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CATECHOLBORANE

A NEW HYDROBORATION REAGENT

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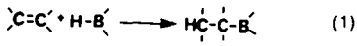
INTRODUCTION

THE first practical synthesis of organoboranes involved the reaction of an organometallic derivative with a boron ester or halide.[1] Since this process required the prior formation of a reactive organometallic followed by its conversion to what was thought to be a less reactive reagent, there was little incentive to explore the synthetic utility of organoboranes.[2] Fortunately, with the development of the hydroboration reaction,[3] this attitude changed dramatically.



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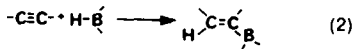

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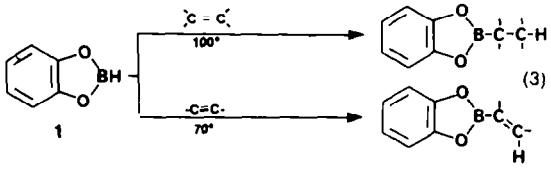
The rapid and quantitative addition of the boron-hydrogen bond to alkenes and alkynes (eqns 1 and 2) has made a wide variety of organoboranes readily available and kindled new interest in exploring organoborane chemistry. Many new reactions of major significance in synthetic organic chemistry have been discovered and this new area of chemistry has been extensively reviewed.[4-6]

During the first six to eight years, the exploratory efforts of Brown and coworkers were directed toward the development of new synthetic reactions for trialkylboranes. These trialkylboranes were derived from both borane (BH_3) and from a number of partially alkylated boranes (R_2BH and $R'BH_2$).[7] Three or four years ago, the research efforts of Brown and coworkers began to shift toward the investigation of various partially substituted, but non-alkylated, boranes as hydroboration reagents.[7] The use of these new reagents for both hydroboration and for organic synthesis was recently reviewed by Brown.[8] This review also contains a large number of experimental procedures and a useful discussion of handling techniques.[8]

One of the most interesting of these new hydroboration reagents is catecholborane (1) (1,3,2-benzodioxaborole).[9] Both alkenes[10] and alkynes[11] react rapidly with catecholborane upon heating to give the corresponding alkyl- and alkenylcatecholboranes in high yield (eqn 3).



(3)

Thus, this reagent provides, for the first time, a convenient synthesis of alkane- and alkeneboronic esters and acids. Alkane- and alkeneboronic acids are a relatively unexplored class of reagents of potential interest in synthetic organic chemistry.

It is hoped that the following review on the chemistry of catecholborane will facilitate the application of this new reagent.

HISTORICAL BACKGROUND

Dialkoxyboranes, such as dimethoxyborane (2)[12] and 1,3,2-dioxaborolane (3),[13] can be readily synthesized from the alcohol and diborane (eqns 4 and 5).

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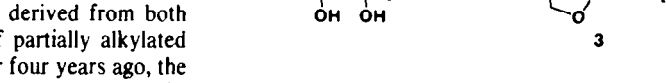

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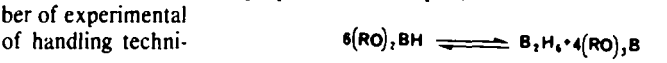
These compounds exist as monomers with no indication of association. They are not spontaneously flammable in air, but are rapidly hydrolyzed. Unfortunately, neither 2 nor 3 is stable and both undergo rapid and reversible disproportionation (eqn 6).



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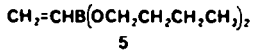
A related dialkoxyborane, 4,4,6 - trimethyl - 1,3,2 - dioxaborinane (4) is reported to be stable toward disproportionation.[14] This reagent can be used for the hydroboration of alkenes[14] and allenes.[15] However, 4 shows a greatly reduced reactivity relative to BH_3 or to

4

alkylboranes as expected due to π-bonding between boron and oxygen.[14] With catecholborane, where oxygen is bound to a benzene ring, a dramatic increase is observed in the rate of hydroboration relative to **4**.[16] This increased rate of hydroboration is expected since the oxygen 2p electrons can resonate into the benzene ring. Consequently, π-bonding between oxygen and boron is less important.

Alkane- and alkeneboronic esters can be prepared from the corresponding organomagnesium or organolithium reagents.[1] However, the yields are often low and the procedure cannot tolerate the presence of many sensitive functional groups. A pair of interesting vinylboronic ester, **5**[17] and **6**,[18] which were prepared from vinylmagnesium chloride, deserve mention because of their interesting chemistry.[19,20]



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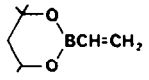

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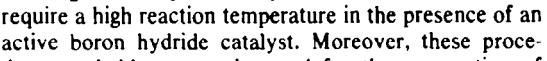
Alternative methods for the preparation of alkyl boronic esters include: (1) hydroboration of an alkene with an excess of borane followed by treatment with methanol,[21] (2) redistribution of a trialkylborane with trimethylene biborate,[22] and (3) redistribution of a trialkylborane with boron trichloride followed by treatment with methanol.[23] Unfortunately, these procedures either give low yields, require careful distillation, or require a high reaction temperature in the presence of an active boron hydride catalyst. Moreover, these procedures probably cannot be used for the preparation of alkenboronic esters due to the large amount of dihydroboration observed for the reaction of alkynes with borane.[24]

Dichloroborane-diethyl etherate is an active hydroboration reagent when the pure complex is treated with boron trichloride in pentane in the presence of an alkene[25] or an alkyne (eqns 7 and 8).[26]



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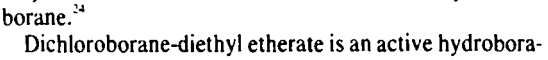
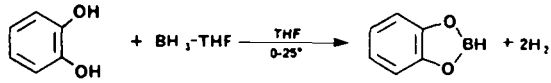


(8)

The alkyl- and alkenyldichloroboranes are readily transformed into alkane- and alkeneboronic esters by simply adding excess alcohol at 0°.[25,26] The development of dichloroborane-diethyl etherate as a hydroboration reagent would appear to make catecholborane obsolete. However, hydroboration with dichloroborane-diethyl etherate requires the neat complex which is unstable on storage.[27] This problem is not present with catecholborane, samples of which have been stored for over a year in a cold room with no detectable deterioration.[28]

PREPARATION AND PROPERTIES

Catecholborane is readily prepared by the reaction of catechol dissolved in tetrahydrofuran (THF) with borane–THF (eqn 9).[9,10] Catecholborane has also been prepared by the reduction of 2 - chloro - 1,3,2 - benzodioxaborole with tributyltin hydride.[29]



(9)

Catecholborane.[9] A 1.0 M solution of BH_3–THF in THF (200 ml, 200 mmol) is placed in a dry, nitrogen-flushed, 500-ml flask. The flask is vented to a hood through a mercury or mineral-oil bubbler. The reaction mixture is stirred in an ice bath and a solution of *o*-dihydroxybenzene (catechol) (22 g, 200 mmol) in THF (50 ml) is added over a 0.5–1 hr period to the borane solution. After completion of the addition, the reaction mixture is stirred at 25° for an additional 0.5–1 hr period. The solvent, THF, is then removed under reduced pressure (40–50 mm) at room temperature. Distillation of the colorless residue under nitrogen provided 16.8–19.2 g (70–80%) of catecholborane; b.p. 50° (26 mm), 76–77° (100 mm); n_D^{20} 1.5070, d 1.27.

Alternative preparations of related cyclic dialkoxyboranes have involved the reduction of a dialkoxychloroborane with sodium borohydride,[14] the reduction of a 2,2'-oxybis (1,3,2-dioxaborinane) with lithium aluminum hydride,[15] and numerous other reactions of less synthetic importance.[30]

Catecholborane displays remarkable stability when compared with other dialkoxyboranes such as **2**[12] and **3**[13] which undergo rapid disproportionation (eqn 4). Catecholborane shows no decomposition by GC analysis for up to 4 hr in refluxing THF solution or for up to 2 hr at 120° as a neat reagent.[9] A sample of catecholborane stored for 28 days at 25° showed an 11% loss in hydride activity.[31] But a sample stored for over one year at 0–5° showed no detectable loss in hydride activity and no observed deterioration by GC analysis.[28] Consequently, it is recommended that catecholborane should be stored in a cold room, where it slowly crystallizes.

A slow pressure build-up during room temperature storage of catecholborane has been observed in our laboratories and elsewhere.[31] When a sample of freshly prepared (eqn 6) catecholborane is stored at room temperature, the pressure within the system increases almost linearly with time for the first 20 days, then slows down and remains constant after 30 days.[31] This pressure build-up is not caused by diborane but is believed to be the result of hydrogen evolved by the slow reaction of catecholborane with an impurity.[31] The catecholborane available from Aldrich Chemical Company is allowed to stand until no further gas evolution is noted and then stored at 0–5°. Such properly aged material has shown no tendency to develop pressure during storage in a cold room for at least one year.

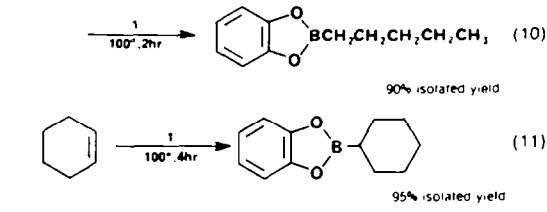
Catecholborane does not spontaneously ignite on exposure to air. However, air hydrolysis occurs with hydrogen evolution and with eventual formation of a white, water-soluble, unreactive residue. Catecholborane (**1**) is remarkably stable in dry air. Only a 6% loss of hydride activity is observed when a solution of **1** in THF is stirred in the presence of dry air at 25° for 8 hr.[9] The reagent undergoes rapid and quantitative hydrolysis with

hydrogen evolution upon injection into excess methanol at 20–25°. This reaction can be used for the quantitative analysis of **1** both neat and in solution.[32] The neat reagent shows a hydride concentration of ~10 M by gas evolution.

To maintain maximum hydride activity, catecholborane must be stored and handled without exposure to atmospheric moisture. Syringe and double-tipped needle transfer techniques are the most convenient. These techniques have been described in detail.[8,33] Cold catecholborane (m.p. *ca.* 10–12°) must be allowed to melt slowly at room temperature upon removal from cold storage before it can be transferred via syringe techniques. Also, since catecholborane is an active hydride, it must be handled with due care and skin contact should be avoided.

HYDROBORATION OF ALKENES[9,10]

Reaction of alkenes with catecholborane is very slow at 25°. Fortunately, at 100° (boiling water bath), the reaction rate is sufficiently rapid so that hydroboration becomes a practical synthetic procedure. The yields of the desired alkaneboronic esters are virtually quantitative when a 10% excess of **1** is used. Specific examples are listed in eqns (10) and (11).



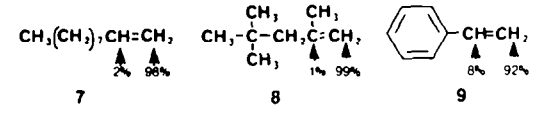
(10)

(11)

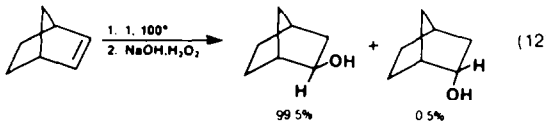
As a standard procedure, internal alkenes are allowed to react with the neat reagent for 4 hr at 100° to give a >98% GC yield of the alkaneboronic ester. Only 2 hr at 100° is required for terminal alkenes. With low boiling alkenes, a sealed ampoule is required to reach the 100° reaction temperature.

B - exo - Norbornylcatecholborane.[9] A 100-ml single-necked flask equipped with a septum inlet, magnetic stirring bar, and outlet tube connected to a mercury bubbler is flushed with nitrogen and charged with 9.4 g (100 mmol) of norbornene. After reflushing the system with nitrogen, 13.2 g (110 mmol) of **1** is added using a dry syringe. The resulting mixture is then stirred for 4 hr at 100°. Direct vacuum distillation using a dry, nitrogen-flushed apparatus provides 20.3 g (95%) of 2 - *exo* - norbornyl - 1,3,2 - benzodioxaborole; b.p. 104° (0.5 mm).

The regioselectivity observed for BH_3–THF in the hydroboration of alkenes is influenced by both steric and electronic effects.[3] For example, hydroboration of a monosubstituted terminal alkene with BH_3–THF proceeds to place the B atom preferentially at the terminal position (94%). Hydroboration of a disubstituted terminal alkene with BH_3–THF proceeds even more selectively to place the boron atom almost exclusively at the terminal position (99%). The powerful electronic directive effect of a phenyl substituent is illustrated by the hydroboration of styrene with BH_3–THF which results in only 81% of the 2-phenylethyl product. A study of directive effects in the hydroboration of alkenes with catecholborane showed that **1** is somewhat more sensitive to steric effects than BH_3–THF, i.e. a higher percentage of B substitution is observed at the less hindered C atom of the alkene. Interestingly, catecholborane is less sensitive to the electronic influence of a phenyl substituent, i.e. a lower percentage of B substitution is observed at the benzylic position. These results are illustrated for 1-decene (**7**), 2,4,4 - trimethyl - 1 - pentene (**8**) and styrene (**9**). The percentage given is the amount of alcohol product observed by GC analysis after hydroboration with **1** followed by standard alkaline hydrogen peroxide oxidation.



Hydroboration of alkenes with catecholborane shows a stereoselectivity comparable to that observed for BH_3–THF. For example, hydroboration–oxidation of norbornene with catecholborane gives predominantly *exo*-norborneol by both GC and NMR analysis (eqn 12).

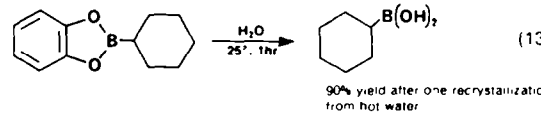


(12)

Hydroboration of alkenes with **1** provides a facile and highly convenient procedure for the preparation of 2 - alkyl - 1,3,2 - benzodioxaboroles (B-alkylcatecholboranes). Some interesting applications in organic synthesis have been reported for these alkaneboronic esters.

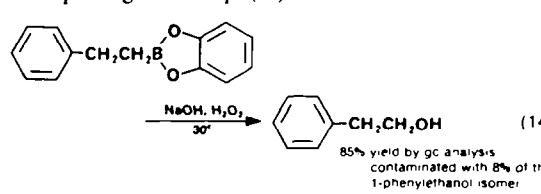
SYNTHETIC APPLICATIONS OF B-ALKYLCATECHOLBORANES

B-Alkylcatecholboranes undergo rapid hydrolysis upon stirring with excess water at 25°.[9,10] The water-insoluble, crystalline alkaneboronic acid is easily removed from the highly water-soluble catechol by-product. Simple filtration gives an essentially quantitative isolated yield of the boronic acid in excellent purity (eqn 13).



(13)

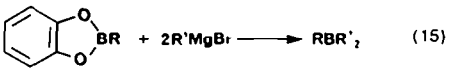
B-Alkylcatecholboranes can be oxidized to alcohols with alkaline hydrogen peroxide if sufficient excess sodium hydroxide is added to react with the liberated catechol to form the corresponding phenolate.[9] A specific example is given in eqn (14).



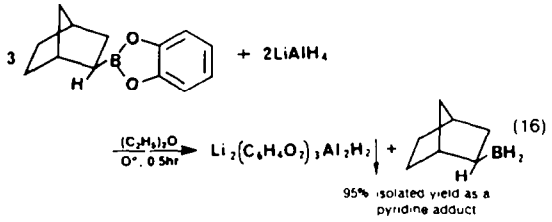
(14)

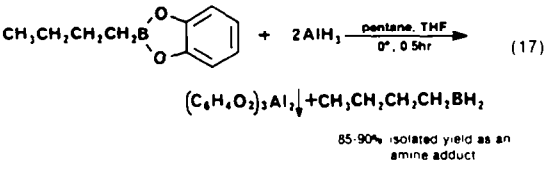
The most important potential use for these B-alkylcatecholborane derivatives is for the preparation of "mixed" trialkylboranes (RBR'_2) which are difficult or impossible to prepare via direct hydroboration with BH_3–THF. These mixed trialkylboranes could prove to be important intermediates in the various synthetic transformations that are possible for organoboranes.[4–6,8]

One method for converting B-alkylcatecholboranes to trialkylboranes is their direct reaction with an alkylmagnesium reagent (eqn 15).[34]



However, a more versatile approach involves the reduction of B-alkylcatecholboranes with either lithium aluminum hydride (LAH) or aluminum hydride.[35] The corresponding monoalkylborane is formed in nearly quantitative yield (eqn 16 and 17).[35,36]

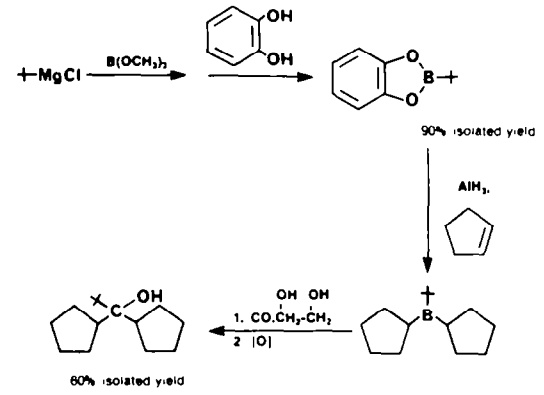




These monoalkylboranes can then be used to prepare mixed trialkylboranes via direct hydroboration of alkenes.[35]

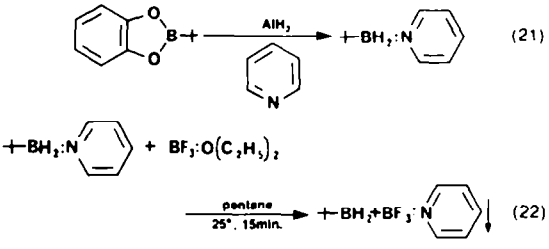
In the reduction using LAH (eqn 16), the lithium aryloxyaluminohydride precipitate retains reactive hydride. Consequently, it must be removed by filtration if the monoalkylborane is used for the hydroboration of alkenes containing reducible functional groups. The aluminum hydride[37] procedure (eqn 17) circumvents the need for this separtion. Thus, the reaction mixture can be used directly to hydroborate functionally substituted alkenes (eqns 18–20).[35]

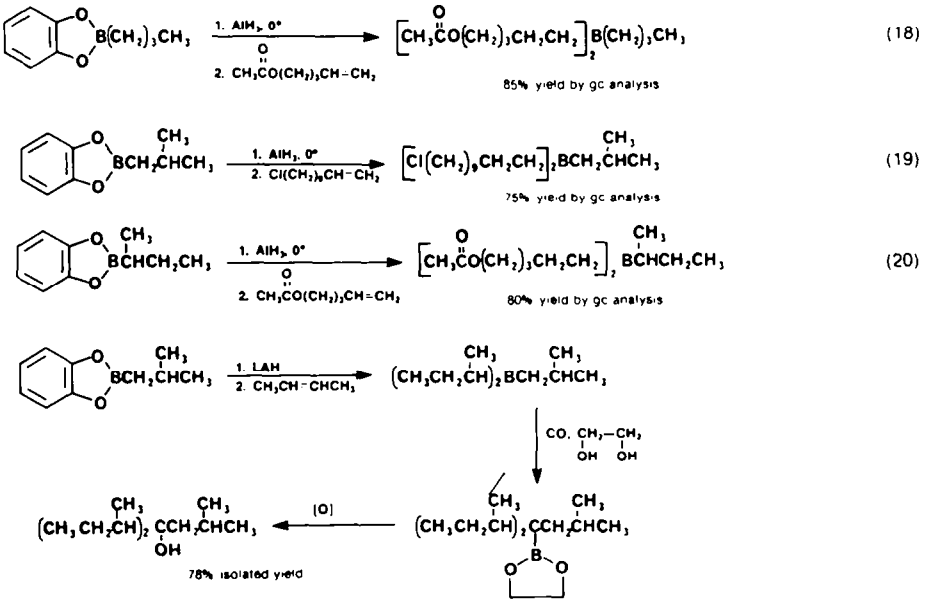
An important synthetic application for these mixed trialkylboranes is conversion into trialkylmethanols via carbonylation (Scheme 1).[38] t-Butylcatecholborane can also be prepared and then converted into a highly branched trialkylmethanol using a related process (Scheme 2).[39]



Scheme 2.

These monoalkylboranes should be utilized as soon as formed, or they should be prepared in the presence of the alkene as shown in Scheme 2. Fortunately, they can be transformed into a relatively stable derivative by carrying out the reduction in the presence of pyridine (eqn 21).[35,39,40] These monoalkylborane–pyridine complexes can be isolated by distillation if desired. They are readily converted to the reactive, free monoalkylborane by treatment with boron trifluoride etherate (eqn 22).[35,39]



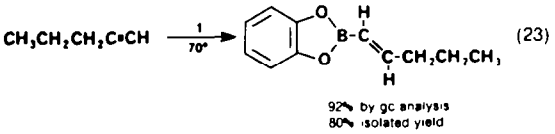


Scheme 1.

These developments, based on catecholborane, provide the first general and convenient synthesis of monoalkylboranes. Numerous transformations are possible for mixed trialkylboranes. Thus, these monoalkylboranes should be of considerable synthetic importance as reaction intermediates.

HYDROBORATION OF ALKYNES[9,11]

Catecholborane reacts only sluggishly with alkynes at 25°. However, hydroboration proceeds at a satisfactory rate at 70° with the neat reagent. Terminal alkynes undergo hydroboration at a rate faster than that observed for internal alkynes. Terminal alkynes require 1 hr at 70° while internal alkynes require 2–4 hr at 70°. The reaction proceeds in a highly satisfactory manner giving nearly quantitative GC yields of the desired 2-alkenyl - 1,3,2 - benzodioxaboroles without any observable dihydroboration (eqns 23 and 24).



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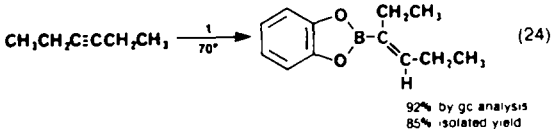
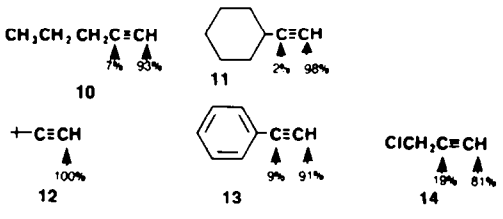


(24)

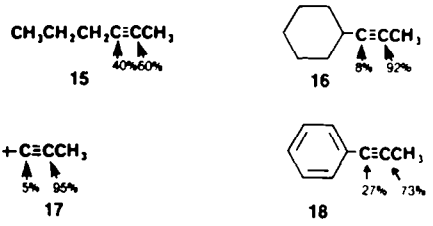
The B-alkenylcatecholboranes are readily isolated by distillation and can be stored under nitrogen for prolonged periods without polymerization or disproportionation.

B - cis - (2 - *Cyclohexyl* - 1 - *methyl)ethenylcatecholborane.*[9] A 100-ml single-necked flask equipped with a septum inlet, magnetic stirring bar, and outlet tube connected to a mercury bubbler is flushed with nitrogen and charged with 12.2 g (100 mmol) of 1-cyclohexylpropyne and 12.0 g (100 mmol) of **1** using a dry syringe. The resulting mixture is then stirred for 4 hr at 70°. Direct vacuum distillation using a dry, nitrogen-flushed apparatus provides 20.8 g (86%) of *cis* - 2(2 - cyclohexyl - 1 - methyl)ethenyl - 1,3,2 - benzodioxaborole; b.p. 124° (0.15 mm), n_D^{20} 1.5400.

Hydroboration of alkynes with catecholborane involves a stereospecific *cis* addition with the B atom being attached regioselectively to the least hindered C atom of the triple bond. Using NMR to determine the presence of isomeric products, 1-pentyne (**10**) gave only 93% of the terminal hydroboration product. Cyclohexylethyne (**11**), with the bulkier cyclohexyl substituent, gave predominantly the terminal hydroboration product. 3,3 - Dimethyl - 1 - butyne (**12**) gave only terminal substitution. In addition to steric effects, electronic effects are also important in directing the bonding of the B atom. For example, phenylethyne (**13**) and 3-chloropropyne (**14**) show significant quantities of the internal substitution product.



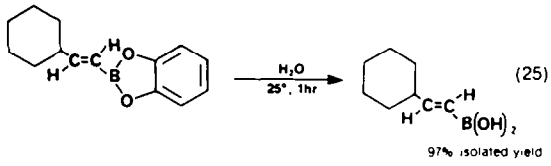
Even with internal alkynes, a pronounced steric effect is observed wherein the B atom is preferentially bonded to the C atom at the less hindered position of the triple bond. This steric effect is illustrated for 2-hexyne (**15**), 1-cyclohexylpropyne (**16**) and 4,4 - dimethyl - 2 - pentyne (**17**). The relative percentage of B substitution is given. The electronic effect of a phenyl substituent partially overcomes the steric effect as shown by the hydroboration of 1 - phenyl - propyne (**18**) with catecholborane. Obtained is a considerable quantity (27%) of the product which results from attachment on the C atom carrying the phenyl ring.



It is now evident that the hydroboration of alkynes with catecholborane provides a facile and highly convenient procedure for the regioselective and stereospecific synthesis of 2 - alkenyl - 1,3,2 - benzodioxaboroles (B-alkenylcatecholboranes). A number of interesting and synthetically useful applications have been reported for these alkeneboronic esters.

SYNTHETIC APPLICATIONS OF B-ALKENYLCATECHOLBORANES

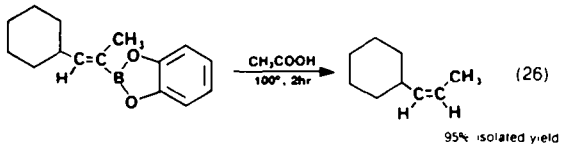
B-Alkenylcatecholboranes undergo rapid hydrolysis upon stirring with excess water at 25° (eqn 25).[9] The alkeneboronic acids are usually crystalline solids of low



(25)

solubility in water and can be conveniently isolated and handled in air without significant deterioration.[41] Since the catechol by-product is highly soluble in water, simple filtration provides the alkeneboronic acid in essentially quantitative yield and in high purity.

Protonolysis and deuterolysis of B-alkenylcatecholboranes proceed readily providing simple, stereospecific syntheses of alkenes (eqns 26 and 27).[9,11]



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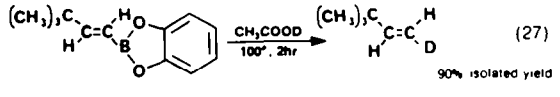
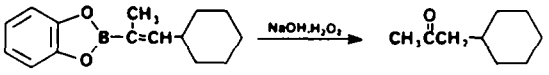


(27)

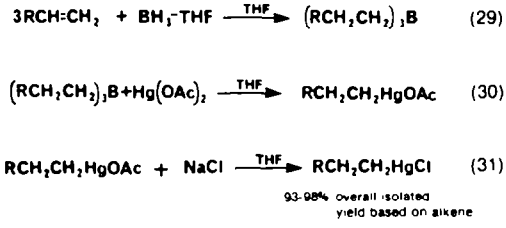
B-alkenylcatecholboranes derived from terminal alkynes could conceivably be oxidized with alkaline (pH 7–9) hydrogen peroxide.[9] Unfortunately, a detailed synthetic procedure is not available. A similar oxidation of B-alkenylcatecholboranes derived from internal alkynes permits a ready synthesis of ketones (eqn 28).[9,11]



(28)

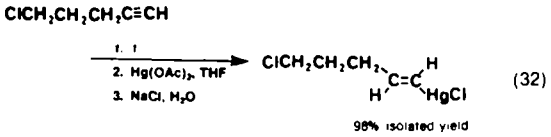
Pyridine reacts rapidly with B-alkenylcatecholboranes to form stable, crystalline 1:1 addition compounds.[9] These complexes can serve as readily identified solid derivatives of B-alkenylcatecholboranes.

Mercury(II) salts are known to react with alkaneboronic acids, alkeneboronic acids, and trialkylboranes to yield a variety of organomercurials. This reaction was used in the development of a convenient hydroboration-mercuration procedure for the conversion of alkenes to alkylmercuric salts (eqns 29–31).[42] A similar



process was utilized for the conversion of terminal alkynes to geminal dimercurials.[43] However, a hydroboration-mercuration procedure has not been developed for the conversion of alkynes to alkenylmercuric salts using BH_3–THF as the hydroboration reagent.[44]

The discovery that catecholborane (1) readily hydroborates alkynes provided a new and convenient route to alkenylmercurials via a hydroboration-mercuration procedure.[45] The mercuration reaction proceeds stereospecifically with retention of configuration. A few representative examples are shown in (eqns 32–34) along with the isolated yields based on distilled B-alkenylcatecholborane.[45]



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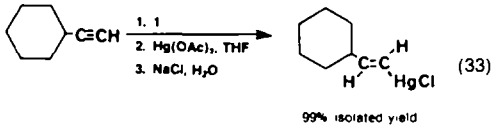

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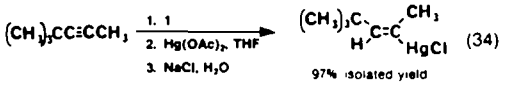
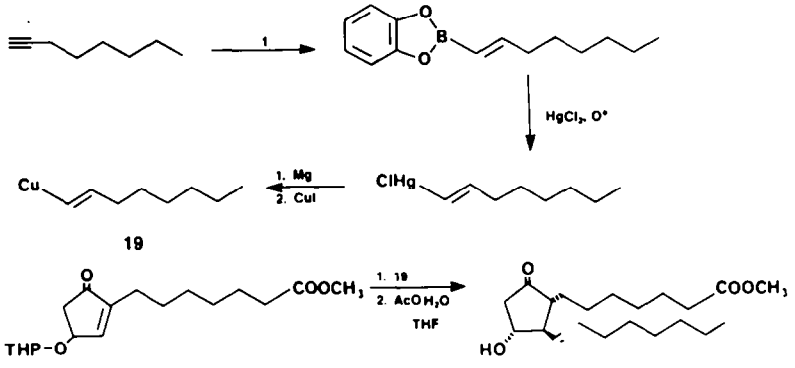


(34)

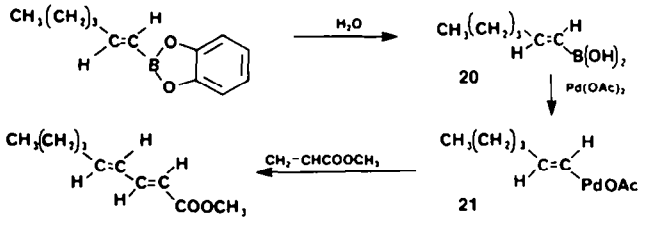
This stereospecific preparation of alkenylmercurials should prove to be very important in organic synthesis. These stable, easily handled compounds can be used directly for the preparation of other alkenyl-metallics. For example, an alkenylmercurial was recently prepared by this procedure and converted into an alkenylcopper reagent (**19**). Reagent **19** was then used in the synthesis of a prostaglandin analog (Scheme 3).[46]

Another metallation reaction was recently reported.[47] *trans*-Hexenylboronic acid (**20**) reacts readily with palladium acetate in the presence of methyl acrylate to give a good yield of the corresponding methyl *trans, trans*-2,4 - nonadienoate.[47] The process (Scheme 4) is believed to involve a stereospecific conversion of **20** to *trans*-hexenylpalladium acetate (**21**). A stoichiometric amount of palladium acetate is required. Consequently, the practical synthetic utility of this interesting diene synthesis is somewhat limited. A related process using an alkenyl halide requires only a catalytic amount of palladium acetate.[47]

An even more important potential synthetic application for B-alkenylcatecholboranes and alkeneboronic acids resulted from a study of the halogenation of these easily



Scheme 3.

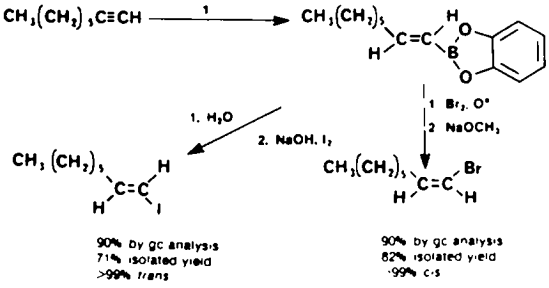


Scheme 4.

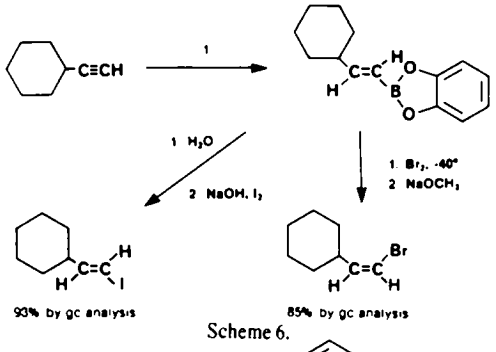
prepared derivatives. Reaction of alkeneboronic acids with iodine in the presence of base gives alkenyl iodides with *retention of configuration*.[48] Reaction with bromine followed by treatment with base gives alkenyl bromides with *inversion of configuration*.[49] Thus, it is now very easy to convert a terminal alkyne into either a *trans*-alkenyl iodide or into a *cis*-alkenyl bromide.

The stereochemical purities were determined by GC analysis.[50] Separation of *cis*- and *trans*-alkenyl iodides was carried out using a 12 ft × 1/4 in. column packed with 20% SE-30 on DMCS treated Chromosorb W. A 2 ft × 1/4 in. column packed with 15% Carbowax 20 M and 0.4% Asmac 18D on Chromosorb W was used to separate *cis*- and *trans*-alkenyl bromides. The identification of the product was done by comparison of the GC retention times with authentic samples or by actual isolation by preparative GC followed by characterization by ir (~700 cm^{-1} for *cis*-isomer, 940–960 cm^{-1} for *trans*-isomer), NMR and mass spectrometry.[50]

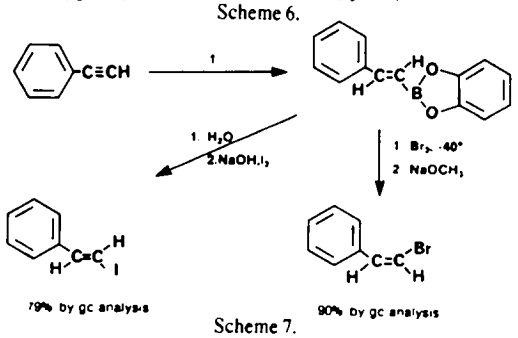
A few specific examples are given in Schemes 5–7. The yields are based on starting alkyne. In all cases, the stereochemical purity of the product is >99% by GC analysis, and there is no question as to the validity of the stereochemical assignments.[50] The stereochemical results are quite remarkable and seem to indicate that two different mechanisms must be involved in these interesting halogenation reactions. Brown and coworkers have proposed possible mechanisms which are capable of explaining the stereochemical results.[49]



Scheme 5.

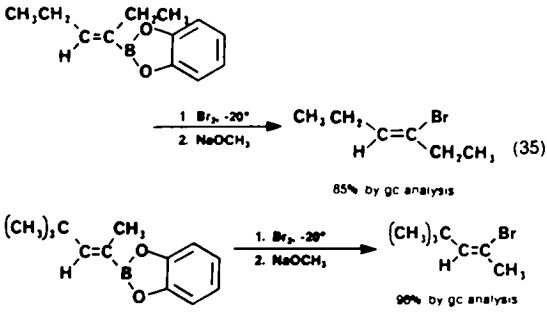


Scheme 6.



Scheme 7.

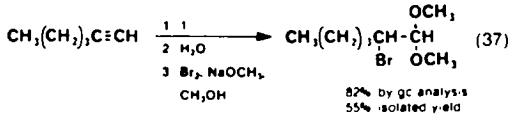
The reaction of alkenylboronic acids derived from internal alkynes with iodine and base fails to give the desired alkenyl iodide. However, the reaction of alkenylboronic acids and esters with bromine followed by base is a general reaction which can also be used to convert internal alkynes into alkenyl bromides. Inversion of configuration again occurs giving a product with a stereochemical purity of >99%. Two examples are shown in eqns (35) and (36) along with yields based on starting alkynes.[49]



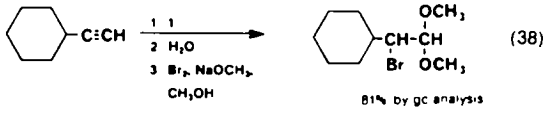
(35)

(36)

1-Alkenylboronic acids are used in the synthesis of *trans* - 1 - iodoalkenes.[48] For the preparation of *cis* - 1 - bromoalkenes, the catechol ester of the alkenylboronic acid can be used directly.[49] When the bromine is first added to the alkenylboronic acid, followed by sodium methoxide, an essentially quantitative yield of pure bromoalkene is obtained.[49] Unexpectedly, bromination in the presence of sodium methoxide in methanol results in the formation of the corresponding alpha-bromo dimethyl acetal.[51] Equations (37) and (38) give two examples. The yield given is based on alkyne.

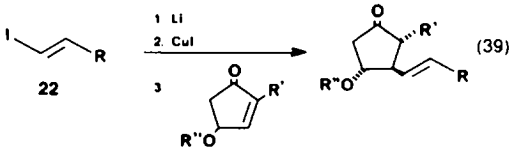


(37)



(38)

The most important use for the alkenyl halides is in the preparation of alkenylmagnesium[12] and alkenyllithium reagents.[53] Fortunately, these reagents are formed stereospecially and react with overall retention of the stereochemistry present in the original alkenyl halide.[52,53] Various *trans*-1-alkenyl iodides proved to be particularly useful in a number of the recently reported syntheses for prostaglandins.[54] All these syntheses contain, as one of the key steps, the conversion of an alkenyl iodide to an alkenyllithium reagent followed by the conjugate addition of the alkenylcuprate to a substituted cyclopentenone with overall retention of stereochemistry (eqn 39).



(39)

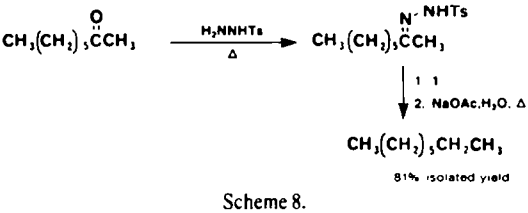
The R group in 22 is usually substituted with a 3-alkoxy group which could influence the direction of hydroboration in the alkyne precursor. The alkenyl iodide 22 might contain a significant amount of the undesired 2-iodo isomer if hydroboration with catecholborane is used in the preparation of 22. Thus, in this specific case, the hydroalumination-iodination procedure may prove to be the method of choice.

REACTIVITY TOWARDS VARIOUS FUNCTIONAL GROUPS

The synthetic utility of B-alkyl-and B-alkenylcatecholboranes is enhanced by the fact that a number of functional groups may be incorporated into the molecules via hydroboration of appropriately substituted alkenes and alkynes. However, certain functional groups might be expected to undergo reduction under hydroboration conditions. Consequently, a knowledge of the reducing properties of catecholborane is important before this reagent should be used for the hydroboration of a functionally substituted alkene or alkyne.

As expected, catecholborane is a milder reducing agent than diborane[55] or dialkylboranes.[56] This diminished reactivity is a consequence of the lower Lewis acidity of boron in boronic esters, which apparently is a result of electron donation from oxygen.

Published results concerning the reducing properties of catecholborane are limited.[57,58] However, some interesting results have recently become available.[59] These investigations seem to indicate that catecholborane is a useful new reducing agent. For example, tosylhydrazones are readily reduced with catecholborane,[57] providing a mild alternative to the Wolff–Kishner process (Scheme 8).



Scheme 8.

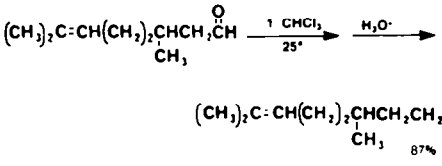
Catecholborane is one of the most convenient boron hydride reducing agents available due to its thermal stability and solubility characteristics. Catecholborane reductions can be carried out in carbon tetrachloride, chloroform, benzene, toluene, diethyl ether, and THF as well as in the absence of solvent. The rate of reduction of a specific functional group varies only slightly in these solvents with the fastest rate being obtained in a THF solution. For example, in THF at room temperature, heptanal is reduced to 1-heptanol in 4 hr while the reduction requires 5.5 hr in chloroform (0.5 M in each reactant).

Hydroboration reactions utilizing catecholborane demonstrate the largest variations in rate among the various solvents. At room temperature 1-octene does not react with catecholborane in chloroform but slowly undergoes hydroboration in THF. Alkynes react with catecholborane in both chloroform and THF, although the rate of hydroboration is faster in THF. For example, in THF at room temperature, the hydroboration of 1-hexyne requires 4 days while the reaction is only 60% complete in chloroform (0.5 M in each reactant). Interestingly, when one equivalent of catecholborane was used in chloroform, it was possible to achieve a selective hydroboration of 1-hexyne in the presence of cyclohexene.

A large number of functional groups do not react with catecholborane. Alkyl and aryl halides, nitro groups, sulfones, disulfides, thiols,[60] primary amides, ethers, sulfides, and alcohols[60] are insensitive to the reagent. Hydroboration of alkenes and alkynes containing these functionalities should proceed in a straightforward fashion provided the functional group is at least two carbon atoms removed from the alkene or alkyne linkage. As in all hydroboration reactions, the regioselectivity of the reaction is influenced by the proximity of functional groups.[61,62] Also, substrates which contain a B atom α, β or γ to an appropriate leaving group are prone to undergo a facile rearrangement, elimination, or cyclization reaction.[4]

Nitriles, esters, and acid chlorides react slowly with catecholborane.[59] The hydroboration of alkenes and alkynes containing these functional groups should be carefully monitered since a simultaneous reduction may occur. It is difficult to predict the extent of reduction vs hydroboration but it does appear that alkynes containing a nitrile, ester, or acid chloride group can be hydroborated with only a modest amount of concurrent reduction. For example, 1-hexyne undergoes complete hydroboration with catecholborane in THF at reflux in approximately 24 hr (0.5 M in each reactant). Under similar conditions, ethyl butyrate is only 30% reduced (0.5 M in ester and 1.0 M in catecholborane). Likewise, acetonitrile is incompletely reduced after as long as 5 days in THF at reflux when the concentration of nitrile is 0.5 M and the catecholborane is 1.5 M.

Certain functional groups are readily reduced by catecholborane[57,59] and would not be expected to survive a hydroboration reaction. Aldehydes, imines, ketones and sulfoxides are reduced in a few hours at room temperature. In these case, it may occasionally be possible to reduce the functional group without concomitant hydroboration of an alkene or alkyne linkage. Thus, citronellal is reduced to the unsaturated alcohol with catecholborane (eqn 40).[59]



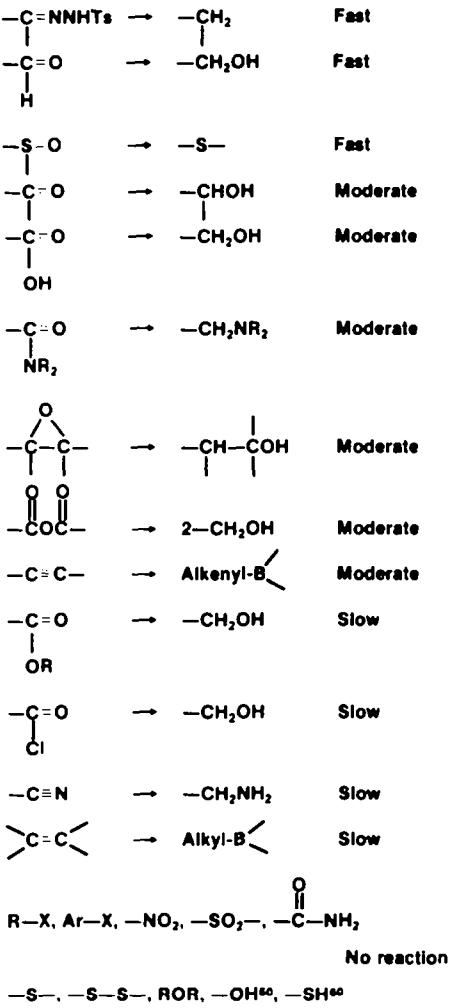
(40)

With other derivatives neither a competitive reduction nor hydroboration is possible directly with catecholborane. Carboxylic acids, N,N-dialkylamides, acid anhydrides, and epoxides are reduced fairly rapidly with catecholborane, requiring approximately 24 hr at room temperature. This rate is faster but still comparable to the rate of hydroboration of alkynes.

Scheme 9 summarizes the reactivity of various functional groups towards catecholborane and should serve as a convenient guide to determine when hydroboration of a functionally substituted alkene or alkyne is possible. However, it must be realized that the relative reactivities are presented only in a general sense and may be altered by modifications in the molecular structure. Also, as expected, the rates are dependent upon concentration and temperature.

CONCLUSIONS

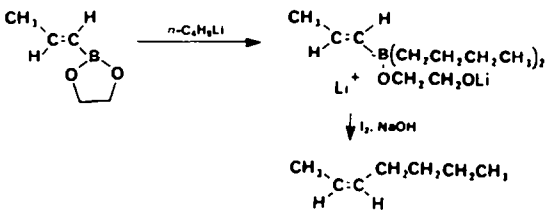
Obviously, catecholborane is a useful hydroboration reagent. The reaction of 1 with alkenes and alkynes provides the first convenient and general synthesis of



Scheme 9. Relative reactivity of catecholborane towards various functional groups.

alkane- and alkeneboronic esters and acids. Many new and exciting synthetic applications have already been discovered for these boronic acid derivatives. With the commercial availability of catecholborane, many additional applications should follow.

Some promising reactions and observations have been reported for analogous systems which should be applicable to catecholborane and its derivatives. For example, Matteson recently reported an interesting *cis*-alkene synthesis (Scheme 10).[63] B-alkenylcatecholboranes could probably also be used for this reaction as well as other alkyllithium reagents. The dialkoxyborane 4 is useful as a blocking agent for active hydrogens.[64] This is also an obvious potential application for catecholborane. Finally, recent investigations have shown that catecholborane is a useful new reducing agent.[57-59]



Scheme 10.

Undoubtedly future developmental efforts will uncover additional areas where this promising new hydroboration reagent can be utilized to solve problems in organic synthesis.

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