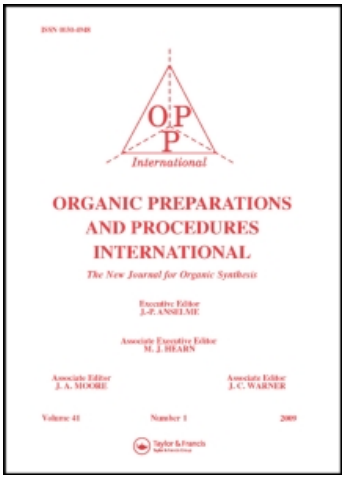


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# CATECHOLBORANE IN ORGANIC SYNTHESIS. A REVIEW

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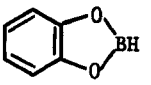
## INTRODUCTION

The utility of diborane and its complexes in organic synthesis has been well documented.[1-4] In recent years a number of substituted borane reagents have been developed and are commercially available.[5-6] The stability and reactivity of the substituted boranes vary dramatically. In general the alkyl substituted borane reagents are more regioselective and stereoselective than the simple borane complexes.[5,7-9] The non-alkylated substituted boranes are less reactive than the borane complexes (as well as the alkylsubstituted boranes) and are often utilized when selectivity is an important factor.[10-11]

One of the more useful substituted boranes is 1,3,2-benzodioxaborole, 1, commonly referred to as catecholborane. Catecholborane is an

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air-stable, moisture sensitive liquid (bp. 76-77/100mm), soluble in nearly all aprotic solvents. It exhibits greatly reduced reactivity relative to the borane complexes and the alkylated boranes. Presumably, the diminished reactivity is a consequence of electron delocalization from the oxygens to boron. This reduced reactivity makes catecholborane valuable in selective reductions and hydroborations.

Catecholborane has some practical advantages over other commonly used borane reagents.

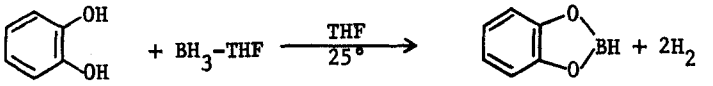
(1) It is a liquid at room temperature and may be used without solvent.

(2) It is soluble and stable in all common aprotic solvents.

(3) It is stable in dry air.

(4) It may be stored for over a year at 0° with no apparent change.

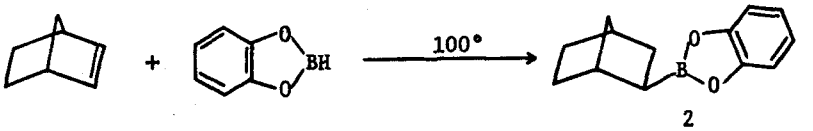
As a hydroborating agent, catecholborane's main disadvantage is its reduced reactivity.[12] It is, however, the reagent of choice in a number of synthetic reactions.[13-15] Catechlborane is readily prepared by the reaction of catechol dissolved in tetrahydrofuran (THF) with borane-THF.




Catecholborane.-A 1.0 M solution of $BH_3$-THF in THF (200 ml, 200 mmols) 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) (22g, 200 mmols) 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 provides 16.8-19.2g (70-80%) of catecholborane; bp. 50°/26 mm, 76-77°/100 mm; $n_D^{20}$ 1.5070, d 1.27.

## 1.-HYDROBORATION

The reaction of catecholborane with alkenes and alkynes is very slow at 25°.[10,12] The reactions do proceed at elevated temperatures so that hydroborations are practical in numerous instances (100° for alkenes and 70° for alkynes). The yields of the boronic esters are essentially quantitative.

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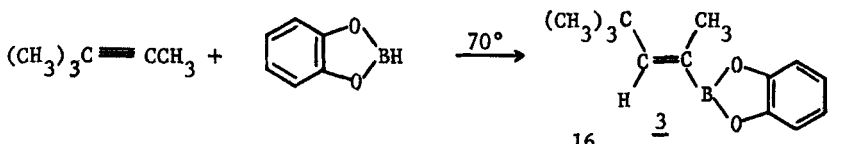


2-exo-Norbornyl-1,3,2-benzodioxaborole (2)[16].-A 100 ml single necked flask equipped with a septum inlet, a magnetic stirring bar and an outlet tube connected to a mercury bubbler is flushed with nitrogen and charged with norbornene (9.4g, 100 mmols). Catecholborane (13.2g, 110 mmols) is added via syringe. The mixture is stirred for 4 hrs at 100°. Direct vacuum distillation (with careful exclusion of air) provides 20.3g (95%) of the product; bp. 104°/0.5 mm.

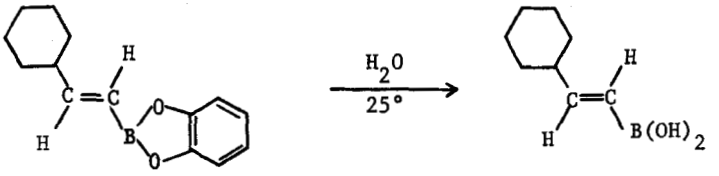
cis-2-(2-t-Butyl-1-methyl)ethenyl-1,3,2-benzodioxaborole (3)[12].-4,4-Dimethyl-2-pentyne (9.6g, 100 mmols) is hydroborated with catecholborane (12g, 100 mmols) providing 18.4 g. (85%) of the product, bp. 86°/0.5 mm. The isomeric 3-alkenyl-1,3-2-benzodioxaborole is formed in 4% yield.

The hydroboration of alkynes with catecholborane involves the stereospecific cis addition of the boron hydrogen moiety.[12] Thus catecholborane exhibits the same stereochemical control reported for all other hydroborating reagents.[5]

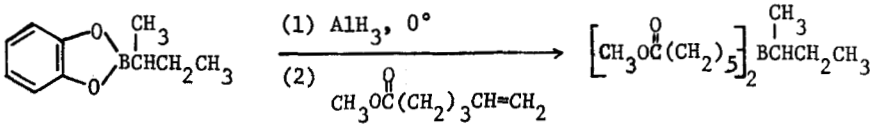
All known hydroborating reagents are regioselective. The boron atom is preferentially placed at the less hindered carbon atom. The regioselectivity is mainly a consequence of steric interactions but electronic effects can become important in certain instances and alter the regiochemistry of the reactions.[2,17] Catecholborane is somewhat more regioselective than borane complexes in the hydroboration of alkenes and alkynes.[12] It does not appear to be quite as regioselective as the dialkylborane reagents such as disiamylborane or 9-borabicyclo[3.3.1]-nonane.[18,19] As an example, it was noted earlier that 4,4-dimethyl-2-pentyne produces an isomeric mixture of the 2- and 3-boraethenes in a 95:5 ratio. The analogous reaction with the borane-THF complex yields the 2- and 3-boraethenes in a 71:29 ratio whereas the reaction with

disiamylborane produces a 97:3 ratio of isomers.[18]

The alkyl and alkenylbenzodioxaboroles which are formed via hydroborations utilizing catecholborane have proven to be valuable synthetic intermediates. They are a ready source of alkyl and alkenylboronic acids due to their facile hydrolysis.[12,13]

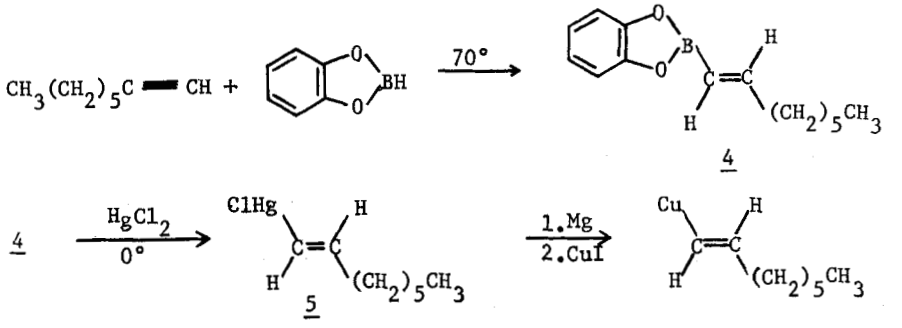


The alkyl derivatives have been used as a source of monoalkylboranes which can then be isolated as their amine complexes[13,20] or used as intermediates in the preparation of mixed trialkylboranes.[13]



The alkenyl derivatives have proven to be useful intermediates. Deuteration (or protonation) produces alkenes of known stereochemistry whereas oxidation produces the corresponding carbonyl compounds.[21]

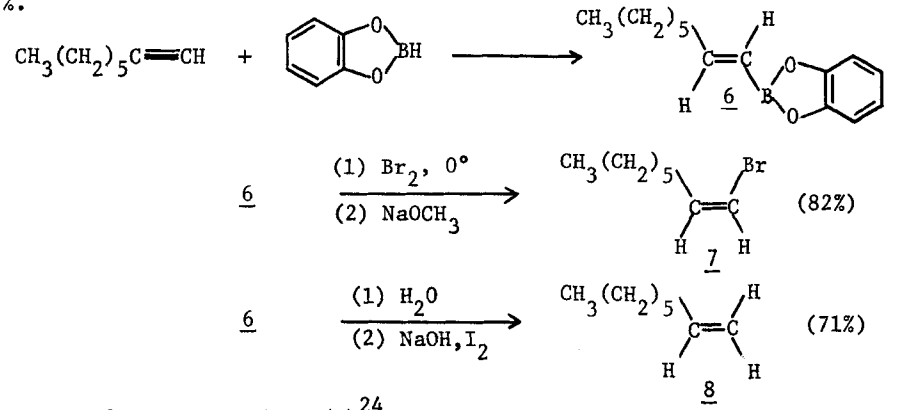
A number of transmetallation reactions have been reported which involve catecholborane.[14,22-23]



cis-4,4-Dimethyl-2-pentenylmercuric Chloride (5).-A solution of cis-2-(2-t-butyl-1-methyl)ethenyl-1,3,2-benzodioxaborole (25 mmols) is prepared as described earlier (p. 135). The solution is cooled to 0°

under a nitrogen atmosphere. Mercuric acetate (7.97g, 25 mmols) is added to the solution. The mixture is stirred until the mercuric acetate has disappeared (a few minutes) and then the solution is poured into 100 ml of ice-water containing 25 mmols of NaCl. The THF is removed and the white solid filtered, washed with water and dried in vacuo. The product is obtained in 97% yield (8.04g); mp. 108-108.5°.

The halogenation reactions of the alkenylbenzodioxaboroles have proven to be most useful. Reaction of these reagents with bromine in the presence of base proceeds with inversion of configuration[15] whereas iodination in the presence of base proceeds with retention of configuration.[24] In all cases, the stereochemical purity of the product exceeds 99%.[24]

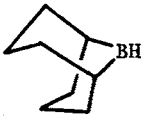



trans-1-Octenyl Iodide (8)[24].-As described earlier a 100 ml single-necked, nitrogen flushed flask is charged with 1-octyne (6g, 50 mmols) and catecholborane (55g, 50 mmols). The mixture is stirred for 2 hrs at 70° (to form the boronic ester) and then cooled to 0°. The white solid is collected by filtration, washed free of catechol using ice-cold water and then dissolved in 50 ml of ether. The ethereal solution is cooled to 0°, aqueous NaOH (50 ml, 3N) added followed by a solution of iodine in ether (60 mmol of $I_2$ in 150 ml of ether). The mixture is stirred at 0° for 0.5 hr. and then an aqueous sodium thiosulfate is added to destroy excess iodine. The ethereal solution is separated, washed with water and dried over anhydrous magnesium sulfate. Distillation yields 16.9g (71%) of the trans product, bp. 58°/0.2 mm.

## 2.-REDUCTIONS

The utility of hydrides in organic synthesis has been demonstrated repeatedly. The complex metal hydrides were the first to be exploited for selective reductions of organic compounds.[25] The most frequently used reagents of this type are sodium borohydride[26] and lithium aluminum hydride,[27] although in recent years, derivatives of these reagents have proven useful in selective reductions.[28,29] It has also become obvious that borane reagents can compete favorably with the complex metal hydrides as reducing agents.[4,6,30-32] The reactions of the borane reagents often parallel those of the complex metal hydrides but, in a number of important instances, their reactions are sometimes quite different. The differences arise because the borane reagents are electron-deficient; being Lewis acids, they attack the electron-rich center in the functional group. Conversely, the complex metal hydride reagents attack the electron-deficient center in the functional group.

The alkyl substituted boranes exhibit reducing characteristics similar to the borane complexes such as $BH_3 \cdot THF$ or $BH_3 \cdot S(CH_3)_2$. In general, the alkyl substituted reagents such as 9-BBN (9) and disiamylborane (10) are most frequently used since they are commercially available and readily prepared.[31-32] The increased steric requirements of the dialkyl substituted boranes often leads to increased selectivity in their reactions.[6]

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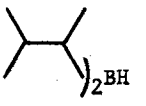


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Catecholborane is the least reactive of the readily available borane reagents.[33] A consequence of this lessened reactivity, is an increased selectivity as compared to the other borane reagents. Catecholborane

reduces most of the functional groups that the other boranes reduce but at diminished rates.

Carbonyl groups and hydroazones are readily reduced by catecholborane. In fact they are reduced faster than alkenes and alkynes (hydroboration) which makes it possible to reduce carbonyl groups or hydrazones in the presence of alkenes and alkynes. [CB represents catecholborane.]

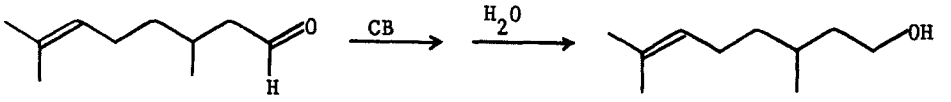


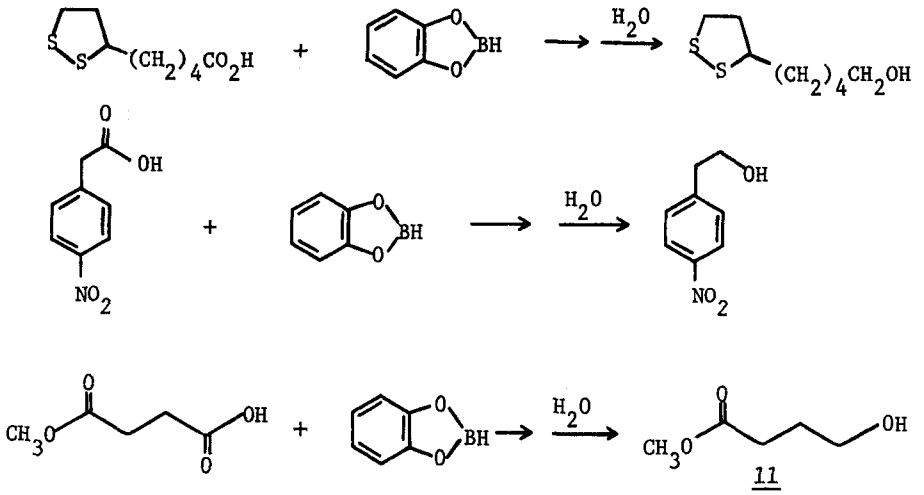

Table I summarizes the reducing properties of catecholborane. The rates of the reductions may be increased by raising the temperature or increasing the concentration of hydride. It is noteworthy that catecholborane will reduce carboxylic acid salts which is not possible with other borane reagents.



1-Hexadecanol[33].-Palmitic anhydride (2.15g, 4.32 mmols) is placed in a dry, nitrogen flushed 25 ml flask, fitted with a magnetic stirring bar, septum inlet and an outlet tube connected to a mercury bubbler. Chloroform (70 ml) is then added followed by the dropwise addition of catecholborane (2.03 ml, 18.6 mmols). The mixture is refluxed until the reaction is complete (3 days). The solution is extracted with 6x25 ml of 1.0 N NaOH to remove catechol, dried over anhydrous magnesium sulfate and separated *via* column chromatography (silica gel, 60-200 mesh). The hexadecanol is eluted using a ligroin-ether mixture (98:2) and is the first material eluted. The isolated yield is 96% (2.02g, 8.24 mmols).

Catecholborane differs from the borane complexes in that it does not reduce esters and primary amides at room temperature. Carboxylic acids are reduced but less readily than aldehydes, ketones, and hydrazones.

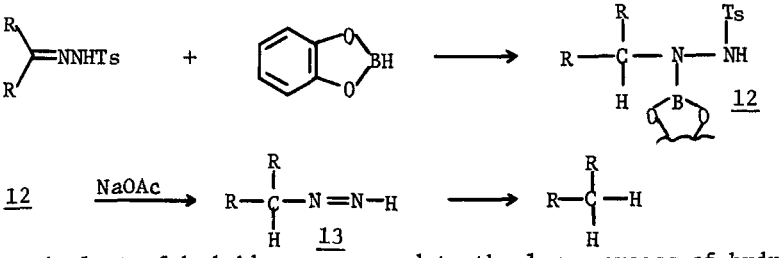
Catecholborane has been shown to be quite versatile in selective reductions.[33]



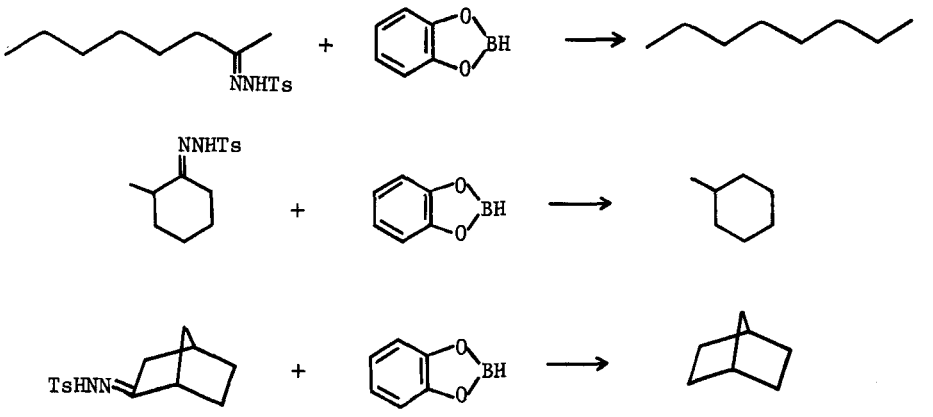
Methyl Ester of 4-Hydroxybutanoic Acid (11).-The monomethyl ester of succinic acid (3.6g, 25 mmols) is dissolved in chloroform (50 ml) contained in a dry, nitrogen flushed, 100 ml flask fitted with a septum inlet and a magnetic stirring bar. Catecholborane (8.6 ml, 80 mmols) is then added and the reaction mixture refluxed for 48 hrs. Sufficient methanol is added to free the product. NMR analysis indicates a 95% (3.0g) yield of the methyl ester of 4-hydroxybutanoic acid. The product was isolated *via* column chromatography (silica gel, 65% - ethyl ether - pet. ether eluent). The reaction mixture yields dihydro-2(3H)-furanone (the lactone) when distillation is attempted, bp. 206°/76° mm.

## 3.-DEOXYGENATION REACTIONS

The reduction of hydrazones (which are readily prepared from the corresponding carbonyl compounds) by catecholborane is very facile. In the presence of mild bases, the resultant hydrazinoborane derivatives, 12, readily decompose to the corresponding diazene, 13, if the original hydrazone contained a good leaving group (eg. a tosyl group). Diazenes, of course, decompose readily to yield the corresponding hydrocarbons.[34] The overall reduction is a convenient, mild alternative to the Wolff-Kishner and Clemmensen reductions. The catecholborane reductions require



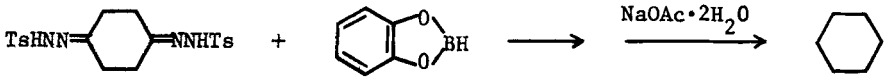
only one equivalent of hydride as compared to the large excess of hydride required by other mild procedures.[35-36] The reaction is applicable to a wide variety of structural types.



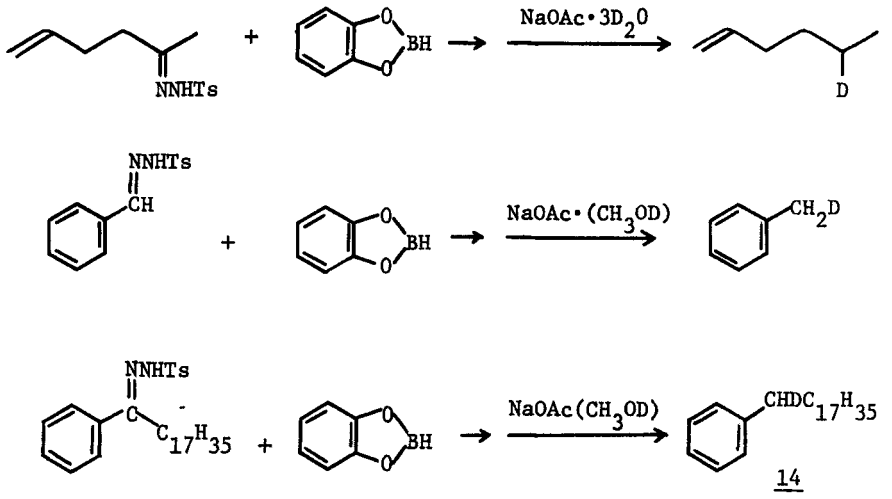
Octane[34].-The tosylhydrazone of 2-octanone (15.64g, 52.7 mmols) is dissolved in 105 ml of chloroform contained in a dry, nitrogen flushed, 250 ml flask fitted with a septum inlet and a magnetic stirring bar. After cooling the solution to -10°, catecholborane (6.31 ml, 58 mmols) is added and the reduction allowed to proceed to completion. (20 min. in this case but the times are variable; NMR is a convenient method for monitering these reductions since the methylene hydrogens α to the imine group disappear as the reaction proceeds.) Sodium acetate trihydrate (21.1g, 155 mmols) is then added and the mixture refluxed gently for 1 hr. (The sodium acetate affects the decomposition of the hydrazinoborane.) GLC analysis indicates a 90.8% yield of octane. A simple distil-

lation yields 81% (4.78g) of the product, bp. 124-127°.

The reaction has also been applied to ditosylhydrazone derivatives.[37]




Available data support a mechanism in which the second hydrogen is delivered as a proton rather than a hydride. The substitution of $D_2O$ or $CH_3OD$ for $H_2O$ affords an inexpensive method for the regiospecific incorporation of deuterium.[38]

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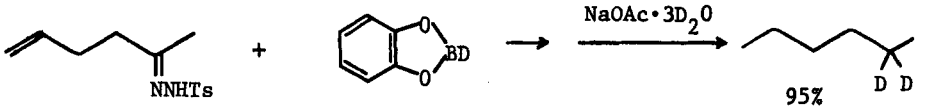
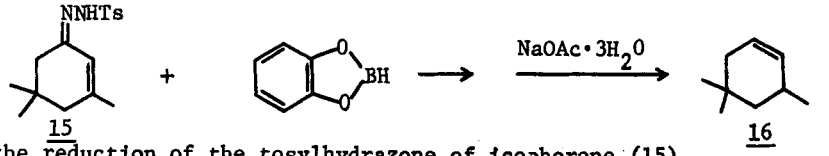
1-Phenyloctadecane-1-d (14)[38].-The tosylhydrazone of stearophenone (5.13g, 10 mmols) is dissolved in deuterochloroform (15 ml) contained in a flame-dried, nitrogen flushed flask fitted with a septum inlet and magnetic stirring bar. Catecholborane (2.18 ml, 20 mmols) is added and the mixture stirred for 1 hr at room temperature. The methanol-OD (2.44 ml, 60 mmols), sodium acetate (0.82g, 10 mmols) and perdeuterodimethylsulfoxide (4 ml) are added and the mixture is refluxed. After 1 hr, an

82% yield is obtained (NMR). The product (2.42g, 73%) is isolated by column chromatography (silica gel, hexane eluent); mp. 36°. The reaction may be used to prepare di-deutero derivatives by utilizing 1,3,2-benzodioxaborole-2-d (deuterated catecholborane) in the reduction step.[38]



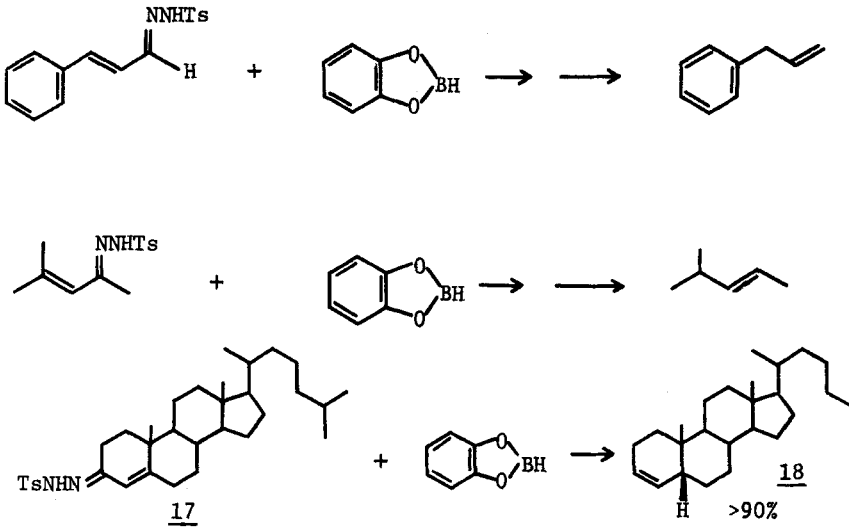

In the original report, it was noted that α,β-unsaturated tosylhydrazone derivatives were reduced with migration of the double bond.[34] A single hydrocarbon product, 3,5,5-trimethylcyclohexene (16) was formed in




15 16

the reduction of the tosylhydrazone of isophorone (15).

The rearrangement reaction was found to be a general one.[39] In every instance, the reduction occurs with a regiospecific migration of the double bond even in cases where the thermodynamically unfavorable product results.[39,40]

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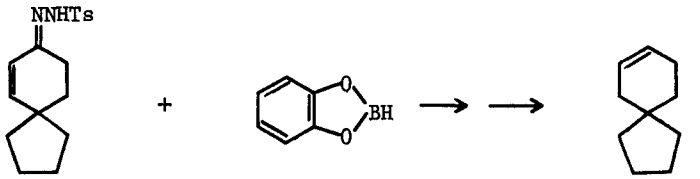
The rearrangement of α,β-unsaturated tosylhydrazone systems also occurs during reductions involving sodium cyanoborohydride.[41] However, sodium cyanoborohydride will not reduce tosylhydrazones of conjugated cyclohexenone derivatives.[41]

The reduction of tosylhydrazones using catecholborane is certainly one of the mildest Wolff-Kischner analogues available and should find increasing use in years ahead. An interesting example of the reaction has been reported involving the synthesis of spiroalkenes.[42]




Current investigations in our laboratories are centered on: (a) the incorporation of tritium, as well as deuterium, via the reduction of tosylhydrazones; (b) the formation of allenes via reduction of acetylenic derivatives.

Table I. Reduction of Functional Groups with Catecholborane[a]

| Functionality | Substrate | Products[b] | Time for 50% Reduction, hours | % Overall yield (time, hrs) |
|---|---|---|---|---|
| Aldehyde | $C_6H_{13}CHO$ | $C_6H_{13}CH_2OH$ | 0.3 | 93(4) |
| | $C_6H_5CHO$ | $C_6H_5CH_2OH$ | 0.5 | 85(2) |
| Hydrazone | $C_6H_{13}C(CH_3)=NNHTs$ | $C_8H_{18}$ | 0.3 | 100(1) |
| Acid Salt | $C_{17}H_{35}CO_2Na$ | $C_{17}H_{35}CH_2OH$ | - | 100(6) |
| Sulfoxide | $(CH_3)_2SO$ | $(CH_3)_2S$ | 0.5 | 93(24) |
| Anhydride | $(C_{15}H_{31}CO)_2O$ | $C_{15}H_{31}CH_2OH$ | 0.5 | 90(24) |
| Epoxide | Propylene oxide | $C_3H_7OH$[c] | 2 | 99(1) |
| | Styrene oxide | $\phi C_2H_4OH$[c] | - | 100(1) |
| Alkyne | $C_4H_9C\equiv CH$ | $C_4H_9CH=CH_2$ | 12 | 79(26) |
| Ketone | Cyclopentanone | $C_5H_9OH$ | 28 | 68(72) |
| | $C_6H_{13}COCH_3$ | $C_6H_{13}CHOHCH_3$ | 40 | 70(163) |
| Alkene (terminal) | $C_6H_{13}CH=CH_2$ | $C_8H_{18}$ | - | 5(44) |
| Acid | $C_6H_5CO_2H$ | $C_6H_5CH_2OH$ | - | 28(20) |
| Amide | $CH_3CON(CH_3)_2$ | $CH_3CH_2N(CH_3)_2$ | - | 40(96) |
| Ester | $C_3H_7CO_2C_2H_5$ | | - | 0(81) |
| Disulfide | $(CH_3S)_2$ | | - | 0(48) |
| Nitro | $CH_3NO_2$ | | - | 0(168) |
| Alkene (internal) | Cyclohexene | | - | 0(46) |
| Halide | n $C_8H_{17}Br$ | | - | 0(48) |

(a) Reactions were run using an initial subtrate concentration of 0.5 M and sufficient hydride to reduce the functional group. The reactions were run at room temperature in $CHCl_3$. (b) Products obtained on protonolysis. (c) The isomeric alcohols are obtained.

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