

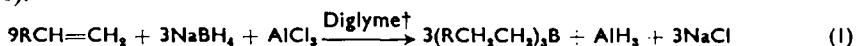
## HYDROBORATION—A POWERFUL SYNTHETIC TOOL\*

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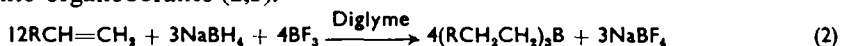
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EARLY observations on the reaction of diborane with unsaturated organic compounds indicated that the reaction required either elevated temperatures or long reaction times,<sup>1-4</sup> and did not provide a convenient synthetic route to the organoboranes. In the course of studying the reducing action of sodium borohydride-aluminum chloride solutions on representative organic molecules,<sup>5</sup> it was observed that unsaturated molecules such as ethyl oleate utilized more than the two "hydrides" required for reduction of the ester grouping. Investigation of the phenomenon revealed that the reagent readily reacts with olefins to convert them into the corresponding organoboranes (1).<sup>6</sup>

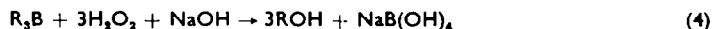


Investigation soon uncovered alternative convenient procedures for the conversion of olefins into organoboranes (2,3).<sup>7</sup>



These reactions are rapid and quantitative at room temperature. They make the organoboranes readily available as intermediates for the synthetic chemist and stimulate a new interest in the chemistry of these reactive compounds.

Although the reactions of organoboranes will be reviewed later in this discussion, it is necessary to call attention to the simple oxidation of organoboranes with alkaline hydrogen peroxide (4).<sup>6-8</sup>



The reaction is essentially quantitative, and appears to proceed without rearrangement, placing an hydroxyl group at the precise position previously occupied by the boron atom in the organoborane. Consequently, it has been of immense value in studying this conversion of olefins into organoboranes.

\* Lecture to the Organic Division at the 137th Meeting of the American Chemical Society in Cleveland, Ohio, April 12, 1960, in connection with the 1960 A.C.S. Award for Creative Work in Synthetic Organic Chemistry.

† Diglyme: diethyleneglycol dimethyl ether; triglyme: triethyleneglycol dimethyl ether.

‡ THF: tetrahydrofuran. EE: ethyl ether.

<sup>1</sup> D. T. Hurd, *J. Amer. Chem. Soc.* **70**, 2053 (1948).

<sup>2</sup> F. G. A. Stone and H. J. Emeleus, *J. Chem. Soc.* 2755 (1950).

<sup>3</sup> A. T. Whatley and R. N. Pease, *J. Amer. Chem. Soc.* **76**, 835 (1954).

<sup>4</sup> F. G. A. Stone and W. A. G. Graham, *Chem. & Ind.* 1881 (1955).

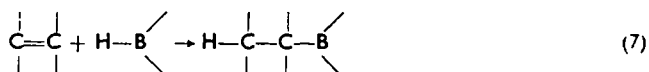
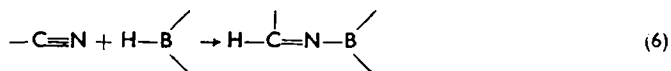
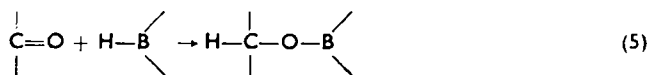
<sup>5</sup> H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 2582 (1956).

<sup>6</sup> H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 5694 (1956); **81**, 6423 (1959).

<sup>7</sup> H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22**, 1136 (1957); *J. Amer. Chem. Soc.* **81**, 6428 (1959).

<sup>8</sup> J. R. Johnson and M. G. Van Campen, Jr. *J. Amer. Chem. Soc.* **60**, 121 (1938).

The addition of the boron-hydrogen bond to multiple linkages of carbon to oxygen, to nitrogen and to carbon, appears to be a general reaction (5-7), as general as the related older reaction involving the addition of hydrogen to these systems.



Whereas the addition of hydrogen generally requires elevated temperatures and catalysts, the addition of the boron-hydrogen bond generally proceeds quite rapidly at room temperature in ether solvents. The term hydroboration (HB) has been suggested as a general term to refer to the addition of the boron-hydrogen bond to multiple linkages. The present discussion will be restricted to the hydroboration of olefins and acetylenes.

#### Hydroboration procedures

Sodium borohydride is essentially insoluble in ethyl ether and tetrahydrofuran, but it is readily soluble in diglyme. Consequently this is the solvent of choice when sodium borohydride is the hydroborating agent. The most convenient procedure is to mix the sodium borohydride with the olefin in diglyme and to add boron trifluoride etherate slowly (exothermic reaction) from a dropping funnel, maintaining an inert atmosphere. The reaction is essentially complete immediately following completion of addition (8).

In many cases where the organoborane is desired simply as an intermediate for further reaction it need not be isolated. Thus it can be oxidized *in situ* with alkaline hydrogen peroxide to the alcohol, which is then readily recovered from the reaction mixture by distillation. In cases where the alcohol desired possesses a boiling point inconveniently near that of diglyme (b.p. 162°), the related solvent, triglyme (b.p. 216°), can be utilized.

Alternatively, diborane may be readily prepared by treating sodium borohydride with boron trifluoride etherate<sup>9</sup> and the gas passed into a solution of the olefin in tetrahydrofuran\* (9). Or a solution of diborane in tetrahydrofuran may be prepared and the olefin added slowly (exothermic reaction) to the solution. These latter procedures yield the pure organoborane in the volatile solvent tetrahydrofuran, and a simple distillation suffices to isolate the organoborane in a state of high purity.

The unavailability of diglyme abroad has led to difficulties in applying these procedures.<sup>10,11</sup> Fortunately, over the years numerous procedures have been developed for the preparation of diborane and the information accumulated makes it possible to circumvent the requirement for any particular solvent or reagent.<sup>12</sup>

\* Tetrahydrofuran is preferred because of the high solubility of diborane in the solvent.

<sup>9</sup> H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.* **80**, 1552 (1958).

<sup>10</sup> R. Dulou and Y. Chrétien-Bessière, *Bull. Soc. Chim. Fr.* **9**, 1362 (1959).

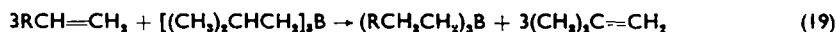
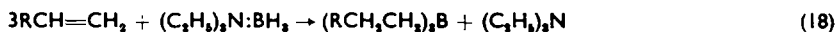
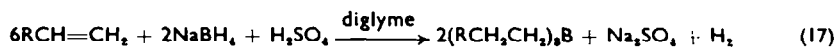
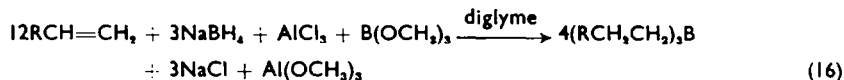
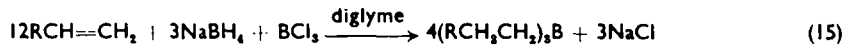
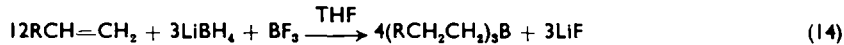
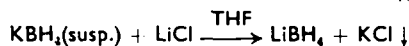
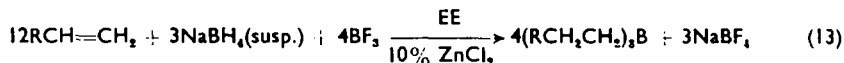
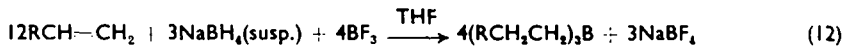
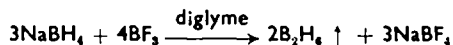
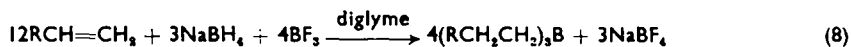
<sup>11</sup> S. Wolfe, M. Nussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.* **24**, 1034 (1959).

<sup>12</sup> H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 4233 (1960).

Thus the reaction of lithium aluminum hydride with boron trifluoride etherate can be used to accomplish hydroboration (10).<sup>10,11</sup> Similarly, lithium borohydride is soluble in both ethyl ether and tetrahydrofuran and can be utilized in these solvents (11).<sup>12</sup> Sodium borohydride, although essentially insoluble in tetrahydrofuran, reacts readily with boron trifluoride etherate and olefin in this medium to produce the organoborane (12).<sup>12</sup> Even ethyl ether can be utilized with sodium borohydride—a small quantity of anhydrous zinc chloride serves to catalyze the hydroboration of olefins by sodium borohydride in ethyl ether suspension (13).<sup>12</sup> Finally, in tetrahydrofuran suspension potassium borohydride reacts with lithium chloride to form lithium borohydride in solution<sup>13</sup> and the latter can be utilized readily for hydroboration (14).<sup>12</sup>

Boron trifluoride etherate is generally applicable as the acid component for these hydroborations. However, it can be replaced by boron trichloride (15),<sup>12</sup> or by a mixture of aluminum chloride and methyl borate (16).<sup>12</sup> Finally, a solution of sulfuric acid in the ether solvent likewise serves to accomplish the hydroboration reaction (17).<sup>12</sup>

The above procedures permit the hydroboration of olefins under mild conditions, 0 to 25°. In cases where elevated temperatures can be tolerated, hydroboration may be accomplished by heating the olefin with amine-boranes at temperatures of 100–200° (18)<sup>14,15</sup> or with triisobutylborane (19).<sup>16</sup>



<sup>10</sup> R. Paul and N. Joseph, *Bull. Soc. Chim. Fr.* 550 (1952).

<sup>11</sup> M. F. Hawthorne, *J. Org. Chem.* 23, 1788 (1958).

<sup>12</sup> E. C. Ashby, *J. Amer. Chem. Soc.* 81, 4791 (1959).

<sup>13</sup> R. Köster, *Liebigs Ann.* 618, 31 (1958).

*Scope and stoichiometry*<sup>7</sup>

The hydroboration reaction has now been applied to an enormous number of olefins of widely different structures. In practically all cases hydroboration proceeds simply and rapidly at room temperature. Representative olefins which have been utilized in this reaction include:

*Terminal olefins:* 1-hexene, 1-octene, 1-decene, 1-tetradecene, 3-methyl-1-butene, 3,3-dimethyl-1-butene, 4,4-dimethyl-1-pentene, 2-methyl-1-butene, 2-methyl-1-pentene and 2,4,4-trimethyl-1-pentene.

*Dialkyl internal olefins:* 2-hexene, 3-hexene, 2-octene, *cis*- and *trans*-4-methyl-2-pentene, *cis*- and *trans*-4,4-dimethyl-2-pentene, and *trans*-2,2,5,5-tetramethyl-3-hexene.

*Cyclic olefins:* cyclopentene, cyclohexene, and norbornene.

*Trialkyl olefins:* 2-methyl-2-butene, 2-methyl-2-pentene, 3-ethyl-2-pentene, 2,4,4-trimethyl-2-pentene, 1-methylcyclopentene, 1-methylcyclohexene and  $\alpha$ -pinene.

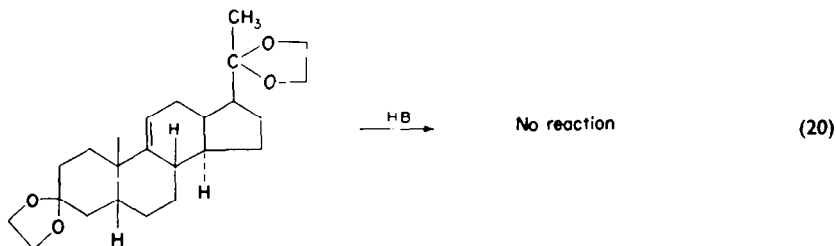
*Tetraalkyl olefins:* 2,3-dimethyl-2-butene, 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene.

*Aryl olefins:* styrene,  $\alpha$ -methylstyrene, 1-phenylcyclohexene, 1,1-diphenylethylene, *trans*-stilbene and triphenylethylene.

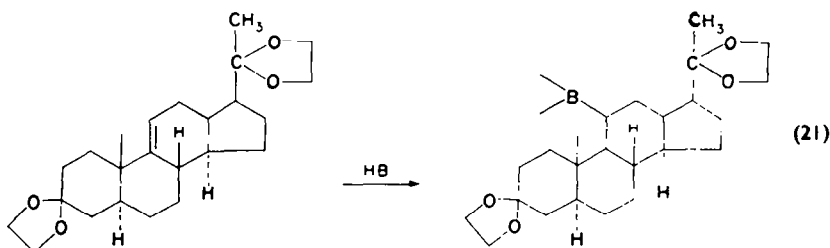
*Substituted olefins:* vinyl chloride, allyl chloride, allyl ethyl ether, ethyl oleate and ethyl cinnamate.

The hydroboration reaction has also been applied to a wide variety of acetylenes and dienes. Since these offer a number of points of special interest, this topic will be considered later.

In only one case to date has it been noted that a double bond resists the hydroboration reaction. Wechter reported that 3,20-biscycloethylenedioxy-5 $\beta$ -pregn-9(11)-ene failed to undergo hydroboration under the usual hydroboration conditions (20).<sup>17</sup>



On the other hand, the analogous compound with the A/B-*trans* junction does undergo hydroboration (21).<sup>18</sup>

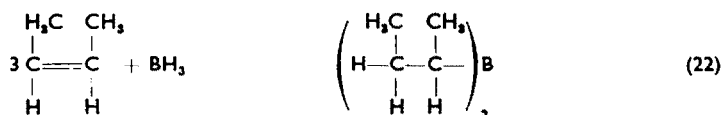


<sup>17</sup> W. J. Wechter, *Chem. & Ind.* 294 (1959).

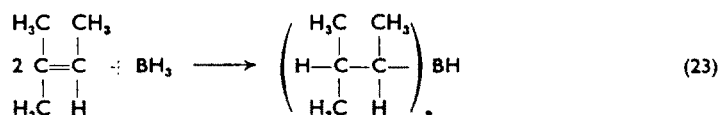
<sup>18</sup> F. Sondheimer and M. Nussim, *Chem. & Ind.* 400 (1960).

The available data support the conclusion that hydroboration is a general reaction of the carbon-carbon double bond with only the most hindered olefins exhibiting any resistance to the addition.

In the case of simple olefins, the reaction commonly proceeds rapidly to the complete utilization of the active hydrogen of the diborane molecule, with the formation of the trialkylborane (22).

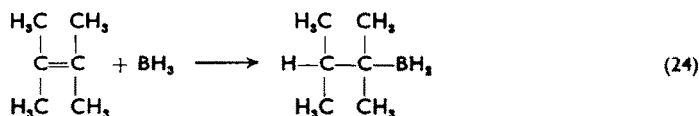


However, trisubstituted olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, react rapidly at room temperature to utilize only two of the active hydrogens of the borane group, yielding a dialkylborane (or its dimer) as the reaction product (23).

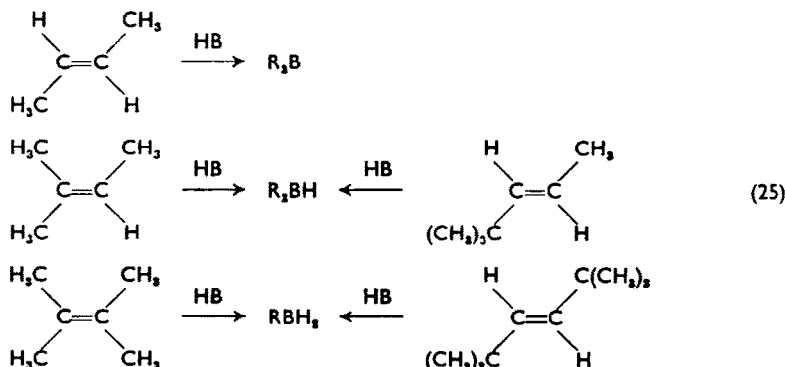


Although further reaction to the trialkylborane stage is possible, the reaction is very slow at room temperature, requiring extended periods of time for completion.

Finally, tetrasubstituted olefins, such as tetramethylethylene, react rapidly only to the first stage.



This phenomenon appears to be largely steric in origin. Thus if the double bond is loaded with groups of much larger steric requirements, such as *t*-butyl, the hydroboration tends to become quite slow at even earlier stages. For example, *trans*-*t*-butylmethylene undergoes hydroboration rapidly only to the dialkylborane stage,<sup>19</sup> while the corresponding reaction of *trans*-di-*t*-butylethylene appears to halt at the monoalkylborane stage (25).<sup>20</sup>



<sup>19</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 1504 (1960).

<sup>20</sup> T. J. Logan and T. J. Flaatt, *Ibid.* **82**, 3446 (1960).

*Directive effects*<sup>19</sup>

The hydroboration of 1-hexene yields an organoborane which, upon oxidation with alkaline hydrogen peroxide, is converted quantitatively into a mixture of hexanols, 94 per cent 1- and 6 per cent 2-hexanol. It is concluded that the addition reaction has proceeded to place the boron atom predominantly at the terminal position, with only a minor amount of the reaction proceeding to place the boron in the 2- position. Similar results are observed with 1-butene, 1-pentene and 1-octene. Branching of the alkyl group, as in 3-methyl-1-butene and 3,3-dimethyl-1-butene, does not alter the distribution (Table 1).

TABLE 1. DIRECTIVE EFFECTS IN THE HYDROBORATION OF TERMINAL OLEFINS AT 20°

Olefin	Alcohol product, %	
	1-ol	2-ol
1-Butene	93	7
1-Pentene	94	6
1-Hexene	94	6
3-Methyl-1-butene	94	6
3,3-Dimethyl-1-butene	94	6
4,4-Dimethyl-1-pentene	93	7
<i>p</i> -Methoxystyrene	91	9
<i>p</i> -Methylstyrene	82	18
Styrene	80	20
<i>p</i> -Chlorostyrene	65	35
Allylbenzene	90	10
2-Methyl-1-butene	99	1
2,4,4-Trimethyl-1-pentene	99	1
$\alpha$ -Methylstyrene	100	trace

Essentially complete addition of the boron atom to the terminal position of disubstituted olefins, such as 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene, is observed. Evidently the combined directive effect of the two alkyl substituents dominates the reaction.

The addition is less one-sided in the case of styrene, with 80 per cent of the boron in the terminal position and 20 per cent on the secondary carbon. Moreover, the direction of addition is strongly modified by substituents in the *para* position.

In the case of internal olefins containing two different alkyl groups there is little discrimination between the two carbon atoms of the double bond. This is true even in the case of molecules, such as *trans*-4-methyl-2-pentene and *trans*-4,4-dimethyl-2-pentene, where the two alkyl groups on the double bond differ markedly in their steric requirements. Only in the case of *trans*-1-phenylpropene, where the phenyl group is opposed to a methyl group, is a marked directive effect indicated, and here the boron atom actually prefers (85 per cent) the carbon atom holding the phenyl substituent.

Finally, in olefins containing three alkyl substituents on the double bond, such as 2-methyl-2-butene and 2,4,4-trimethyl-2-pentene, the addition proceeds to place the boron atom predominantly on the less substituted of the two carbon atoms of the double bond.

The data are summarized in Table 2.

The results clearly show that a change in the bulk of the alkyl group attached to the double bond, as in "ethylethylene" (93 per cent 1-), "isopropylethylene" (94 per cent 1-) and t-butylethylene (94 per cent 1-), does not influence the direction of addition. Consequently, the results argue against steric control of the direction of addition. The marked influence of *para* substituents on the direction of addition likewise supports the conclusion that the direction of addition must be controlled primarily by electronic factors.

TABLE 2. DIRECTIVE EFFECTS IN THE HYDROBORATION OF INTERNAL OLEFINS AT 20°

Olefin	Alcohol product, %	
	2-ol	3-ol
<i>cis</i> -2-Pentene	55	45
<i>trans</i> -2-Pentene	51	49
<i>cis</i> -2-Hexene	50	50
<i>trans</i> -2-Hexene	46	54
<i>cis</i> -3-Hexene		100
<i>trans</i> -4-Methyl-2-pentene	57	43
<i>trans</i> -4,4-Dimethyl-2-pentene <sup>a</sup>	58	42
<i>trans</i> -1-Phenylpropene	85 <sup>b</sup>	15 <sup>c</sup>
2-Methyl-2-butene <sup>a</sup>	2	98 <sup>d</sup>
2,4,4-Trimethyl-2-pentene <sup>a</sup>	2	98 <sup>e</sup>

<sup>a</sup> Hydroboration to the dialkylborane stage.

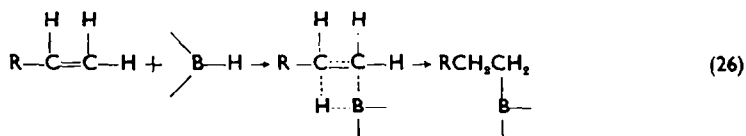
<sup>b</sup> 1-Phenyl-1-propanol.

<sup>c</sup> 1-Phenyl-2-propanol.

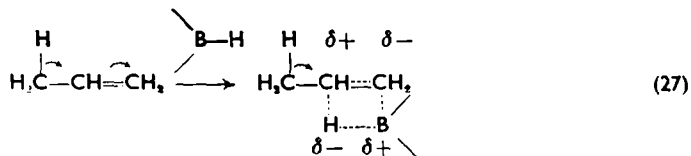
<sup>d</sup> 3-Methyl-2-butanol.

<sup>e</sup> 2,4,4-Trimethyl-3-pentanol.

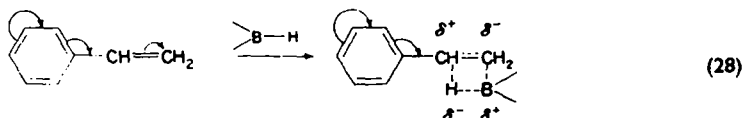
The available evidence supports the conclusion that the addition reaction must involve a simple four-center transition state (26).



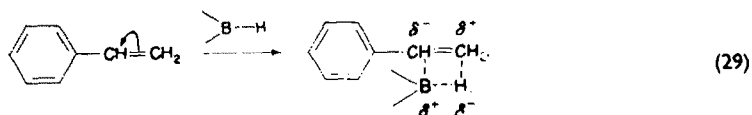
The boron-hydrogen bond is presumably polarized, with the hydrogen having some hydridic character. In view of the electronic shifts generally utilized to account for the normal addition of hydrogen chloride to propylene, the preference of the boron atom for the terminal position is readily understood (27).



A similar discussion can be used to rationalize the observed preference of the boron atom for the terminal position of styrene (28).



It is generally recognized that a phenyl group cannot only serve to supply electrons to an electron deficient center, but it can also serve as an electron sink. This provides a simple explanation for the increased substitution in the  $\alpha$  position observed in styrene (29).

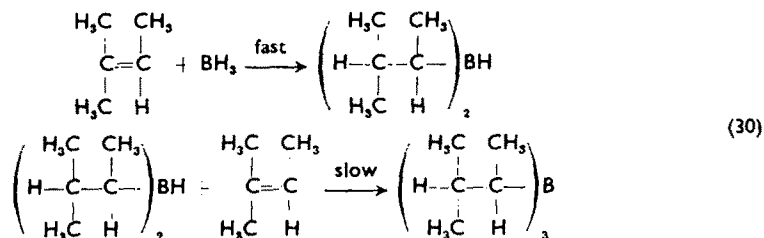


Electron withdrawing substituents, such as *p*-chloro, should stabilize, and electron supplying substituents, such as *p*-methoxy, should destabilize such a transition state. This is in accord with the influence of these substituents on the hydroboration of the substituted styrenes (Table 2).

At the present time there is little quantitative information on the influence of other substituents on the direction of the addition reaction. It is evident that major effects will be encountered. Thus trimethylvinylsilane undergoes hydroboration to place 37 per cent of the boron in the secondary position<sup>21</sup> as compared to 6 per cent for *t*-butylethylene.<sup>19</sup> This problem is currently under investigation in our laboratory.

#### *Bis-3-methyl-2-butylborane as a selective hydroborating agent*<sup>22</sup>

It was pointed out earlier that highly substituted olefins, such as 2-methyl-2-butene, undergo hydroboration rapidly to the dialkylborane stage, with further reaction to the trialkylborane stage being relatively slow (30).



The slowness of the last stage in this particular case, in contrast to the high speed with which other olefins undergo reaction to the trialkylborane stage, is presumably a result of the large steric requirements of the intermediate dialkylborane. It appeared that such a reagent might exhibit an enhanced sensitivity to the steric requirements of the substituents on double bonds and thereby exert a steric influence on the direction of hydroboration.

Bis-3-methyl-2-butylborane, conveniently synthesized by the hydroboration of 2-methyl-2-butene, was selected for study. 1-Hexene reacts rapidly with the reagent, and oxidation of the product yielded 1-hexanol in an isomeric purity of at least 99 per cent, in contrast with the 94 per cent isomeric purity realized with diborane itself. Similarly, styrene yielded less than 2 per cent of the secondary alcohol, whereas diborane results in the formation of 20 per cent. Finally, *cis*-isopropylmethylene yielded 97 per cent of the less hindered isomer, 4-methyl-2-pentanol.

The experimental data are summarized in Table 3.

<sup>21</sup> D. Seyferth, *J. Inorg. Nucl. Chem.* 7, 152 (1958).

<sup>22</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* 82, 3222 (1960).



In the course of these studies it was noted that there was a vast difference in the ease with which different olefins reacted with the reagent. Thus, the reaction with 1-hexene was complete in a matter of minutes at 0°, whereas the reactions of internal olefins were much slower, with cyclopentene reacting faster than *cis*-2-hexene and the latter reacting considerably faster than cyclohexene. *Cis*-2-hexene reacted considerably faster than the *trans* isomer. Trisubstituted olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, reacted very slowly.

TABLE 3. DIRECTIVE EFFECTS IN THE HYDROBORATION OF UNSYMMETRICAL OLEFINS WITH DIBORANE AND BIS-3-METHYL-2-BUTYLBORANE

Olefin	Hydroborating agent	Temp., °C	Time, hr	Alcohol distribution, %		
				1-ol	2-ol	3-ol
1-Hexene	Diborane	25	1	94	6	
	R <sub>2</sub> BH	0	1	99	1	
Styrene	Diborane	25	1	80	20	
	R <sub>2</sub> BH	25	2	98	2	
<i>p</i> -Methoxy-styrene	Diborane	25	1	91	9	
	R <sub>2</sub> BH	25	2	98	2	
<i>trans</i> -4-Methyl-2-pentene	Diborane	25	1		57	43
	R <sub>2</sub> BH	25	12		95	5
<i>cis</i> -4-Methyl-2-pentene	R <sub>2</sub> BH	25	12		97	3

The results may be expressed in the following series: 1-hexene ≥ 3-methyl-1-butene > 2-methyl-1-butene > 3,3-dimethyl-1-butene > *cis*-2-hexene ≥ cyclopentene > *trans*-2-hexene > *trans*-4-methyl-2-pentene > cyclohexene ≥ 1-methylcyclopentene > 2-methyl-2-butene ≥ 1-methylcyclohexene ≥ 2,3-dimethyl-2-butene.

The differences in reactivities are quite large and can be utilized for the selective hydroboration of a more reactive olefin in the presence of a less reactive structure. Thus, treatment of 1-pentene and 2-pentene with a controlled quantity of the reagent yielded the 2-pentene free of the 1-isomer. Similarly, a mixture of 1-hexene and cyclohexene yielded essentially pure cyclohexene. Treatment of an equimolar mixture of cyclopentene and cyclohexene yielded a product which was nearly pure cyclohexene, with only minor amounts of the more reactive cyclopentene remaining. Even more exciting, it proved possible to treat a commercial mixture of *cis*- and *trans*-2-pentene (18 per cent *cis*- and 82 per cent *trans*-) with the reagent, realizing a product which contained better than 97 per cent of the *trans* isomer.

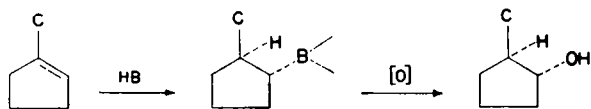
The reagent should be particularly useful to accomplish the selective hydroboration of complex molecules containing two or more reactive centers. Considerable success has been realized in this direction. It is evident that the reagent should be a very useful synthetic tool in the terpene and steroid fields.

#### *Stereochemistry of hydroboration*<sup>23</sup>

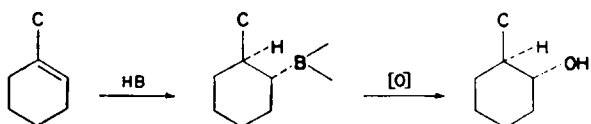
The hydroboration of cyclic olefins provides a means of observing the stereochemistry of the reaction. Thus, the hydroboration of 1-methylcyclopentene and

<sup>23</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 247 (1959).

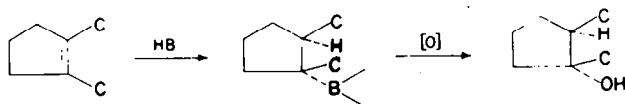
1-methylcyclohexene, followed by oxidation with alkaline hydrogen peroxide, results in the formation of pure *trans*-2-methylcyclopentanol and *trans*-2-methylcyclohexanol. The available evidence indicates that the hydrogen peroxide oxidation proceeds with retention of configuration. Consequently, the hydroboration must involve a *cis*-addition of the hydrogen-boron bond to the double bond of the cyclic olefin (31).



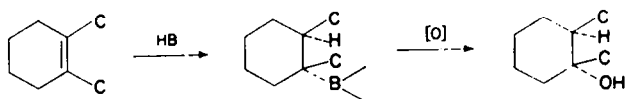
(31)



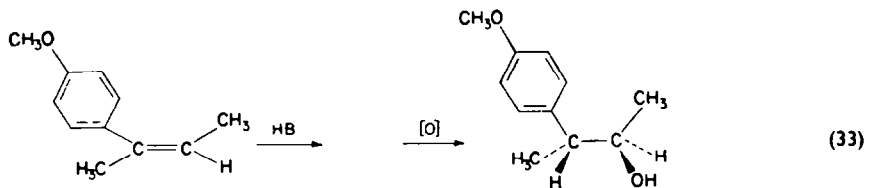
The products in these hydrations are the thermodynamically stable isomers. However, this cannot be the controlling factor in the reaction since the hydroboration of 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene produces pure *cis*-1,2-dimethylcyclopentanol and *cis*-1,2-dimethylcyclohexanol, both of which are the thermodynamically less stable isomers (32).



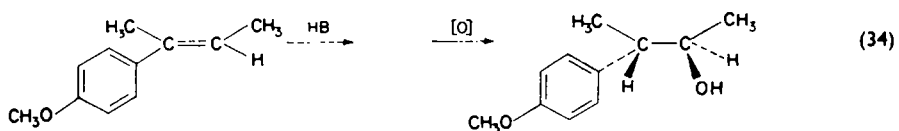
(32)



This *cis* hydration has been utilized to achieve a convenient synthesis of diastereomeric alcohols (33,34).<sup>24</sup>



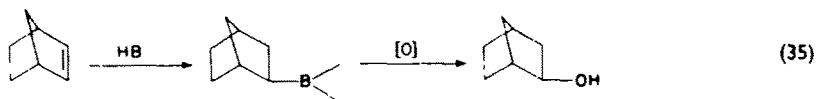
(33)



(34)

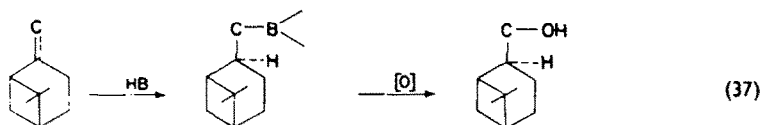
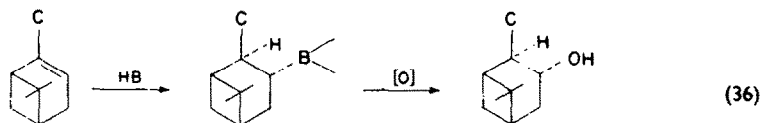
<sup>24</sup> E. L. Allred, J. Sonnenberg and S. Winstein, *J. Org. Chem.* **25**, 25 (1960).

The hydroboration of norbornene proceeds to give *exo*-norborneol almost exclusively (35).

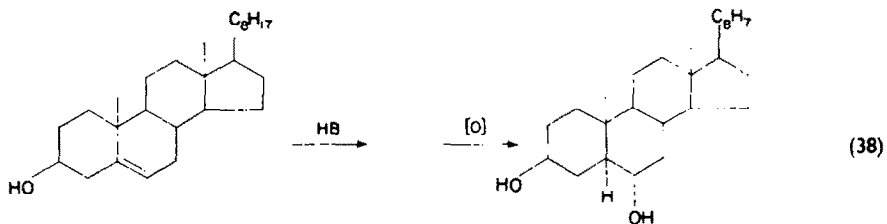


It appears, therefore, that hydroboration proceeds via a *cis* addition, preferentially from the less hindered side of the double bond.

This generalization is now supported by a considerable number of independent observations. Thus  $\alpha$ -pinene is readily converted by this procedure into isopinocampheol (36),<sup>23</sup> and  $\beta$ -pinene into *cis*-myrtanol (37).<sup>25</sup>



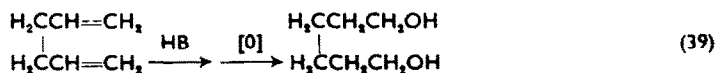
Similarly, the hydroboration of cholesterol produces cholestane-3 $\beta$ ,6 $\alpha$ -diol preferentially, clearly the result of a preferential *cis* addition from the less hindered under side of the molecule (38).<sup>17</sup>



This simple synthesis of stereochemically defined products should make the hydroboration reaction of especial value for the synthesis of steroid derivatives and related natural products,<sup>11,17,18,26</sup>

#### Dienes<sup>27</sup> and acetylenes<sup>28</sup>

Hydroboration provides a convenient synthetic route to diols. Thus 1,3-butadiene is transformed into 1,4-butanediol and 1,5-hexadiene is converted into 1,6-hexanediol (39).



<sup>25</sup> Research in progress with M. V. Bhatt.

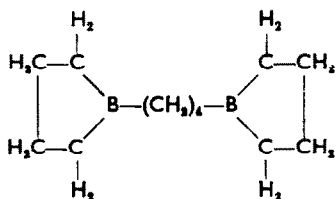
<sup>26</sup> P. Bruck, D. Thompson and S. Winstein, *Chem. & Ind.* 405 (1960).

<sup>27</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 5832 (1959).

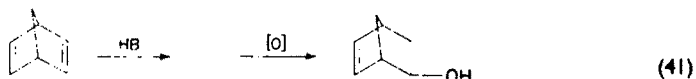
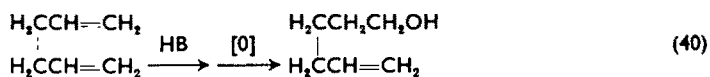
<sup>28</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 1512 (1959).

The generality of this synthesis has been demonstrated for a considerable number of additional dienes.<sup>29</sup>

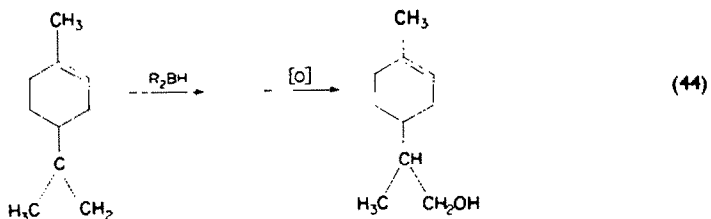
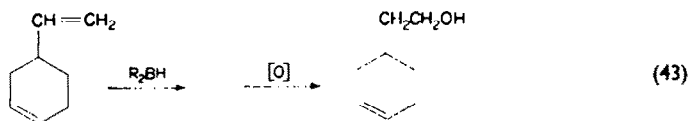
Köster has isolated the organoborane from butadiene and has assigned it a cyclic structure.<sup>30</sup>



The partial hydroboration of dienes provides a valuable synthetic route to the synthesis of unsaturated alcohols (40,<sup>27</sup> 41,<sup>27</sup> 42<sup>24</sup>).



The reagent, bis-3-methyl-2-butylborane, provides a convenient means to achieve the partial hydroboration of the less hindered double bond in a diene.<sup>22</sup> Thus, the more active exocyclic double bonds in vinylcyclohexene and D-limonene are readily hydrated without attack on the less active double bond in the ring (43, 44).

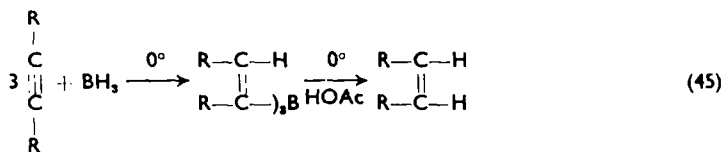


The hydroboration of internal acetylenes proceeds readily and can be controlled to give predominantly a single addition of a boron-hydrogen bond per acetylene

<sup>29</sup> K. A. Saegebarth, *J. Amer. Chem. Soc.* **82**, 2081 (1960).

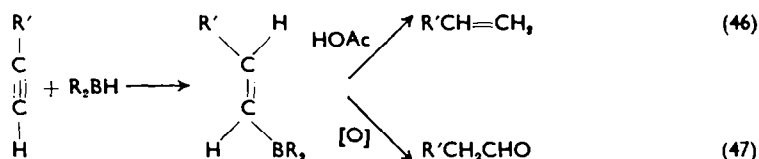
<sup>30</sup> R. Köster, *Angew. Chem.* **71**, 520 (1959).

molecule. The resulting products are readily converted to the corresponding *cis* olefins in high purity by treatment at 0° with acetic acid (45).<sup>28</sup>



The corresponding reaction is less simple in the case of 1-alkynes, apparently proceeding predominantly to the dihydroboration stage. However, here also, the reagent bis-3-methyl-2-butylborane circumvents the difficulty and permits the formation of the monohydroborated product.

Treatment of this product with acetic acid yields the 1-alkene in 90 per cent yield (46) while oxidation of the organoborane forms the corresponding aldehyde in similar yield (47).



The dihydroboration of acetylenes appears to place two boron atoms on the same carbon atom. Oxidation of the products yields the ketone predominantly from an internal acetylene and the aldehyde from a terminal acetylene. The precise nature of these organoboranes is under investigation.

#### Oxidation of organoboranes

The lower alkylboranes are spontaneously inflammable in air, whereas tri-*n*-butylborane and the higher members react with oxygen, but do not inflame. Considerable study has been devoted to uncovering the precise course of the reaction with oxygen.<sup>8,31,32</sup> However, since air oxidation has not proven to be valuable in synthetic work, the results will not be discussed here.

On the other hand, the oxidation of organoboranes by alkaline hydrogen peroxide,<sup>6-8</sup> has proven to be of immense practical value in synthetic work. Accordingly, a detailed study of the reaction was undertaken.<sup>33</sup>

It was established that the oxidation of the organoborane is essentially quantitative at 25° in the usual hydroboration solvents—diglyme and tetrahydrofuran. Consequently, the oxidation can be carried out directly on the newly synthesized organoborane *in situ*, without isolation. In cases where the solvent is ethyl ether or a similar medium not miscible with water, the addition of ethanol as a co-solvent likewise results in essentially quantitative yields.

Wide variation in the structure of the olefin can be tolerated in this reaction. No instance has yet turned up of an organoborane which resists this oxidation under the usual mild conditions.

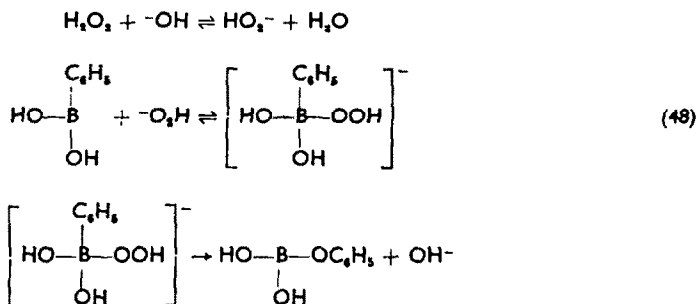
<sup>21</sup> R. C. Petry and F. H. Verhoek, *J. Amer. Chem. Soc.* **78**, 6416 (1956).

<sup>22</sup> A. G. Davies and R. B. Moodie, *Chem. & Ind.* 1622 (1959).

<sup>23</sup> H. C. Brown, C. Snyder, B. C. Subba Rao and G. Zweifel, manuscript in preparation.

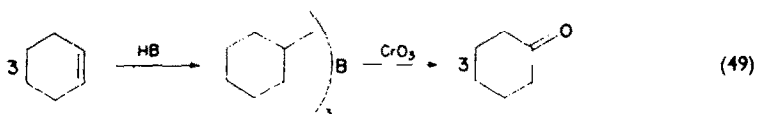
Numerous substances, such as olefins, acetylenes, dienes, esters, ketones and nitriles, may be present in the reaction mixture without influencing the yield of oxidation product from the organoborane, or exhibiting any attack on themselves. This indicates that the reaction will be applicable not only to simple organoboranes, but also to their functional derivatives now readily available by the hydroboration of unsaturated compounds.

A detailed kinetic study of the reaction has not yet been reported. However, Kuivila *et al.* have examined the closely related reaction of benzeneboronic acid with hydrogen peroxide.<sup>34</sup> They propose the mechanism (48):



An identical mechanism, in three successive stages, is consistent with all of the available data for the oxidation with alkaline hydrogen peroxide.<sup>17</sup> In this mechanism the organic group shifts with its pair of electrons from boron to oxygen. This is consistent with the retention of configuration which is observed in the hydroboration-oxidation of cyclic olefins.

The direct oxidation of organoboranes to ketones with chromic acid has been accomplished.<sup>35</sup> Thus, a cyclic olefin such as cyclohexene, can be hydroborated and directly oxidized *in situ* with aqueous chromic acid to cyclohexanone in satisfactory yield (49).<sup>36</sup>



### Protonolysis<sup>37</sup>

The trialkylboranes are remarkably stable toward hydrolysis with water. Even in the presence of strong mineral acids the hydrolysis is slow and incomplete. Thus the treatment of tributylborane with 48 per cent hydrobromic acid under reflux results in loss of but one of the three alkyl groups, with the formation of a quantitative yield of dibutylboronic acid.<sup>38</sup>

<sup>34</sup> H. G. Kuivila, *J. Amer. Chem. Soc.* **76**, 870 (1954); *Ibid.* **77**, 4014 (1955); H. G. Kuivila and R. A. Wiles, *Ibid.* **77**, 4830 (1955); H. G. Kuivila and A. G. Armour, *Ibid.* **79**, 5659 (1957).

<sup>35</sup> R. Pappo, *J. Amer. Chem. Soc.* **81**, 1010 (1959).

<sup>36</sup> Research in progress with C. P. Garg.

<sup>37</sup> H. C. Brown and K. J. Murray, *J. Amer. Chem. Soc.* **81**, 4108 (1959).

<sup>38</sup> J. R. Johnson, H. R. Snyder and M. G. Van Campen, Jr., *J. Amer. Chem. Soc.* **60**, 115 (1938).

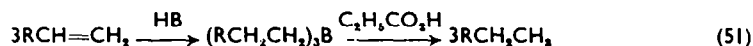
It is quite remarkable that the organoboranes are far more susceptible to attack by carboxylic acids than by the mineral acids.

For example, under relatively mild conditions triethylborane reacts with acetic acid to form diethylboron acetate and ethane (50).<sup>39</sup>



A detailed study of the action of carboxylic acids on organoboranes has demonstrated that two of the three groups can be removed by excess dry acetic or propionic acid at room temperature, and all three groups can generally be removed by heating the organoborane in diglyme solution with a slight excess of the carboxylic acid for 2 to 3 hours.<sup>37</sup> (Propionic acid is preferred over acetic acid because of its lower volatility).

Consequently, hydroboration of olefins in diglyme, followed by addition of propionic acid and refluxing, provides a convenient non-catalytic procedure for the hydrogenation of double-bonds (51).



Secondary alkyl groups undergo protonolysis less readily than primary. Consequently, in hydroborating internal olefins, it is preferable that the boron be transferred to the terminal position by heating under reflux prior to addition of the acid. (This isomerization of organoboranes is discussed later.)

It has been established that olefins containing relatively active sulfur, chlorine and nitrogen substituents undergo hydroboration readily. Consequently, hydroboration followed by protonolysis opens up the possibility of hydrogenating double bonds in molecules containing such labile groups. Indeed, the conversion of allylmethyl sulfide into n-propylmethyl sulfide by this method proceeds in good yield, whereas hydrogenation with the usual metal catalysts results in the loss of the thiomethyl group.<sup>37</sup>

As was indicated earlier, organoboranes of the vinyl type, readily obtained by the hydroboration of acetylenes, undergo protonolysis much more readily. These compounds undergo complete protonolysis with acetic acid in a matter of minutes at 0°, and the reaction provides a convenient means of converting acetylenes into *cis* olefins of high purity.<sup>28</sup>

#### *Mercuration. Grignard-like reactions*

The ability of trialkylboranes to function as a Grignard reagent has as yet received little attention. Consequently, considerable interest attaches to the report by Honeycutt and Riddle that they have synthesized diethylmercury by treating mercuric oxide with triethylborane and sodium hydroxide in water at 75°. The reaction was fast, complete in 10 minutes, with a yield of 95 per cent based on the mercuric oxide.<sup>40</sup>

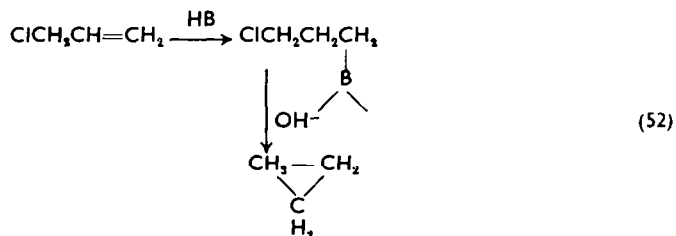
More recently these authors have demonstrated the synthesis of di-n-hexylmercury and of tetraethyllead by related procedures.<sup>41</sup>

<sup>39</sup> J. Goubeau, R. Epple, D. D. Ulmschneider and H. Lehmann, *Angew. Chem.* **67**, 710 (1955).

<sup>40</sup> J. B. Honeycutt, Jr. and J. M. Riddle, *J. Amer. Chem. Soc.* **81**, 2593 (1959).

<sup>41</sup> J. B. Honeycutt, Jr. and J. M. Riddle, *J. Amer. Chem. Soc.* **82**, 3051 (1960).

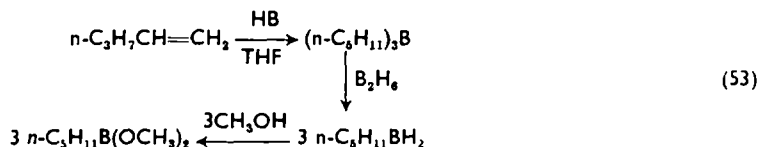
An unusually interesting Grignard-like reaction was discovered by Hawthorne and Dupont. They noted that treatment of the hydroboration product from allyl chloride with alkali brought about cyclization to form cyclopropane (52).<sup>42</sup>



This reaction offers promise as a general synthesis of substituted cyclopropanes.<sup>43</sup>

#### Redistribution reactions

Equilibration of trialkylboranes with excess diborane provides a convenient route to the monoalkylboranes (or their dimers). These monoalkylboranes are readily alcoholized to the corresponding boronic esters or hydrolyzed to the boronic acid. Consequently, hydroboration provides a convenient route to these derivatives (53).<sup>44</sup>



By controlling the amount of excess diborane, it is possible to direct the equilibration reaction to the dialkylborane stage. Alternatively, addition of the olefin to excess diborane in tetrahydrofuran solution at 0° results in the formation of the dialkylborane in good yield. In this way hydroboration likewise provides convenient routes to the dialkylborinic acids and esters.<sup>44</sup>

Boron trichloride reacts rapidly with trialkylboranes at temperatures above 100° to give nearly quantitative yields of dialkylchloroboranes.<sup>45,46</sup> The reaction has been demonstrated for tri-*n*-butylborane, triisobutylborane, and tri-*sec*-butylborane, so that it is relatively insensitive to the structure of the alkyl group. At elevated temperatures the redistribution can be carried one step further—to the monoalkyldichloroboranes. These reactions provide an alternative route to the boronic and borinic acids and their derivatives.

#### Isomerization of organoboranes<sup>47</sup>

At elevated temperatures secondary organoboranes are slowly isomerized into the primary derivatives. Thus, Hennion *et al.* observed that tri-*sec*-butylborane was transformed into tri-*n*-butylborane by heating at 200–215° for 48 hours.<sup>48</sup>

<sup>42</sup> M. F. Hawthorne and J. A. Dupont, *J. Amer. Chem. Soc.* **80**, 5830 (1958).

<sup>43</sup> M. F. Hawthorne, *J. Amer. Chem. Soc.* **82**, 1886 (1960).

<sup>44</sup> H. C. Brown, A. Tsukamoto and D. B. Bigley, *J. Amer. Chem. Soc.* **82**, 4703 (1960).

<sup>45</sup> V. W. Buls, O. L. Davis and R. I. Thomas, *J. Amer. Chem. Soc.* **79**, 337 (1957).

<sup>46</sup> P. A. McCusker, G. F. Hennion and E. C. Ashby, *J. Amer. Chem. Soc.* **79**, 5192 (1957).

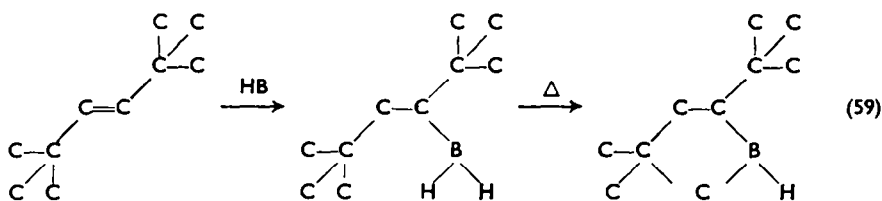
<sup>47</sup> H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22**, (1957); *J. Amer. Chem. Soc.* **81**, 6434 (1959).

<sup>48</sup> G. F. Hennion, P. A. McCusker, E. C. Ashby and A. J. Rutkowski, *J. Amer. Chem. Soc.* **79**, 5190 (1959).

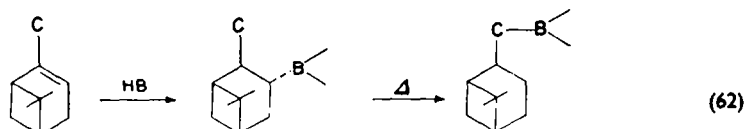
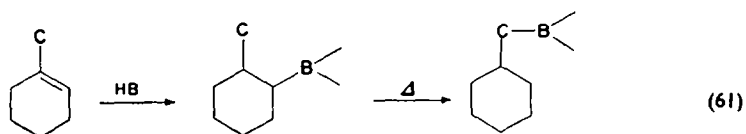
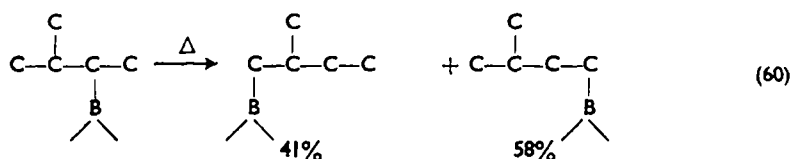




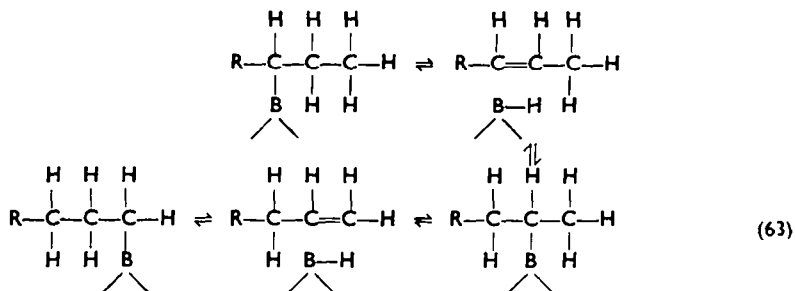
Logan and Flautt attempted to examine the behaviour of a boron atom trapped between two quaternary carbon atoms. However, in this case a cyclization reaction occurred under relatively mild conditions (59).<sup>20</sup>



In the usual isomerization, the boron atom migrates preferentially to the least hindered position in the molecule (60, 61, 62).



The isomerization of the boron atom from an internal position on a carbon chain to the terminal position can be formulated as a succession of eliminations and additions (63).<sup>47</sup>



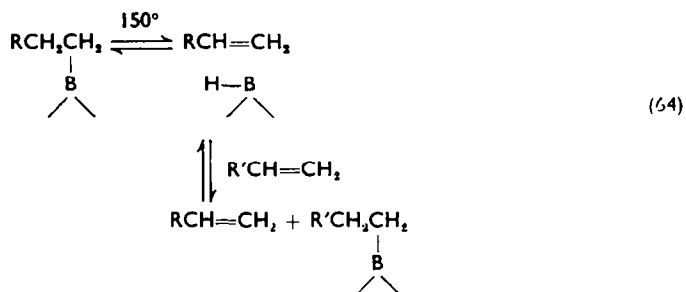
The preference of the boron for the terminal position is postulated to be the result of decreased steric interactions in that location. All of the available data for the

<sup>20</sup> H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 1504 (1960).

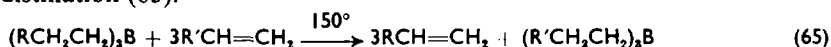
isomerization of organoboranes are consistent with this elimination-addition mechanism.

*Displacement reactions*<sup>16,47,51</sup>

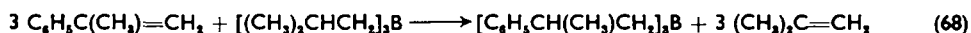
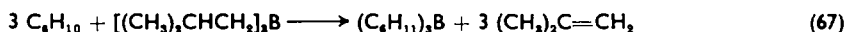
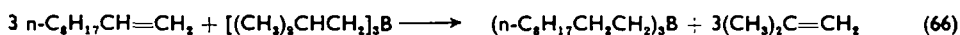
It is a consequence of the mechanism outlined above for the isomerization of organoboranes that a high concentration of an olefin of similar or greater reactivity should result in the displacement of some or all of the olefin formed in the elimination stage. Ultimately there would result an equilibrium mixture of all of the possible organoboranes and the two olefins (64).



A large excess of the displacing olefin shifts the equilibrium far toward the formation of the new organoborane. Alternatively, in cases where the displacing olefin is less volatile than the product olefin produced from the organoborane, the reaction is conveniently completed by removing the more volatile olefin from the reaction mixture by distillation (65).



This reaction has been utilized by Köster as a convenient synthesis of organoboranes.<sup>16</sup> Commonly triisobutylborane, readily available from the reaction of triisobutylaluminum with methyl borate, was heated with various olefins to displace isobutylene and to form the corresponding organoborane. In this way he has synthesized numerous organoboranes, such as tri-*n*-decylborane (66), tricyclohexylborane (67) and tri-(2-phenylpropyl)-borane (68).



The emphasis has been different in our studies. Hydroboration provides such a convenient route to the organoboranes that the displacement reaction has been explored primarily as a new type of elimination reaction which permits the preparation of olefins under relatively moderate reaction conditions with very mild reagents.

The utility of this reaction to produce pure olefins of representative structural types was tested as follows. The olefins were hydroborated to form the corresponding trialkylboranes. 1-Decene was added to the reaction mixture and the olefin product was distilled out of the refluxing reaction mixture. In each case the purity of the product was established by vapor phase chromatography. The yields averaged  $80 \pm 10$  per cent.

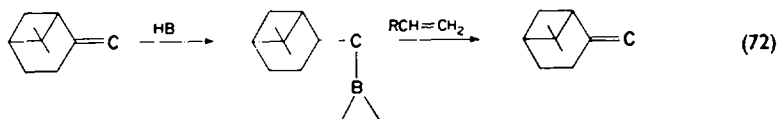
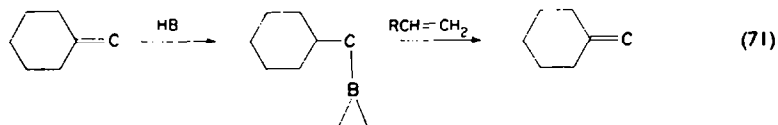
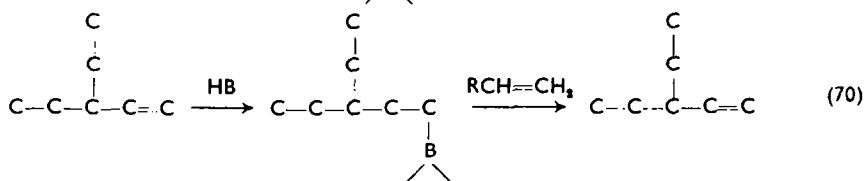
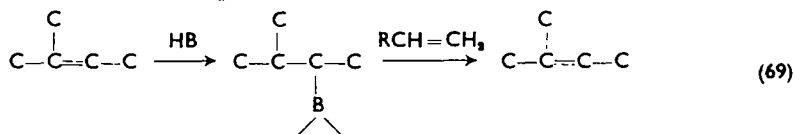
<sup>51</sup> H. C. Brown and M. V. Bhatt, *J. Amer. Chem. Soc.* **82**, 2074 (1960).

Terminal olefins, such as 1-pentene, 1-hexene, 3-methyl-1-butene and 3-ethyl-1-pentene required approximately 6–8 hours for completion. The products were 90–96 per cent pure 1-olefins with 5–10 per cent of the 2-olefin. The 2-olefin was contained in the initial fractions of the distillation. Evidently, this side-product arises from the 6–7 per cent of the 2-alkylboron derivative formed in the hydroboration of a terminal olefin and this structure must undergo displacement more readily than the 1-alkylborane present.

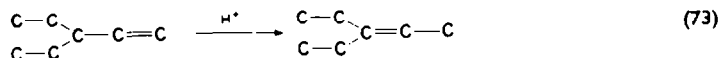
Terminal olefins containing two alkyl substituents, such as 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene, are displaced more readily, with 2 to 4 hours being adequate for completion of the reaction. In these cases the olefin products exhibit a purity of 98–99 per cent.

Finally, internal olefins, such as 2-methyl-2-butene (69), 3-ethyl-2-pentene (70), 2,4,4-trimethyl-2-pentene, cyclopentene and cyclohexene, undergo displacement to produce the corresponding olefin in high purity.

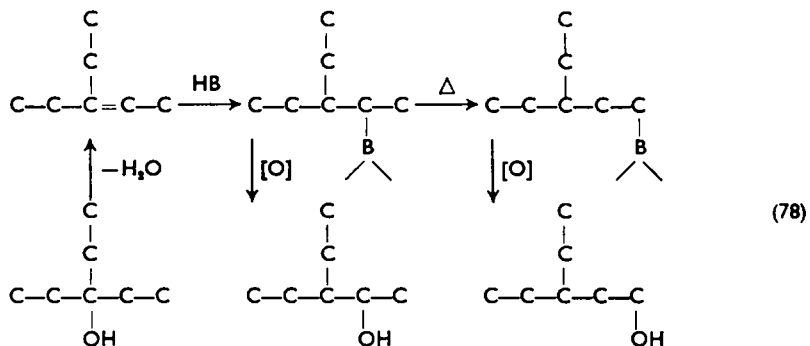
Even such labile structures, such as methylenecyclohexene (71) and  $\beta$ -pinene (72), can be hydroborated and then displaced without rearrangement.



The usual acid-catalyzed isomerization of terminal olefins results in a preferential migration of the double bond into the chain or ring, with the final product being predominantly the more thermodynamically stable, most highly substituted olefin (73, 74).







The first report of a simple laboratory procedure for the hydroboration of olefins dates back only to late 1956.<sup>6</sup> Since that time the literature dealing with this subject has grown enormously, and it was not possible within the limits of this discussion to present a complete review. It is hoped that any injustices resulting from these limitations may largely be remedied in a more detailed review of this topic now under preparation.

Finally, it should be pointed out that even though developments have been rapid they show no signs of abating.<sup>52,53</sup> We can be confident that new, important synthetic procedures based on the hydroboration reaction will be forthcoming. The hydroboration reaction promises to become one of the major synthetic tools at the disposal of the organic chemist.

*Acknowledgements*—Finally, it is a pleasure to acknowledge that these studies were greatly facilitated by grants from Parke, Davis and Co., The Upjohn Co., American Cyanamid Co., and the Ethyl Corporation.

<sup>52</sup> K. A. Saegebarth, *J. Amer. Chem. Soc.* **82**, 2081 (1960).

<sup>53</sup> R. Köster and G. Rotermund, *Angew. Chem.* **72**, 138, 563 (1960).