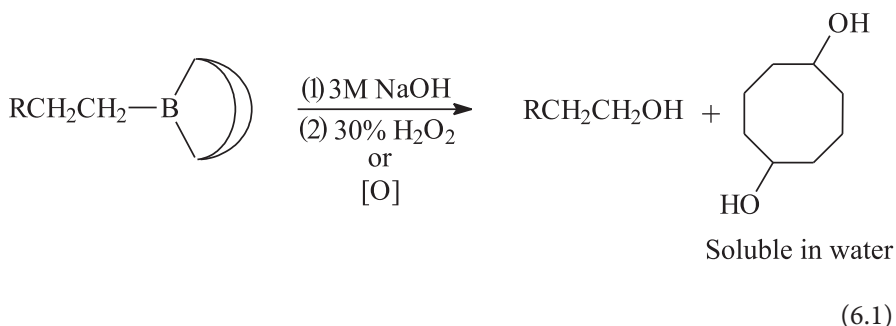# 6 Synthesis of Alcohols

6.1
Synthesis of Saturated Alcohols

Hydroboration-oxidation is now a standard method for *anti*-Markovnikov's *cis*-hydration [1] of alkenes from the less hindered side of the double bond. The hydroboration of olefins, mainly in THF solvent, affords conveniently the corresponding organoboranes. Oxidation of the intermediate organoboranes is most conveniently carried out by successive addition of 3 M NaOH and 30% hydrogen peroxide (depicted as [O], Eq. 6.1). Other oxidation procedures, e.g., H_2O_2 in buffer solutions, H_2O_2 in NaOAc, per acids, and trimethyl-*N*-oxides are used in certain cases when the organoboranes are unstable to water or contain functionalities sensitive to alkaline medium.

$$\text{RCH}_2\text{CH}_2\text{—B} \quad \xrightarrow[\substack{(2)\ 30\%\ \text{H}_2\text{O}_2 \\ \text{or} \\ [\text{O}]}]{(1)\ 3\text{M NaOH}} \quad \text{RCH}_2\text{CH}_2\text{OH} \ + \quad \text{(cyclooctane diol, OH / HO)}$$

Soluble in water

$$(6.1)$$

Among all boranes, 9-BBN shows the highest sensitivity to subtle differences in steric environment. Though, disiamylborane is sterically more hindered than 9-BBN, but surprisingly, the hydroboration of 1-hexene with 9-BBN in THF at 25 °C is more regioselective than is disiamylborane. The comparative data are given in Table 6.1 [2].

In general, the intermediate organoboranes on usual oxidation afford the corresponding alcohols, essentially in quantitative yields. Only in the case of 2,3-dimethyl-2-butene is the primary alcohol (<0.5%) derived from an isomerized organoborane. The results are summarized in Table 6.2 [2].

Table 6.1. Hydroboration-oxidation products in the reaction of unsymmetrical olefins with diborane, disiamylborane and 9-boracyclo[3.3.1]nonane (9-BBN) [2]

Olefin	Hydroborating agent	Product distribution (%)[a]		
		1-ol	2-ol	3-ol
1-Hexene	BH_3	94	6	
	Sia_2BH	99	1	
	9-BBN	>99.9		
Styrene	BH_3	80	20	
	Sia_2BH	98	2	
	9-BBN	98.5	1.5	
cis-4-Methyl-2-pentene	BH_3		57	43
	Sia_2BH		97	3
	9-BBN		99.8	0.2

[a] Total yields of products are 95±5%.

Table 6.2. Products from the hydroboration–oxidation of representative olefins with 9-BBN in THF [2]

Olefin	Time (h)	Temp (°C)	Product distribution (%)[a]
1-Hexene	2	25	1-Hexanol, >99.9
3,3-Dimethyl-1-butene	2	25	3,3-Dimethyl-1-butenol, >99.7 3,3-Dimethyl-2-butanol, <0.3
Styrene	4	25	1-Phenylethanol, 98.5 2-Phenylethanol, 1.5
2-Methyl-1-pentene	2	25	2-Methyl-1pentanol, >99.8
cis-3-Hexene	1	65	3-Hexanol, 100
cis-4-Methyl-2-pentene	1	65	4-Methyl-2-pentanol, 99.8 2-Methyl-3-pentanol, 0.2
cis-4,4-Dimethyl-2-pentene	1	65	4,4-Dimethyl-2-pentanol, 99.9 2,2-Dimethyl-3-pentanol, 0.1
2-Methyl-2-butene	1	65	3-Methyl-2-butanol, >99.8
Cyclopentene	2	25	Cyclopentanol, 100
Cycloheptene	2	25	Cycloheptanol, 100
Cyclooctene	2	25	Cyclooctanol, 100
Norbornene	2	25	*exo*-Norborneol, 99.5 *endo*-Norborneol, 0.5
Cyclohexene	1	65	Cyclohexanol
1-Methylcyclohexene	8	65	*trans*-2-Methylcyclohexanol, >99.8
2,3-Dimethyl-2-butene	8	65	2,3-Dimethyl-2-butanol, 99.5 2,3-Dimethyl-1-butanol, 0.5

[a] The combined yield of alcohols is >97%, except for 2,3-dimethyl-2-butene, where it is 95%.

Table 6.3 Products from the hydroboration-oxidation of representative olefins with 9-BBN in refluxing benzene and hexane solvents[2]

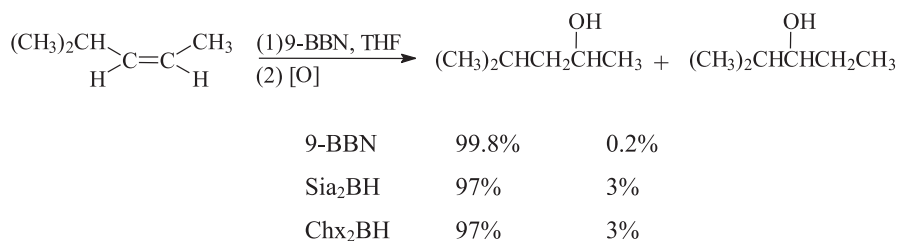| Olefins	Product	Yield (%)[a,b]	
		Benzene	Hexane
1-Hexene	1-Hexanol	>99.5	>99.5
	2-Hexanol	<0.5	Trace
3,3-Dimethyl-1-butene	3,3-Dimethyl-1-butanol	>99.5	>99.5
	3,3-Dimethyl-2-butanol	Trace	Trace
Styrene	2-Phenylethanol	98	98
	1-Phenylethanol	2	2
cis-3-Hexene	3-Hexanol	100	100
2,3-Dimethyl-2-butene[c]	2,3-Dimethyl-2-butanol	99.5	99.5
		0.5	0.5
Cyclopentene	Cyclopentanol	100	100
Cyclohexene	Cyclohexanol	100	100
1-Methylcyclohexene[d]	trans-2-Methyl-cyclohexanol	>99.5	>99.5
	Cyclohexanemethanol	Trace	Trace
Norbornene	exo-Norborneol	99.5	99.5
	endo-Norborneol	0.5	0.5

[a] Reaction times are 8 h.
[b] Total yields of 93–100% are obtained.
[c] Reaction time of 12 h. Total yield of alcohols is 71% in benzene and 40% in hexane.
[d] Reaction time of 12 h.

The results of hydroboration-oxidation in solvents benzene and hexane are summarized in Table 6.3 [2]. Hydroboration is slower in non-ether solvents.

The cis-4-methyl-2-pentene reacts to place 99.8% (Chart 6.1) of the boron of 9-BBN at the less hindered of the two carbon atoms of the double bond. It is significant to mention that no selectivity is observed with either thexylborane or diborane.

$$(CH_3)_2CH \underset{H}{\overset{}{C}} = \underset{H}{\overset{CH_3}{C}} \xrightarrow[\text{(2) [O]}]{\text{(1)9-BBN, THF}} (CH_3)_2CHCH_2\overset{OH}{\underset{|}{C}}HCH_3 \; + \; (CH_3)_2CH\overset{OH}{\underset{|}{C}}HCH_2CH_3$$

|		
9-BBN	99.8%	0.2%
Sia$_2$BH	97%	3%
Chx$_2$BH	97%	3%

Chart 6.1

Hydroboration of the *trans* isomer is much less regioselective.

The hydroboration of substituted cycloalkenes proceeds with exceptionally high regio- and stereoselectivity. The addition of B–H occurs *cis*. Consequently, hydroboration of 1-substituted cycloalkenes cleanly produce the *trans*-2-alkyl-cyclo-9-BBN, which on oxidation produces the corresponding *trans*-alcohols (Chart 6.2) [3].

9-BBN	>99.9%	~0%
BH_3	98.5%	1.5%
$HBCl_2$	>99.8%	<0.2%

9-BBN	>99.9%	~0%
BH_3	98%	<2%
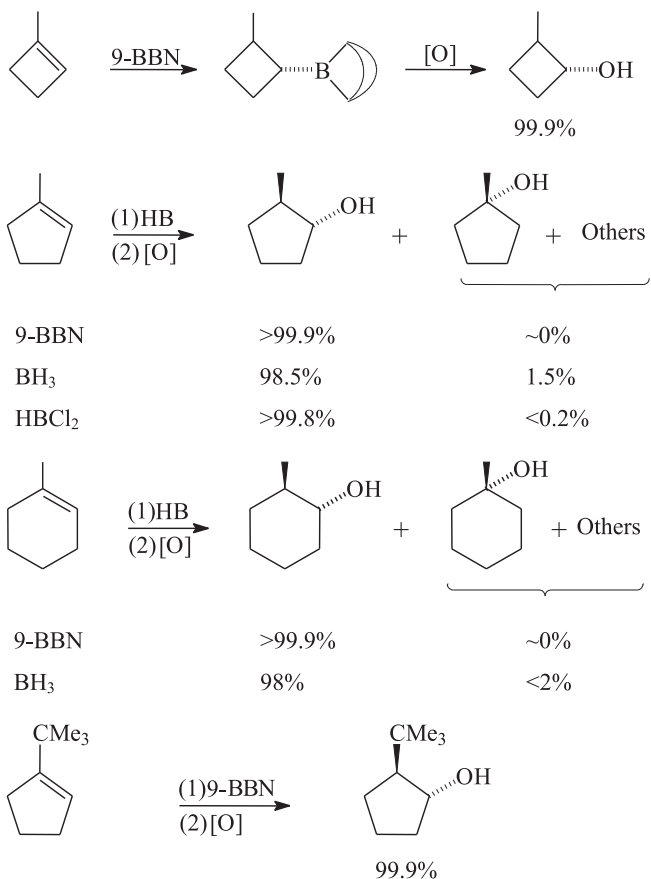
Chart 6.2

The stereoselectivities of 9-BBN, IPC$_2$BH, Sia$_2$BH, and BH$_3$ toward 3-substituted cycloalkenes are of little significant, as the addition of B–H occurs from both the faces. Among these hydroborating agents 9-BBN, however, gives the highest regioselectivity (Chart 6.3) [3].
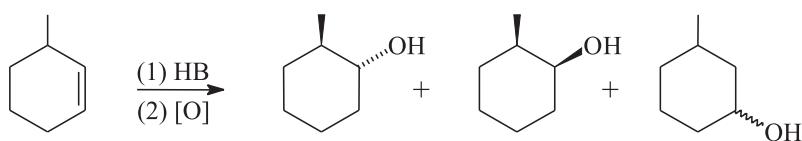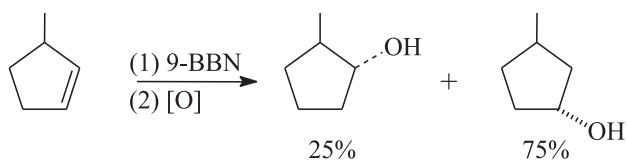
	trans	*cis*	
9-BBN	20%	0%	80%
Sia$_2$BH	30%	18%	52%
BH$_3$	34%	16%	50%

Chart 6.3

The regioselectivity of 9-BBN and BH$_3$ toward 4-methylcyclohexene is nei-
ther stereoselective *nor* regioselective. 4-Methylcyclopentene, however, under-
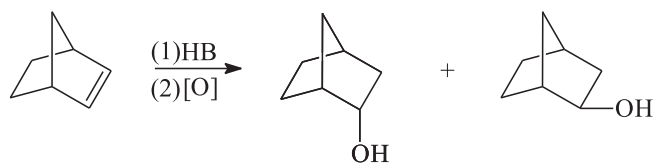goes hydroboration with 9-BBN, with high stereo- and regioselectivities (Chart
6.4) [3].

9-BBN   95%   5%

BH$_3$ 83%   17%

>99%   trace
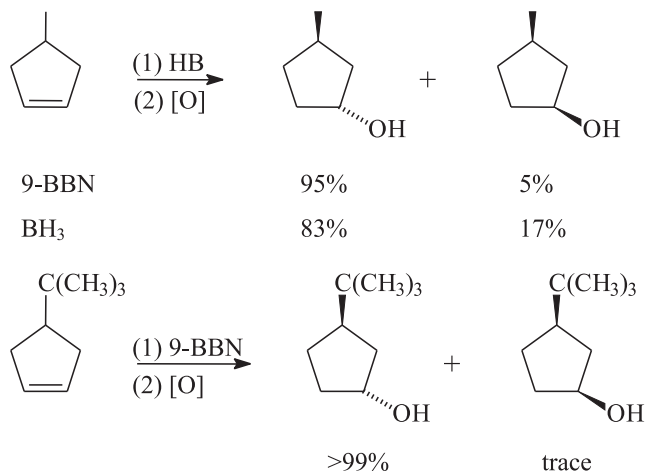
Chart 6.4

Stereoisomeric purities from 97–99.9% have been realized in bicyclic systems
where the attack of 9-BBN occurs from the less hindered side (Chart 6.5) [3, 4].

9-BBN is a reagent of choice for high stereoselective hydroboration of 1,3-
dimethlcycloalkenes, affording only 2,ω-dimethylcycloalkyl-9-BBN, with both
methyl groups *trans* to the 9-BBN moiety (Chart 6.6) [5].

B-Alkyl-9-BBN derivatives are exceptionally resistant to thermal isomeriza-
tion. *B*-3-Hexyl-9-BBN requires heating at 150 °C for 168 h to attain the equi-
librium distribution of the boron along the hexyl chain, whereas isomerization
of tri-3-hexylborane is complete in 1 h at the same temperature. The sluggish
migration of 9-BBN along the carbon skeleton makes possible the successful
hydroboration of certain labile system, not readily handled by other hydrobo-
rating reagents. For example, 1-methylcyclooctene with borane-THF produces
mixtures of products arising from the facile isomerization of the organoborane
intermediates. However, 9-BBN hydroborates [1] these alkenes cleanly (Chart
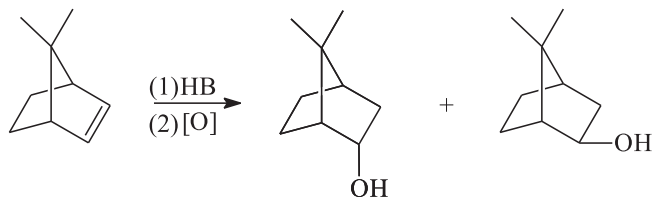6.7) [3].

The stereocontrolled addition of 9-BBN has been elegantly provided in the
synthesis of the steroidal alcohols [6], where the attack occurs from the less hin-
dered α-face. Aldehydes derived from these alcohols are assigned the stereo-
structures (Scheme 6.1) as the proton of equatorial -CHO absorbs at δ 9.73,
whereas axial -CHO appears at δ 9.96 in the ^{1}H NMR spectrum [7].

BH$_3$	87%	13%
9-BBN	99.5%	0.5%
BH$_2$Cl	99.8%	0.2%

BH$_3$	79%	21%
9-BBN	97%	3%

BH$_3$	98%	2%
9-BBN	>99.9%	—

BH$_3$	98%	2%
9-BBN	99.9%	—

Chart 6.5

Chart 6.6

| 9-BBN | 98% | 2% |
| BH$_3$ | 97% | 3% |

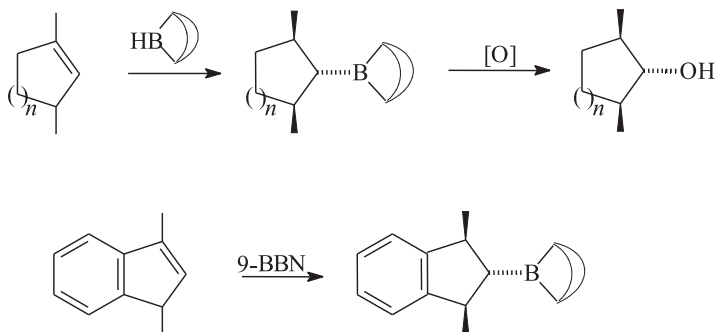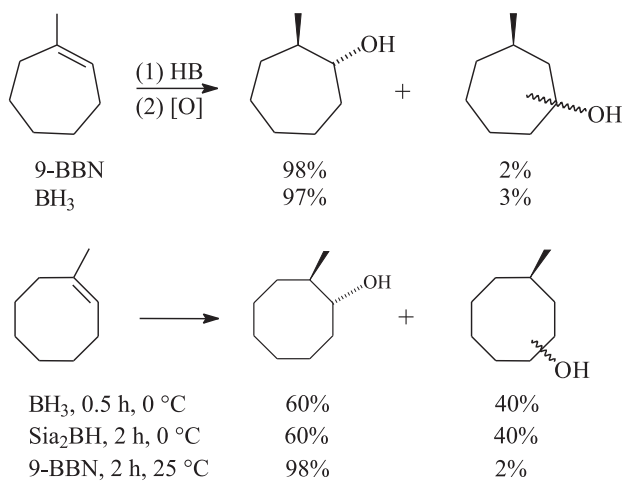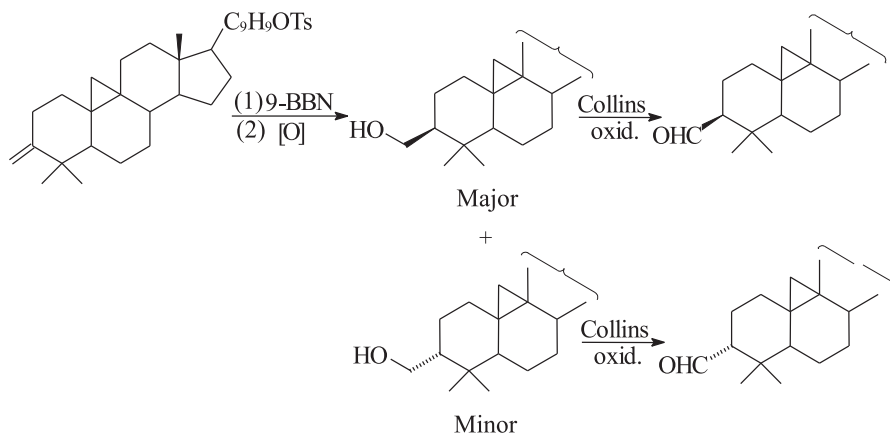| BH$_3$, 0.5 h, 0 °C | 60% | 40% |
| Sia$_2$BH, 2 h, 0 °C | 60% | 40% |
| 9-BBN, 2 h, 25 °C | 98% | 2% |
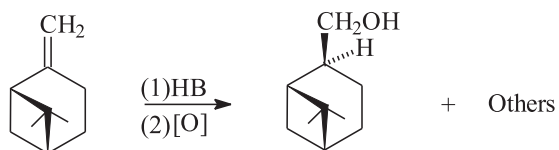
Chart 6.7

Scheme 6.1

Brown *et al* [8] have devised a general, convenient, and simple synthesis of straight-chain alcohols from internal alkynes. Long-chain internal alkynes, prepared by Eiter's procedure [9] by metalating 1-alkynes, followed by treatment with alkyl halides, are isomerized to 1-alkynes on treatment with potassium-3-aminopropylamide (KAPA) [10] in 1,3-diaminopropane (APA). KAPA is prepared by the quantitative reaction of potassium hydride with excess of (APA) [10]. This difunctional "superbase" produces exceptionally rapid migration of internal C≡C to the terminal C≡C position. The terminal alkynes thus obtained are subjected to dihydroboration with 2 equiv of 9-BBN. The dibora intermediate on alkaline hydrogen peroxide oxidation provides 61–80% yield (Table 6.4) [8] of the corresponding alcohols (Eq. 6.2).
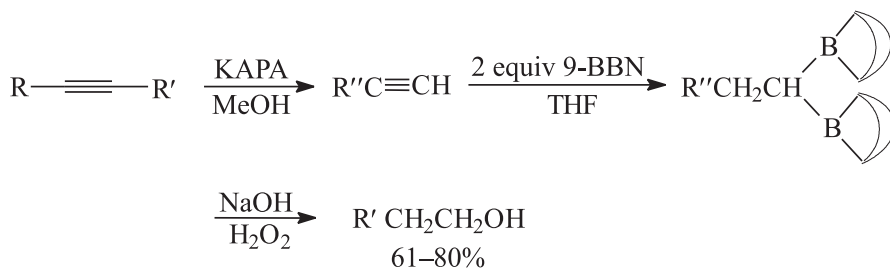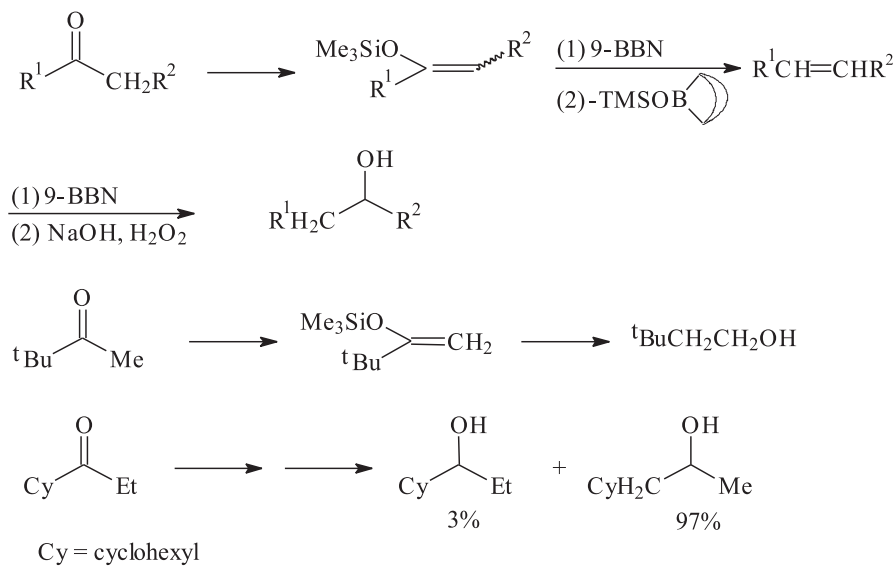

$$(6.2)$$

Table 6.4 Long-chain alcohols *via* KAPA method [8]

Alcohols	Number of carbon atoms	Yield (%)	m.p. (°C)
1-Tetracosanol	24	80	74–76
1-Triacontanol	30	76	86–88
1-Hentriacontanol	31	74	84–86
1-Tritriacontanol	33	73	86–88
1-Hexatriacontanol	36	76	90–92
1-Dotetracontanol	42	68	96–98
1-Octatetracontanol	48	61	102–104

The 1,2 transposition of oxygen functionality is an important reaction methodology in the synthesis of various organic compounds. 9-BBN enables the clean achievement of this transposition [11] in several cases, as illustrated in Scheme 6.2.

Scheme 6.2