2,2,6,6-Tetramethyl-4-heptyn-3-ol: mp 38–40 °C [lit.[22] mp 38.5–40 °C]; MS, m/z 168 (M^+); IR ($BrCCl_3$) 3475 (OH), 2246 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 9 H), 1.23 (s, 9 H), 1.99–2.1 (m, 1 H), 3.96 (b s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.44, 27.53, 31.16, 35.93, 71.43, 94.32.

1-(3,3-Dimethyl-1-butynyl)cyclohexanol: mp 44.5–46 °C; MS, m/z 180 (M^+); IR ($BrCCl_3$) 3299 (OH), 2240 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.3–2.1 (m, 10 H), 2.73 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.69, 25.52, 27.37, 31.27, 40.57, 68.51, 82.77, 93.17.

1-(3,3-Dimethyl-1-butynyl)cyclopentanol: n^{20}_D 1.4655; MS, m/z 166 (M^+); IR (film) 3370 (OH), 2244 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.66–2.1 (m, 8 H), 2.5 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.53, 27.33, 31.21, 42.82, 74.55, 82.95, 91.50.

2,5,5-Trimethyl-3-hexyn-2-ol: bp 75 °C (16 mm); n^{20}_D 1.4299; MS m/z 140 (M^+); IR (film) 3375 (OH), 2280, 2244 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.46 (s, 6 H), 2.9 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.22, 31.19, 32.01, 65.02, 84.11, 90.36.

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Registry No. 1 (R = C≡C$(CH_2)_3CH_3$), 62459-81-8; 1 (R = C≡CPH), 62459-78-3; 1 (R = C≡C$(CH_2)_3$Cl), 62459-80-7; 1 (R = C≡CC(CH_3)=CH_2), 62248-79-7; 2, 62276-26-0; 5, 95764-75-3; 7, 999-70-2; 8, 15332-33-9; 9, 76014-98-7; 11, 17689-03-1; HCHO, 50-00-0; PhCHO, 100-52-7; $CH_3CH_2CH(OH)C$≡CPh, 27975-78-6; $Cl(CH_2)_3C$≡$CCH(OH)CH_2CH_3$, 999-71-3; CH_2=$C(CH_3)C$≡CCH$(OH)CH_2CH_3$, 95764-76-4; $(CH_3)_3CC$≡CCH_2OH, 52323-98-5; $(CH_3)_3CC$≡CCH(Ph)OH, 17474-12-3; $(CH_3)_3CC$≡CCH$(OH)C(CH_3)_3$, 30338-48-8; $(CH_3)_3CC$≡C$C(CH_3)_2OH$, 1522-16-3; propionaldehyde, 123-38-6; 3-cyclohexene-1-carboxaldehyde, 100-50-5; piraldehyde, 630-19-3; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; acetone, 67-64-1; 1-(3-cyclohexen-1-yl)-4,4-dimethyl-2-pentyn-1-ol, 95764-77-5; 1-(3,3-dimethyl-1-butynyl)cyclohexanol, 95764-78-6; 1-(3,3-dimethyl-1-butynyl)cyclopentanol, 95764-79-7.

Hydroboration. 71. Hydroboration of Representative Heterocyclic Olefins with Borane–Methyl Sulfide, 9-Borabicyclo[3.3.1]nonane, Dicyclohexylborane, and Disiamylborane. Synthesis of Heterocyclic Alcohols

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The hydroboration of representative heterocycles bearing an endocyclic double bond with borane–methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), and disiamylborane (Sia_2BH) was investigated systematically to establish the optimum conditions for clean and quantitative hydroboration. The hydroboration of 2,3- and 2,5-dihydrofurans with BMS (3:1 molar ratio) at 25 °C for 1 h affords the trialkylborane, readily oxidized to 3-hydroxytetrahydrofuran in excellent yield. However, preparation of the corresponding dialkylboranes from these olefins using 2 olefin/BMS was not possible even at 0 °C. Excess hydride and prolonged reaction time cause ring cleavage of the alkylboranes to yield both unsaturated alcohol and the dihydroborated products 1,3- and 1,4-pentanediols. Hydroboration of both 2,3-dihydrothiophene and 2-methyl-4,5-dihydrofuran with BMS proceeds cleanly to the trialkylborane stage, oxidized to the corresponding alcohols in almost quantitative yields. Hydroboration of 3-pyrroline with BMS could not be achieved with the unprotected nitrogen atom. Such hydroboration could be accomplished by protecting the nitrogen atom with the benzyloxycarbonyl group affording the trialkylborane, readily converted to *N*-(benzyloxycarbonyl)-3-pyrrolidinol in good yield. Conditions for a clean hydroboration of these heterocyclic five-membered olefins with 9-BBN, Chx_2BH, and Sia_2BH were also established. In all cases clean trialkylboranes were obtained, readily oxidized to heterocyclic alcohols in high yields. 3,4-Dihydropyran, on hydroboration with BMS, followed by oxidation, affords 3-hydroxytetrahydropyran in good yield. However, ring cleavage in this case is greater when compared to 2,3-dihydrofuran. 2-Methoxy- or 2-ethoxy-3,4-dihydro-2*H*-pyran readily undergo hydroboration with BMS to the trialkylboranes, oxidized to the corresponding trans and cis alcohols in a 7:3 ratio. As the steric requirements of the dialkylborane are increased, more trans alcohol is formed. Thus at 0 °C, the ratios of trans to cis alcohols were increased from 1:1 to 7:3 and then to 8:2 with 9-BBN, Chx_2BH, and Sia_2BH_2, respectively. *N*-(Benzyloxycarbonyl)-1,2,3,6-tetrahydropyridine is readily hydroborated with BMS, 9-BBN, Chx_2BH, and Sia_2BH to the corresponding trialkylboranes, readily oxidized to *N*-(benzyloxycarbonyl)-3- and -4-piperidinols in good yield. Strongly basic groups in the heterocyclic ring can greatly reduce the ease of hydroboration, and the introduction of boron β to the heteroatom can lead to elimination. However, both problems can be avoided to provide ready hydroboration–oxidation of heterocyclic olefins.

Hydroboration is a synthetically useful reaction.[2-4] The intermediate organoboranes thus produced undergo a wide variety of carbon–carbon bond forming and other reactions to afford almost all types of organic compounds.[5,6] In the

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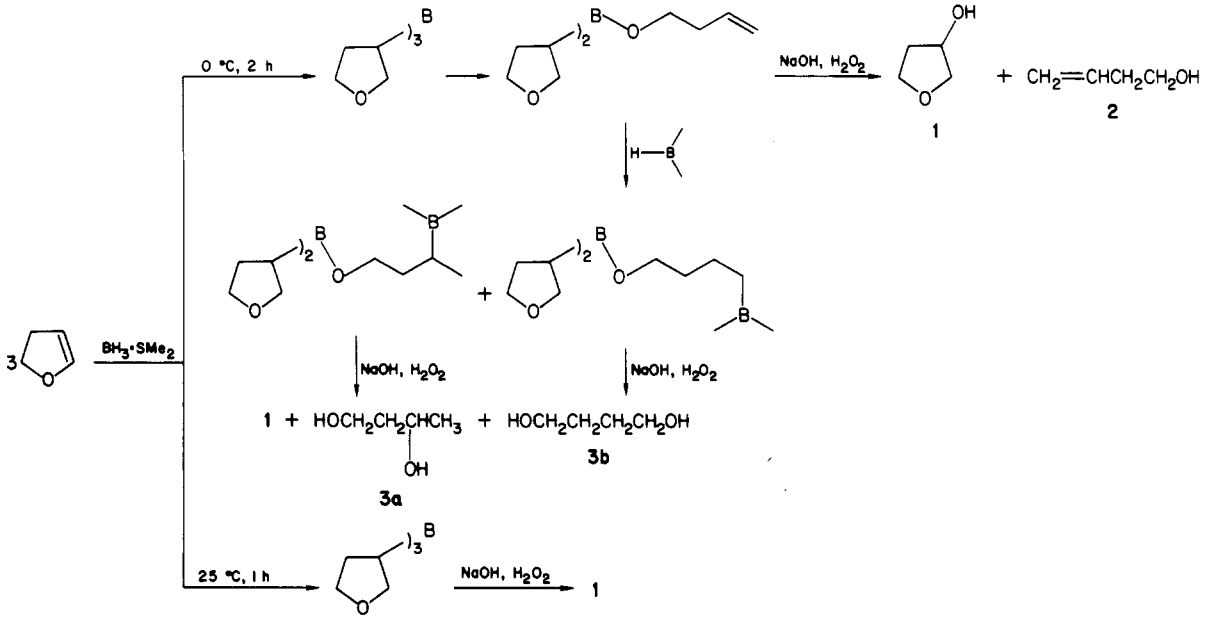
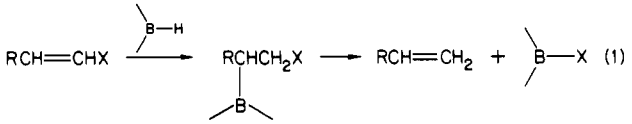
0022-3263/85/1950-1582$01.50/0

Scheme I

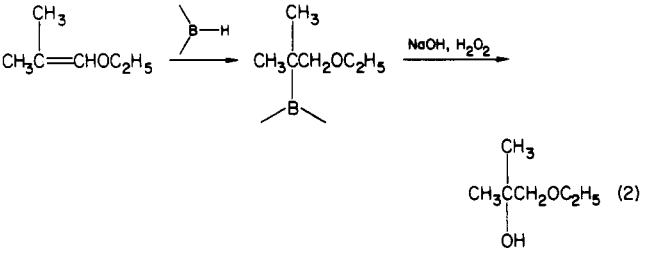


past, there were numerous reports on the hydroboration of cis olefins, trans olefins, trisubstituted olefins, dienes, acetylenic compounds, and functionalized unsaturated substrates. A wide range of hydroborating agents, such as borane–methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), disiamylborane (Sia_2BH), thexylborane (Thx_2BH), catecholborane, and haloboranes, were developed to achieve the hydroboration in a desired and convenient fashion, and their hydroboration properties were studied systematically.[7] These hydroborating agents were often complementary to each other, thus providing powerful procedures to the synthetic organic chemist for selective hydroboration of various compounds.

The hydroboration of 3-butenyl,[8] 2-butenyl,[9] and 1-butenyl[10] derivatives containing representative substituents were studied systematically in our laboratory. It was reported that organoboranes containing a heteroatom at the β-position tended to undergo 1,2-elimination (eq 1).[8-15]



The extent of elimination depends upon a number of factors, such as the leaving group, the temperature, and the solvent. If X is a good leaving group, such as OTs, Cl, or OAc, then elimination occurs rapidly.[8-10] Elimination can be minimized for poor leaving groups, such as OR and OAr. It was observed that such hydroborations can proceed with a remarkable regioselectivity, placing essentially all of the boron atom at the β-position.[10,14-16] Thus, 1-ethoxy-2-methyl-1-propene yields 88% of 1-ethoxy-2-methyl-2-propanol on hydroboration–oxidation, indicating the selectivity of the boron atom for a β-carbon atom even though it is tertiary (eq 2).[10]



Although there have been individual reports on the hydroboration of heterocyclic olefins containing oxygen,[16-22] sulfur,[23] and nitrogen,[24-34] a clear understanding of the optimum conditions required for clean and efficient hydroboration of heterocyclic olefins is truly lacking. Therefore, we undertook a systematic study of the hydroboration of representative heterocyclic olefins with

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Table I. Hydroboration of 2,3- and 2,5-Dihydrofurans

olefin	hydroborating agent	olefin to hydroborating agent ratio	reactn, temp, °C	reactn time, h	product distribution,[a] mol %			
					3-hydroxy-tetrahydrofuran (1)	3-buten-1-ol (2)	butanediols 1,3 (3a)	butanediols 1,4 (3b)
	$BH_3 \cdot SMe_2$	3:1	0	2	88	4	2	4
	$BH_3 \cdot SMe_2$	3:1	25	1	98	trace	0	trace
	$BH_3 \cdot SMe_2$	3:1	25	4	65	27	0	4
	$BH_3 \cdot SMe_2$	2:1	0	8	54	19	2	3
	$BH_3 \cdot SMe_2$	2:1	0	4	62	19	5	7
	$BH_3 \cdot SMe_2$	2:1	0	0.5	54	19	2	3
	9-BBN	1:1	25	1	100	0	0	0
	9-BBN	1:1	25	4	94	6	0	0
	9-BBN	1:1	25	22	28	70	0	0
	9-BBN	1:1	65	4	31	27	0	21
	Chx_2BH	1:1	25	1	100	0	0	0
	Sia_2BH	1:1	0	2	100	0	0	0
	$BH_3 \cdot SMe_2$	3:1	0	10	63	7	0	0
	$BH_3 \cdot SMe_2$	3:1	25	1	95	0	0	0
	$BH_3 \cdot SMe_2$	3:1	25	2	76	3	7	13
	9-BBN	1:1	25	1.5	82	5	0	0
	9-BBN	1:1	25	4	65	22	0	6
	Chx_2BH	1:1	25	1	92	2	0	trace
	Sia_2BH	1:1	0	2	96	0	0	0

[a] By GC analysis.

BMS, 9-BBN, Chx_2BH, and Sia_2BH in order to establish optimum conditions for the hydroboration.

Results and Discussion

The following five-membered and six-membered heterocyclic olefins were selected for study: 2,3-dihydrofuran, 2,5-dihydrofuran, 2-methyl-4,5-dihydrofuran, 2,3-dihydrothiophene, 3-pyrroline, *N*-(trimethylsilyl)-3-pyrroline, *N*-methyl-3-pyrroline, *N*-(benzyloxycarbonyl)-3-pyrroline, 3,4-dihydro-2-ethoxy-2*H*-pyran, 1,2,3,6-tetrahydropyridine, *N*-methyl-1,2,3,6-tetrahydropyridine, and *N*-(benzyloxycarbonyl)-1,2,3,6-tetrahydropyridine.

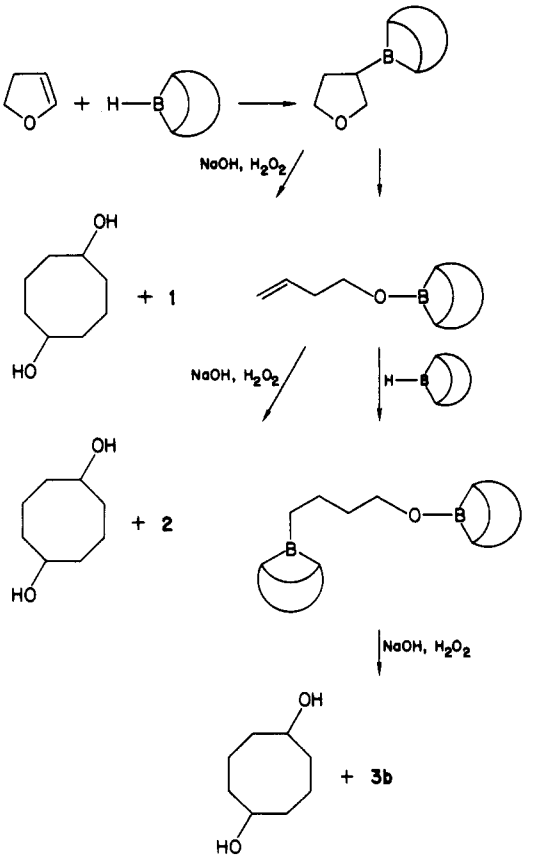
Five-Membered Oxygen Heterocycles. The hydroboration of 2,3-dihydrofuran with BMS (3:1 molar ratio) at 0 °C for 2 h proceeded to give a mixture of trialkylborane and borinate. Oxidation afforded a mixture of 3-hydroxytetrahydrofuran (**1**, 88%), 3-buten-1-ol (**2**, 4%), and 1,3- and 1,4-butanediols (**3a** and **3b**, 6%). The formation of the ring cleavage products **2** and **3** can be rationalized as shown in Scheme I.

Ring cleavage could be eliminated by performing the hydroboration at 25 °C for 1 h, as evidenced by ^{11}B NMR, which indicated the presence of trialkylborane only. Oxidation of the reaction mixture afforded the alcohol **1** in 98% yield. When the reaction was kept at 25 °C for 4 h, ring cleavage occurred, as evidenced by analysis of the reaction mixture following oxidation, which revealed the presence of 31% of the ring cleavage product **2**.

Dialkylboranes often are preferred reagents for hydroboration. The hydroboration of 2,3-dihydrofuran with BMS in a 2:1 molar ratio was carried out at 0 °C in order to prepare the heterocyclic dialkylborane, which might be a valuable hydroborating agent. However, the reaction could not be halted at the dialkylborane stage. The ^{11}B NMR spectrum after 2 h showed two peaks corresponding to BMS and borinate. Even reduction of the reaction time failed to yield clean dialkylborane.[35]

Hydroboration of 2,3-dihydrofuran with 9-BBN proceeded cleanly to trialkylborane at 25 °C for 1 h. Oxidation afforded the alcohol **1** essentially in quantitative yield. The trialkylborane is not very stable at 25 °C in THF. It gradually rearranges to the unsaturated acyclic borinate, which, after oxidation, gave unsaturated alcohol **2** (Scheme II). Thus the reaction mixture in 4 h and 22 h yielded 6% and 70% of the unsaturated alcohol **2**. Hydroboration in refluxing THF for 4 h yielded 51% of cleavage products **2** and **3b** and 31% of the alcohol **1**. Hydroboration of 2,3-dihydrofuran with Chx_2BH and Sia_2BH proceeded cleanly at 25 °C and 0 °C, respectively, to afford the alcohol **1** in essentially quantitative yields. No ring cleavage was observed. Hydroboration of 2,5-dihydrofuran with BMS, 9-BBN, Chx_2BH, and Sia_2BH gave similar results.

Scheme II



(35) For the sake of comparison, the reaction of 2,3-dihydrofuran with BH_3·THF (2:1 molar ratio) was also performed, which gave similar results.

Table II. Hydroboration of 2-Methyl-4,5-dihydrofuran, 2,3-Dihydrothiophene, and *N*-(Benzyloxycarbonyl)-3-pyrroline

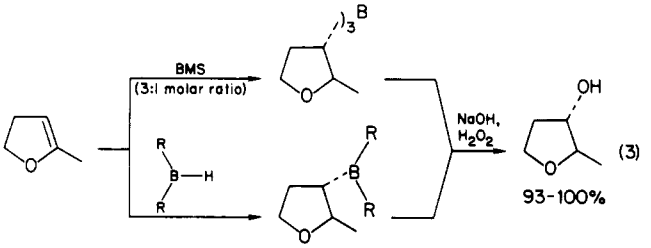
olefin	hydroborating agent	olefin to hydroborating agent ratio	reactn temp, °C	reactn time, h	product	yield,[a] %
	$BH_3 \cdot SMe_2$	3:1	25	1	*trans*-2-methyl-3-hydroxytetrahydrofuran	100
	9-BBN	1:1	25	1	*trans*-2-methyl-3-hydroxytetrahydrofuran	93
	Chx_2BH	1:1	25	1	*trans*-2-methyl-3-hydroxytetrahydrofuran	98
	Sia_2BH	1:1	0	2	*trans*-2-methyl-3-hydroxytetrahydrofuran	97
	$BH_3 \cdot SMe_2$	3:1	25	1	3-hydroxytetrahydrothiophene	94
	9-BBN	1:1	25	1	3-hydroxytetrahydrothiophene	98
	Chx_2BH	1:1	25	1	3-hydroxytetrahydrothiophene	100
	Sia_2BH	1:1	0	2	3-hydroxytetrahydrothiophene	100
	$BH_3 \cdot SMe_2$	3:1	25	1	*N*-(benzyloxycarbonyl)-3-pyrrolidinol	88
	9-BBN	1:1	25	1	*N*-(benzyloxycarbonyl)-3-pyrrolidinol	92
	Chx_2BH	1:1	25	1	*N*-(benzyloxycarbonyl)-3-pyrrolidinol	82
	Sia_2BH	1:1	0	3	*N*-(benzyloxycarbonyl)-3-pyrrolidinol	84

[a] By GC analysis.

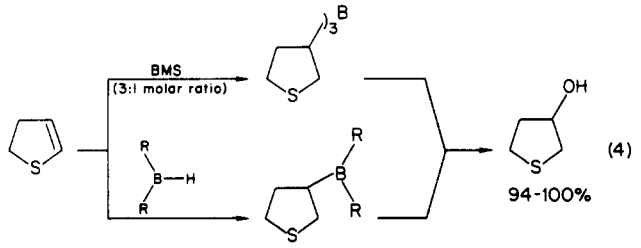
The results are summarized in Table I.

Similarly, the preferred condition for hydroboration of 2,3- and 2,5-dihydrofurans with BMS to form the desired trialkylborane is 25 °C in THF for 1 h. Reaction time and control of temperature is crucial for a clean reaction. We observed slightly more cleavage at 0 °C than at 25 °C. We believe that at 0 °C there is a higher concentration of intermediates, such as BH_3, RBH_2, and R_2BH, and that the cleavage arises from the Lewis acidity of such intermediates in interacting with the R_3B product.

The trisubstituted heterocyclic olefin 2-methyl-4,5-dihydrofuran underwent hydroboration cleanly with all of the hydroborating agents chosen for the present study, BMS (3:1 molar ratio), 9-BBN, Chx_2BH, and Sia_2BH (1:1 molar ratio), and afforded the corresponding trialkylboranes. Oxidation yielded *trans*-2-methyl-3-hydroxytetrahydrofuran in almost quantitative yields (eq 3). No ring cleavage was observed under the experimental conditions utilized for these hydroborations (Table II).

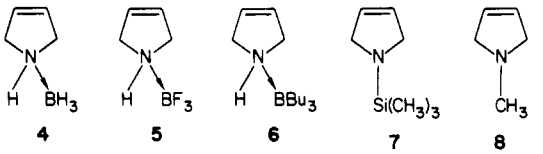


Five-Membered Sulfur Heterocycle. The hydroboration of 2,3-dihydrothiophene with BMS (3:1 molar ratio) at 25 °C for 1 h proceeded cleanly to give the trialkylborane, oxidized to 3-hydroxytetrahydrothiophene in excellent yield. Similarly, hydroboration of this olefin with 9-BBN, Chx_2BH, and Sia_2BH was also clean. Oxidation of the trialkylboranes obtained in each case gave 3-hydroxytetrahydrothiophene in essentially quantitative yields (eq 4, Table II).

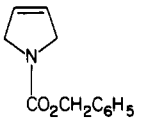


Five-Membered Nitrogen Heterocycles. 3-Pyrroline, on treatment with BMS (1:1 molar ratio), formed amine–borane complex **4** (as evidenced by the ^{11}B NMR signal at δ −18.1) and no hydroboration was observed. 3-Pyrroline was then treated with 1.33 equiv of BMS and the reaction mixture was stirred at 25 °C in THF for 6 h. No reaction was observed, even under these conditions. Moreover, the reaction failed to proceed even in refluxing THF (65 °C) for 2 h. Similar results were obtained for the reactions with 9-BBN and Sia_2BH, respectively.

The nitrogen atom of 3-pyrroline was next protected in several ways. Thus the amine–BF_3 complex **5**, amine–*n*-BBu_3 complex **6**, the *N*-trimethylsilyl derivative **7**, the *N*-methyl derivative **8**, and the *N*-benzyloxycarbonyl derivative **9** were prepared to study their hydroboration.



4 **5** **6** **7** **8**



9

The 3-pyrroline–BF_3 complex **5** was prepared by treating 3-pyrroline with boron trifluoride etherate (1:1 molar ratio) at 0 °C for 1 h. The complex thus formed, **5** (evidenced by ^{11}B NMR signal at δ −0.53), was treated with BMS (3:1 molar ratio) at 25 °C for 12 h, followed by refluxing in THF for 2 h. Unfortunately, the reaction did not proceed even under these vigorous experimental conditions. In a separate experiment, the 3-pyrroline–tri-*n*-butylborane complex, **6**, was prepared by adding tri-*n*-butylborane to 3-pyrroline (1:1 molar ratio) in THF at 25 °C (^{11}B NMR signal at δ −2.7). The complex **6** was treated with BMS (3:1 molar ratio) in THF at 25 °C for 4 h, followed by refluxing in THF for 1 h, but no hydroboration could be observed. Similarly, neither the *N*-(trimethylsilyl)-3-pyrroline (**7**) nor the *N*-methyl-3-pyrroline (**8**), underwent hydroboration with BMS at room temperature.

However, not all of our attempts were unsuccessful. Fortunately, *N*-(benzyloxycarbonyl)-3-pyrroline (**9**) underwent successful hydroboration with BMS (3:1 molar ratio) in THF at 25 °C for 1 h. Oxidation provided *N*-(benzyloxycarbonyl)-3-pyrrolidinol in 88% yield (eq 5).

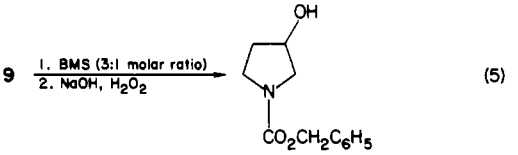
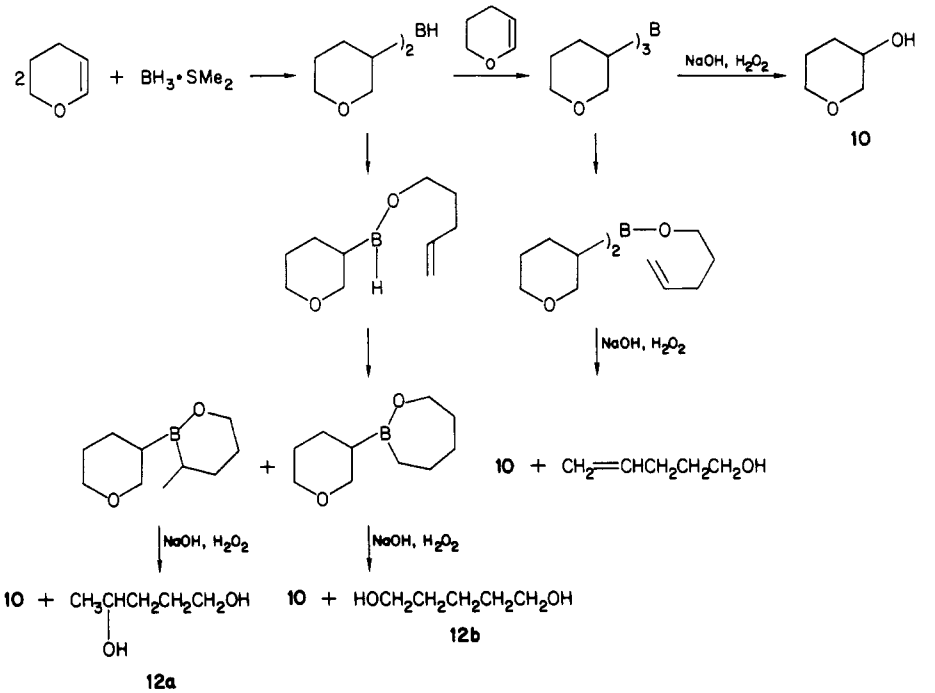


Table III. Hydroboration of 3,4-Dihydropyran

hydroborating agent	olefin to hydroborating agent ratio	reactn temp, °C	reactn time, h	product distribution,[a] mol % 3-hydroxytetrahydropyran (8)	4-penten-1-ol (9)	1,5- and 1,4-pentanediols 10a and 10b
BH_3·SMe_2	3:1	25	1	82	15	3
BH_3·SMe_2	3:1	25	4	51	1	20
BH_3·SMe_2	3:1	65	4	47	4	22
BH_3·SMe_2	2:1	25	4	37		56
BH_3·SMe_2	2:1	0	4	44		50
BH_3·THF	2:1	0	3	90		
9-BBN	1:1	25	2	92		
Chx_2BH	1:1	25	1.5	98		2
Sia_2BH	1:1	0	18	96	2	trace

[a] By GC analysis.

Scheme III

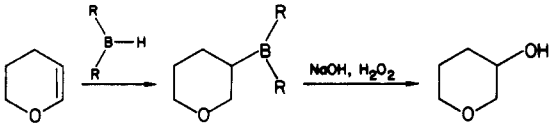


Similarly, the derivative **9** was successfully hydroborated with 9-BBN, Chx_2BH, and Sia_2BH, and oxidation of the trialkylboranes thus produced provided *N*-(benzyloxycarbonyl)-3-pyrrolidinol in excellent yields. The results are summarized in Table II.

Six-Membered Oxygen Heterocycles. The hydroboration of 3,4-dihydropyran with BMS (3:1 molar ratio) proceeded to trialkylborane and borinate. Oxidation yielded 3-hydroxytetrahydrofuran (**10**, 57–51%), 4-penten-1-ol (**11**, 1–4%), 1,4-pentanediol (**12a**), and 1,5-pentanediol (**12b**, 10–11%). The results of the experiments are shown in Table III. We established that initially both dialkylborane and trialkylborane are formed. These then undergo cleavage to form borinates (as evidenced by ^{11}B NMR). The formation of cleavage products **11** annd **12** could be accounted for as shown in Scheme III.

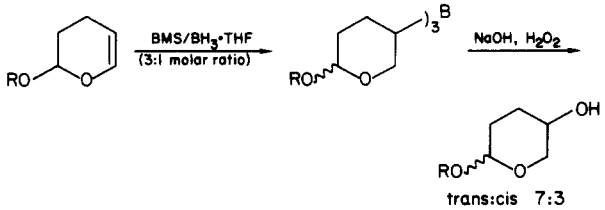
Hydroboration of 3,4-dihydropyran with BMS in a 2:1 molar ratio at 25 °C or 0 °C for 4 h produced the dialkylborane along with borinate. Oxidation of these organobornes yielded the alcohol **10** (37–44%) and diols **12a** (25–27%) and **12b** (25–29%). The reaction could not be stopped at the dialkylborane stage. However, all of the hydride was consumed in the reaction. Another experiment in THF at 0 °C using BH_3·THF was performed to compare the reaction with that of BH_3·THF in a 2:1 molar ratio. The reaction yielded a slight gray precipitate of bis(3-tetrahydropyranyl)borane. Oxidation of this yielded the alcohol **10** in 90% yield.

The hydroboration of 3,4-dihydropyran with dialkylboranes, 9-BBN, Chx_2BH, and Sia_2BH proceeded very cleanly to afford the corresponding trialkylboranes, which on further oxidation gave the alcohol **10** in excellent yields (eq 6). The results are summarized in Table III.



(6)

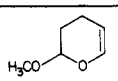
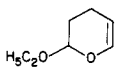
Hydroboration of 2-methoxy-3,4-dihydro-2*H*-pyran with either BH_3·THF or BMS in a 3:1 molar ratio in THF at 25 °C for 4 h proceeded cleanly to afford the trialkylborane, oxidized to *trans*- and *cis*-2-methoxy-5-hydroxytetrahydropyran in a 8:3 ratio (eq 7, R = CH_3).



(7)

R=CH_3, C_2H_5

Table IV. Hydroboration of 2-Methoxy-3,4-dihydro-2*H*-pyran and 2-Ethoxy-3,4-dihydro-2*H*-pyran

olefin	hydroborating agent	olefin to hydroborating agent ratio	reactn temp, °C	reactn time, h	total yield,[a] %	% of alcohols[a]	
	BH_3·THF	3:1	25	3	80	27	73
	BH_3·SMe_2	3:1	25	3	90	32	68
	9-BBN	1:1	25	12	96	49	51
	9-BBN	1:1	0	48	92	53	47
	Chx_2BH	1:1	25	2	96	47	53
	Chx_2BH	1:1	0	24	88	34	66
	Sia_2BH	1:1	0	48	98	21	79
olefin	hydroborating agent	olefin to hydroborating agent ratio	reactn temp, °C	reactn time, h	total yield,[a] %	% of alcohols[a]	
	BH_3·THF	3:1	25	5	70	28	72
	BH_3·SMe_2	3:1	25	1	94	32	68
	9-BBN	1:1	25	12	100	56	44
	Chx_2BH	1:1	25	2	96	48	52
	Sia_2BH	1:1	0	48	96	21	79
	Sia_2BH[b]	1:1	0		92	20	80

[a] By GC analysis. [b] The result was taken from Zweifel, G; Plamondon, J. *J. Org. Chem.* **1970**, *35*, 898.

Table V. Hydroboration of *N*-(Benzyloxycarbonyl)-1,2,3,6-tetrahydropyridine

hydroborating agent	olefin to hydroborating agent ratio	reactn temp, °C	reactn time, h	total yield,[a] %	product distribution,[a] %	
					N-(benzyloxycarbonyl)-3-piperidinol	*N*-(benzyloxycarbonyl)-4-piperidinol
BH_3·SMe_2	3:1	25	1	80	85	15
9-BBN	1:1	25	24	75	85	15
Chx_2BH	1:1	25	6	84	75	25
Sia_2BH	1:1	0	96	69	75	25

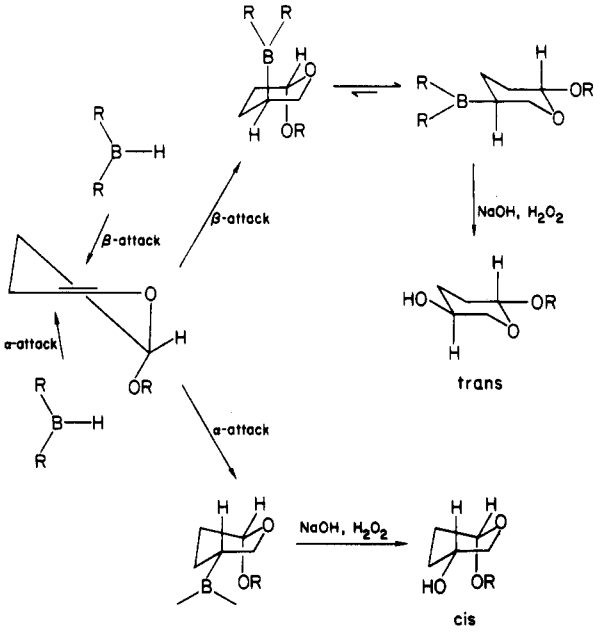
[a] By GC analysis.

Similarly, hydroboration of 2-methoxy-3,4-dihydro-2*H*-pyran with 9-BBN, Chx_2BH, and Sia_2BH at 0 °C cleanly formed the corresponding trialkylboranes. Oxidation of these organoboranes yield trans and cis alcohols in ratios of 1:1, 7:3, and 8:2, respectively. Thus it appears that the trans to cis alcohol ratio varies with the steric requirements of the dialkylborane. In the case of Chx_2BH it was noted that decrease in the temperature to 0 °C increased the trans/cis ratio from 1:1 to 2:1. A similar ratio of alcohols was obtained in the hydroboration of 2-ethoxy-3,4-dihydro-2*H*-pyran with 9-BBN, Chx_2BH, and Sia_2BH. The results are summarized in Table IV and can be rationalized as shown in Scheme IV.

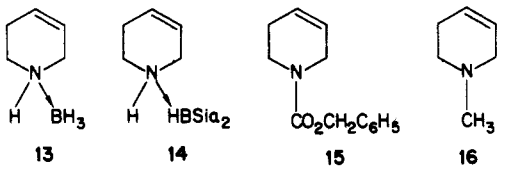
It is known that the 2-alkoxytetrahydropyrans prefer the more sterically encumbered axial conformation (anomeric effect).[36] The hydroboration of 2-alkoxy-3,4-dihydro-2*H*-pyran is very regioselective. The hydroborating agent can attack either from the α-side or the β-side. However, α-side attack should be more sterically disfavored due to the axial alkoxy group. Hence, when the steric requirements of the dialkylborane are relatively high, it prefers to attck the double bond from the β-side. Since 9-BBN is very much less sensitive to steric factors,[37] this factor is less important.

Six-Membered Nitrogen Heterocycles. The six-membered nitrogen heterocycle 1,2,3,6-tetrahydropyridine behaved in a manner similar to that of the five-membered nitrogen heterocycle, as described previously. No hydroboration was achieved at 25 °C with BMS or Sia_2BH, even though an excess of the hydroborating agent was used. Only formation of the amine–Lewis acid complexes **13** and **14** were observed. In this case also the hydroboration occurred readily following deactivation of the amino moiety as the benzyloxycarbonyl derivative **15**. In this case, treatment with BMS (3:1 molar ratio) at 25 °C for 1 h provided the hydroboration product, readily oxidized in the usual manner to give 85% of *N*-(benzyloxycarbonyl)-3-

Scheme IV



(36) Armarego, W. L. F. "Stereochemistry of Heterocyclic Compounds"; Part II; Wiley: New York, 1977.
(37) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.



13 14 15 16

and -4-piperidinols in a ratio of 85:15. Similarly, hydroboration of this olefin, **15**, with 9-BBN, Chx_2BH, and Sia_2BH followed by oxidation afforded *N*-(benzyloxycarbonyl)-3- and -4-piperidinols in good yields. However, in the case of Chx_2BH and Sia_2BH, a slightly different ratio of the isomeric products 3- and 4-piperidinols, 75:25, is obtained. The results are summarized in Table V.

On the other hand, *N*-methyl-1,2,3,6-tetrahydropyridine (**16**) behaved differently than the five-membered analogue **8**. In this case, **16** underwent slow hydroboration with BMS (1:1.33 molar ratio) at 25 °C. Similarly, Sia_2BH (1:2 molar ratio) successfully hydroborated the double bond of **16**.

We have not attempted to explore the cause for this interesting difference in the behavior of **8** and **16**. Possibly, in the five-membered derivative **8** the deactivation produced by the donor bond of the borane adduct is more effectively transmitted to the double bond through the five-membered ring of **8** than is the case with the six-membered ring of **16**.

Conclusion

The hydroboration–oxidation of heterocycles is synthetically highly useful, affording the corresponding alcohols in excellent yields. In the case of heterocyclic olefins containing a double bond α to the heteroatom, the hydroboration reaction is highly regioselective, placing boron 100% on the β-carbon atom. The many heterocyclic trialkylboranes synthesized in this study should be applicable in the many known organoborane reactions.[6] Thus, B-heterocyclic 9-BBN derivatives should be convertable into their corresponding aldehydes via carbonylation and should be applicable in the α-alkylation reactions to form α-substituted esters, α-halo esters, carbonyl compounds, nitriles, etc., and to the synthesis of 1,4-conjugated addition products (Scheme V).

Hydroboration of various heterocyclic olefins provides the trialkylboranes very cleanly. This study suggested that it should be possible to hydroborate these heterocyclic olefins with diisopinocampheylborane to achieve the synthesis of chiral heterocyclic compounds. Currently we are exploring the asymmetric hydroboration of these and other heterocyclic olefins with a number of chiral hydroborating agents.

Experimental Section

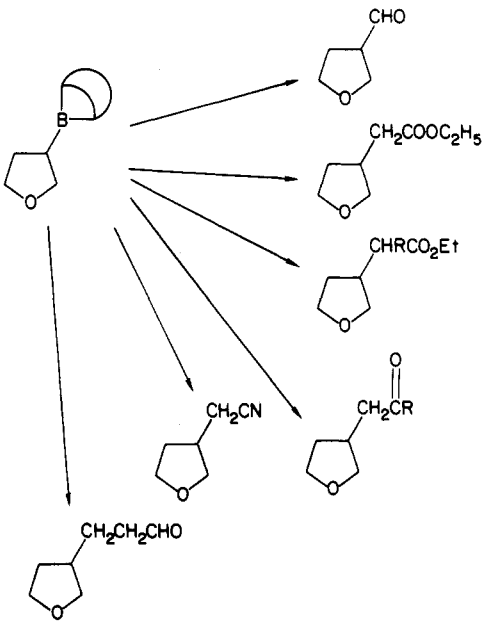
The reaction flasks and other glass equipment were stored in an oven at 150 °C overnight and assembled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled in a stream of dry nitrogen gas. Special techniques used in handling air-sensitive materials are described in detail elsewhere.[6]

Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3{\cdot}OEt_2$. ^1H NMR (90 MHz), ^{13}C NMR (80 MHz), IR, and mass spectra were recorded on Perkin-Elmer R-32, Varian FT-80A, Perkin-Elmer 137, and Finnegan GC/mass spectrometers, respectively.

GLC Analyses. All GLC analyses were carried out with a Hewlett-Packard 5750 chromatography using 9 ft and 12 ft × 0.125 in columns packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh) or 12 ft × 0.125 in. column packed with 10% SE-30 on Chromosorb W (100–120 mesh).

Materials. Borane–methyl sulfide (BMS) and 9-borabicyclo[3.3.1]nonane (9-BBN) were purchased from Aldrich Chemical Company. BMS was estimated according to the standard procedure.[6] Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. 2,3-Dihydrofuran, 2,5-dihydrofuran, 2-methyl-4,5-dihydrofuran, 3,4-dihydropyran, 3,4-dihydro-2-methoxy-2*H*-pyran, and 3,4-dihydro-2-ethoxy-2*H*-pyran were kept over anhydrous potassium carbonate overnight and distilled in nitrogen atmosphere. 2,3-Dihydrothiophene was prepared according to the literature procedure.[38] *N*-(Benzyloxycarbonyl)-3-pyrroline (contains 25% of *N*-(benzyloxycarbonyl)-3-pyrrolidine) and *N*-(benzyloxycarbonyl)-1,2,3,6-tetrahydropyridine were prepared by the reaction of 3-pyrroline (contains 25% of pyrrolidine, Aldrich) and 1,2,3,6-tetrahydropyridine with benzyl chloroformate in the presence of sodium hydroxide.[39] The internal standard tridecane (Phillips) was kept over 4-Å molecular sieves under nitrogen atmosphere and used as such.

Scheme V



Preparation of Dialkylboranes. Dicyclohexylborane was prepared according to the literature procedure.[40] Disiamylborane was prepared as follows. In a 50-mL, round-bottomed flask equipped with a septum inlet and magnetic stirring bar was placed 20 mmol (1.12 mL of 8.98 M) of BMS. The flask was cooled to −10 °C. To it was added 40 mmol (2.24 mL) of 2-methyl-2-butene dropwise via syringe. The flask was kept at 0 °C under stirring for 3 h. The ^{11}B NMR of the reaction mixture after methanolysis showed a clean signal at δ 53.8, characteristic of R_2B–O species.

Hydroboration with BMS. A typical experiment is as follows. In a 25-mL flask equipped with a septum inlet, magnetic stirring bar, and connecting tube leading to a mercury bubbler was placed 1.1 mL (15 mmol) of 2,3-dihydrofuran in 12.6 mL of THF. To it was added 0.74 mL (3 mmol) of tridecane. The reaction flask was cooled to 0 °C. To it was added 0.56 mL (5 mmol) of BMS (8.98 M) dropwise via syringe. The reaction mixture was kept at room temperature and the reaction was followed by ^{11}B NMR. After 1 h, the reaction mixture was cooled to 0 °C and oxidized by using 5 mL of 3 N sodium hydroxide and 30% hydrogen peroxide. The reaction mixture was kept at 25 °C for 6 h. The aqueous phase was saturated with 8 g of anhydrous potassium carbonate. A small amount of the organic phase was dried over 4-Å molecular sieves and analyzed by GC. The percentage of the products was calculated by using a correction factor. The results are summarized in Table I.

The following is representative for isolating the heterocyclic alcohols. In a 100-mL flask equipped with a septum inlet, a magnetic stirring bar, and a connecting tube leading to a mercury

(38) Sosnovsky, G. *Tetrahedron* **1962**, *18*, 15 and 903.
(39) Izumiya, N.; Francis, J. E.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1962**, *84*, 1702.
(40) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, *42*, 1392.

bubbler was placed 1.9 mL (25 mmol) of 2,3-dihydrofuran in 20.3 mL of THF. The reaction flask was cooled to 0 °C and 2.8 mL (25 mmol) of BMS (8.98 M) was added dropwise via syringe under magnetic stirring. After 1 h at 25 °C, the reaction mixture was cooled to 0 °C and oxidized with 8.3 mL of 3 N sodium hydroxide and 4 mL of 30% hydrogen peroxide. The reaction mixture was stirred at 25 °C for 6 h. The aqueous phase was saturated with 12.5 g of anhydrous potassium carbonate. The organic layer was separated. The aqueous layer was extracted with 3 × 15 mL of ether and the combined ether extracts were dried over anhydrous $MgSO_4$. The ether was evaporated. The residue on distillation under vacuum afforded 2 g of 3-hydroxytetrahydrofuran: yield 91%; bp 80 °C (15 mm) [lit.[41] bp 93–96 °C (26 mm)]; n^{20}_D 1.4465, [lit.[41] n^{25}_D 1.4497]; IR (neat), 3413, 2939, 2878, 1441, 1272, 1120, 1065; ^{1}H NMR ($CDCl_3$) δ 4.3 (m, 1 H), 4.0 (m, 2 H), 3.7 (d, 2 H), 1.9 (m, 2 H); ^{13}C NMR ($CDCl_3$) ppm 75.32, 71.33, 66.76, 55.33; mass spectrum, *m/e* (relative intensity) 88, M, (6), 71 (10), 70 (11), 58 (67), 57 (100), 44 (15), 43 (39).

Hydroboration with 9-BBN. In the usual experimental setup was placed 1.2 g of solid 9-BBN (10 mmol) in THF and 3.7 g (2 mmol) of tridecane added. To it was added 10 mmol of heterocyclic olefin dropwise. The reaction mixture was kept under stirring at 25 °C and the reaction was followed by ^{11}B NMR. After the reaction was completed, the reaction mixture was oxidized with 10 mL of 3 N sodium hydroxide and 4.25 mL of 30% hydrogen peroxide. The contents were maintained at 55 °C for 1 h to insure the completion of oxidation. The reaction mixture was cooled to 25 °C, and 15 g of anhydrous potassium carbonate was added. After the reaction mixture was stirred for 15 min, the organic layer was taken and dried over molecular sieves and analyzed by GC.

Hydroboration with Chx_2BH. The reactions were done as described above for 9-BBN.

Hydroboration with Sia_2BH. The hydroborations were performed at 0 °C and the procedure is as described for 9-BBN.

The physical data and spectral properties of heterocyclic alcohols are as follows.

3-Hydroxytetrahydrothiophene: bp 42 °C (0.3 mm) [lit.[42] bp 44–48 °C (0.3 mm)]; IR (neat) 3473, 2932, 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.6 (m, 1 H), 2.95 (m, 4 H), 2.7 (s, exchangeable with D_2O, 1 H), 2.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) ppm 74.67, 39.85, 38.11, 28.16; mass spectrum, *m/e* (relative intensity) 105 M + 1 (25), 104, M (100), 87 (40), 86 (27), 85 (18), 76 (24), 60 (32), 59 (20), 57 (22), 48 (47), 45 (32), 43 (18).

***trans*-2-Methyl-3-hydroxytetrahydrofuran**: bp 91–92 °C (15 mm) [lit.[16] bp 91 °C (21 mm)]; n^{20}_D 1.4415 [lit.[16] n^{22}_D 1.4420]; IR (neat) 3413, 2965, 2885, 1445, 1374, 1308, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.93 (m, 5 H), 2.0 (m, 2 H), 1.23 (d, 3 H), 3.0 (s, exchangeable with D_2O, 1 H); ^{13}C NMR ($CDCl_3$) ppm 81.92, 76.86, 66.19, 34.49, 18.93; mass spectrum, *m/e* (relative intensity) 103, M + 1 (58), 85 (100), 58 (47), 57 (53), 45 (13), 43 (40).

***N*-(Benzyloxycarbonyl)-3-pyrrolidinol.** From the crude reaction mixture, the alcohol was isolated by column chromatography using silica gel; 40% ether in pentane eluents removed *N*-(benzyloxycarbonyl)-3-pyrrolidine, whereas, the ether eluents afforded pure *N*-(benzyloxycarbonyl)-3-pyrrolidinol: n^{20}_D 1.5406; IR (neat) 3413, 2945, 2892, 1685, 1431, 1361, 1201, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 5.1 (s, 2 H), 4.2 (m, 1 H), 4.1 (s, exchangeable with D_2O, 1 H), 3.6 (m, 4 H), 1.86 (m, 2 H); mass spectrum, *m/e* (relative intensity) 222, M + 1 (5), 221, M (16), 114 (6), 92 (10), 91 (100), 86 (4), 65 (8), 42 (5.4).

3-Hydroxytetrahydropyran: bp 90 °C (20 mm) [lit.[16] bp 90 °C (21 mm)]; n^{20}_D 1.4570 [lit.[16] n^{20}_D 1.4572]; IR (neat) 3386, 2935, 2848, 1441, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.26–3.93 (m, 5 H), 3.06 (s, exchangeable with D_2O, 1 H), 1.66–2.13 (m, 4 H); ^{13}C NMR ($CDCl_3$) ppm 72.90, 67.91, 65.69, 31.53, 23.33; mass spectrum, *m/e* (relative intensity) 103, M + 1 (6), 102 (17), 85 (31), 84 (14), 70 (26), 58 (19), 57 (34), 45 (34), 44 (100), 43 (62), 42 (17), 41 (21).

***cis*- and *trans*-2-Methoxy-5-hydroxytetrahydropyran**: bp 98–101 °C (12 mm) [lit.[17] bp 100 °C (10 mm)]; n^{20}_D 1.4550 [lit.[17] n^{20}_D 1.4559]; IR (neat) 3419, 2939, 1435, 1370, 1272, 1120, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.6 (m, 1 H), 3.4 (s, 3 H), 3.3–4.0 (m, 4 H), 1.5–2.1 (m, 4 H); ^{13}C NMR ($CDCl_3$) ppm 99.36, 98.20, 65.67, 65.46, 65.30, 64.75, 55.17, 54.80, 28.31, 27.82, 26.30, 25.81; mass spectrum, *m/e* (relative intensity) 131, M-H (6), 115 (3), 101 (100), 83 (23), 71 (16), 59 (21), 58 (52), 57 (12), 43 (31).

***cis*- and *trans*-2-Ethoxy-5-hydroxytetrahydropyran**: bp 92–93 °C (0.6 mm) [lit.[16] bp 64–66 °C (1 mm)]; n^{20}_D 1.4515 [lit.[16] n^{22}_D 1.4505]; IR (neat) 3413, 2932, 1440, 1370, 1206, 1130, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.5 (m, 1 H), 3.25–4.05 (m, 5 H), 3.0 (s, exchangeable with D_2O, 1 H); ^{13}C NMR ($CDCl_3$) ppm 97.90, 97.16, 65.98, 65.79, 65.35, 64.94, 63.17, 62.92, 28.26, 28.01, 26.50, 26.06, 15.08; mass spectrum, *m/e* (relative intensity) 145 M + 1 (1), 116 (15), 101 (42), 83 (26), 75 (26), 72 (71), 57 (36), 55 (22), 47 (36), 44 (100), 43 (84).

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Registry No. **2**, 627-27-0; **8**, 19752-84-2; **9**, 821-09-0; **10A**, 111-29-5; **10B**, 626-95-9; BMS, 13292-87-0; 9-BBN, 280-64-8; Chx_2BH, 1568-65-6; Sia_2BH, 1069-54-1; *N*-(benzyloxycarbonyl)-3-pyrroline, 31970-04-4; *trans*-2-methyl-3-hydroxytetrahydrofuran, 20086-88-8; 3-hydroxytetrahydrothiophene, 3334-05-2; *N*-(benzyloxycarbonyl)-3-pyrrolidinol, 95656-88-5; *cis*-2-methoxy-5-hydroxytetrahydropyran, 95908-97-7; *trans*-2-methoxy-5-hydroxytetrahydropyran, 95908-98-8; *cis*-2-ethoxy-5-hydroxytetrahydropyran, 95798-20-2; *trans*-2-ethoxy-5-hydroxytetrahydropyran, 95798-21-3; *N*-(benzyloxycarbonyl)-1,2,3,6-tetrahydropyridine, 66207-23-6; *N*-(benzyloxycarbonyl)-3-piperidinol, 95798-22-4; *N*-(benzyloxycarbonyl)-4-piperidinol, 95798-23-5; 2,3-dihydrofuran, 1191-99-7; 2,5-dihydrofuran, 1708-29-8; 3-hydroxytetrahydrofuran, 453-20-3; 1,3-butanediol, 107-88-0; 1,4-butanediol, 110-63-4; 5-methyl-2,3-dihydrofuran, 1487-15-6; 2,3-dihydrothiophene, 1120-59-8; 3,4-dihydropyran, 110-87-2; 2-methoxy-3,4-dihydro-2*H*-pyran, 4454-05-1; 2-ethoxy-3,4-dihydro-2*H*-pyran, 103-75-3; 2-methyl-2-butene, 513-35-9; BH_3·THF, 14044-65-6.

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