Thexylborane—A Highly Versatile Reagent for Organic Synthesis via Hydroboration

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The present review discusses the chemistry of thexylborane pertinent to organic synthesis, and summarizes scattered results of organic synthesis involving thexylborane.

Der vorliegende Übersichtsartikel beschreibt die Chemie von Thexylboran in organischen Synthesen und faßt die Ergebnisse zusammen.

It has become increasingly clear that the organoboranes are highly useful as intermediates in organic synthesis[1]. These organoboranes are conveniently prepared by the hydroboration of olefins[2]. It should be noted, however, that the reaction of borane (BH_3) in tetrahydrofuran with less hindered olefins, such as 1-butene, isobutylene and cyclopentene, tends to form the corresponding symmetrical trialkylboranes (R_3B) as the initial products, irrespective of the reactant ratio[2,3]. On the other hand, with moderately hindered olefins, such as cyclohexene, 2-methyl-2-butene, and α-pinene, the reaction proceeds rapidly to the dialkylborane stage. (Nearly all dialkylboranes exist as their bridged dimers. However, it is often more convenient to treat them as the monomers.)

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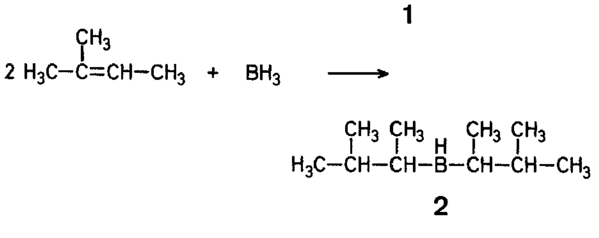

$$2\ H_3C-\overset{\overset{CH_3}{|}}{C}=CH-CH_3 + BH_3 \longrightarrow H_3C-\overset{\overset{CH_3}{|}}{CH}-\overset{\overset{CH_3}{|}}{CH}-\overset{\overset{H}{|}}{B}-\overset{\overset{CH_3}{|}}{CH}-\overset{\overset{CH_3}{|}}{CH}-CH_3$$

2

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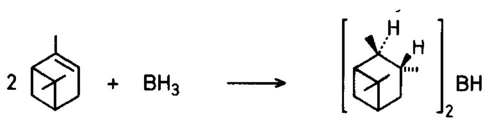
[1] H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, New York, 1972.

[2] H. C. Brown, *Hydroboration*, W. A. Benjamin, New York, 1962.

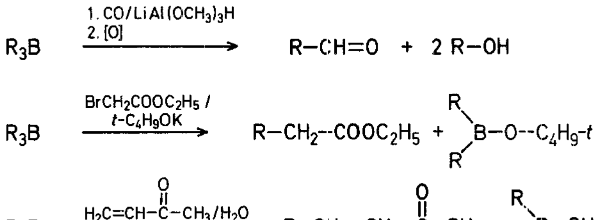
[3] H. C. Brown, A. Tsukamoto, D. B. Bigley, *J. Amer. Chem. Soc.* **82**, 4703 (1960).



3

With highly hindered olefins, such as 2,3-dimethyl-2-butene, the reaction proceeds rapidly only to the monoalkylborane (or dialkyldiborane) stage[2,4,5].

In applying the organoboranes to organic synthesis, it is often undesirable to use symmetrical trialkylboranes (R_3B). First, these symmetrical trialkylboranes are, in most cases, not applicable to the syntheses of unsymmetrical ketones, unsymmetrical alkenes, and unsymmetrical secondary and tertiary alcohols. Second, many reactions of organoboranes involve utilization of only one of the three alkyl groups[1].



$$R_3B \xrightarrow[2.\ [O]]{1.\ CO/LiAl(OCH_3)_3H} R{-}CH{=}O + 2\ R{-}OH$$

$$R_3B \xrightarrow[t\text{-}C_4H_9OK]{BrCH_2COOC_2H_5\ /} R{-}CH_2{-}COOC_2H_5 + R_2B{-}O{-}C_4H_9\text{-}t$$

$$R_3B \xrightarrow{H_2C{=}CH{-}\overset{O}{\overset{\|}{C}}{-}CH_3/H_2O} R{-}CH_2{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}CH_3 + R_2B{-}OH$$

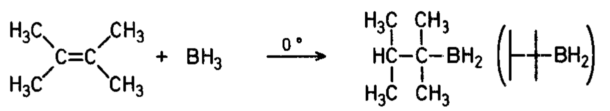
Use of symmetrical trialkylboranes in these cases limits the maximum yield of products to 33.3% based on the starting olefins, which can be a serious problem when the olefins are highly precious.

Use of the partially alkylated boranes has been found effective in circumventing these difficulties[1]. It may even be stated that *selection of the most suitable partially alkylated borane is the key to the successful application of organoboranes to organic synthesis.* The present review summarizes the chemistry of thexylborane pertinent to organic synthesis and its synthetic applications.

1. Chemistry of Thexylborane

1.1. Preparation and Characterization of Thexylborane

The reaction of 2,3-dimethyl-2-butene, or tetramethylethylene, with an equimolar quantity of borane in tetrahydrofuran at 0° produces quantitatively 2,3-dimethyl-2-butylborane (**4**) *(thexylborane)*[4,5].



$$(H_3C)_2C{=}C(CH_3)_2 + BH_3 \xrightarrow{0°} HC(CH_3)_2{-}C(CH_3)_2{-}BH_2$$

4

Thexylborane[6]:

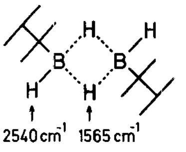
A 300-ml, three-necked flask, with a magnetic stirring bar, a thermometer well, a septum inlet, and a condenser, the tip of which is connected to a mercury bubbler, is flushed with nitrogen. Borane in tetrahydrofuran (2.71 *M*, 74 ml, 200 mmol) is placed in the flask, and tetramethylethylene (16.8 g, 23.8 ml, 200 mmol) is slowly added while maintaining the reaction temperature at 0–5°. The reaction mixture is stirred for 1 hr at 0°. The concentration of thexylborane in this case is 2.08 *M*.

A stock solution of thexylborane in tetrahydrofuran may safely be stored in a refrigerator for a week to 10 days without any noticeable change. However, the reaction of tetramethylethylene with borane in tetrahydrofuran is followed by a slow isomerization of the thexyl group into the 2,3-dimethyl-1-butyl group. It is therefore important not to store a solution of thexylborane over an extended period of time. Data on the thermal stability of thexylborane are summarized in Table 1[7].

Table 1. Stability of Thexylborane at 20–25° in Tetrahydrofuran

Time (days)	Retention of hydride (%)	Distribution of 2,3-dimethylbutanol after oxidation (%): 2-ol	1-ol
0	100	99	1
8	99	97	3
16	100	91	9

Thexylborane exists as its dimer, dithexyldiborane (**5**), in various solvents, such as tetrahydrofuran and cyclohexane, as well as in neat form[5].



5

A molecular weight of 193 was observed in tetrahydrofuran. The calculated value for the dimer **5** is 197. The infrared spectrum exhibits a strong band at 1565 cm^{-1} for the B—H—B stretching and a single sharp band at 2540 cm^{-1} characteristic of the terminal BHR moiety.

Water and alcohols, such as methanol, readily react with thexylborane with the evolution of hydrogen. Dimethoxythexylborane serves as a convenient derivative for the quantitative analysis of thexylborane. It can readily be detected by G.L.C. using an inert non-polar column, such as SE-30[8], and its N.M.R. spectrum exhibits a characteristic sharp peak for the methoxy protons at 3.61 ppm.

1.2. Reaction of Thexylborane with Olefins

The synthetically most important derivatives of thexylborane are those obtained by its reaction with olefins. When two mols of olefins are reacted with a

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[4] H. C. Brown, A. W. Moerikofer, *J. Amer. Chem. Soc.* **84**, 1478 (1962).

[5] H. C. Brown, G. J. Klender, *Inorg. Chem.* **1**, 204 (1962).

[6] H. C. Brown, E. Negeshi, *J. Amer. Chem. Soc.* **94**, 3561 (1972).

[7] G. Zweifel, H. C. Brown, *J. Amer. Chem. Soc.* **85**, 2066 (1963).

[8] H. C. Brown, E. Negeshi, J. J. Katz, unpublished results.

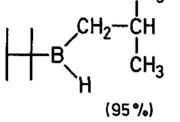
mol of thexylborane, the first mol of most of the olefins examined so far is taken up within 30 min to 1 hr at 0°[7]. Approximate rates of the reaction of thexylborane with two molar equivalents of olefins at 0° are summarized in Table 2.

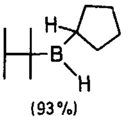
Table 2. Reaction of Various Olefins with Theyxlborane in Diglyme at 0° in the Molar Ratio of 2:1

Olefin	Olefin reacted (%) after: 0.5 hr	1 hr	2 hr	4 hr	24 hr	Tetramethylethylene dehydroborated (%)
1-Hexene	72	87	95	–	–	trace
2-Methyl-1-pentene	69	86	92	–	–	trace
Styrene	73	91	94	–	–	trace
cis-2-Hexene	76	84	90	96	–	28
Cyclohexene	53	62	73	79	90	57
2-Methyl-2-butene	46	59	66	76	94	65
1-Methylcyclopentene	59	64	73	85		53
1-Methylcyclohexene	18	32	41	53	77	50

The directive effects in the hydroboration of olefins with thexylborane closely parallel those with borane in tetrahydrofuran[7]. Thus, the hydroboration of 1-hexene with thexylborane in the 2:1 ratio produces, after oxidation, a 95:5 mixture of 1- and 2-hexanols.

Recently, a detailed structural study of the reaction of thexylborane with olefins in the molar ratio of 1:1 has been made[8]. The study has established that a majority of olefins react with thexylborane at −20 to −25° to produce the corresponding thexylmonoalkylboranes in nearly quantitative yields.


(95%)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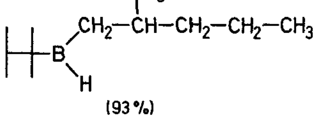
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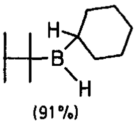
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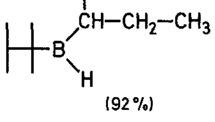
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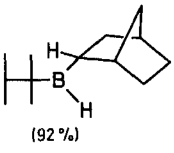
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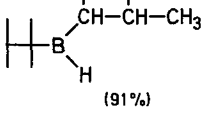
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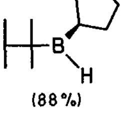
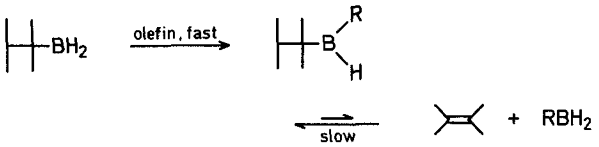
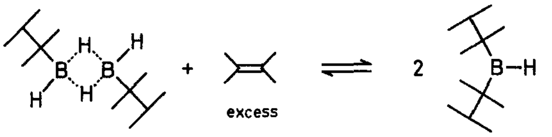

(88%)

It should be noted, however, that the reaction of thexylborane with these olefins even in the 1:1 molar ratio tends to be accompanied by the dehydroboration of tetramethylethylene.



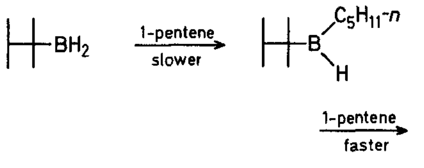
The dehydroboration has been shown to be an equilibrium reaction, at least in one case, and the rate at which the equilibrium is reached depends very much on the reaction temperature. Consequently, *it is highly recommended to prepare these thexylmonoalkylboranes at a low temperature, such as −20 to −25°, and consume them as soon as they are formed.*

When an olefin is highly hindered, the dehydroboration of 2,3-dimethyl-2-butene can compete with the hydroboration of the olefin with thexylborane. As a result, the yields of the thexylmonoalkylboranes obtained by the reaction of thexylborane with 1-methylcyclohexene and α-pinene are 80 and < 75%, respectively. However, dithexylborane (**6**) can be prepared by the reaction of a large (sixteenfold) excess of tetramethylethylene with borane in tetrahydrofuran[9].



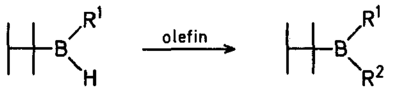
5 **6**

Unlike all dialkylboranes studied previously, dithexylborane exists exclusively or nearly exclusively as an unassociated monomer, as evidenced by I.R. (2470 cm^{-1}), ^{11}B-N.M.R. [81.3 ppm ($J = 110$ Hz) downfield relative to $BH_3 \cdot O(C_2H_5)_2$], molecular weight measurement, and the conversion of **6** into methoxydithexylborane[9]. Somewhat unexpectedly, the reaction of thexylborane with a monosubstituted terminal olefin produces a mixture of the corresponding thexylmonoalkylborane and thexyldialkylborane. Evidently, the thexylmonoalkylborane effectively competes with thexylborane for the remaining olefin.



The best observed yields of thexyl(*n*-pentyl)borane and thexyl(2-phenylethyl)borane are 24 and 61%, respectively.

Thexylmonoalkylboranes can hydroborate a number of olefins to form the corresponding totally "mixed" trialkylboranes.



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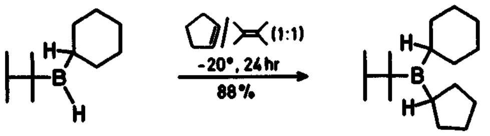
[9] E. Negishi, J. J. Katz, H. C. Brown, *J. Amer. Chem. Soc.* **94**, 4025 (1972).

In preparing thexyldialkylboranes containing two secondary alkyl groups it is desirable to carry out the second stage of the hydroboration at − 20° in the presence of tetramethylethylene to suppress the undesirable dehydroboration of tetramethylethylene[8].



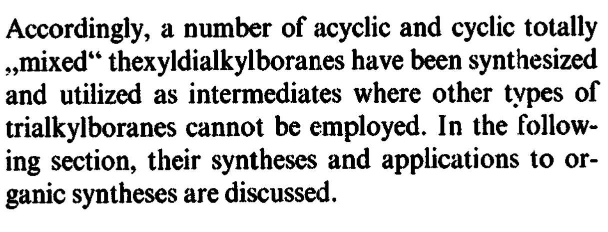
At present, these thexyldialkylboranes represent the only class of readily available totally "mixed" trialkylboranes with various unique possibilities.

Accordingly, a number of acyclic and cyclic totally „mixed" thexyldialkylboranes have been synthesized and utilized as intermediates where other types of trialkylboranes cannot be employed. In the following section, their syntheses and applications to organic syntheses are discussed.

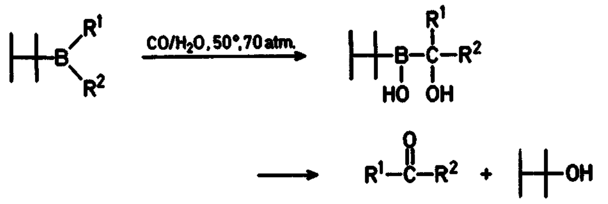
2. Synthetic Applications of Thexylborane

2.1. Synthesis of Unsymmetrical Ketones—A Multi-Carbon Homologation of Olefins

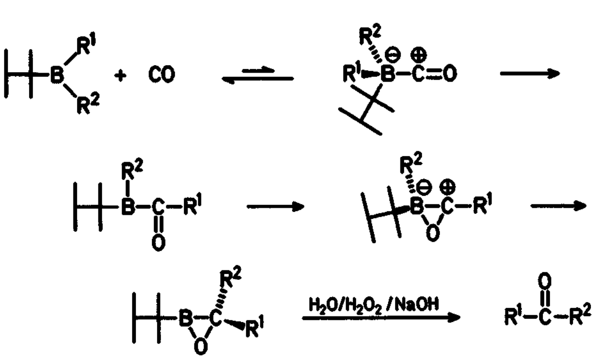
Carbonylation of trialkylboranes[10] in the presence of water provides a novel route to ketones[11].



In this reaction, only two of the three alkyl groups of a trialkylborane are utilized. A more important problem is how to synthesize unsymmetrical ketones by this reaction. Fortunately, it has been found that, in the carbonylation of readily available totally "mixed" thexyldialkylboranes, the thexyl group exhibits a very low migratory aptitude, thereby permitting a simple synthesis of unsymmetrical ketones[12].



In no case has the migration of the thexyl group been observed to any significant extent. Although the mechanism of the reaction has not been established, the following is consistent with the experimental data.



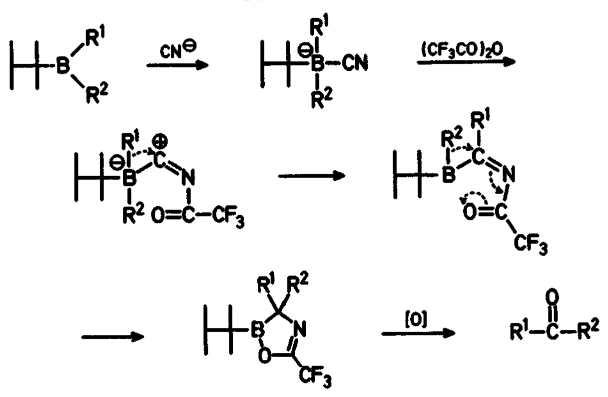
Based on this mechanism, there does not appear to be any steric reason which should favor the migration of the less bulky R^1 and R^2 groups over that of the thexyl group. The observed migratory aptitude order (primary > secondary ≫ tertiary)[12,13] appears to correlate with the stability of the alkyl groups as their anions.

The procedure can accommodate a variety of functional groups as shown in Table 3. In these cases, use of sodium acetate in place of sodium hydroxide in the oxidation step avoids possible complication arising from the use of the stronger base.

7-Cyclopentyl-7-oxoheptyl Acetate[14]:
To a 2.0 M solution of borane (50 ml, 100 mmol) in tetrahydrofuran in a 200-ml flask was added 2,3-dimethyl-2-butene (12.0 ml, 100 mmol) at 0°. The mixture was stirred for 1 hr. Cyclopentene (6.8 g, 100 mmol) was then added at 0°, followed 30 min. later by the addition of 5-hexenyl acetate (14.2 g, 100 mmol). The cooling bath was removed and the mixture was stirred at 25° for 2 hr. After the addition of water (2.7 ml, 150 mmol), the reaction mixture was transferred into a 250-ml autoclave and reacted with carbon monoxide at 70 atm and 50° for 6 hr. The cooled carbonylated mixture was oxidized with 3 N sodium acetate (34 ml)/30% hydrogen peroxide (34 ml) at 30–40°. After an exothermic reaction subsided, the mixture was heated at 45–50° for 1 hr. After the usual work-up; distillation provided essentially pure *7-cyclopentyl-7-oxoheptyl acetate*; yield: 17.5 g (73%); b.p.: 140°/3 torr; $n_D^{20} = 1.4597$.

It should be noted that this procedure provides a general method for the homologation of olefin chains by four or more carbon chains with terminal functionalization (Table 3)[12,14].

Recently, an alternate procedure to convert thexyldialkylboranes into the corresponding unsymmetrical ketones has been reported[15]. The following mechanism has been suggested[15,16].



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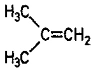
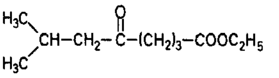
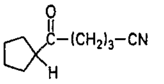
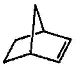
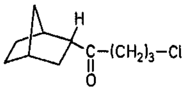
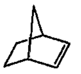
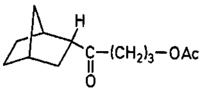
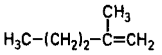
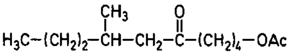
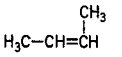
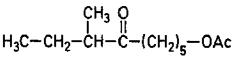
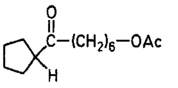
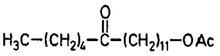
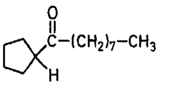
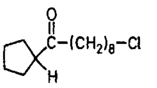
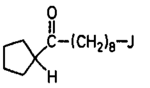
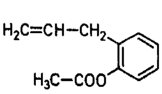
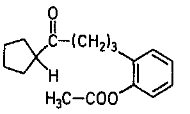
[10] H. C. Brown, *Accounts Chem. Res.* **2**, 65 (1969).

[11] H. C. Brown, M. W. Rathke, *J. Amer. Chem. Soc.* **89**, 2738 (1967).

[12] H. C. Brown, E. Negishi, *J. Amer. Chem. Soc.* **89**, 5285 (1967).

Table 3. Synthesis of Unsymmetrical Ketones via Thexyldialkylboranes

Olefin A	Olefin B	Product	Yield (%)	Reference
	$H_2C=CH-CH_2-COOC_2H_5$	 $(H_3C)_2CH-CH_2-CO-(CH_2)_3-COOC_2H_5$	84	12
	$H_2C=CH-CH_2-CN$		45	12
	$H_2C=CH-CH_2-Cl$		63	12
	$H_2C=CH-CH_2-OAc$		66	14
 $H_3C-(CH_2)_2-C(CH_3)=CH_2$	$H_2C=CH-(CH_2)_2-OAc$	 $H_3C-(CH_2)_2-CH(CH_3)-CH_2-CO-(CH_2)_4-OAc$	61	14
 $H_3C-CH=CH-CH_3$	$H_2C=CH-(CH_2)_3-OAc$	 $H_3C-CH_2-CH(CH_3)-CO-(CH_2)_5-OAc$	63	14
	$H_2C=CH-(CH_2)_4-OAc$		73	14
$H_3C-(CH_2)_2-CH=CH_2$	$H_2C=CH-(CH_2)_9-OAc$	 $H_3C-(CH_2)_4-CO-(CH_2)_{11}-OAc$	42[a]	14
	$H_2C=CH-(CH_2)_5-CH_3$		83	15
	$H_2C=CH-(CH_2)_6-Cl$		76	15
	$H_2C=CH-(CH_2)_6-J$		76	15
			80	15

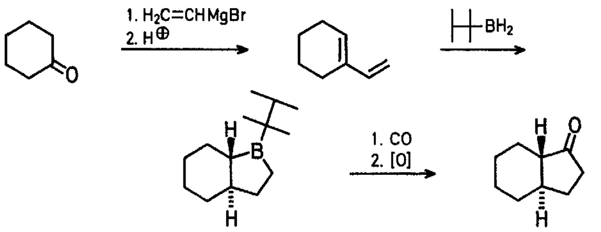
[a] Thexylborane was added to a 1:1 mixture of the olefins A and B

The thexyl group does not migrate competitively in this case either. The results are summarized in Table 3.

2.2. Synthesis of Cyclic Ketones – A New Annelation Reaction

Thexylborane has proven to be a convenient reagent for the cyclic hydroboration of dienes to form the corresponding *B*-thexylboracyclanes[7,17–19].

The carbonylation-oxidation of these *B*-thexylboracyclanes readily produces the corresponding cyclic ketones[20]. This cyclic ketone synthesis provides a highly promising, stereoselective annelation reaction[21].



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[13] H. C. Brown, M. W. Rathke, *J. Amer. Chem. Soc.* **89**, 4528 (1967).

[14] E. Negishi, H. C. Brown, *Synthesis* **1972**, 196.

[15] A. Pelter, M. G. Hutchings, K. Smith, *Chem. Commun.* **1971**, 1048.

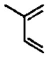
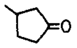
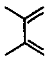
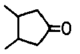
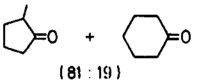
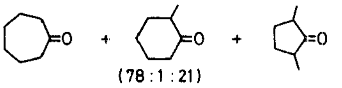
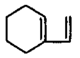
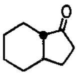
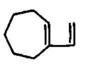
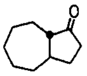
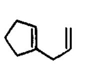
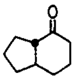
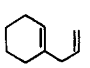
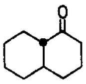
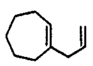
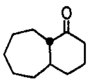
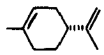
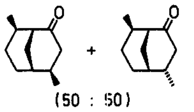
[16] A. Pelter, M. G. Hutchings, K. Smith, *Chem. Commun.* **1970**, 1529.

[17] H. C. Brown, C. D. Pfaffenberger, *J. Amer. Chem. Soc.* **89**, 5475 (1967).

[18] H. C. Brown, E. Negishi, *J. Amer. Chem. Soc.* **94**, 3567 (1972).

[19] H. C. Brown, E. Negishi, *Pure Appl. Chem.* **1972**, 527.

Table 4. Syntheses of Cyclic and Bicyclic Ketones via *B*-Thexylboracyclanes

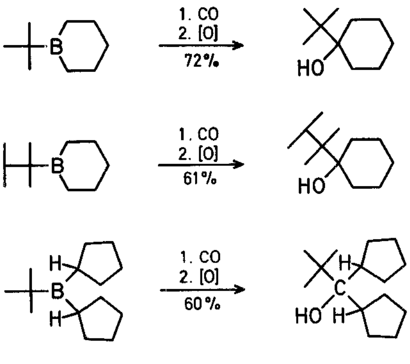
Diene	Product	Yield (%)	Reference
		46	20
	 (*cis* : *trans* = 69 : 71)	69	20
	 (81 : 19)	75	20
	 (78 : 1 : 21)	80	20
		60	20
		67	21
		40	21
		66	21
		62	21
	 (50 : 50)	95	15

Fusion of a six-membered ring is also possible. A noteworthy aspect of the synthetic method is the formation of the *trans* ketones with stereoisomeric purities of nearly 100%. It appears that this is the first stereoselective synthesis of such ketones, applicable to the construction of a wide range of structures. The results of cyclic and bicyclic ketone syntheses via *B*-thexylboracyclanes are summarized in Table 4.

***trans*-1-Hydrindanone**[20]:

In a 300-ml flask was introduced dry tetrahydrofuran (50 ml), followed by the simultaneous slow addition at 20 to 25°, over a period of 3 hr, of thexylborane[6] (28.2 ml of 1.77 M solution, 50 mmol) and 1-vinylcyclohexene (5.95 g, 55 mmol) in tetrahydrofuran (25 ml). After stirring at room temperature for 5 hr to complete the cyclization, water (1.8 ml, 100 mmol) was added, and the mixture was transferred into a 250 ml autoclave under nitrogen and carbonylated at 70 atm and 50° (3 hr). The reaction mixture was oxidized with sodium acetate (20 ml of 3 *M* solution) and hydrogen peroxide (20 ml of 30% solution). After the usual work-up, distillation of a 45-mmol aliquot yielded *trans*-1-hydrindanone; yield: 3.7 g (60%); b.p. 40–43°/0.5 torr; $n_D^{20} = 1.4782$; m.p. of oxime: 145–146°.

We have so far emphasized that the thexyl group has a very low migratory aptitude in the carbonylation and related reactions. It is worth noting, however, that under the reaction conditions permitting the formation of tertiary alcohols, the thexyl and other tertiary groups can be transferred from boron to carbon without isomerization[22]. A few such examples are shown below.



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[20] H. C. Brown, E. Negishi, *J. Amer. Chem. Soc.* **89**, 5477 (1967).

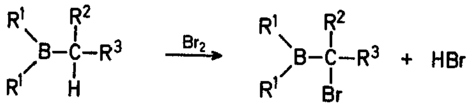
[21] H. C. Brown, E. Negishi, *Chem. Commun.* **1968**, 594.

[22] E. Negishi, H. C. Brown, *Synthesis* **1972**, 197.

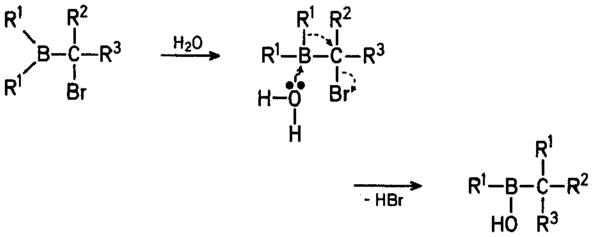
[23] C. F. Lane, H. C. Brown, *J. Amer. Chem. Soc.* **92**, 7212 (1970)

2.3. Coupling of Two Unlike Alkyl Groups via Bromination of Thexyldialkylboranes

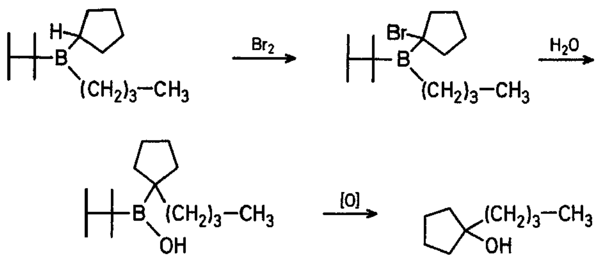
The reaction of organoboranes with bromine involves the following free-radical alpha bromination mechanism[23].



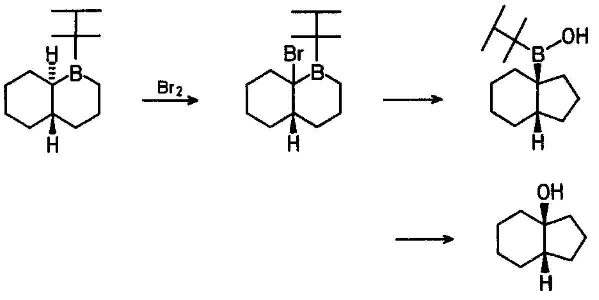
In the presence of a nucleophile, such as water, a further ionic migration reaction takes place[24].



Thus, the whole sequence provides a means of coupling two alkyl groups of organoboranes. Oxidation of the coupled products yields the corresponding alcohols. The thexyl group does not have an alpha hydrogen to be abstracted. Moreover, it exhibits the low migratory aptitude also in this reaction. Consequently, the totally "mixed" thexyldialkylboranes are ideal intermediates for the coupling of two unlike alkyl groups with simultaneous introduction of a hydroxyl group at the point of coupling[25]. An alkyl group capable of yielding the more stable free radical in the alpha position is preferentially brominated.



Application of the bromination-oxidation reaction to cyclic thexyldialkylboranes results in a ring contraction[26].



At present, it is not clear why *cis*-8-hydrindanol is formed preferentially in the above reaction. However, based on related results obtained recently with norbornylborane derivatives[27], it is likely that this is a rare and novel example of the migration of an alkyl group from the boron atom to an adjacent carbon atom with retention of the configuration at the migration terminus.

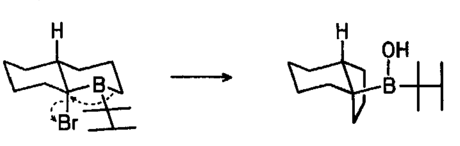
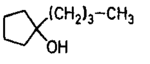
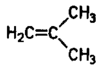
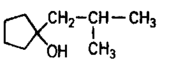
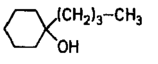
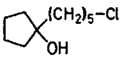
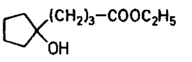
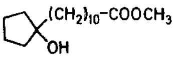
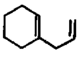
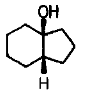
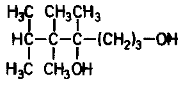
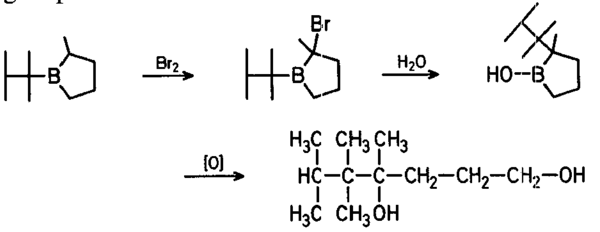


Table 5. Coupling of Two Unlike Alkyl Groups via Bromination-Oxidation of Thexyldialkylboranes

Olefin A	Olefin B	Product	Yield (%)	Reference
	$H_2C=CH-CH_2-CH_3$		85	25
	 $H_2C=C(CH_3)_2$		70	25
	$H_2C=CH-CH_2-CH_3$		51	25
	$H_2C=CH-(CH_2)_3-Cl$		89	25
	$H_2C=CH-CH_2-COOC_2H_5$		72	25
	$H_2C=CH-(CH_2)_8-COOCH_3$		75	25
			60	26
		 $$\begin{array}{l}H_3C\ CH_3CH_3\\ HC-C-C-(CH_2)_3-OH\\ H_3C\ CH_3OH\end{array}$$	55	26

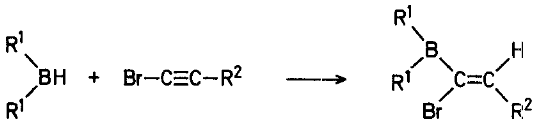
The ring contraction reaction is not applicable to the synthesis of four-membered rings. Thus, the bromination-oxidation of *B*-thexyl-2-methylborolane results in the migration of the bulky thexyl group[26].



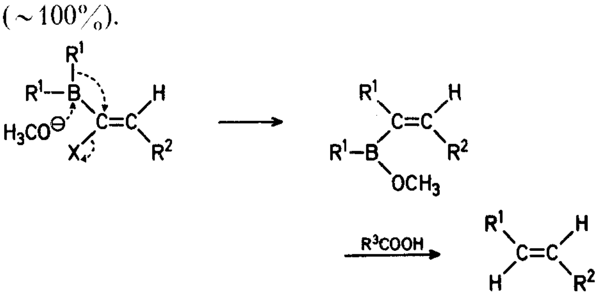
The results of the bromination-oxidation of thexyldialkylboranes are summarized in Table 5.

2.4. Synthesis of *trans*-Disubstituted Olefins

Dialkylboranes hydroborate 1-halo-1-alkynes in a regio- and stereoselective manner fo form the corresponding haloalkenylborane. Four entirely different groups can be placed around a carbon-carbon double bond in one step in a predictable fashion[28].



Moreover, the base-induced migration of an alkyl group from the boron atom to the bromine-bearing carbon atom involves an exclusive or nearly exclusive inversion at the carbon atom[28,29]. Stereospecific protonolysis of the product provides the corresponding *trans* olefin with a high stereoisomeric purity (~100%).



Although *trans* disubstituted olefins may readily be obtained by the partial reduction of acetylenes with sodium in liquid ammonia[30], this novel olefin synthesis via hydroboration has a unique advantage over the conventional method in that four consecutive stereocenters can be created in a predictable manner as shown by the following example[31].

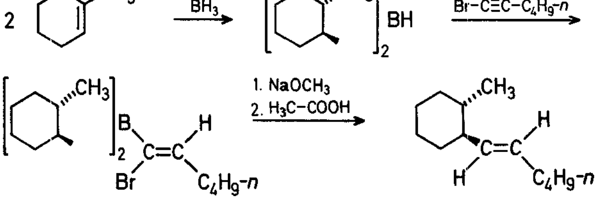
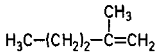
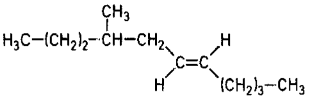
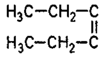
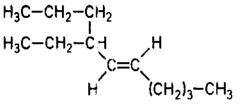
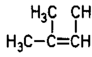
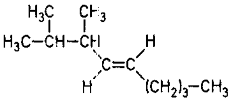
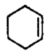
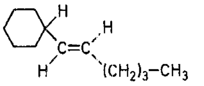
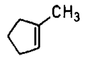
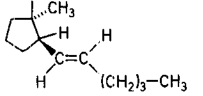
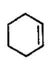
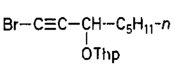
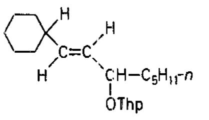
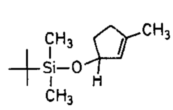
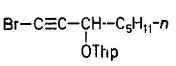
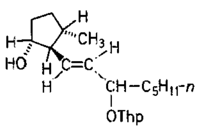
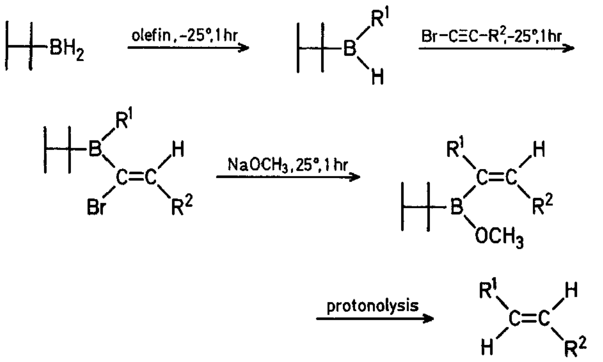


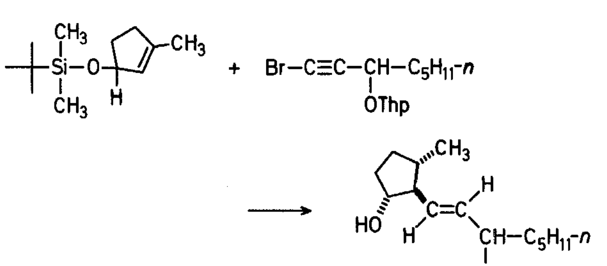
Table 6. Synthesis of *trans*-Disubstituted Olefins via Thexylmonoalkylboranes.

Olefin	Acetylene	Product	Yield (%)	Reference
 $H_3C-(CH_2)_2-\overset{CH_3}{C}=CH_2$	$Br-C\equiv C-(CH_2)_3-CH_3$		94	32
 $\begin{array}{l}H_3C-CH_2-CH\\ \qquad\quad\ \|\\ H_3C-CH_2-CH\end{array}$	$Br-C\equiv C-(CH_2)_3-CH_3$		93	32
 $H_3C-\overset{H_3C}{C}=\overset{CH_3}{CH}$	$Br-C\equiv C-(CH_2)_3-CH_3$		86	32
	$Br-C\equiv C-(CH_2)_3-CH_3$		85	32
	$Br-C\equiv C-(CH_2)_3-CH_3$		94	32
	 $Br-C\equiv C-\underset{OThp}{CH}-C_5H_{11}\text{-}n$		65	33
	 $Br-C\equiv C-\underset{OThp}{CH}-C_5H_{11}\text{-}n$		—	33

Unfortunately, there are two apparent difficulties in the original procedure. First, it requires dialkylboranes whose availability by simple hydroboration has been relatively limited. Second, only one of the two alkyl groups of the dialkylboranes is utilized. These difficulties can now be circumvented by employing thexylmonoalkylboranes in place of the simple dialkylboranes[32,33].



The thexyl group migrates to the extent of only 2–7%. Protonolysis of the methoxythexylalkenylboranes can be achieved either with carboxylic acids[32], such as acetic acid (refluxing overnight to 24 hr.), propanoic acid (several hours), and isobutyric acid (1–2 hr.), or with aqueous silver ammonium nitrate (8 hr. at 75–80°)[33]. The latter reagent has been reported to be compatible with acid-sensitive groups. This procedure appears promising as a simple stereoselective route to prostaglandins as indicated by the following synthesis of a model compound[33].

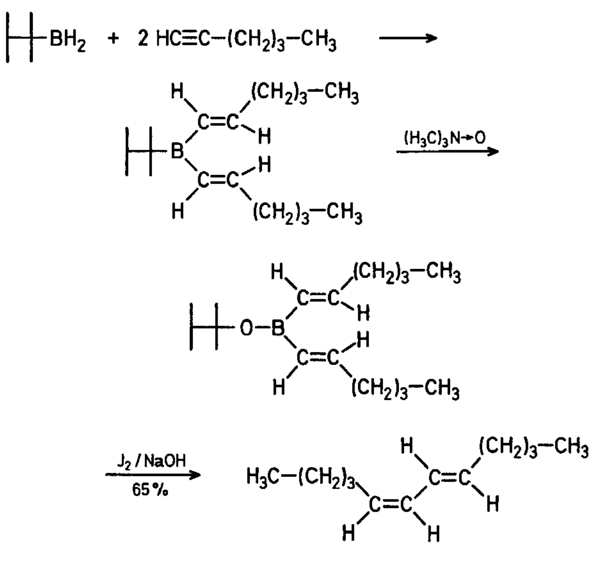


***trans*-3-Propyl-4-nonene**[32]:

To 2.05 *M* thexylborane[6] (14.7 ml, 30 mmol) in a 100-ml flask were added sequentially *trans*-3-hexene (2.52 g, 30 mmol, −25°, 1 hr), 1-bromo-1-hexyne (4.83 g, 30 mmol, −25°, 1 hr), and sodium methoxide (2.43 g, 45 mmol) in methanol (30 ml), (−25°, 5 min, then 25°, 1 hr). After evaporation the volatile substances (25°/15 torr, 1 hr), isobutyric acid (30 ml) was added. The reaction mixture was refluxed for 1 hr, cooled, poured into water (100 ml), and extracted with pentane (3 × 50 ml). The organic layer was washed with water (2 × 50 ml) and a saturated aqueous solution of potassium carbonate (2 × 50 ml) and was dried with magnesium sulfate. Distillative work-up provided *trans*-3-propyl-4-nonene, yield: 3.93 g (78%); b.p. 49–51°/0.4 torr; $n_D^{20} = 1.4319$. The product was >99% pure by G.L.C.

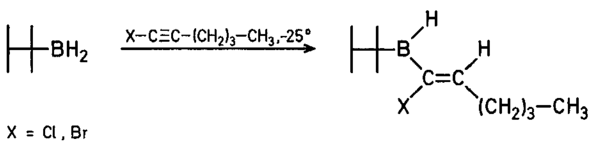
2.5. Syntheses of Conjugated Dienes

The hydroboration of acetylenes with thexylborane has not been subjected to detailed investigation. However, an earlier study has established that the addition of thexylborane to 1-hexyne in the ratio of 1:2 yields the corresponding thexyldivinylborane[7]. After selectively oxidizing the thexyl group, treatment of the oxidation product with iodine and sodium hydroxide produces *cis,trans*-5,7-dodecadiene (98% pure)[34].



It is somewhat unfortunate that the procedure appears suitable only for the synthesis of symmetrically substituted *cis,trans*-conjugated dienes. Unlike the case of the *trans* olefin synthesis, the thexyl group participates in the migration reaction and a nearly 1:1 mixture of the expected diene and 2,3,3-trimethyl-4-nonene is formed, unless the thexyl group is oxidized prior to this reaction[34].

A preliminary study indicates that the hydroboration of 1-hexyne with thexylborane in the ratio of 1:1 does not produce thexylhexenylborane in high yield[35]. On the other hand, the reaction with 1-chloro- or 1-bromo-1-hexyne (but not with 1-iodo-1-hexyne) produces the corresponding thexylhaloalkenylborane in high yield[35].



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[24] C. F. Lane, H. C. Brown, *J. Amer. Chem. Soc.* **93**, 1025 (1971).

[25] H. C. Brown, Y. Yamamoto, C. F. Lane, *Synthesis* **1972**, 304.

[26] Y. Yamamoto, H. C. Brown, unpublished results.

[27] Y. Yamamoto, H. C. Brown, unpublished results.

[28] G. Zweifel, H. Arzoumanian, *J. Amer. Chem. Soc.* **89**, 5086 (1967).

[29] G. Köbrich, H. R. Merkle, *Angew. Chem.* **79**, 50 (1967); *Angew. Chem. Internat. Edit.* **6**, 74 (1967).

[30] H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, Menlo Park, California, 1972, p. 205.

[31] G. Zweifel, R. P. Fisher, J. T. Snow, C. C. Whitney, *J. Amer. Chem. Soc.* **93**, 6309 (1971).

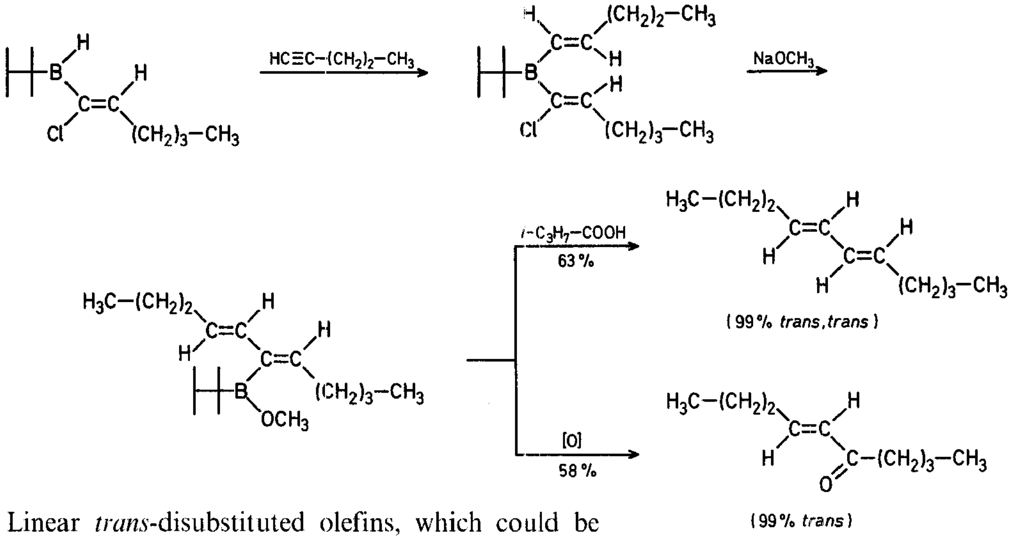
[32] E. Negishi, J. J. Katz, H. C. Brown, *Synthesis* **1972**, 555.

[33] E. J. Corey, T. Ravindranathan, *J. Amer. Chem. Soc.* **94**, 4013 (1972).

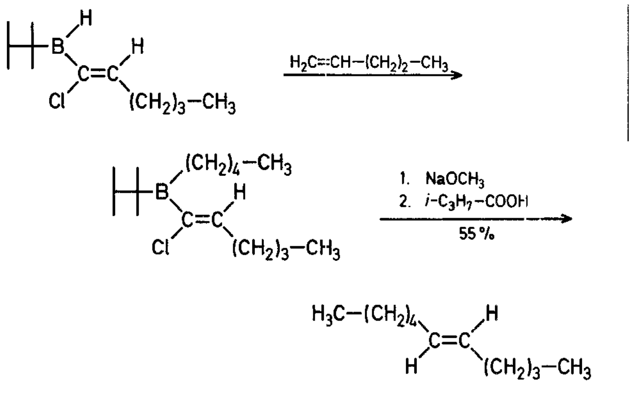
[34] G. Zweifel, N. L. Polston, C. C. Whitney, *J. Amer. Chem. Soc.* **90**, 7139 (1968).

[35] E. Negishi, T. Yoshida, *Chem. Commun.* **1973**, 606.

This has opened up a number of unique possibilities. A few of them are shown below.



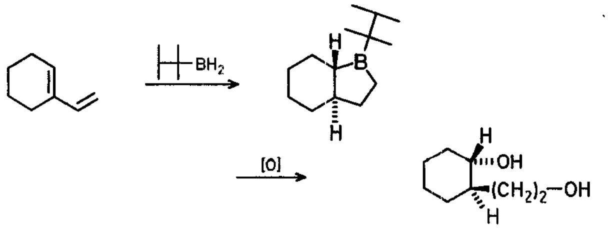
Linear *trans*-disubstituted olefins, which could be obtained only in low yields by the methods discussed earlier (Section 2.4.) can be prepared in good yields[35].



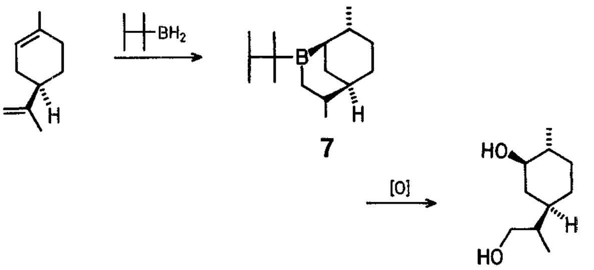
It now is clear that the stereoselective nature of the hydroboration reaction makes various olefin syntheses via hydroboration highly attractive procedures and that thexylborane is indispensable in expanding the scope of these synthetic procedures.

2.6. Stereoselective Syntheses of Diols from Dienes

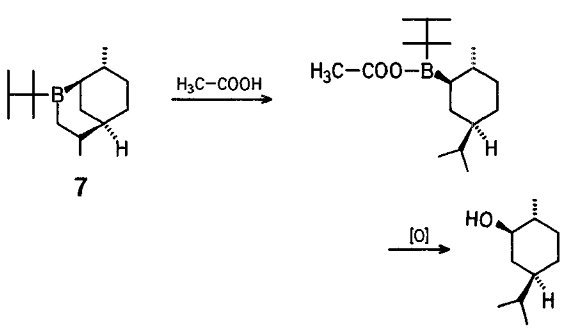
The cyclic hydroboration of dienes containing at least one endocyclic double bond can yield bicyclic organoboranes which, on oxidation, produce either *trans* or *cis* diols in a stereoselective manner. Thus, 1-vinyl- or 1-allyl-1-cycloalkenes react with thexylborane to form only the *trans*-fused bicyclic organoboranes[21], as discussed earlier (Section 2.2.). Oxidation of the borane intermediate yields the corresponding *trans* diols.



On the other hand, the cyclic hydroboration-oxidation of other dienes, such as 1,5-cyclooctadiene and limonene, form only the *cis* diols[17,18].



It should be noted that the protonolysis of **7** followed by oxidation permits a remarkably simple and stereoselective conversion of D-(+)-limonene to D-(−)-carvomenthol in 75% yield[17].



In principle, borane in tetrahydrofuran can also be used in achieving similar stereoselective transformations[36]. However, results with thexylborane are often much more favorable mainly due to its difuntional nature.

2.7. Synthesis of 1,5-Diols from Monoolefins

Thexylmonoalkylboranes having hydrogen on a carbon atom epsilon to the boron atom can form the corresponding six-membered boracyclanes on heating.

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[36] H. C. Brown, E. Negishi, P. L. Burke, *J. Amer. Chem. Soc.* **94**, 3561 (1972).

Oxidation of the cyclic products yields the corresponding 1,5-diols[37] (Table 7).

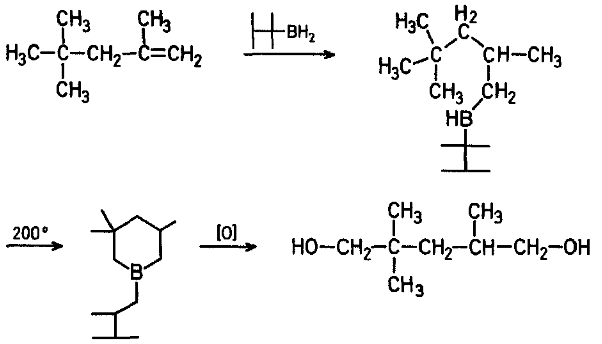
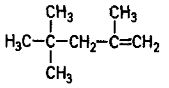
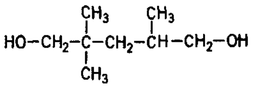
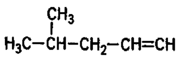
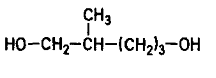
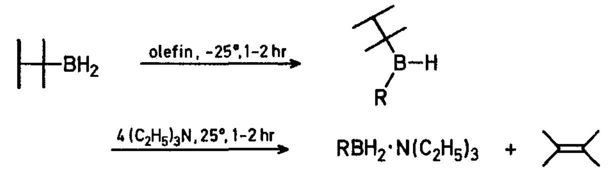


Table 7. Synthesis of 1,5-Diols from Monoolefins

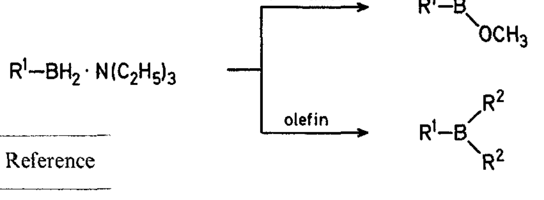
Olefin	Product	Yield (%)	Reference
 $H_3C-C(CH_3)_2-CH_2-C(CH_3)=CH_2$	 $HO-CH_2-C(CH_3)_2-CH_2-CH(CH_3)-CH_2-OH$	81	37
$H_3C-(CH_2)_2-CH=CH_2$	$HO-(CH_2)_5-OH$	55	37
 $H_3C-CH(CH_3)-CH_2-CH=CH_2$	 $HO-CH_2-CH(CH_3)-(CH_2)_3-OH$	68	37
$H_3C-(CH_2)_3-CH=CH_2$	four diols	40	37

2.8. Synthesis of Monoalkylboranes as Triethylaminates

As mentioned earlier, simple hydroboration of most olefins with borane in tetrahydrofuran does not produce the corresponding monoalkylboranes cleanly. Only in 1971 was the first general synthesis of monoalkylboranes reported[38]. An alternate, more convenient method to prepare monoalkylboranes as their triethylaminates has since been developed. It takes advantage of the finding that the thexyl group can be selectively dehydroborated from thexylmonoalkylboranes[39] (Table 8).

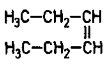
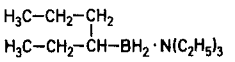
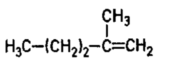
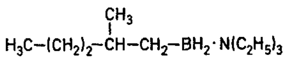
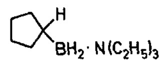
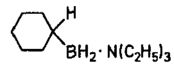
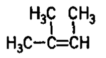
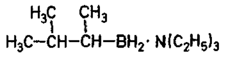
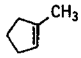
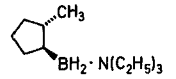


These monoalkylborane triethylaminates function as monoalkylboranes in disguise. They can readily be solvolyzed to form the corresponding boronic acids and their derivatives, and can hydroborate olefins to produce a variety of "mixed" trialkylboranes[39].



These products have proven to be valuable intermediates in organic synthesis via hydroboration[1].

Table 8. Preparation of Monoalkylborane Triethylaminates

Olefin	Product	Yield (%)	Reference
	 $H_3C-CH_2-CH_2-CH(CH_2-CH_3)-BH_2\cdot N(C_2H_5)_3$	96	39
 $H_3C-(CH_2)_2-C(CH_3)=CH_2$	 $H_3C-(CH_2)_2-CH(CH_3)-CH_2-BH_2\cdot N(C_2H_5)_3$	90	39
		98	39
		95	39
 $H_3C-C(CH_3)=CH-CH_3$	 $H_3C-CH(CH_3)-CH(CH_3)-BH_2\cdot N(C_2H_5)_3$	95	39
		95	39

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[37] H. C. Brown, K. J. Murray, H. Muller, G. Zweifel, *J. Amer. Chem. Soc.* **88**, 1443 (1966).

[38] H. C. Brown, S. K. Gupta, *J. Amer. Chem. Soc.* **93**, 4062 (1971).

[39] H. C. Brown, E. Negishi, J. J. Katz, *J. Amer. Chem. Soc.* **94**, 5893 (1972).

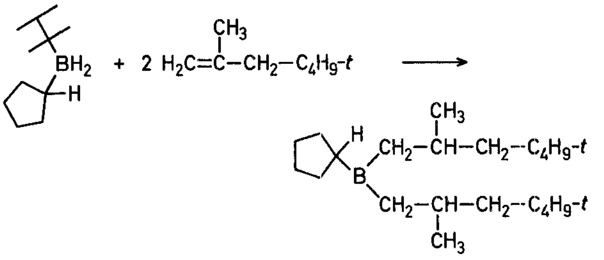
[40] C. F. Lane, H. C. Brown, *J. Organomet. Chem.* **34**, C29 (1972).

Cyclopentylborane Triethylaminate and Cyclopentyldi-*n*-pentylborane[39]:

To 1.77 *M* thexylborane solution (5.65 ml, 10 mmol) was added cyclopentene (0.68 g, 10 mmol) at −25°. One hour later triethylamine (5.6 ml, 40 mmol) was added, and the mixture was stirred for 1–2 hr at 25°. For most purposes direct use of this reaction mixture is satisfactory, as described below.

To the crude mixture containing cyclopentylborane triethylaminate was added 1-pentene (1.4 g, 20 mmol) at 25°. More than 90% of the 1-pentene was taken up in 16 hr at 25°. The product was identified as 2-(cyclopentyldi-*n*-pentylcarbinyl)-2-bora-1,3-dioxolane, formed by the carbonylation of the crude product in the presence of ethylene glycol; b.p. 127–128°/0.7 torr; $n_D^{20} = 1.4675$.

In certain favorable cases, preparation of "mixed" trialkylboranes $[R^1B(R^2)_2]$ can be achieved without the separate synthesis of monoalkylborane triethylaminates. Thus, the reaction of thexylcyclopentylborane with two molar equivalents of 2,4,4-trimethyl-1-pentene produces predominantly cyclopentylbis(2,4,4-trimethylpentyl)borane[40].



However, the applicability of this procedure appears rather limited.

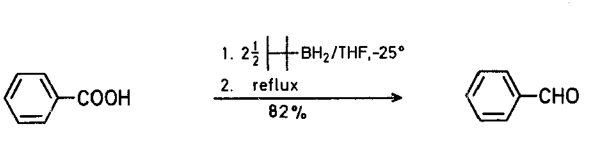
2.9. Selective Reduction with Thexylborane

A detailed study of the reactions of a wide variety of organic compounds with thexylborane has been reported[41]. Except for relatively minor differences, the results more or less parallel those obtained with borane in tetrahydrofuran[1,2,42]. The acidic hydrogens are attacked by thexylborane at varying rates. In general, compounds containing —COOH, —OH, and $—SO_3H$ groups react with evolution of hydrogen at rapid-to-moderate rates[41]. On the other hand, amines rapidly react with thexylborane to form the corresponding 1:1 complexes[5,8]. Little or no hydrogen evolution accompanies at 0° even when primary amines are reacted[41]. The reactivity of thiols appears to lie between those of alcohols and primary amines.

The reactivity of the carbonyl group toward thexylborane also varies. Aldehydes generally react rapidly with thexylborane. However, most other carbonyl functions react at much slower rates. Therefore, in many instances, the hydroboration of olefins and acetylenes with thexylborane can be achieved in the presence of these groups. On the other hand, the aldehyde group of cinnamaldehyde is attacked by thexylborane more rapidly than the olefinic double bonds[41]. The experimental results with carbonyl derivatives and other derivatives may be summarized as follows.

aldehyde	$\xrightarrow{\text{rapid}}$	alcohol
ketone	$\xrightarrow{\text{slow}}$	alcohol
carboxylic acid	$\longrightarrow$	aldehyde, etc.
acid chloride	$\xrightarrow{\text{very slow}}$	reduction
acid anhydride	$\longrightarrow$	reduction
ester	$\xrightarrow{\text{very slow}}$	reduction
lactone	$\xrightarrow{\text{slow}}$	reduction
amide	$\xrightarrow{\text{slow to moderate}}$	reduction
nitrile	$\xrightarrow{\text{slow}}$	reduction
epoxide	$\xrightarrow{\text{slow}}$	reduction
aromatic nitro	$\xrightarrow{\text{slow}}$	reduction
aliphatic nitro	$\longrightarrow$	no reaction
sulfone	$\longrightarrow$	no reaction
tosylate	$\longrightarrow$	no reaction

Preliminary results indicate that, under carefully controlled conditions, both aliphatic and aromatic carboxylic acids can be converted into the corresponding aldehydes in excellent yields[41].



2.10. Selective Reduction with Trialkylborohydrides Containing the Thexyl Group

Certain trialkylborohydrides have emerged as a new class of reducing agents, whose reactivity and unique selectivity are unequalled by any other previously known boron and aluminum containing reducing agents[43–45]. The bulky nature of the thexyl group appears to render those trialkylborohydrides which contain the thexyl group highly effective in achieving

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[41] H. C. Brown, P. Heim, N. M. Yoon, *J. Org. Chem.* **37**, 2942 (1972).

[42] H. C. Brown, P. Heim, N. M. Yoon, *J. Amer. Chem Soc.* **92**, 1637 (1970).

[43] H. C. Brown, W. C. Dickason, *J. Amer. Chem. Soc.* **92**, 709 (1970).

[44] H. C. Brown, S. Krishnamurthy, R. A. Coleman, *J. Amer. Chem. Soc.* **94**, 1750 (1972).

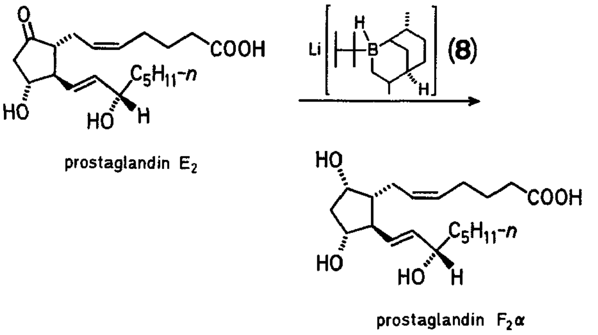
[45] H. C. Brown, S. Krishnamurthy, *J. Amer. Chem. Soc.* **94**, 7159 (1972).

[46] E. J. Corey, R. K. Varma, *J. Amer. Chem. Soc.* **93**, 7319 (1971).

[47] See appropriate references cited in Ref. 46.

[48] E. J. Corey, K. B. Becker, R. K. Varma, *J. Amer. Chem. Soc.* **94**, 8616 (1972).

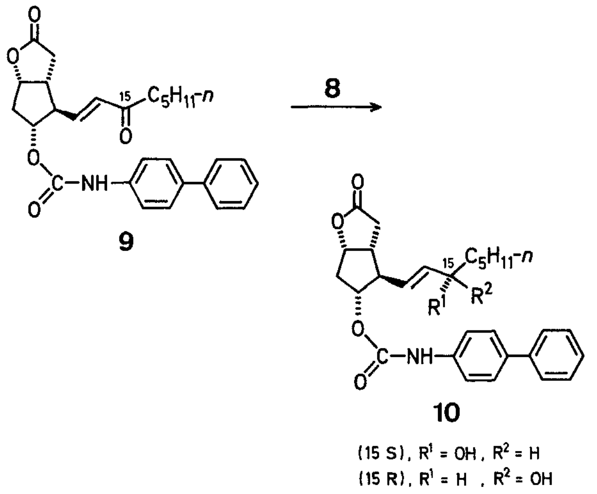
the stereoselective reduction of the carbonyl group. Thus, the reduction of prostaglandin E_2 with the bulky trialkylborohydride (**8**) produces stereoselectively prostaglandin $F_2\alpha$. No appreciable formation of prostaglandin $F_2\beta$ is observed[46].



It should be noted that the reduction with sodium borohydride yields a nearly 1:1 mixture of prostaglandin $F_2\alpha$ and $F_2\beta$[47].

Similarly, the reduction of **9** with **8** produces **10** with a ratio 15*S*:15*R* of 92:8[48].

Undoubtedly, it is the large steric requirement of trialkylborohydrides, such as **8**, which is mainly responsible for the remarkable stereoselectivity. In any case, it is clear that these trialkylborohydrides are revolutionalizing the art of selective reduction.



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