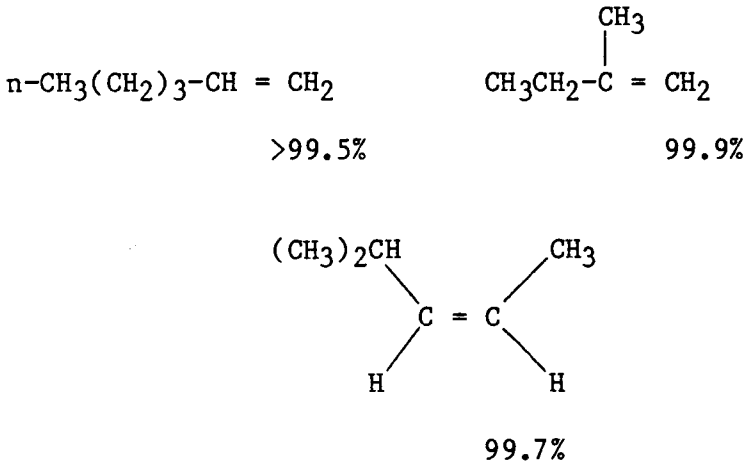
(12)

Finally, dichloroborane and monochloroborane complexes are useful regioselective hydroborating reagents. These reagents are prepared by reacting lithium borohydride with boron trichloride in diethyl ether (Equations 13 and 14).[10]

$$LiBH_4 + BCl_3 + 2Et_2O \longrightarrow LiCl\downarrow + 2ClBH_2{:}OEt_2 \qquad (13)$$

$$LiBH_4 + BCl_3 + 4Et_2O \longrightarrow LiCl\downarrow + 4Cl_2BH{:}OEt_2 \qquad (14)$$

The chloroboranes react with olefins at 0°C to produce the corresponding organoboranes. The boron atom is selectively placed at the terminal position.[10]



C. Oxidation of Organoboranes

1. Oxidation with Molecular Oxygen (Autoxidation)

The reaction of organoboranes with oxygen to form peroxyboranes, alcohols, and hydroperoxides has been extensively investigated. Trialkylboranes are very sensitive to oxygen. Lower alkylboranes spontaneously inflame when exposed to molecular oxygen, while higher homologs react slowly with oxygen.[15] Arylboranes are less reactive towards oxygen. [It should be noted that 9-BBN (see Hydroboration Section, page 8) is relatively stable in an oxygen environment.] Organoboranes containing bulky groups, such as trimesitylborane, are relatively stable.[10]

Johnson and Van Campen reported that the autoxidation of trialkylboranes proceeds through a "borinate-peroxide" intermediate (Equation 15).[15] They further showed that water inhibited autoxidation

$$R_3B + O_2 \longrightarrow R_3\overset{-}{B} - \overset{+}{O} = O \qquad (15)$$

of organoboranes. Amines (for example, propylamine) also inhibit the reaction.[16,17] This is most likely attributed to the competition of these reagents with oxygen for co-ordination to the boron atom.[16] Later workers established that autoxidation proceeds through the initial formation of alkylborinic peroxide esters (Equation 16).[16] The

$$R_3B + O_2 \longrightarrow R_2B(O_2R) \qquad (16)$$

reaction is very fast, with the first boron-carbon bond being oxidized faster than the second, which is oxidized much faster than the third.[18]

The autoxidation of organoboranes was first thought to proceed by an ionic rather than a radical mechanism, since early efforts to inhibit the reaction by using common radical scavengers, such as hydroquinone,[16,19] iodine,[20] and methyl methacrylate,[20] were unsuccessful. However, later investigations revealed that powerful radical scavengers, galvinoxyl,[21-23] and elemental iodine,[24] efficiently inhibit autoxidation of organoboranes. Further evidence to support a radical mechanism is the fact that stereoisomeric groups tend to racemize during the reaction. For example, optically active 1-phenylethylboronic acid reacts with oxygen to produce racemic dihydroxy-1-phenylethylperoxyborane.[21] Also, sec-butanol formed from

the autoxidation of optically active diisopinocampheyl-sec-butylborane shows a high degree of racemization.[22] The autoxidation of epimeric mixtures of trinorbornylboranes results in racemic norborn-2-ylbis(norborn-2-ylperoxy)borane containing 76% exo- and 24% endo-norbornyl-oxygen bonds.[25] The high degree of exo isomer is due to the preferential attack by oxygen at the less hindered side of the norbornyl radical.[25]

The following homolytic chain mechanism has been proposed (Equation 17).[26] The initial alkylperoxyborane, RO_2BR_2, produced may

$$\begin{aligned} &\text{Initiation:} && R_3B + O_2 \rightarrow R\cdot + \cdot O_2BR_2 \\ &\text{Propagation:} && R\cdot + O_2 \rightarrow RO_2\cdot \\ & && RO_2\cdot + R_3B \rightarrow RO_2BR_2 + R\cdot \\ &\text{Termination:} && 2ROO\cdot \text{ (or } 2R\cdot) \rightarrow \text{stable products} \end{aligned} \qquad (17)$$

further react with a second mole of oxygen to give the dialkylperoxyborane, $(RO_2)_2BR$, or may undergo an intermolecular reaction with unreacted R_3B to form the borinate ester, $ROBR_2$.[16,27] The borinate ester may then react with oxygen to produce the $ROB(O_2R)R$ species.[16]

Brown and coworkers have studied the initiation reaction by utilizing iodine as a radical scavenger.[24] They conclude that the reaction of oxygen with organoboranes initially involves the relatively slow attack of molecular oxygen on the boron atom.[24] The rate of this initiation is retarded by increasing the crowding about the boron atom.[28] Thus, the order of reactivity for initiation is

1°>2° (e.g., n-Bu_3B; sec-Bu_3B, iso-Bu_3B), which is opposite the order displayed for the overall autoxidation process (i.e., 3°>2°>1°).[29] Thus the chain propagation step occurs more readily for tri-sec-alkylboranes than for corresponding primary alkylborane.[24,30] The relative rates of autoxidation of organoboranes follow the general series (Equation 18):[16,17,28-30]

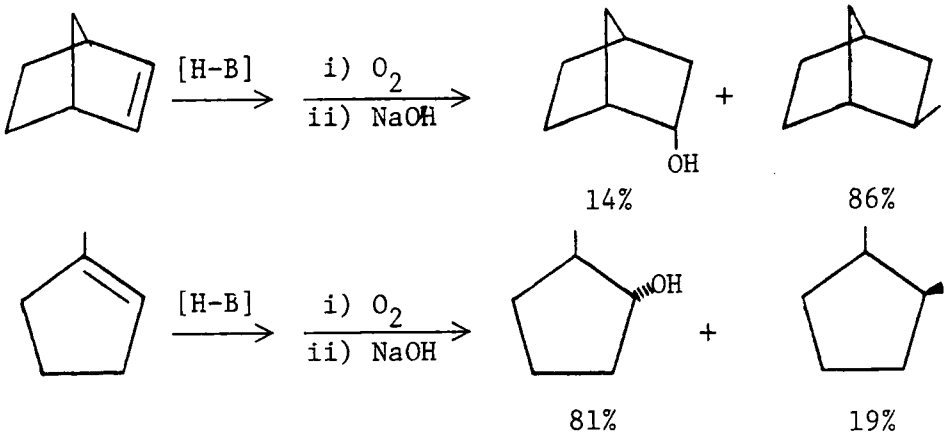
$$\begin{aligned}
&\text{Alkyl-B}\lessdot > \text{Vinyl-B}\lessdot \sim \text{Aryl-B}\lessdot \\
&R_3B > R_2B\text{-}OR > RB(OR)_2 \\
&R_2BOH > R_2BOR > R_2B\text{-}O^-Na^+ \\
&R_3B > R_2BCl > RBCl_2 \\
&\text{t-alkyl-B}\lessdot > \text{s-alkyl-B}\lessdot > \text{p-alkyl-B}\lessdot > CH_3\text{-B}\lessdot
\end{aligned} \qquad (18)$$

Any substituent that has the ability to donate electrons to the unfilled shell of the boron atom causes the organoborane to be less reactive towards oxygen.[16]

The addition of stoichiometric amounts of oxygen (1.5 moles O_2 per mole R_3B) to organoborane solutions followed by treatment with sodium hydroxide affords a convenient and mild route to the corresponding alcohols in quantitative yields (Equation 19).[29]

$$R_3B + 1.5O_2 \longrightarrow [(RO)_3B] \xrightarrow{3H_2O} 3ROH + B(OH)_3 \qquad (19)$$

Since this reaction proceeds via a radical chain mechanism, some loss in stereospecificity is observed (Equations 20 and 21).[29]



Alkyl hydroperoxides are conveniently prepared, in high yields, by reacting the intermediates of autoxidation with aqueous hydrogen peroxide, in the absence of base (Equation 22).[31]

$$R_3B + 2O_2 \rightarrow RB(O_2R)_2 + H_2O_2 \rightarrow 2RO_2H + ROH + B(OH)_3 \qquad (22)$$

2. Oxidation with Peroxides

a. Alkaline hydrogen peroxide. Alkaline hydrogen peroxide oxidation of organoboranes has been the most widely studied oxidation method. This has resulted in the extensive use of this procedure in the synthesis of alcohols via the hydroboration of olefins. It has been reported that both perbenzoic acid (in chloroform) and hydrogen peroxide, in the presence of dilute alkali, react with tri-n-butylborane to achieve complete dealkylation, which results in the formation of boric acid and n-butyl alcohol, in quantitative yields.[15]

The oxidation of organoboranes with alkaline hydrogen peroxide is the most convenient route for the anti-Markovnikov hydration of unsaturated molecules (Equation 23).[32] The reaction is clean and

$$R_3B + 3H_2O_2 + NaOH \rightarrow 3ROH + NaB(OH)_4 \qquad (23)$$

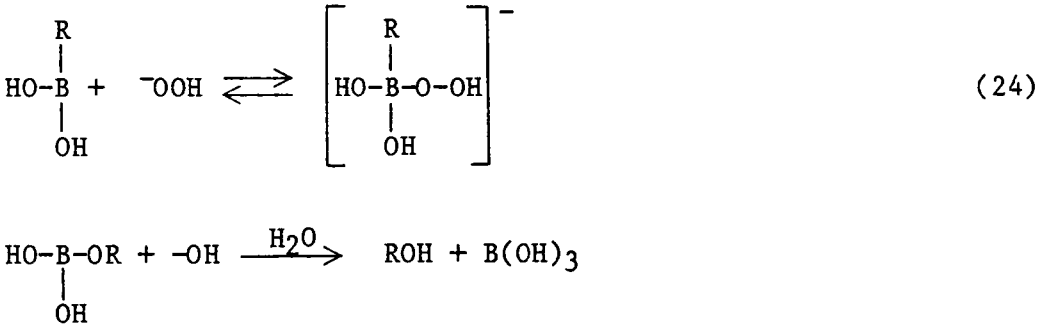
takes place in solvents (ether, THF, and diglyme) typically utilized in hydroboration.[10] Ethanol should be added as a cosolvent when performing oxidations in diethyl ether, due to ether's immiscibility in water.[33]

The first reported alkaline hydrogen peroxide oxidation of organoboranes[34] and early applications of this process[35] employed heating the organoborane with excess hydrogen peroxide and concentrated sodium hydroxide under reflux. Later studies determined that milder conditions lead to better yields of the desired alcohol.[33] The concentration of hydrogen peroxide, concentration of base, and the reaction temperature can be varied over a wide range without significantly affecting the yield.[33]

Oxidation reactions using peroxides can tolerate a wide variety of functionalities present in the organoborane, such as alkenes, alkynes, aldehydes, ketones, esters, halides, and nitriles.[9] These groups generally remain unchanged at the completion of the reaction. In addition, this oxidation method is not affected by the steric requirements of the alkyl or aryl groups of the organoborane.[33] The oxidation of organoboranes with alkaline hydrogen peroxide proceeds with complete retention of configuration (see Hydroboration Section, page 6).[12]

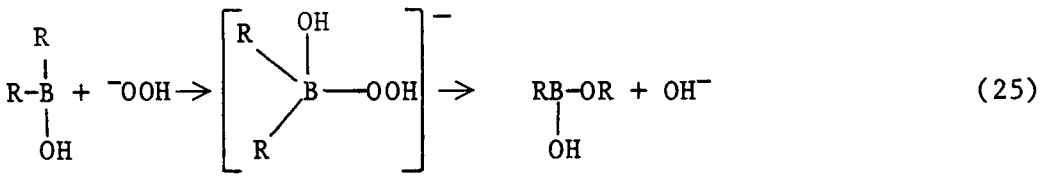
The oxidation reactions are convenient; the organoborane is treated with 3N sodium hydroxide followed by drop-wise addition of 20% excess hydrogen peroxide (30%) at room temperature. The reaction mixture is normally heated to 50°C for one hour, after which the product is isolated.[10]

A detailed kinetic study of the oxidation of alkylboranes, with alkaline hydrogen peroxide, has not been reported. However, a mechanism has been proposed for the related reaction of alkyl- and arylboronic acids with alkaline hydrogen peroxide (Equation 24).[36]



(24)

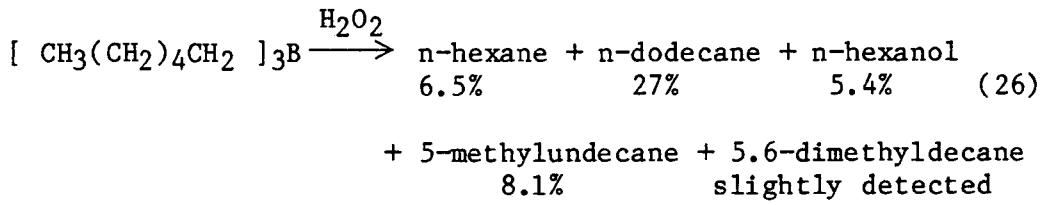
An identical mechanism was reported by Wechter (Equation 25).[37]



(25)

The R group migrates, with its pair of electrons, from boron to oxygen. The successive migration of the three alkyl groups results in the formation of boronic acid and alcohol.

b. Neutral hydrogen peroxide. The reaction of neutral hydrogen peroxide with tri-n-butylborane, in equimolar proportions, gives a mixture of dimeric and monomeric hydrocarbons and alcohols (Equation 26).[38]



(26)

When the reaction mixture is treated further with excess alkaline hydrogen peroxide, an additional 34% n-hexanol, 1.6% n-dodecane, and 2.3% 2-hexanol are realized.[38] These results indicate that one boron-carbon bond is not cleaved by neutral hydrogen peroxide.[38] If the reaction is performed in carbon tetrachloride, 27.3% hexyl chloride is produced as one of the products.[38] Similarly, 25.8% hexyl iodide is detected when tetrahydrofuran solution containing iodine is used.[38] In both cases, a marked decrease in the amount of n-dodecane and 5-methylundecane and a noticeable increase in the alcohol products are observed.[38] Bigley and Payling suggest that these results indicate radicals are being formed during the reaction.[38] The formation of n-dodecane results via coupling of primary radicals, whereas formation of 5-methylundecane and 5,6-dimethyldecane occur via coupling of secondary radicals (tri-n-hexylborane contains approximately 7% of the 1-methylpentyl group).[38]

The reaction of alkylboranes containing secondary or tertiary boron-carbon bonds results in some cleavage of the third boron-carbon bond (addition of alkaline hydrogen peroxide only gave an additional 12.6% hexanol).[38] Analysis of the reaction mixture shows a definite increase in the amount of n-hexane and hexanols and drastic decrease in the formation of the dimeric species.[38] These results indicate that most of the n-hexane formation is attributed to H- abstraction and not radical disproportionation.[38] The following mechanism has been proposed (Equation 27).[38]

$$R_2B\text{-}OOH + R_3B \rightarrow R_2B\text{-}O\cdot + R\cdot + R_2B\text{-}OH$$

$$R_2B\text{-}O\cdot + H\text{-}OO\text{-}H \rightarrow R_2B\text{-}OH + \cdot O\text{-}O\text{-}H$$

$$R_2B\text{-}O\cdot + H\text{-}O\text{-}O\text{-}H \rightarrow R_2B\text{-}O_2H + \cdot OH \qquad (27)$$

$$R_3B - \cdot O\text{-}O\text{-}H \rightarrow R_2B\text{-}O_2H + R.$$

The production of alcohols is likely to arise from the attack of a hexyl radical on hydrogen peroxide or by combination with a hydroxyl radical.[38] However, Davies and Tudor reported that epimeric trinorbornylboranes react with equimolar amounts of aqueous hydrogen peroxide to produce epimeric norbornanols, which are structurally similar to the reactant norbornylboranes.[39] They conclude that a competition exists between the homolytic (norbornyl radical involvement) and heterolytic (polar process) processes, with the majority of the product arising from the latter process.[39]

3. Oxidation with Amine N-Oxides

The oxidation of trialkyl- and triarylboranes with anhydrous tertiary amine N-oxides (trimethylamine oxide and pyridine 1-oxide) occurs readily and yields the corresponding alkoxy- and aryloxyboranes (Equation 28).[40] Transesterfication of the borates with methanol

$$R_3B + 3 \text{ Amine oxide} \longrightarrow B(OR)_3 + 3 \text{ Amine} \qquad (28)$$

affords the alcohols in nearly quantitative yield.[40] In certain circumstances, oxidation with tertiary amine N-oxides is more desirable than peroxide oxidations. For example, some substituents on functionally substituted organoboranes may be sensitive to the harsh

basic conditions employed with alkaline hydrogen peroxide oxidation.[41] Oxidation of organoboranes with molecular oxygen causes some loss in stereospecificity.[29]

A mechanism has been proposed by Davies and coworkers for the tertiary amine N-oxide oxidation method, which is similar to the one accepted for the alkaline hydrogen peroxide oxidation of organoboranes (Equation 29).[42] This mechanism consists of a co-ordination of oxygen

$$R_3B + {}^{-}O\text{-}\overset{+}{N}(CH_3)_3 \rightleftharpoons \left[\begin{array}{c} R \\ | \\ R_2B\text{-}O\text{-}N(CH_3)_3 \end{array}\right]^{-} \rightarrow R_2B\text{-}OR + {:}NMe_3 \qquad (29)$$

to boron, forming the "ate complex," succeeded by 1,2-migration of the alkyl or aryl group from boron to oxygen.[42] The R_2B-OR species may then react further with amine oxide to form the trialkyl- or triaryloxyborane, $B(OR)_3$.

Although oxidation of organoboranes with anhydrous tertiary amine oxides appears to have great use as mild oxidizing reagents, there are drawbacks to their use. These reagents are wearisome to prepare and reported oxidation procedures specify hydrocarbon solvents (hydroboration reactions employ etheral solvents).[41]

Kabalka and coworkers have reported that trimethylamine N-oxide dihydrate (TMAO) is an exceptionally mild oxidizing reagent.[41] Unlike anhydrous amine N-oxides, TMAO is commercially available and is easier to handle.[41] This reagent provides for the nearly quantitative conversion of organoboranes to the corresponding alcohols, in yields

as good or better than those utilizing alkaline hydrogen peroxide.[41] A wide variety of functionalities remain unchanged after oxidation with this reagent.[41]

TMAO oxidation can be carried out in either ethereal or hydrocarbon solvents.[41,43] A variety of solvents may be used without affecting the rate of oxidation greatly, especially at higher temperatures.[43]

Oxidation with TMAO is temperature dependent.[43] This results in increased yields of alcohol with increasing temperature. For tri-n-hexylborane, the first alkyl group is readily removed at 25°C. However, the second and third groups require temperatures of 66° and 138°C, respectively.[43]

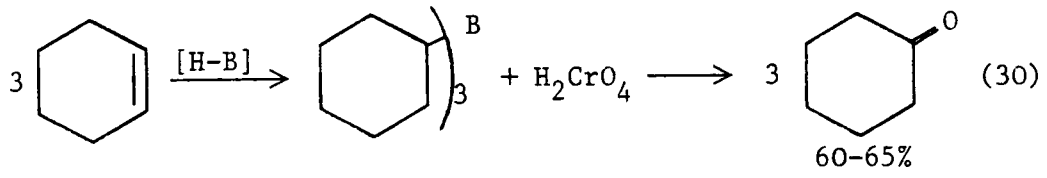
The general procedure for the TMAO oxidation method is very simple. To the organoborane, which is dissolved in a suitable solvent, is added TMAO. The solution is then heated under reflux for two hours, after which the product is isolated.[41]

4. Oxidation with Chromic Acid

It has been reported that conessine, 3β-dimethylamino-con-5-enine, is readily convertd to 3β-dimethylaminoconanin-6-one via hydroboration with sodium borohydride and aluminum chloride followed by oxidation, of the hydroborated conine derivative with chromic acid,[44] in the presence of aqueous acetic acid.[45] Organoboranes have been found to undergo protonolytic cleavage in the presence of acetic acid and other carboxylic acids, such as propionic acid and capyrlic acid,[46] but are relatively stable to aqueous mineral acids.[45]

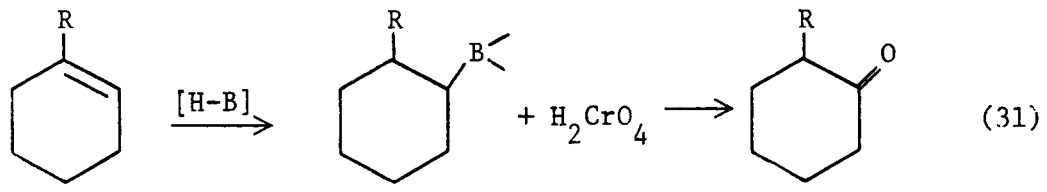
Brown and coworkers have reported that organoboranes are successfully converted to ketones by oxidation with aqueous 8N chromic acid (prepared with sodium dichromate dihydrate and concentrated sulfuric acid) in moderate to good yields.[45] The experimental procedure is simple and common hydroborating solvents are employed. Diethyl ether is the solvent of choice since it facilitates the isolation of ketones.[45] A representative procedure involves the slow addition of 10% excess aqueous 8N chromic acid to the organoborane followed by heating to reflux for two hours.[45]

The use of this reagent makes it possible to convert cyclic olefins, such as cyclohexene (Equation 30), to the corresponding



(30)

ketones.[45] Also, 2-alkyl- and 2-arylcycloalkanones are conveniently prepared by the hydroboration of 2-alkylcycloalkenes followed by oxidation with aqueous chromic acid (Equation 31).[45]

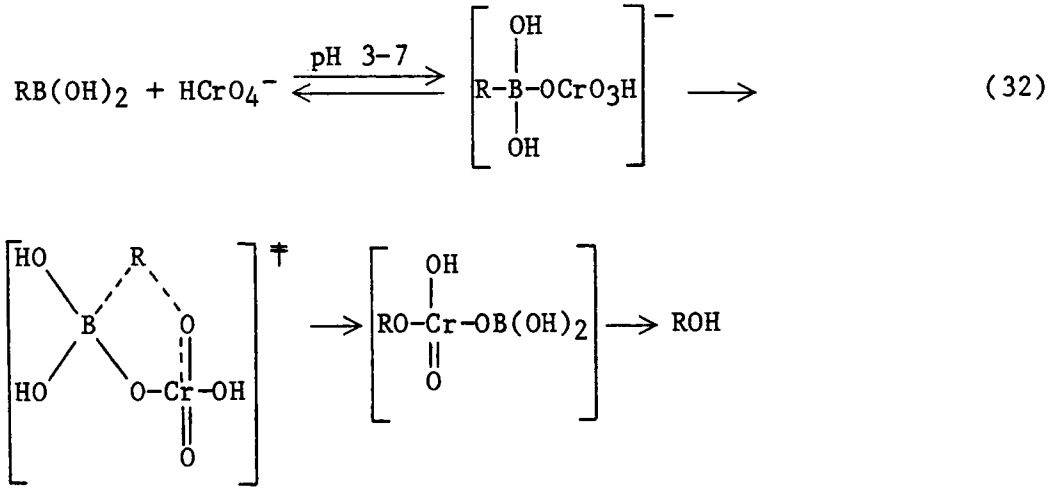


(31)

The rate of chromic acid oxidation has been investigated and found to be sensitive to the structure of the alkyl groups of the organoborane.[47] For instance, the second order rate constants in

0.114 M perchloric acid at 30°C are 7.5×10^{-2} (R=t-butyl), 6.6×10^{-4} (R=ethyl), and 2.4×10^{-7} liter/mole·sec (R = methyl).[47]

Mechanistic studies on chromic acid oxidation of alkylboranes have not been reported. However, studies on alkylboronic acids, ($RB(OH)_2$), have been performed.[47] Ware and Traylor showed that oxidation at pH values between 3 and 7 result in the formation of alcohols. Ketones are formed at lower pH values (2N acid).[47] The following mechanism has been proposed (Equation 32).[47]



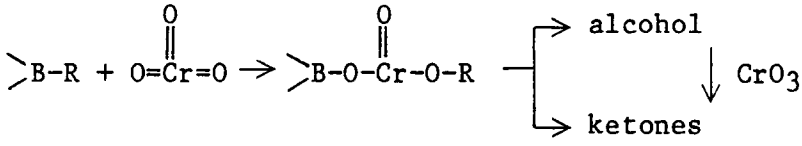
(32)

5. Oxidation with Pyridinium Chlorochromate

Pyridinium chlorochromate has been shown to oxidize organoboranes to the corresponding ketones and aldehydes in good yields.

In a preliminary report, Ramana Rao and coworkers presented a facile synthesis of ketones via a one-step oxidation or organoboranes, derived from cyclic alkenes, with pyridinium chlorochromate.[48] The anhydrous reaction conditions and easy workup procedures make this a convenient oxidation method.[48]

A tentative mechanism has been proposed for this reaction (Equation 33).[48] The oxidation probably progresses via the formation of alcohols, which are subsequently oxidized to ketones.[48]



(33)

It has been reported that pyridinium chlorochromate oxidation of organoboranes, derived from terminal olefins, conveniently affords the production of the corresponding aldehydes (Equation 34).[49] Since this

$$RCH = CH_2 \xrightarrow{BH_3 \cdot SMe_2} (RCH_2CH_2)_3B \xrightarrow{Py \cdot HCl \cdot CrO_3} RCH_2CHO \qquad (34)$$

reagent efficiently oxidizes borate esters to aldehydes and ketones,[49] the possibility of a one-step oxidation procedure seems conceivable. Indeed, organoboranes are oxidized directly by pyridinium chlorochromate to the corresponding aldehydes without isolation of any intermediates.[49] ^{11}B-NMR spectra of incomplete reaction mixtures shows that the oxidation proceeds via the initial formation of borate ester intermediates.[49]

This oxidation method provides for anhydrous reaction conditions, easy workup procedures, and high yield of aldehyde product.[49]

D. Statement of the Problem

Synthesis of oxygen-17 labeled alcohols are usually performed by hydrolysis of the appropriate acetals or ketals with oxygen-17 labeled water followed by reduction of the resulting oxygen-17 labeled carbonyl compound with lithium aluminum hydride or sodium borohydride.[50] Although this procedure allows for the production of simple oxygen labeled alcohols, in high yields, it has limitations in the synthesis of functionally substituted alcohols. A more desirable procedure would, therefore, result in high yields of products and tolerate a wide variety of functional substituents present in reactant molecules. The oxidation of organoborane intermediates with molecular oxygen has been shown to result in high yields of the corresponding alcohols containing a wide variety of functional substituents.

The synthesis of oxygen-17 enriched alcohols by the oxidation of organoboranes with a limited amount of oxygen-17 enriched molecular oxygen has advantages over procedures using excess or stoichiometric amounts of oxygen; the introduction of a limited quantity of oxygen allows for the full utilization of the oxygen-17 isotope. We decided to adapt the well-documented reaction of molecular oxygen with organoboranes for the synthesis of oxygen-17 enriched alcohols.

Two studies were conducted. The first involved the oxidation of trialkylboranes with a limited amount of isotopically normal molecular oxygen. This was done to standardize a procedure that was subsequently used for the incorporation of the oxygen-17 isotope into alcohols.

The second study was a preliminary investigation of improvements in the regioselectivity of the hydroboration reaction.

CHAPTER II

SYNTHESIS OF ISOTOPICALLY NORMAL ALCOHOLS

A. Results and Discussion

A representative series of functionally substituted alkenes, 1-decene(I), cyclohexene(II), 3-(3,4-methylenedioxyphenyl)-1-propene(III), 3-p-tolylthio-2-methyl-1-propene(IV) and methyl-10-undecenoate(V), were each hydroborated with BH_3-THF, the resulting organoborane oxidized with a limited quantity of isotopically normal molecular oxygen, and the reaction mixture treated with glacial acetic acid (Equation 35). The alcohol products were isolated via column

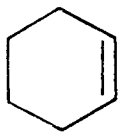
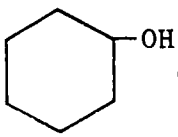
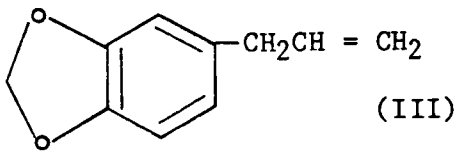
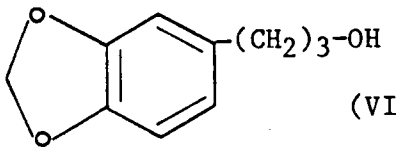
$$R\text{-}CH = CH_2 \xrightarrow[\text{ii) } O_2 \\ \text{iii) } H\ddot{O}Ac]{\text{i) } BH_3\text{:THF}} R\text{-}CH_2CH_2\text{-}OH \qquad (35)$$

chromatography and the percent yields calculated based on the quantity of oxygen introduced. The results are summarized in Table I.

Since less than a stoichiometric amount of oxygen was introduced to the trialkylborane solutions, some boron-carbon bonds remained unreacted. These bonds would presumably be oxidized during aqueous workup procedures in an air environment; this would result in artificially high yields of product. In order to circumvent this, glacial acetic acid was added to ensure protonolytic cleavage of any unreacted boron-carbon bonds.[46] Control experiments were performed to demonstrate that alcohol was formed only when oxygen was introduced to

TABLE I

PERCENT YIELDS OF ISOTOPICALLY NORMAL ALCOHOL PRODUCTS

Alkene[a]	Product[b]	% Yield[c]
$H_3C-(CH_2)_7-CH = CH_2$ (I)	$H_3C-(CH_2)_9-OH$ (VI)	93
 (II)	 (VII)	97
 (III)	 (VII)	78
$p\text{-}MeC_6H_4SCH_2C(CH_3)=CH_2$ (IV)	$p\text{-}MeC_6H_4SCH_2CH(CH_3)CH_2\text{-}OH$ (IX)	89
$CH_3OC(=O)\text{-}(CH_2)_8\text{-}CH = CH_2$ (V)	$CH_3OC(=O)(CH_2)_{10}\text{-}OH$ (X)	91

[a]The alkenes were converted into the corresponding trialkylboranes by hydroboration with BH_3-THF.

[b]The products contained small quantities of the secondary hydroxyl isomer.

[c]Isolated yields; yields are based on 2 mmoles of oxygen, theoretically, yielding 4 mmoles of alcohol.

the trialkylborane in a controlled manner. The results indicate that only insignificant quantities of alcohol (<10%) were formed unless oxygen was purposely added.

An additional set of experiments was performed to check the efficiency of the hydroboration reaction, workup procedure, and product isolation technique employed in this work. The hydroboration of 1-decene followed by alkaline hydrogen peroxide oxidation of the resulting tridecylborane was carried out. Isolation of the product via column chromatography indicated a 97% yield of decanol.

The isolated products (Table I) contained small quantities of the secondary hydroxyl isomer due to incomplete regiospecificity in the hydroboration stage. For example, comparison of the proton NMR (^{1}H-NMR) spectra recorded for the products obtained from both the hydroboration/ molecular oxygen oxidation sequence and oxymercuration-demercuration (regiospecific for the formation of the secondary isomer) of 3-(3,4-methylenedioxyphenyl)-1-propene(III) clearly showed that small quantities of the secondary hydroxyl isomer were present in the former case.

The oxidation of tridecylborane with both an excess and a stoichiometric amount of oxygen ($\geq$ 1.5 mmole O_2 per mmole R_3B) resulted in approximately 70% yield of decanol. Further oxidations with less than stoichiometric amounts of oxygen gave similar yields of decanol. These results are consistent with incomplete oxidation of the trialkylborane and corresponds to only two of three alkyl groups being converted to product (Equation 36). Thus, only two alkyl groups

$$R_3B \xrightarrow[\text{excess}]{O_2} (RO)_2BR \qquad (36)$$

readily migrate and are subsequently converted to the corresponding alcohol. Consequently, labeling experiments were designed to utilize two of the three R groups. The percent yields recorded in Table I (page 27) are therefore based on oxygen as the limiting reagent (1 mmole O_2 per mmole of R_3B).

During the development of this oxidation procedure, it was observed that a small amount of impurity was present in the isolated product. The ^{1}H-NMR spectra of the alcohol formed from the oxidation of tridecylborane showed a quartet at δ3.6 (H^1-NMR of pure 1-decanol shows a triplet at δ3.55). The product also burned with a green flame which indicates the presence of boron. Further oxidation of the isolated products with alkaline hydrogen peroxide resulted in pure 1-decanol being formed. These results indicate that the impurity was most likely decylboronic and/or decylborinic esters and/or peroxides which were produced during the reaction and were not efficiently separated during the chromatography. Refinement of the column chromatography, by using smaller percentages of ethyl acetate in petroleum ether, allowed for the isolation of pure 1-decanol free from the boron ester and/or peroxide impurities.

These results indicate that the formation of alcohol initially proceeds through alkyl borinic peroxide intermediates. This is in agreement with reported mechanistic data for the oxidation of

organoboranes with molecular oxygen (see Chapter I, page 12). The low yields obtained for the oxidation of tridecylborane with both an excess and stoichiometric amounts of oxygen can be rationalized based on the fact that the first boron-carbon bond is oxidized easier than the second, which is oxidized easier than the third (see Chapter I, page 11). The experimental conditions employed evidently did not allow for the complete oxidation of the third boron-carbon bond. This resulted in only two of the alkyl groups of the trialkylborane being converted to product.

B. Conclusion

The syntheses of isotopically normal alcohols were readily achieved by the reaction of trialkylboranes with a limited quantity of molecular oxygen. The alcohols were isolated in high yields.

C. Experimental

1. General

The alcohol products were isolated by column chromatography on 60-200 mesh silica gel (Davison Chemical). The solvent system employed was a mixture of petroleum ether and ethyl acetate. Thin layer chromatography on silica gel (2000 μL Fisher Uniplate) was utilized to indicate the eluent composition. ^{1}H-NMR spectra were recorded on a Varian T-60A spectrometer. The samples were dissolved in deuteriochloroform ($CDCl_3$, Aldrich Chemical Company), and tetramethylsilane (TMS) was used as the reference compound. Chemical shifts are reported in parts per million downfield from TMS.

The commercially available chemicals listed in Table II were used without further purification unless otherwise noted.

2. Procedures

a. Preparation of diborane.[10] A two-liter, three-necked, round-bottomed flask was equipped with a 500-mL pressure-equalizing dropping funnel, a mechanical stirrer with a mercury seal, and a Dry-Ice condenser fitted with a three-way stopcock exit port. The condenser exit leads to a mercury/acetone bubbler and two traps connected in series. A sintered-glass dispersion tube was inserted into a one-liter round-bottomed flask, which was equipped with a magnetic stirrer and a septum inlet leading to a mercury/acetone bubbler, and was connected to the exit port of the second trap. The entire apparatus was flame-dried while being flushed with dry nitrogen. While maintaining a nitrogen atmosphere, dry diglyme (500 mL) and sodium borohydride (1.9 moles, 74.1 g) were added to the three-necked flask, boron trifluoride etherate (2.5 moles, 315 ml) was added to the dropping funnel, and dry THF (1 liter) was added to the single-necked flask. The first trap was charged with sodium borohydride (1 g) and approximately 3 cm of diglyme, while the second trap was immersed in a Dry-Ice/acetone bath. The reaction was initiated by the dropwise addition of boron trifluoride etherate over a 4-5 hour period. A gentle stream of nitrogen was maintained until the generation of diborane had begun. After the addition was completed, the reaction mixture was heated to 60°C for one hour in order to drive the remaining diborane from the diglyme. The system was then flushed

TABLE II

GRADE, MANUFACTURER, AND METHODS OF PURIFICATION OF COMMERCIALLY AVAILABLE CHEMICALS

Chemicals	Grade[a]	Manufacturer[b]	Methods of purification[c]
Acetic acid, glacial, (CH_3COOH)	C	Fi	K
Boron dimethylsulfide, [$H_3B{:}S(CH_3)_2$]		Al	
Boron trifluoride etherate, [$(C_2H_5)O{:}BF_3$]		Al	I, J
Calcium hydride (CaH_2)		Al	
3-Chloro-2-methylpropene		Al	
Cyclohexene		Ea	
1-Decene		Al	I, J
Diethylene glycol dimethylether (diglyme)		An	F, H
Diethyl ether, (ether)	A,C	Fi	
Ethyl acetate, ($CH_3OOC_2H_5$)	C	Fi	
Hexadecane		Al	
1-Hexanol		Al	
2-Hexanol		ICN	
1-Hexene		Al	
Hydrogen peroxide, 30% (H_2O_2)	C	Fi	
Lithium aluminum hydride, ($LiAlH_4$)		Ve	
(+)-Longifolene		Ca	I, J
Magnesium sulfate	A,C	Fi	
Methanol	C	Fi	
Mercuric acetate, [$Hg(CH_3COOH)_2$]		Ba	
3-(3,4-Methylenedioxyphenyl)-1-propene, (Safrole)		Al	
Methyl-10-undecenoate		Ea	
Nitrogen gas	E	Li	
Oxygen	B	Li	
Oxygen-17 enriched oxygen, (20 atom %-^{17}O)		Me	
Petroleum ether, (ligroine)	D	Fi	I
Potassium hydroxide, (KOH)	C	Fi	
Sodium borohydride, ($NaBH_4$)		Fi	
Sodium carbonate, (Na_2CO_3)	C	Fi	
Sodium hydroxide, (NaOH)	C	Fi	
Tetrahydrofuran, (THF)	C	Fi	G, H
p-Tolylthiol		Al	

TABLE II (Continued)

[a]Grades: (A) = Anhydrous
(B) = Research grade
(C) = Certified ACS
(D) = Drum grade
(E) = Prepurified

[b]Manufacturers: (Fi) = Fisher Scientific Company
(Al) = Aldrich Chemical Company
(Ea) = Eastman Chemical Company
(An) = Ansul
(Ve) = Ventron
(Li) = Linde Specialty Gases
(Me) = Merck and Company, Inc.
(Ba) = C. P. Baker
(Ca) = Camphor and Allied Products, Ltd.
(ICN)= ICN Pharmaceuticals

[c]Methods of purification:
(F) = Predried over CaH_2
(G) = Predried over KOH then CaH_2
(H) = Distilled from $LiAlH_4$
(I) = Distilled from CaH_2
(J) = Distilled under reduced pressure
(K) = Deoxygenated by bubbling with dry N_2 gas

with nitrogen for one-half hour. The single-necked flask was removed under a stream of nitrogen and capped with a glass stopper. The mercury bubbler was removed and the septum inlet was capped with a rubber septum.

The concentration of the BH_3-THF solution was determined by hydrolyzing aliquots of the solution in a 50-50 mixture of glycerine and water. The amount of hydrogen evolved was measured using a gas buret. The molarity (M) of the BH_3-THF solution was calculated using the following equation (Equation 36):

$$M = \frac{(V_{H_2},\ L)(P_{bar} - P_{H_2O},\ atm)}{(V_{soln},\ L)(3\ moles\ H/mole\ BH_3)(0.082\ L\text{-}atm/mole\cdot deg)(T,\ ^\circ K)} \quad (36)$$

b. Preparation of 3-p-tolylthio-2-methylpropene.[41] Aqueous sodium hydroxide (50 ml, 6 N) was added to p-tolylthiol (0.3 mmoles, 24.2 g). The mixture was stirred at room temperature for four hours, after which the water was removed under reduced pressure. The residual salt was mixed with methanol (50 ml), treated with 3-chloro-2-methylpropene (0.3 mmoles, 27.5 g), and stirred overnight. The mixture was added to water (100 ml), and the product extracted with three aliquots of ether (50 ml each). The ether layer was dried over anhydrous magnesium sulfate and the product isolated by distillation: bp. 67° (0.3 mm Hg); ^{1}H-NMR ($CDCl_3$) δ1.8 (S, 3, CH_3-C = C), 2.2 (S, 3, CH_3-Ar), 3.4 (S, 2,-CH_2-S), 4.8 (broad s, 2, H_2C = C), 7.2 ($A'_2X'_2$, 4, ArH).

c. Hydroboration of alkenes with diborane. An oven-dried, 25-ml round-bottomed flask with a sidearm inlet, was equipped with a magnetic stirring bar, two rubber septums, and a gas outlet to a mercury bubbler. The flask was flame-dried while flushing with nitrogen. The appropriate alkene (9 mmoles) and a sufficient quantity of THF, to make an approximately 0.75 M solution, were added via oven-dried, nitrogen flushed syringes. The solution was cooled to 0°C by means of an ice-water bath, and stirring was initiated. The BH_3-THF (3 mmoles) was added dropwise via an oven-dried, nitrogen flushed syringe. After the addition was complete, the solution was allowed to stir under the conditions specified below.

Tri-n-decylborane. 1-decene(I) (9 mmoles, 1.71 ml) in 0.92 ml THF was hydroborated with BH_3-THF (3 mmoles, 1.37 ml of a 2.19 M solution). The mixture was stirred at 0°C for one-half hour and then allowed to warm to room temperature (25°C).

Tri-cyclohexylborane. Cyclohexene(II) (9 mmoles, 0.90 ml) in 1.72 ml THF was hydroborated with BH_3-THF (3 mmoles, 1.37 ml of a 2.19 M solution). The reaction was allowed to proceed at 50°C for three hours.

Tri-[3-(3,4-methylenedioxyphenyl)-1-propyl]borane (safrole). Safrole (9 mmoles, 1.33 ml) in 1.3 THF was hydroborated with BH_3-THF (3 mmoles,, 1.37 ml of a 2.19 M solution). The reaction mixture was stirred at 0°C for one-half hour and then stirred at room temperature (25°C) for two hours.

Tri-(3-p-tolylthio-2-methylpropyl)borane. 3-p-Tolylthio-2-methylpropene(IV) (9 mmoles, 1.61 ml) in 1.0 ml THF was hydroborated with BH_3-THF (3 mmoles, 1.37 ml of a 2.19 M solution). The reaction mixture was stirred at 0°C for one-half hour, and then stirred at room temperature (25°C) for one hour.

Tri-(methyl-11-undecyloate)borane. Methyl-10-undecenoate(V) (9 mmoles, 2 ml) in 0.63 ml THF was hydroborated with BH_3-THF (3 mmoles, 1.37 ml of a 2.19 M solution). The reaction mixture was stirred at 0°C for one-half hour and then stirred at room temperature (25°C) for one hour.

d. Oxidations of trialkylboranes with molecular oxygen. The trialkylborane solution (approximately 0.75 M), prepared via the hydroboration of the appropriate alkene, was cooled to 0°C by means of an ice-water bath and stirring was initiated. A nitrogen-flushed, rubber bladder gas reservoir was attached to the reaction flask to maintain the nitrogen atmosphere while accommodating temporary increases in pressure. Molecular oxygen (2 mmoles) was slowly added to the solution via a gas-tight syringe. After the addition was complete, the solution was allowed to stir at 0°C for 20 minutes. Deoxygenated glacial acetic acid (2.0 ml) was then added and the reaction mixture heated to 60°C for one hour. The mixture was cooled to room temperature (25°C), treated with saturated sodium chloride solution (10 ml), and extracted three times with anhydrous ether (50 ml aliquots). The ether layer was washed with sodium carbonate, dried

over anhydrous magnesium sulfate, reduced in volume, and the product isolated.

Decanol(VI). Tri-n-decylborane was prepared as described. The product (VI) was isolated via column chromatography: 0.588 g, 93% yield; ^{1}H-NMR ($CDCl_3$)δ0.9 (t, 3,-CH_3), 1.3(s, 16, -CH_2-), 3.25 (s, 1, -OH), 3.58 (t, 2, -CH_2OH).

Cyclohexanol(VII). Tricyclohexylborane was prepared as described. The product (VII) was isolated via column chromatography: 0.388 g, 97% yield; ^{1}H-NMR ($CDCl_3$)δ0.90-2.40 (broad m, 10, -CH_2-), 3.50 (m, 1, H-C(OH)-), 4.7 (s, 1, -OH).

3-(3,4-methylenedioxyphenyl)-1-propanol(VIII). Tri-[3-(3,4-methylenedioxyphenyl)-1-propyl]borane was prepared as described. The product (VIII) was isolated via column chromatography: 0.560 g, 78% yield; ^{1}H-NMR ($CDCl_3$) δ1.2 (t, 3,-CH_3), 1.8 (m, 2,-CH_2-), 2.55 (t, 2, ArCH_2-), 3.6 (t, 2,-CH_2O), 5.0 (s, 1, -OH), 5.8 (s, 2, OCH_2O), 6.6 (s, 3, ArH).

3-p-tolylthio-2-methyl-1-propanol(IX). Tri-(3-p-tolylthio-2-methyl-1-propyl)borane was prepared as described. The product (IX) was isolated via column chromatography: 0.633 g, 89% yield; ^{1}H-NMR ($CDCl_3$)δ1.0 (d, 3, -CH_3), 1.9 (broad m, 1, -CH), 2.3 (s, 3, ArCH_3), 2.9 [m(AB), 2, S-CH_2], 3.5 (s, 1, -OH), 3.55 (d, 2, -CH_2O), 7.2 ($A'_2X'_2$, 4, ArH).

Methyl-11-hydroxy-undecanoate(X). Tri(methyl-11-undecyloate) borane was prepared as described. The product (X) was isolated via column chromatography: 0.785 g, 91% yield; ^{1}H-NMR ($CDCl_3$) δ1.1-1.6

(broad s, 16, $-CH_2-$), 2.2 (t, 2, $-CH_2CO_2$), 3.4 (t, 2, $-\underline{CH_2}-OH$), 3.5 (s, 3, $-OCH_3$).

e. Oxidation of trialkylboranes with alkaline hydrogen peroxide. The trialkylborane, prepared via the hydroboration of the appropriate alkene, was cooled to 0°C by means of an ice-water bath. The reaction flask was vented to a mercury bubbler, and stirring was initiated. Aqueous sodium hydroxide (4 mmoles, 1.33 ml of a 3 N solution) was added, followed by the slow addition of 30% aqueous hydrogen peroxide (9 mmoles, 1.02 ml). After the addition was complete, the mixture was heated to 60°C for one hour. The mixture was then treated with saturated sodium chloride solution (10 ml) and extracted three times with anhydrous ether (75 ml aliquots). The ether layer was dried over anhydrous magnesium sulfate, the volume reduced, and the product isolated.

f. Oxymercuration-demercuration of alkenes.[51] A 50-ml round-bottomed flask, equipped with a magnetic stirrer, was charged with THF (14.0 ml), H_2O (7.0 ml) and mercuric acetate (10 mmoles, 3.2 g). The mixture was treated with the appropriate alkene (10 mmoles) at room temperature (25°C). After 10 minutes, aqueous sodium hydroxide (10 ml of a 3 N solution) was added, followed by the addition of sodium borohydride in 3 N sodium hydroxide (10 ml of a 0.5 M solution). The reaction mixture was stirred for 15 minutes, filtered, washed with saturated sodium chloride, extracted three times with anhydrous ether, dried over anhydrous magnesium sulfate, and the volume reduced.

g. Control experiment. The trialkylborane, prepared via the hydroboration of the appropriate alkene, was cooled to 0°C by means of an ice-water bath. The reaction flask was vented to a nitrogen-flushed, rubber bladder gas reservoir, and stirring was initiated. Deoxygenated glacial acetic acid (2 ml) was added and the reaction mixture heated to 60°C for one hour. After cooling to room temperature (25°C), the solution was treated with saturated sodium chloride solution (10 ml) and extracted three times with ether. The ether layer was washed with sodium carbonate, dried over anhydrous magnesium sulfate, and reduced in volume. The material obtained was isolated via column chromatography.

CHAPTER III

SYNTHESIS OF OXYGEN-17 ENRICHED ALCOHOLS

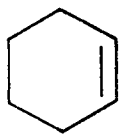
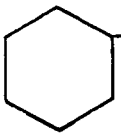
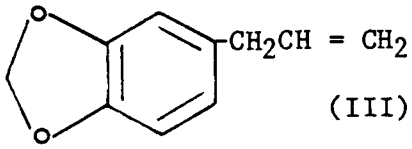
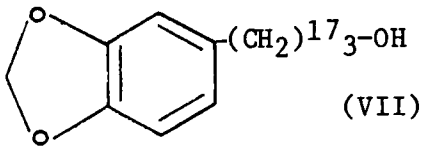
A. Results and Discussion

The series of alkenes employed for the synthesis of the corresponding isotopically normal alcohols (Chapter II, page 26) were also used for the synthesis of the corresponding oxygen-17 enriched alcohols. Each alkene was hydroborated with BH_3-THF, the resulting trialkylborane was then oxidized with a limited quantity of oxygen-17 enriched molecular oxygen, and the mixture treated with deoxygenated glacial acetic acid. The alcohol products were isolated by column chromatography and the percent yields calculated based on the amount of oxygen introduced (i.e., 2 mmoles O_2 would yield 4 mmoles alcohol). The results are summarized in Table III.

Oxygen-17 NMR measurements were performed on each isolated product and the oxygen-17 chemical shifts summarized in Table IV. (Oxygen-17 NMR spectra were also recorded on the isotopically normal alcohols reported in Chapter II (page 26). In the normal alcohols, no oxygen-17 peak was realized.) The ^{1}H-NMR spectra (Figure 1), the carbon-13 NMR spectra (Figure 2), and the oxygen-17 NMR spectra (Figure 3) for oxygen-17 enriched decanol(XI) are provided for comparison purposes. The oxygen-17 NMR spectrum exhibits broad lines. This is due to the large nuclear quadrupole moment associated with the oxygen-17 isotope ($I = 5/2$).[52]

TABLE III

PERCENT YIELDS OF OXYGEN-17 ENRICHED ALCOHOL PRODUCTS

Alkene[a]	Product[b]	% Yield[c]
$H_3C-(CH_2)_7-CH = CH_2$ (I)	$H_3C-(CH_2)_9{}^{17}-OH$ (VI)	93
 (II)	 (XII)	90
 (III)	 (VII)	76
$p-MeC_6H_4SCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}} = CH_2$ (IV)	$p-MeC_6H_4SCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2{}^{17}-OH$ (XIV)	92
$CH_3O\overset{\displaystyle O}{\overset{\Vert}{C}}-(CH_2)_8-CH = CH_2$ (V)	$CH_3O\overset{\displaystyle O}{\overset{\Vert}{C}}-(CH_2)_{10}{}^{17}-OH$ (XV)	96

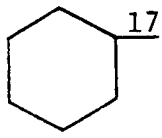
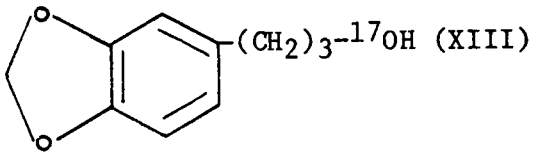
[a]The alkenes were converted into the corresponding trialkylboranes by hydroboration with BH_3-THF.

[b]The products contained small quantities of the secondary hydroxyl isomer.

[c]Isolated yields; yields based on 2 mmoles of oxygen, theoretically yielding 4 mmoles of alcohol.

TABLE IV

OXYGEN-17 CHEMICAL SHIFTS FOR OXYGEN-17 ENRICHED ALCOHOL PRODUCTS

Products	^{17}O-Chemical Shifts[a]
$H_3C-(CH_2)_9-{}^{17}OH$ (XI)	-1.0
 (XII)	+33.3
 (XIII)	-3.6
$p\text{-}MeC_6H_4SCH_2C(CH_3)CH_2-{}^{17}OH$ (XIV)	-11.5
$H_3COC-(CH_2)_{10}-{}^{17}OH$ (XV)	-2.2

[a]NMR spectra were obtained on a JEOL FX-90Q spectrometer; products were dissolved in acetone-d_6 [$\delta(^{17}O)$ 572] and referenced to $H_2{}^{17}O$.

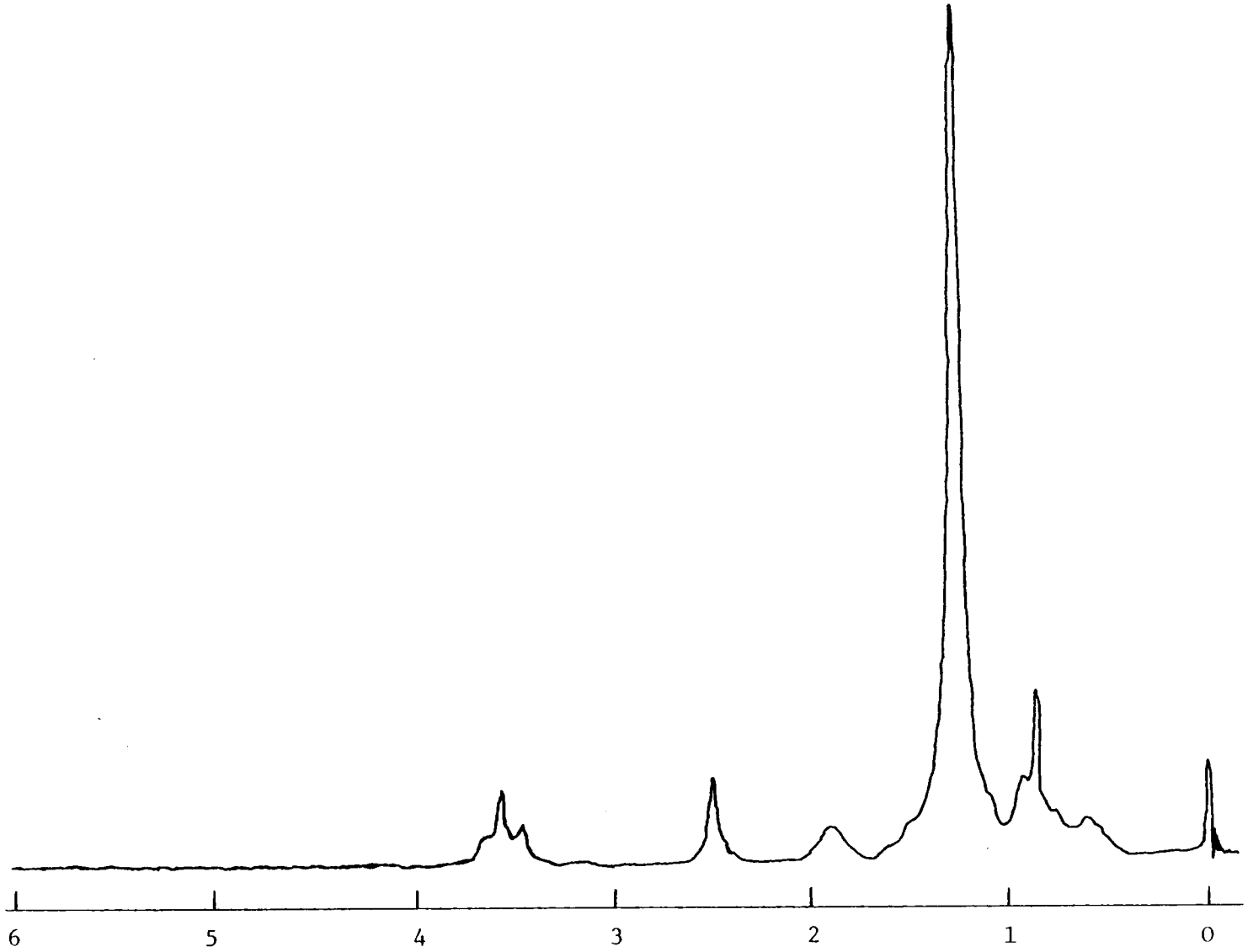


Figure 1. Proton NMR spectra for oxygen-17 enriched decanol.

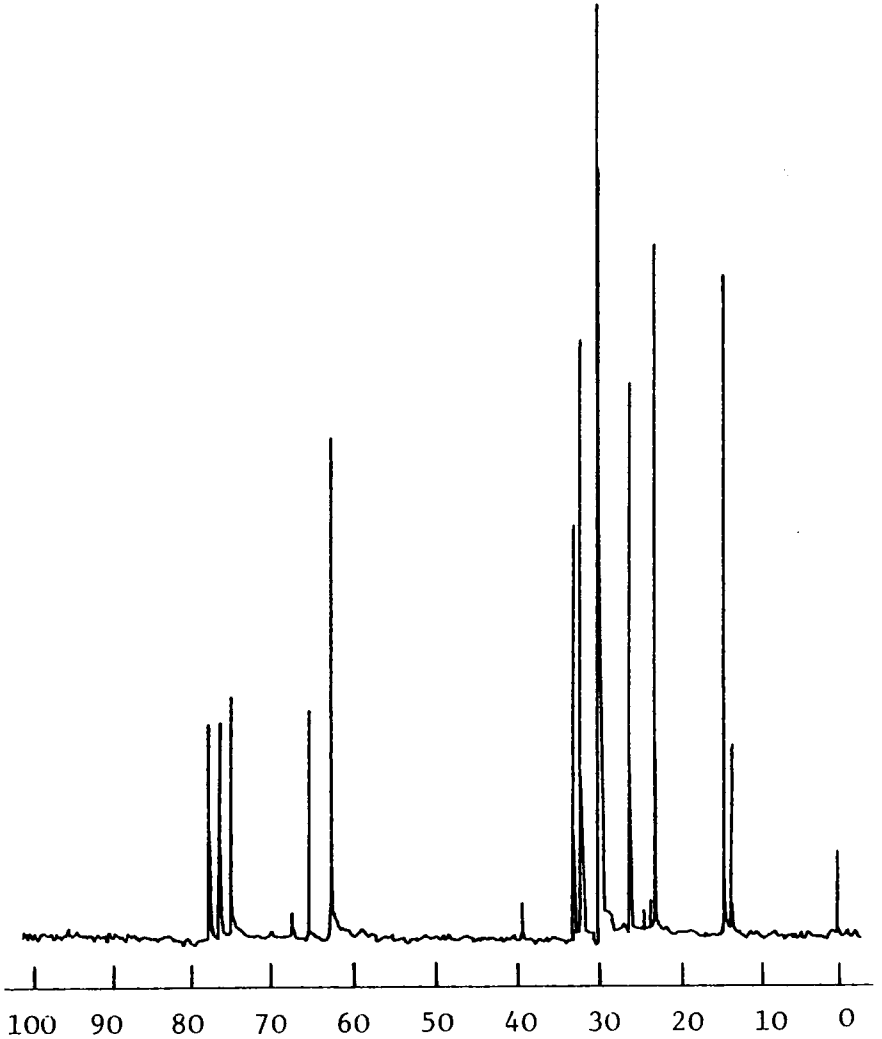


Figure 2. Carbon-13 NMR spectra for oxygen-17 enriched decanol.

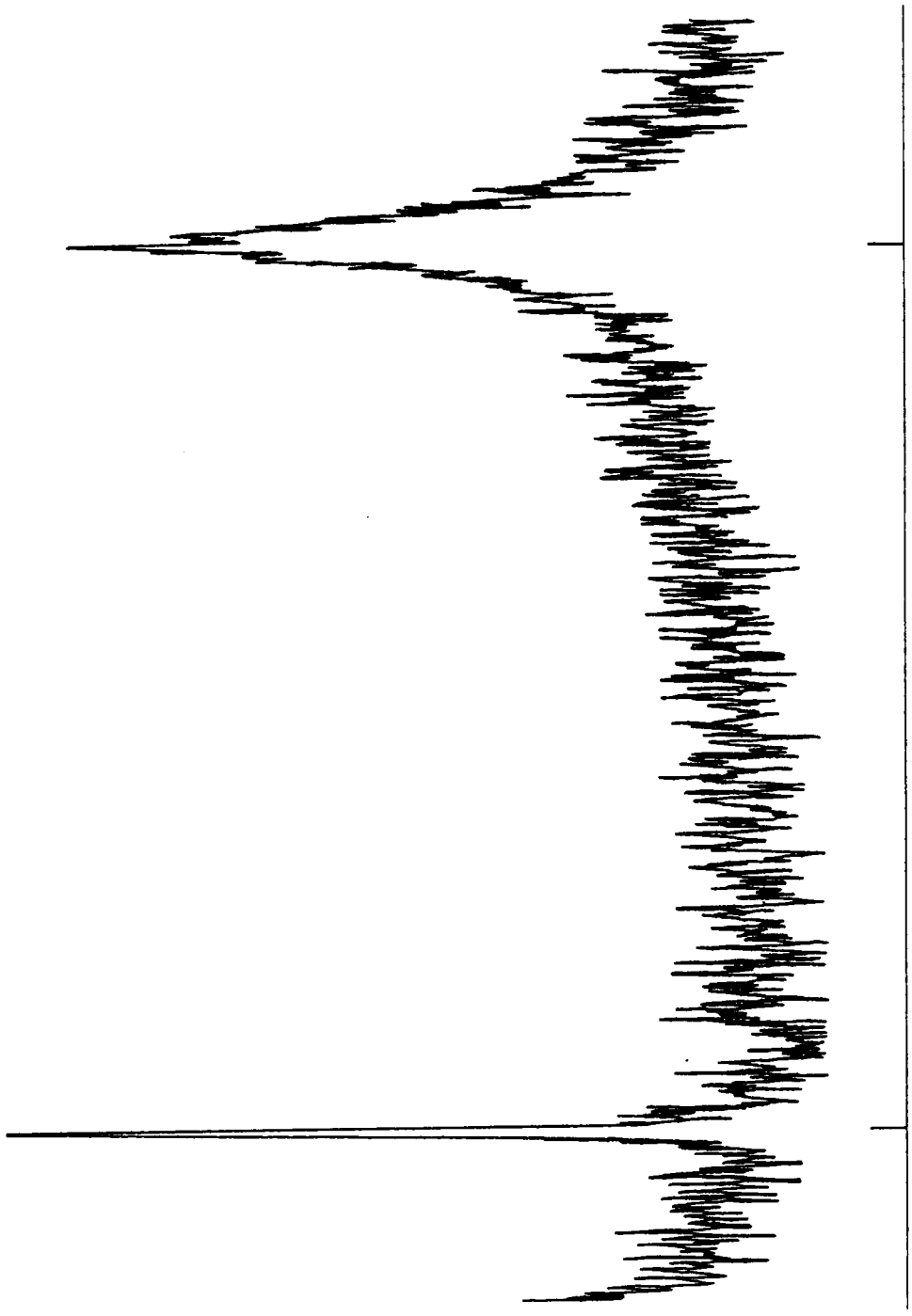


Figure 3. Oxygen-17 NMR spectra for oxygen-17 enriched decanol.

It has been reported that oxygen-17 NMR characteristics of the hydroxyl group depend on the structure of the molecule.[53] The magnitude of oxygen-17 chemical shifts (positive values represent downfield shifts relative to the reference; negative values represent upfield shifts) are influenced by the type and position of substituents groups in the molecule. This is known as the substituent chemical shift concept and is widely used to relate perturbations in chemical shifts with structural changes at various positions in a molecule.[53]

For a series of substituted methanols (MeOH, $MeCH_2OH$, Me_2CHOH, Me_3COH), the introduction of each methyl substituent results in deshielding about the oxygen atom. This produces a downfield chemical shift in the oxygen-17 NMR with addition of each methyl group. This effect is typical for β substitutions and is known as the β-effect.[53]

The successive introduction of methyl substituents, at the β-carbon of ethanol, increases shielding. This is known as the γ-effect and produces upfield chemical shifts with each substituent addition.[53] This effect is rationalized in terms of 1,4-gauche interactions; with increased gauche interactions between the hydroxyl group and the methyl group, increased shielding is displayed.[53]

The downfield chemical shift in the oxygen-17 NMR of cyclohexanol can also be rationalized based on γ interactions. Due to the rigid nature of the cyclohexane ring, the hydroxyl group of cyclohexanol is not involved with gauche interactions and has a similar chemical shift to isopropyl alcohol which contains no γ substituents.[53]

δ-Alkyl groups do not generally cause significant changes in oxygen-17 chemical shifts of alcohols.[53] The introduction of heteroatomic substituents on the γ-carbon of alcohols causes shielding, which is usually larger than that of methyl substituents.[53]

The oxygen-17 chemical shifts reported in Table IV (page 42) are consistent with literature values. The chemical shift obtained for decanol(XI) is essentially the literature value reported for hexanol[$\delta(^{17}O)$-0.8].[53] Both of these alcohols contain δ-alkyl substituent groups. A chemical shift value for cyclohexanol [$\delta(^{17}O)$ + 36] has been reported in the literature.[54] The value obtained for cyclohexanol(XII) is in good agreement with the literature value. The chemical shift obtained for 3-p-tolylthio-2-methyl-1-propanol(XIV) can be rationalized based on the combined β-methyl substituents, and γ-heteroatom (presence of sulfur atom on the γ-carbon) effects, which both cause shielding. For 3-(3,4-methylenedioxyphenyl)-1-propanol(XIII), the presence of the aryl group at the γ-carbon results in shielding. The chemical shift for methyl-11-hydroxy-undecanoate(XV) is mainly due to δ-alkyl effect. The ester function has little effect because of the distance between it and the hydroxyl group.

B. Conclusion

The reaction of trialkylboranes with a limited quantity of oxygen-17 enriched molecular oxygen is a convenient synthetic procedure for the production of oxygen-17 enriched alcohols.

Oxygen-17 NMR measurements indicated that the isotope had been successfully incorporated into the alcohol products in all cases.

C. Experimental

1. General

The oxygen-17 enriched alcohol products were isolated by column chromatography (see Chapter II, page 30). Oxygen-17 NMR spectra were obtained at 12.11 MHz on a JEOL FX-90Q pulse FT-NMR spectrometer. The products were dissolved in acetone-d_6[$\delta(^{17}O)$ 572] (Aldrich Chemical Company), in a 10-mm tube, and referenced to $H_2{}^{17}O$ [$\delta(^{17}O)$ 0.0]. The chemical shifts (Table IV, page 42) are reported in parts per million. Carbon-13 NMR spectra were obtained on a Joel FX-90Q pulse FT-NMR spectrometer. The samples were dissolved in deuteriochloroform and referenced to tetramethylsilane. ^{1}H-NMR spectra were also obtained for each product on a Varian T-60A spectrometer (Chapter II, page 30).

The commercially available chemicals used are listed in Table II (Chapter II, page 32).

2. Procedures

a. Preparation of diborane. The procedure is outlined in Chapter II (page 31).

b. Preparation of 3-p-tolylthio-2-methyl-1-propene. The procedure is outlined in Chapter II (page 34).

c. Hydroboration of alkenes with diborane. The procedure is outlined in Chapter II (page 35).

d. Oxidation of trialkylboranes with oxygen-17 enriched molecular oxygen. The trialkylborane solution, prepared via the hydroboration of the appropriate alkene, was cooled to 0°C by means of an ice-water bath, and stirring was initiated. A nitrogen flushed, rubber bladder gas reservoir was attached to the reaction flask to maintain the nitrogen atmosphere and accommodate temporary increases in pressure. Oxygen-17 enriched molecular oxygen gas (2 mmoles of a 2:1 mixture of isotopically normal molecular oxygen and oxygen-17 enriched molecular oxygen) was slowly added to the solution via a gas-tight syringe. After the addition was complete, the solution was allowed to stir at 0°C for 20 minutes. Deoxygenated glacial acetic acid (2.0 ml) was then added and the reaction mixture heated to 60°C for one hour. The mixture was cooled to room temperature (25°C), treated with saturated sodium chloride solution (10.0 ml), and extracted three times with anhydrous ether (50 ml aliquots). The ether layer was washed with sodium carbonate, dried over anhydrous magnesium sulfate, reduced in volume, and the product isolated.

Decanol(XI). Tri-n-decylborane was oxidized as described. The product (XI) was isolated via column chromatography: 0.588 g, 93% yield; ^{17}O-NMR $\delta(^{17}O)$-1.0; ^{1}H-NMR (see Chapter II, page 37); ^{13}C-NMR($CDCl_3$)δ14.3 ($-CH_3$), 22.9 ($CH_3\underline{C}H_2-CH_2-$), 26.0 ($-\underline{C}H_2CH_2CH_2-OH$), 29.9 ($-(CH_2)-_4$), 32.1 ($CH_3CH_2\underline{C}H_2-$), 33.0 ($-\underline{C}H_2CH_2-OH$), 63.1 ($CH_2OH$).

Cyclohexanol(XII). Tricyclohexylborane was oxidized as described. The product (XII) was isolated via column chromatography: 0.354 g, 90% yield; ^{17}O-NMR$\delta(^{17}O)$ + 33.3, ^{1}H-NMR (see Chapter II, page 37).

3-(3,4-methylenedioxyphenyl)-1-propanol (XIII). Tri-[3,4-methylenedioxyphenyl)-1-propyl] borane was oxidized as described. The product (XIII) was isolated via column chromatograph: 0.547 g, 76% yield; ^{17}O-NMR$\delta(^{17}O)$ - 3.6, ^{1}H-NMR (see Chapter II, page 37).

3-p-tolylthio-2-methyl-1-propanol(XIV). Tri-(3-p-tolylthio-2-methyl-1-propyl)borane was oxidized as described. The product (XIV) was isolated via column chromatography: 0.652 g, 92% yield; ^{17}O-NMR $\delta(^{17}O)$-11.5, ^{1}H-NMR (see Chapter II, page 37).

Methyl-11-hydroxy-undecanoate(XV). Tri-(methyl-11-undecyloate) borane was oxidized as described. The product (XV) was isolated via column chromatography: 0.835 g, 96% yield; ^{17}O-NMR$\delta(^{17}O)$-2.2, ^{1}H-NMR (see Chapter II, page 37).

CHAPTER IV

PRELIMINARY INVESTIGATION OF IMPROVEMENTS IN REGIOSPECIFICITY OF THE HYDROBORATION REACTION

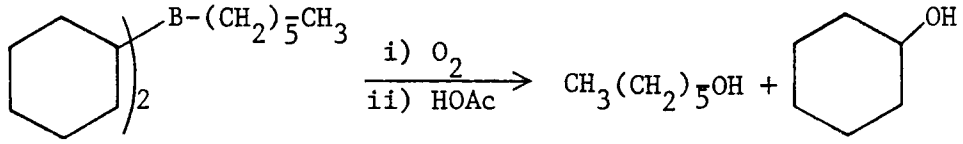
A. Background

The reaction of oxygen-17-enriched molecular oxygen with trialkylboranes has been shown to be an excellent method for preparing oxygen-17 labeled primary alcohols (Chapter III, page 40). However, the products are often contaminated with traces of the secondary alcohol due to the incomplete regiospecificity of the hydroboration reaction (Equation 37).

$$[CH_3(CH_2)_4CH_2]_3B \xrightarrow[HOAc]{^{17}O_2} CH_3(CH_2)_5{}^{17}OH + CH_3(CH_2)_3\underset{\text{trace}}{\overset{|}{{}^{17}C}}HCH_3 \qquad (37)$$

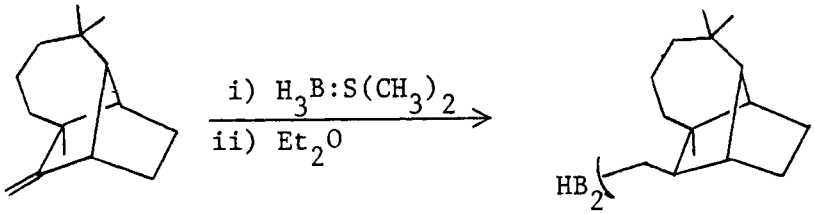
The regiospecificity of the hydroboration of olefins can be improved by using hydroboration agents that specifically allow for the placement of the boron atom at the terminal carbon. Oxidation of the resulting organoboranes produces oxidation products in high isomeric purity (Chapter I, page 7). A procedure developed to synthesize isotopically enriched alcohols, in high isomeric purity, would be advantageous, because it would eliminate the secondary hydroxyl isomer; this would more efficiently utilize the oxygen-17 isotope.

Unfortunately, the boron reagents currently available (Chapter I, page 8) contain boron atoms attached to secondary and tertiary carbon atoms. Since the oxidation reaction is a free radical process, these secondary and tertiary carbons would be expected to compete effectively for the oxygen (Equation 38).



(38)

It has been reported that readily available (+)-longifolene is an effective hydroborating agent.[55] Hydroboration of longifolene with borane dimethylsulfide stops at the dialkyl stage due to the large steric requirements of the molecule (Equation 39).[55] The longifolene



(39)

molecule contains an exo-methylene double bond so that the boron atom attaches to a primary carbon atom in the hydroboration stage.[55] This is unique. Other regiospecific hydroborating agents, such as 9-BBN (Chapter I, page 8), contain boron atoms attached to secondary carbons. Since longifolene contains a substituted bicyclo-[2.2.1]-heptane structure with a large bridge head shielding the exo-face of the double bond, hydroboration proceeds exclusively from the less hindered endo side.[55]

We felt that dilongifolylborane might be an effective regio-specific hydroborating agent which could be useful for oxygen-17 incorporation. The steric bulk of the longifolene groups should direct the boron atom to the most open site of the alkene being hydroborated. Further, the resultant organoborane might yield the least hindered alcohol product during oxidations.

B. Results and Discussion

The alkene, 1-hexene, was hydroborated with dilongifolylborane followed by oxidation of the resulting organoborane with alkaline hydrogen peroxide. Gas chromatographic (GC) analysis of the reaction mixture indicated an overall yield (95%) of 1-hexanol in >99.9% isomeric purity.

The sensitivity of the GC was established by analyzing 0.1 M, 0.01 M, 0.001 M, and 0.0001 M solutions of 2-hexanol. It was determined that 0.001 mmoles of 2-hexanol could be detected on the GC.

The percent of 2-hexanol present in the reaction mixture was determined as follows. A GC analysis was performed on the reaction mixture. At high attenuation, a very small 2-hexanol peak was indicated. The reaction mixture was charged with 0.0001 mmoles of 2-hexanol (1 ml of a 0.0001 M solution). GC analysis indicated that the 2-hexanol peak area was not changed. Addition of 0.001 mmoles of 2-hexanol (1 ml of 0.001 M solution) resulted in the increase of the 2-hexanol peak area. This corresponded to approximately 0.1% 2-hexanol present in the reaction mixture.

C. Conclusion

These preliminary results indicate that the hydroboration of alkenes with dilongifolylborane followed by oxidation of the resulting organoborane, is a convenient synthetic method for the production of alcohols in high isomeric purity. The use of dilongifolylborane in

the synthesis of oxygen-17 enriched alcohols could result in isomerically pure products.

D. Experimental

1. General

Gas chromatographic analysis was performed on a Varian Model 1700 dual column instrument utilizing a 1.8 x 1/4 in. 10% Carbowax, C-20M on Chromosorb W column. Hexadecane was used as the internal standard. GC's of 1- and 2-hexanol standards were performed to authenticate reaction product peaks. Melting point measurements were taken on a Laboratory Devises Mel-Temp. utilizing standard thermometers.

The commercially available chemicals used are listed in Table II (page 32).

2. Procedures

a. Preparation of dilongifolylborane.[55] A 100-ml round-bottomed flask was flame-dried while flushing with nitrogen. After cooling, borane dimethylsulfide (50 mmoles, 5.25 ml) and anhydrous ether (46.4 ml) were added to the flask via dry, nitrogen flushed syringes, and stirring was initiated. The mixture was cooled to 0°C by means of an ice-water bath, and (+)-longifolene (108 mmoles, 23.6 ml) was added dropwise. The mixture was allowed to stand at 25°C for 24 hours. The dilongifolylborane crystallized as a heavy white solid. The solid was washed with anhydrous ether and filtered in a sintered glass filter

funnel under a nitrogen atmosphere. The dilongifolylborane (m.p. 150-153°C) was isolated (10.1 g, 48%), and stored under nitrogen.

b. Preparation of hexyl(dilongifolyl)borane. A 50-ml round-bottomed flask was flame-dried while flushing with nitrogen. The flask was charged with 10% excess dilongifolylborane (1.4 mmoles, 0.59 g) and THF (6 ml). The mixture was cooled to 0°C by means of an ice-water bath and stirring was initiated. 1-hexene (1.3 mmoles, 0.16 ml) was added dropwise and the mixture stirred at 25°C overnight.

c. Oxidation of hexyl(dilongifolyl)borane. The trialkylborane, prepared as described above, was cooled to 0°C by means of an ice-water bath and stirring was initiated. The solution was treated with aqueous sodium hydroxide (4.4 mmoles, 1.4 ml of a 3 M solution), followed by addition of hydrogen peroxide (5.6 mmoles, 0.64 ml of a 30% solution). The solution was allowed to stir at 25°C for one hour; GC anlaysis indicated a 95% yield of 1-hexanol in >99.9% isomeric purity.

CHAPTER V

SUMMARY AND CONCLUSIONS

A convenient method for the synthesis of oxygen-17 enriched alcohols has been presented in this work. The reaction of a limited quantity of oxygen-17 enriched molecular oxygen with trialkylboranes results in high yields of labeled alcohols. The reaction tolerates a wide range of functional substituents.

Future applications of this procedure include the synthesis of radioactive isotopically labeled compounds. Preliminary studies are planned for incorporation of oxygen-15 (half life of 124 seconds)[56] into molecules via the reaction of organoboranes with a limited quantity of oxygen-15 enriched molecular oxygen gas.

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