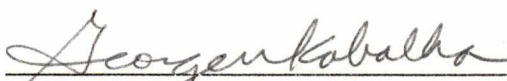
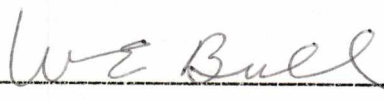


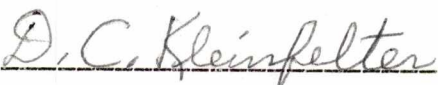
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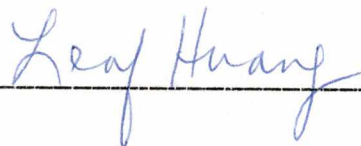
I am submitting herewith a dissertation written by Zhe Wang entitled "Synthesis of Amines via Organoborane Chemistry." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirement for the degree of Doctor of Philosophy, with a major in Chemistry.


George W. Kabalka, Major Professor

We have read this dissertation
and recommend its acceptance:







Accepted for the Council:



Associate Vice Chancellor
and Dean of The Graduate School

SYNTHESIS OF AMINES VIA ORGANOBORANE CHEMISTRY

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Zhe Wang

May 1991

DEDICATION

I wish to dedicate this work to the Chinese youths who sacrificed themselves for the future of China.

I also wish to dedicate this work to my parents, Zhen Wang (王真) and Qi Jiang (蒋琦) who provided me with a fully loving family atmosphere and invaluable educational opportunities. I wish further to dedicate this work to my wife, Dr. Xian-Jun Meng (孟宪君), and my son, Meng-Xin Wang (王孟辛) for their love, sacrifice and support during this work. Finally, I wish to dedicate this work to my sisters, Yin Wang (王颖), Rui Wang (王芮), Peng Wang (王萍) and Jue Wang (王珏) for their many years of steadfast support and encouragement.

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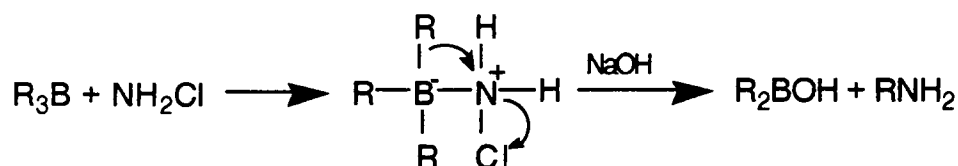
I also wish to express my thanks to Professor Du Li (Chairman of the Chemistry Department at Lanzhou University) who provided me with the opportunity to study at U.T. as an exchange student.

I would like to thank the faculty of the Department of Chemistry of The University of Tennessee for their help and assistance during my Ph.D. study and to Dr. Edward Buonocore (Chairman of the Radiology Department at the University of Tennessee Medical Center in Knoxville) for the opportunity to carry out my radiopharmaceutical research. A warm acknowledgement is also extended to Dr. Gary. W. McCollum for his hospitality at the time I first joined Dr. Kabalka's research group.

ABSTRACT

Organoboranes have proven to be valuable in organic synthesis. They are readily available due to the facile reaction of olefins, dienes and acetylenes with a variety of hydroborating agents. In addition to their ready availability, the organoboranes tolerate a wide variety of functional groups and exhibit defined reaction stereospecificity which has resulted in a number of new syntheses.

The boron atom in organoboranes can be readily converted into a wide variety of organic functional groups under mild conditions via stereospecific rearrangements. Many of the borane rearrangements involve anionotropic rearrangements of appropriately substituted organoborate complexes; generally, an alkyl group migrates from an organoborate complexes; generally, an alkyl group migrates from an electron-rich atom to an electron-deficient neighboring atom. The reaction has been used to prepare a large variety of organic molecules including those in which the migration terminus is a nitrogen atom.



The nature of the leaving groups and the groups attached to nitrogen have been varied extensively. Chloramine has been shown to be one of the best amination reagents but its use in amination reactions

is complicated by the fact that it is difficult to prepare and it is unstable. Amination reactions are also complicated by the fact that simple hydroboration reactions are regioselective but not regiospecific which often leads to isomeric mixtures.

Solutions to these problems are presented in this thesis; they involve the *in situ* generation of chloramine and/or alkylchloramines and the utilization of regiospecific hydroborating agents. These methods have been developed and successfully applied to the syntheses of dialkylamines, isomerically pure primary and secondary amines, diamines and amino acids. As a part of a continuing program involving the syntheses of nitrogen-13 labeled amino derivatives as diagnostic agents for positron emission tomography, we extended the new, convenient, and easy to manipulate, one-pot amination reaction to the syntheses of isomerically pure nitrogen-13 labeled diamines and amino acids.

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Chapter I

Synthetic Applications of Organoboranes

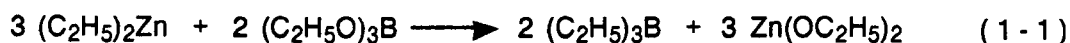
Introduction:

The research described in this dissertation is focused on the development of a rapid, convenient, easy to manipulate, one-pot reaction methodology to aminate organic compounds via organoborane chemistry. A variety of organic transformation strategies are discussed: (a) the syntheses of secondary amines via trialkylborane precursors; (b) the syntheses of isomerically pure primary and secondary amines through dimethylborane precursors; (c) the syntheses of isomerically pure diamines; and (d) the syntheses of isomerically pure amino acids. A detailed review of borane chemistry is beyond the scope of this dissertation; the area has been summarized in several excellent books^{1,2,3,4,5,6} and a number of outstanding reviews^{7,8,9,10,11,12,13}. However, a brief description of organoborane chemistry will provide the appropriate background for this dissertation.

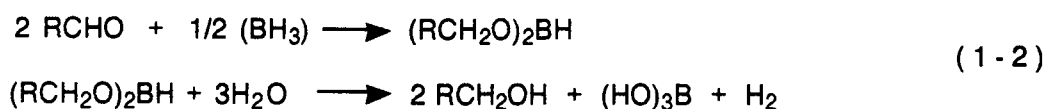
Section 1. The Development of Borane Chemistry.

A. Historical.

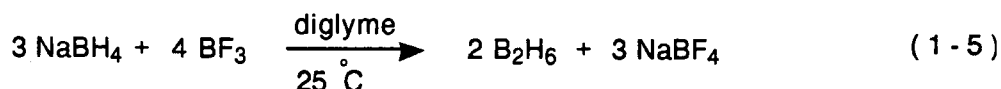
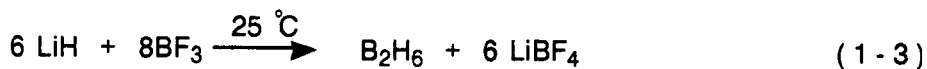
Organoboranes were first synthesized by Frankland in 1859 using the reaction of dialkylzinc compounds with triethoxyborane^{14,15} (1-1). He



discovered that the products from this reaction were stable to water and flammable in air. During the period 1910-1930, the hydrogen borane compounds, such as B_2H_6 , B_4H_{10} , B_5H_{11} and $\text{B}_{10}\text{H}_{14}$, were isolated by Alfred Stork¹⁶. Subsequently, it was observed that aldehydes and ketones reacted rapidly with diborane to give alkoxyboranes which produced the corresponding alcohols on hydrolysis¹⁷⁽¹⁻²⁾. However, the boron hydrides

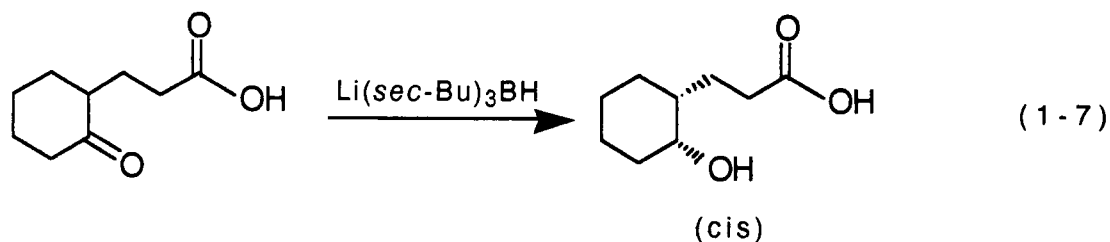
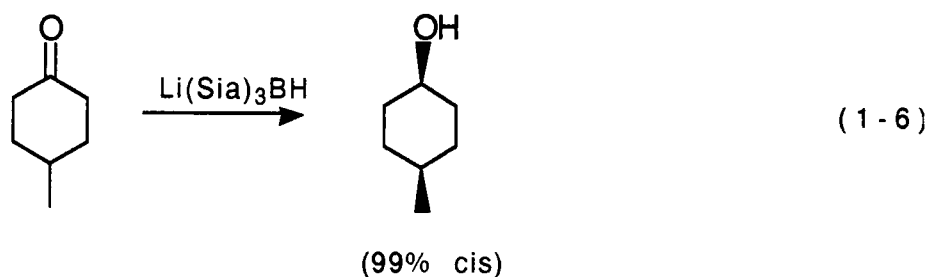


remained of little interest to chemists due to their lack of availability. Over the period 1940-1945, H. I. Schlesinger, H. C. Brown, and their co-workers developed convenient procedures for the preparation of diborane and sodium borohydride¹⁸ (1-3), (1-4), (1-5).



Subsequent studies using sodium borohydride established it as an alternative reducing agent to lithium aluminium hydride¹⁹. The former is a very gentle reducing agent, readily reducing only aldehydes, ketones and acid

chlorides, whereas the latter is a most powerful reducing agent, rapidly reducing the great majority of organic functional groups. In order to achieve selective reducing agents whose reactivity fell between the two extremes, other metal borohydride^{1,6,9} were developed; their reactivity fell in the following order $\text{NaBH}_4 < \text{LiBH}_4 < \text{Mg}(\text{BH}_4)_2 < \text{Al}(\text{BH}_4)_3$. There was also a need for sterically controlled reducing reagents and these were developed by introducing large organic reagents such as $\text{Li}(\text{sec-Bu})_3\text{BH}$ and $\text{Li}(\text{Sia})_3\text{BH}$. These reagents now make sterically controlled reductions possible^{9,20}(1-6, 1-7).

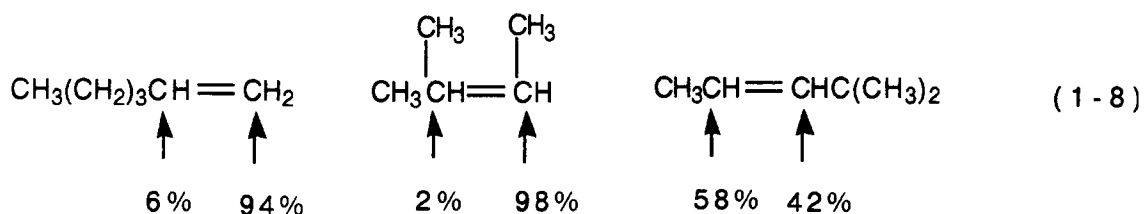


The discovery of the hydroboration reaction, in 1956, by H. C. Brown and B. C. Subba Rao provided a new and convenient route to organoborane derivatives and led to a new realm of chemistry^{1,22}. The ease of preparation, the versatile transformations, and the tolerance of various functional groups to hydroboration conditions have made the organoboranes the most useful intermediates in organic synthesis^{1,2,3}.

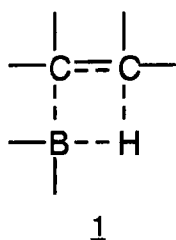
B. Hydroboration.

Organoboranes are generally obtained by addition of borane to alkenes and alkynes. The hydroboration takes place by *syn*-addition of the B-H moiety to a carbon-carbon multiple bond^{1,2}. Diborane reacts very sluggishly with olefins in the gas²³ phase and in hydrocarbon solvents²⁴, but the presence of weak Lewis bases enhances the reaction rate^{22,25}. Borane is normally utilized in complex form, e.g. $\text{BH}_3\cdot\text{THF}$, $\text{BH}_3\cdot\text{SMe}_2$, and $\text{BH}_3\cdot\text{NR}_3$ ^{26,27}. Several BH_3 -Lewis base complexes are commercially available.

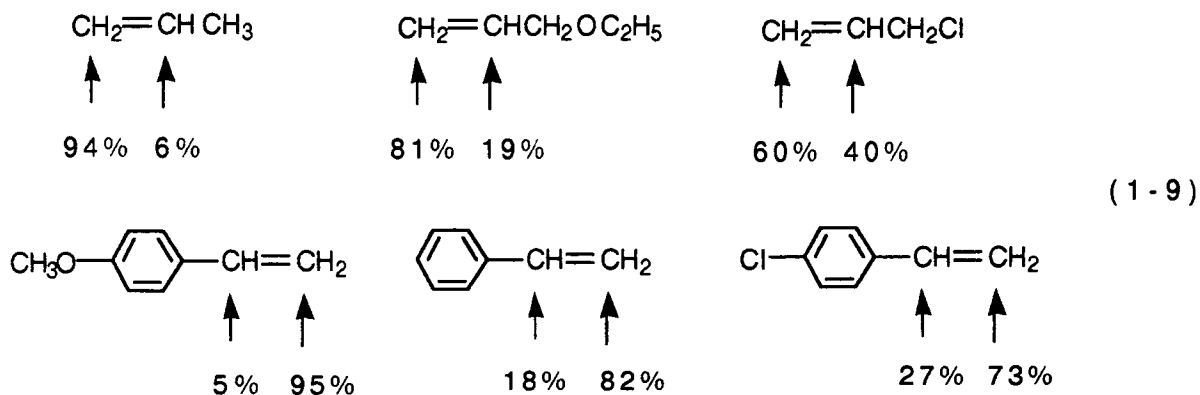
Addition of borane to an unsymmetrical alkene gives rise to two different products with boron becoming attached to both sides of the original double bond. However, in the absence of strong polar neighboring substituents, the hydroboration reactions are highly regioselective and predominantly produce the isomer in which boron is placed at the less substituted carbon atom²⁸. With disubstituted internal alkenes, there is little discrimination¹ (1-8).



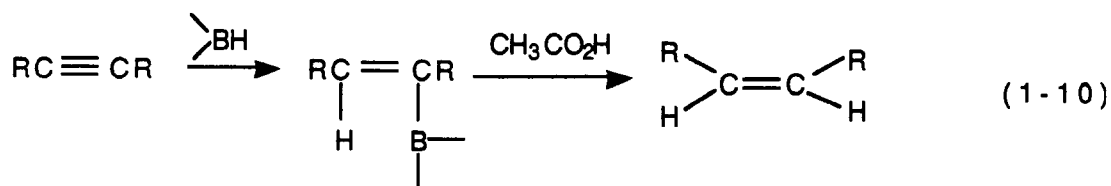
All the available evidence suggests that the hydroboration reaction is a concerted process¹ and takes place through a four-membered cyclic transition state, 1, formed by the addition, to the double bond, of a polarized B-H bond in



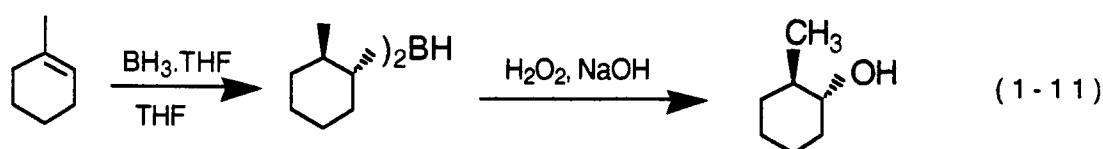
which the boron atom is the more positive. There is some evidence to suggest the formation of a π -complex prior to reaction¹. A concerted mechanism is also supported by the stereochemistry of the reactions (*syn* addition of B and H) and by the directive effect of polar substituents. Thus, in alkyl derivatives and in substituted styrenes the proportion of products formed by addition of boron to the *alpha*-carbon increases with the electronegativity of the substituent (1-9)²⁹.



Hydroboration of alkenes and alkynes is highly stereoselective and takes place by *syn* addition to the less hindered side of the multiple bond. Thus, hydroboration of alkynes followed by protonolysis affords *Z*-alkenes (1-10).



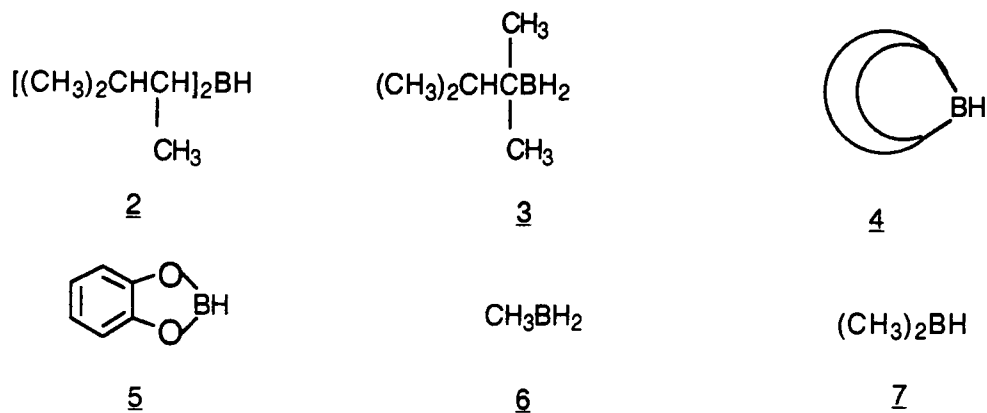
Hydroboration of 1-alkylcycloalkenes yield *trans*-2-alkylcycloalkanols after oxidation (1-11). Both the oxidation and the protonolysis of the boron-carbon



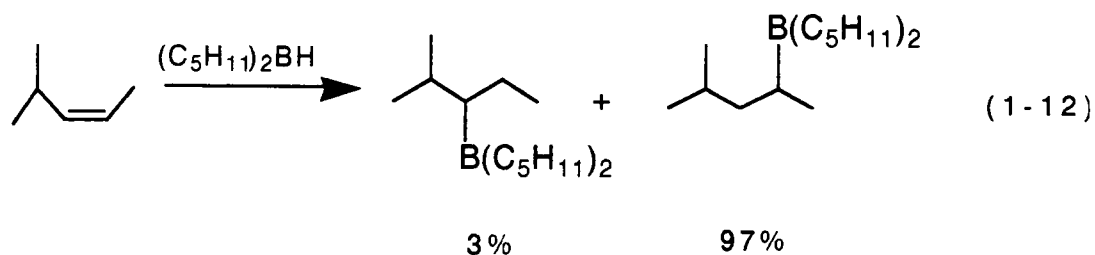
bond are known to occur with retention³⁰ of configuration; this establishes the *syn* nature of the original boron-hydride addition^{1,2,3,31}.

Hydroboration with borane, although valuable and extensively used, has limitations. For example, the hydroboration of terminal alkenes is regioselective but not regiospecific²⁸; the situation is even more complex when 1,2-disubstituted alkenes are utilized since there is little to distinguish between two carbons of the double bond^{1,2}. In addition, there is little variance in the rates of reaction of borane with different double bonds^{1,2,32}, so that it is rarely possible to achieve a selective hydroboration of one double bond in the presence of another. Another serious limitation is found in the hydroboration of terminal alkynes which often proceeds past the desired alkenylborane stage by addition of a second molecule of borane to the previously formed vinylborane^{33,34}. Many of these difficulties can be overcome by using substituted boranes rather than borane itself^{1,2,3,6}. The most frequently used reagents are disiamylborane, 2, thexylborane, 3, the stable crystalline

derivative 9-borobicyclo[3,3,1]nonane (9-BBN), 4, catecholborane, 5, and the recently developed methylboranes, 6 and 7.

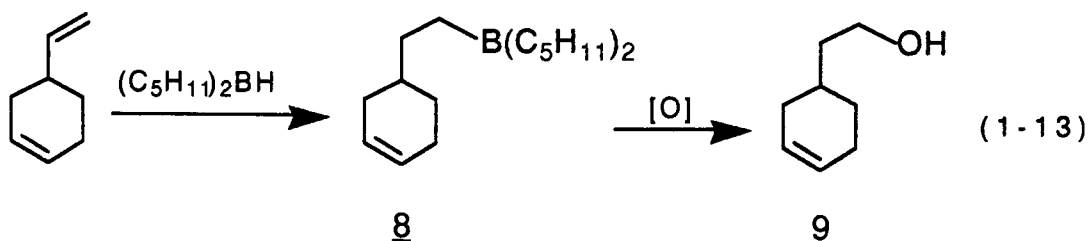


These reagents are less reactive and more selective than borane⁶. Disiamylborane $[(C_5H_{11})_2BH]$, for example, hydroborates 1-hexene with 99% of the boron becoming attached to the C-1 atom. The large steric requirement of the reagent results in excellent regioselectivity between the two carbon atoms of the double bond in *cis*-4-methyl-2-pentene (1-12); Even greater



discrimination is shown by 9-BBN³⁵. Disiamylborane is also more sensitive to the structure of alkenes than borane. Terminal alkenes react more rapidly than internal alkenes and (Z)-alkenes more rapidly than their (E)-isomers. This sometimes allows the selective hydroboration of one double bond in a

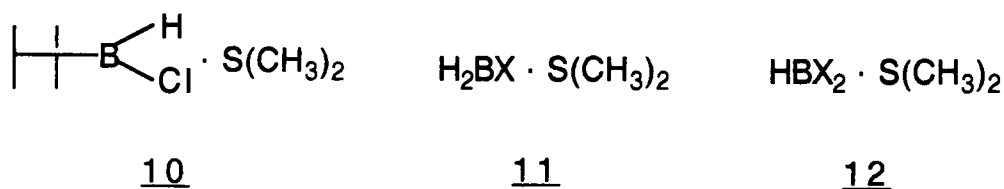
compound which contains several double bonds. Vinylcyclohexene, for example, can be monohydroborated to 8, and subsequently oxidized to alcohol 9 (1-13).



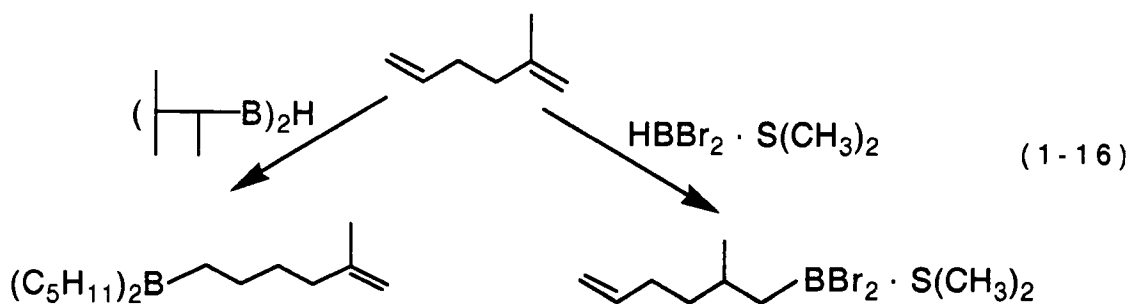
Similar results were obtained in hydroborations with 9-BBN. Dialkylboranes also permit the monohydroboration of alkynes, thus making available the corresponding alkenylboron derivatives³⁶. Similar results are obtained with other substituted boranes such as catecholborane³⁷, dibromoborane³⁸, hexylmonochloroborane³⁹ and dimethylborane⁴⁰. Oxidation of the products with alkaline hydrogen peroxide⁴¹ or sodium perborate⁴² affords aldehydes (1-14, 1-15). Reaction of terminal alkynes with borane yields mainly dihydroboration products but, with substituted hydroborating agents, high yields of monohydroboration products can be obtained. These compounds are synthetically useful. The series of reactions, hydroboration followed by oxidation, thus complements the usual acid-catalyzed hydration of terminal alkynes which leads to methyl ketones⁴³.



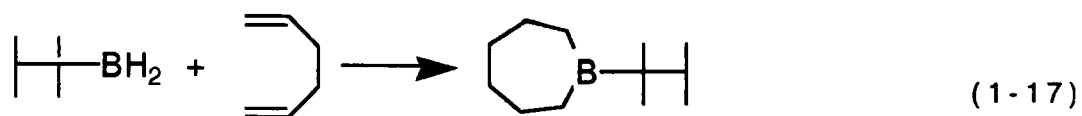
Thexylborane, 3, and the derived thexylchloroborane-methylsulfide complex, 10, catecholborane, 5, mono- and dihalogenoborane-methylsulfide complexes, 11, and 12, are also valuable selective hydroborating agents⁴⁴. The latter two reagents are readily available and are more stable than the ether



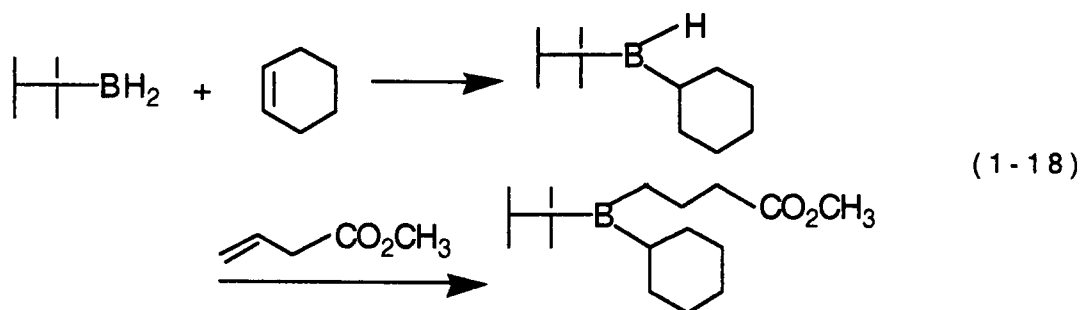
complexes. Both types of complexes react selectively at the less substituted end of a carbon-carbon double bond and at C-1 of terminal alkynes. The much higher reactivity of dibromoborane^{45,46} towards $-\text{C}(\text{CH}_3)=\text{CH}_2$ as compared with $-\text{CH}=\text{CH}_2$, in contrast to disiamylborane, makes possible the selective hydroboration of either double bond in 2-methyl-1,5-hexadiene (1-16).



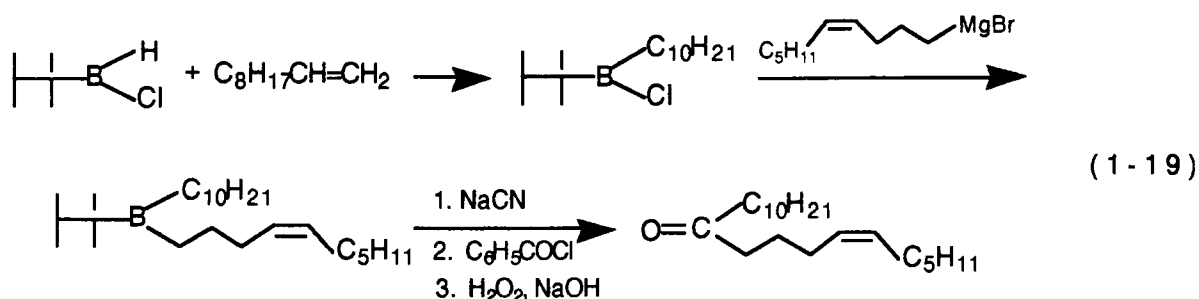
Thexylborane, the most readily available of the monoalkylboranes, is unique: it is useful for the cyclic hydroboration of dienes. Hydroboration of dienes with borane usually leads to the formation of polymers,⁴⁷ but with thexylborane, cyclic organoboranes are formed^{7,48} (1-17). Thexylborane can also be used to make trialkylboranes containing three different alkyl groups



by stepwise addition to two different alkenes (1-18). However the first alkene



must be relatively unreactive. This limitation can be overcome by the use of thexylchloroborane which can be prepared from thexylborane with hydrogen chloride or by monohydroboration of 2,3-dimethyl-2-butene with the monochloroborane-dimethylsulfide complex³⁹. Its reaction with an alkene gives an alkylthexylchloroborane which can be converted into a dialkylthexylborane by reaction with one equivalent of a Grignard reagent or an alkyl lithium. The dialkylthexylboranes are valuable reagents in organic synthesis (1-19).



Mono- and dimethylboranes are now readily available⁴⁰. The outstanding regiospecific hydroboration characteristics and the migratory resistance of the methyl group have made these reagents useful in synthetic transformations. The details of these reagents will be discussed in Chapter III.

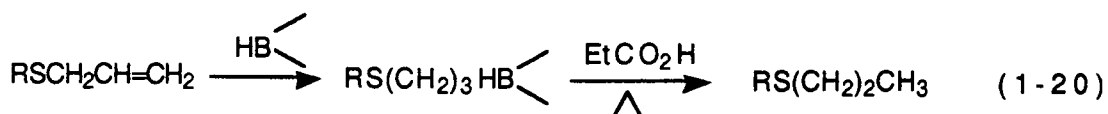
C. Organoboranes for Organic Synthesis.

The usefulness of the hydroboration reaction in synthesis arises from the fact that the resultant alkylboranes can be converted into a variety of organic functional groups under mild conditions, providing simple versatile methods for syntheses of organic compounds. Investigations of these substitution reactions reveal that, with rare exception, the organoboranes transfer the alkyl groups from boron to other elements with complete retention of stereochemistry. A practical advantage of these reactions is that it is often unnecessary to isolate the intermediate organoboranes.

1. Protonolysis.

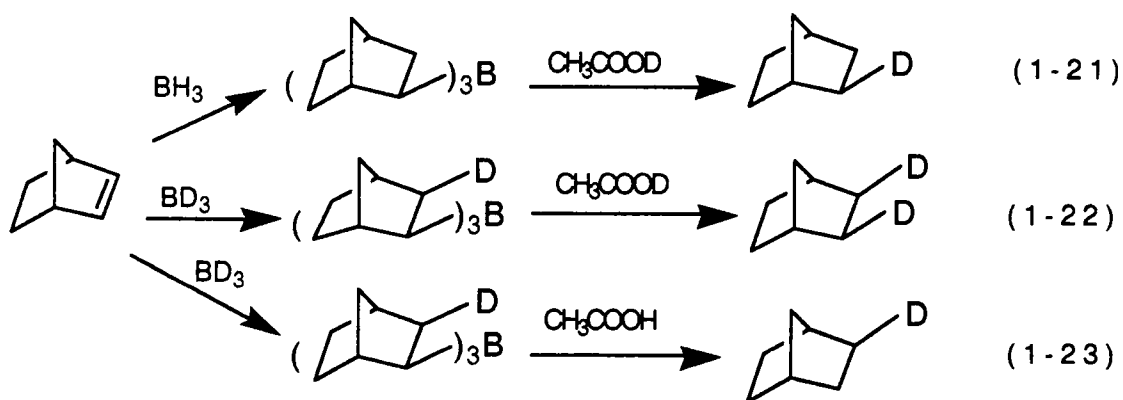
The organoboranes are remarkably stable to water, aqueous bases, and aqueous mineral acids. However, they are susceptible to protonolysis by

carboxylic acids⁴⁹. Protonolysis provides a convenient method for the reduction of carbon-carbon multiple bonds and affords an alternative to catalytic hydrogenation reactions⁵⁰ (1-20).



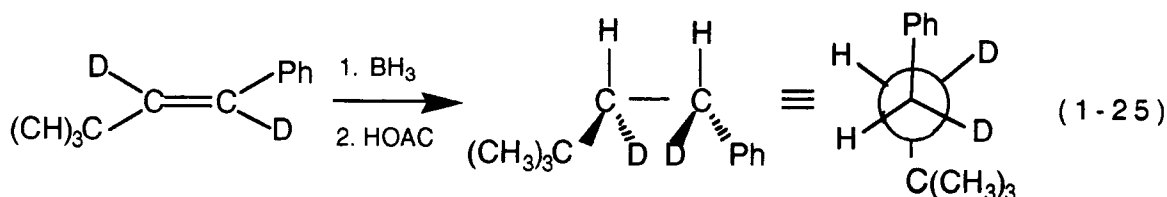
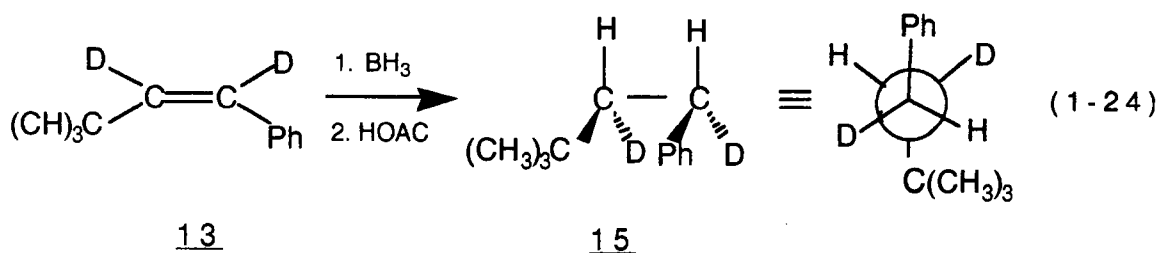
In general, a refluxing carboxylic acid, in diglyme, is used to protonate alkylboranes; alkenylboranes are much more reactive and often undergo rapid protonolysis with acetic acid at room temperature (1-10).

The protonolysis occurs with retention of configuration at the carbon attached to boron^{51, 52}. Thus the deuteriolysis of chiral dibutyl phenylethylboronate produces chiral *alpha*-deuterioethylbenzene and the hydroboration-deuteriolysis of norbornene yields 2-*exo*-deuterionorbornane (1-21, 1-22, 1-23).



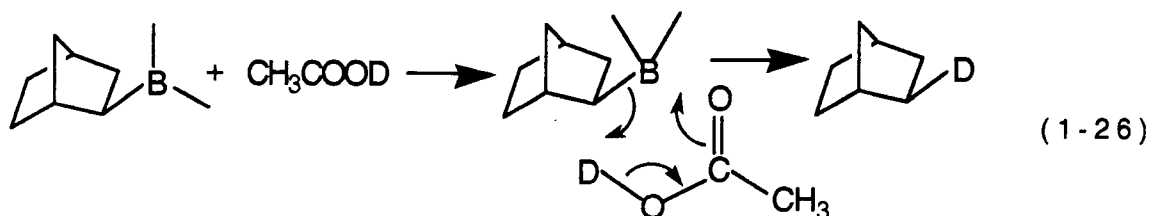
Kabalka⁵³ utilized nuclear magnetic resonance spectroscopy to analyze the stereochemistry of the hydroboration/protonolysis sequence. (Z)- and (E)-1-phenyl-3,3-dimethyl-1-butene-1,2-d₂ (13 and 14 respectively) were hydro-

borated and the intermediate organoboranes were protonolyzed. An overall *syn* hydrogenation (retention of configuration during protonolysis) would produce *erythro*- and *threo*-1-phenyl-3,3-dimethyl-1,2-d₂ (15 and 16 respectively). An overall *anti* hydrogenation (inversion of configuration during protonolysis) would produce the opposite stereochemical results (1-24, 1-25). The ²H-decoupled ¹H-NMR spectra clearly demonstrate that *erythro*-15



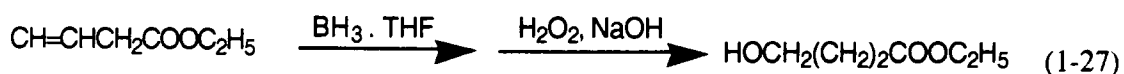
(³J = 12.5 Hz) is produced from 13 and *threo*-16 (³J = 5.0 Hz) is produced from 14 by the hydroboration-protonolysis sequence.

The high reactivity of organoboranes with carboxylic acids was unexpected. The enhanced reactivity is ascribed to an initial coordination of the electron-rich carbonyl oxygen of the acid with electron-deficient boron⁵⁴ (1-26).

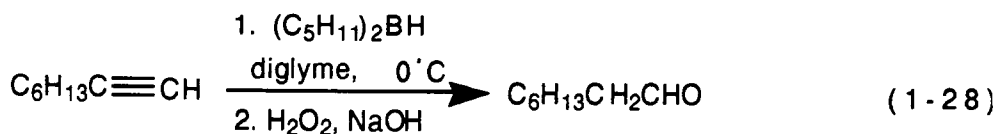


2. Oxidation.

Oxidation of organoboranes to alcohols is usually affected by alkaline hydrogen peroxide,⁴¹ although other methods^{55,56,57,58} can be used. The reaction is of wide applicability; many functional groups are unaffected by the reaction conditions, so that a variety of substituted alkenes can be converted into alcohols by this procedure (1-27). A valuable feature of the reaction is that it results in overall anti-Markovnikov addition of water to a double or triple

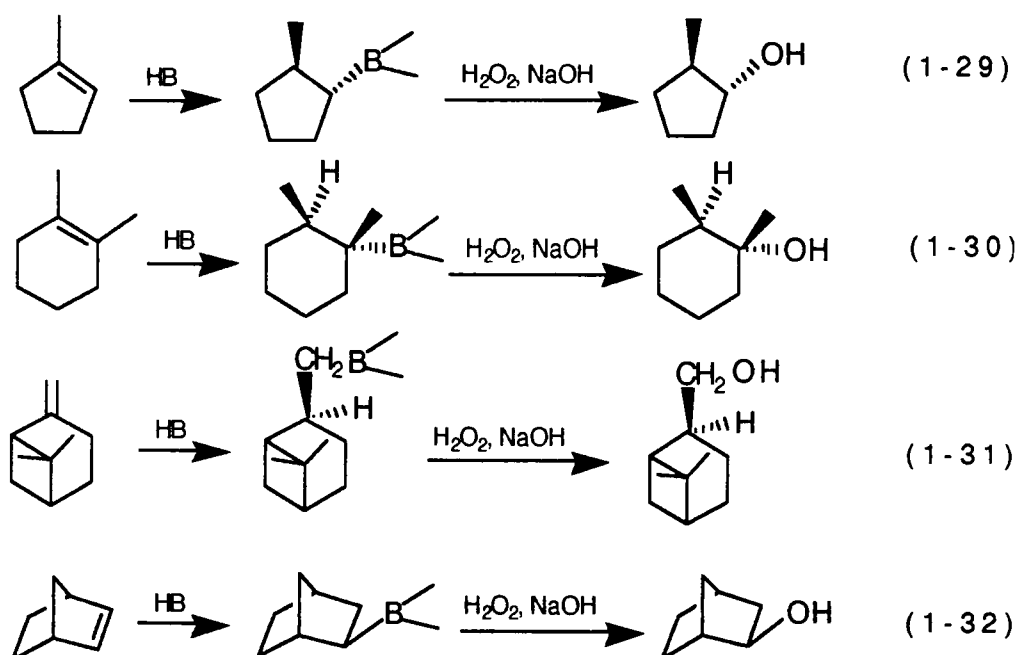


bond; thus, it complements the acid-catalyzed hydration reaction. This follows from the fact that, in the hydroboration step, the boron atom adds to the less substituted carbon of the multiple bond. Terminal alkynes, for example, give aldehydes in contrast to methylketones, which are obtained by acid-catalyzed hydration⁴² (1-28).

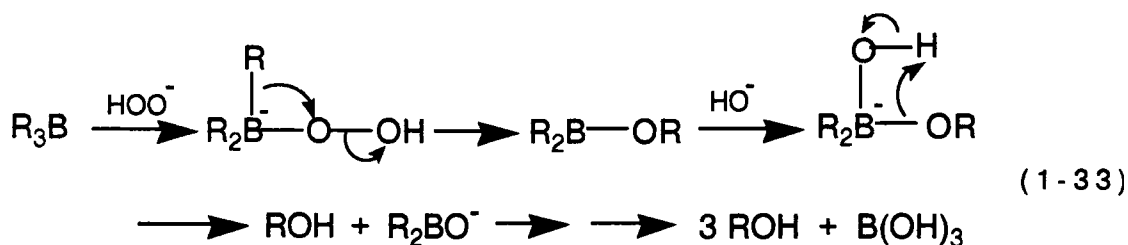


Another noteworthy feature of the reaction is that it leads to *syn* addition

of the elements of water to the double bond. This is determined by the reaction pathway and not by the stability of the product; therefore, the thermodynamically more stable product is not invariably formed. Thus, hydroboration-oxidation of 1-methylcyclopentene affords the more stable *trans*-2-methylcyclopentanol (1-29), but 1,2-dimethylcyclohexene yields the less stable *cis*-1,2-dimethylcyclohexanol (1-30). *Beta*-pinene similarly gives the less stable *cis*-myrtanol (1-31). Hydroboration-oxidation of cyclic and bicyclic alkenes led to the generalization that these reactions proceed with complete retention of configuration (1-29, 1-30, 1-31 and 1-32).



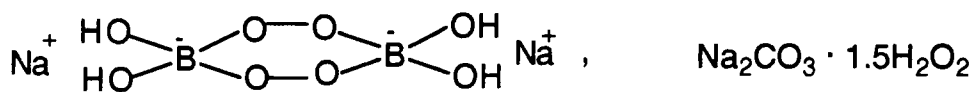
A reaction pathway involving intramolecular transfer of an alkyl group from boron to carbon in an "ate" complex has been proposed⁵⁹ (1-33).



Direct oxidation of primary trialkylboranes to aldehydes and secondary trialkylboranes to ketones, without isolation of the intermediate alcohols, is possible using pyridinium chlorochromate or aqueous chromic acid⁶⁰.

Other reagents have been used to oxidize organoboranes to the corresponding alcohols; these include amine N-oxides^{56,57}, perbenzoic acid⁵⁵, and sodium perchlorate⁵⁸. The most fascinating recent developments regarding the oxidation of organoboranes to the corresponding alcohols involve sodium perborate⁴² and sodium percarbonate⁶¹.

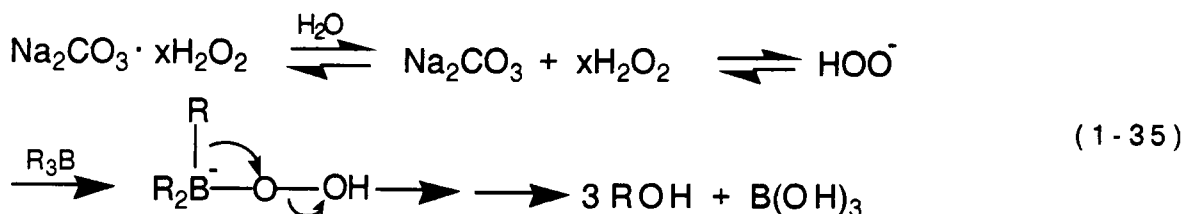
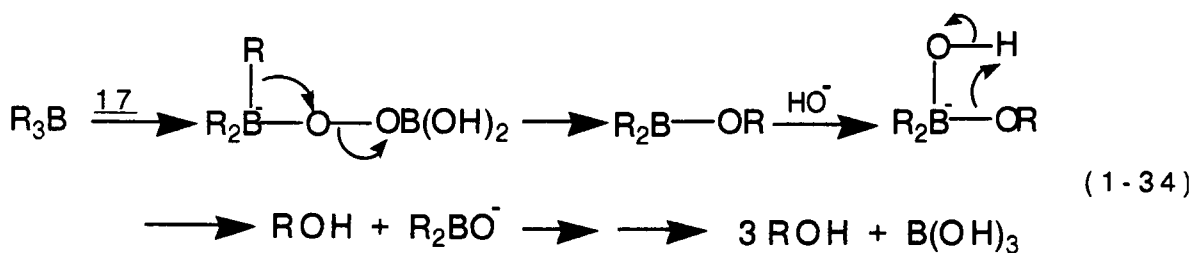
Sodium perborate, 17, and sodium percarbonate, 18, are both inexpensive, large scale industrial chemicals which are stable and easily handled. The reagents have been shown to be mild oxidizing agents, and sodium percarbonate is extensively used in the detergent industry as a bleaching agent⁶².

1718

Interestingly, both sodium perborate and sodium percarbonate oxidize organoboranes and vinylboranes to produce the corresponding products with yields as good, or better, than those obtained using the peroxide procedure. The

oxidations proceed at room temperature for most of the organoboranes studied; highly hindered boranes and those complexed with dimethyl sulfide require heating (50 °C).

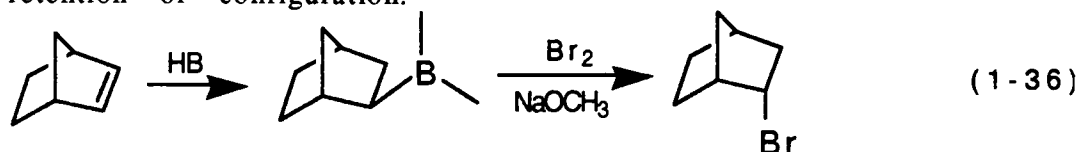
The oxidations of organoboranes with sodium perborate and sodium percarbonate presumably proceed through a mechanism (1-35, 1-36) similar to that of hydrogen peroxide. However, since the reagents are mildly basic, the addition of external base is not required. The rate of the oxidation is temperature dependent.



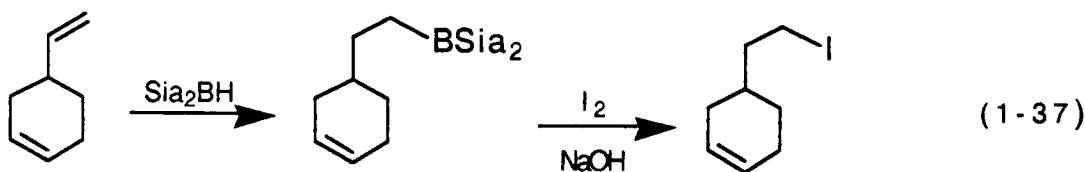
3. Halogenolysis.

Organoboranes exhibit a remarkable sluggishness towards rupture of the carbon-boron bond by direct reaction with halogens. However, in the presence of base, the replacement by bromine or iodine proceeds readily at 0 °C with

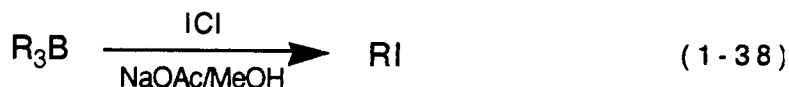
inversion of the configuration at the migrating carbon⁶³ (1-37). This is one of the very few substitution reactions of organoboranes that does not proceed with retention of configuration.



The iodination of organoboranes is a useful synthetic operation. Two of the three alkyl groups are utilized in the organoborane-iodination transformations; the maximum yield is 67%⁶⁴. The use of borane derived hydroborating agents such as disiamylborane can circumvent this disadvantage and also allow the selective iodination of a terminal olefin (1-37). Catecholborane is a widely used hydroborating agent in the hydroboration-iodination reactions.



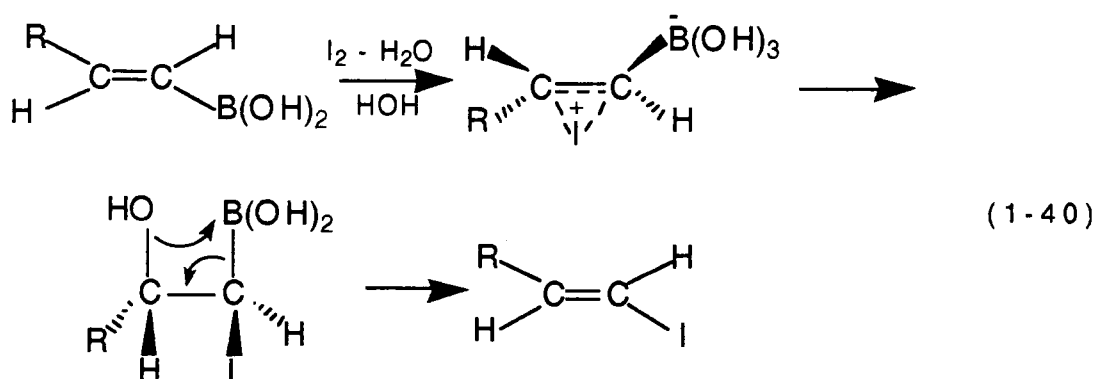
In order to employ the iodination sequence for radiopharmaceutical applications, Kabalka and his co-workers developed a mild alternative procedure utilizing iodine monochloride as the electrophilic iodine source⁶⁵ (1-38). Inversion of configuration is also observed.



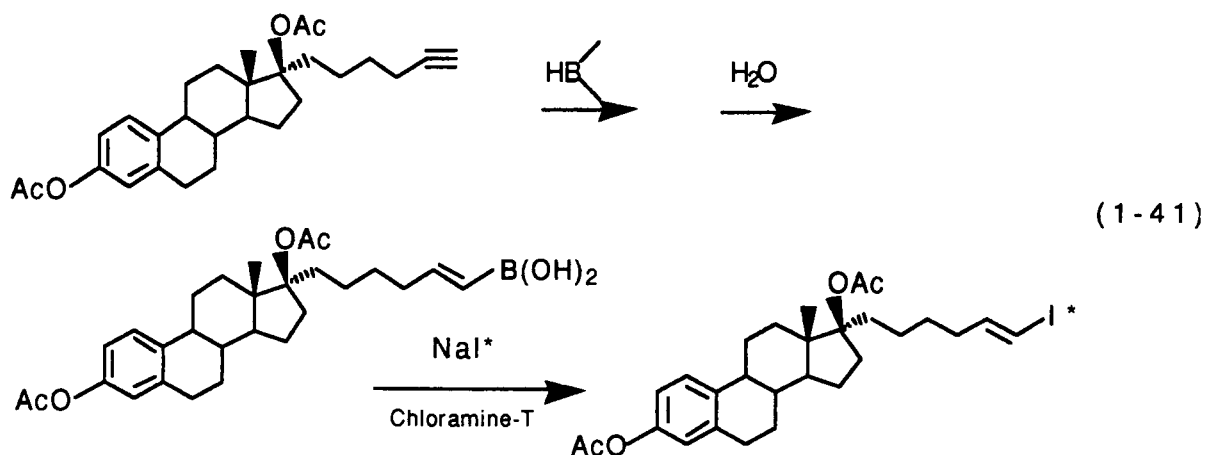
More recently, Kabalka's group used sodium iodide as the iodine source and a mild oxidizing agent (e.g. chloramine-T) to generate electropositive iodine *in situ*⁶⁶(1-39).



A mechanism has been proposed which involves an iodonium ion intermediate, nucleophilic attack by base, followed by *syn* elimination of boric acid. The proposed mechanism is in accordance with the observed stereochemistry⁶⁷ (1-40).

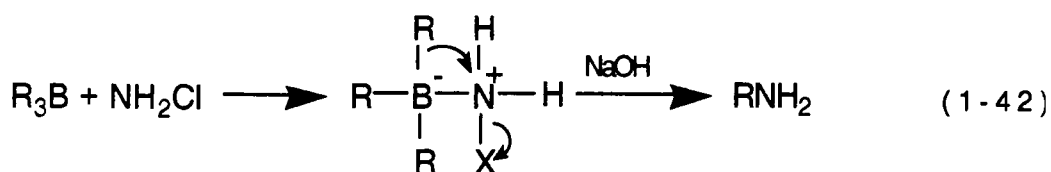


The *in situ* methodology utilizing the sodium iodide-chloramine-T reagent has been applied to the iodination of vinylboronic acids, and currently is used in the syntheses of a series of radioactive iodine labeled single photon emission computer tomography (SPECT) diagnostic agents⁶⁸ (1-41).



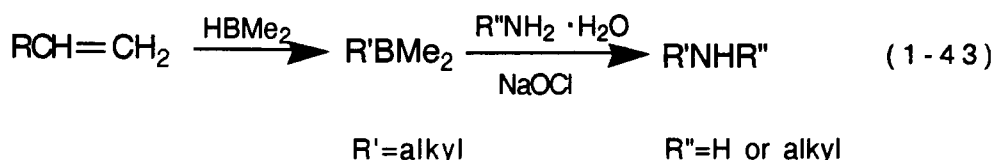
4. Amination.

The synthesis of amines via organoborane chemistry is an important synthetic transformation. Several reactions are known in which an alkyl group is transferred from the organoborane to a nitrogen atom leading to primary amine derivatives^{69,70,71,72}. Trialkylboranes, on treatment with chloramine or hydroxylamine O-sulfonic acid, generate primary amines in 40-60% yield (1-42). Two of the three alkyl groups are utilized and the cleavage occurs with retention of configuration. Unfortunately, the third alkyl group on boron fails to react⁷³, decreasing the yield to a maximum 67% based on the alkene used to generate trialkylborane. A recent development⁷⁴⁻⁷⁸ utilizing



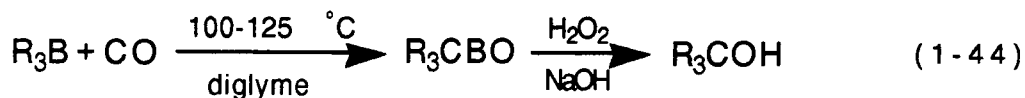
X=Cl, OSO₃H, etc.

dimethylborane as hydroborating agent can be used to solve this problem. The methyl group resists transfer from boron to nitrogen so that higher yields of the desired product are readily obtained (1-43). The details of this reaction will be discussed in Chapters III and IV.

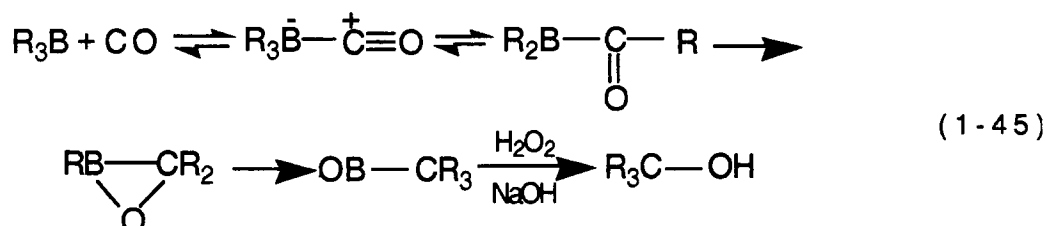


5. Carbonylation.

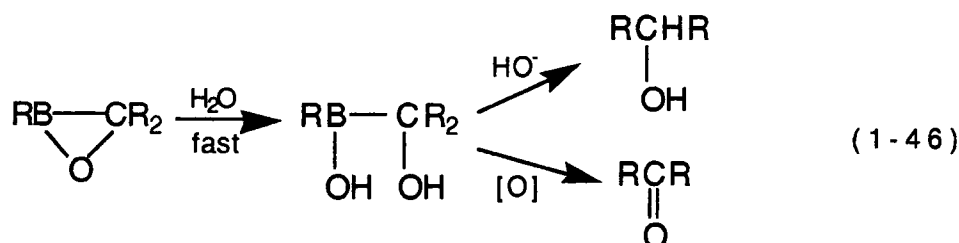
One of the most useful reactions of organoboranes is their reaction with carbon monoxide which, under appropriate conditions, can be directed to give primary, secondary and tertiary alcohols, aldehydes, as well as open chain, cyclic, and polycyclic ketones. At a temperature of 100-125 °C in diglyme solution, organoboranes absorb one equivalent of carbon monoxide at atmosphere pressure to form intermediates which are oxidized to tertiary alcohols by alkaline hydrogen peroxide in excellent yield (1-44). The reaction is of wide applicability, and for trialkylcarbinols containing bulky groups gives much higher yields than other methods^{1,2,6}.



The reaction involves migration of alkyl groups from boron to the carbon atom of carbon monoxide. This has been shown to occur intramolecularly by the fact that carbonylation of an equimolecular mixture of triethylborane and tributylborane gives, after oxidation, only triethylcarbinol and tributylcarbinol; no 'mixed' carbinols are formed^{1,79}. A stepwise pathway (1-45) involving three successive intramolecular transfers has been proposed.

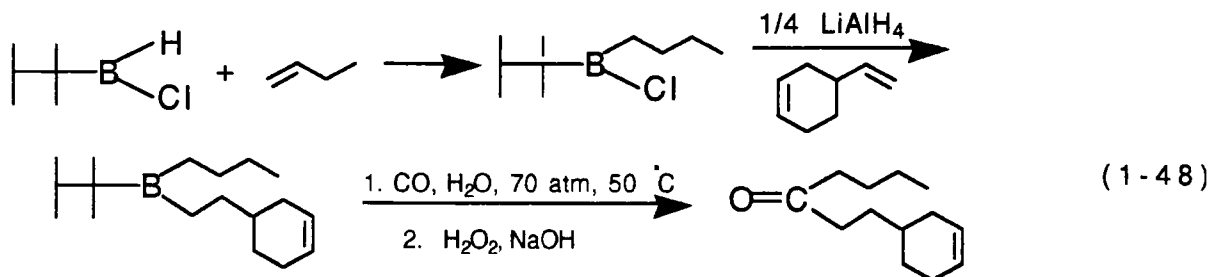
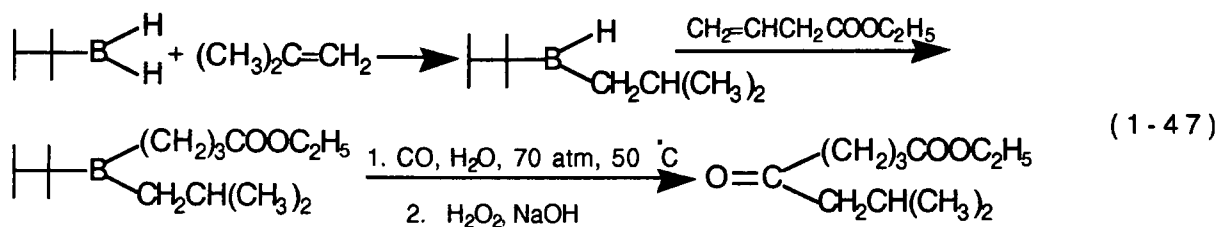


If the carbonylation is conducted in the presence of a small amount of water, migration of the third alkyl group is inhibited. Oxidation of the hydrate produced then gives the dialkyl ketone instead of the trialkylcarbinol (1-46). Alkaline hydrolysis leads to secondary alcohols; yields are generally high and the sequence provides a convenient synthetic route to ketones. The method can

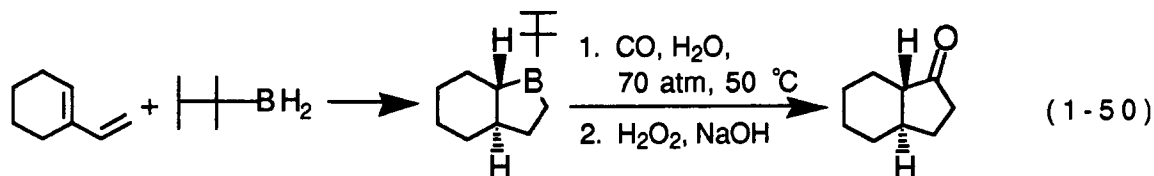
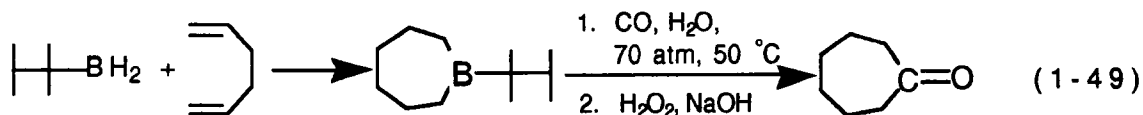


also be extended to the syntheses of unsymmetrical ketones by using "mixed" organoboranes prepared from thexylborane or thexylchloroborane. The thexyl group shows an exceptionally low aptitude for migration⁸⁰, and carbonylation

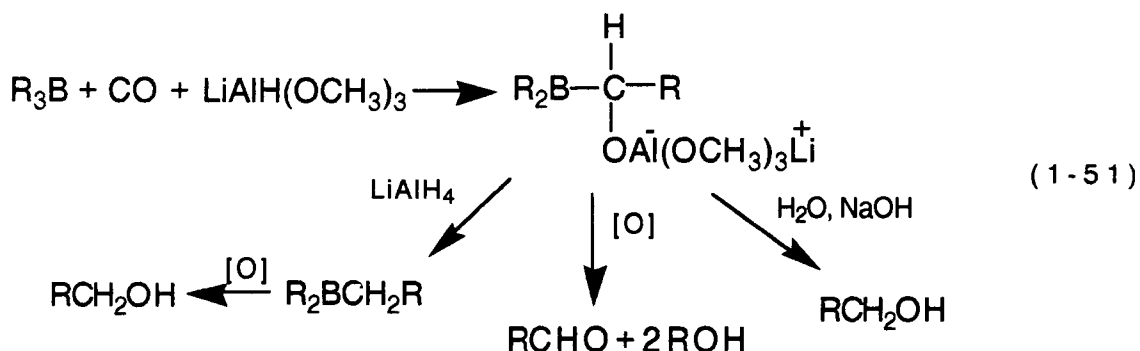
of trialkylboranes containing a hexyl group, in the presence of water, leads to high yields of ketone. Many functional groups in the alkene do not interfere with the reaction, and the procedure can be used to synthesize ketones from many different alkenes (1-47, 1-48).



Dienes yield cyclic ketones (1-49); the reaction has been utilized⁸¹ for the stereospecific generation of thermodynamically disfavored *trans*-perhydroindanone (1-50).

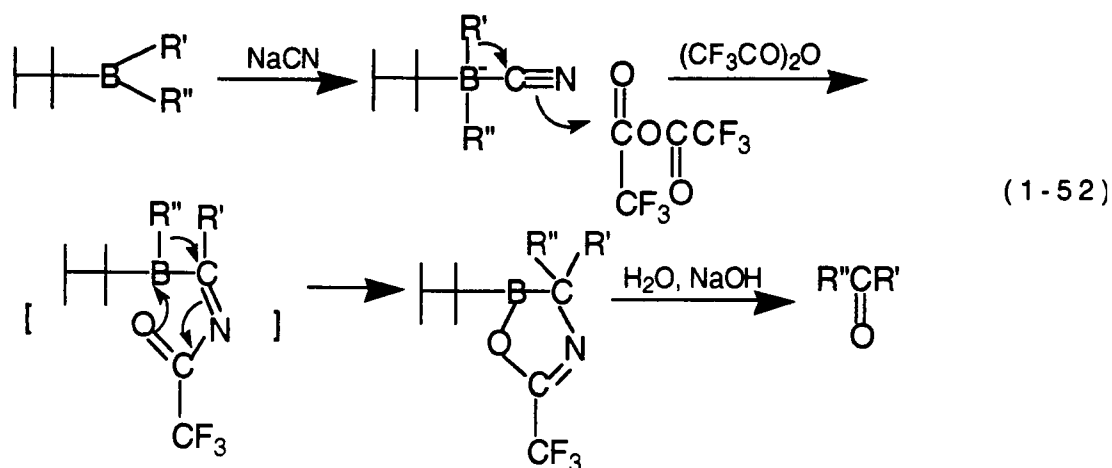


The carbonylation reaction can also be used for the preparation of aldehydes and primary alcohols^{82,83}. In the presence of hydride reducing agents such as lithium trimethoxyaluminum hydride, the rate of reaction of carbon monoxide with organoboranes is greatly increased, and the products, on oxidation with buffered hydrogen peroxide, afford aldehydes. Alkaline hydrolysis gives the corresponding primary alcohols containing one more carbon atom than the original alkenes, and thus differ from the products obtained on direct oxidation of the original alkylboranes (1-51).



There is a useful alternative to the carbonylation route to ketones and trialkylmethanols^{84,85}. In this sequence the key intermediate is a cyanoborate, and the carbon atom which eventually becomes the carbonyl group of the

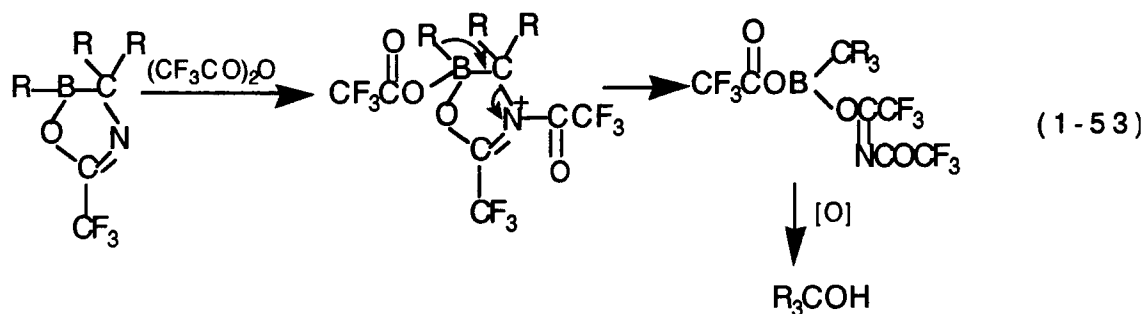
ketone or the "methanol" carbon of the trialkylmethanol originates in the cyanide ion. In the reaction, the addition of one equivalent of benzoyl chloride or, better, trifluoroacetic anhydride induces two successive migrations of alkyl groups from boron to the adjacent carbon atom of the cyanide (1-52). As in the



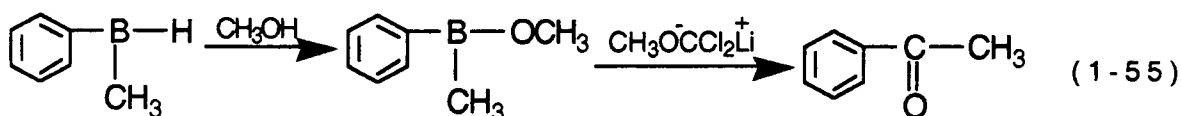
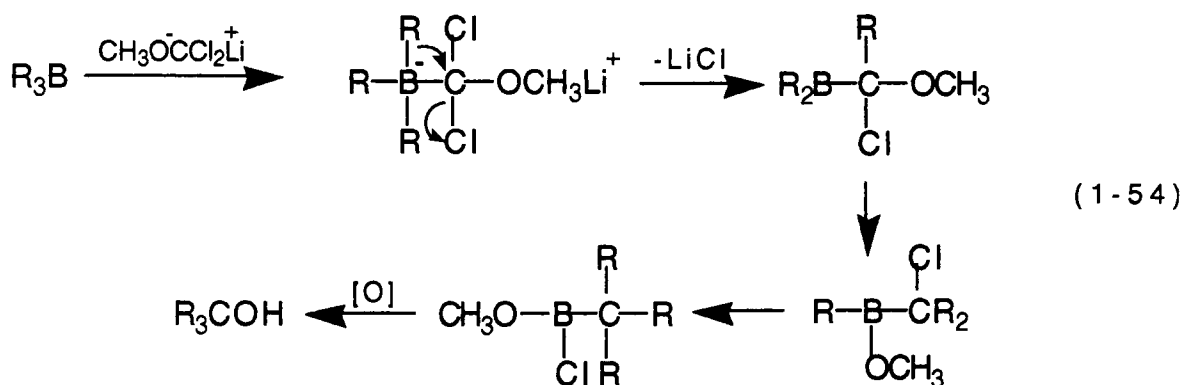
carbonylation reaction, maximum utilization of the alkyl groups on the borane is achieved by using thexylborane or thexylchloroborane as hydroborating agents; the thexyl group does not migrate and unsymmetrical ketones are easily obtained from two different alkenes. If an excess of trifluoroacetic anhydride is employed, the reaction takes place in a different manner; the third alkyl group migrates from boron to carbon, and after oxidation, produces a trialkylmethanol (1-53).

Another convenient procedure for the preparation of tertiary alcohols and ketones involves the use of the reaction of organoboranes with dichloromethyl methyl ether⁸⁶ (DCME) in the presence of a strong hindered base such as lithium triethylcarboxide. All three groups of the alkylborane are transferred to the halogenated carbon atom of the ether; oxidation of the product

affords the corresponding tertiary alcohol. It is not clear whether the reaction takes place through the *alpha*-halocarbanion or the corresponding carbene,

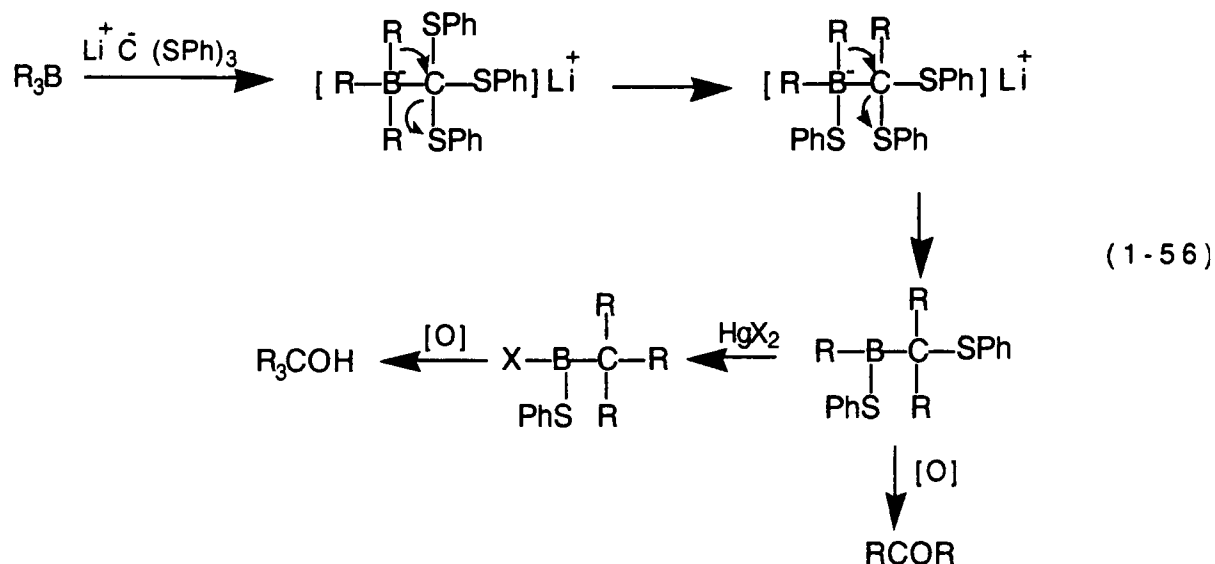


but the anion route has been proposed (1-54). This sequence has been used to prepare ketones starting from dialkylboronic esters⁸⁷ (1-55).

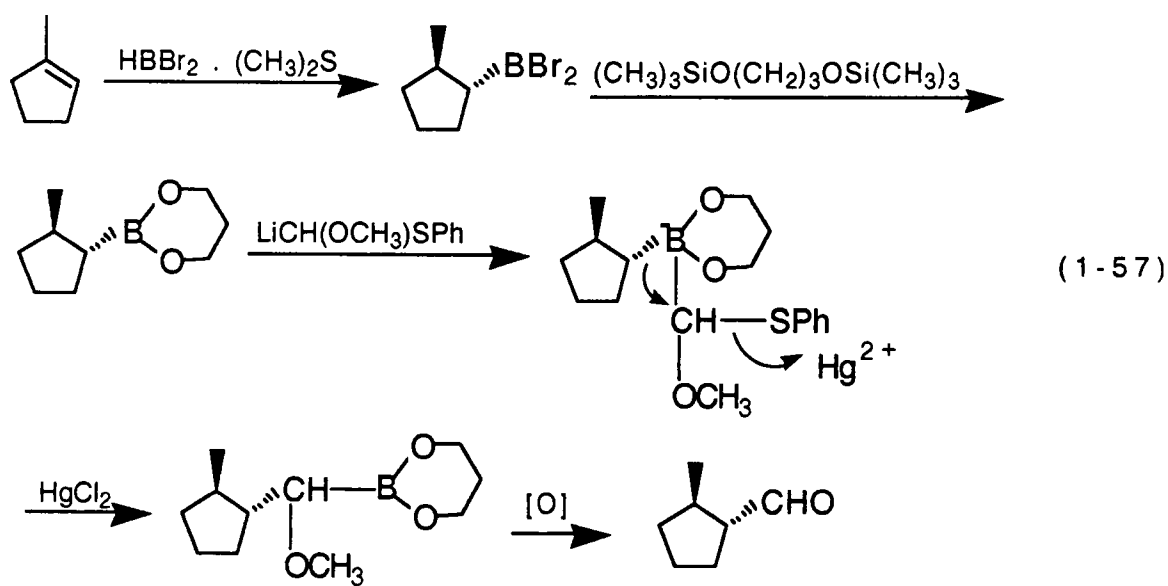


Another approach to ketones and carbinols involves reaction of trialkylboranes with the readily available anion of tri(phenylthio)methane⁸⁸. Two alkyl groups migrate spontaneously from boron to the carbon to yield a product which produces the ketone after oxidation. A third migration can be

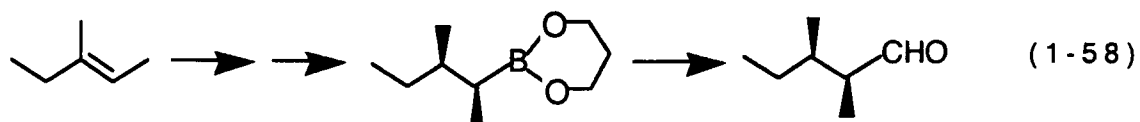
induced by treatment with mercuric ion which affords a trialkyl carbinol after oxidation (1-56).



Aldehydes can also be obtained by reaction of alkylboronic esters with methoxy(phenylthio)methyl lithium, $\text{LiCH}(\text{OMe})\text{SPh}$ ⁸⁹ (1-57). The migration

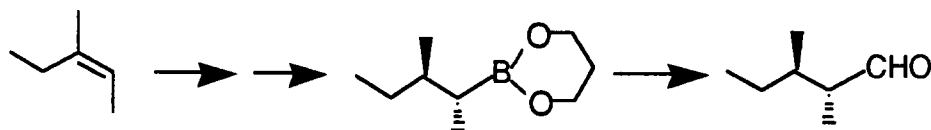


step proceeds with retention of configuration of the migrating carbon atom. This reaction has proven to be valuable in the stereoselective synthesis of disubstituted aldehydes (1-58, 1-59).



(1-58)

96% threo

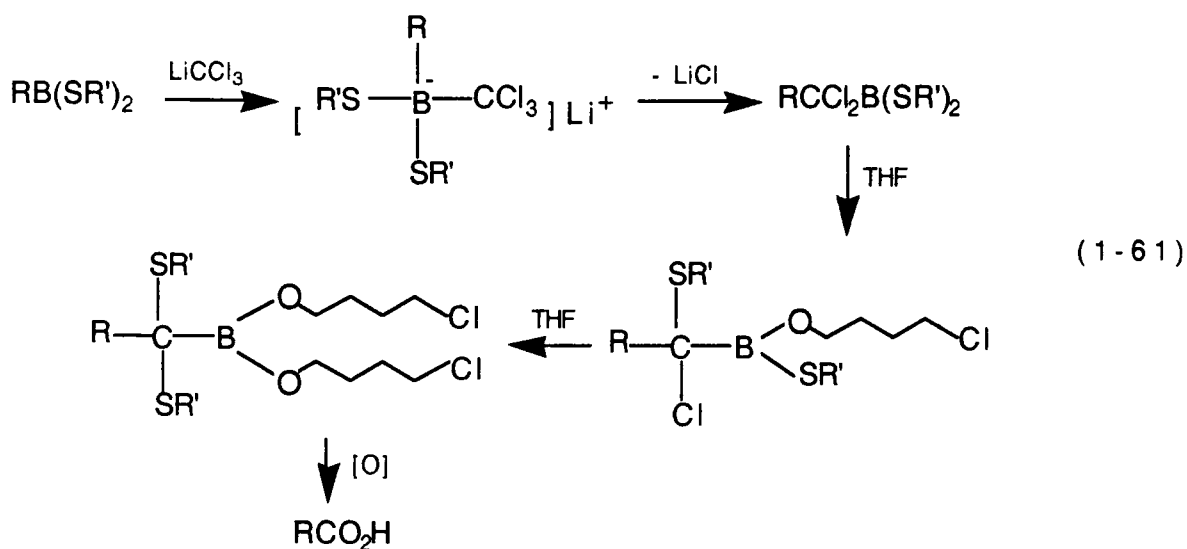
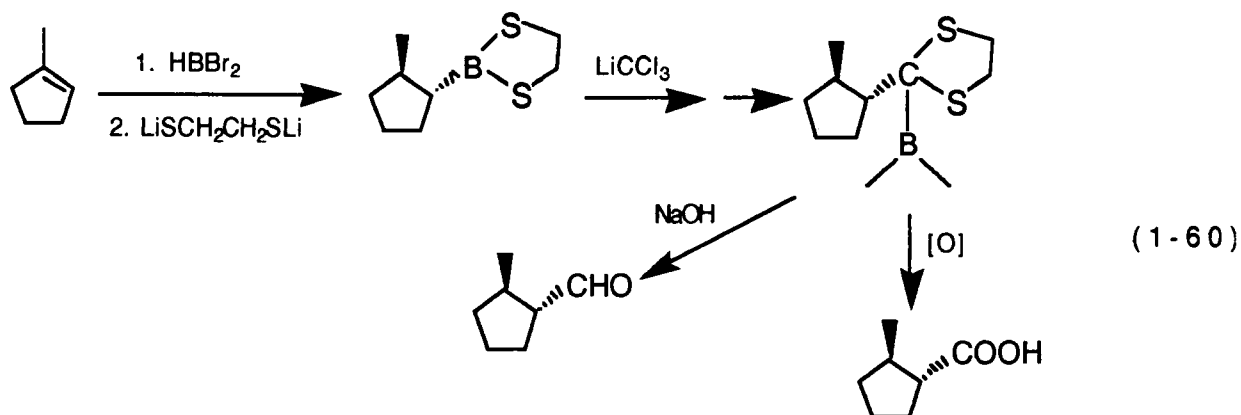


(1-59)

96% erythro

6. Oxycarbonylation.

Alkenes hydroborated with dibromoborane-dimethylsulfide complex and then treated with dilithio 1,2-ethanedithiolate yield alkylthioboronic esters. The boronic esters can be treated with trichloromethyl lithium to provide intermediates which are oxidized to carboxylic acids or hydrolyzed to aldehydes^{90,91} (1-60). This reaction is believed to proceed as shown in equation (1-61).



Alternatively, the aldehydes obtained from the formylation of organoboranes can be easily oxidized by a two-phase chromic acid procedure to furnish carboxylic acids.

D. Summary.

The systematic study of organoboranes has revealed that they are among the most versatile intermediates available to the synthetic organic chemist. It is

now possible to utilize organoboranes to synthesize essentially all structural types of organic compounds. Typical transformations are summarized in Figure 1-1.

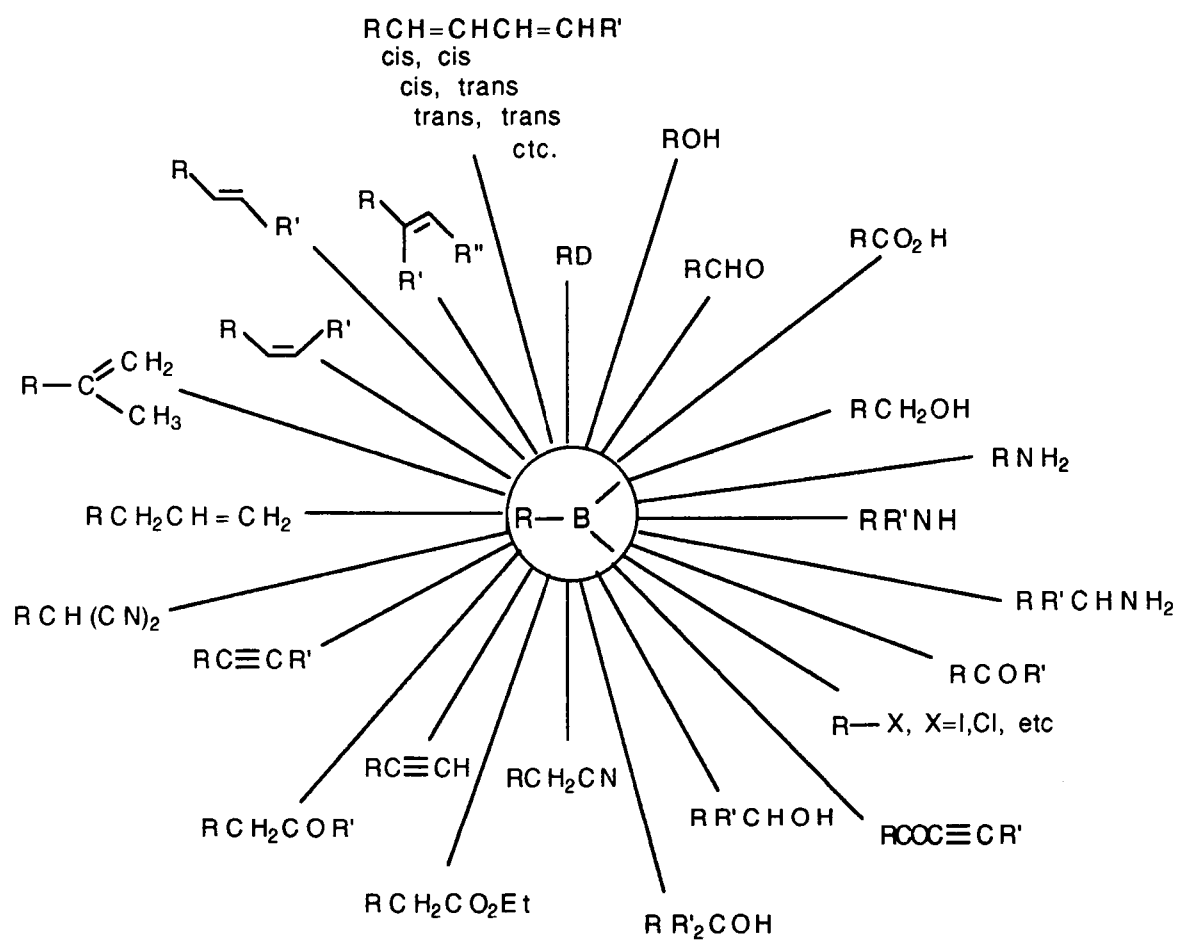


Figure 1-1. The Versatile Organoborane Transformations.

Section II: General Asymmetric Synthesis via Organoborane Chemistry.

The unique chemistry of organoboranes has made possible a three-pronged approach to asymmetric synthesis: (1) asymmetric hydroboration; (2) asymmetric reduction; and (3) asymmetric allyl- and crotylboration. These reactions make possible unique general syntheses of pure enantiomers and complex optically active compounds that have broad applications in synthesis⁹².

The successful hydroboration of *cis*-2-butene by diisopinocampheylborane (92% enantiomeric excess) in 1961 provided a boron intermediate which was oxidized to optically active 2-butanol (87% ee). This was the first successful organoborane asymmetric synthesis⁹³. Improvements in the reagent raised the ee to 98.4%⁹⁴. Since then, a number of asymmetric hydroborations have yielded products in the 100% ee range. Monoisopinocampheylborane has been synthesized and used to achieve asymmetric hydroborations of more hindered alkenes (*trans*, trisubstituted) in the 60-100% ee range. Recent developments involving a simple crystallization of the boron intermediate provide the desired chiral R* group in 100% ee.⁹⁵ These chiral groups attached to boron can be transferred with complete retention of configuration. Consequently, it is now possible to prepare a large range of optically active compounds in essentially 100% ee⁹².

Chiral organoboranes have also made possible chiral syntheses via reduction of carbonyl groups. These reagents have been vastly improved and chiral reductions involving optical purities approaching 100% are now readily available⁹⁶. Finally, allyl- and crotylboration have been developed to

permit chiral syntheses of the allyl and crotyl products in optical purities approaching 99+% ee⁹⁷.

It is evident that the boron chemistry is in the initial phase of a new era in synthetic organic chemistry. Boron chemistry will be an essential part of the realm of the organic chemist of the future⁹².

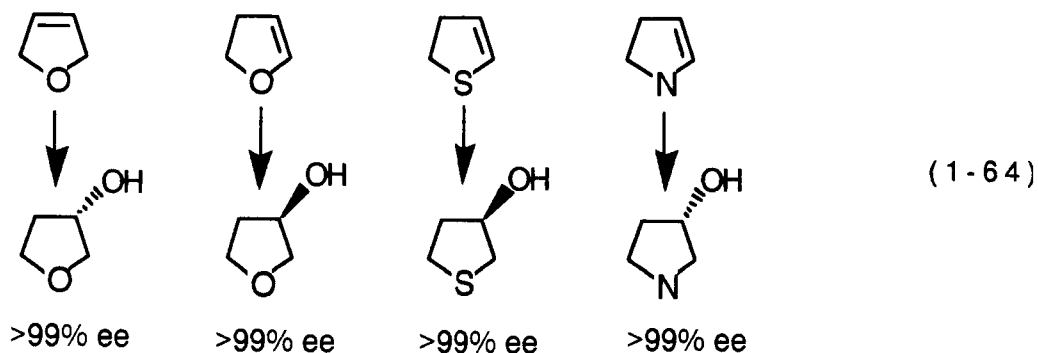
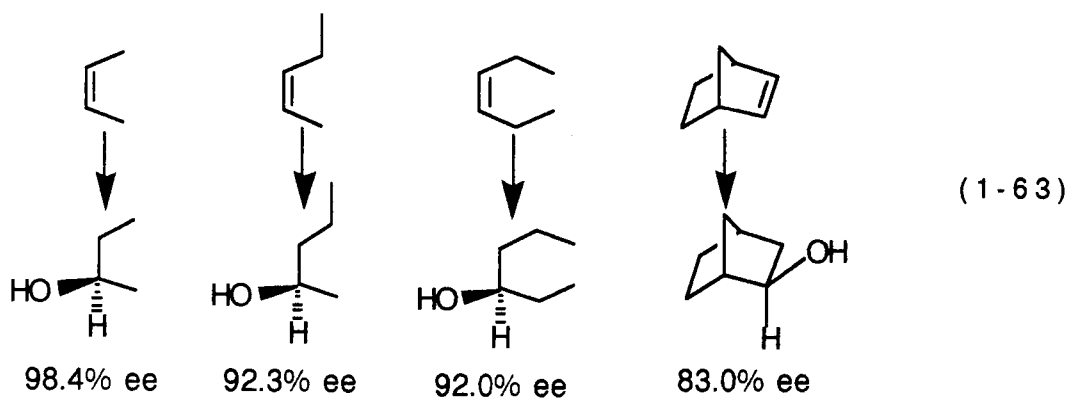
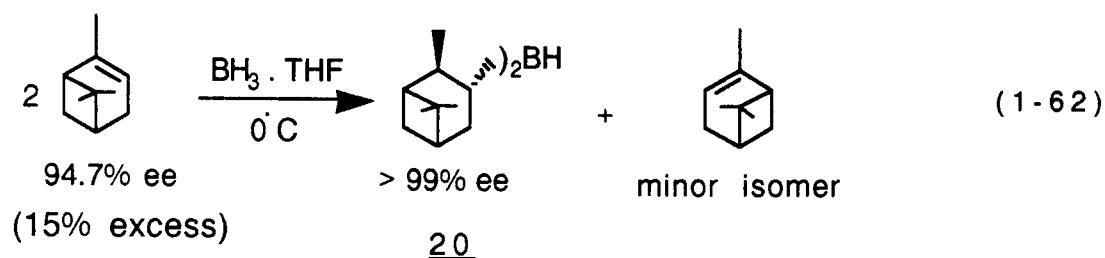
A. Asymmetric Hydroboration.

Hydroboration of alkenes with optically active alkylboranes has been used in the asymmetric syntheses of optically active secondary alcohols. The best results to date have been obtained with diisopinocampheylborane and monoisopinocampheylborane, which are readily available in either chiral form by reaction of borane with (+)- or (-)-*alpha*-pinene under appropriate conditions.

1. Asymmetric Hydroboration with Diisopinocampheylborane.

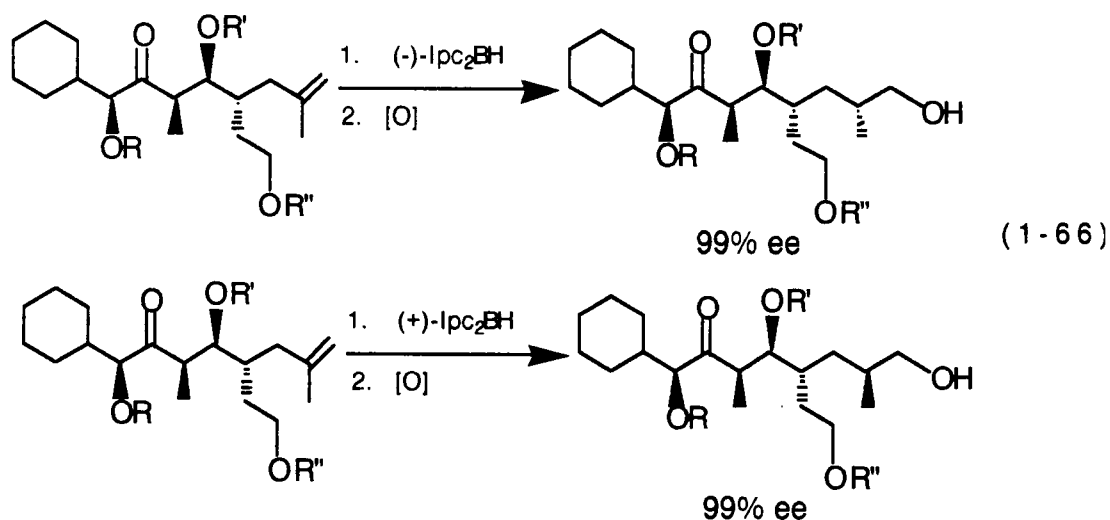
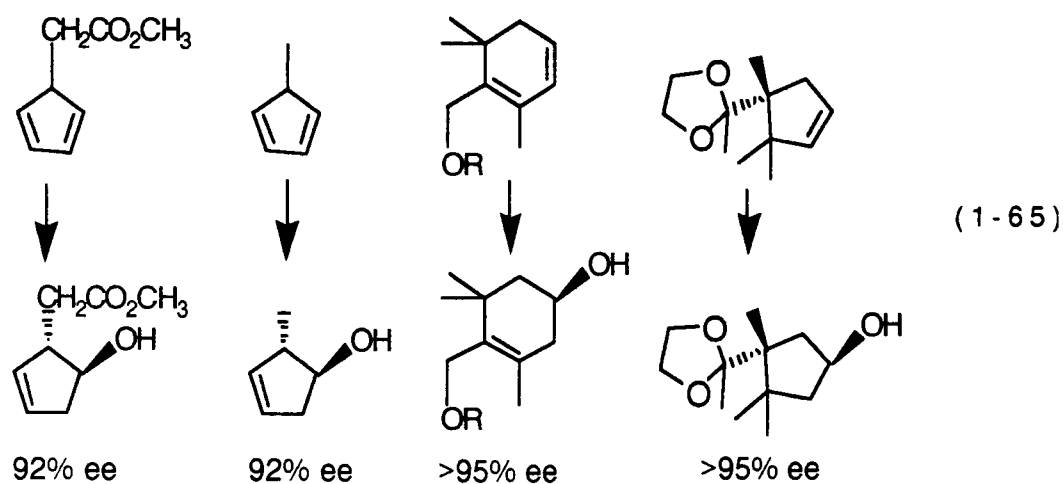
Diisopinocampheylborane (Ipc₂BH, 20) is one of the most versatile chiral reagents available for asymmetric synthesis⁹⁸. It has been applied to the asymmetric hydroboration of alkenes and subsequent transformations of the resultant organoborane intermediates into a variety of chiral products such as alcohols⁹⁹, amines¹⁰⁰, halides¹⁰¹, ketones¹⁰², and other products¹⁰³. The excellent asymmetric induction achieved with *cis*-alkenes has been applied to the synthesis of natural products¹⁰⁴.

Commercial *alpha*-pinene is only 92% optically pure. However, the crystalline Ipc_2BH formed on hydroboration of *alpha*-pinene (92% ee) is recrystallized at 0 °C in the presence of a slight excess of *alpha*-pinene; after the recrystallization the reagent is obtained in nearly 100% ee, (1-62). Excellent asymmetric induction is obtained in the hydroboration-oxidation of *cis*-olefins with Ipc_2BH of high enantiomeric purity¹⁰⁵ (1-63).



This reaction has also been successfully applied to the asymmetric hydroboration of heterocyclic olefins in both high regio- and enantio-selectivities¹⁰⁶ (1-64).

Similarly, several synthetic intermediates have been prepared by using asymmetric hydroboration with Ipc_2BH followed by oxidation¹⁰⁷ (1-65).



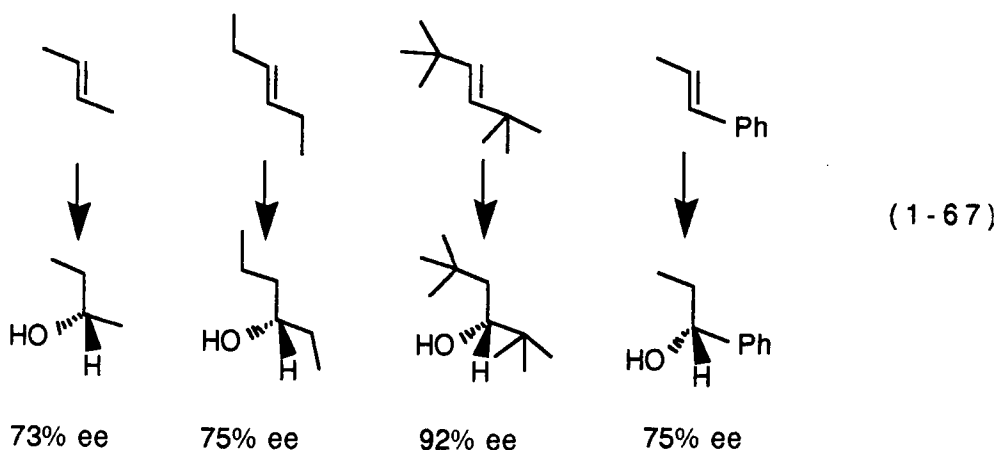
Diisopinocampheylborane hydroborates *cis*-alkenes very effectively. However, it is not a good asymmetric hydroborating agent for 2-substituted-1-

alkenes; very high selectivities have been achieved only when one of the two substituents is very bulky. A tylenolide precursor was obtained from the asymmetric hydroboration-oxidation of a complex 2-methyl-1-olefinic compound with (-)-Ipc₂BH¹⁰⁴ (1-66).

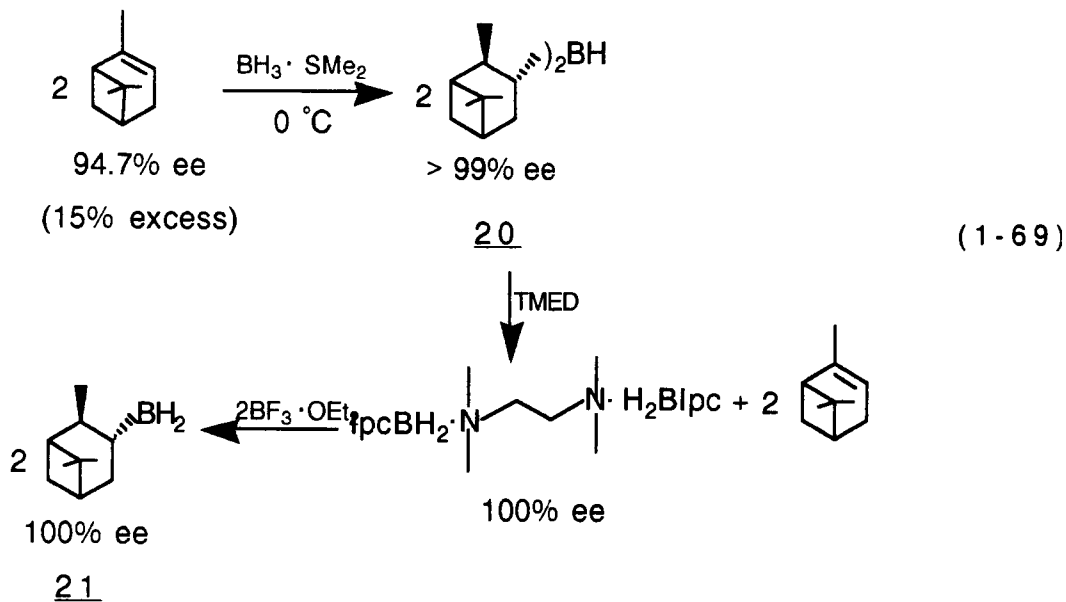
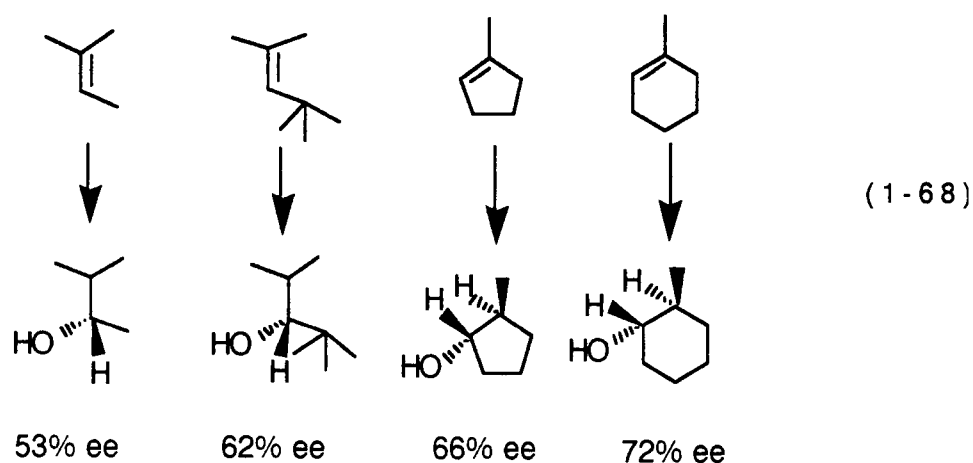
The steric requirements¹⁰⁸ of *trans*- and trisubstituted alkenes appear too large for the Ipc₂BH. This problem is partially solved by the synthesis and application of monoisopinocampheylborane (IpcBH₂, 21) for the asymmetric hydroboration of *trans*- and trisubstituted alkenes.

2. Asymmetric Hydroboration with Monoisopinocampheylborane.

With (E)-disubstituted alkenes the best results have been obtained using monoisopinocampheylborane, 21 (equation 1-69), but the reaction is strongly dependent on the bulk of the alkyl substituents attached to the double bond of the alkene. The effective asymmetric hydroboration-oxidation of *trans*-olefins with IpcBH₂ is shown in (1-67)¹⁰⁹.



Similarly, the hydroboration of trisubstituted alkenes with IpcBH_2 , followed by oxidation, provides the corresponding alcohols in reasonable enantiomeric purities (1-68)¹⁰⁹. It is worth noting that enhancement in the enantiomeric purity is observed for trisubstituted olefins containing a phenyl group^{109,110}.



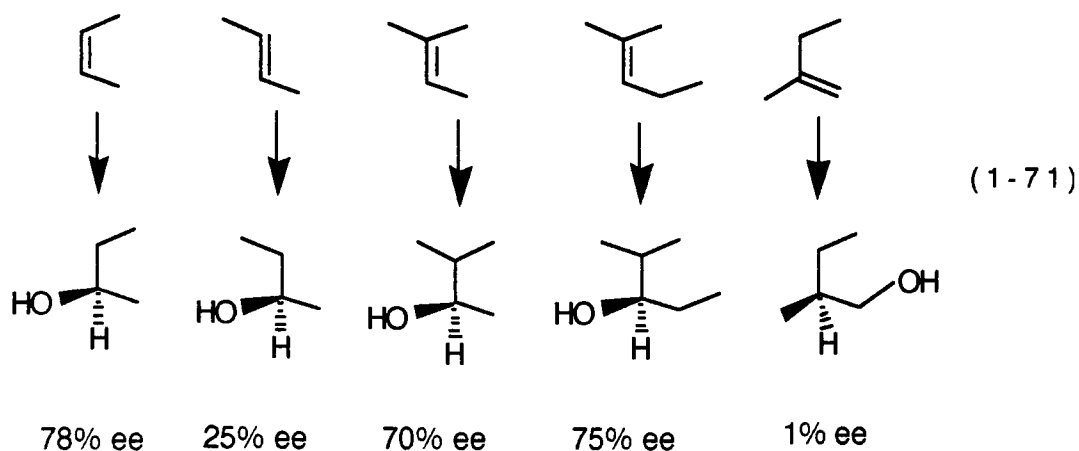
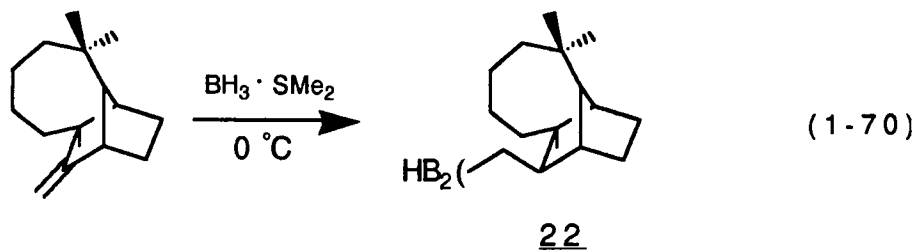
The preparation of IpcBH_2 is quite readily achieved from Ipc_2BH .

Hydroboration of *alpha*-pinene cannot be controlled to yield IpcBH_2 . The reaction generally proceeds rapidly past the IpcBH_2 to give Ipc_2BH . However, treatment of Ipc_2BH with 0.5 equivalent of N,N,N',N' -tetramethylethylenediamine (TMED) provides the 1:2 adduct, $\text{TMED} \cdot 2\text{BH}_2\text{IPC}$, with the liberation of one equivalent of *alpha*-pinene. The adduct crystallizes in enantiomerically and diastereomerically pure form. The reagent IpcBH_2 is readily liberated by treating the adduct with boron trifluoride etherate¹⁰⁸ (1-69).

Ipc_2BH and IpcBH_2 complement each other. However, they fail to provide access to high ee from alkenes of relatively low steric requirements.

3. Asymmetric Hydroboration with Dilongifolylborane.

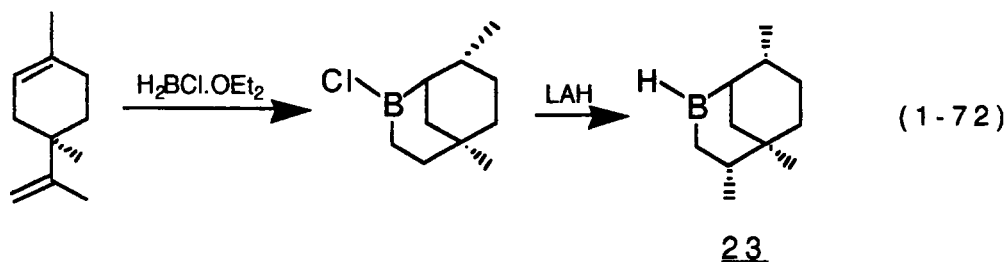
Dilongifolylborane^{95,111} (Lgf_2BH , 22) is prepared by the hydroboration of (+)-longifolene with borane dimethyl sulfide complex (1-70). Due to a large bridge effectively shielding the double bond from the *exo*-face of the longifolene, the hydroboration with borane occurs exclusively from the less hindered *endo*-side. Lgf_2BH has proven to be a very effective chiral hydroborating agent for *cis*-alkenes and trisubstituted alkenes (1-71). The asymmetric hydroboration of alkenes of different structure with Lgf_2BH helps in deducing the effect of steric requirements of the alkenes in achieving asymmetric induction.



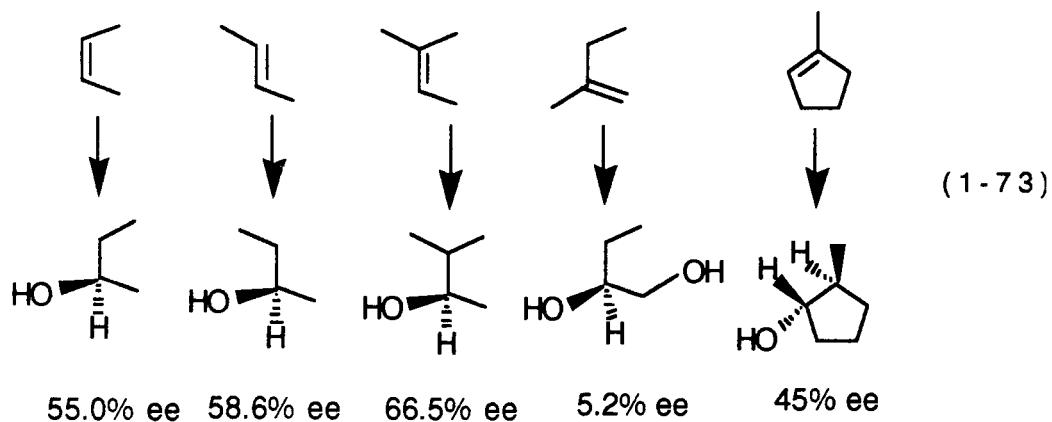
4. Asymmetric Hydroboration with Limonylborane.

Limonylborane^{95,112}, 2-bora-4,8-dimethylbicyclo[3.3.1]nonane (LimBH, 23), is another chiral hydroborating agent. It was the first boraheterocycle to be studied as a chiral hydroborating agent. In contrast to two other chiral dialkylboranes, Ipc₂BH and Lgf₂BH, the two alkyl groups in LimBH are unsymmetrical.

The synthesis of LimBH (1-72) is readily achieved by the cyclic hydroboration of limonene with monochloroborane followed by hydridation with LAH. The reagent is generated *in situ* by the hydridation of LimBCl in the presence of the olefin to be hydroborated.



LimBH achieves a high degree of asymmetric induction in the hydroboration of *cis*- and *trans*-alkenes and trisubstituted alkenes (1-73). It is interesting that the asymmetric induction in the hydroboration of both *cis*-2-butene and *trans*-2-butene is good and comparable (55 and 58% ee, respectively), in contrast to the other chiral hydroborating agents, which give excellent results only with *cis*-2-butene (Ipc₂BH and Lgf₂BH) or only with *trans*-2-butene (IpcBH₂). Both enantiomers of limonene are readily available. Consequently, chiral centers of the opposite configuration can be generated using LimBH derived from the appropriate antipode of limonene.



5. Asymmetric Hydroboration with Mono(2-ethylapoisopinocampheyl)-borane.

Brown postulated that increasing the steric bulk at the 2-position of pinene might lead to a favorable increment in the optical induction¹¹³. He prepared mono(2-ethylapoisopinocampheyl)borane (EapBH₂, 24) in a procedure similar to that used for the preparation of the IpcBH₂ reagent but utilizing (-)-(2)-ethylapopinene as starting material (1-74). A comparison of product alcohols resulting from the hydroboration-oxidation sequence using EapBH₂ and IpcBH₂ as hydroborating agents revealed that the new reagent provides significantly better ee than IpcBH₂ (Table 1-1). This indicates that further modification in the pinanyl moiety may provide even better chiral auxiliaries for asymmetric hydroboration.

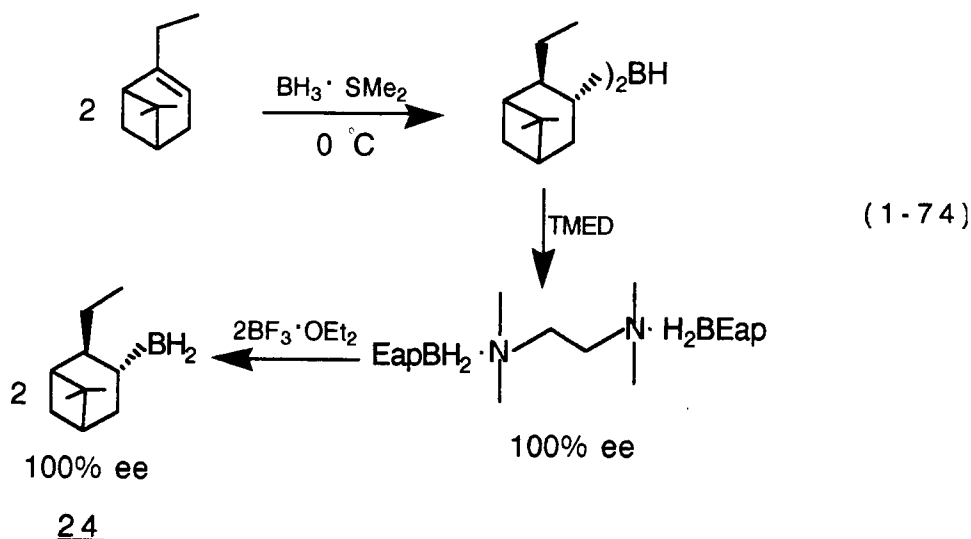
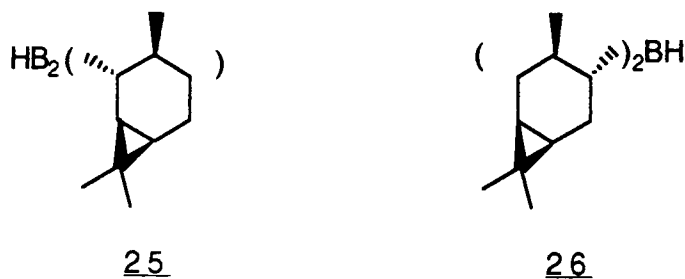


Table 1-1. Asymmetric Hydroboration of Representative Alkenes with EapBH₂ and IpcBH₂

Alkene	IpcBH ₂ %ee of product	EapBH ₂
2-methyl-1-butene	1.5	2.0
<i>cis</i> -2-butene	24	30
<i>trans</i> -2-butene	73	76
2-methyl-2-butene	53	68
1-methylcyclopentene	66	68
1-methylcyclohexene	72	78

6. Asymmetric Hydroboration with [1S]-Di-2-isocaranylborane and [1S]-Di-4-isocaranylborane.

The continuing efforts to develop new asymmetric hydroboration agents have resulted in two new hydroborating agents 2-Icr₂BH (25) and 4-Icr₂BH (26)¹¹⁴. The reagents are conveniently prepared by the

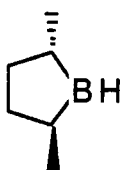
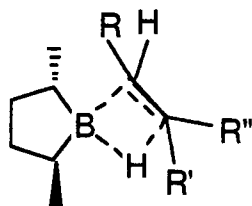


hydroboration of (+)-2- and (+)-(3)-carene with borane-dimethylsulfide in tetrahydrofuran. The reagents crystallize out of solution and are isolated by decantation.

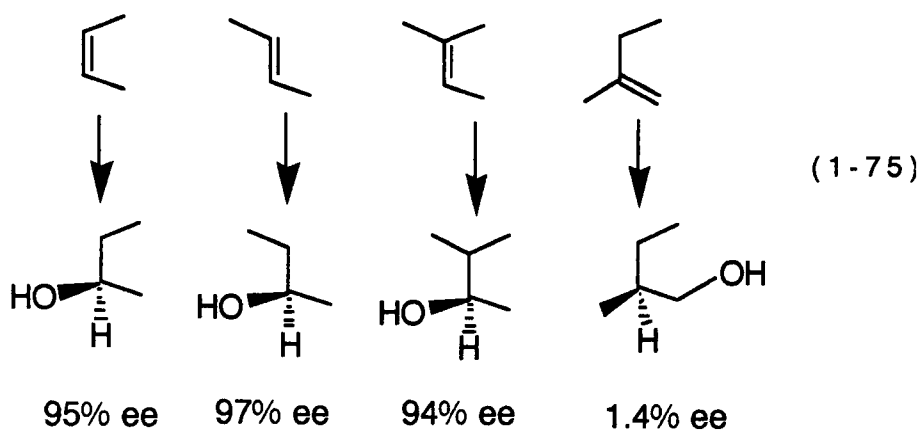
The hydroboration-oxidation of prochiral *cis*-olefins with 2-Icr₂BH (25) and 4-Icr₂BH (26) afford alcohols of opposite absolute configuration¹¹⁰. Enantioselectivity in the hydroboration of these alkenes with 2-Icr₂BH (25) is comparable to that achieved with 2-Ipc₂BH (20) and considerably higher than with 4-Icr₂BH (26). Both reagents hydroborate more rigid *cis*-olefins, e.g., norbornene, with good asymmetric induction. The hydroboration of simple heterocyclic five-membered ring olefins with 2-Icr₂BH (25) and 4-Icr₂BH (26) is facile and leads to the corresponding chiral alcohols of 27-85% ee.

7. Asymmetric Hydroboration with *trans*-2,5-Dimethylborolane.

A fascinating development has recently been reported by Masamune and his co-workers¹¹⁵. A new asymmetric hydroborating agent, *trans*-2,5-dimethylborolane, (27), has been synthesized and resolved. The C₂ symmetry which makes both faces of the boron atom equivalent, is an important feature in this reagent. This reagent appears to be superior to those mentioned previously in terms of chiral induction and thus the diastereoselectivity. Unfortunately the synthesis is quite complex. However, the reagent provides valuable information as to the transition state geometry of the hydroboration reaction. Investigations using the reagent reveal that the monoborane rather than the diborane is the reacting species and that the reaction involves a four-membered ring transition state 28.

2728

This reagent produces excellent results in the asymmetric hydroboration of three of the four representative classes of olefins. However, the 2-substituted-1-alkenes proved resistant (1-75).



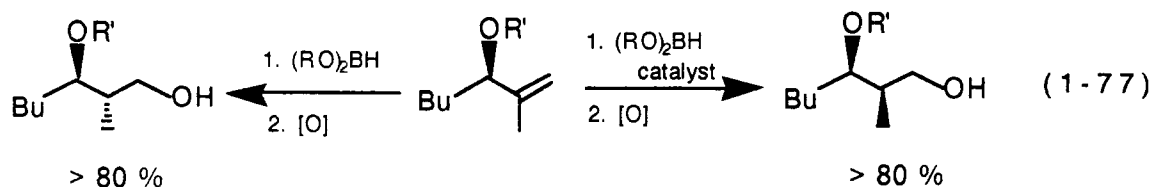
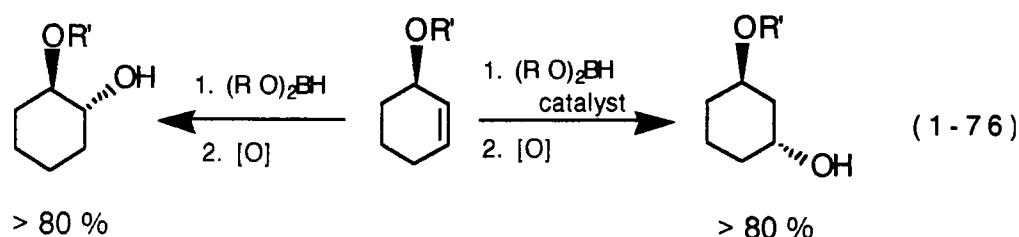
8. Asymmetric Hydroboration with Boranes in the Presence of Catalysts.

Until 1970¹¹⁶ it was generally assumed that only enzymes could function as effective asymmetric catalysts. Until that time, no non-enzyme, chiral catalyst had been found which would transform prochiral molecules into optically active chiral products. The dramatic discoveries of the chiral catalysts by Horner, Knowles and others^{117,118,119,120} opened the way to the syntheses of optically pure amino-acids and led to non-enzyme, catalyzed asymmetric syntheses.

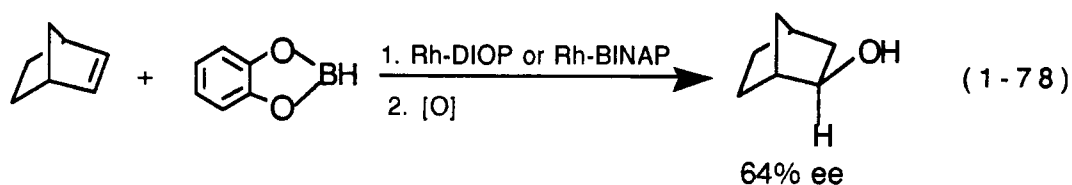
There have been several reports concerning the use of transition metal catalysts to deliver a B-H bond to a double bond. Examples include catalytic hydroboration with rhodium carboranes¹²¹, transition-metal promoted reaction of polyhedral boranes and carboranes¹²², as well as rhodium catalyzed addition of borazine to alkynes¹²³. However, these reactions are not practical for routine syntheses.

Evans and his co-worker¹²⁴ reported a rhodium-catalyzed, hydroboration process using catecholborane in the presence of Wilkinson's catalyst, $\text{Rh}(\text{PPh}_3)_3\text{Cl}$, which possessed better regio- and diastereoselective

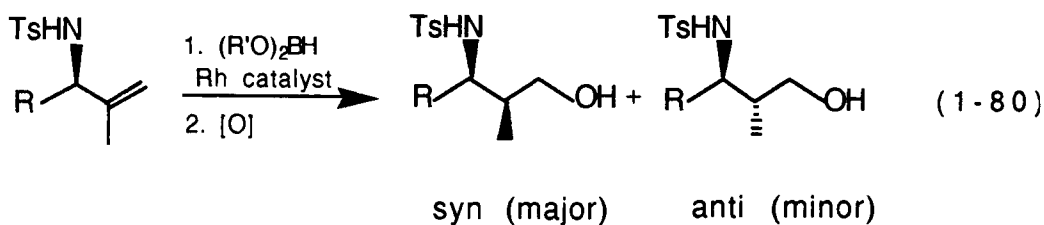
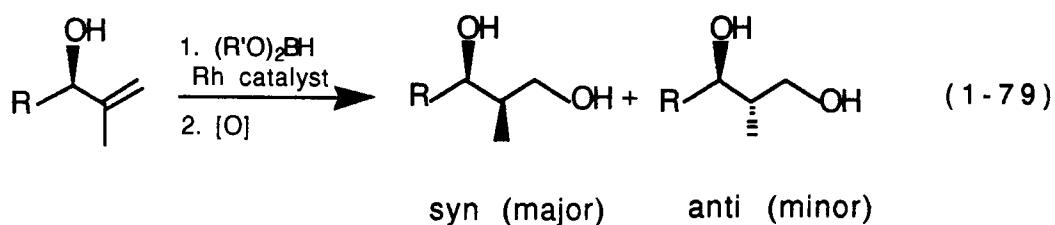
properties than $[\text{Rh}(\text{nbd})(\text{diphos-4})]\text{BF}_4$. The investigations revealed that in the hydroboration of cyclic 1,2-disubstituted allylic alcohol derivatives, the regioselectivity of the catalyzed reaction is opposite to that of the uncatalyzed variant (1-76). They also showed that the $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ -catalyzed hydroboration of 1,1-disubstituted allylic alcohol derivatives takes place with a high level of stereoselectivity but in a complementary sense to that observed with dialkylborane (1-77).



Burgess and Ohlmeyer¹²⁵ recently reported that the homochiral rhodiumphosphene complex [(2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, DIOP, or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, BINAP.) was employed to obtain enantioselective hydroborations (1-78).



Burgess and Ohlmeyer also reported the rhodium-catalyzed, diastereoselective hydroboration of protected allylic alcohols¹²⁶ (1-79) and allylic amine derivatives¹²⁷ (1-80). They proposed a model to rationalize the substrate-controlled diastereoselectivity in catalyzed hydroboration of chiral allylic alcohols and amines¹²⁸.



B. Asymmetric Reduction.

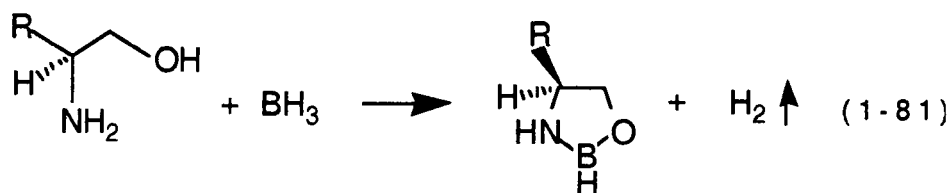
The syntheses of optically active molecules have traditionally fallen into three categories^{96,129}: stereoselective transformation of optically active starting materials, resolution of racemic mixtures, and asymmetric syntheses from prochiral substrates. Each of these methods has its own particular advantages and disadvantages that must be weighed in a synthesis¹³⁰.

One of the most useful asymmetric reactions is the reduction of a prochiral ketone to an optically active alcohol¹³¹; subsequently the resultant

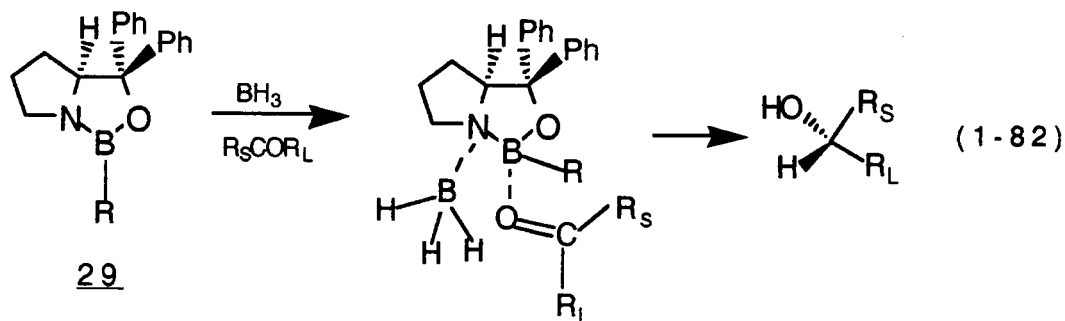
alcohol may serve as a chiral building block in a synthesis¹³². Boron derived asymmetric reagents have played important roles in asymmetric reduction.

1. Asymmetric Reduction Using Aminoborane Reagents.

The aminoborane complex $R^*NH_2 \cdot BH_3$ was the first reported borane agent for the chiral reductions¹³³. A similar approach involved the use of an aminoalcohol-treated borane complex to achieve chiral reductions¹³⁴ (1-81).

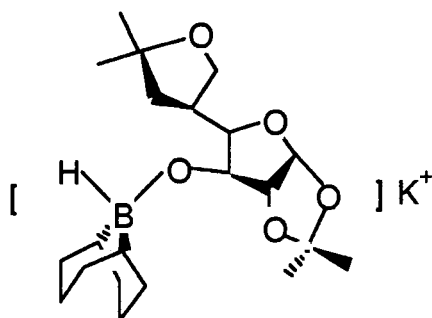


Corey and his co-workers¹³⁵ developed a series of highly effective reagents for enantioselective reductions of ketones, using borane as reducing agent in the presence of the chiral aminoalcohol-boron complex, oxazaborolidines, (29), as a catalyst, (1-82).



2. Asymmetric Reduction Using Alkoxyborohydrides.

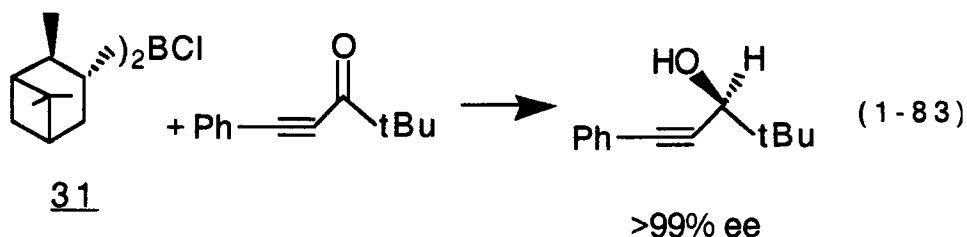
Hirao and co-workers¹³⁶ reported that sodium borohydride in the presence of a hydroxy monosaccharide is a modestly effective reducing agent¹³⁷. Their reports opened a new approach of asymmetric reduction. Brown's group developed a highly effective chiral borohydride reagent, K-glucoride, (30)¹³⁸.



30

3. Asymmetric Reduction Using Organoborane Derivatives.

Brown¹³⁸ and Midland⁹⁶ developed a series of organoborane derived reducing agents including B-chlorodiisopinocampheylborane (Ipc₂BCl, 31), which reduces a wide variety of prochiral ketones to optically active alcohols. For example, Ipc₂BCl reduces *alpha,beta*-acetylenic ketones to propargylic alcohols in very high enantiomeric excess¹³⁹ (1-83).

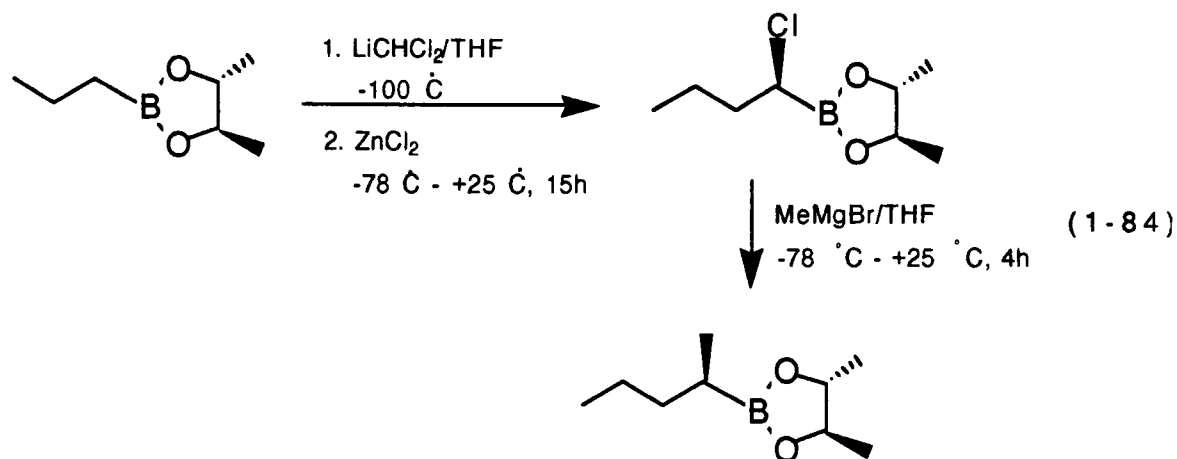


C. Asymmetric Synthesis via Boronic Esters.

An advantage of boronic esters (or acids) is that the single organic group is totally differentiated from alkoxy ligands so that the carbon-boron linkage can be utilized very efficiently¹⁴⁰. The stability of boronic esters generally allows rigorous purification, which provides a simple approach to pure boron derivatives. Boronic esters have been extensively applied in asymmetric organic syntheses of insect pheromones, carbohydrates, amino acids, etc. This topic has been reviewed by D. S. Matteson^{141,142}.

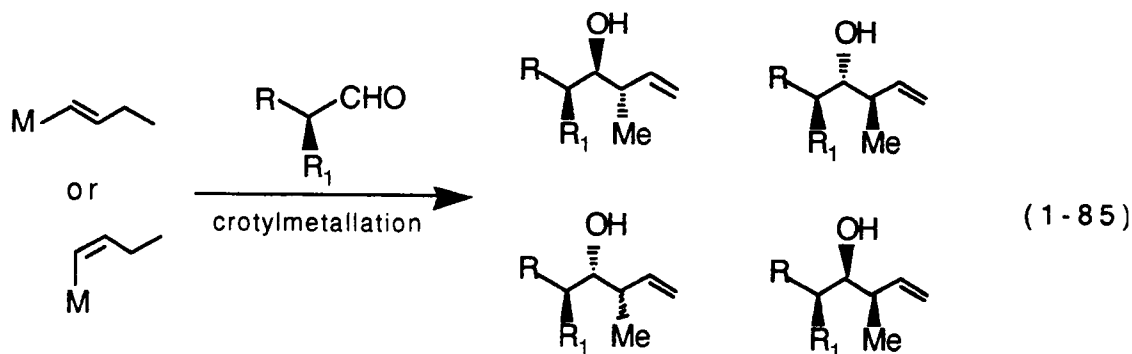
Homologation¹⁴³ is one of the most widely used applications of boronic esters in asymmetric organic synthesis. It is a simple but efficient procedure for the sequential installation of chiral carbon atoms in a highly stereoselective manner (1-84).

The treatment of the asymmetric Ipc_2BH or IpcBH_2 hydroboration products with acetaldehyde¹⁴⁴ removes the isopinocampheyl group as *alpha*-pinene and yields the optically active boronic ester. The resultant boronic ester intermediates have been widely used in organic synthesis^{140,141,143}.

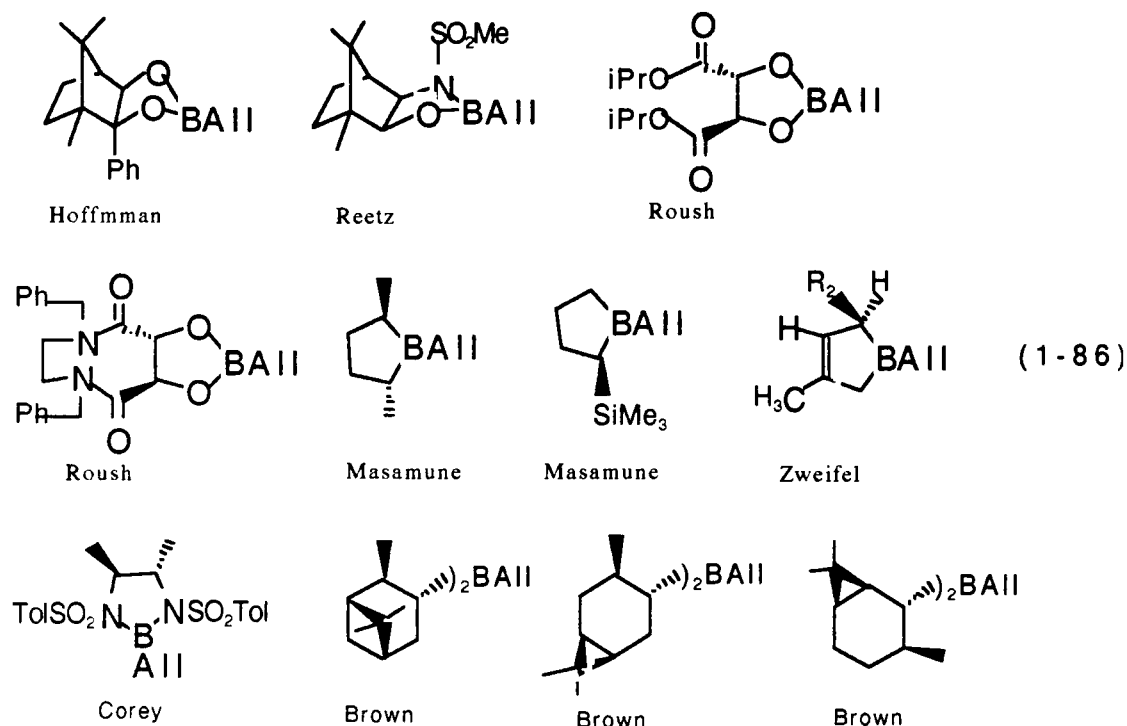


D. Asymmetric Allyl- and Crotylboration.

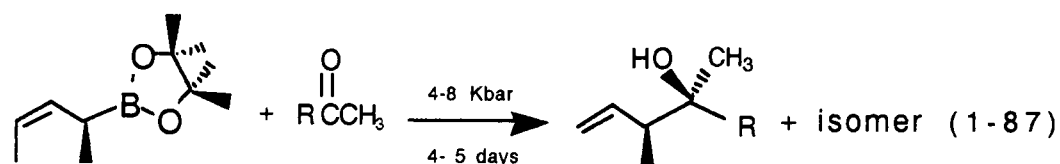
The development of new methods for acyclic diastereo- and enantiomeric control of chiral centers is of current importance in synthetic organic chemistry^{145,146,147}. The stereoselective allylation of prostereogenic carbonyl compounds is one of the most useful stereoselective reactions in that several stereogenic centers can be generated in a single step^{148,149} (1-85). Over the past few years, allyl- and crotylboration have



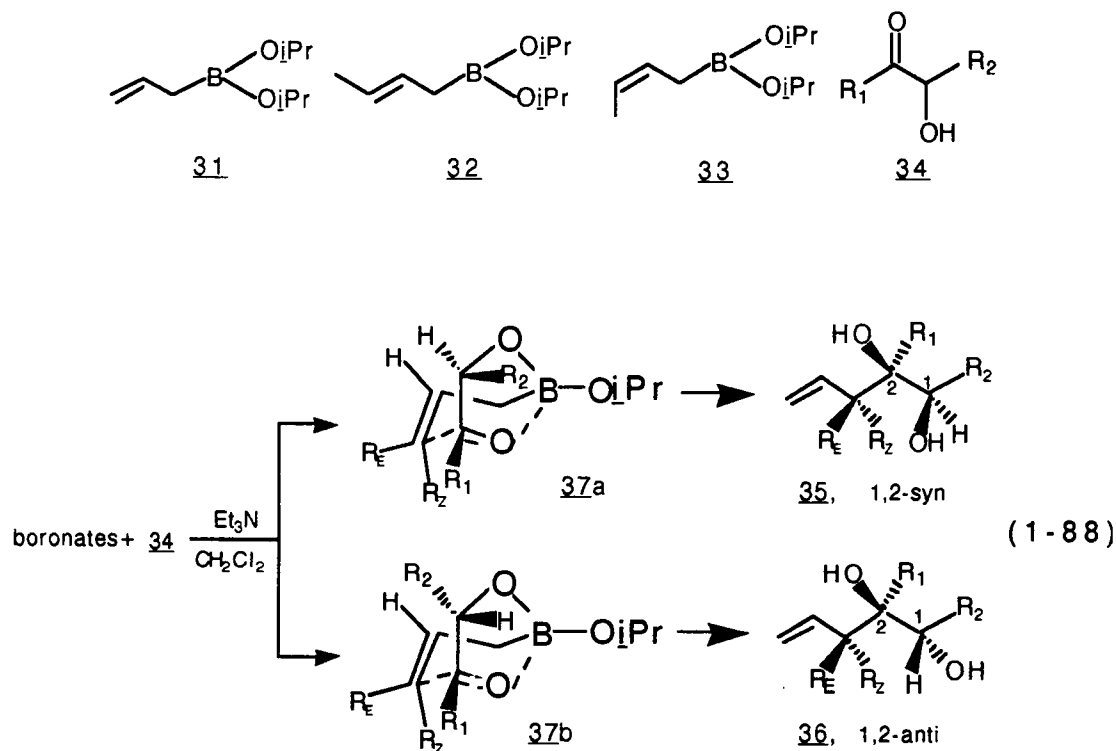
proven to be valuable in asymmetric and double asymmetric syntheses¹⁵⁰. Several chiral reagents (1-86) have been devised in recent years from which enantio- and diastereoselectivities approaching 100% have been achieved¹⁵¹.



There are few reports on the allylation of ketones due to the low reactivity of ketones and the low stereoselectivity of ketone reactions. For example, Hoffmann reported the addition of (E)- and (Z)-pentenylboronates to ketones¹⁵². The reactions proceeded under a high pressure and for a period of 4-5 days (1-87).

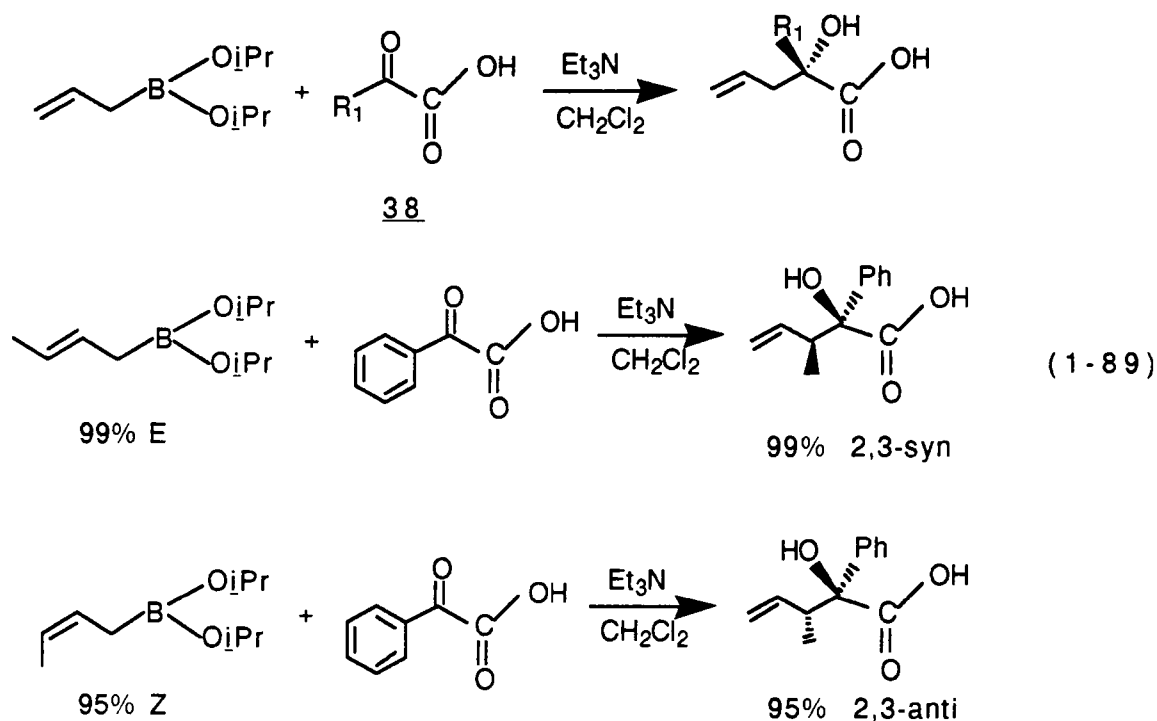


Kabalka and his co-workers have found that allylboronate, (31), (E)-crotylboronate, (32), and (Z)-crotyl-boronate, (33), react with *alpha*-hydroxyketones, (34), to yield tertiary homoallylic alcohols, (35), stereoselectively¹⁵³. The essential functions of the OH group in this case are: (1) activating the carbonyl group, and (2) directing the incoming reagents. The allylic addition of ketones is promoted by base. Our results suggest that the reaction proceeds through a rigid bicyclic transition state (1-88). Bulkier R₂ groups favor the transition state 37a over that of 37b and lead to a *syn/anti* ratio approaching 100%.



Kabalka and his co-workers have also found that allyl- and crotylboration of *alpha*-oxocarboxylic acids, 38, yield tertiary homoallylic,

alpha-hydroxy-carboxylic acid regio-, chemo- and stereoselectively (1-89)^{154,155}. The excellent selectivities suggest that the reaction proceeds through a bicyclic transition state, and the transition state results in regio-, chemo- and stereoselectivities approaching 100%.



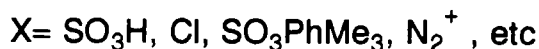
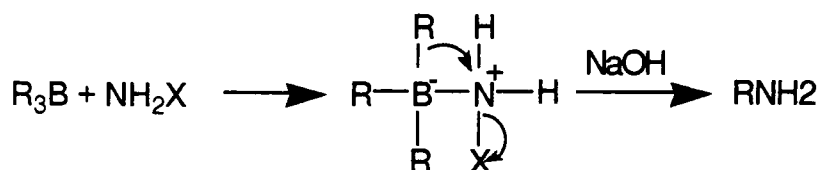
E. Summary.

A wide variety of organic groups of 100% ee can be attached to boron and are now readily available in organic synthesis. They can be easily converted into reagents such as $R^*B(OR)_2$, LiR^*BH_2 , R^*BH_2 , R^*BHX , R^*BX_2 , R^*RBOR , $R^*HBC(CH_3)_2CH(CH_3)_2$, LiR^*RBH_2 , R^*RBH , and R^*RBX .

The important characteristic of the reaction of organoboranes (and these of organoboron reagents) is that the organic group transfers from boron to other elements, including carbon, with defined stereochemistry. Consequently, remarkable synthetic transformations are now possible which provide general methods for the synthesis of enantiomerically pure products.

Section III: Statement of the Problem.

The syntheses of primary amines via organoborane intermediates has been extensively studied by both Brown and Kabalka. The studies have established that trialkylboranes can be converted into primary amines on treatment with hydroxylamine-O-sulfonic acid, chloramine, O-mesitylene hydroxylamine, chloramine-T, and azide derivatives.



However, the reactions are often not practical in organic syntheses due to the harsh reaction conditions and the long reaction times. Amination reactions of trialkylboranes are also complicated by the fact that hydroborations involving BH_3 are regioselective but not regiospecific; furthermore, only one or two of the three alkyl groups are utilized in the amination reactions. Moreover, the reaction of the more hindered

alkylborane derivatives are very sluggish and yields are decreased. The practical need for isotopically labeled nitrogen compounds revealed a demand for the development of a procedure for the syntheses of a variety of amines. It was, therefore, decided to investigate the synthesis of dialkylamines via a hydroboration-amination reaction sequence utilizing the reaction of trialkylboranes with alkylchloramines generated *in situ* (Chapter II).

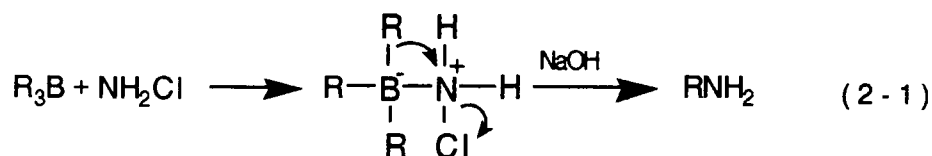
As a part of a program involving the syntheses of nitrogen-13 labeled amino compounds, a rapid, convenient and easy to manipulate one-pot method to prepare isomerically pure amino compounds was required. Therefore, the syntheses of isomerically pure primary and secondary amines via the reaction of dimethylalkylboranes with *in situ* generated chloramine and alkylchloramines were investigated (Chapter III). Reactions of functional olefins using dimethylborane were also investigated; the resultant organoboranes were subsequently converted to diamines and amino acids (Chapter IV). Finally, the hydroboration-amination reaction was extended to the syntheses of isomerically pure nitrogen-13 labeled amines, diamines and amino acids (Chapter V).

Chapter II.

Reaction of Trialkylboranes with Alkylamines: Syntheses of Dialkylamines

A. Introduction:

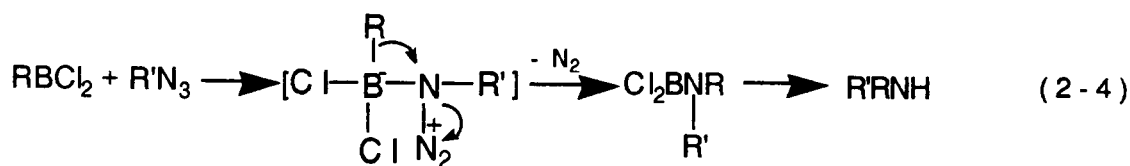
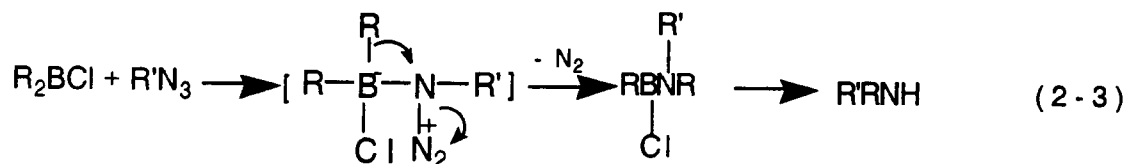
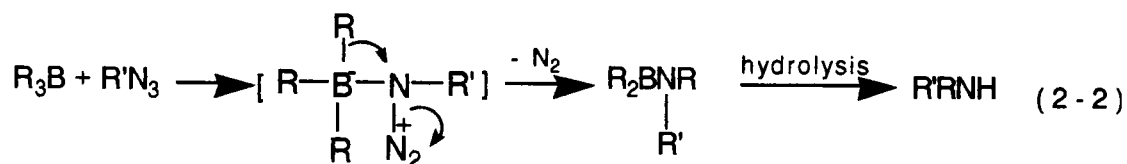
Organoboranes have proven to be valuable synthetic intermediates due to their ease of formation and facile reactivity.^{1,2} Many of the borane rearrangements involve anionotropic rearrangements of appropriately substituted organoborate complexes; generally, an alkyl group migrates from an electron-rich boron atom to an electron-deficient neighboring atom.^{6,21} The reaction has been used to prepare a wide variety of organic molecules including those in which the migration terminus is a nitrogen atom.⁶⁹ The nature of the leaving group^{6,72} and the groups^{72,156,157,158,159,160,161} attached to the nitrogen have been varied extensively. The reaction of chloramine with organoboranes is representative of these reactions and provides a unique method for the preparation of alkylamines (2-1)^{162,163}.



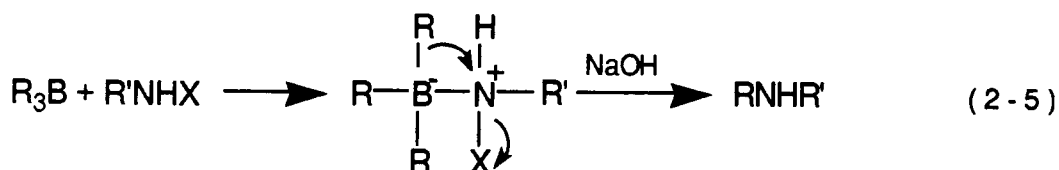
However, the preparation of the precursor chloramine is tedious and the reagent is not stable^{162,164}. In general, the reaction of trialkylboranes with

freshly prepared chloramine proceeds in the presence of aqueous sodium hydroxide and only one or two out of three alkyl groups in R_3B is utilized. Kabalka and his co-workers reported an improved procedure to synthesize alkylamines by utilizing the reaction of trialkylboranes with chloramine generated *in situ*^{71,165}.

Dialkylamines can also be synthesized by reaction of trialkylboranes¹⁶⁶, dialkylchloroboranes¹⁶⁷ and alkylchloroboranes¹⁶⁸ with various organic azides (2-2, 2-3, 2-4).¹⁶⁹



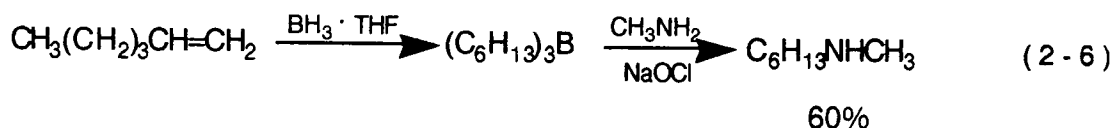
In this chapter we describe the first successful preparation of dialkylamines via the reaction of trialkylboranes with alkylchloramines (2-5).



B. Results And Discussion.

Organoboranes do not readily react with sodium hypochlorite whereas alkylamines react with sodium hypochlorite instantaneously at low temperature to generate N-chloroalkylamines^{162,163,164,170}. The reaction of aqueous methylamine with sodium hypochlorite in the presence of trihexylborane was examined under a variety of conditions.

Initial studies of the *in situ* process revealed that alkylamines were produced in approximately 60% yield when trialkylboranes, methylamine and sodium hypochlorite were used in approximately equimolar amounts (2-6)

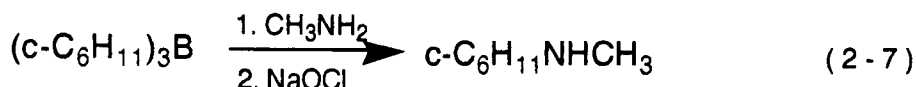


1. Investigation of the Reaction of Trialkylboranes with N-Alkylchloramines Generated *In Situ*.

Studies designed to optimize the reaction conditions were carried out. The investigations involved two different methods for preparing the N-chloroalkylamines: Method A (one-pot reaction) in which the sodium hypochlorite was added dropwise to a mixture of organoborane and alkylamine and Method B (two-pot reaction) in which the sodium hypochlorite was first added to the alkylamine and this solution was then added to the organoborane.

a. One-Pot Procedure: Method A.

Methylamine (1 equivalent) was added slowly to a solution of an organoborane, such as tricyclohexylborane, freshly generated in THF at 0 °C. An aqueous solution of sodium hypochlorite (1 equivalent) was then added dropwise at 0 °C. The reaction mixture was maintained at 0 °C for 10 minutes, allowed to warm to room temperature, and then stirred for 1 hour. The desired product, N-methylcyclohexylamine, was formed in good yield (67%) (2-7).



b. Two-Pot Procedure: Method B.

In a parallel experiment, methylamine was mixed with sodium hypochlorite at 0 °C in a flask. After stirring the mixture for 2 minutes at 0 °C, the solution was then added dropwise to another flask containing one equivalent of a trialkylborane such as tricyclohexylborane (freshly produced) in THF at 0 °C. The reaction mixture was maintained at 0 °C for 10 minutes, allowed to warm to room temperature, and then stirred for 1 hour. The desired product, N-methylcyclohexylamine, was formed in good yield (75%)

Both methods were utilized throughout the study. In general, Method B produce slightly higher yields (10 percent) of the desired product. However,

Method A is operationally simpler, faster, and more suitable for radiolabeling studies.

2. Stoichiometry.

In an attempt to attain maximum efficiency, the stoichiometry of the reaction was examined. The initial reactions were carried out by adding aqueous methylamine followed by aqueous sodium hypochlorite (Method A) or a mixture of methylamine and sodium hypochlorite (Method B) to a solution of trialkylborane in THF under an inert atmosphere. Preliminary experiments revealed that an excess (50% and 100%) of amine and hypochlorite did not increase the reaction yields. In fact, excess hypochlorite was found to be deleterious in a number of ways, each of which depended on the addition sequence. In the absence of the borane, the alkylamine reacts with hypochlorite to form alkyl-N,N-dichloramine (in addition to the desired alkylchloramine), which then reacts with a trialkylborane to generate alkylchloride via a free radical pathway. Alternatively, hypochlorite may react with the product dialkylamine to form N-chloro-derivatives.

Excess organoborane did not increase reaction yields; instead, it reduced them. This may be a consequence of a competition between the organoborane and the alkylamine for the sodium hypochlorite (this will be discussed later). However, in Method B, excess trialkylborane did not reduce the reaction yield significantly. These studies are summarized in Table 2-1 and Table 2-2.

Table 2-1. Stoichiometry Study--Method A

Entry ^a	R ₃ B ^b (mmol)	MeNH ₂ ^c (mmol)	NaOCl (mmol) ^d	yield% ^e
1)	10	10	10	68
2)	10	15	15	70
3)	10	20	20	65
4)	15	10	10	50
5)	10	10	20	30

a) Reactions were run at 0 °C under a nitrogen atmosphere, allowed to stir for 10 minutes, and then stirred an additional hour at room temperature.

b) Trihexylborane was used in this investigation.

c) 40% aqueous methylamine was used as alkylamine source.

d) Standardized commercial bleach (0.74 M) was used as sodium hypochlorite source.

e) Isolated yields were based on one R group migration from R₃B.

Table 2-2. Stoichiometry Study--Method B^a

Entry ^b	R ₃ B ^c (mmol)	MeNH ₂ ^d (mmol)	NaOCl (mmol) ^e	Yield% ^f
1)	10	10	10	78
2)	10	15	15	79
3)	10	20	20	80
4)	15	10	10	55
5)	10	10	20	30

- a) The N-methylchloramine was formed by mixing methylamine and sodium hypochlorite at 0 ° C, and then adding trialkylborane in THF dropwise after 2 minutes.
- b) Reactions were run at 0 ° C under a nitrogen atmosphere for 10 minutes and then stirred an additional hour at room temperature.
- c) Trihexylborane was used in this investigation.
- d) 40% Aqueous methylamine was used as alkylamine source.
- e) Standardized commercial bleach (0.74 M) was used as sodium hypochlorite source.
- f) Isolated yields were based on one R group migration from R₃B.

3. Order of Addition.

The amination reaction was normally carried out by adding N-alkylchloramine to a trialkylborane solution (Methods A and B). However, a reverse addition experiment was performed in which a trihexylborane-THF solution (1 equivalent) was added to an aqueous solution of N-methylchloramine at 0 °C. After work up, the reaction yield was decreased (30%) probably due to the temporary excess of the concentration of alkylamine and sodium hypochlorite.

4. Temperature Effect:

A series of experiments were performed in which the reaction temperature was varied using Method A. In this study, the same ratios of trihexylborane, methylamine, and sodium hypochlorite were utilized. Our investigations (Table 2-3) revealed that the amination reaction was not very sensitive to temperature in the range of -20 °C - 80 °C.

The effect of temperature on the yields obtained using Method B was also investigated under similar reaction conditions. The results verified that Method B was insensitive to temperature. Initiating the reaction at 0 °C and then allowing the reaction mixture to warm to room temperature was found to be the optimum reaction condition.

Table 2-3. Effect of Reaction Temperature-Method A.

Entry ^a	Temperature range (°C)	Yield% ^b
1	0° to 22°	67
2	-20° to 22°	60
3	0° to 80°	62

- a) Reactions were carried out at the indicated temperature for 5 minutes, allowed to warm to the final temperature, and then stirred for one hour.
- b) Isolated yields based on one R group migration from R₃B.

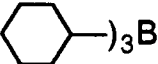
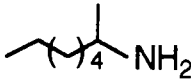
5. Steric Effects.

The hydroboration-amination reactions are sensitive to certain steric interactions as shown in (Table 2-4). Trihexylborane and tricyclohexylborane gave good yields of the corresponding methylalkylamines on treatment with N-methylchloramine; tri-*exo*-norbornylborane also produced the desired N-methylnorbornylamine in good yield. These observations indicate that the reaction does not appear to be sensitive to the steric requirements of the organoborane. On the other hand, the reaction cannot be utilized with hindered amines, such as 1-methylheptylamine. These observations are consistent with the proposed formation of a complex between the organoborane and the N-chloramine, which would form more slowly, if at all, when the complexing chloramines are sterically crowded. Retardation of complex formation is presumably responsible for the dichotomy observed for the reactions of trialkylboranes with amination reagents; N-chlorodialkylamines react with trialkylboranes to yield chloroalkanes rather than the expected trialkylamines.

6. The Effect of Free Radical Inhibitors.

A. G. Davis, et al studied the reactions of N,N-dimethylchloramines with boranes in great detail¹⁷¹. They reported that, in the absence of free radical inhibitors, the principle reaction of dimethylchloramine with trialkylboranes was a radical chain reaction which converted the alkylborane to an alkylchloride. When a free radical inhibitor such as galvinoxyl was added, the

Table 2-4. Steric Effects in Amination Reactions

Entry ^a	Trialkylborane ^b	Alkylamine	Yield% ^c
1	 ₃ B	CH ₃ NH ₂	67
2	 ₃ B	CH ₃ NH ₂	68
3	 ₃ B	CH ₃ NH ₂	66
4	 ₃ B	 NH ₂	0
5	 ₃ B	(CH ₃) ₂ NH	0

- a) Reactions were carried out using equal molar quantities of trialkylborane, alkylamine, and sodium hypochlorite using method A.
- b) Trialkylboranes were freshly prepared.
- c) Isolated yields based on one R group migration from R₃B.

free radical reaction was suppressed, and the major product was the tertiary amine.

In preliminary studies, the reaction yields were normally in the range of 60%-80%. Consequently, it was suspected that a competitive free radical chlorination reaction might be a competing side reaction^{172,173}. Analysis of the reaction mixture of trihexylborane with N-methylchloramine by gas chromatography revealed up to 15.3% yield of hexylchloride. Examination of a reaction of N-butylchloramine with trihexylborane revealed 14.5% hexylchloride.

The borane-amination reaction was investigated in the presence of galvinoxyl. Both Method A and Method B were examined. The reaction conditions were similar to the normal reaction procedures except for the addition of 0.1 - 0.4 equivalent of galvinoxyl to the reaction mixture after mixing the alkylamine and sodium hypochlorite (Method A) or prior to reaction with the organoborane (Method B).

The results support the postulation that a competitive free radical pathway is involved in reactions of trialkylboranes with chloramine reagents. Gas chromatographic analyses of the various reaction mixtures (Table 2-5 and 2-6) indicate that modest quantities of chloroalkanes (5-15%) are formed as byproducts in all reactions. Upon addition of galvinoxyl, the chloroalkane byproducts essentially disappear (<3%) and a concomitant increase in the yields of desired dialkylamine products is observed (2-8).

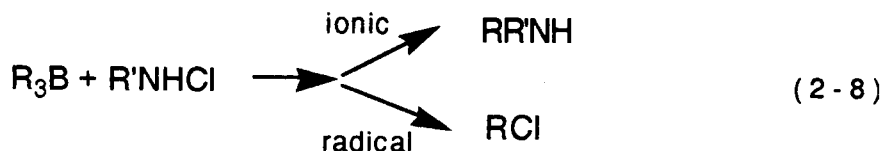
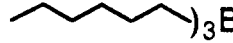


Table 2-5. The Effect of Free Radical Inhibitors-Method A^a.

Entry ^b	Organoborane 1 equivalent	Alkylchloramine 1 equivalent	Galvinoxyl equivalent	Yield % ^c	
				amine	chloralkane
1	 B	MeNHCl	0.0	82.5	15.7
2	 B	MeNHCl	0.1	88.0	11.8
3	 B	MeNHCl	0.2	95.0	2.7
4	 B	MeNHCl	0.4	94.8	2.0
5	 B	n-BuNHCl	0.0	82.0	10.8
6	 B	n-BuNHCl	0.2	90.0	8.0
7	 B	n-BuNHCl	0.4	91.0	5.0
8	 B	Me ₂ NCl	0.0	0.0	80.0
9	 B	Me ₂ NCl	0.2	8.0	75.0
10	 B	Me ₂ NCl	0.4	10.0	76.0

- a) Reactions were started at 0 °C (Method-A), followed by the immediate addition of galvinoxyl in the amount indicated under a nitrogen atmosphere; the mixture was stirred for 10 minutes and then kept an additional hour at room temperature.
- b) The reactions were run on a 3.0 mmol scale.
- c) GC yields.

Table 2-6. The Effect of Free Radical Inhibitors-Method B^a.

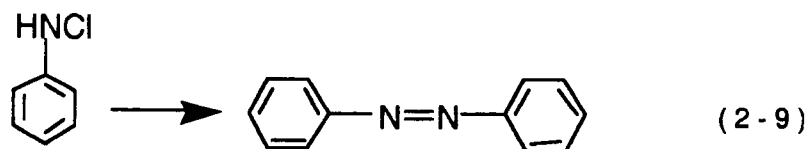
Entry ^b	Organoborane 1 equivalent	Alkylchloramine 1 equivalent	Galvinoxyl equivalent	Yield % ^c	
				amine	chloroalkane
1	 _3B	MeNHCl	0.0	85.0	13.1
2	 _3B	MeNHCl	0.1	92.0	7.0
3	 _3B	MeNHCl	0.2	96.0	2.0
4	 _3B	MeNHCl	0.4	96.0	1.3
5	 _3B	n-BuNHCl	0.0	86.0	9.0
6	 _3B	n-BuNHCl	0.2	92.0	4.0
7	 _3B	n-BuNHCl	0.4	92.0	3.0
8	 _3B	Me ₂ NCl	0.0	0.0	75.0
9	 _3B	Me ₂ NCl	0.2	11.0	72.0
10	 _3B	Me ₂ NCl	0.4	11.0	71.0

- a) Reactions were started at 0 °C (Method-B), followed by the immediate addition of galvinoxyl in the amount indicated above under a nitrogen atmosphere; the mixture was stirred for 10 minutes and then kept an additional hour at room temperature.
- b) The reactions were run on a 3.0 mmol scale.
- c) GC yields.

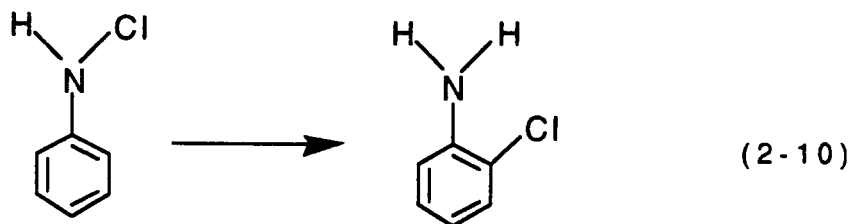
As anticipated, the reaction involving the more sterically demanding N-chlorodimethylamine produced only a trace of the desired trialkylamine; 1-chlorohexane was the only product identified (75% yield).¹⁷¹ Interestingly, the addition of galvinoxyl to this reaction mixture had no significant effect on the product distribution. These studies are summarized in Table 2-5 (Method A) and Table 2-6 (Method B).

7. Aromatic Amines.

Aromatic compounds, such as aniline, were examined as the organic chloramine source. The reaction of trihexylborane with aniline, in the presence of sodium hypochlorite, did not produce any of the desired product using both Method A and Method B because the desired N-hexylaniline could not be prepared. Instead, the reaction mixture became dark black. This is presumably due to the formation of azobenzene (2-9)¹⁷⁴ through a coupling reaction of N-chloramine. Using both Method A and Method B, the desired



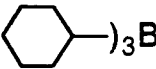
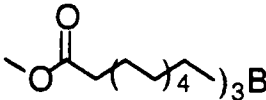
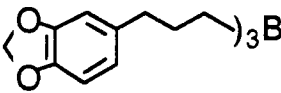
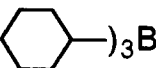
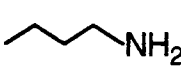
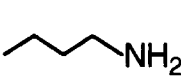
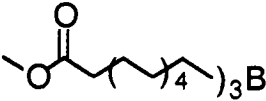
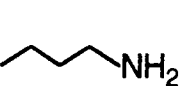
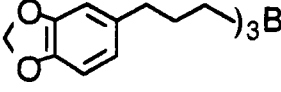
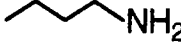
N-hexylaniline. The failure of the amination reaction might also be due to the rearrangement of the N-chloroaniline¹⁷⁵(2-10).



8. Syntheses of Dialkylamines via the Reaction of Trialkylboranes with the Alkylchloramines Generated *In Situ*.

After the preliminary studies, a series of representative dialkylamines were synthesized. Both Methods A and B were employed throughout the study. In general, Method B produces slightly higher yields of the desired product. The reactions were run at 0°C utilizing equimolar quantities of organoboranes, alkylamines and sodium hypochlorite, and then warmed to room temperature. The alkenes were each hydroborated with BH₃-THF, and then the resulting organoboranes, illustrated in Tables 2-7 and 2-8, were aminated. The amine products were isolated via a standard acid-base work up followed by chromatographic purification. The yields were calculated based on the amount of alkylamine added. The results are summarized in Tables 2-7 and 2-8. The data demonstrate that the reaction tolerates various functional groups in the organoboranes, an important consideration in many syntheses. The reaction is not sensitive to steric factors in the organoboranes. In addition, the mild and convenient reaction conditions make this procedure ideally suited for the use in important organic syntheses.

Table 2-7. Reaction of Trialkylboranes (R_3B) with Alkylamines ($R'NH_2$) to yield $RNHR'$ [Method A.]]^a

Entry	Organoborane ^b	Amine	Yield% ^c
1	 $_3B$	CH_3NH_2	67
2	 $_3B$	CH_3NH_2	68
3	 $_3B$	CH_3NH_2	66
4	 $_3B$	CH_3NH_2	68
5	 $_3B$	CH_3NH_2	68
6	 $_3B$		56
7	 $_3B$		65
8	 $_3B$		53
9	 $_3B$		59
10	 $_3B$		66

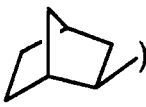
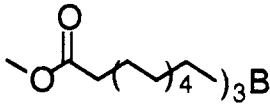
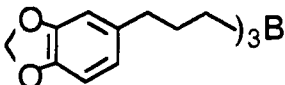
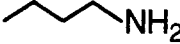
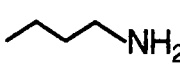
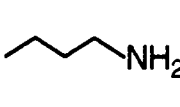
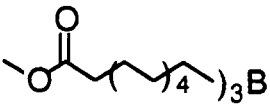
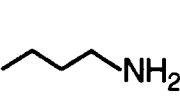
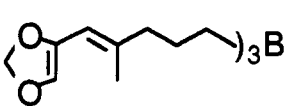
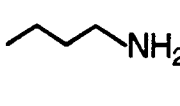
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Table 2-7. ... continued

Entry	Organoborane ^b	Amine	Yield% ^c
11			57
12			43
13			48
14			56
15			0
16			0
17		$(\text{CH}_3)_2\text{NH}$	0

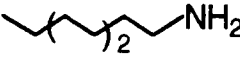
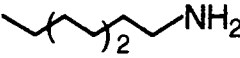
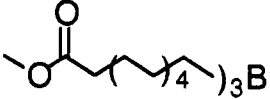
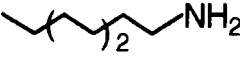
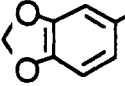
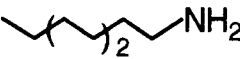
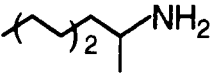
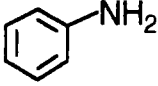
- a) The reactions were run at 0°C utilizing equimolar quantities of organoboranes, alkylamines and sodium hypochlorite, and then warmed to room temperature.
- b) The organoboranes were freshly prepared.
- c) Yields were based on one R group being transferred.

Table 2-8. Reaction of Trialkylboranes (R_3B) with Alkylamines ($R'NH_2$) to yield $RNHR'$ [Method B.]^a

Entry	Organoborane ^b	Amine	Yield% ^c
1	 $_3B$	CH_3NH_2	78
2	 $_3B$	CH_3NH_2	77
3	 $_3B$	CH_3NH_2	67
4	 $_3B$	CH_3NH_2	57
5	 $_3B$	CH_3NH_2	83
6	 $_3B$		72
7	 $_3B$		83
8	 $_3B$		59
9	 $_3B$		48
10	 $_3B$		61

cont'd.

Table 2-8. ... continued

Entry	Organoborane ^b	Amine	Yield% ^c
11	 ₃ B	 NH ₂	62
12	 ₃ B	 NH ₂	55
13	 ₃ B	 NH ₂	39
14	 ₃ B	 NH ₂	35
15	 ₃ B	 NH ₂	0
16	 ₃ B	 NH ₂	0
17	 ₃ B	(CH ₃) ₂ NH	0

- a) The reactions were run at 0°C utilizing equimolar quantities of organoboranes, alkylamines and sodium hypochlorite, and then warmed to room temperature.
- b) The organoboranes were freshly prepared.
- c) Yields were based on one R group being transferred.

C. Conclusion.

The present study led to the development of a simple and practical procedure for the conversion of alkenes and alkylamines into the corresponding dialkylamines. This synthetic method for preparing secondary amines from trialkylborane intermediates provides a fast and convenient general method for introducing N-alkylamino functionalities into olefins in a stereodefined manner.

D. Experimental Section.

All glassware, syringes, and syringe needles were thoroughly oven-dried prior to use. Gas chromatographic analyses were performed on a Varian Model 3700 gas chromatograph (10% SE30 on Chromosorb W80/100, 10 ft.). Both H-1 and C-13 NMR were recorded on a JEOL-FX 90 Q spectrometer and referenced to TMS. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Commercial bleach was used as the oxidant after titration to determine the concentration of sodium hypochlorite.¹⁷⁶ When applicable, commercially available chemicals, their manufacturers, and the methods of purification used, unless otherwise specified, are listed in Table 2-9.

Hydroboration. General Procedure. The alkene (30.0 mmol), in 10.0 mL of dry THF, was placed in a dry, 100-mL, nitrogen-flushed flask fitted with a septum inlet. The flask was cooled to 0 °C and BH₃·THF (10.0 mmol, 10.0 mL of a

Table 2-9. Manufacturer and Methods of Purification of Commercially Available Chemicals

Chemical	Manufacturer ^a	Method of Purification ^b
Acetic Acid	F	
Acetone	F	
Ammonium chloride	F	
Aqueous Ammonia	F	
Aniline	A	
Benzophenone	A	
Borane-THF	A	
Borane methyl sulfide	A	
Boron trifluoride	A	
n-Butylamine	A	
t-Butylamine	A	
Calcium hydride	A	
Calcium chloride	F	
Cyclohexene	A	1
Cyclohexylamine	A	2
Cyclopentylamine	A	2
1-Decene	A	1
Dichloromethane	M	3

cont'd

Table 2-9. ... continued

Chemical	Manufacturer ^a	Method of Purification ^b
Diglyme	A	
2,3-Dimethyl-1-butene	A	
Diethyl ether	M	4
Ethylene glycol	A	
1-Hexene	A	1
Hydrochloric acid	F	
Iodine	A	
Lithium aluminum hydride	A	
Magnesium, turnings	A	
Magnesium sulfate	F	
Methanol	F	
2-Methyl-1-butene	A	1
Methylamine (aqueous, 40%)	A	
Methyl iodide	A	
2-Methyl-1-pentene	A	1
Methyl 10-undecenoate	A	6
Mercury	A	
4A Molecular sieves	F	7
Dimethylamine	A	

cont'd

Table 2-9. ... continued

Chemical	Manufacturer ^a	Method of Purification ^b
Norbornene	A	
1-Octene	A	1
1-Octylamine	A	2
2-Octylamine	A	2
Pentene	A	1
Picric acid	A	
Potassium hydroxide	F	
Safrole	A	8
Silica gel	D	
Sodium	A	
Sodium bicarbonate	F	
Sodium chloride	F	
Sodium hydroxide	F	
Sodium sulfate	F	
Sodium thiosulfate	A	
Tetrahydrofuran	M	4
Triethylamine	A	5
Trimethylchlorosilane	A	3
Undecane	A	

a) Manufacturer:

A = Aldrich

D = Davison Chemical Company

F = Fisher

M = Mallinckrodt Chemical Company

b) Methods of Purification:

1 = Distilled from LAH

2 = Simple distillation

3 = Distilled from calcium hydride

4 = Distilled from sodium and benzophenone

5 = Distilled from potassium hydroxide

6 = Predried from molecular sieves

7 = Oven-dried

8 = Dried from molecular sieves

1.0 M solution) was added dropwise over a period of 3 min. The solution was allowed to warm to room temperature and stirred for 60 min.

Synthesis of Dialkylamines. General Procedure.

Method A. The trialkylborane (10.0 mmol in 10.0 mL of THF) was cooled to 0 °C under a nitrogen atmosphere; monoalkylamine (10.0 mmol) was slowly added followed by the slow addition of sodium hypochlorite (10.0 mmol). The solution was allowed to warm to room temperature and stirred at room temperature for 1 hours.

Method B. Sodium hypochlorite (10.0 mmol) was added dropwise to a solution of alkylamine (10.0 mmol) contained in a 25-mL flask cooled to 0 °C. This mixture was transferred into the flask containing the trialkylborane (10.0 mmol in 10.0 mL of THF) at 0 °C. The solution was allowed to warm to room temperature and stirred for 1 hours. [In reactions involving free radical inhibitors, galvinoxyl (0.29 mmol, 0.84 g) was added to the trialkylborane solution prior to the addition of the chloramine.]

Isolation. The reaction mixture (Method A or Method B) was then acidified to pH=1 (10% HCl) and then washed with diethyl ether. The free amines were obtained via the addition of sodium hydroxide (6.0 N) to the aqueous layer (pH > 13) and extraction of the product into ether. The ether layer was dried over potassium hydroxide and the product obtained, after removal of solvents, was

purified by chromatography (silica gel; chloroform/methanol/ammonia eluant).

1-(Methylamino)hexane. 1-Hexene (30. mmol, 2.5 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 1 hour. Methylamine (10 mmol, 0.78 g of a 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 0.77 g (67%) [Method A] and 0.90 g (78%) [Method B]; bp 137°C (lit⁶⁹ bp $138\text{--}140^\circ\text{C}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 52.5 (C-1), 31.8 (C-2), 27.0 (C-3), 29.9 (C-4), 22.6 (C-5), 14.0 (C-6), 36.5 (C-1'); ^1H NMR (CDCl_3), (ppm) 0.95 (3 H, CH_3), 1.17 (s, 1 H, NH, D_2O exchangeable), 1.26-1.60 (b, 8 H, $(\text{CH}_2)_4$), 2.43 (s, 3H, CH_3N), 2.62 (b, 2H, CH_2N).

(Methylamino)cyclohexane. Cyclohexene (33 mmol, 2.7 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 3 hour. Methylamine (10 mmol, 0.78 g of a 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 0.77 g (68%) [Method A] and 0.87 g (77%) [Method B]; bp 148°C (lit⁶⁹ bp $147\text{--}148^\circ\text{C}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 58.4 (C-1), 33.2 (C-2, 6), 26.2 (C-4), 25.0 (C-3, 5), 33.5 (C-1'); ^1H NMR (CDCl_3), (ppm) 0.92-2.02 (11 H, d. b, H's of cyclohexane), 2.25 (s, 1 H, NH, D_2O exchangeable), 2.40 (s, 3H, CH_3N).

Methyl 11-(Methylamino)undecanoate. Methyl 10-undecenoate (30 mmol, 6.0 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 80 minutes.

Methylamine (10 mmol, 0.78 g of 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 2.0 g (81%) [Method A] and 1.3 g (57%) [Method B]; mp (hydrochloride, recrystallized from acetone) 140-141 °C (lit⁶⁹ mp 139-141 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 52.0 (C-1), 30.0 (C-2), 27.1 (C-3), 29.3 (C-4), 29.0 (C-5), 29.1 (C-6), 29.7 (C-7), 29.0 (C-8), 25.0 (C-9), 33.7 (C-10), 173.6 (C-11), 51.0 (C-12), 36.6 (C-1'); ^1H NMR (CDCl_3), (ppm) 3.66 (s, 3 H, CH_3O), 2.60-2.20 (m 8 H, COCH_3 , CH_2NHCH_3), 1.70-1.15 envelope, 16 H, aliphatic).

exo-2-(Methylamino)norborane. Norbornylene (33 mmol, 3.1 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 2.5 hours. Methylamine (10 mmol, 0.78 g of a 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 0.81 g (65%) [Method A] and 0.84 g (67%) [Method B]; mp (hydrochloride) 198-202 °C (lit⁶⁹ mp 199-201 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 63.7 (C-1), 40.0 (C-2), 39.6 (C-3), 34.5 (C-4), 28.3 (C-5), 26.6 (C-6), 34.2 (C-7), 35.3 (C-1'); ^1H NMR (CDCl_3), (ppm) 2.80-2.46 (m, 1 H, CHN), 2.37 (s, 3 H, CH_3N), 2.2 (b, 2 H, bridgehead Hs), 0.90-1.90 (m, 8 H, aliphatic), 0.85 (s, 1 H, NH, D_2O , exchangeable).

1-(Methylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (30 mmol, 4.9 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 80 minutes. Methylamine (10 mmol, 0.78 g of a 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.3 g (68%) [Method A] and 1.6 g (83%) [Method B]; bp 104-106° C/35 mmHg; ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 51.4 (C-1), 31.6 (C-2), 33.4 (C-3), 135.9 (C-4), 108.2 (C-5), 147.7 (C-6), 145.7 (C-7), 108.9 (C-8), 121.1 (C-9), 100.8 (C-10), 36.3 (C-1'); ^1H NMR (CDCl_3), (ppm) 6.66 (s, 3 H, ArH), 5.86 (s, 2 H, OCH_2O), 2.80-2.30 (m, 4 H, CH_2N , ArCH_2), 2.38 (s, 3 H, NCH_3), 1.85-1.60 (m, 3 H, CH_2CNH , D_2O exchange, one H less).

1-(Butylamino)hexane. 1-Hexene (30 mmol, 2.5 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 1 hour. *n*-Butylamine (10 mmol, 0.73 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 0.88 g (56%) [Method A] and 1.1 g (72%) [Method B]; bp 202 ° C (740 mmHg) (lit⁶⁹ bp 202 ° C/740 mmHg); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts, the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 50.3 (C-1), 30.3 (C-2), 27.2 (C-3), 32.5 (C-4), 22.7 (C-5), 14.1 (C-6), 49.9 (C-1'), 32.8 (C-2'), 20.2 (C-3'), 14.1 (C-4'); ^1H NMR (CDCl_3), (ppm) 2.62 (b, 2 H, CH_2N), 2.55 (2 H NCH_2), 1.90-1.10 (13 H, aliphatic), 0.92 (6 H, CH_3).

(*n*-Butylamino)cyclohexane. Cyclohexene (33 mmol, 2.7 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 3.5 hour. *n*-Butylamine (10 mmol, 0.73 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.0 g (65%) [Method A] and 1.3 g (83%) [Method B]; bp 207 °C (740 mmHg) (lit⁶⁹ bp 207 °C /740.mmHg); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 57.1 (C-1), 33.7 (C-2, 6), 26.4 (C-4), 25.3 (C-3, 5), 46.8 (C-1'), 32.7 (C-2'), 20.8 (C-3'), 14.1 (C-4'); ^1H NMR (CDCl_3), (ppm) 2.75 (m, 4 H, NH, CHNCH_2 , D_2O exchange, one H less), 2.0-0.9 (m, 17 H, aliphatic).

Methyl 11-(1-Butylamino)undecanoate. Methyl 10-undecenoate (30 mmol, 6.0 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 70 minutes. *n*-Butylamine (10 mmol, 0.73 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.8 g (hydrochloride) (59%) [Method A] and 1.31 g (48%) [Method B]; mp (hydrochloride) 182 °C dec. (lit⁶⁹ mp 182 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 47.9 (C-1), 26.0 (C-2), 27.0 (C-3), 29.4 (C-4), 29.1 (C-5), 29.7 (C-6), 29.4 (C-7), 29.1 (C-8), 21.5 (C-9), 34.1 (C-10), 174.2 (C-11), 51.4 (C-12), 47.6 (C-1'), 27.9 (C-2'), 20.2 (C-3'), 13.6 (C-4'); ^1H NMR (CDCl_3), (ppm) 9.56 (b 1 H, NH(HCl), D_2O exchangeable), 3.65 (s, 3 H, CH_3O), 2.92 (m, 4 H, CH_2NHCH_2), 2.30 (m, 2 H, COCH_2), 1.90-1.15 (envelope, 20 H, aliphatic), 0.84 (t, 3 H CH_3).

exo-2-(Butylamino)norbornane. Norbornylene (33 mmol, 3.1 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 2.5 hours. *n*-butylamine (10 mmol, 0.73 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 0.88 g (53%) [Method A] and 0.98 g (59%) [Method B]; mp (hydrochloride) 226.0 °C, dec. (lit⁶⁹ mp 226.0 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts, the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 62.0 (C-1), 40.6 (C-2), 40.3 (C-3), 35.6 (C-4), 28.6 (C-5), 27.0 (C-6), 34.8 (C-7), 47.7 (C-1'), 32.6 (C-2'), 20.6 (C-3'), 13.9 (C-4'); ^1H NMR (CDCl_3), (ppm) 2.82-2.50 (m, 1 H, CHN), 2.37 (m, 2 H, CH_2N), 2.20 (b, 2 H, bridgehead Hs), 2.20-0.90 (m, 12 H, aliphatic), 0.85 (m, 4 H, CH_3 , NH, after D_2O exchange, one H less).

1-(Butylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (30 mmol, 4.9 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 80 minutes. *n*-Butylamine (10 mmol, 0.73 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.6 g (66%) [Method A] and 1.4 g (61%) [Method B]; mp 182.0 °C, dec; ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkyl-amine are 1', 2', 3', ...) (ppm) 47.1 (C-1), 27.8 (C-2), 32.6 (C-3), 133.7 (C-4), 108.3 (C-5), 147.7 (C-6), 146.1 (C-7), 108.8 (C-8), 121.3 (C-9), 100.9 (C-10), 47.8 (C-1'), 27.6 (C-2'), 20.1 (C-3'), 13.5 (C-4'); ^1H NMR (CDCl_3), (ppm) 6.68 (s, 3 H, ArH), 5.91 (s, 2 H,

OCH₂O), 2.90-1.70 (m, 7 H, CH₂NCH₂, ArCH₂, NH, after D₂O exchange, one H less), 1.60-1.10 (b, 3 H, aliphatic), 0.87-1.10 (t, 3 H, CH₃).

1-(1-Octylamino)hexane. 1-Hexene (30 mmol, 2.5 g) was hydroborated with BH₃·THF (10 mmol) for 1 hour. *n*-Octylamine (10 mmol, 1.3 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.2 g (57%) [Method A] and 1.3 g (62%) [Method B]; bp 251-253 °C (740 mmHg) (lit⁶⁹ bp 255-257 °C); ¹³C NMR (CDCl₃) (¹³C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 50.1 or 52.3 (C-1), 30.2 (C-2), 26.8 (C-3), 29.2 (C-4), 22.0 (C-5), 13.9 (C-6), 52.3 or 50.1 (C-1'), 30.2 (C-2'), 26.8 (C-3'), 29.2 (C-4') 29.5 (C-5'), 31.8 (C-6'), 22.6 (C-7'), 13.9 (C-8'); ¹H NMR (CDCl₃), (ppm) 2.73 (2t, 4 H, CH₂NCH₂), 1.27-1.12 (b, 21 H, aliphatic Hs and N-H after D₂O exchange, 20 Hs), 0.88 (t, 6 H, 2xCH₃).

(*n*-Octylamino)cyclohexane. Cyclohexene (33 mmol, 2.7 g) was hydroborated with BH₃·THF (10 mmol) for 3.5 hour. *n*-Butylamine (10 mmol, 1.3 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product as hydrochloride: 1.1 g (43%) [Method A] and 1.4 g (55%) [Method B]; mp 210-212 °C (lit⁶⁹ mp 212 °C); ¹³C NMR (CDCl₃) (¹³C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...) (ppm) 57.1 (C-1), 29.0 (C-2, 6), 24.8 (C-4), 24.5 (C-3, 5), 44.5 (C-1'), 27.0 (C-2'), 26.0 (C-3'), 29.0 (C-4', C-5'), 31.6 (C-6'), 22.5 (C-

7'), 14.0 (C-8'); ^1H NMR (CDCl_3), (ppm) 2.90-2.60 (2t, 4H, CH_2NCH_2), 2.20-1.12 (b, m, 22 H, aliphatic H), 0.88 (t, 3H, CH_3).

Methyl 11-(1-Octylamino)undecanoate. Methyl 10-undecenoate (30 mmol, 6.0 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 80 minutes. 1-Octylamine (10 mmol, 1.3 g) and sodium hypochlorite (10.0 mmol) were then added as described in the general procedures to yield the desired product: 1.8 g (48%) (hydrochloride) [Method A] and 1.3 g (39%) [Method B]; mp (hydrochloride) 178-180 °C (lit⁶⁹ mp 181-183 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkyl-amine are 1', 2', 3', ...) (ppm) 47.8 (C-1), 26.0 (C-2), 27.1 (C-3), 29.5 (C-4), 29.2 (C-5, 6, 7, 8), 25.2 (C-9), 34.3 (C-10), 174.2 (C-11), 51.4 (C-12), 47.8 (C-1'), 27.1 (C-2'), 26.0 (C-3'), 29.2 (C-4'), 29.5 (C-5'), 32.0 (C-6'), 22.8 (C-7'), 14.1 (C-8'); ^1H NMR (CDCl_3), (ppm) 9.56 (b, 1 H, $\text{NH}(\text{HCl})$, D_2O exchangeable), 3.66 (s, 3 H, CH_3O), 2.92-2.60 (m, 5 H, CH_2NHCH_2), 2.31 (m, 2 H, COCH_2), 1.90-1.15 (envelope, 28 H, aliphatic), 0.87 (t, 3 H, CH_3).

1-(1-Octylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (30 mmol, 4.9 g) was hydroborated with $\text{BH}_3\cdot\text{THF}$ (10 mmol) for 80 minutes. *n*-Octylamine (10 mmol, 1.3 g) and sodium hypochlorite (10 mmol) were then added as described in the general procedures to yield the desired product: 1.8 g (56%) [Method A] and 1.2 g (35%) [Method B]; mp 220-222 °C (lit⁶⁹ mp 221-223 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original

monoalkylamine are 1', 2', 3', ...) (ppm) 47.1 (C-1), 27.7 (C-2), 32.5 (C-3), 133.6 (C-4), 108.5 (C-5), 147.8 (C-6), 146.1 (C-7), 108.8 (C-8), 121.2 (C-9), 100.8 (C-10), 48.0 (C-1'), 27.0 (C-2'), 26.0 (C-3'), 29.1 (C-4', C-5'), 31.7 (C-6'), 22.6 (C-7'), 14.0 (C-8'); ^1H NMR (CDCl_3), (ppm) 6.67 (s, 3 H, ArH), 5.90 (s, 2 H, OCH_2O), 2.80-2.40 (m, 6 H, CH_2NCH_2 , ArCH_2), 2.30-1.50 (b, 3 H, CH_2CNH), 1.50-1.00 (b, 12 H, aliphatic), 0.87-1.10 (t, 3 H, CH_3).

Chapter III.

The Syntheses of Isomerically Pure Primary and Secondary Amines via Organoborane Chemistry.

A. Introduction.

The reactions of trialkylboranes with aqueous ammonia and alkylamines in the presence of sodium hypochlorite have been discussed in Chapters I and II. The amination reactions are simple and practical methods for the conversion of trialkylborane intermediates into amino and alkylamino functionalities. However, the reactions are complicated by the fact that hydroborations involving BH_3 are regioselective but not regiospecific.^{1,2} Under normal conditions, approximately six percent of the alkyl groups in the organoboranes are attached to the boron at the more substituted carbon of the original double bond.^{1,2} The fact that only one of the three alkyl groups is normally utilized in the amination reaction means that up to eighteen percent of the incorrect (internal) amine can be formed.

In order to increase both the regioselectivity and reaction yield, regiospecific hydroborating agents⁶, such as dicyclohexylborane, can be used to hydroborate alkenes. Unfortunately, the use of dicyclohexylalkylborane intermediates in amination reactions results in contamination of the desired amine products by the cyclohexyl derivative.¹⁷⁷

Brown and his co-workers¹⁷⁸ recently reported a practical procedure for the preparation of dimethylborane. This reagent is also a regioselective hydroborating reagent, placing the boron at the most open side of a double bond.¹⁷⁹ Moreover, methyl groups are less reactive than other alkyl groups in organoborane transformations.^{178,179,180,181} Brown's group also utilized dimethylalkylborane intermediates to generate amines via an azide reaction.¹⁸² We felt that the recently developed dimethylborane reagent could be utilized to prepare primary amines regioselectively. The resultant reactions would also be of value for the syntheses of radiolabeled amines.

B. Results and Discussion.

The initial investigation focused on the amination reactions of dimethylalkylborane intermediates with *in situ* generated chloramine or alkylchloramines. Dimethylborane was produced *in situ* during the hydroboration by treating dimethylborohydride with trimethylsilyl chloride or hydrogen chloride etherate.¹⁷⁹ The resulted dimethylalkylboranes were subsequently treated with ammonium hydroxide or alkylamines in the presence of sodium hypochlorite to yield alkylamines or dialkylamines regiospecifically.

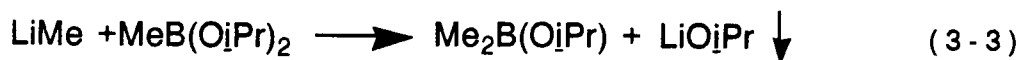
1. Preparation of Dimethylborane.

Methylborane, MeBH_2 , and dimethylborane, Me_2BH , are the simplest of the monoorganylboranes and diorganylboranes.^{182,183} However, the

traditional routes to these compounds are experimentally tedious,^{183,184,185} difficult to perform on a large scale, and produce mixtures of products. Furthermore, these boranes readily disproportionate in a relatively short period of time, producing a complex mixture of boron-containing compounds.¹⁸⁶

Unlike dimethylborane, the corresponding borohydride is thermodynamically stable and readily stored under an inert atmosphere over a period of months without hydride loss. Hence, the most useful method for preparing dimethylborane involves the preparation of lithium dimethylboro-hydride and its subsequent conversion to dimethylborane.¹⁷⁹

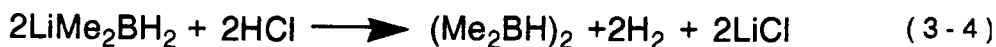
The method was first used to prepare dimethylborane in high purity and high yield in 1985.¹⁸⁷ The procedure involves the reduction of dimethylmonoisopropoxyborane with one equivalent of lithium monoethoxyaluminum hydride (3-1). [The precursor dimethylmonoisopropoxyborane was prepared by a two step-wise addition reaction sequence of methyl lithium to triisopropylborate (3-2, 3-3).^{187,188,189,190,191,192}



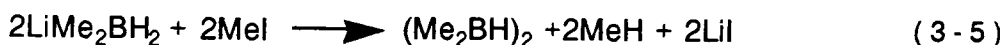
Because of the practical needs of dimethylborane and monomethylborane, the liberation of the corresponding borane from the borohydride had also been investigated in detail by Brown's group.¹⁷⁹ The conversion can be

achieved from the borohydride by treatment with four reagents: anhydrous hydrogen chloride in diethyl ether, trimethylsilyl chloride, methyl iodide, and trimethylsilyl methanesulfonate.

Hydrogen chloride reacts very rapidly with dimethylborohydride in pentane, ether, and THF to form dimethylborane, an equivalent hydrogen, and lithium chloride (3-4).



The rates of the reactions of methyl iodide and trimethylsilyl chloride with lithium dimethylborohydride are strongly dependent on the solvent. The reactions are much faster in THF than in ether and are relatively slow in pentane (3-5, 3-6).



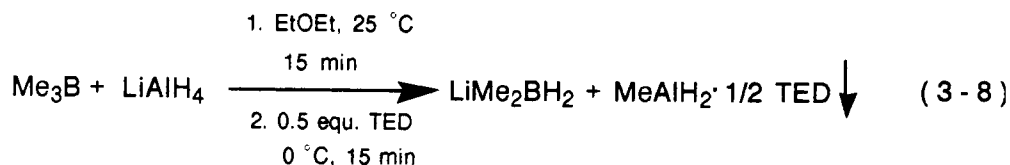
The lithium dimethylborohydride can also be readily converted to dimethylborane with trimethylsilyl methanesulfonate (3-7). The advantage



of this reagent is that the lithium methanesulfonate is essentially insoluble, both in diethyl ether and in THF, permitting the formation of a dimethylborane reagent solution free of dissolved salt. The borane is formed as a dimer; the B-11

NMR reveals a signal at +25.0 ppm referenced to boron trifluoride etherate in common ether solvents which is in accord with literature reports¹⁷⁹.

More recently, a more convenient and quantitative method using readily available starting material, trimethylborane, has been developed. The reaction sequence^{178,179,193} involves the reduction of trimethylborane by lithium aluminum hydride in ether solution followed by the treatment of the reaction mixture with an ether solution of triethylenediamine (0.5 equivalent). The alane precipitates as the bis(monoethylalane)triethylenediamine complex (3-8). After filtration, a clean solution of lithium dimethylborohydride is obtained in quantitative yield; B-11 NMR reveals an absorption at -21.8 ppm relative to boron trifluoride etherate in accord with literature reports¹⁷⁹.

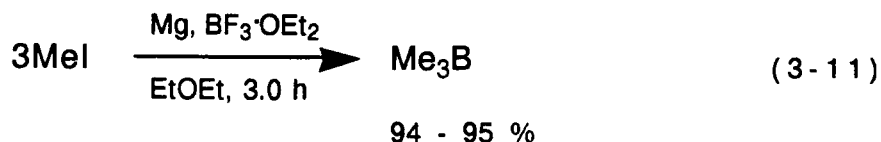


Trimethylborane can be obtained by the reaction of a preformed methyl magnesium halide with boron trifluoride etherate (3-9, 3-10).⁵



We employed a newly developed synthetic method involving the direct reaction of methyl iodide, magnesium, and boron trifluoride etherate to prepare trimethylborane. The reaction involves the *in situ* generation of methyl

magnesium iodide and the subsequent reaction with boron trifluoride etherate (3-11).

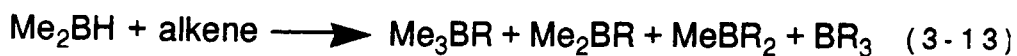


Trimethylborane is a spontaneously flammable and volatile (bp. -20°C) borane^{194,195} which can be collected as a gas in anhydrous ether at 0°C .

2. Hydroboration of Olefins Using Dimethylborane.

Dimethylborane, like other sterically nonhindered dialkylboranes, is not stable in solution. Dimethylborane undergoes a fast disproportionation to form a mixture of methylboranes. Solvents greatly affect the stability of the dimethylboranes; redistribution is faster in THF than in ether or pentane solutions.^{178,179,193}

The hydroboration progress can be monitored by B-11 NMR. The hydroboration mixtures reveal a single peak at approximately +85 ppm relative to boron trifluoride etherate, which indicates that trialkylborane is present. This does not establish whether the desired dimethylalkylborane (3-12) is formed exclusively since the various redistributed alkyl dimethylboranes would be expected to resonate near 85 ppm (3-13). The conversion of these



organoborane intermediates into stable carbon compounds via the carbonylation, cyanidation, and related reactions, demonstrated that hydroboration products formed in THF result in a mixture of redistributed tertiary alcohols after carbonylation-oxidation. On the other hand, in diethyl ether, the hydroborations are complete within 1 hour at 0 °C, exhibit a single peak at approximately 85 ppm in the B-11 NMR spectra, and carbonylation-oxidation of the organoboranes produce only one tertiary alcohol. Therefore, diethyl ether was used as solvent instead of THF in the preparation of the dimethylalkylboranes prepared from the reaction of dimethylborane with alkenes.^{178,179}

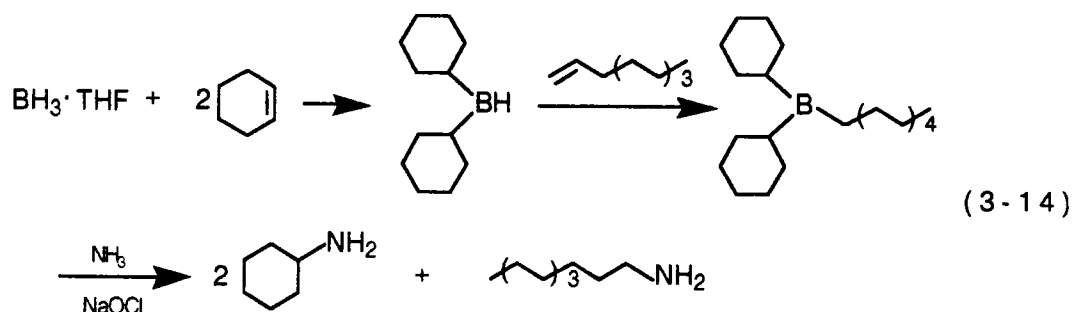
3. Initial Study of the Syntheses of Isomerically Pure Primary Amines from Dimethylalkylborane via Amination Reactions Using Chloramine.

The reactions of trialkylboranes with amination reagents suffer from two major disadvantages: (1) only one or two of the three alkyl groups on boron can be used; and (2) they are not regiospecific. A number of dialkylboranes have been used as hydroborating agents to overcome such problems. Initial investigation involved a comparison of the amination of organoboranes derived from dicyclohexylborane and dimethylborane.

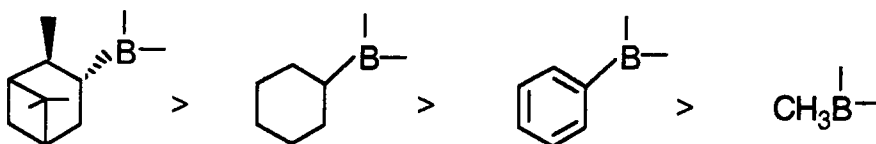
a. Amination of Dicyclohexyldecylborane - Comparative Studies.

Dicyclohexylborane is a rather stable, white crystalline solid which is prepared using either borane-THF or borane-dimethylsulfide; it is used

immediately after formation⁶. In this experiment, the dicyclohexylborane was made using one equivalent of borane-THF to hydroborate two equivalents of cyclohexene at 0 °C for three hours. The dicyclohexylborane reagent was directly used to hydroborate 1-decene to produce dicyclohexyldecylborane. The resultant organoborane was subsequently subjected to amination reaction using aqueous ammonia and sodium hypochlorite to give a mixture of amines. After isolation, the ratio of cyclohexylamine to *n*-decylamine was found to be approximately 2:1 (3-14) which is consistent with literature reports that the cyclohexyl group migrates as readily as the *n*-decyl group.¹⁷⁷

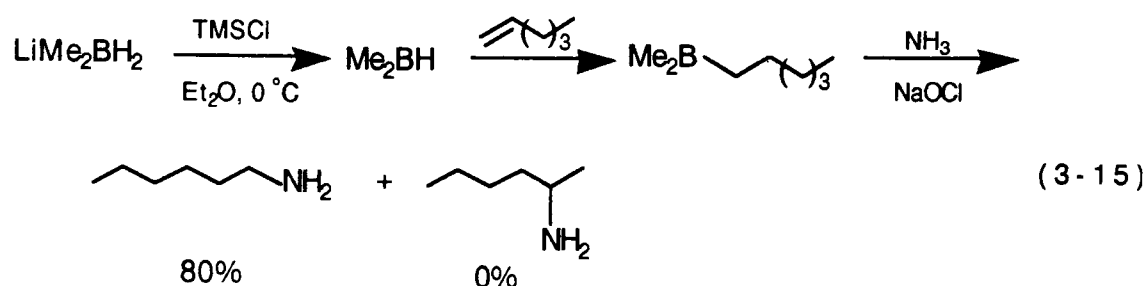


Brown and his co-workers^{177, 182} also investigated the migrating tendency of different alkyl groups in amination reactions using a series of mixed organoborane intermediates to react with hydroxylamine O-sulfonic acid. They demonstrated that the methyl group was a non-migrating group in amination reactions.



b. Amination of Dimethylhexylborane - Initial Study.

Dimethylhexylborane was used in our preliminary studies. The borane intermediate was obtained via the hydroboration of 1-hexene using dimethylborane generated from lithium dimethylborohydride and trimethylsilyl chloride *in situ* at 0 °C. The resultant dimethylborane produced a clean signal at +25.0 ppm in the B-11 NMR. The hydroboration was carried out at 0 °C in the same reaction flask. After hydroboration, the B-11 NMR revealed a new peak at +85.0 ppm and the disappearance of the peak at +25.0 ppm. After 30 to 45 minutes the dimethylborane peak disappeared and indicating that the dimethylhexylborane was formed completely. The amination was carried out by the slow addition of aqueous ammonia followed by the dropwise addition of sodium hypochlorite to the organoborane solution at 0 °C. The reaction mixture was kept at 0 °C for 5 minutes, and then allowed to warm to room temperature, and then stirred for 30 minutes. After work up, 80% of the desired *n*-hexylamine was obtained with greater than 99% regioselectivity. No detectable regioisomer was found. Fortunately, the methylamine, if produced, does not get extracted into the diethyl ether under the experimental conditions (3-15).



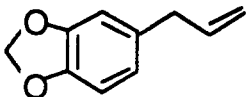
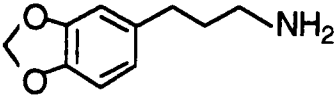
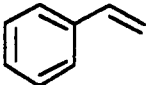
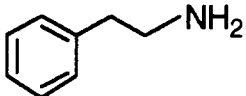
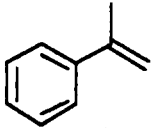
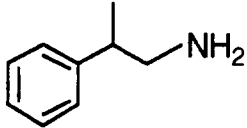
4. Regioselectivity.

Regioselectivity is a very important feature in organic synthetic chemistry. The regiochemical studies using dimethylalkylborane intermediates as precursors to produce isomerically pure amino compounds involved olefins such as 1-hexene, safrole, styrene and 2-methylstyrene, etc. All of the Me_2BR compounds employed in this study were synthesized by hydroboration of the corresponding olefins with dimethylborane prepared *in situ* from lithium dimethylborohydride and trimethylsilyl chloride in diethyl ether solution at 0°C . The resultant dimethylalkylboranes were then converted into alkylamines on treatment with ammonium hydroxide and sodium hypochlorite. The reaction mixtures were acidified and washed with ether. The aqueous layers were made basic and extracted with ether. The desired products were obtained from organic layers after evaporation of the solvent. The regioselectivities were determined by GC analyses of the corresponding N-methyl-N-(trimethylsilyl)-trifluoroacetamide (MSTFA) derivatives (3-16).⁷⁴



These studies (Table 3-1) revealed excellent regioselectivities for all alkenes used. As illustrated in Table 3-1, the straight chain terminal alkene (entry 1) generates the amine with excellent regioselectivity (>99%). However, if the double bond is adjacent to an electron withdrawing group, such as a phenyl group (entry 3), the regioselectivity is decreased; the effect diminishes

Table 3-1. Regioselectivity of The Reaction of Dimethylalkylboranes with Chloramine^a.

Entry ^b	Olefin	Product	Yield% ^c	Regio-selectivity% ^d
1			80	>99
2			60	94
3			62	90
4			60	>99

a) The reactions were run on a 5.0 mmol scale.

b) Lithium dimethylborohydride was freshly prepared.

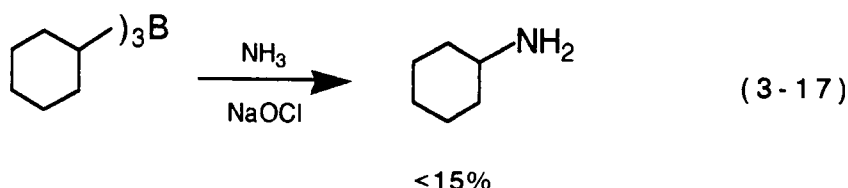
c) Isolated yields.

d) Regioselectivity was determined by GC analysis using *n*-decane as the internal standard.

if an electron withdrawing group is placed at the allylic position of the double bond (entry 2). As expected (entry 4), branching at the internal position of the alkene restores the regioselectivity of the reaction. In every instance, the regioselectivity is greater than that observed in hydroboration using BH_3 .

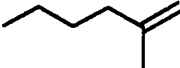
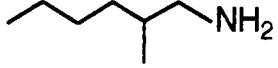
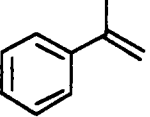
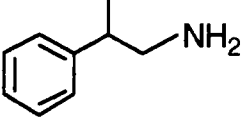
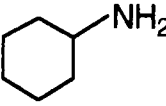
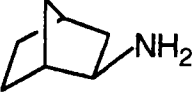
5. Steric Effect.

In addition to the aforementioned two major disadvantages, limited yield and low regioselectivity in amination reactions using trialkylboranes, the amination of hindered trialkylboranes, such as 2-methyl-1-hexene, have never produced satisfactory yields. Furthermore, unlike the reaction of tricyclohexylborane with N-methylamine (Table 2-6), the amination of tricyclohexylborane with aqueous ammonia and sodium hypochlorite produces a very low yield of the desired cyclohexylamine (3-17).



Brown concluded that although amination reactions work well for unhindered organoboranes, they are not applicable for more hindered organoboranes.¹⁰ This problem can now be solved using readily available dimethylalkylborane intermediates in the amination procedure. Our studies are summarized in Table 3-2.

Table 3-2. Steric Effects of the Reaction of Dimethylalkylboranes with Chloramine^a.

Entry ^b	Alkene	Product	Yield% ^c	Regioselectivity% ^d
1			80	>99
2			60	>99
3			56	>99
4			60	>99
5			65	>99, exo-

- a) The reactions were run on a 5 mmol scale under standard conditions using *in situ* generated dimethylborane.
- b) The chloramine was generated *in situ*.
- c) Isolated yields.
- d) Regioselectivity was determined by GC analysis using n-decane as the internal standard.

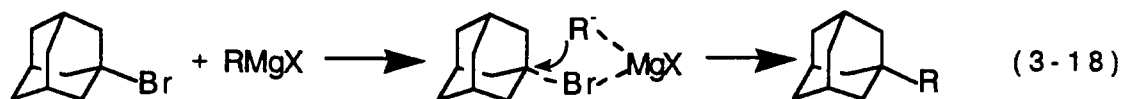
The success of the dimethylalkylborane reactions is presumably due to the fact that these reagents are less sterically hindered than normal trialkylboranes. These reactions proceed with complete retention of configuration (Entry 5).

6. Syntheses of Adamantane-Derived Primary Amines.

Adamantane-derived amino compounds are important in pharmaceutical research^{196,197,198,199,200}: (1) introducing an adamantyl group can increase the therapeutic activity of a drug; and (2) the adamantyl group can improve the lipophilicity of a drug. In conjunction with our boron-amination research, we felt that the new amination reaction would be advantageous in synthesizing adamantyl-derived amines.

a. Preparation of Adamantylalkenes.

The preparation of adamantylalkenes involves carbon-carbon bond formation through the use of organometallic reactions.^{201,202,203} The reaction proceeds via a S_E2 reaction between a Grignard reagent and an organic halide. In this reaction, the Grignard reagent acts both as a nucleophile and as a Lewis acid, complexing the Lewis acidic magnesium center with a bridgehead halide followed by reaction of the organic group bound to the magnesium with the weakly positive adamantane bridgehead carbon center (3-18). In order to maximize the formation of the complex, non-Lewis base solvents were



employed. Methylene dichloride was used as the solvent. The reaction of 1-bromoadamantane with terminal bromomagnesium alkenyl derivatives proceeded smoothly, and the cross-coupling products, 1-alkenyl-1'-adamantanes, were obtained in reasonable yields.

The Grignard reagents used in the study were prepared in ether by the standard procedure,²⁰⁴ and then the solvent was removed and replaced with methylene dichloride. Results are summarized in Table 3-3.

b. Syntheses of the Adamantane-Derived Primary Amines.

The hydroborations were carried out using lithium dimethylborohydride and TMSCl in the presence of the alkenes. The hydroboration reactions were monitored by B-11 NMR spectrum which revealed a signal at +85.0 ppm relative to boron trifluoride etherate; the reactions were run at 0 °C in ether for 45 minutes. Then aqueous ammonia and sodium hypochlorite were added to the organoboranes (Table 3-4). The NMR spectra are presented in Figures 3-1, 3-2, and 3-3.

Table 3-3. Syntheses of 1-Alkenyl-1'-adamantanes^a.

Entry	Bromoalkene ^b	Product	Yield% ^c
1			38
2			44
3			48

- a) The methylene dichloride solution of the Grignard reagent was refluxed gently and 1-bromoadamantane was slowly added. The reaction solution was refluxed for 5 hours.
- b) The Grignard reagents were freshly prepared.
- c) Nonoptimized isolated yields.

Table 3-4. The Syntheses of Adamantane-Derived Isomerically Pure Primary Amines^a.

Entry	Alkene	Product	Yield % ^b	Regio selectivity % ^c
1			60	100
2			55	100
3			58	100

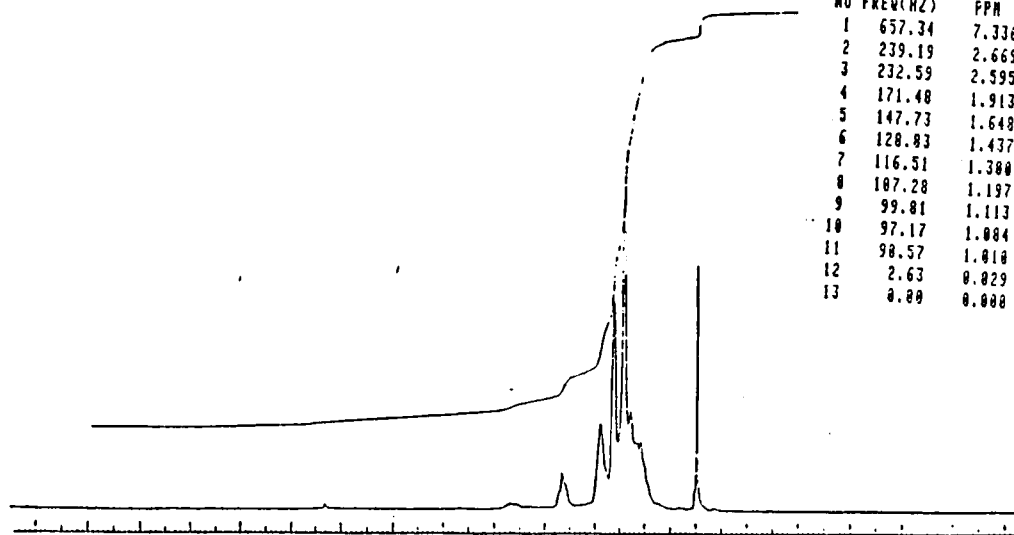
a) The hydroboration-amination reactions were run under standard conditions.

c) Isolated yields.

c) The regioselectivities were determined by C-13 and H-1 NMR analyses.

TOTAL 13
 RESOL 43961 -4 HZ
 EXREF 0.0000PPM
 OBS 337.2478 HZ
 NGAIN 2

NO	FREQ(HZ)	PPM	INT2
1	657.34	7.336	174
2	239.19	2.669	1080
3	232.59	2.595	737
4	171.48	1.913	2446
5	147.73	1.648	5804
6	128.83	1.437	8992
7	116.51	1.380	2784
8	107.28	1.197	1986
9	99.81	1.113	1882
10	97.17	1.084	1949
11	98.57	1.018	1276
12	2.63	0.029	595
13	0.00	0.000	6865



TOTAL 11
 RESOL 61838 -4 HZ
 EXREF 77.1800PPM
 OBS 547.4653 HZ
 NGAIN 11

NO	FREQ(HZ)	PPM	INT2
1	1763.04	78.508	603
2	1784.96	75.664	575
3	999.99	44.389	1474
4	949.34	42.132	6378
5	943.23	41.861	1412
6	832.17	36.931	6024
7	755.86	33.545	1031
8	716.21	31.784	1542
9	639.88	28.397	7646
10	619.74	27.503	1412
11	493.40	21.856	1434

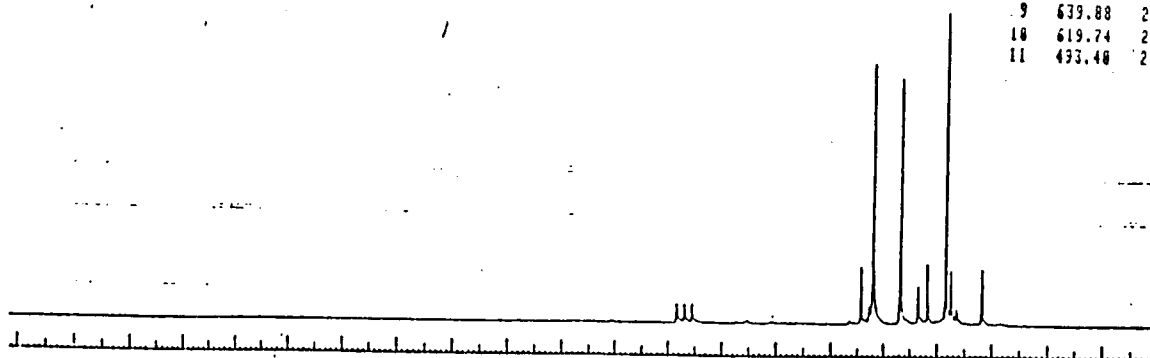
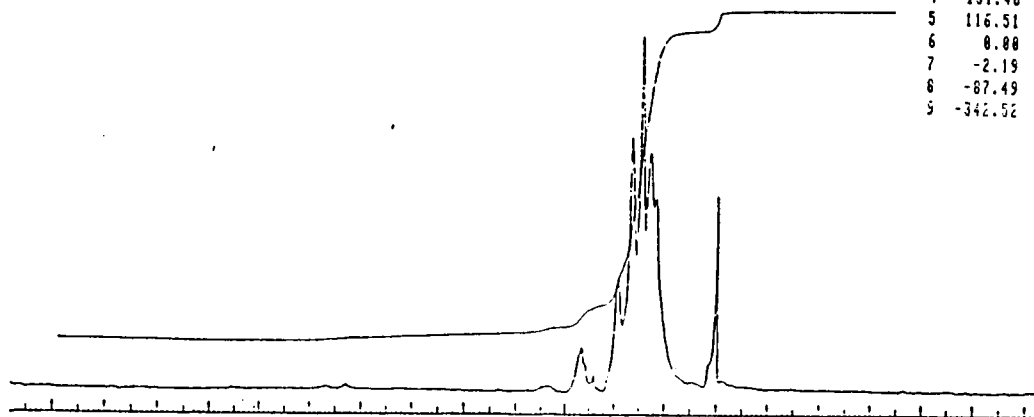


Figure 3-1. ^1H and ^{13}C NMR Spectra of 5-(Adamantyl)-1-aminopentane.

TOTAL 9
 RESOL 43961 -4 HZ
 EXREF 0.0000PPM
 OBS 336.3684 HZ
 NGAIN 0

NO	FREQ(HZ)	PPM	INT1
1	240.51	2.664	1294
2	175.87	1.962	3251
3	158.81	1.683	7262
4	131.46	1.467	9760
5	116.51	1.300	6279
6	0.00	0.000	5827
7	-2.19	-0.824	-271
8	-87.49	-0.576	-219
9	-342.52	-3.622	-222



TOTAL 12
 RESOL 61031 -4 HZ
 EXREF 77.1000PPM
 OBS 552.9785 HZ
 NGAIN 8

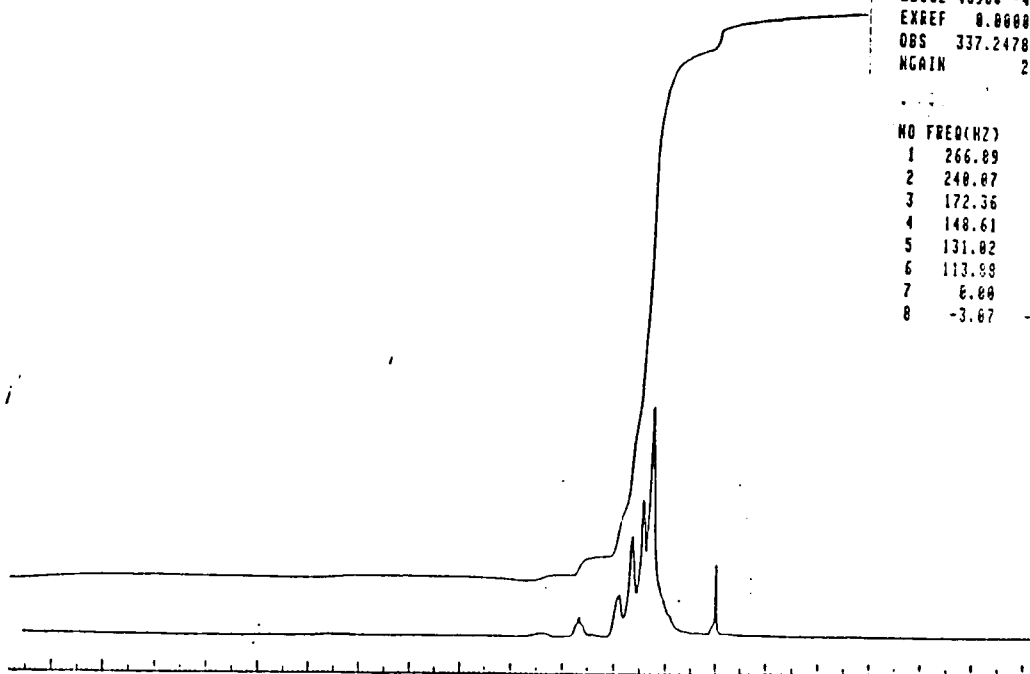
NO	FREQ(HZ)	PPM	INT1
1	1769.84	76.568	2408
2	1736.69	77.072	2395
3	1704.96	75.664	2212
4	1607.93	44.732	1921
5	958.49	42.538	7287
6	848.72	37.310	7721
7	765.03	33.951	1361
8	725.97	32.218	1266
9	686.88	30.483	1610
10	649.04	28.803	9310
11	626.32	26.934	1660
12	583.16	22.336	1755



Figure 3-2. ^1H and ^{13}C NMR Spectra of 6-(Adamantyl)-1-aminohexane.

TOTAL 8
 RESOL 43968 -4 HZ
 EXREF 0.0000PPM
 OBS 337.2478 HZ
 NGAIN 2

NO	FREQ(HZ)	PPM	INT2
1	266.89	2.978	-95
2	240.87	2.679	551
3	172.36	1.923	1169
4	140.61	1.658	2785
5	131.02	1.462	3765
6	113.98	1.270	6375
7	6.00	0.000	2629
8	-3.67	-0.034	151



TOTAL 14
 RESOL 61831 -4 HZ
 EXREF 77.1000PPM
 OBS 552.3631 HZ
 NGAIN 6

NO	FREQ(HZ)	PPM	INT2
1	4067.16	181.365	-1013
2	1769.84	78.588	1149
3	1737.38	77.190	1234
4	1704.96	75.664	1229
5	1690.54	41.753	1595
6	557.38	42.511	5613
7	342.11	37.283	5268
8	763.20	33.870	1131
9	724.75	32.164	1541
10	638.71	30.564	1629
11	657.35	29.616	3803
12	648.43	28.776	6068
13	605.79	25.988	1514
14	582.55	22.302	1782



Figure 3-3. ^1H -1 and ^{13}C -13 NMR Spectra of 8-(Adamantyl)-1-aminooctane.

7. Syntheses of Typical Isomerically Pure Primary Amines via the Reaction of Dimethylalkylborane with Chloramine Generated *In Situ*.

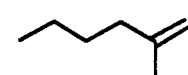
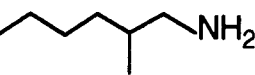
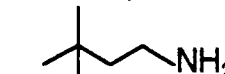
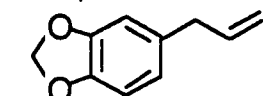
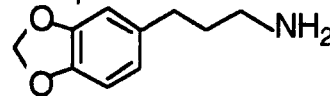
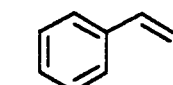
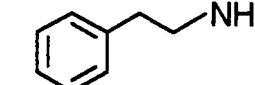
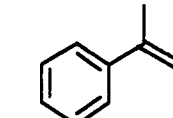
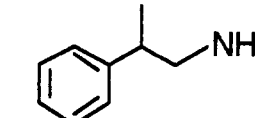
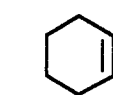
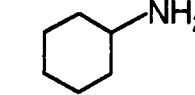
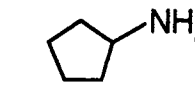
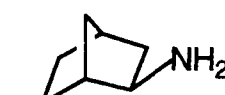
A series of representative primary amines were synthesized using dimethylalkylborane intermediates. The dimethylborane was produced by treatment of lithium dimethylborohydride with trimethylsilyl chloride in the presence of the alkenes at 0 °C for 5 minutes. The reaction mixture was then stirred for an additional 45 to 60 minutes at the same temperature. The formation of dimethylalkylborane intermediates were confirmed by B-11 NMR spectra with signals in the range of +84.5 to +87.0 ppm using boron trifluoride etherate as external standard. The amination reactions were carried out at 0 °C followed by stirring at room temperature for 1 hour. The investigations are summarized in Table 3-5.

8. Syntheses of Isomerically Pure Dialkylamines via the Reaction of Dimethylalkylboranes with Chloralkylamines Generated *In Situ*.

There were few reports in the literature concerning the synthesis of dialkylamines via organoborane chemistry. We felt that the reaction of dimethylalkylboranes with chloralkylamine would be an excellent method to synthesize isomerically pure dialkylamines (3-19).

The initial study was carried out by reacting dimethylhexylborane with methylamine and sodium hypochlorite. The hydroboration of 1-hexene was monitored with B-11 NMR (sharp signal at +86.0 ppm). An equivalent of

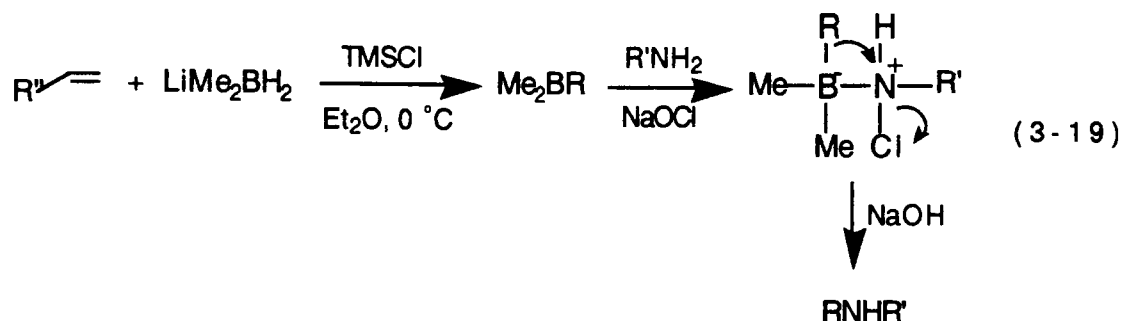
Table 3-5. The Syntheses of Isomerically Pure Primary Amines from Dimethylalkylboranes^a.

Entry	Alkene	Product	Yield% ^b	Regio-selectivity % ^c
1			80	>99
2			74	>99
3			60	>99
4			61	>99
5			59	>99
6			62	90
7			56	>99
8			60	
9			78	
10			65	>99, <i>exo</i> -

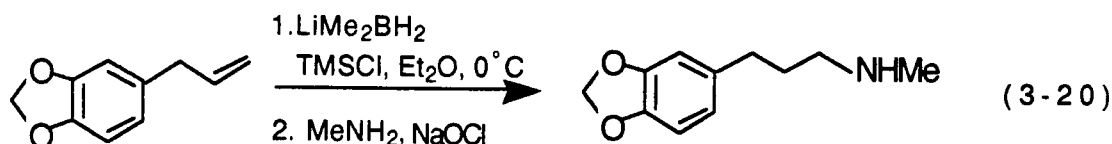
a) The hydroboration-amination reactions were run under normal conditions.

b) Isolated yields.

c) The regioselectivities were determined by C-13 and H-1 NMR analyses.

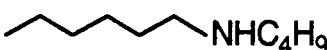
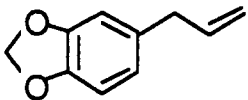
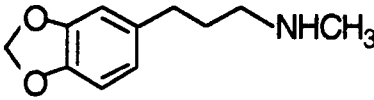
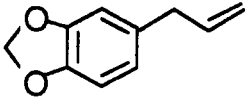
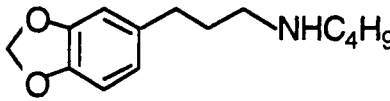
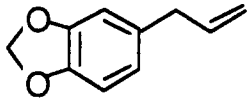
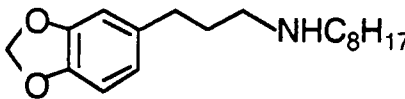
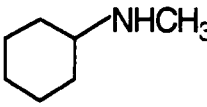
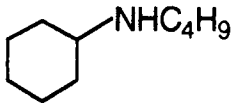
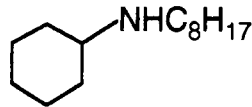
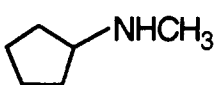
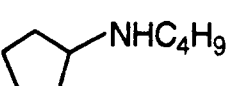


methylamine and then sodium hypochlorite were added slowly at 0 °C. The reaction was stirred at room temperature for 1 hour and then worked up using the normal acid-base procedure. The desired N-methyl-1-hexylamine was obtained in 80% yield. The safrole was then hydroborated with dimethylborane and subsequently aminated with chloromethylamine; the desired amine product was obtained with a regioselectivity (3-20) consistent with the results obtained earlier (Table 3-6, Entry 3).



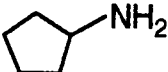
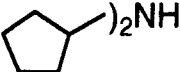
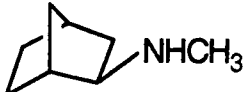
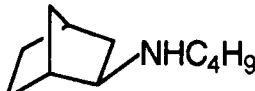
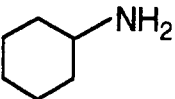
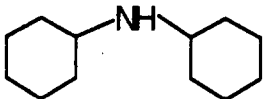
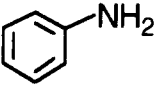
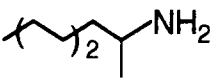
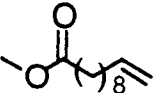
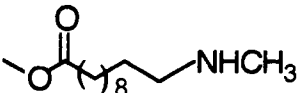
A series of N,N-dialkylamines were synthesized via the *in situ* hydroboration-amination reaction as summarized in Table 3-6. As illustrated in Table 3-6, upon treatment with different alkylamines, the dimethylcyclohexylborane and 2-*exo*-norbornyldimethylborane intermediates produced the desired dialkylamines in good yields (Entries 6, 7, 8, 12 and 13). When dimethylcyclopentylborane was treated with cyclopentylamine and sodium hypochlorite (Entry 11), N,N-dicyclopentylamine was produced in nearly 50% yield. These results indicate that the amination reaction is not as sensitive to the steric

Table 3-6. The Syntheses of Isomerically Pure Secondary Amines from Dimethylalkylboranes^a.

Entry	Alkene ^b	Amine	Product	Yield% ^c
1		CH ₃ NH ₂		77
2		n-C ₄ H ₉ NH ₂		62
3		CH ₃ NH ₂		59
4		n-C ₄ H ₉ NH ₂		62
5		n-C ₈ H ₁₇ NH ₂		50
6		CH ₃ NH ₂		73
7		n-C ₄ H ₉ NH ₂		67
8		n-C ₈ H ₁₇ NH ₂		48
9		CH ₃ NH ₂		74
10		n-C ₄ H ₉ NH ₂		68

cont'd

Table 3-6. ...continued

Entry	Alkene ^b	Amine	Product	Yield% ^{b,c}
11				46
12		CH_3NH_2		63
13		$n\text{-C}_4\text{H}_9\text{NH}_2$		60
14				10
15			$n\text{-C}_6\text{H}_{13}\text{NH}$ - 	0
16		$(\text{CH}_3)_2\text{NH}_2$	$n\text{-C}_6\text{H}_{13}\text{NH}(\text{CH}_3)_2$	0
17			$n\text{-C}_6\text{H}_{13}\text{NH}$ - 	0
18		CH_3NH_2		0

a) The hydroboration-amination reactions were run under standard conditions.

b) Isolated yield.

c) The regioselectivities were determined by C-13 and H-1 NMR analyses.

requirement of the dimethylalkylboranes, relative to reagents such as tricyclohexylborane probably due to the smaller size of the two methyl groups. Treatment of dimethylcyclohexylborane with cyclohexylchloramine (Entry 14) resulted in a very poor yield of the desired N,N-dicyclohexylamine. When dimethyl-hexylborane was treated with 1-methylheptylchloramine (Entry 17), only a trace amount product was detected. These results indicate that the reaction is sensitive to the steric requirement of the alkylchloramine agent; only terminal primary amine agents produce good yields. Dimethylhexylborane did not react with N,N-dimethylamine (Entry 16); instead, the alkyl chloride was formed.

The reaction (*in situ* generation of dimethylborane from lithium dimethylborohydride and trimethylsilyl chloride) does not tolerate ester groups (Entry 18) since they tend to be reduced by lithium dimethylborohydride.

C. Conclusion.

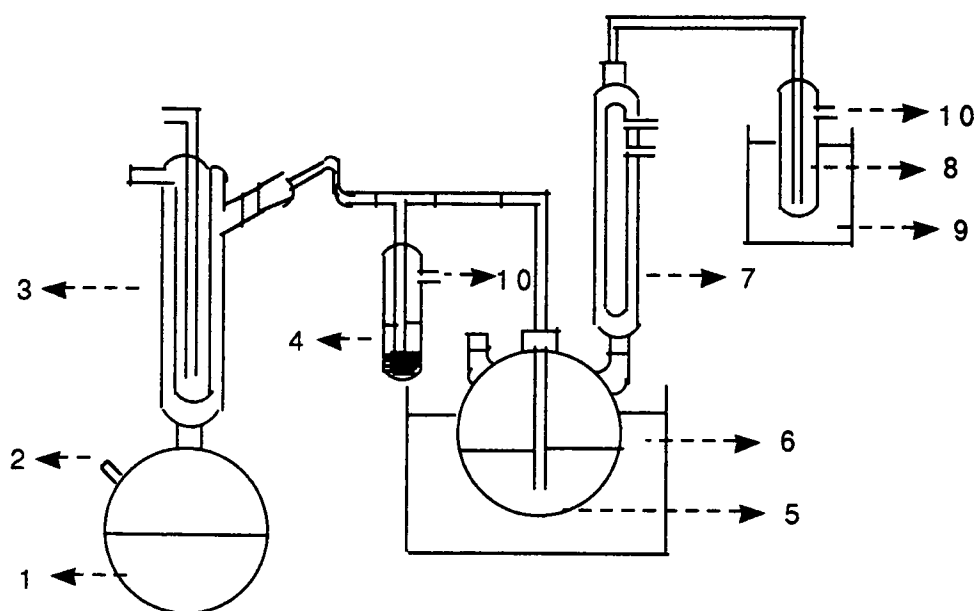
We have developed a practical synthesis of isomerically pure mono- and dialkylamines via the reaction of dimethylalkylborane intermediates with chloramine or chloralkylamines.^{74,75} The reaction were run under mild conditions with excellent regioselectivity and complete retention of configuration.

D. Experimental Section.

Glassware was thoroughly oven-dried and cooled under a stream of nitrogen just before use. Gas chromatographic analyses were performed with a Varian Model 3700 gas chromatograph (10% SE30 on Chromosorb W80/100, 10 ft.). Both PMR and C-13 NMR were recorded on a JEOL-FX 90 Q spectrometer using deuteriochloroform as the solvent and are referenced to TMS. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. All alkenes were distilled prior to use. All of the alkylamines were purchased commercially and used without further purification. Commercial bleach was used as the source of sodium hypochlorite after determination of its concentration by titration.¹⁷⁶ N-Methyl-N-(trimethylsilyl)trifluoroacetamine (Aldrich Chemical Co.) was used without further purification. Other chemicals were used and purified as described in Table 2-9.

Preparation of Trimethylborane. The experimental setup shown in Figure 3-4 was used for the preparation of trimethylborane. Mg turnings (9.72 g, 400 mmol) were placed in the reaction flask (1000 mL). The flask was heated on an open flame, and then cooled under a stream of nitrogen. A crystal of iodine, $\text{BF}_3 \cdot \text{OEt}_2$ (14.2 g, 100 mmol), and anhydrous ether (360 mL) were next introduced into the flask. Into the first safety trap (30 mL) was added a solution of ethylenediamine (3.0 g, 50 mmol) in THF (20 mL) above the level of the mercury. Anhydrous ether (200 mL) was placed in the collector flask (500 mL) and cooled to 0 °C. The second safety trap (50 mL) containing THF (20 mL) which was maintained at -78 °C by using a dry ice-acetone bath. Methyl iodide

(49.7 g, 350 mmol) was then added slowly to the well-stirred mixture of Mg turnings and $\text{BF}_3 \cdot \text{OEt}_2$ in ether over a period of 1 hour. The reaction began instantly and the ether refluxed gently; Me_3B bubbled very smoothly into the ether at 0°C .



(1) reaction flask, (2) side arm, (3) water condenser (double-walled), (4) safety trap, (5) collector flask, (6) ice bath, (7) reflux condenser, (8) safety trap, (9) dry ice-acetone trap, and (10) fumehood.

Figure 3-4. Apparatus used for the preparation of Me_3B

Following completion of the addition of methyl iodide, the reaction mixture was stirred for 0.5 hour at 25°C , and then warmed by a lukewarm water bath so as to distill the residual Me_3B from the reaction flask into the collector flask. Me_3B

was prepared essentially quantitatively. The formation of Me_3B was confirmed by B-11 NMR (86.3 ppm).

Preparation of LiMe_2BH_2 . Me_3B (100 mmol) was prepared as described above in a 500 mL flask. Subsequently, LiAlH_4 in diethyl ether (100 mL, 1.0 M, 100 mmol), which was initially cooled to 0°C , was added dropwise while the reaction mixture was stirred. The reaction mixture was stirred for 15 minutes at 0°C and then a cooled solution (0°C) of triethylenediamine in diethyl ether (100 mL, 0.50 M, 100 mmol) was slowly added to the reaction mixture via a double-ended needle under a pressure of nitrogen. A voluminous white precipitate of bis-(monomethylalane)-triethylenediamine instantly precipitated. The reaction mixture was vigorously stirred for 25 minutes at 0°C and then allowed to settle overnight at room temperature. The reaction mixture was filtered through a dry, sintered glass, fritted funnel capped with a rubber septum into another dry flask as a receiver at 0°C . The precipitate in the glass funnel was thoroughly washed with ether (2 x 50 mL) and the washings were combined with the ethereal solution contained in the receiving flask. Once again, the B-11 NMR analysis of the ethereal solution confirmed the formation of LiMe_2BH_2 (-21.8 ppm); the yield was established to be 91% by hydride analysis described as below.

Hydride Analysis.² The concentration of the lithium dimethylborohydride was determined by hydrolyzing aliquots of the lithium dimethylborohydride solution with a 50/50 mixture of alcohol and water. The amount of hydrogen

evolved was measured using a gas buret. The molarity (M) of the LiMe_2BH_2 -ether solution was calculated using the following equation:

$$M = \frac{(V_{\text{H}_2}, \text{L}) (P_{\text{bar}} - P_{\text{H}_2\text{O}}, \text{atm})}{(T^{\circ}, \text{K}) (V_{\text{soln}}, \text{L}) (2 \text{ moles H/mole LiMe}_2\text{BH}_2) (0.0821 \text{ L} \cdot \text{atm/mole} \cdot \text{K})}$$

Hydroboration of Alkenes with Dimethylborane.

General Procedure. In a dry, 25-mL, nitrogen-flushed flask fitted with a septum-covered side arm inlet and a magnetic stirring bar was placed 5.0 mmol of lithium dimethylborohydride in ether. The flask was cooled to 0 °C. The alkene (6.0 mmol), was introduced into the flask followed by a dropwise addition of trimethylsilyl chloride (5.0 mmol, 0.54 g) over a period of 2 min. There was an immediate precipitate of lithium chloride. The reaction was stirred for 45 - 70 minutes. The B-11 NMR spectrum revealed a single peak at ca. +86 ppm.

Synthesis of Alkylamines.

General Procedure. The dimethylalkylborane (5.0 mmol prepared freshly in ether) was cooled to 0 °C. The chloramine (6.0 mmol) was generated by adding sodium hypochlorite (6.0 mmol) dropwise to a solution of aqueous ammonia (6.0 mmol) contained in a 25-mL flask cooled to 0 °C. This mixture was added dropwise, with stirring, to the flask containing the dimethylalkylborane. The

solution was stirred at 0 °C for 3 minutes, allowed to warm to room temperature, and then stirred for 1 hour.

The reaction mixture was then acidified to pH=1 (10% HCl) and washed with diethyl ether. The free amines were obtained via the addition of sodium hydroxide (6 M) to the aqueous layer (pH=13) and extraction of the product into ether. The ether layer was dried over potassium hydroxide, and the product was purified by chromatography (silica gel using chloroform/methanol/methylamine as the elution system). The regioselectivity of the essentially pure product was determined by GLC analysis. The amine was analyzed by mixing it with N-methyl-N-(trimethylsilyl)-trifluoroacetamide at room temperature, followed by warming in a lukewarm water bath for 5 minutes. The reaction mixture was used directly for the GLC analysis.

1-Aminohexane. 1-Hexene (6.1 mmol, 0.51 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 45 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedures to yield the desired product: 0.41 g (80%); mp (hydrochloride) 220 °C (lit.⁷⁴ mp 220 °C); ¹³C NMR (CDCl₃) (ppm) 42.3 (C-1), 33.7 (C-2), 26.8 (C-3), 32.0 (C-4), 22.6 (C-5), 14.0 (C-6); ¹H NMR (CDCl₃), (ppm) 2.70 (m, 2H, CH₂N), 1.58 (s, 2 H, NH₂, D₂O exchangeable), 1.26-1.00 (b, 8 H, (CH₂)₄), 0.91 (t, 3 H, CH₃).

1-Amino-2-methylpentane. 2-Methyl-1-pentene (6.1 mmol, 0.51 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl

ether) and TMSCl (5.0 mmol, 0.54 g) for 45 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.30 g (60%); bp 63-66 °C/94mmHg (lit.⁷⁴ bp 64 °C/90mmHg); ^{13}C NMR (CDCl_3) (ppm) 48.5 (C-1), 36.6 (C-2), 36.1 (C-3), 20.2 (C-4), 14.3 (C-5), 17.4 (C-6); ^1H NMR (CDCl_3), (ppm) 2.40 (s, 2 H, NH_2 , D_2O exchangeable), 2.32-2.10 (m, 2 H, CH_2N), 1.45-1.05 (b, 5 H, aliphatic), 0.95-0.70 (m, 6 H, $2\times\text{CH}_3$).

1-Aminodecane. 1-Decane (5.8 mmol, 0.81 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 60 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.57 g (74%); mp 181 °C (hydrochloride) (lit.⁷⁴ mp 182 °C); ^{13}C NMR (CDCl_3) (ppm) 41.9 (C-1), 33.4 (C-2), 26.8 (C-3), 29.5 (C-4, 5, 6, 7), 31.8 (C-8), 22.5 (C-9), 14.0 (C-10); ^1H NMR (CDCl_3), (ppm) 2.90-2.70 (m, 2 H, CH_2N), 2.00 (s, 2 H, NH_2 , D_2O exchangeable), 1.55-1.00 (envelop, 16 H, $(\text{CH}_2)_8$), 0.87 (3 H, CH_3).

1-Amino-3,3-dimethylhexane. 3,3-Dimethyl-1-butene (6.1 mmol, 0.51 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 60 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.31 g (61%); bp 113-114 °C (lit.⁷⁴ bp 115-116 °C); ^{13}C NMR (CDCl_3) (ppm) 48.3 (C-1), 29.9 (C-2), 38.4 (C-3), 29.6 ($3\times\text{C-4}$); ^1H NMR (CDCl_3), (ppm) 2.75-2.50 (, 2 H,

CH₂N), 1.52-1.30 (m, 2 H, CH₂), 1.23 (s, 2 H, NH₂, D₂O exchangeable), 0.93 (s, 9 H, 3xCH₃).

1-Amino-2-phenylethane. Styrene (6.0 mmol, 0.63 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 60 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6 mmol) were then added as described in the general procedure to yield the desired product: 0.36 g (62%); mp 218 °C (picrate) (lit.⁷⁴ mp 220 °C); ¹³C NMR (CDCl₃) (ppm) 43.1 (C-1), 39.7 (C-2), (aromatic C-1, C-4, C-2 and 6, C-3 and 5): 139.5, 125.8, 128.1, 128.8. ¹H NMR (CDCl₃), (ppm) 7.22 (s, 5 H, ArH₅), 3.10-2.45 (m, 4 H, ArCH₂CH₂N), 0.95 (s, 2 H, NH₂, D₂O exchangeable).

1-Amino-2-phenyl-propane. 2-Methylstyrene (6.0 mmol, 0.71 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 60 minutes. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.38 g (56%); mp 181 °C (picrate) (lit.⁷⁴ mp 182 °C); ¹³C NMR (CDCl₃) (ppm) 49.2 (C-1), 43.2 (C-2), 19.2 (C-3), (aromatic C-1, C-4, C-2 and 6, C-3 and 5): 144.7 126.3, 127.2 , 128.4 ; ¹H NMR (CDCl₃), (ppm) 7.22 (s, 5 H, ArH₅), 2.85-2.60 (b, 3 H, ArCHCH₂N), 2.20-1.95 (s, 2 H, NH₂, D₂O exchangeable), 1.13 (d, 3 H, CH₃).

Aminocyclohexane. Cyclohexene (6.1 mmol, 0.50 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0

mmol, 0.54 g) for 2.5 hours. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.30 g (60%); mp 157 °C (picrate) (lit.⁷⁴ mp 158 °C); ¹³C NMR (CDCl₃) (ppm) 50.1 (C-1), 36.9 (C-2, 6), 26. (C-4), 25.0 (C-3, 5); ¹H NMR (CDCl₃), (ppm) 2.90-2.40 (s, H, CHN), 2.10-0.90 (m, b, 12 H, aliphatic and NH₂).

Aminocyclopentane. Cyclopentene (6.3 mmol, 0.43 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. Aqueous ammonia (6 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.33 g (78%); mp 106 °C (picrate) (lit.⁷⁴ mp 105 °C); ¹³C NMR (CDCl₃) (ppm) 58.0 (C-1), 33.6 (C-2, 5), 24.1 (C-3, 5); ¹H NMR (CDCl₃), (ppm) 3.30-3.00 (s, 1 H, CHN), 1.48 (s, 2 H, NH₂), 2.10-1.00 (m, b, 10 H, aliphatic). 1.48 (s, 2 H, NH₂).

exo-2-Aminonorbornane. Norbornylene (6.2 mmol, 0.58 g) was hydroborated with LiMe₂BH₂ (5 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1.5 hours. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.36 g (65%); mp 174 °C (picrate) (lit.⁷⁴ mp 174 °C); ¹³C NMR (CDCl₃) (ppm) 54.8(C-1), 45.2 (C-2), 42.1 (C-3), 35.8 (C-4), 28.1 (C-5), 26.6 (C-6), 34.1 (C-7); ¹H NMR (CDCl₃), (ppm) 2.90-2.70 (m, 1 H, CHN), 2.40 (s, 2 H, NH₂, D₂O, exchangeable), 2.2 (b, 2 H, bridgehead Hs), 1.90-0.90 (m, 8 H, aliphatic).

1-Amino-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (6.0 mmol, 0.97 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. Aqueous ammonia (6.0 mmol, 3.1 mL of 1.93 M solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.53 g (59%); mp 176 °C (hydrochloride) (lit.⁷⁴ mp 174 °C); ^{13}C NMR (CDCl_3) (ppm) 41.3 (C-1), 32.8 (C-2), 35.3 (C-3), 135.6 (C-4), 107.9 (C-5), 147.4 (C-6), 145.4 (C-7), 108.6 (C-8), 121.1 (C-9), 100.5 (C-10); ^1H NMR (CDCl_3), (ppm) 6.65 (s, 3 H, ArH), 5.88 (s, 2 H, OCH_2O), 2.80-2.30 (m, 4 H, CH_2N , ArCH_2), 2.23 (s, 2 H, NH_2 , D_2O exchangeable), 2.00-1.50 (m, 2 H, CH_2CN).

Synthesis of Dialkylamines.

General Procedure. The dimethylalkylborane (5.0 mmol prepared freshly in ether) was cooled to 0 °C. The alkylchloramine (6.0 mmol) was generated by adding sodium hypochlorite (6.0 mmol) dropwise to a solution of alkylamine (6.0 mmol) contained in a 25-mL flask cooled to 0 °C. This mixture was added dropwise, with stirring, to the flask containing the demethylalkylborane (5.0 mmol in ether) at 0 °C. The solution was stirred at 0 °C for 5 minutes, allowed to warm to room temperature, and then stirred for 1 hour.

The reaction mixture was then acidified to pH=1 (10% HCl) and washed with diethyl ether. The free amines were obtained via the addition of sodium hydroxide (6 M) to the aqueous layer (pH=13) and extraction of the product into ether. The ether layer was dried over potassium hydroxide and the product was

purified by chromatography (silica gel using chloroform/methanol/methylamine as the elution system). The regioselectivity of the essentially pure product was determined by GLC analysis: the amine was mixed with N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature followed by warming in lukewarm water bath for 5 minutes; The reaction mixture was then analyzed by GLC.

1-(Methylamino)hexane. 1-Hexene (6.1 mmol, 0.51 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 45 minutes. Methylamine (6 mmol, 0.52 mL of 40% solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.45 g (77%); bp 137°C (lit.⁷⁵ bp 138°C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 52.5 (C-1), 31.8 (C-2), 27.0 (C-3), 29.9 (C-4), 22.6 (C-5), 14.0 (C-6), 36.5 (C-1'); ^1H NMR (CDCl_3), (ppm) 0.95 (3 H, CH_3), 1.17 (s, 1 H, NH, D_2O exchangeable), 1.26-1.60 (b, 8 H, $(\text{CH}_2)_4$), 2.43 (s, 3 H, CH_3N), 2.62 (t, 2 H, CH_2N).

(Methylamino)cyclohexane. Cyclohexene (6.1 mmol, 0.50 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 2.5 hours. Methylamine (6.0 mmol, 0.52 mL of 40% solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.41 g (73%); bp 148°C (lit.⁷⁵ bp 148°C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two

parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 58.4 (C-1), 33.2 (C-2, 6), 26.2 (C-4), 25.0 (C-3, 5), 33.5 (C-1'); ^1H NMR (CDCl_3), (ppm) 0.92-2.02 (9 H, d, b, H's of cyclohexane), 2.25 (s, 1 H, NH, D_2O exchangeable), 2.40 (s, 3 H, CH_3N).

(Methylamino)cyclopentane. Cyclopentene (6.3 mmol, 0.43 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. Methylamine (6.0 mmol, 0.52 mL of 40% solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.37 g (73%); bp 123°C (lit.⁷⁵ bp 124°C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 59.4 (C-1), 33.0 (C-2, 5), 23.7 (C-3, 5), 34.1 (C-1'); ^1H NMR (CDCl_3), (ppm) 3.10-2.80 (m, 1 H, CHN), 2.43 (s, 1 H, NCH_3), 1.90-1.40 (m, b, 8 H, aliphatic), 1.50 (s, 1 H, NH, D_2O exchangeable).

exo-2-(Methylamino)norbornane. Norbornylene (6.2 mmol, 0.58 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1.5 hours. Methylamine (6.0 mmol, 0.52 mL of 40% solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.40 g (63%); mp (hydrochloride) $200\text{-}202^\circ\text{C}$ (lit.⁷⁵ mp 199°C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 63.7 (C-1), 40.0 (C-2), 39.6 (C-3), 34.5 (C-4), 28.3 (C-5), 26.6 (C-6), 34.2 (C-7), 35.3 (C-1');

^1H NMR (CDCl_3), (ppm) 2.80-2.46 (m, 1 H, CHN), 2.37 (s, 3 H, CH_3N), 2.2 (b, 2 H, bridgehead Hs), 0.90-1.90 (m, 8 H, aliphatic), 0.85 (s, 1 H, NH, D_2O , exchangeable).

1-(Methylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (6.0 mmol, 0.97 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. Methylamine (6.0 mmol, 0.52 mL of 40% solution) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.58 g (59%); bp $106^\circ\text{C}/35\text{mmHg}$ (lit.⁷⁵ bp $108^\circ\text{C}/35\text{mmHg}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 51.4 (C-1), 31.6 (C-2), 33.4 (C-3), 135.9 (C-4), 108.2 (C-5), 147.7 (C-6), 145.7 (C-7), 108.9 (C-8), 121.1 (C-9), 100.8 (C-10), 36.3 (C-1'); ^1H NMR (CDCl_3), (ppm) 6.66 (s, 3 H, ArH), 5.86 (s, 2 H, OCH_2O), 2.80-2.30 (m, 4 H, CH_2N , ArCH_2), 2.38 (s, 3 H, NCH_3), 1.85-1.60 (m, 3 H, CH_2CNH , D_2O exchangeable, one H less).

1-(Butylamino)hexane. 1-Hexene (6.1 mmol, 0.51 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 45 minutes. *n*-Butylamine (6.0 mmol, 0.44 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.49 g (63%); bp $202^\circ\text{C}/740\text{mmHg}$ (lit.⁷⁵ bp $201^\circ\text{C}/738\text{mmHg}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 50.3 (C-1), 30.3 (C-2), 27.2 (C-3), 32.5 (C-4), 22.7 (C-5), 14.1 (C-6), 49.9 (C-1'), 32.8 (C-2'), 20.2 (C-3'), 14.1 (C-4'); ^1H

NMR (CDCl_3), (ppm) 2.62 (m, 2H, CH_2N), 2.55 (m, 2 H, NCH_2), 1.90-1.10 (envelope, 13 H, aliphatic), 0.92 (t, 3H, CH_3).

(n-Butylamino)cyclohexane. Cyclohexene (6.1 mmol, 0.50 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 2.5 hours. *n*-Butylamine (6.0 mmol, 0.44 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.53 g (67%); bp $207^\circ\text{C}/740$ mmHg (lit.⁷⁵ bp $207^\circ\text{C}/740\text{mmHg}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 57.1 (C-1), 33.7 (C-2, 6), 26.4 (C-4), 25.3 (C-3, 5), 46.8 (C-1'), 32.7 (C-2'), 20.8 (C-3'), 14.1 (C-4'); ^1H NMR (CDCl_3), (ppm) 2.75 (m, 4 H, NH, CHNCH_2 , D_2O exchangeable, one H less), 2.0-0.9 (m, 17 H, aliphatic).

(Butylamino)cyclopentane. Cyclopentene (6.3 mmol, 0.43 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. *n*-Butylamine (6.0 mmol, 0.44 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.37 g (73%); bp 186°C (lit.⁷⁵ bp 186°C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 59.8 (C-1), 33.1 (C-2, 5), 23.9 (C-3, 4), 48.3 (C-1'), 32.4 (C-2'), 20.4 (C-3'), 13.8 (C-4'); ^1H NMR (CDCl_3), (ppm) 3.20- 2.80

(m, 1 H, CHN), 2.70-2.40 (m, 3 H, NH, NCH₂, D₂O exchangeable, one H less), 1.90-1.05 (envelope, 12 H, aliphatic), 0.91 (t, 3 H, CH₃).

exo-2-(Butylamino)norbornane. Norbornylene (6.2 mmol, 0.58 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1.5 hours. n-Butylamine (6.0 mmol, 0.44 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.57 g (68%); mp (hydrochloride) 226° C, dec.; ¹³C NMR (CDCl₃) (¹³C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 62.0 (C-1), 40.6 (C-2), 40.3 (C-3), 35.6 (C-4), 28.6 (C-5), 27.0 (C-6), 34.8 (C-7), 47.7 (C-1'), 32.6 (C-2'), 20.6 (C-3'), 13.9 (C-4'); ¹H NMR (CDCl₃), (ppm) 2.82-2.50 (m, 1 H, CHN), 2.37 (m, 2 H, CH₂N), 2.20 (b, 2 H, bridgehead Hs), 2.20-0.90 (m, 12 H, aliphatic), 0.85 (m, 4 H, CH₃, NH, after D₂O exchangeable, one H less).

1-(Butylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (6.0 mmol, 0.97 g) was hydroborated with LiMe₂BH₂ (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. n-Butylamine (6.0 mmol, 0.44 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.73 g (62%); mp 182° C, dec; ¹³C NMR (CDCl₃) (¹³C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 47.1 (C-1), 27.8 (C-2), 32.6 (C-3), 133.7 (C-4), 108.3 (C-5), 147.7 (C-6), 146.1 (C-7), 108.8 (C-8), 121.3 (C-9), 100.9 (C-

10), 47.8 (C-1'), 27.6 (C-2'), 20.1 (C-3'), 13.5 (C-4'); ^1H NMR (CDCl_3), (ppm) 6.68 (s, 3 H, ArH), 5.91 (s, 2 H, OCH_2O), 2.90-1.70 (m, 7 H, CH_2NCH_2 , Ar CH_2 , NH, after D_2O exchangeable, one H less), 1.60-1.10 (b, 3 H, aliphatic), 0.87-1.10 (t, 3 H, CH_3).

(n-Octylamino)cyclohexane. Cyclohexene (6.2 mmol, 0.51 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 2.5 hours. n-Octylamine (6.0 mmol, 0.77 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.51 g (48%); mp 210-212 °C (lit.⁷⁵ mp 212 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 57.1 (C-1), 29.0 (C-2, 6), 24.8 (C-4), 24.5 (C-3, 5), 44.5 (C-1'), 27.0 (C-2'), 26.0 (C-3'), 29.0 (C-4', C-5'), 31.6 (C-6'), 22.5 (C-7'), 14.0 (C-8'); ^1H NMR (CDCl_3), (ppm) 2.90-2.60 (2t, 4 H, CH_2NCH_2), 2.20-1.12 (b, m, 22 H, aliphatic H), 0.88 (t, 3 H, CH_3).

1-(1-Octylamino)-3-[3,4-(methylenedioxy)phenyl]propane. Safrole (6.0 mmol, 0.97 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. n-Octylamine (6.0 mmol, 0.77 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.70 g (50%); mp 220-222 °C (lit.⁷⁵ mp 221 °C); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 47.1 (C-1), 27.7 (C-2), 32.5 (C-3), 133.6 (C-4), 108.5 (C-5), 147.8 (C-6), 146.1 (C-7), 108.8 (C-8), 121.2

(C-9), 100.8 (C-10), 48.0 (C-1'), 27.0 (C-2'), 26.0 (C-3'), 29.1 (C-4', C-5'), 31.7 (C-6'), 22.6 (C-7'), 14.0 (C-8'); ^1H NMR (CDCl_3), (ppm) 6.67 (s, 3 H, ArH), 5.90 (s, 2 H, OCH_2O), 2.80-2.40 (m, 6 H, CH_2NCH_2 , ArCH_2), 2.30-1.50 (b, 3 H, CH_2CNH), 1.50-1.00 (b, 12 H, aliphatic), 0.87-1.10 (t, 3 H, CH_3).

(Cyclopentylamino)cyclopentane. Cyclopentene (6.3 mmol, 0.43 g) was hydroborated with LiMe_2BH_2 (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) and TMSCl (5.0 mmol, 0.54 g) for 1 hour. Cyclopentylamine (6.0 mmol, 0.52 g) and sodium hypochlorite (6.0 mmol) were then added as described in the general procedure to yield the desired product: 0.73 g (46%); bp $87^\circ\text{C}/10\text{mmHg}$ (lit.⁷⁵ bp $86^\circ\text{C}/10\text{mmHg}$); ^{13}C NMR (CDCl_3) (^{13}C NMR data are presented in two parts: the carbons in the original alkene are numbered 1, 2, 3, ...; the carbons in the original monoalkylamine are 1', 2', 3', ...). (ppm) 58.2 (C-1, 1'), 33.1 (C-2, 5, 2', 5'), 23.6 (C-3, 4, 3', 4'); ^1H NMR (CDCl_3), (ppm) 3.12 (m, 2 H, CHNCH), 2.61 (s, 1 H, NH, D_2O exchangeable), 2.20-1.12 (m, envelope, 16 H, aliphatic).

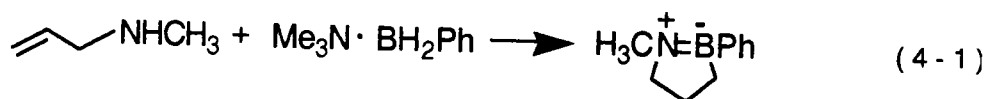
Chapter IV

Syntheses of the Isomerically Pure Diamines and Amino Acids *via* the Reaction of Functionalized Alkyldimethylboranes with Chloramine or Chloralkylamines.

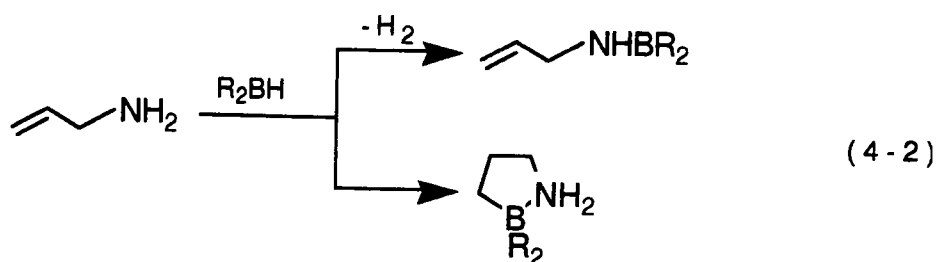
A. Introduction.

One of the most significant features of the hydroboration reaction is the fact that a large number of functional groups tolerate various hydroborating agents.^{1,2} Consequently, organoboranes are rather unique synthetic intermediates in that functionalities can be introduced rather early in a multistep synthetic sequence.

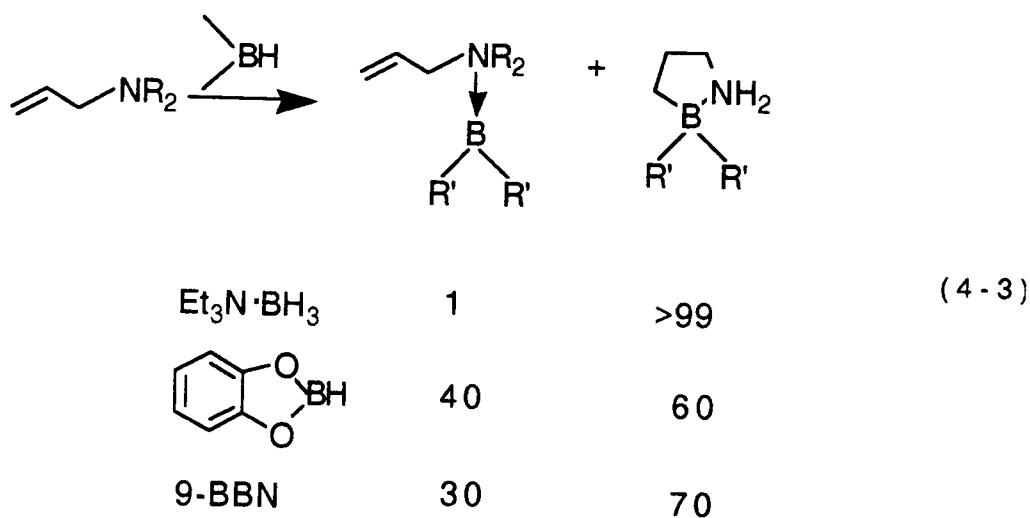
The hydroboration of N-methyl derived olefinic amines using trimethylaminoborane was first reported in 1963 (4-1).^{205,206} The reaction



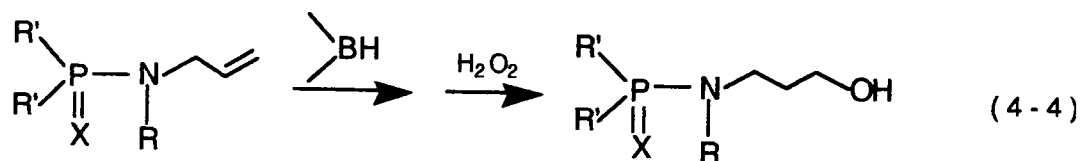
of allylamine with tetraalkyldiboranes was also studied at that time.²⁰⁷ The studies revealed that the hydroborations could produce an amineborane with loss of hydrogen or a cyclic monoalkylborane(4-2),²⁰⁸ depending on the reaction conditions. Unlike reactions with simple unsaturated hydrocarbons, hydroboration of unsaturated amines proceeds only to the monoalkylborane stage. The resultant cyclic monoalkylboranes are very stable.^{209,210,212,213}



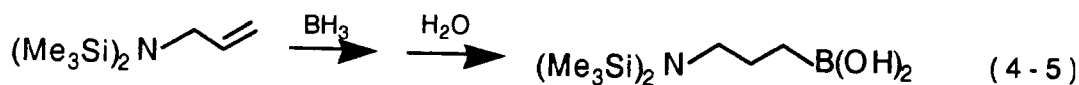
A systematic investigation²¹⁴ of the hydroboration of allylic amines with a series of hydroborating agents revealed that the choice of hydroborating agent was a critical factor in determining the equilibrium between the linear amineborane and cyclic amineborane (4-3).



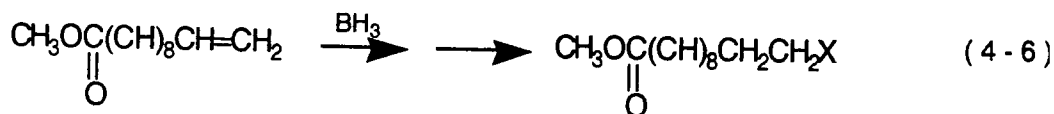
The hydroboration of nitrogen-protected olefinic amines has also been studied.³ The hydroboration of olefinic phosphoramides^{215,216,217} resulted in phosphorus organoborane intermediates, which in turn could be transformed into functionalized phosphoramides derivatives (4-4). The removal of the protecting groups required harsh conditions and long reaction times, both of which limited the usefulness of the reaction.^{218,219}



A recent investigation by Montury and co-workers^{220,221} revealed that the trimethylsilyl group could effectively protect the N-H bonds in olefinic amines during the hydroboration reaction. The resultant organoboranes provided a convenient route to aminoboronic acids. However, the regioselectivity remained a problem in this reaction (4-5).

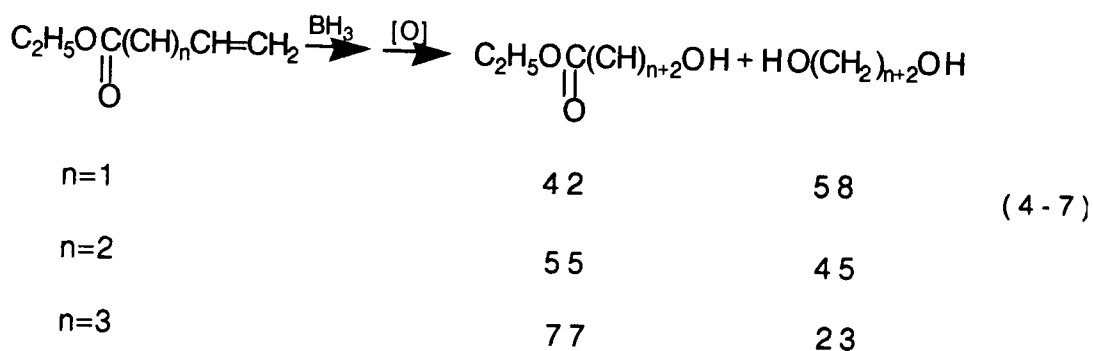


The hydroboration of esters is also complicated by competitive reactions involving reduction of the ester functionalities. Esters are slowly reduced by diborane, requiring 12-24 hours for complete uptake of two hydrides.²²² Since the rate of hydroboration is much faster than ester reduction, hydroboration in the presence of an ester functionality is possible provided careful control of the reaction temperature is maintained.^{24,222,224} Thus, methyl 10-undecenoate has been hydroborated and subjected to subsequent transformations^{69,225} (4-6).

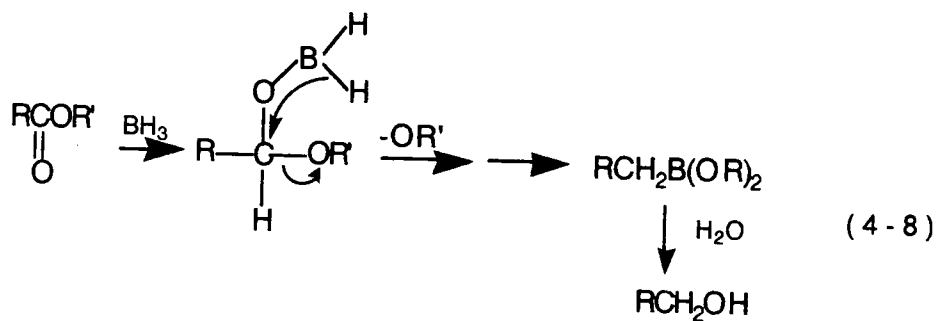


X = OH, NH₂, RNH, etc.

Brown's group^{226,227,228} has carried out a detailed study of the hydroboration of terminal unsaturated esters. They reported that a significant amount of diol is formed due to competitive reduction of esters. The amount of diol formed was inversely proportional to the distance between the ester and olefin functionalities (4-7).

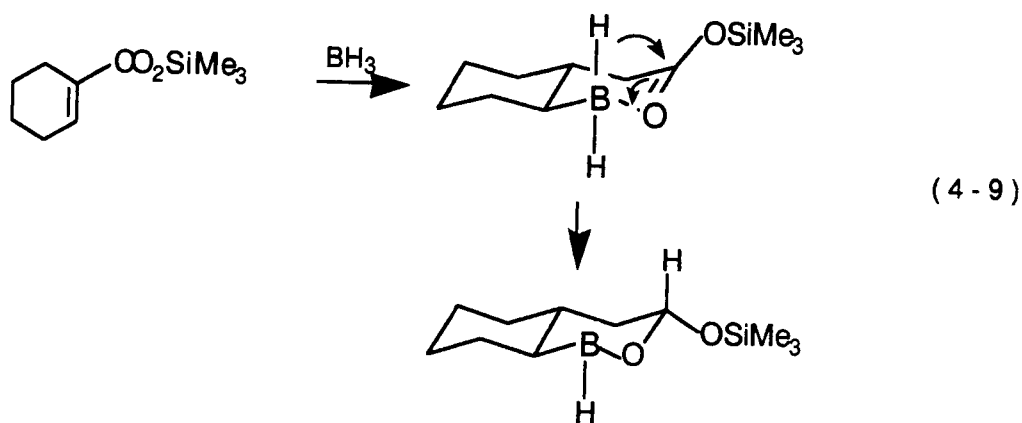


The reduction of esters by boranes is presumed to occur via an intramolecular hydride transfer mechanism²²⁵ shown in (4-8). In the

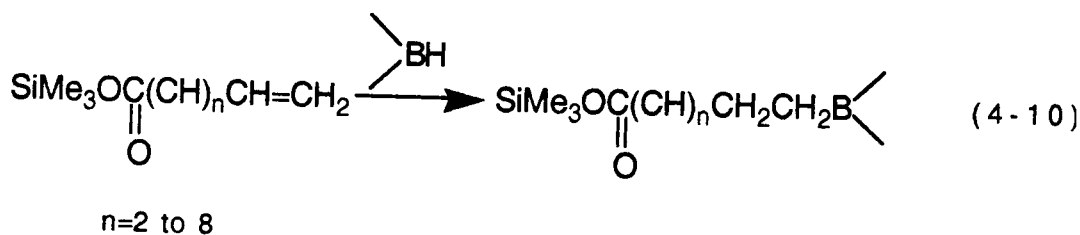


case of olefinic esters, the first step is the rapid addition of the borane to the olefin. Then a rapid intramolecular reaction of the borane intermediate with the ester functionality occurs to form a cyclic intermediate. The greatly enhanced reactivity of ester groups near double bonds is accounted

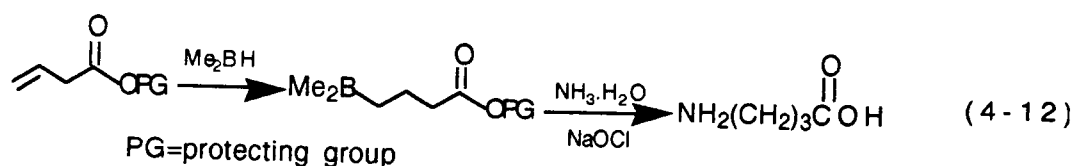
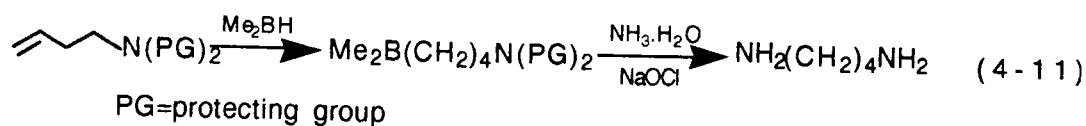
for by this cyclic transition state. It also explains why the amount of ester reduction decreases with increasing chain length. Since five and six membered rings are more stable thermodynamically, unsaturated esters are capable of forming five and six membered rings, such as 1-cyclohexenyl-acetoxytrimethylsilane (4-9).²²⁹



Kabalka's group²²⁵ has systematically studied the hydroboration of olefinic trimethylsilylcarboxylic esters. These studies revealed that trimethylsilyl esters of carboxylic acids were stable to a variety of hydroborating agents. These readily available carboxylic acid derivatives can be utilized to prepare a number of mixed trialkylboranes that can then be converted to functionalized carboxylic acids via well-known organoborane transformations (4-10).⁶



As part of the project involving the syntheses of nitrogen-13 labeled compounds as potential positron emission tomography agents, there has been great interest in developing methodologies for synthesizing diamines and amino acids, particularly putrescine (1,4-butyldiamine) and *gamma*-aminobutyric acid. Since it has been demonstrated that the reaction of dimethylalkylboranes with chloramine or chloralkylamines could produce primary and secondary amines regiospecifically and in good yields, it was felt that dimethylborane would be an ideal reagent to hydroborate N-protected olefinic amines and unsaturated carboxylic acid esters. The resultant organoboranes would appear to be ideal precursors to isomerically pure diamines and amino acids (4-11, 4-12).



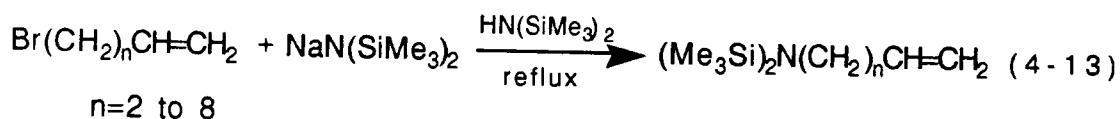
B. Results and Discussion.

The syntheses of amines and *omega*-amino acids have been studied extensively via organoborane chemistry.^{206,225} Interestingly, the

preparation of diamines and *gamma*-amino acids have never been reported. The results of our investigation involving the syntheses of diamines and amino acids are summarized in the next sections.

1. Preparation of N,N-bis(trimethylsilyl)aminoalkenes.

The preparation of disilylated aminoalkenes was carried out according to the literature procedure.²³⁰ Upon the treatment of terminal bromo-1-alkenyl compounds at 80 °C for eight to sixteen hours with sodium bis(trimethylsilyl)amide using hexamethyldisilazane as solvent, the desired N,N-bis(trimethylsilyl)aminoalkenes were formed. After filtration and vacuum distillation, the pure products were obtained in good yield. The reaction is postulated to proceed through an S_N2 mechanism (4-13). As



illustrated in Table 4-1, the reaction of 4-bromo-1-butene with sodium bis(trimethylsilyl)amide generated the desired 4-[bis(trimethylsilyl)amino]-1-butene in a low yield, which was probably due to elimination and ring closure side reactions.

Table 4-1. Preparation of N,N-bis(trimethylsilyl)aminoalkenes^a.

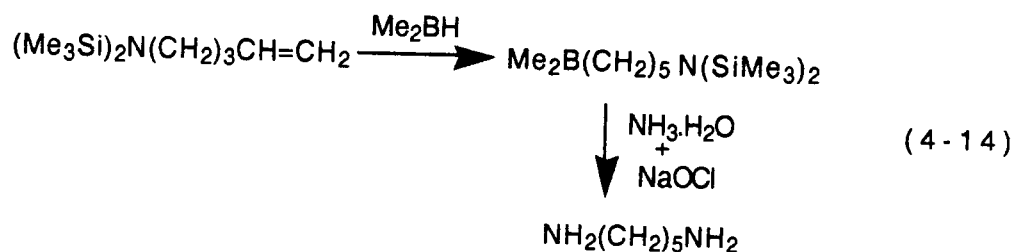
Entry	Bromoalkene ^b	Product	Yield% ^c
1	$\text{BrCH}_2\text{CH}=\text{CH}_2$	$(\text{Me}_3\text{Si})_2\text{NCH}_2\text{CH}=\text{CH}_2$	41
2	$\text{Br}(\text{CH}_2)_2\text{CH}=\text{CH}_2$	$(\text{Me}_3\text{Si})_2\text{N}(\text{CH}_2)_2\text{CH}=\text{CH}_2$	19
3	$\text{Br}(\text{CH}_2)_3\text{CH}=\text{CH}_2$	$(\text{Me}_3\text{Si})_2\text{N}(\text{CH}_2)_3\text{CH}=\text{CH}_2$	50
4	$\text{Br}(\text{CH}_2)_4\text{CH}=\text{CH}_2$	$(\text{Me}_3\text{Si})_2\text{N}(\text{CH}_2)_4\text{CH}=\text{CH}_2$	60
5	$\text{Br}(\text{CH}_2)_6\text{CH}=\text{CH}_2$	$(\text{Me}_3\text{Si})_2\text{N}(\text{CH}_2)_6\text{CH}=\text{CH}_2$	58

- a) The reactions were run using equimolar quantities with stirring at 80 °C for 8 to 16 hours.
- b) The bromoalkenes were distilled prior to use.
- c) Unoptimized distillation yields.

2. Preliminary Investigations for the Syntheses of Diamines: Route A.

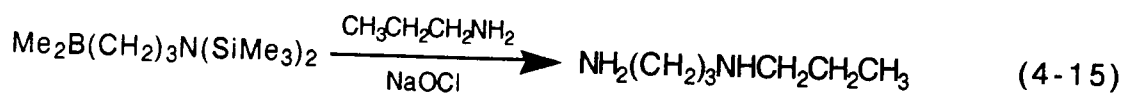
The preliminary studies were carried out using 5-[bis(trimethylsilyl)-amino]-1-pentene. The 5-[bis(trimethylsilyl)amino]-1-pentene was hydroborated at 0 °C in diethyl ether with dimethylborane generated *in situ* from lithium dimethylborohydride and trimethylsilyl chloride under a nitrogen atmosphere. The hydroboration was maintained at 0 °C and monitored by B-11 NMR. Initially, only one peak corresponding to dimethylborane was present at +25.2 ppm. After the reaction mixture was stirred at 0 °C for 30 minutes, a new peak at +86.0 ppm appeared as the signal at +25.2 ppm decreased in size. After 1 hour stirring at 0 °C, the dimethylborane's signal disappeared; only the dimethylalkylborane's resonance at +86.0 ppm was present, indicating that the hydroboration reaction was complete in 1 hour.

The chloramine was generated in a separated flask, and the aqueous chloramine solution was added dropwise to the organoborane solution. The amination reaction was continued at room temperature for 30 minutes. After acid-base work up, a 60% yield of the desired 1,5-diaminopentane was obtained (4-14).



3. Syntheses of Diamines via the Reaction of N,N-bis(trimethylsilyl)-aminoalkyl-dimethylboranes with Chloramine: Route A.

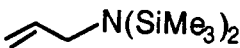
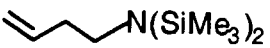
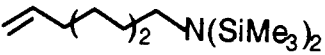
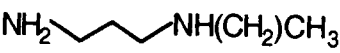
Each of the N,N-protected aminoalkenes were hydroborated using dimethylborane generated *in situ*. The subsequent dimethylalkylboranes were aminated via the *in situ* amination process. In these cases, the chloramine was prepared in a separate flask and then introduced into the organoborane containing flask under an inert atmosphere via a syringe. This process is also applicable to the preparation of N-substituted unsymmetric secondary diamines, such as N-propyl-1,3-diaminopropane (4-15). The propylchloramine was generated in a fashion analogous to that employed for the chloramine. These results are summarized in Table 4-2.



4. Syntheses of Isomerically Pure Diamines from Dienes and Chloramine: Route B.

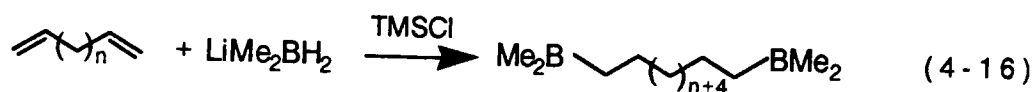
A more direct approach to diamine compounds involves hydroboration of terminal nonconjugated dienes and subsequent amination of the resultant organoboranes. The hydroboration of dienes using dimethylborane has never been reported. However, the hydroboration of dienes using other hydroborating agents has been studied. Based on the nature of the dimethylborane agent (only one hydride available, high regioselectivity),

Table 4-2. Syntheses of Isomerically Pure Diamines via the Reaction of N,Nis(trimethylsilyl)aminoalkyldimethylboranes with Chloramine or Chloralkylamine: Route A^a.

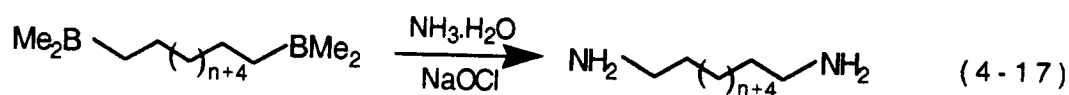
Entry	Alkene ^b	Product	Yield% ^c
1			64
2			60
3			68
4			66
5			58 ^d

- a) The amination reactions were run at room temperature for 45 to 60 minutes followed by an acid-base work up procedure.
- b) Alkenes were freshly prepared.
- c) Isolated yields.
- d) The reaction of the dimethyl(N-silylatedamino)propylborane with chloropropylamine was run at room temperature for 1 hour.

it was felt that diene hydroboration using dimethylborane (4-16) would be possible; and the resultant bis[dimethylboryl]alkanes would be ideal intermediates for conversions to diamines.



1,4-Pentadiene was chosen as the model compound for the initial experiment. One equivalent of 1,4-pentadiene was introduced into a flame-dried flask, containing diethyl ether as solvent, under a nitrogen atmosphere at -78°C . The solution was warmed to 0°C by an ice-water bath. The diene was then hydroborated with 2 equivalents of dimethylborane generated *in situ* from lithium dimethylborohydride and trimethylsilyl chloride. The progress of the hydroboration was monitored by B-11 NMR. The disappearance of the resonance at $+25.0$ ppm indicated that the hydroboration was complete after one hour at 0°C . The resultant organoborane was immediately aminated using *in situ* generated chloramine; the initial reaction temperature was 0°C but the reaction mixture was allowed to warm to room temperature for 30 minutes followed by the acid-base work up. The desired 1,5-diaminopentane was obtained (4-17) in approximately 70% yield.



1,5-Hexadiene and 1,7-octadiene were then hydroborated using dimethylborane. The resultant organoboranes were each aminated employing chloramine; the reaction mixtures were worked up using the acid-base procedure. The desired 1,6-diaminohexane and 1,8-diaminooctane were obtained in good yields.

The 1,6-bis[dimethylboryl]hexane was also treated with methylamine and sodium hypochlorite; the desired 1,6-bis[dimethylamino]hexane was obtained in a reasonable yield. The results are summarized in Table 4-3.

In summary⁷⁶, our investigations involved two different protocols for preparing diamines. In one, Route A, trimethylsilyl protected aminoalkenes were hydroborated by dimethylborane and then treated with ammonium hydroxide and sodium hypochlorite to produce diamines. In the other, Route B, dienes were hydroborated utilizing dimethylborane. The resultant organoboranes reacted with *in situ* generated chloramine to yield the desired diamines. This approach was also used to prepare N,N'-disubstituted symmetrical diamines (Entry 4, Table 4-3).

In general, Route B gave slightly higher yields of the desired products and was more convenient than Route A. However, Route A was more flexible; thus N-monosubstituted secondary diamines, such as N-propyldiaminopropane, could be prepared in reasonable yield (Entry 5, Table 4-2).

Table 4-3. Syntheses of Isomerically Pure Diamines via the Reaction of Bis[dimethylboryl]alkenes with Chloramine or Chloralkylamines: Route B^a.

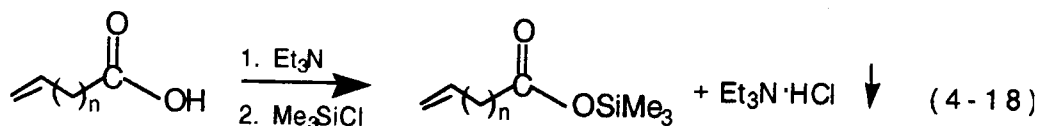
Entry	Alkene ^b	Product	Yield% ^c
1			74
2			78
3			76
4			49

- a) The amination reactions were run at room temperature for 45 to 60 minutes using 1 equivalent of organoborane and two equivalents of chloramine.
- b) Isolated yields.
- c) The reaction of the organoborane with chloromethylamine was run at room temperature for 1 hour.

5. Hydroboration of Alkenes in the Presence of Protected Carboxylic Acid Functionality Using Dimethylborane.

A good protecting group must be easily introduced, unreactive to reagents, and easily removed.²³² Methyl esters have been proven to be stable during hydroboration-amination reactions if the chain length between one double bond and the ester group is greater than three,^{69,225} but the ester group is somewhat difficult to hydrolyze. Silicon protecting groups, such as the trimethylsilyl group, are easily prepared and have proven to be one of the most useful protecting groups.

Trimethylsilyl esters were prepared from alkenyl carboxylic acids by sequential treatment of the acids with triethylamine and trimethylsilyl chloride (one equivalent of each).²²⁵ The resulting precipitate (triethylamine hydrochloride) was filtered off under nitrogen and the filtrate distilled under vacuum to produce the desired trimethylsilyl alkenoate (4-18).



Initial studies of the dimethylborane hydroboration of alkenyl carboxylic acid silyl esters were carried out using trimethylsilyl pentenoate. The hydroboration of trimethylsilyl pentenoate using a borane-THF complex had been performed previously.²²⁵ The first attempt at hydroborating trimethylsilyl pentenoate using equimolar dimethylborane generated from lithium dimethylborohydride and TMSCl was not successful. The failure was

due to the fact that lithium dimethylborohydride is also a reducing agent which reduced the ester functionalities. To circumvent this problem the dimethylborane was generated in a separate flask and then transferred into the flask containing the trimethylsilyl pentenoate. The hydroboration was successful as indicated by B-11 NMR.

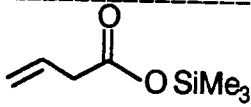
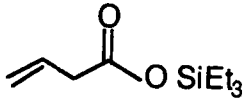
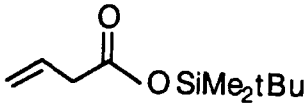
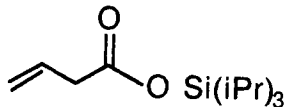
The hydroboration of trimethylsilyl butenoate using dimethylborane generated in a separate flask was studied next. The hydroboration was started at -78°C and was gradually increased to room temperature.

Unfortunately, when the temperature reached -30°C , one B-11 NMR spectrum revealed a major peak at 54.0 ppm which corresponded to the resonance of the dimethylalkoxylborane reduction product; after 2 hours, the peak increased slightly. In a parallel experiment, when the reaction temperature was quickly raised from -78°C to -25°C and stirred for 2 hours at -25°C , only one peak at +54.0 was present in the B-11 NMR spectrum. The results indicate that the reduction occurred at -25°C . Various reaction temperatures were tried, but only a very low yield (10%) of hydroboration product was obtained after the organoborane intermediates were aminated.

Since the hydroboration reaction of trimethylsilyl butenoate using dimethylborane failed, it was felt that an increased size of the silyl protecting groups might reduce hydride attack on the ester group due to steric hindrance. A variety of trialkylsilyl butenoates were then synthesized, as shown in Table 4-4.

Subsequently, the hydroboration of the trialkylsilyl butenoates were performed using dimethylborane as the hydroborating agent. Upon

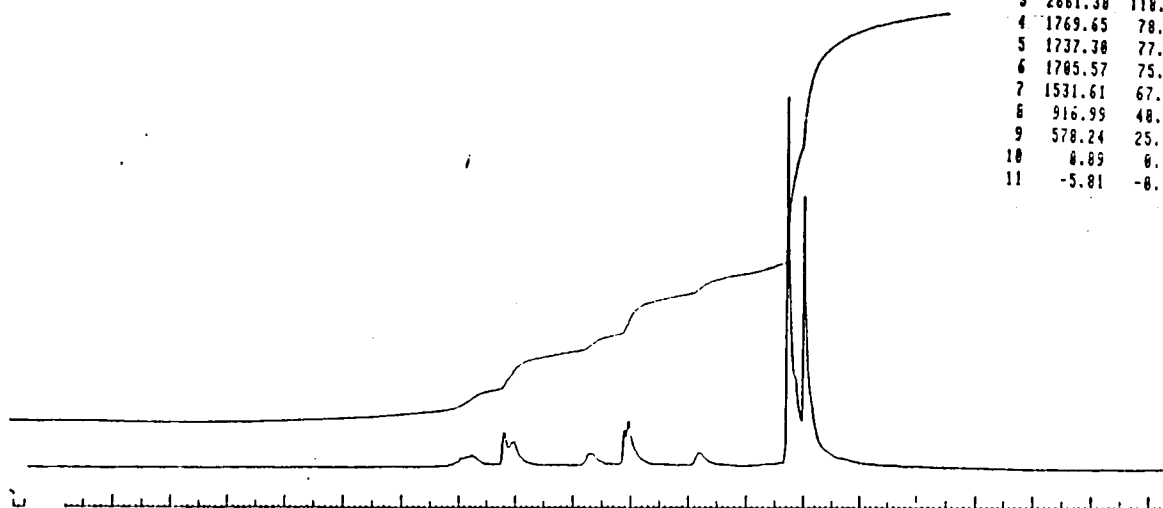
Table 4-4. The Preparation of Trialkylsilylbutenoates^a.

Entry	Silicon Reagent ^b	Product ^c	Yield% ^d
1	Me ₃ SiCl		88.6
2	Et ₃ SiCl		90.0
3	Me ₂ tBuSiCl		94.3
4	(iPr) ₃ SiCl		91.5

- a) The reactions were carried out using equimolar quantities.
- b) Trialkylsilyl chlorides were distilled prior to use.
- c) The NMR spectra of new compounds are presented in Figures 4-1 to 4-4.
- d) Distillation yields.

TOTAL 11
 RESOL 61031 -4 HZ
 EXREF 77.1000PPM
 OBS 554.8095 HZ
 NGAIN 9

NO	FREQ(HZ)	PPM	INT1
1	3077.20	172.067	612
2	2947.63	130.814	2335
3	2661.30	110.110	2769
4	1769.65	78.535	1737
5	1737.30	77.100	1766
6	1705.57	75.691	1632
7	1531.61	67.972	681
8	916.95	40.696	3078
9	570.24	25.661	680
10	0.89	0.840	3234
11	-5.81	-0.257	5745



TOTAL 11
 RESOL 61031 -4 HZ
 EXREF 77.1000PPM
 OBS 554.8095 HZ
 NGAIN 9

NO	FREQ(HZ)	PPM	INT1
1	3077.20	172.067	612
2	2947.63	130.814	2335
3	2661.30	110.110	2769
4	1769.65	78.535	1737
5	1737.30	77.100	1766
6	1705.57	75.691	1632
7	1531.61	67.972	681
8	916.95	40.696	3078
9	570.24	25.661	680
10	0.89	0.840	3234
11	-5.81	-0.257	5745



Figure 4-1 The H-1 and C-13 NMR Spectra of Trimethylsilyl Ester of 3-Butenoic Acid.

TOTAL 22
 RESOL 43963 -4 HZ
 EXREF 0.0000PPM
 OBS 333.2965 HZ
 NGAIN 4

NO	FREQ(HZ)	PPM	INT1
1	528.51	5.898	336
2	518.84	5.798	375
3	512.24	5.716	226
4	467.83	5.221	914
5	465.63	5.196	960
6	454.28	5.669	645
7	288.96	3.135	1578
8	274.37	3.062	1527
9	95.41	1.064	1576
10	93.21	1.040	1465
11	90.57	1.010	1907
12	87.06	0.971	7752
13	81.34	0.907	7145
14	77.82	0.868	3687
15	76.58	0.853	4021
16	72.11	0.804	4957
17	65.95	0.736	1755
18	63.31	0.706	1881
19	57.60	0.642	729
20	53.64	0.596	395
21	3.07	0.034	310
22	0.00	0.000	3324

TOTAL 11
 RESOL 61034 -4 HZ
 EXREF 77.1000PPM
 OBS 554.1952 HZ
 NGAIN 9

NO	FREQ(HZ)	PPM	INT1
1	3874.15	171.932	606
2	2948.85	130.868	2330
3	2668.16	110.855	3178
4	1769.84	76.568	895
5	1737.38	77.109	851
6	1704.96	75.664	982
7	915.77	40.642	3174
8	144.69	6.432	7578
9	131.46	5.637	531
10	101.55	4.589	8474
11	-0.93	-0.040	704

Figure 4-2 The H-1 and C-13 NMR Spectra of Triethylsilyl Ester of 3-Butenoic Acid.

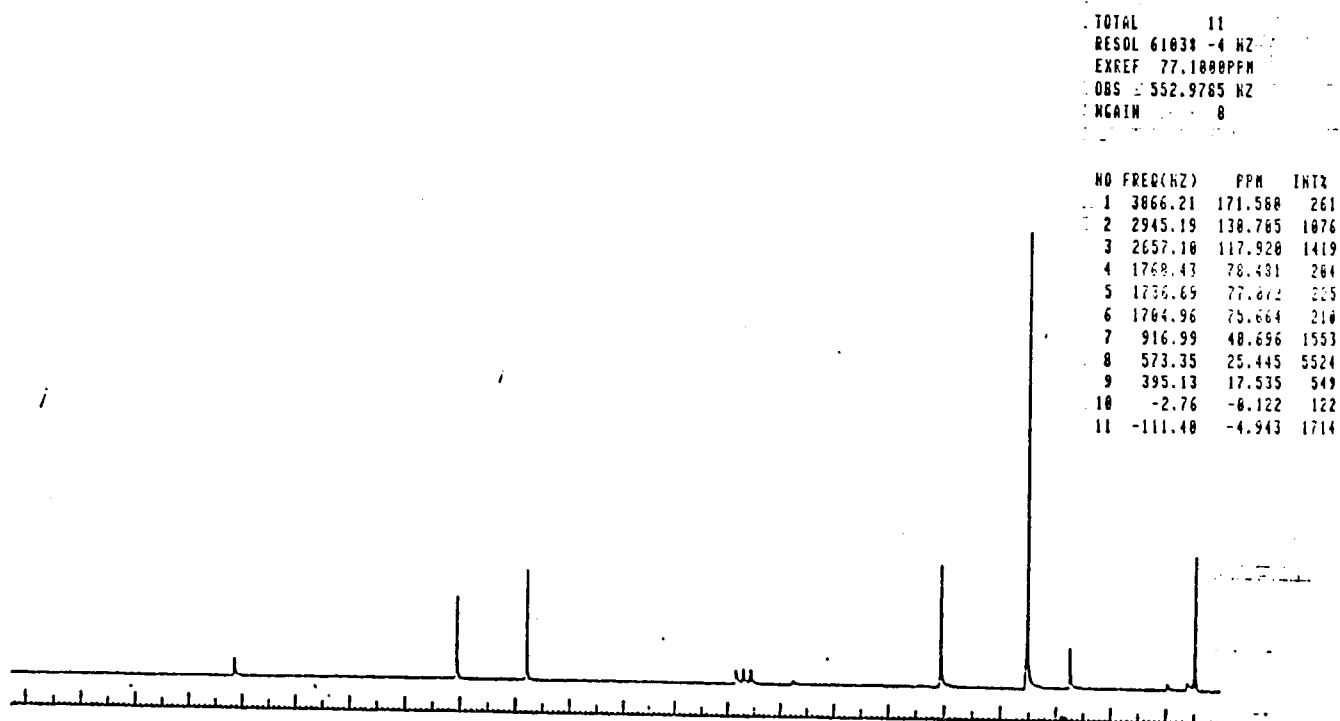
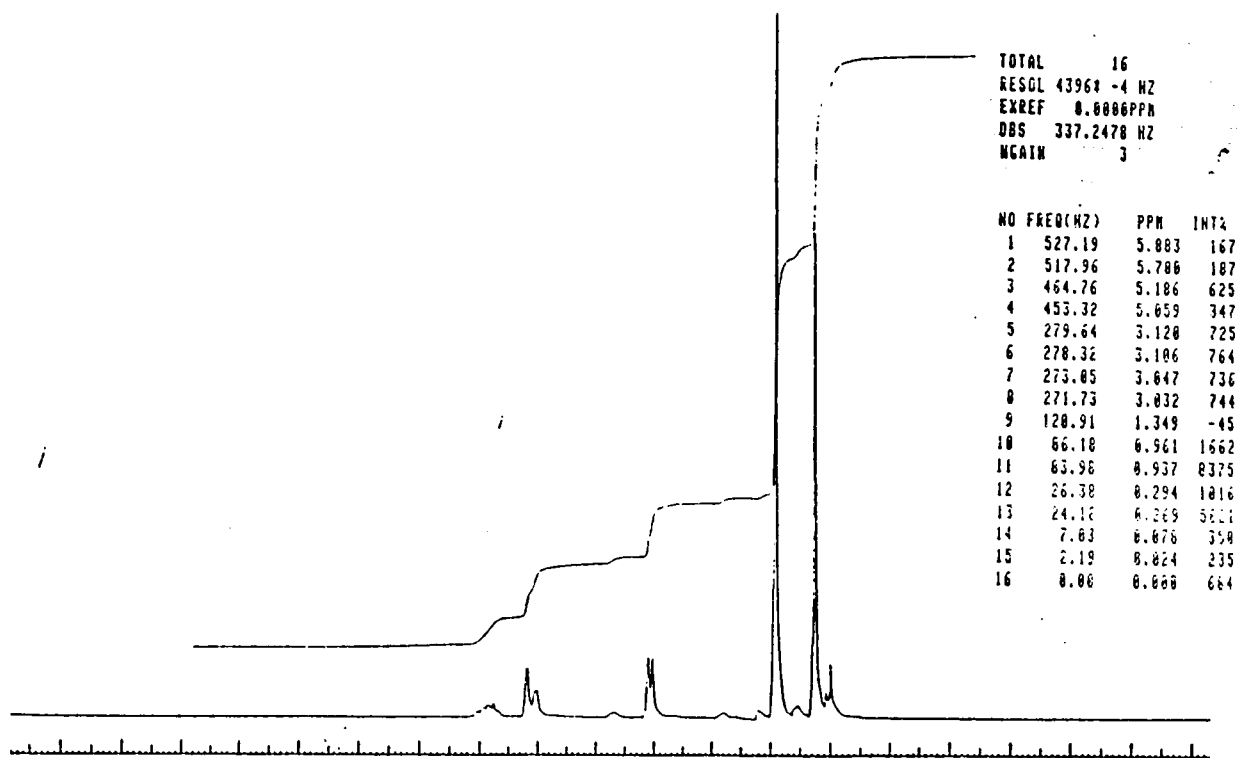
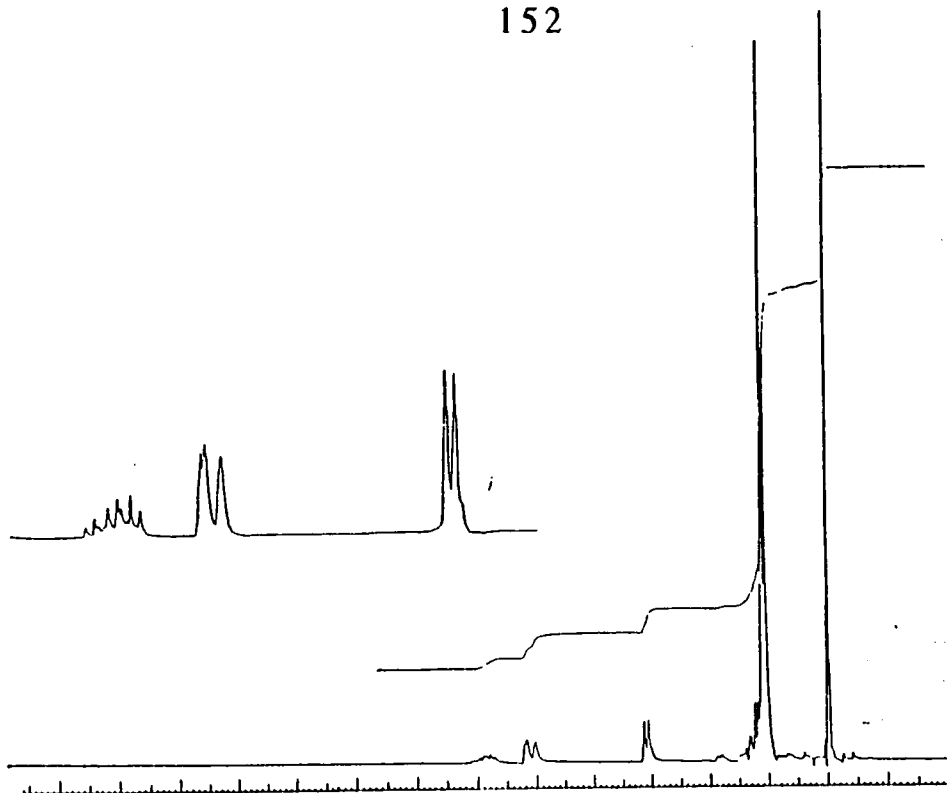


Figure 4-3 The ^1H -1 and ^{13}C -13 NMR Spectra of Dimethylmono-*t*-butylsilyl Ester of 3-Butenoic Acid.

TOTAL 25
 RESOL 43964 -4 HZ
 EXREF 0.0000PPM
 OBS 335.9237 HZ
 NGAIN 3



NO	FREQ(HZ)	PPM	INTX
1	529.33	5.913	146
2	520.16	5.885	123
3	467.83	5.221	322
4	282.28	3.150	553
5	275.25	3.071	537
6	124.07	1.393	152
7	119.15	1.329	427
8	110.80	1.236	873
9	105.96	1.132	837
10	99.37	1.109	8832
11	94.89	1.058	4910
12	88.81	0.991	487
13	78.70	0.878	-163
14	34.73	0.337	92
15	21.99	0.245	-112
16	20.22	0.225	100
17	14.51	0.161	-89
18	7.93	0.276	103
19	4.93	0.453	-239
20	3.87	0.834	322
21	0.00	0.000	8617
22	-3.95	-0.844	-206
23	-5.27	-0.858	344
24	-12.75	-0.142	-125
25	-20.66	-0.230	-180

TOTAL 10
 RESOL 61033 -4 HZ
 EXREF 77.1000PPM
 OBS 557.2589 HZ
 NGAIN 13

NO	FREQ(HZ)	PPM	INTX
1	3852.78	178.364	245
2	2953.13	131.857	924
3	2654.66	117.812	975
4	1769.84	78.508	227
5	1736.69	77.872	214
6	919.43	40.804	1295
7	398.79	17.698	8896
8	284.05	12.608	195
9	273.67	12.148	4122
10	-2.76	-0.122	1614

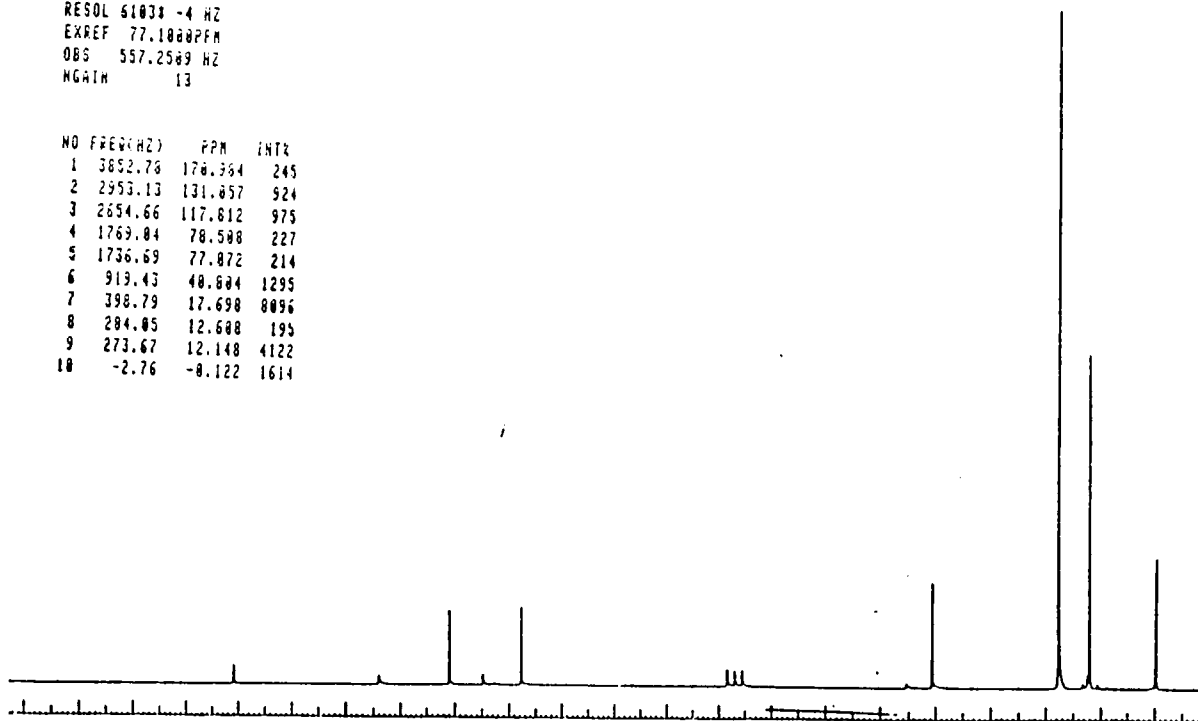


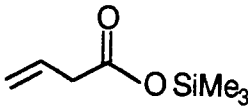
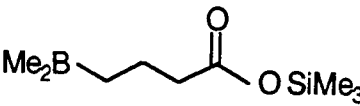
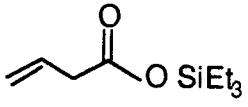
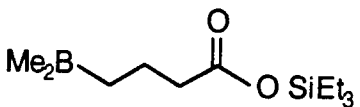
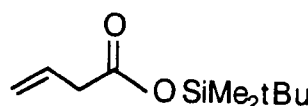
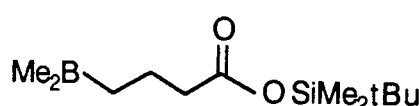
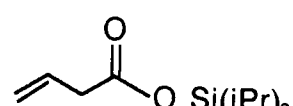
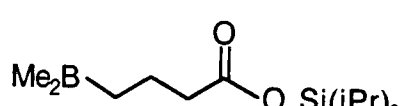
Figure 4-4 The ^1H -1 and ^{13}C -13 NMR Spectra of Triisopropylsilyl Ester of 3-Butenoic Acid.

treatment with aqueous ammonia and sodium hypochlorite, the resultant organoboranes were then converted to the *gamma*-amino acids. After purification, the desired products were obtained in high yields (Table 4-5).

Successful hydroboration conditions were developed using triisopropylsilyl butenoic esters and dimethylborane. Temperature was an important factor, and its effect was thoroughly investigated employing B-11 NMR to monitor the reaction progress. The NMR spectra were recorded initially beginning with the freshly prepared lithium dimethylborohydride, (a sharp resonance at -21.8 ppm), and at subsequent stages. The NMR studies revealed that dimethylborane was generated on treatment with TMSCl in ether in 2 minutes at 0 °C, as evidenced by the appearance of a sharp resonance at +25.6 ppm and the disappearance of the peak at -21.8 ppm. The reaction of lithium dimethylborohydride with TMSCl was also temperature dependent. No dimethylborane was produced at -78 °C to -50 °C for 5 hours. At -30 °C, a small amount of dimethylborane appeared within 30 minutes. The dimethylborane was easily generated at -10 °C to 0 °C in 5 minutes.

The hydroboration of triisopropylsilyl butenoate involved the generation of dimethylborane at 0 °C, followed by cooling the solution to -78 °C under a stream of argon, and transferring the solution into a reaction flask containing the butenoate ester in diethyl ether at -78 °C. The NMR studies revealed only a single dimethylborane peak at +25.6 ppm at -78 °C to -50 °C. As the temperature was raised to -50 °C, a small peak at +54.4 ppm,

Table 4-5. Use of Silicon Protecting Groups in Hydroboration of Unsaturated Carboxylic Acids^a.

Entry	Protected Ester ^c	Organoborane	Yield ^c (%) of Gamma-Amino Butyric Acid
1			12
2			24
3			31
4			53

- a) The hydroboration reactions were run at -78°C for 5 minutes, and then the reaction mixture was warmed to room temperature, and then stirred for 45 minutes to 1 hour.
- b) Starting materials were freshly prepared.
- c) Isolated yields.

corresponding to the reduced product Me₂BOR, developed after 5 minutes. This peak increased gradually in size with time. As the reaction mixture was warmed to -25 °C, a second peak at 87.1 ppm, corresponding to the desired product, appeared. A further increase in temperature to 0 °C (30 minutes), led to the gradual disappearance of the peak at +25.6 ppm, while the peaks at +87.1 ppm and +54.4 ppm increased in size. The peak at +87.1 ppm increased faster than that at +55.4 ppm. Amination of the organoborane, followed by work up of the reaction mixture, gave approximately 40% yield of *gamma*-aminobutyric acid. In other experiments started at -35 °C and -25 °C, both peaks (+87.1 ppm and +54.4 ppm) appeared simultaneously. It was found that the best hydroboration conditions involve introducing the dimethyl-borane into the butenoate-containing flask maintained at -78 °C followed by exchange of the dry ice-acetone bath for an ice-water bath. Amination of the organoboranes led then to 50% yields of the desired amino acid (Table 4-6).

C. Conclusion.

Successful hydroboration-amination methodologies were developed for the preparation of isomerically pure diamines and amino acids (*gamma*-amino acids). The one-pot methods are easy and convenient. The reactions give the desired products in good yields. The methods are generally applicable to the syntheses of nitrogen-13 labeled diamines and amino acids and proceed with complete retention of configuration.

Table 4-6. Temperature Effects on Hydroboration of Triisopropylsilyl butenoate Using Dimethylborane Reagent^a.

Entry	Starting Temp.	Final Temp.	Yield ^b (%) of Amino Acid
1	-25 °C	0 °C	35
2	-35 °C	0 °C	> 35
3	-50 °C	0 °C	< 40
4	-78 °C	0 °C	> 50

a) Hydroboration reactions were run at the temperature indicated for 45 minute to 1 hour followed by amination under normal conditions.

b) Isolated yields.

D. Experimental Section.

The H-1 and C-13 NMR spectra were recorded on a Jeol FX-90Q spectrometer using deuteriochloroform or deuteriomethanol as solvent and are referenced to TMS. The B-11 NMR spectra of the organoborane precursors were recorded on the same spectrometer using BF₃-etherate as an external reference. Glassware was thoroughly oven-dried and cooled under a stream of dry nitrogen just prior to use. Bromoalkenes and alkenylcarboxylic acids (Aldrich Chemical Company) were distilled prior to use. Sodium bis(trimethylsilyl)amide, triethylsilyl chloride, dimethylbutylsilyl chloride, triisopropylsilyl chloride, boron trifluoride etherate, methyl iodide, and lithium aluminum hydride (1.0 M solution in ether) were used as purchased (Aldrich Chemical Co.). Commercial bleach was used as the source of sodium hypochlorite after determination of its concentration. Dimethylborane was prepared according to the procedure described in Chapter III. Other chemicals were used and purified as described in Table 2-9.

General Procedure for the Preparation of [N,N-bis(trimethylsilyl)-amino]alkenes: Preparation of 5-[N,N-bis(trimethylsilyl)amino]-1-pentene.

The preparation of 5-[N,N-bis(trimethylsilyl)amino]-1-pentene serves as an example of the general procedure for the preparation of [N,N-bis(trimethylsilyl)-amino]alkenes. A 100-mL round-bottomed flask, fitted

with a septum inlet, was equipped with a magnetic stirring bar, addition funnel, and a gas outlet connected to a mercury bubbler. Sodium bis(trimethylsilyl)amide (50 mmol, 9.7 g, 95% purity) in 25 mL of 1,1,1,3,3,3-hexamethyldisilazane was placed in the flask by a cannula. 5-bromo-1-pentene (50 mmol, 7.7 g, 97% purity) was then added and the solution was warmed at 84 °C (oil bath temperature) for 16 hours.

A separate apparatus consisting of a 100-ml round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass, fritted funnel capped with a septum was assembled while hot and then flushed with nitrogen. The reaction mixture was then filtered under nitrogen by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate with 1,1,1,3,3,3-hexamethyldisilazane, the solvent was removed from the filtrate by slow distillation under nitrogen. The residue was distilled under vacuum to yield the desired product. 6.1 g, (50%) as a colorless oil: bp 48-51°C/1 mmHg. ¹H-NMR (CDCl₃) (ppm): 6.00-5.51 (m, 1H, CH₂=CH), 5.10-4.75 (m, 2H, CH₂=CH), 2.90-2.60 (d, 2H, CH₂), 2.01-1.70, (m, 2H, CH₂), 1.60-1.25 (m, 2H, CH₂), 0.09 (s, 18H, 6xCH₃-Si). ¹³C-NMR (ppm): 138.6 , 114.5 , 45.4, 34.7, 31.7, 2.3.

Preparation of 3-[N,N-bis(trimethylsilyl)amino]propene. Sodium bis(trimethylsilyl)amide (25 mmol, 4.8 g, 95% purity) reacted with allylbromide (25 mmol, 3.1 g) using 1,1,1,3,3,3-hexamethyldisilazane (15 mL) as solvent and according to the general procedure described above to produce the desired product, 2.2 g (41%), as colorless oil : bp 35-37 °C/0.5 mmHg. ¹H-NMR (CDCl₃) (ppm): 6.00-5.50 (m, 1H, CH₂=CH), 5.25-4.80 (m, 2H,

$\text{CH}_2=\text{CH}$), 3.79 (m, 2H, CH_2), 0.10 (s, 18H, $6\times\text{CH}_3\text{-Si}$). $^{13}\text{C-NMR}$ (ppm): 141.5, 113.4, 47.6, 2.1.

Preparation of 4-[N,N-bis(trimethylsilyl)amino]-1-butene. Sodium bis(trimethylsilyl)amide (50 mmol, 9.7 g, 95% purity) reacted with 4-bromo-1-pentene (50 mmol, 6.9 g) using 1,1,1,3,3,3-hexamethyldisilazane (25 ml) as solvent according to the general procedure to produce the desired product, 2.1 g (19%) as a colorless oil : bp 54-57 °C/10 mmHg. $^1\text{H-NMR}$ (CDCl_3) (ppm): 5.90-5.30 (m, 1H, $\text{CH}_2=\text{CH}$), 5.15-4.80 (m, 2H, $\text{CH}_2=\text{CH}$), 3.40-1.55 (envelop, 4H, CH_2), 0.10 (s, 18H, $6\times\text{CH}_3$). $^{13}\text{C-NMR}$ (ppm): 136.6, 115.5, 45.4, 40.0, 2.6.

General Procedure for the Preparation of Putresine (1,4-diaminobutane).

The preparation of putresine serves as an example of the general procedure for preparing diamines. To a dry 25-ml flask fitted with a septum inlet and equipped with a magnetic stirring bar and a gas outlet, lithium dimethylborohydride (5.0 mmol, 10.4 mL of 0.48 M solution in diethyl ether) was added, and the reaction flask was cooled to 0 °C. Then 4-[bis(trimethylsilyl)amino]-1-butene (5.1 mmol 1.2 g) was added, followed by the addition of TMSCl (5.5 mmol, 0.60 g). The reaction mixture was stirred for 1 hr at 0 °C, after which the $^{11}\text{B-NMR}$ of the reaction mixture was recorded (signal at 86.0 ppm). In a separate flask, sodium hypochlorite (5.0 mmol, 6.8 mL of 0.74 M solution) was added dropwise to aqueous ammonia (5.0 mmol, 2.6 mL of 1.92 M solution). To the organoborane solution, the chloroamine solution was added

slowly with stirring. The reaction mixture was allowed to warm to room temperature and stirred for 60 minutes. The mixture was then acidified to pH=1.0 and washed with diethyl ether. The free amine was obtained via the addition of sodium hydroxide (6 M) to the aqueous layer (pH > 13) followed by extraction of the product into n-butanol or chloroform. The organic layer was dried over sodium sulfate and the product was purified by column chromatography to obtain the desired product; yield 0.27 g (60%): mp. 28-30 °C (lit.⁷⁶ mp 27-28 °C); ¹H-NMR (MeOD/D₂O) (ppm): 3.90-2.50 (t, 4H, 2xCH₂N), 2.4-1.5 (m, 4H, CH₂CH₂). ¹³C-NMR (ppm): 41.0, 38.0.

Preparation of 1,3-Diaminopropane. 3-[Bis(trimethylsilyl)amino]-1-propene (5.1 mmol, 1.1 g) was hydroborated with dimethylborane (6.0 mmol) using diethyl ether as solvent, and the resultant organoborane was aminated according to the general procedure to produce the desired product, 0.24 g (64%): mp (dihydrochloride) 244-247 °C (lit.⁷⁶ mp 246-250 °C); ¹H-NMR (MeOD/D₂O) (ppm): 5.00 (s, 6H, 2xNH₂·HCl), 3.16 (t, 4H, 2xCH₂N), 2.14 (m, 2H, CH₂). ¹³C-NMR (ppm): 37.8, 26.1.

Preparation of 1,5-Diaminopentane. 5-[bis(trimethylsilyl)amino]-1-pentene (5.0 mmol, 1.22 g) was hydroborated with dimethylborane (6.0 mmol) using diethyl ether as solvent, and the resultant organoborane was aminated according to the general procedure to produce the desired product, 0.34 g (66%): mp (dihydrochloride) 258-260 °C (lit.⁷⁶ mp 260-262 °C); ¹H-NMR (MeOD) (ppm): 5.16 (s, 6H, 2xNH₂·HCl), 2.97 (t, 4H, 2xCH₂N), 1.90-1.30 (m, 6H, CH₂). ¹³C-NMR (ppm): 40.3, 27.6, 24.1.

Preparation of 1,6-Diaminohexane. Sodium bis(trimethylsilyl)amide (10 mmol, 1.9 g, 95% purity) reacted with 6-bromo-1-hexene (10 mmol, 1.6 g) using 1,1,1,3,3,3-hexamethyldisilazane (10 mL) as solvent and according to the general procedure to produce the desired product, 1.8 g (68%). The 6-[bis(trimethylsilyl)-amino]-1-hexene was directly hydroborated with dimethylborane (6.0 mmol), using diethyl ether as solvent, and the resultant organoborane was aminated according to the general procedure to produce the desired product, 0.39 g (68%): mp (dihydrochloride) 255-256 °C (lit.⁷⁶ mp 256-257 °C); ¹H-NMR (CDCl₃) (ppm): 2.68 (b, 4H, 2xCH₂N), 1.35 (b, 8H, CH₂), 1.14 (s, 4H, NH₂, D₂O exchangeable). ¹³C-NMR (ppm): 41.8, 33.5, 26.4

Preparation of 1,8-Diaminooctane. Sodium bis(trimethylsilyl)amide (10 mmol, 1.9 g, 95% purity) reacted with 8-bromo-1-octene (10 mmol, 1.8 g), using 1,1,1,3,3,3-hexamethyldisilazane (10 mL) as solvent according to the general procedure to produce the desired product, 1.7 g (58%). The 8-[bis(trimethylsilyl)-amino]-1-octene was directly hydroborated with dimethylborane (5.0 mmol) using diethyl ether as solvent, and the resultant organoborane was aminated according to the general procedure to produce the desired product, 0.48 g (66%): mp 49-52 °C (lit.⁷⁶ mp 50-52 °C); ¹H-NMR (CDCl₃) (ppm): 2.67 (b, 4H, 2xCH₂N), 1.32 (b, 12H, CH₂), 1.08 (s, 4H, NH₂, D₂O exchangeable). ¹³C-NMR (ppm): 42.0, 33.7, 29.2, 26.6.

Preparation of 3-(n-Propylamino)-1-aminopropane. 3-[Bis(trimethylsilyl)amino]propene (5.0 mmol, 1.1 g) was hydroborated with

dimethylborane (6.0 mmol), using diethyl ether as solvent, and the resultant organoborane was aminated with *n*-propylamine (5.0 mmol, 0.30 g) and sodium hypochlorite (5.0 mmol, 2.6 mL of 1.9 M solution) according to the general procedure to produce the desired product, 0.34 g (58%): bp 168-171 °C (lit.⁷⁶ bp 169 °C); ¹H-NMR (CDCl₃) (ppm): 2.67 (p, 6H, 3xCH₂N), 1.62 (h, 4H, CH₂), 1.08 (s, 3H, NH, NH₂, D₂O exchangeable), 0.91 (t, 3H, CH). ¹³C-NMR (ppm): 51.6, 47.3, 39.9, 33.4, 22.8, 11.5.

Hydroboration of Dialkenes with Dimethylborane.

General Procedure. To a dry, 25-mL, nitrogen-flushed flask fitted with a septum-covered side arm inlet and a magnetic stirring bar was added lithium dimethylborohydride (12.0 mmol) in ether. The flask was cooled to 0 °C and the dialkene (5.0 mmol), was introduced into the flask followed by the dropwise addition of trimethylsilyl chloride (12.0 mmol, 1.30 g) over a period of 2 min. There was an immediate precipitate of lithium chloride. The reaction was stirred for an appropriate period of time to complete the reaction. The B-11 NMR spectrum revealed a resonance at ca. +87 ppm.

Synthesis of Diaminoalkanes: Route B.

General Procedure. The bis(dimethylboryl)alkane (5.0 mmol freshly prepared in ether) was cooled to 0 °C. The chloramine (10.0 mmol) was generated by adding sodium hypochlorite (10.0 mmol) dropwise to a solution of aqueous ammonia (6.0 mmol) contained in a 25-mL flask cooled to 0 °C.

This mixture was added dropwise, with stirring, to the flask containing the bis(dimethylboryl)alkane (5.0 mmol in ether) at 0 °C. The solution was stirred at 0 °C for 3 minutes, allowed to warm to room temperature and then stirred for 1 hour.

The reaction mixture was then acidified with 10% HCl to pH=1 and washed with diethyl ether. The free amines were obtained via the addition of sodium hydroxide (6 M) to the aqueous layer (pH>13) and extraction of the product into chloroform or *n*-butanol. The organic layer was dried over magnesium sulfate and the product was purified by chromatography.

Preparation of 1,6-Diaminohexane. 1,5-Hexadiene (5.1 mmol, 0.42 g) was hydroborated with LiMe₂BH₂ (12 mmol, 25 mL of 0.48 M solution in diethyl ether) and TMSCl (12 mmol, 1.3 g) for 45 minutes. Aqueous ammonia (10 mmol, 5.3 mL of 1.9 M solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedure to yield the desired product: 0.45 g (78%).

Preparation of 1,5-Diaminopentane. 1,4-Pentadiene (5.2 mmol, 0.35 g) was hydroborated with LiMe₂BH₂ (12 mmol, 25 mL of 0.48 M solution in diethyl ether) and TMSCl (12 mmol, 1.3 g) for 45 minutes. Aqueous ammonia (10.0 mmol, 5.3 mL of 1.9 M solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedure to yield the desired product: 0.47 g (74%).

Preparation of 1,8-Diaminooctane. 1,7-Octadiene (4.9 mmol, 0.54 g) was hydroborated with LiMe_2BH_2 (12 mmol, 25 mL of 0.48 M solution in diethyl ether) and TMSCl (12 mmol, 1.3 g) for 45 minutes. Aqueous ammonia (10 mmol, 5.3 mL of 1.9 M solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedure to yield the desired product: 0.55 g (76%).

Preparation of 1,6-N,N'-Dimethylaminohexane. 1,5-Hexadiene (5.1 mmol, 0.42 g) was hydroborated with LiMe_2BH_2 (12 mmol, 25 mL of 0.48 M solution in diethyl ether) and TMSCl (12 mmol, 1.3 g) for 45 minutes. Methylamine (10 mmol, 0.78 g of a 40% solution) and sodium hypochlorite (10 mmol) were then added as described in the general procedure to yield the desired product: 0.35 g (49%); bp 100-102 °C/15mmHg (lit.⁷⁶ bp 96 °C/14mmHg) $^1\text{H-NMR}$ (CDCl_3) (ppm): 2.41 (t, 4H, $2\times\text{CH}_2\text{N}$), 2.26 (s, 6H, $2\times\text{CH}_3$), 1.75 (s, 2H, $2\times\text{NH}$, D_2O exchangeable), 1.22 (b, 8H, CH_2). $^{13}\text{C-NMR}$ (ppm): 51.4, 35.8 29.3 26.8.

General Procedure for the Preparation of Silyl Esters:

Preparation of the Triisopropylsilyl Ester of 3-Butenoic Acid.

The preparation of the triisopropylsilyl ester of 3-butenic acid is a representative example for the general procedure used to prepare silyl esters. A 250-mL round-bottomed flask, fitted with a septum inlet, was equipped with a magnetic stirring bar, addition funnel, and a gas outlet connected to a mercury bubbler. 3-Butenoic acid (52 mmol, 4.5 g) in 10 mL of

THF was placed in the flask by a cannula. Tetrahydrofuran (50 mL) and triethylamine (52 mmol, 7.2 g) were then added and the solution was cooled to 0 °C. A mixture of triisopropylsilyl chloride (52 mmol, 10 g, predried over molecular sieves) and dry THF (25 mL) was added dropwise over a period of 25 minutes. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hr.

A separate apparatus consisting of a 25-mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel capped with a septum was assembled while hot and then flushed with nitrogen. The reaction mixture was then filtered under nitrogen by transferring it into the fritted funnel using a 12 ga. double-ended needle. After the precipitate of the triethyl ammonium chloride was washed with dry THF, the solvent was removed from the filtrate by slow distillation under nitrogen. The residue was distilled under vacuum to yield the desired product, 9.6 g (76%) as colorless oil : bp 64-65 °C/0.12 mmHg. ¹H-NMR (CDCl₃) (ppm): 5.71 (m, 1H, CH₂=CH), 5.15 (m, 2H, CH₂=CH), 3.11 (d, 2H, CH₂-C=O), 1.30-0.90 (m, 3xCH-(CH₃)₂), 1.1 (d, 18H, 6xCH₃-CH). ¹³C-NMR (ppm): 171.0 (C=O), 131.1 (CH₂=CH), 117.8 (CH₂=CH), 40.8 (CH₂-CH), 17.7 (C-CH₃), 12.2 (Si-CH). ²⁹Si-NMR (CDCl₃, ppm, referenced to TMS) 21.7.

Preparation of the Trimethylsilyl Ester of 3-Butenoic Acid. 3-Butenoic acid (100 mmol, 8.6 g) reacted with trimethylsilyl chloride (100 mmol, 11 g) in the presence of triethylamine (100 mmol, 10 g) in tetrahydrofuran (100 mL) according to the general procedure to produce the desired product, 14 g (89%): bp 48-50 °C/15 mmHg. ¹H-NMR (CDCl₃) (ppm):

5.89 (m, 1H, $\text{CH}_2=\text{CH}$), 5.16 (m, 2H, $\text{CH}_2=\text{CH}$), 3.06 (d, 2H, $\text{CH}_2-\text{C}=\text{O}$), 0.94 (s, 9H, $3\times\text{CH}_3-\text{C}$), 0.27 (s, 6H, $2\times\text{CH}_3-\text{Si}$). ^{13}C -NMR (ppm): 172.1 (C=O), 130.8 ($\text{CH}_2=\text{CH}$), 118.1 ($\text{CH}_2=\text{CH}$), 40.1 (CH_2-CH), -0.3 ($\text{Si}-\text{CH}_3$). ^{29}Si -NMR (CDCl_3 , ppm, referenced to TMS) 25.5.

Preparation of the Triethylsilyl Ester of 3-Butenoic Acid. 3-

Butenoic acid (20 mmol, 1.7 g) reacted with triethylsilyl chloride (20 mmol, 3.0 g) in the presence of triethylamine (20 mmol, 2.1 g) in tetrahydrofuran (30 mL) according to the general procedure to produce the desired product 3.6 g, (90%): bp 46-48 °C/3 mmHg. ^1H -NMR (CDCl_3) (ppm): 5.90 (m, 1H, $\text{CH}_2=\text{CH}$), 5.15 (m, 2H, $\text{CH}_2=\text{CH}$), 3.07 (d, 2H, $\text{CH}_2-\text{C}=\text{O}$), 0.94 (t, 9H, $3\times\text{CH}_3-\text{C}-\text{Si}$), 0.83 (m, 6H, $3\times\text{CH}_2-\text{Si}$). ^{13}C -NMR (ppm): 171.9 (C=O), 130.9 ($\text{CH}_2=\text{CH}$), 118.1 ($\text{CH}_2=\text{CH}$), 40.6 (CH_2-CH), 6.4 ($\text{Si}-\text{CH}_2$), 4.5 ($\text{Si}-\text{CH}_3$). ^{29}Si -NMR (CDCl_3 , ppm, referenced to TMS) 25.9.

Preparation of the Dimethyl-*t*-butylsilyl Ester of 3-Butenoic Acid.

3-Butenoic acid (20.0 mmol, 1.72 g) reacted with dimethylmono-*t*-butylsilyl chloride (20 mmol, 3.1 g) in the presence of triethylamine (20.0 mmol, 2.05 g) in tetrahydrofuran (30 mL) according to the general procedure to produce the desired product 3.77 g (94.3%): bp 47-49 °C/3 mmHg. ^1H -NMR (CDCl_3) (ppm): 5.90 (m, 1H, $\text{CH}_2=\text{CH}$), 5.15 (m, 2H, $\text{CH}_2=\text{CH}$), 3.07 (d, 2H, $\text{CH}_2-\text{C}=\text{O}$), 0.94 (t, 9H, $3\times\text{CH}_3-\text{C}-\text{Si}$). ^{13}C -NMR (ppm): 171.6 (C=O), 130.7 ($\text{CH}_2=\text{CH}$), 117.9 ($\text{CH}_2=\text{CH}$), 40.7, (CH_2-CH), 25.5 $3\times\text{CH}_3-\text{C}$), 17.5 ($\text{Si}-\text{CH}$), -4.9 ($\text{Si}-\text{CH}_3$). ^{29}Si -NMR (CDCl_3 , ppm, referenced to TMS) 25.9.

Preparation of Triisopropylsilyl 4-(Dimethylboro)butanoate. A 25-mL round-bottomed flask, fitted with a septum inlet and equipped with a magnetic stirring bar and gas outlet connected to mercury bubbler, was flame dried, purged with argon, and allowed to cool to $-5\text{ }^{\circ}\text{C}$ under a stream of argon. Lithium dimethylborohydride (5mmol, 10.4 mL of a 0.48 M solution) was added followed by a dropwise addition of TMSCl (5.5 mmol, 0.60 g); a white precipitate was formed. After the mixture was stirred at $-5\text{ }^{\circ}\text{C}$ for 5 minutes, the ^{11}B -NMR revealed a signal at +25.4 ppm which corresponded to dimethylborane. The dimethylborane solution was then cooled to $-78\text{ }^{\circ}\text{C}$ under argon.

A separate apparatus consisting of a 25-mL round-bottomed flask fitted with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel capped with a septum was assembled, flame dried, and cooled to $-78\text{ }^{\circ}\text{C}$ under a stream of argon. Dry ether (3 mL) and triisopropylsilyl 3-butenate were introduced by a syringe. The dimethylborane solution was then filtered under argon into the reaction flask through the filtering funnel by using a double-ended needle. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 minutes; the dry ice-acetone bath was removed, and the mixture was stirred at room temperature for 10 minutes. The solution (in diethyl ether) was analyzed by ^{11}B -NMR, which revealed a signal at +85 ppm.

Preparation of *Gamma*-Aminobutyric Acid.

The triisopropylsilyl 4-(dimethylboro)butanoate solution was cooled to $0\text{ }^{\circ}\text{C}$, while maintaining an argon atmosphere. Aqueous ammonia (5.0 mmol,

2.6 mL of 1.9 M solution) was slowly added to the flask followed by the slow addition with stirring of sodium hypochlorite (5.0 mmol, 6.8 mL of 0.74 M solution) . The solution was allowed to warm to room temperature and was then stirred for an additional 10 minutes. The reaction mixture was acidified with 15 % HCl to pH=1 and then neutralized with 6 N NaOH. The solvents were removed under reduced pressure, and the residue was passed through a silica gel column using methanol as the eluting solvent. Removal of the methanol under reduced pressure gave the expected *gamma*-amino acid in 53% yield (0.28 g); mp. 200 °C (dec.) (lit.⁷⁸ mp 203 °C dec.) ¹H-NMR (MeOD/D₂O) (ppm): 3.10 (t, 2H), 2.45 (t, 2H), 2.0 (q, 2H). ¹³C-NMR (ppm): 183.0, 40.6, 35.8, 26.4. R_f : 0.53 (MeOH as eluant).

Chapter V.

Synthesis of Isomerically Pure Nitrogen-13 Labeled *Gamma*-Aminobutyric Acid and Putresine**A. Introduction.**

Isotopically labeled compounds have played an important role in chemistry, biology, and medicine since Hevesy pioneered their use as tracers²³². Because of the influence of amines on various physiological functions, the syntheses of nitrogen labeled amines have also attracted interest. As a part of a continuing program involving syntheses of nitrogen-13 labeled diamines and amino acids as potential diagnostic agents for positron emission tomography, a rapid, convenient, and easy to manipulate one-pot method for preparing diamines and amino acids was sought^{76,77,78}. Since organoboranes are known to react with chloramine and hydroxylamine O-sulfonic acid to produce organic amines^{69,72}, this makes them ideal candidates for use in the syntheses of nitrogen labeled compounds. Organoboranes are versatile intermediates in organic synthesis^{1,2} and have been used to incorporate isotopes of carbon, nitrogen, oxygen, and halogens^{233,234,235}. Investigations revealed that organoboranes can be utilized to introduce a variety of positron emitting nuclides into functionally substituted materials via the direct reaction of organoboranes with the appropriate, cyclotron-produced radiolabeled agent²³⁶.

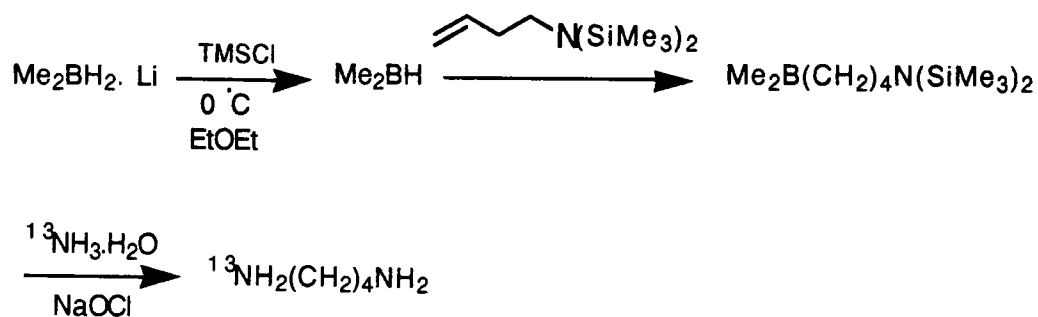
Organoborane reactions have been used to prepare nitrogen-13 labeled primary amines^{237,238}. However, under normal conditions, approximately six percent of the regioisomer is produced due to the nature of the hydroboration reaction. Recently, it was reported that dimethylboranes react regioselectively with chloramine to produce alkylamines^{74,75}. These investigations provided an attractive approach to the regioselective preparation of nitrogen-13 labeled diamines and amino acids.

The synthesis of nitrogen-13 labeled putresine and *gamma*-amino-butyric acid from the corresponding 4-(dimethylboro)-1-[bis(trimethylsilyl)amino]butane and triisopropylsilyl 4-(dimethylboro)butanoate are outlined in this chapter.

B. Results and Discussion:

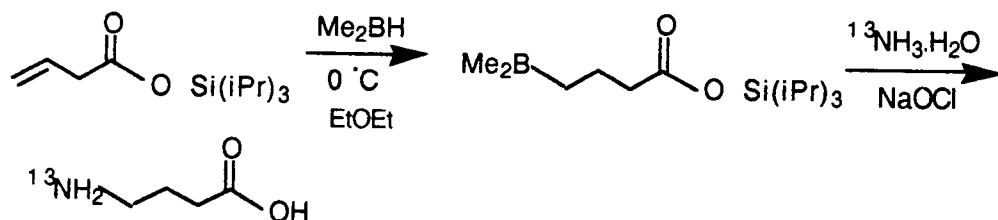
The amination of organoboranes provides a convenient procedure for synthesizing amines. The mild reaction conditions make this process suitable for the synthesis of functionally substituted amines. Furthermore, the application of dimethylborane as a hydroboration reagent overcomes the isomeric impurity problem, and the lessened reactivity provided by the methyl group leads to high yields of the desired product [see chapters III and IV]. The reaction sequence reported in this chapter provides an excellent method for the preparation of highly pure radioactive compounds. The preparation of putrescine (1,4-diaminobutane) is the first application of the hydroboration-amination sequence in the presence of an amine, Scheme 5-1.

Scheme 5-1. Preparation of N-13 Labeled Putrescine (1,4-Diaminobutane) via the Hydroboration-Amination Sequence.



Hydroboration of unsaturated esters using BH_3 is complicated by lessened regioselectivity and by competing reduction reactions^{225,229,239}. Investigations have shown that larger silicon protecting groups lead to higher reaction yields (Chapter IV). The preparation of N-13 labeled *gamma*-aminobutyric acid is the first successful hydroboration-amination of a *beta,gamma*-unsaturated ester and is shown in Scheme 5-2.

Scheme 5-2. Preparation of N-13 labeled *Gamma*-Aminobutyric Acid.



C. Conclusion.

N-Trimethylsilyl protected aminobutene and the triisopropylsilyl ester of butenoic acid were reacted with dimethylborane. The organoboranes were subsequently reacted with *in situ* generated nitrogen-13 labeled chloramine to yield isomerically pure nitrogen-13 labeled *gamma*-aminobutyric acid and putresine (1,4-diaminobutane).

The hydroboration-amination sequence provides a rapid, convenient, and easy to manipulate one-pot method for preparing diamines and *gamma*-amino acids. It also provides a promising method for preparing nitrogen-13 labeled functionally substituted amines which are potentially valuable as agents for use in positron emission tomography.

D. Experimental Section.

The H-1 and C-13 NMR spectra of the non-labeled compounds were recorded on a Jeol FX-90Q spectrometer using deuteriochloroform or deuteriomethanol as solvent and are referenced to TMS. The B-11 NMR spectra of the precursors were recorded on the same spectrometer using BF₃-etherate as an external reference. Glassware was thoroughly oven-dried and cooled under dry nitrogen just prior to use. Commercial bleach was used as the source of sodium hypochlorite after determination of its concentration¹⁷⁶.

Dimethylborane was prepared according to the procedure described in Chapter III. The dimethylalkylborane intermediates were prepared according to the procedure described in Chapter IV.

Preparation of Nitrogen-13 Labeled Ammonia

Aqueous nitrogen-13 labeled ammonia was produced using the UTMCK 11 MeV negative ion cyclotron by the ^{13}C (p,n) and ^{16}O (p, α) reactions on a slurry of [C-13] enriched carbon powder in water. The target assembly employs a 0.00254 cm aluminum vacuum window and a 0.00254 cm titanium target window which reduces extracted proton energy from 11.2 MeV to 10.7 MeV entering the [C-13] carbon powder and [O-16] water. Carbon powder (0.11 g, 99% enriched with carbon-13) was loaded into the target and [O-16] water was passed through the carbon powder in the beam strike using a HPLC pump at a flow rate of 1.5 mL/min (150-375 psi) to saturate the powder with water. The resulting carbon bed is 1.22 mm thick when saturated with water. Twenty mCi of [N-13] ammonia, no-carrier added, in 6 ml of water was produced by irradiating the target with protons at a beam current of 3.5 microamperes for 9 minutes after pressurizing the target with water to 400 psi, followed by 4 minutes during which the flow of water was 1.5 mL/min (125-200 psi) through the target chamber.

Preparation of Nitrogen-13 Labeled *Gamma*-Aminobutyric Acid

To a predried serum vial flushed with nitrogen, equipped with a magnetic stirring bar and connected to mercury bubbler, triisopropylsilyl 4-(dimethylboro)butanoate (0.25 mmol, 0.63 mL of 0.40 M solution in ether) was introduced via a syringe [see Chapter IV]. Nitrogen-13 labeled ammonia (0.25

mmol, 3.5 mCi in 1 mL H₂O) was added, followed by the dropwise addition of sodium hypochlorite (0.25 mmol, 0.34 mL of 0.74 M solution). The mixture was allowed to stir at room temperature for 10 minutes. The stirring was discontinued and the ether layer was analyzed by thin layer chromatography. The TLC analysis was performed on precoated silica gel plates (Analtech, 150 micron) using CH₃OH as eluant. The R_f value of ¹³N-labeled *gamma*-aminobutyric acid was 0.53. After elution, the TLC plate was scanned using a Bioscan System 200 Imaging Scanner. The ratio of the number of counts in the product section of the plate to the total number of counts gave the radiochemical yield of the product. The average (n=2) yield of nitrogen-13 labeled *gamma*-aminobutyric acid was 84.5%.

Preparation of Nitrogen-13 Labeled Putrescine (1,4-diaminobutane)

The same procedure was employed to synthesize nitrogen-13 labeled putrescine using 4-(dimethylboro)-1-[bis(trimethylsilyl)amino]butane (0.25 mmol, 0.63 mL of 0.40 M solution in ether) [see Chapter IV]. This was followed by amination with nitrogen-13 labeled ammonia (0.25 mmol, 3.5 mCi in 1 mL H₂O and 0.25mmol sodium hypochlorite, 0.34 mL of 0.74 M solution) at room temperature for 10 minutes. The product was analyzed by TLC using a mixture of 85% methanol and 15% methylamine (40% solution in water) as the TLC eluant. The R_f value of putrescine is 0.61. The average (n=2) radiochemical yield of nitrogen-13 labeled putrescine was 70.5%.

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VITA

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