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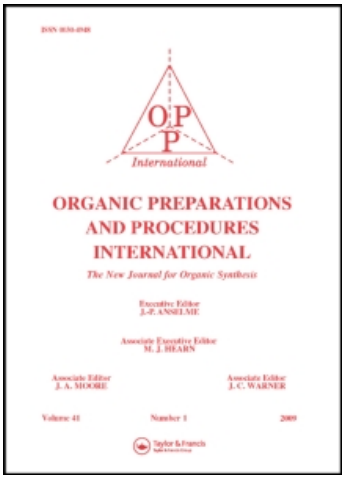

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
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AMINE BORANES AS SELECTIVE REDUCING AND HYDROBORATING AGENTS. A REVIEW

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To cite this Article Hutchins, Robert O. , Learn, Keith , Nazer, Behrooz , Pytlewski, David and Pelter, Andrew(1984) 'AMINE BORANES AS SELECTIVE REDUCING AND HYDROBORATING AGENTS. A REVIEW', Organic Preparations and Procedures International, 16: 5, 335 — 372
To link to this Article: DOI: 10.1080/00304948409457891
URL: http://dx.doi.org/10.1080/00304948409457891

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ORGANIC PREPARATIONS AND PROCEDURES INT. 16(5), 335-372 (1984)

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INTRODUCTION

Although complexes between amines and borane have been known for many years and several are commercially available, they have not seen the widespread usage as reducing or hydroborating agents enjoyed by their chemical cousins borane-THF,[1] borane-dimethylsulfide,[2] borohydride[3] and cyanoborohydride.[4] In fact, recent reviews devoted to selective reductions report only sparse applications.[2,5] Nevertheless, the available evidence suggests that the reducing abilities of amine boranes in some instances mimics the chemistry of borohydride[3] or cyanoborohydride[4] and, in addition, often offers unique reducing properties. Indeed, during the past few years, exploration of the synthetic potential of amine boranes has rapidly expanded and this has in turn augmented their potential for the future. This Review updates the short article which appeared in 1973[6] and hopefully will stimulate further investigations of this important but relatively neglected class of reagents. Coverage will primarily focus on the literature since 1973, but some overlap with the previous review[6] is essential for completeness.

I. PREPARATION AND PROPERTIES

Schlesinger and Burg prepared the first amine borane complex in 1937 by the direct reaction of diborane with trimethylamine[7](eq. 1). Since this initial discovery, numerous complexes have been synthesized employing many different reagents and methods.[8] Currently, most simple amine boranes commonly used as reducing agents are produced commercially on large scale so that demand for even tonage quantities can be met.[9]

$$2(CH_3)_3N + B_2H_6 \longrightarrow 2(CH_3)_3NBH_3 \quad (1)$$

In general, stable amine borane complexes will form if the pK_a of the amine is above 5.0-5.5. This means that ammonia borane as well as almost all primary, secondary and tertiary aliphatic amine boranes can be synthesized since nearly all aliphatic amines fall within or above the critical pK_a range. The major exceptions are branched chain tertiary amines such as tri-isobutylamine, where steric hindrance of the alkyl groups prevents stable bonding.[10] The stereochemistry of complexation between borane and substituted piperidines has been explored.[11] With aromatic amines, pK_a values below 5.0 are more frequently encountered and the corresponding amine boranes are less common. Aniline, for example, has a pK_a of 4.6 and consequently aniline borane cannot be readily isolated. N,N-Dimethylaniline (pK_a 5.1) and pyridine (pK_a 5.2) are borderline; both form stable complexes with borane but the B-N bond is weak in both cases.[10] More recently the synthesis of complexes between amines and alkylboranes has received appreciable attention. Thus, Brown and coworkers obtained triethylamine thexylborane by direct reaction between the components[12a] and N,N-diethylaniline thexyl borane is also available *via* this route.[12a] Furthermore, triethylamine thexylborane reacts rapidly with many alkenes to form new alkylborane triethylamine complexes (eq. 2) which are readily recovered by removal of solvent and tetramethylethylene under vacuum.[12a]

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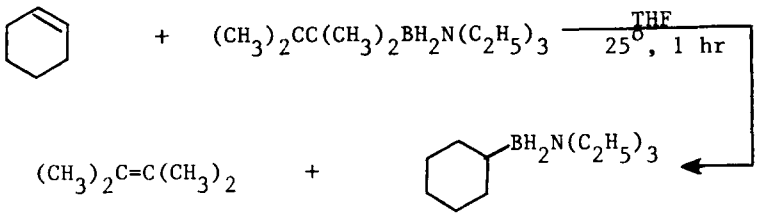

(2)

Several dialkylborane amine complexes have also been synthesized, usually by direct reaction. Thus, commercially available 9-borabicyclo-[3.3.1]nonane (9-BBN) complexes with trimethylamine, pyridine or α-picoline and the corresponding amine boranes precipitate from pentane.[13] Investigations have also resulted in simple procedures for the preparation of pyridine phenylborane,[14] triethylamine 1-methylcyclopentylborane[15] and chiral derivatives between iso- and diisopinocampheyl boranes and amines.[16]

The majority of aliphatic amine boranes are white crystalline solids which are stable indefinitely at room temperature and practically unaffected by air or moisture. Aniline derivatives are less stable and generally react with protic media and moist air.[10] Primary and secondary amine boranes, which contain a hydrogen bonded to nitrogen, are thermaly unstable above about 70°C giving aminoboranes and hydrogen (eq. 3). The decomposition is generally slow at 70°C, but quite rapid at 100°C.[17] Notable exceptions include t-butylamine borane which is stable until melting (95°C) and dimethylamine borane which is stable to at least 110°C.[18]

$$RNH_2BH_3 \xrightarrow{\Delta} RNHBH_2 + H_2 \qquad (3)$$

Aliphatic amine boranes are at least slightly soluble in and

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unreactive toward a wide range of protic and aprotic solvents including water, methanol, ether, THF, hexane, methylene chloride and toluene as illustrated in Table I.[6] This expands the utility of the reagents since most other hydride reagents are restricted to either polar (i.e. $NaBH_4$, $NaBH_3CN$) or nonpolar (and aprotic) solvents (i.e. $LiAlH_4$, $(i\text{-}Bu)_2AlH$). The aliphatic reagents react with carboxylic acid solvents to liberate 2 moles of H_2 and afford solutions of $HB(O_2CR)_2$ or $RNH_2HB(O_2CR')_2$.[19]

TABLE I. Solubilities of Amine Borane Complexes (25°C.) [a,b]

Borane Complex	H_2O	CH_3OH	Et_2O	THF	Hexane	Benzene	Toluene	CH_2Cl_2
ammonia	VS	VS	VS	VS	SS	S		VS
t-butylamine	S	VS	S	VS	I	S	S	S
dimethylamine	VS	VS	VS	VS	I	VS	VS	VS
trimentylamine	SS	VS	VS	VS	I	VS	VS	VS
triethylamine	SS	VS	VS	VS	VS	VS	VS	VS
morpholine	VS	VS	S	VS	I	S	S	VS
N,N-diethylaniline	R	R	VS	VS	VS	VS	VS	VS
N-phenylmorpholine	R	R	VS	VS	I	VS	S	VS
pyridine	SS	VS	VS	VS	I	VS	VS	VS
2,6-lutidine	SS	VS	S	VS	I	VS	VS	VS

a. refs. 6 and 17. b. R = reacts; I = insoluble, <0.1g/100 mL; SS = slightly soluble, 0.1-1.0g/100 mL; S = soluble, 1.0-3.0g/100 mL; VS = very soluble, >3.0g/100 mL.

II. HYDROLYSIS AND DEUTERIUM EXCHANGE

As mentioned, the weak arylamine borane complexes are readily hydrolyzed by water and alcohols and thus must normally be used under dry, aprotic conditions. On the other hand, alkylamine boranes are stable in water and alcohols at near neutrality for over 12 hrs. at 25°C.[17] Hydrolysis occurs in acidic media at varying rates depending on the

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stability of the complex and generally follows the order: NH_3BH_3 RNH_2BH_3 R_2NHBH_3 R_3NBH_3. Thus, in 1M HCl 50% aqueous ethylene glycol, $(CH_3)_3CNH_2BH_3$, $(CH_3)_2NHBH_3$ and $(CH_3)_3NBH_3$ are completely hydrolyzed in 2, 9 and 1000 min., respectively.[17] In synthetic applications, therefore, excess hydride may be destroyed with aqueous acid.

The boron hydrogens of $(CH_3)_3NBH_3$ undergo rapid exchange with deuterium in acidic D_2O (eq. 4) to produce $(CH_3)_3NBD_3$ which can be isolated by extraction with ether.[21] Thus, exchange occurs much more rapidly than hydrolysis since after 6 hours, the amineborane was 98% deuterated and only 6% hydrolyzed. Although similar exchanges involving more acid sensitive complexes have not been investigated, the process potentially provides for the ready procurement of deuterium (and presumably tritium) labeled reagents for introducing D or T by reductions. Trimethylamine borane-d_3 has been used to prepare $NaBD_4$[22a] and B_2D_6.[22b]

$$(CH_3)_3NBH_3 \xrightarrow[DCl,\ 0.5\text{-}5\ min.]{D_2O} (CH_3)_3NBD_3 \qquad (4)$$

III. AMINE BORANES AS REDUCING REAGENTS

a. General Reducing Properties

Although the ability of amine boranes to reduce a number of functional groups has been known for many years,[6] widespread usage has lagged. This is probably partly due to emphasis in the earlier works on the relatively unreactive tertiary amine boranes which behave as reducing agents only with reluctance.[6] Recent investigations with more reactive examples have uncovered a variety of useful, selective and unique reducing capabilities which should insure amine boranes their proper inclusion in the arsenal of reductive weapons available to chemists.

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In general, the reducing abilities of amine boranes are tempered compared to either borane[1,2] or borohydride[3] due to the electron withdrawing effect of the electron-deficient nitrogen and thus, in some respects, the complexes resemble cyanoborohydride.[4] On the other hand, the reducing ability is greatly dependent on the complexing amine. In aliphatic amine boranes the reducing ability decreases with alkyl substitution in the order: $H_3NBH_3 > RH_2NBH_3 > R_2HNBH_3 > R_3NBH_3$. In the case of aryl and heteroaryl amine boranes, the reducing ability appears more dependent on the base strength of the amine. As a general rule, the lower the pK_a of the amine, the stronger the reducing agent. Thus, a range of reduction capabilities are obtainable and, coupled with the compatibility of the reagents toward acid, provide high versatility for reductive selectivity. Applications to various functional group reductions are discussed separately in the following sections. However, it should be noted that much room for further investigation remains.

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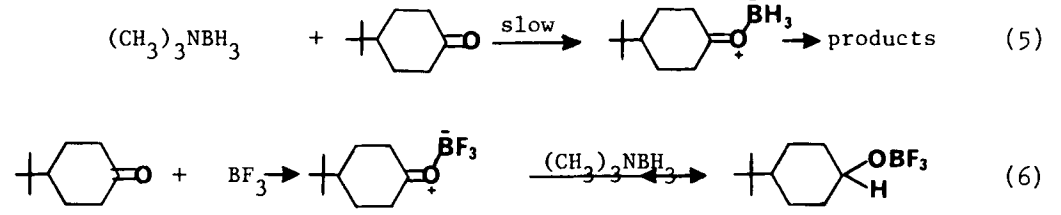
b. Reductions of Carbonyl Groups

Early studies with amine boranes focused on their ability to reduce carbonyl compounds in neutral media. Pyridine borane was shown to reduce aldehydes, aryl ketones and acid chlorides to the corresponding alcohols in refluxing benzene or toluene in yields ranging from 21 to 94%.[23] Better results were obtained with this reagent using pyridine as solvent at 100°C.[24] Under these conditions benzaldehyde and benzoyl chloride were reduced to benzyl alcohol in respective yields of 90 and 96% but only one of the three available hydrides of pyridine borane was active.[24] Similar results were obtained employing ethyl-, i-propyl-, t-butyl- and dimethylamine boranes in refluxing ether or benzene; aldehydes, ketones and acid chlorides were reduced to the corresponding alcohols in good to excellent yields by these more reactive reagents,[25] but other carbonyl derivatives (carboxylic acids, esters, amides) were inert.

In 1959, Jones[26] reported a catalytic effect of BF_3 on the reduction of 4-t-butylcyclohexanone with trimethylamine borane. In the presence of BF_3, this ketone was reduced in two minutes quantitatively by $(CH_3)_3NBH_3$ (0°C., diglyme). In the absence of the Lewis Acid catalyst, the reduction was incomplete even after three days (55% reduction, 100°C., in diglyme). Boron trifluoride also seemed to alter the reduction stereochemistry (Table II). The fact that $(CH_3)_3NBH_3$, in the absence of the BF_3 and diborane, gave the same product distribution in the reduction of 4-t-butylcyclohexanone suggests a common intermediate for both cases involving an initial, slow formation of a ketone-borane complex followed by a rapid intramolecular hydride transfer (eq. 5). In contrast, the acid catalyzed reduction was reported[26,27] to proceed via an initial complexation of BF_3 with the carbonyl followed by an intermolecular hydride transfer from the amine borane (eq. 6). Steric approach control[28] was suggested to explain the observed stereochemistry. Boron trifluoride also catalyzes reductions with a polymer bound amine borane which reduces aldehydes and ketones to the corresponding alcohols in moderate yields.[29]



(5)

(6)

Encouraged by the catalytic effect of Lewis acids cited above ($AlCl_3$ also serves as a catalyst[26]), Kelly and coworkers[30] demonstrated that amine boranes (particularly morpholine, N-methylmorpholine and trimethylamine boranes) are highly effective in reducing carbonyl compounds even in highly

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TABLE II. Reduction of 4-t-Butylcyclohexanone in Diglyme[26]

Hydride	Lewis Acid	Conditions	% Reduction	Ratio cis/tr.
$(CH_3)_3NBH_3$	-	100°C., 3 days	55	16/84
B_2H_6	-	100°C., -	100	16/84
$(CH_3)_3NBH_3$	BF_3	0°C., 2 min.	100	46/54
B_2H_6	BF_3	0°C., -	100	15/85

acidic aqueous media (HCl, pH 2). The reaction rates of amine boranes with aldehydes and ketones were found to increase with increasing acidity of the medium. From kinetic studies with morpholine borane, it was calculated that protonation renders the carbonyl group ca. 10^{11} times more reactive toward reduction.[31] Further mechanistic studies indicated that reduction occurs by two pathways, one independent of, and the other first order in, the hydrogen ion concentration. Kinetic data for the acid-catalyzed pathway are consistent with a rate-determining attack of amine borane on a protonated carbonyl which is formed in a rapid pre-equilibrium. The acid-independent pathway was suggested to involve a rate-determining attack of amine borane on the neutral, unprotonated carbonyl. A four-centered transition state has been proposed for the reduction of aliphatic ketones with morpholine borane.[32] The related derivative, morpholine cyanoborane, failed to show any reactivity towards carbonyl compounds even under highly acidic conditions, an effect presumably due to the electron withdrawing inductive effect of the cyano group.[32]

Trimethylamine borane in methanolic HCl selectively reduced the carbonyl group of 2,3-diphenylcyclopropenone to form 1,2-diphenylcyclopropene.[33] In contrast, $LiAlH_4$ or catalytic hydrogenation gave dibenzylketone, presumably through a cyclopropanone intermediate (eq. 7).

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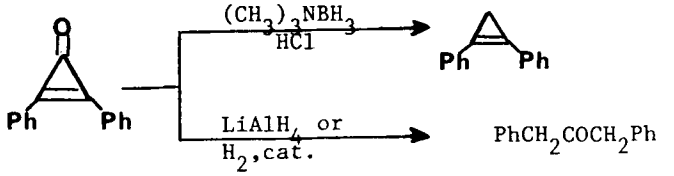
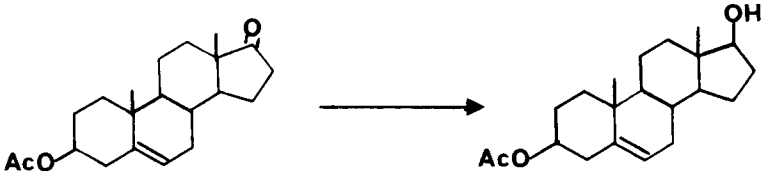


(7)

Johnson and coworkers[34] demonstrated the ability of pyridine borane in acetic acid to reduce the 17-keto group of various steroids. Dihydroepiandrosterone acetate, for example, was reduced by this system (3 hrs., 25°C.) to afford $\Delta^{5,6}$-androsten-3β-17β-diol-3-acetate (eq. 8). Furthermore, pyridine borane in acetic acid has been established as a tool for ascertaining the C/D ring configuration of 17-ketosteroids[34,35] in that compounds containing a trans C/D ring juncture (i.e. eq. 8) are reduced by pyridine borane in acetic acid while those with a cis C/D fusion remain inert.



(8)

In trifluoroacetic acid (TFA), pyridine borane reduces aldehydes to symmetrical ethers.[36] The absence of normal alcohol products may result because the electron withdrawing trifluoroacetoxy group stabilizes boron-oxygen bonds allowing further reaction to occur to give ethers. Alcohols are obtained from aromatic aldehydes bearing strong electron withdrawing groups (i.e. m-nitro) and from dialkylketones.[36b] Reduction of aldehydes in the presence of alcohols provides unsymmetrical ethers while analogous conversions in the presence of thiols affords sulfides[36c](eq. 9). The reduction of aryl-alkyl ketones with pyridine borane in TFA produces the

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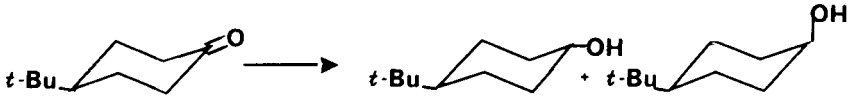
corresponding methylene compounds and aryl alcohols are similarly reduced to arenes.[36b] Such conversions suggest the formation of intermediate ions which are sufficiently stable in aryl cases to be trapped by hydride.

$$\begin{aligned} &\text{RCHO} \xrightarrow{C_5H_5NBH_3,\ TFA} RCH_2OCH_2R \\ &\text{RCHO} + \text{R'OH} \xrightarrow{C_5H_5NBH_3,\ TFA} RCH_2OR' \\ &\text{RCHO} + \text{R'SH} \xrightarrow{C_5H_5NBH_3,\ TFA} RCH_2SR' \end{aligned} \qquad (9)$$

Andrews and Crawford[37] have demonstrated that NH_3BH_3 and primary and secondary amine boranes are mild, highly effecient and stereoselective reducing agents for aldehydes and ketones in polar protic and aprotic solvents. In contrast, less reactive tertiary and aromatic amine complexes exhibited inferior reactivity and selectivity. The order of reactivity toward 4-t-butylcyclohexanone was shown to be: $NH_3BH_3 > t\text{-}C_4H_9NH_2BH_3 > (CH_3)_2NHBH_3 > C_5H_5NBH_3 > (CH_3)_3NBH_3$ (Table III).

TABLE III. The Relative Reactivity and Stereoselectivity of Amine Boranes in the Reduction of 4-t-Butylcyclohexanone in CH_3OH/H_2O at 25°C



I II III

Reagent	Time		
	15 min. II:III (yield)	85 min. II:III (yield)	18hrs II:III (yield
NH_3BH_3	91:9(99)		
$t\text{-}C_4H_9NH_2BH_3$	92:8(99)		
$(CH_3)_2NHBH_3$	90:10(73)	92:8(99)	
2,6-Lutidine.borane	82:18(33)	85:15(42)	86:14(99)
$C_5H_5NBH_3$	(0)		81:19(29)
$(CH_3)_3NBH_3$	(0)	(0)	80:20(6)

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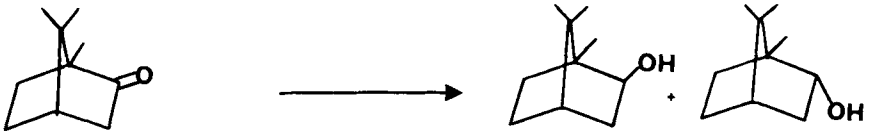
Table III illustrates the stereochemical features of amine borane reductions of cyclic ketones. Ammonia, primary and secondary amine boranes demonstrate high preferences for axial attack (> 90%) to afford equatorial alcohols. This approach preference is in line with similar results obtained with other "small" reagents (i.e. $LiAlH_4$ and $NaBH_4$ afford ca. 90 and 85% axial attack, respectively). However, with the hindered ketone camphor the stereoselectivity of attack was greatly diminished compared to $NaBH_4$. The reason for this is not obvious, perhaps dissociated borane becomes implicated and competes when long reaction times are required (eq.



(10)

NH_3BH_3/7 hrs.	49	:	51 (99% yield)
$NaBH_4$/7 days	85	:	15 (53% yield)

The synthetic utility of ammonia and t-butylamine boranes for the chemoselective reduction of several structurally varient carbonyl compounds has also been examined.[37] The reagents show excellent selectivity in the reduction of ketoesters to alcohol esters and α,β-unsaturated ketones to allylic alcohols (Table IV). t-Butylamine borane has also been employed in the stereoselective reduction of several 12-keto-α-cholanic acid esters.[38] Attack of the amine borane invariably occurs on the α-face to afford the equatorial alcohol.

Competitive experiments have indicated that ammonia borane and t-butylamine borane effectively discriminate between aldehydes and ketones.[39] Thus, in both protic and aprotic solvents, benzaldehyde is chemoselectively reduced in the presence of acetophenone (Table V) and all three hydrides of the amine borane are available for reaction.[39] In acetic acid, a polymer bound amine borane (Amborane) revealed similar although lower selectivity

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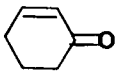
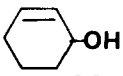
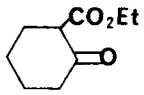
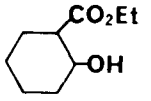
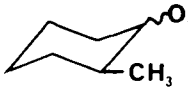
TABLE IV. Chemoselective Reduction of Aldehydes and Ketones

Compound	Amine Borane	Solvent	°C (Time)	Product(% yield)
	t-$C_4H_9NH_2BH_3$	Et_2O	25(16 hrs)	 (87)
	t-$C_4H_9NH_2BH_3$	Et_2O	25(16 hrs)	 (65)
C_6H_5CHO	NH_3BH_3	CH_3OH/H_2O	0(10 min)	$C_6H_5CH_2OH$ (83)
$C_6H_5COCO_2Et$	NH_3BH_3	Et_2O	25(4 hrs)	$C_6H_5CHOHCO_2Et$ (84)
$C_6H_5CH=CHCOCH_3$	t-$C_4H_9NH_2BH_3$	$CHCl_3$	25(1 hr)	$C_6H_5CH=CHCHOHCH_3$ (79)
	NH_3BH_3	Et_2O	0(1 hr)	 87 (30% cis)

(Table V).[40]

The ability of diisopropylamine borane to reduce a ketone in the presence of an ester and a β-lactam was recently exploited in the synthesis of thienamycin from penicillin.[41a] In addition, the reduction was highly stereoselective and afforded one diastereomer in high predominance (eq. 11).[41a] Likewise, ammonia borane (in aqueous methanol) was successfully utilized in the synthesis of lubimin and oxylubimin to selectively reduce a ketone in the presence of a cyano group[41b] and t-butylamine borane was used to reduce a ketone in the presence of a lactone and to reduce an aldehyde in the presence of both a lactone and a ketone in the synthesis of sesquiterpene natural products.[41c]

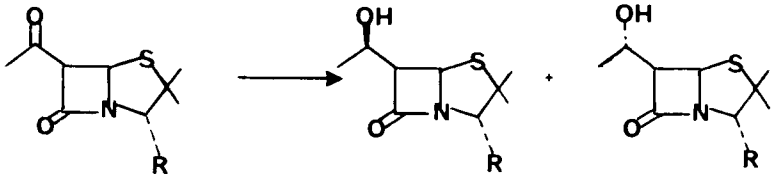


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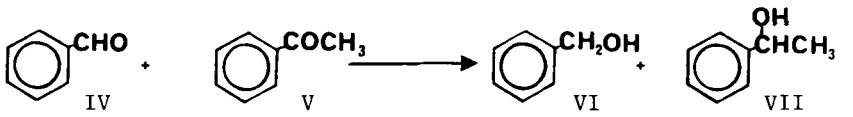
TABLE V. The Selective Reduction of Benzaldehyde in the Presence of Acetophenone with Amine Borane Reagents [a]



IV V VI VII

Reagent	Solvent	T°C.	Ratio VI:VII	% Yield
$t\text{-}C_4H_9NH_2BH_3$	$CH_3OH/H_2O(1:1)$	0	98:2	81
"	THF	0	95:5	84
"	$CHCl_3$	0	97:3	87
"	$C_6H_5CH_3$	0	94:6	95
NH_3BH_3	$CH_3OH/H_2O(1:)$	0	97:3	97
"	"	25	97:3	90
2,6-lutidine BH_3	$CHCl_3$	25	55:45	9
pyridine BH_3	"	25	35:65	11
$(CH_3)_3NBH_3$	"	25	N.R.	0
Amborane	CH_3CO_2H	25	87:13	91[b]

a. ref. 39 unless indicated otherwise. b. ref. 40.

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The alkylborane amine complex 9-borabicyclo[3.3.1]nonane pyridine (9-BBN pyridine) also selectively reduces aldehydes in the presence of ketones and other functional groups including esters, lactones, amides, nitriles, alkyl and benzylic halides, epoxides, alkenes, alkynes and nitroalkanes.[42] However, thexylborane N,N-diethylaniline (TBDA) appears less discriminatory and reduces carboxylic acids (to alcohols) and amides (to amines) in addition to reduction of aldehydes and ketones.[12b]

A number of chiral amine boranes have been synthesized and utilized in the asymmetric reduction of prochiral ketones. Borane complexes of (S)-amphetamine,[43] (S)-deoxyephedrine,[43] and (R) or (S)-1-phenylethylamine[44] were shown to enantioselectively reduce 2-heptanone and acetophenone to the

corresponding alcohols although in low optical yields (1.5-5% e.e.). Better results were obtained employing amine boranes derived from optically active α-aminoesters. Thus, in the presence of BF_3 etherate, various prochiral ketones were reduced by α-amino ester boranes to the respective alcohols in moderate optical yields (14.7-22.5% e.e.).[45] Likewise, chiral sodium salts of α-amino acid complexes with borane effected the asymmetric reduction of several ketones (2-62% e.e.) with sodium prolinate borane affording the best results (Table VI).[46a] Similarly, amino alcohols (produced by reduction of α-amino acids) forms complexes with borane which reduced ketones to alcohols in optical yields up to 60%[46b] while borane complexes with (S)-2-amino-3-methyl-1,1-diphenyl-1-ol reduced aryl ketones in high enantiomeric excesses (94-100% e.e.)[46c] Another highly successful asymmetric synthesis of chiral alcohols has been obtained with borane complexes of the chiral β-hydroxy sulfoximines VIII and IX.[47] These reagents, utilized at -78°C., reduced a broad range of prochiral ketones to chiral alcohols in enantiomeric excesses from 3 to 82%. The highest enantiomeric excesses were obtained with arylalkyl ketones as indicted in Table VII.[47]

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c. Reduction of Imines, Iminium Salts and Enamines

Several years ago, Billman and McDowell[48] demonstrated that dimethylamine borane in glacial acetic acid reduces aryl imines (Schiff Bases) to the corresponding secondary amines in high yields (Table VIII). Numerous other functional groups including chloro, nitro, ester, sulfoamido and carboxy were not affected by the reagent.[48] However, the reduction of imines with trimethylamine borane in refluxing acetic acid afforded the acetyl derivative of the corresponding amines as illustrated in Table IX.[49] The yields varied considerably and depended on the substituents attached to the nitrogen bearing phenyl ring with electron donating groups increasing the amount of acylation.[49] Imines (and enamines) are also reduced by

TABLE VI. Reduction of Prochiral Ketones with the Sodium Salts of α-Amino Acid Borane Complexes in THF at Room Temperature [46]

Ketone	α-Amino Acid	% Yield	% Enant. Excess
$C_6H_5COCH_3$	D-valine	75	1.8
$C_6H_5COCH_3$	D-leucine	77	5.1
$C_6H_5COCH_3$	L-phenylalanine	76	1.8
$C_6H_5COCH_3$	L-proline	92	32
$(CH_3)_2CHCH_2COCH_3$	L-proline	66	17
$CH_3(CH_2)_4COCH_3$	L-proline	66	15
$C_6H_5COCH_2CH_3$	L-proline	92	50

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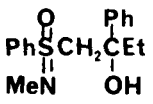
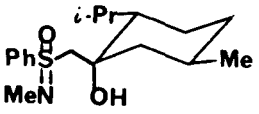


VIII (2 diastereomers, a,b)



IX(2 diastereomers, a,b)

TABLE VII. Reduction of Prochiral Ketones with β-Hydroxysulfoximine Borane Complexes [47]

Ketone	Ligand	% Yield	% Enant. Excess (Abs. Config.)
$C_6H_5COCH_3$	VIIIa	80	60(S)
$C_6H_5COCH_3$	VIIIb	92	57(R)
$C_6H_5COCH_3$	IXa	66	82(S)
$C_6H_5COCH_2CH_3$	VIIIb	74	74(R)
$C_6H_5CO(CH_2)_2CH_3$	VIIIb	81	70(R)
$C_6H_5COCH(CH_3)_2$	VIIIb	53	8(R)
$n\text{-}C_6H_{13}COCH_3$	VIIIb	79	8(R)
$i\text{-}C_3H_7COCH_3$	VIIIb	46	9(R)
$i\text{-}C_4H_9COCH_3$	VIIIb	48	3(R)
$t\text{-}C_4H_9COCH_3$	VIIIb	60	22(R)

TABLE VIII. The Reduction of Imines with Dimethylamine Borane in Glacial Acetic Acid [48]

$ArCH{=}NAr' + (CH_3)_2NHBH_3 \longrightarrow ArCH_2NHAr'$

Ar	Ar'	% Yield
C_6H_5	C_6H_5	84
C_6H_5	$p\text{-}ClC_6H_5$	97
$p\text{-}ClC_6H_5$	$p\text{-}ClC_6H_5$	90
C_6H_5	$o\text{-}ClC_6H_5$	84
$p\text{-}O_2NC_6H_5$	$p\text{-}O_2NC_6H_5$	89
$m\text{-}O_2NC_6H_5$	$m\text{-}O_2NC_6H_5$	95
$m\text{-}O_2NC_6H_5$	$o\text{-}O_2NC_6H_5$	89
$p\text{-}CH_3OC_6H_5$	C_6H_5	91
$m\text{-}HOC_6H_5$	C_6H_5	82
C_6H_5	$p\text{-}C_2H_5O_2CC_6H_5$	93
C_6H_5	$p\text{-}H_2NO_2SC_6H_5$	80
$p\text{-}CH_3OC_6H_5$	$p\text{-}HO_2CCH_2SC_6H_5$	85

TABLE IX. Reductive Acylations of Imines with Trimethylamine Borane in Acetic Acid [49]

$ArCH{=}NAr' + (CH_3)_3NBH_3 \xrightarrow{RCOOH} ArCH_2N(COR)Ar'$

Ar	Ar'	R	T,Hrs	% Yield Amide
C_6H_5	C_6H_5	CH_3	11	61
C_6H_5	C_6H_5	$n\text{-}C_3H_7$	11	65
C_6H_5	C_6H_5	C_6H_5	12	26
C_6H_5	$p\text{-}ClC_6H_4$	CH_3	11	67
$p\text{-}O_2NC_6H_4$	$p\text{-}O_2NC_6H_4$	CH_3	18	23
C_6H_5	$p\text{-}HOC_6H_4$	CH_3	11	88
C_6H_5	$p\text{-}CH_3OC_6H_4$	CH_3	9	69
C_6H_5	$p\text{-}C_2H_5O_2CC_6H_4$	CH_3	12	35

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polymer bound boranes (Amborane). The best results were obtained in acetic acid where yields for reductions of imines to amines ranged from 41-89%. However, long reaction times were required (Table X).[40]

The stereochemical outcomes of reductions of various 2-, 3-, and 4-substituted cyclohexyl and cyclopentyl imines, iminium salts and enamines (via iminium ions) with a variety of amine boranes have been investigated.[19] In acetic acid, where the actual active reagent is probably $HB(OAc)_2$, predominately equatorial attack of 3- and 4-substituted systems was observed while 2-alkylsubstituted derivatives gave cis-2-alkyl cyclic amines. The results imply that diacetoxyboranes behave as bulky reagents with carbon-nitrogen pi systems, in direct contrast to results observed for the same reagents with the corresponding ketones.[19,50] Several examples of the reductions are illustrated in Table XI.[19] Pyridine borane in the presence of acetic acid has been observed to provide an excellent system for the reductive amination of aldehydes and ketones (Table XII).[51a] A variety of amine boranes has also been successfully utilized to methylate protein amino groups via reductive amination with formaldehyde.[51b]

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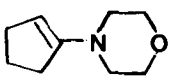
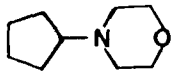
The reduction of imines by amine boranes, usually in acidic media, has been employed in several synthetic applications. Dimethylamine borane in glacial acetic acid was utilized as a selective reducing agent in the preparation of analogues of actinomycin D, a potent antibiotic possessing anti-tumor activity (eq. 12) The sodium salt (or the methyl ester) of 3-phenoxy-1,2-dehydroproline was reduced by amine boranes in acetic acid to 3-phenoxyproline. The ratio of cis/trans products produced was ca. 2:3 with all three amine boranes employed (eq. 13).[53a]

Pyridine borane in acetic acid was utilized to reductively capture imines from 4-methoxy-3-acyloxy-2-hydroxybenzaldehyde and amino acids[53b] while dimethylamine borane was used for imine reduction enroute to

TABLE X. Reduction of Imines and Enamines with Amborane in Acetic Acid

Imine	T°C. (Time,days)	% Yield Amine[a]
$C_6H_5CH{=}NC_6H_5$	25(2)	82
$C_6H_5CH{=}NC_6H_4$-p-Cl	25(2)	41
$C_6H_5CH{=}NC_6H_4$-o-Cl	25(2)	76
$C_6H_5CH{=}NC_6H_4$-p-OCH_3	25(2)	68
	118(0.5)	 47

a. isolated as the HCl salt.

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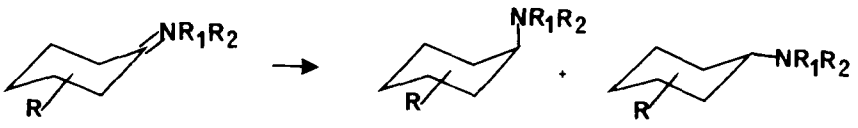
TABLE XI. Reductions of Cyclohexyl Imines and Iminium Salts in Acetic Acid



R	R_1	R_2	Ratio cis/trans (% Yield) $(CH_3)_3CNH_2BH_3$	$(CH_3)_2NHBH_3$
4-t-C_4H_9	C_6H_5	-	84/16 (89)	72/28 (89)
4-t-C_4H_9	cyclohex.	-	77/23 (84)	66/34 (70)
4-t-C_4H_9	$C_6H_5CH_2$	-		66/34 (74)
4-CH_3	C_6H_5	-	77/23 (85)	71/29 (70)
4-CH_3	cyclohex.	-	73/27 (81)	48/52 (81)
2-CH_3	C_6H_5	-	89/11 (76)	
2-CH_3	cyclohex.	-	83/17 (63)	
2-CH_3	$-(CH_2)_4-$		79/21	
2-CH_3	$-[(CH_2)_2]_2O$		82/18	

TABLE XII. Reductive Amination of Aldehydes and Ketones with Pyridine Borane

$$RCOR' + R''NH_2 \xrightarrow{C_5H_5NBH_3,\ HOAc} RR'CHNHR''$$

R	R'	R''	% Yield
C_6H_5	H	cyclohex.	93
C_6H_5	H	n-C_8H_{17}	74
n-C_7H_{15}	H	cyclohex.	54
n-C_7H_{15}	H	n-C_8H_{17}	82
-$(CH_2)_5$-		C_6H_5	97
-$(CH_2)_4CH(CH_3)$-		C_6H_5	83
-$(CH_2)_5$-		cyclohex.	63

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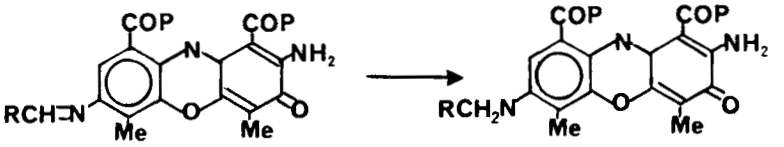
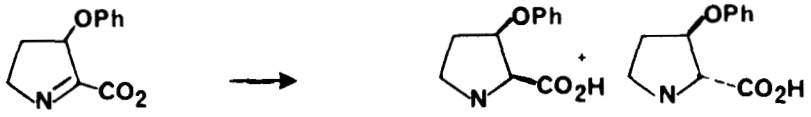


(12)

P = Thr.-D-val.-pro.-sar.-me.val.- (O)

R = C_6H_5 72%; n-C_7H_{13} 82%



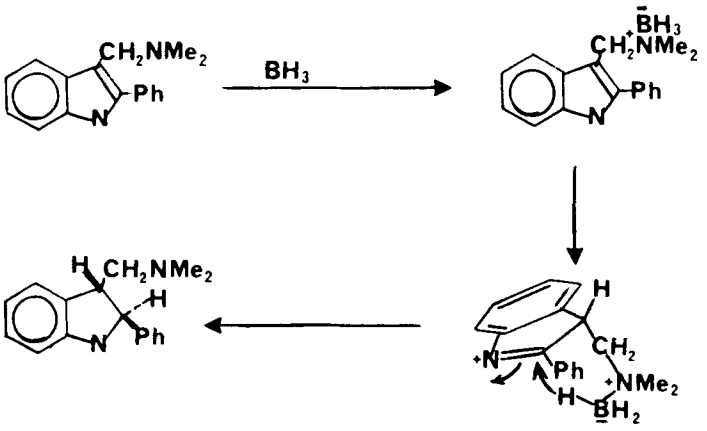
(13)

$(CH_3)_2NHBH_3$	40	60
$(C_2H_5)_3NBH_3$	43	57
$C_5H_5NBH_3$	46	54

pteroyltyrosine.[53c]

d. Reduction of Indoles and Other Heterocyclic Compounds

The relative stability of amine boranes in acidic media has been exploited for the reduction of indoles to indolines *via* initial protonation to give 3H-indolenium ions. Thus, trimethylamine borane in dioxane-10% aqueous HCl reduces indoles to indolines in generally high yields. Likewise, tetrahydrocarbazoles are similarly reduced by this system (Table XIII).[54] With most examples the reductions afford products in which the relative stereochemistry at the 2 and 3 positions is *cis* (Table XIII). The unusual *trans* stereochemistry observed in the reductions of certain indoles bearing nitrogen containing side chains has been attributed to the formation of intermediate amine borane complexes which subsequently reduce the carbon-nitrogen double bond (eq. 14).[55]



(14)

Pyridine borane in ethanolic HCl selectively reduces the indole ring without affecting other functional groups including amides, esters, and nitriles. For acid-labile indoles, reverse addition (i.e. addition of the indole to a preformed solution of the acid and amine borane) has effectively been employed (Table XIV).[56] The reduction of N-acyl trytophan derivatives with pyridine borane in ethanolic 20% HCl was not as successful. However, in CF_3CO_2H pyridine borane afforded N-protected-2,3-

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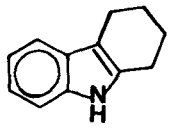
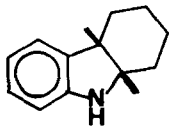
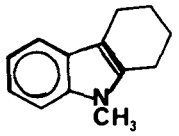
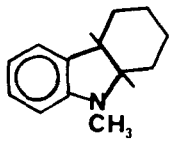
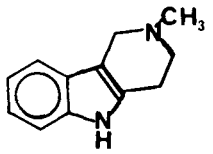
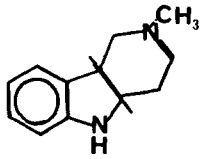
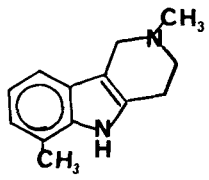
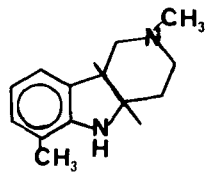
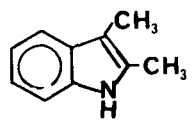
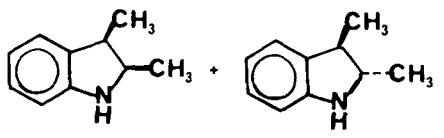
TABLE XIII. Reduction of Indoles and Tetrahydrocarbazoles with Trimethylamine Borane [54]

Reactant	Product(s)	% Yield
		87
		72
		68
		53
	 57 : 43	72

dihydro-L-tryptophan derivatives in high yield.[57] Notably, carboxy groups and sulfur-sulfur bonds were unaffected by the reaction conditions (Table XV).[57] A similar reduction of N-benzoyltryptamine was employed in the synthesis of serotonin, a vasoconstrictor found in blood and other tissues.[58]

The combination of $NaBH_4$ and $AlCl_3$ in pyridine at room temperature has successfully been employed in the reduction of several indole derivatives, presumably via pyridine borane.[59] Interestingly, the reduction was only partially complete until the addition of 10% HCl. In the absence of the Lewis acid catalyst, pyridine borane in pyridine did not effect the

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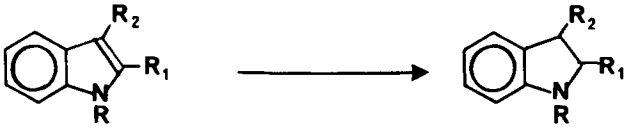
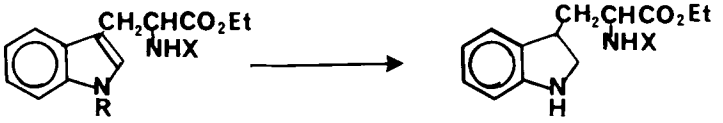
TABLE XIV. Reduction of Indoles with Pyridine Borane in Ethanolic HCl



R	R_1	R_2	Addition[a]	T(min.)	Solvent[b]	% Yield[c]
H	H	H	R	10	A	82
H	H	H	N	5	B	0[d]
CH_3	H	H	R	10	A	54
H	CH_3	H	R	10	A	98
H	H	CH_3	R	10	A	82
H	C_6H_5	H	N	20	C	56(37)
H	H	$(CH_2)_3CO_2C_2H_5$	N	10	C	93
H	H	$(CH_2)_2NHBz$	N	20	C	90(6)
H	H	CH_2CN	N	10	C	57(33)

a. R = reverse addition; N = normal addition. b. A = 10% HCl:C_2H_5OH; B = conc. HCl:C_2H_5OH(2:1); C = 20% (w/w) HCl:C_2H_5OH. c. fig. in parentheses indicate recovered starting material. d. indole dimer obtained quantitatively

TABLE XV. Reduction of Tryptophan Derivatives with Pyridine Borane [57]



X	% Yield(rec. st. mat.)	
	C_2H_5OH-20% HCl	CF_3CO_2H
$C_6H_5CH_2$	75(14)	95
CH_3CO	35(48)	90
$C_6H_5CH_2CO$	50(30)	96
HCO	32(58)	85
H	0(98)	95
z-ala-trp-OMe	58(33)	85
z-trp-ala-OMe		95

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reduction.[59]

Pyridine borane in acetic acid reduced quinoline, isoquinoline, indole and other heterocyclic compounds at room temperature.[60] With quinolines, the presence of a 4-substituent apparently prevents hydride delivery at this position (Table XVI). Pyridine borane in CF_3CO_2H has also been found effective for the reduction of indole derivatives (eq. 15).[61]

e. Reduction of Oximes and Tosylhydrazones

Pyridine borane reduces oximes to the corresponding hydroxylamines in the presence of numerous other functional groups which are unaffected by the reagent (i.e. esters, nitriles, nitros, amides and halides).[62] O-Acyl and O-methyl oximes are similarly reduced in high yield with pyridine borane to the corresponding O-substituted hydroxylamines without over-reduction (Table XVIII).[63]

α-Oximino acid esters and amides were reduced to the corresponding N-hydroxyamino acid analogues with pyridine borane or trimethylamine borane under strongly acidic conditions (C_2H_5OH, 7N HCl) as depicted in eq. 16.[64] Reductions with the latter reagent of O-benzyl oximino acid esters was strategicaly employed in the synthesis of several 1,4-dihydroxy-2,5-dioxopiperazines (eq. 17)[65a] and trytophan dervatives.[65b]

Pyridine borane in ethanolic 20% HCl also effected the reduction of the carbon-nitrogen double bond in tosylhydrazones.[66] The tosylhydrazine products could be further converted to the corresponding hydrocarbons via standard procedures[67] (Table XIX).[66]

f. Reductions of Carbon-carbon Double Bonds

Highly polarized alkenes bearing two strongly electron withdrawing groups at one end may be reduced by amine boranes. Thus, substituted aminomethylene derivatives of cyclic β-dicarbonyl compounds are reduced to the corresponding methyl derivatives[68] and Meldrum's acid has been reductively alkylated via tandem condensation with carbonyl compounds and

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TABLE XVI. Reduction of Heterocyclic Compounds with Pyridine Borane in Acetic Acid at Room Temperature [60]

Heterocycle	Product	% Yield[a]
Quinoline	1,2,3,4-tetrahydroquinoline	71(17)
2-methylquinoline	2-methyl-1,2,3,4-tetrahydroquinoline	73(19)
4-methylquinoline	4-methyl-1,2,3,4-tetrahydroquinoline	6(88)
isoquinoline	1,2,3,4-tetrahydroisoquinoline	48(13)
indole	indoline	86
quinoxaline	1,2,3,4-tetrahydroquinoxaline	95
phthalazine	2-acetyl-1,2,3,4-tetrahydrophthalazine	57[b]

a. Figures in parentheses indicate recovered starting material; b. 5 min. at reflux.

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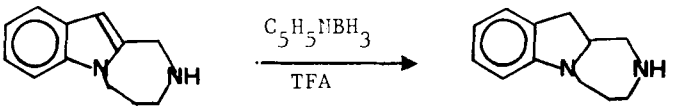
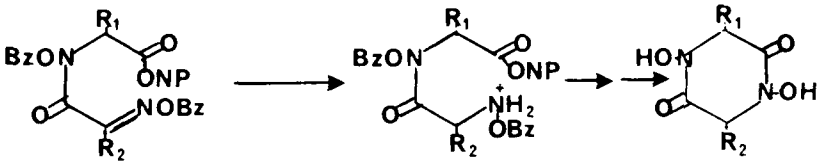


(15)

$$R_1ON{=}C(R_2)CO_2Et \xrightarrow[(CH_3)_3NBH_3]{C_6H_5NBH_3 \text{ or}} R_1ONHCH(R_2)CO_2Et \qquad (16)$$

$$R_1ON{=}C(R_2)CONHCH_3 \xrightarrow[(CH_3)_3NBH_3]{C_6H_5NBH_3 \text{ or}} R_1ONHCH(R_2)CONHCH_3$$



(17)

TABLE XVII. Reduction of Oximes with Pyridine Borane

$$RR_1C{=}NOH \xrightarrow[10\%\ HCl,\ EtOH]{C_5H_5NBH_3} RR_1CHNHOH$$

R	R_1	% Yield
C_6H_5	H	87
C_6H_5	$n\text{-}C_3H_7$	91
$C_6H_5(CH_2)_2$	CH_3	92
$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	91
$m\text{-}O_2NC_6H_4$	H	91
$p\text{-}CH_3O_2CC_6H_4$	H	74
$p\text{-}CNC_6H_4$	H	85
$p\text{-}ClC_6H_4$	H	92
$p\text{-}(CH_3)_2NCOC_6H_4$	H	88

TABLE XVIII. Reduction of O-Acyl- and O-Methyloximes with Pyridine Borane

$$RR_1C{=}NOR_2 \xrightarrow{C_5H_5NBH_3\ H^+} RR_1CHNHOR_2$$

R	R_1	R_2	% Yield
C_6H_5	H	Ac	69
$-(CH_2)_5$		Ac	74
$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	Ac	73
C_6H_5	$n\text{-}C_3H_7$	Ac	74
$C_6H_5(CH_2)_2$	CH_3	Ac	82
C_6H_5	C_6H_5	Ac	95
$-(CH_2)_5-$		Bz	87
$C_6H_5(CH_2)_2$	CH_3	CH_3	83
$p\text{-}ClC_6H_4$	H	CH_3	92
C_6H_5	C_6H_5	CH_3	98

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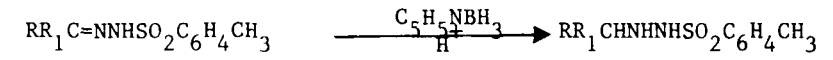
TABLE XIX. Reduction of Tosylhydrazones with Pyridine Borane [66]



R	R_1	% Yield
C_6H_5	CH_3	96
-$(CH_2)_5$		98
p-CNC_6H_4	H	94
$C_6H_5CH{=}CH$	H	94
$C_6H_5CH{=}CH$	CH_3	91

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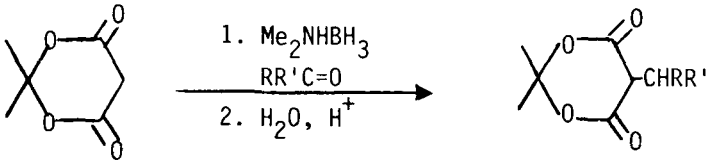
TABLE XX. Reductive Alkylation of Meldrum's Acid [69]



R	R'	%Yield
CH_3	H	87
$CH_3(CH_2)_6$	H	77
$H_2C{=}CH(CH_2)_8$	H	66
C_6H_5	H	94
2-Furyl	H	88
CH_3	CH_3	72
-$(CH_2)_4$		58

reduction of the resulting alkene intermediates with the borane complexes of dimethylamine or trimehtylamine (Table XX).[69]

IV. AMINE BORANES AS HYDROBORATING REAGENTS

Since amine borane complexes are relatively stable, easily handled carriers of borane, it is not surprising that the use of such complexes as hydroborating reagents has attracted attention.[6] However, the same factors which lower borane reactivity and increase stability also concomitantly decreases the ability of borane to attack alkenes since hydroboration must occur via free, dissociated borane. Thus, the ease of hydroboration of alkenes with amine boranes varies with the strength of the complex which, in turn, is a function of the basicity and steric requirements of the amine[10,11,70] as previously discussed. The rate of hydrolysis of amine boranes[6,17] may be taken as a rough guide to the ease of hydroboration, but ^{11}B nmr data must be examined with caution (vide infra).[71] Also, a clear distinction must be made between amines such as pyrrole[72] and aniline[71] that readily yield aminoboranes, which may be excellent hydroborating agents, and those amines that give amine borane adducts; these latter form the subject of this section.

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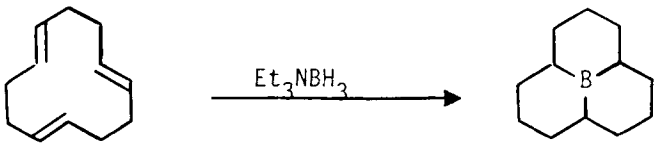
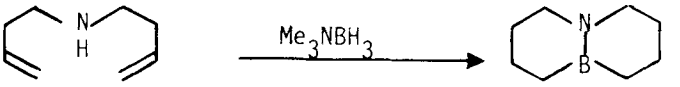
Amine boranes derived from highly basic amines of small steric bulk are sources of nucleophilic hydride and, as such, are poor hydroborating agents. As mentioned, hydroboration in such cases depends on prior disociations to the free amine and borane (eq. 18).

$$R_3NBH_3 \rightleftharpoons R_3N + BH_3 \qquad (18)$$

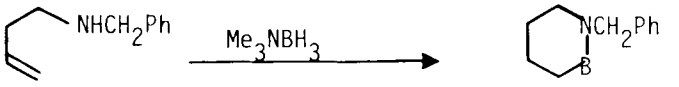
In the case of strongly basic amines of low steric congestion the equilibrium in eq. 18 is displaced largely in favor of the complex and hydroborations are very slow. However, this can be an advantage for the hydroboration of di- and trienes as the equivalent of high dilution conditions is obtained when such amine boranes are used and these become



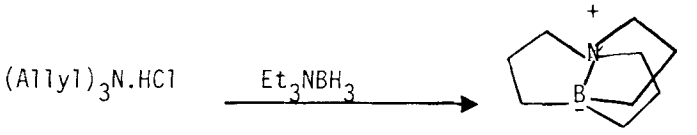
(19)[73]



(20)[74]



(21)[75]



(22)[76]

the reagents of choice (eqs. 19-22).[73-75]

Most amine boranes hydroborate simple alkenes only at elevated temperatures. For example, pyridine borane in diglyme hydroborates alkenes at ca. 100°C.[77] Alkylamine derivatives successfully hydroborate terminal alkenes (no solvent) at temperatures between 124-200°C[77] However, as expected, such relatively drastic conditions often result in isomerization of internal alkylboranes. Thus, 2-hexene gives only tri-n-hexylborane resulting from complete isomerization of the initially produced 2- and 3-isomers at 200°C.[77] Likewise, hydroboration of 2-methyl-2-pentene affords substantial isomerization at higher temperatures (eq. 23).

Clearly, isomerization cannot be avoided with Et_3NBH_3 because of the relatively strenuous conditions required. However, the related derivative Et_3NBH_2Cl hydroborates without isomerization.[78] Since this chloroborane

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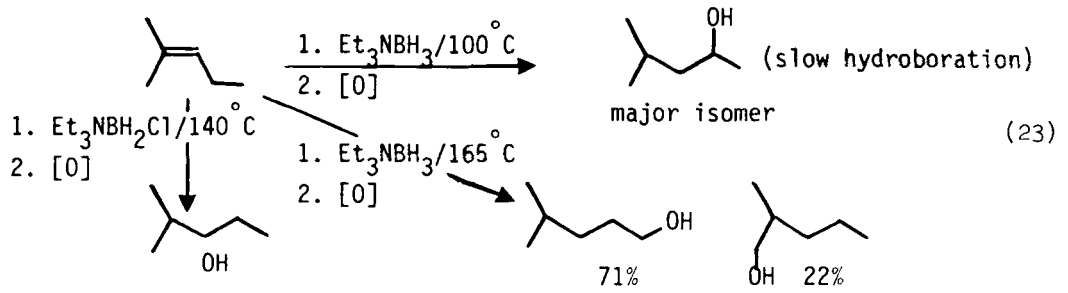
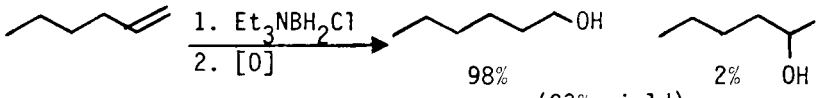


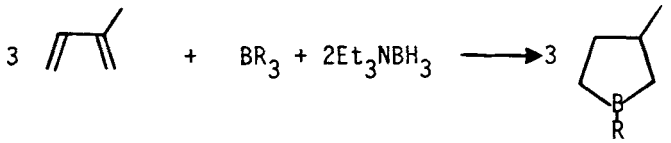
(23)



(24)

complex is a hydrolytically stable solid which is readily produced from the borane adduct,[79] hydroboration studies should be extended. The regioselectivity of hydroboration by Et_3NBH_2Cl is high as illustrated in eq. 24.

An early observation illustrates some further points concerning isomerizations (eq. 25):[80]



(25)

(1) equilibrium clearly exists between R_3B and Et_3NBH_3 to give Et_3NBH_2R.

(2) Et_3NBH_2R hydroborates faster than does Et_3NBH_3, and this is reasonable on steric grounds.

(3) Et_3NBH_2R appears to be an excellent reagent for cyclic hydroborations to give ring alkylboranes.

A further observation[80] implies equilibrium between all types of borane species present (eq. 26).

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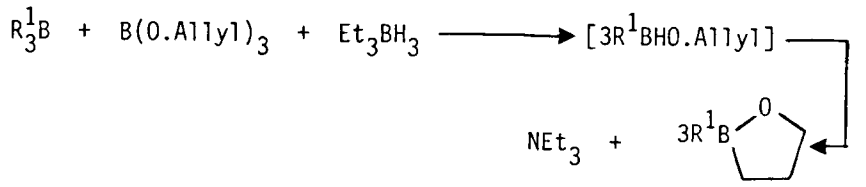

(26)

The relative inertness of amine boranes toward hydroborations at lower, non-isomerizing temperatures has led to several investigations aimed at increasing the reactivity of the adducts. An early attempt to achieve this involved the combine use of Lewis acids and amine boranes.[81] The most efficient combination was pyridine borane and boron trifluoride etherate which gave 90% hydroboration of 1-octene in 16 h in refluxing benzene. However, this is still very slow and other functional groups could be affected by the Lewis acid. Attempts to utilize protic acids were also unsuccessful.[71] The use of the alkylating agent methyl iodide to displace the equilibrium in eq. 18 by converting the amine into the methiodide salt was more successful with Et_3NBH_3. Thus, in the presence of methyl iodide, hydroboration of 1-octene was complete in 6 h in refluxing THF (66°C.) or in 2 h in refluxing glyme (85°C.).[82] Furthermore, the quaternary salt does not interfere with oxidation or separation of the product alcohols. In the absence of methyl iodide, hydroboration in glyme was only 41% complete after 2 h at 85°.[71] Thus, stable aliphatic amine borane complexes appear capable of hydroborations under mild conditions. However, the presence of methyl iodide did not enhance hydroborations with pyridine borane.[71]

As expected, borane complexes with weakly basic amines show enhanced reactivity compared to their strongly basic counterparts as illustrated in Table XXI.[71] As seen, although there is some correlation between hydrolysis and hydroboration rates for pairs of similar derivatives, the correlation is much less secure between differing structural types. Moreover, ^{11}B nmr chemical shifts do not correlate with rates of hydroboration. Synthetically, diethylaniline borane appears to offer

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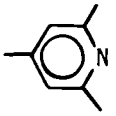
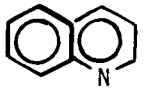
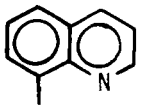
TABLE XXI. Data for Aromatic Amineborane Complexes

AmineBH_3	$^{11}B^a$(p.p.m)	T_{min}(100% hyd.)^b	% Hydroboration of 1-Octene^c
	-11.9	12	0
	-18.4	52	11
	-13.2	42	2.5
	-8.2	6	91
$PhNMe_2$	-6.0	15	56
$PhNEt_2$	-11.6	2	93

a. Rel. to $F_3B.OEt_2$ ext. ref. b. Hyd. by 3M HCl/glycerol/THF, 25°C.
c. THF, 25°C.

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advantages as a relatively stable source of borane which hydroborates efficiently at room temperature. Table XXI presents the striking difference in hydroboration rates between quinoline borane and 8-methylquinoline borane, presumably induced by steric compression by the peri-methyl group. In all cases of hydroborations with amine boranes, the regioselectivity parallels that of borane-THF.

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(Received June 22, 1984; in revised form August 1, 1984)

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