Synthetic Applications of Zinc Borohydride

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Outline

1. Introduction

Although numerous literature references are available on the synthetic applications of various metal borohydrides,[1] only sodium borohydride has gained commercial status, in spite of its poor solubility in organic solvents and lesser reactivity. Moreover, the reagent is inevitably used in excess quantities. To overcome these drawbacks, soluble metal borohydrides such as lithium borohydride,[2] calcium borohydride,[2] and zinc borohydride have been developed. Among these reagents zinc borohydride is unique because: (i) Zn^{2+} is a soft Lewis acid as compared to Ca^{2+}, Li^+, and Na^+ which are hard acids, and (ii) Zn^{2+} has a better coordinating ability and is thus expected to impart selectivity in hydride transfer reactions. Indeed, literature reports on $Zn(BH_4)_2$ indicate that the chemoselective reduction of β-keto esters to the corresponding β-hydroxy esters can be easily achieved with better isomeric control because of the better coordinating ability of zinc with the carbonyl group of the ester.[3] This reaction has been utilized in the synthesis of certain natural products and in prostaglandin synthesis. Ranu[4] has reported $Zn(BH_4)_2$ to be a mild reducing agent capable of reducing aldehydes in the presence of ketones,[5] and ketones in the presence of enones.[6] Under these conditions, $Zn(BH_4)_2$ does not reduce carboxylic acids or esters. However, in the presence of trifluoroacetic anhydride, $Zn(BH_4)_2$ reduces carboxylic acids but not esters.[7] The reduction of esters by $Zn(BH_4)_2$ requires longer reaction times (24 h) and the influence of ultrasonic irradiation. Understandably, aromatic esters and benzyl esters are not at all reduced under these conditions thus allowing selectivity in the reduction of esters.[8] Furthermore, $Zn(BH_4)_2$–silica reduces enones to the corresponding allylic alcohols[9] and epoxides to alcohols.[10]

It would appear from the preceding reports that $Zn(BH_4)_2$ is a mild reagent with only a limited scope. However, the unique properties of $Zn(BH_4)_2$ come to light when subjected to tandem reduction-hydroboration, discovered by Brown and Narasimhan.[11,12] In this reaction, when an unsaturated ester is treated with a metal borohydride, the ester group is reduced much faster than that of a saturated ester, and the double bond also gets hydroborated. However, this depends on the extent of polarization of the borohydride ion by the counter ion. The feasibility of the tandem reduction-hydroboration reaction can be inferred from the reaction of the borohydride reagent with methyl 10-undecenoate which would be rapidly converted to 1,11-undecanediol. Exploring this reaction with $Zn(BH_4)_2$ has enhanced the potential of this reagent in synthetic applications.

2. Preparation of $Zn(BH_4)_2$[13,14]

In a typical procedure, a 500-mL round-bottom flask, equipped with a magnetic pellet and fitted with a reflux condenser carrying a take-off adapter, is flame-dried while a stream of nitrogen is passed through the system. The assembly is allowed to cool to room temperature while the flow of nitrogen is maintained. Freshly fused $ZnCl_2$ (18g;125mmol) is added followed by $NaBH_4$ (11g ; 291mmol). 250 mL of dry THF is then added through a double-ended needle and the contents are stirred at room temperature for

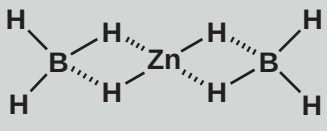


Chart 1

72 hours. The clear supernatant layer is used as such for reactions after estimating its hydride strength (4.4 M in H^-). The absence of chloride is confirmed as reported earlier.[15] Atomic absorption measurements indicate the presence of Na^+, in addition to zinc and boron, and confirm the analogous results reported in the literature.[15] $Zn(BH_4)_2$ can be thought of as a complex having the structure shown in **Chart 1**.

Interestingly, the ^{11}B NMR spectrum shows a quintet at $\delta = -45$ corresponding to the BH_4^- ion when $BF_3 \cdot Et_2O$ is used as the external standard. The reagent is stable over a period of 6 months when stored under nitrogen at room temperature.

3. Synthetic Applications

3.1. Tandem Reduction–Hydroboration of Esters

Earlier reports have indicated that the reduction of aliphatic esters by $Zn(BH_4)_2$ in DME is very slow. However, under vigorous conditions, it is possible to reduce aliphatic esters in the presence of aromatic esters. In addition, $Zn(BH_4)_2$ in THF reduces esters in the following order: unsaturated ester >> aliphatic ester >> aromatic ester (**Table 1**).[16] These rate differences have been exploited in the facile reduction of a number of aliphatic esters in the presence of aromatic esters under simple reaction conditions and without employing ultrasonic irradiation (**Table 2**). The intermediate borate esters can also be oxidized to the corresponding aldehydes (entries 8 and 9).[17]

Interestingly, the rapid reduction of the unsaturated ester methyl 10-undecenoate indicated autocatalysis; this meant that the addition of olefin might catalyze the reduction of esters. When this idea was applied to the reduction of methyl benzoate, a remarkable rate enhancement was observed (**Table 3**).[18] The ^{11}B NMR spectrum of the reaction mixture indicated that hydroboration of the olefin occurred prior to reduction of the ester; i.e., the propensity of $Zn(BH_4)_2$ to hydroborate the alkene was greater than its propensity to reduce the ester. The peak at $\delta = 56$ indicated that the hydroboration of cyclohexene led to a dialkylboron species which could catalyze the reduction of the ester as depicted in **Scheme 1**.

Consequently, several aromatic esters were reduced in good yields and the reduction was tolerant of other reducible groups such as chloro, bromo, nitro, etc. (**Table 4**).[16] The organoboron intermediates can also be oxidized with dichromate solution to the corresponding aldehydes providing a one-pot conversion of esters to aldehydes. This

Table 1. Reduction of esters by $Zn(BH_4)_2$ in THF.

		% reaction[a]					
Entry	Methyl Ester	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Myristate	1.5	4.5	15	61	94	98
2	Benzoate	-	-	-	4	9	
3	Pivalate	4	8	27	46	71	93[b]
4	10-Undecenoate	-	gel	98			

[a]Percent reaction is the number of mmoles of ester that were reduced divided by the number of mmoles of ester used. It was determined by analysis of residual hydride in the reaction mixture and by assuming an uptake of two hydrides per ester reduced. [b]after 8 h.

Table 2. Facile reduction of aliphatic esters by $Zn(BH_4)_2$.

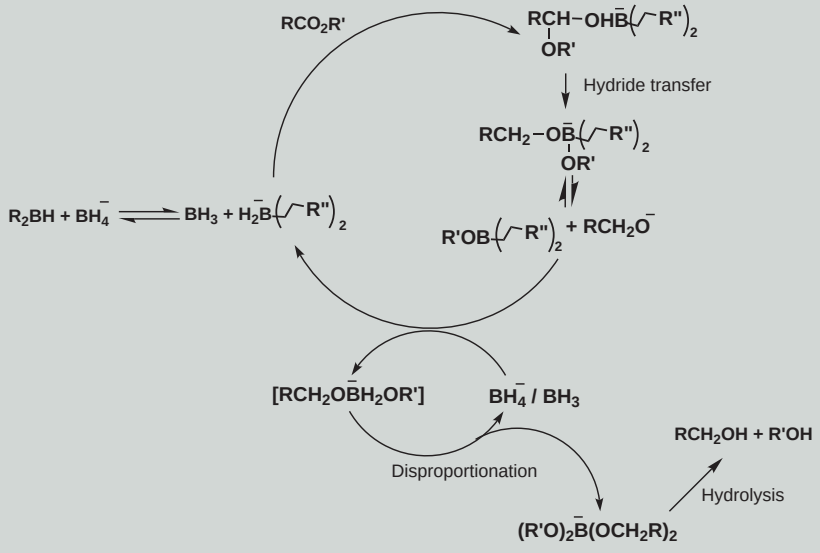
Entry	Ester[a]	Time, h	Product	% Yield
1	Methyl 10-undecenoate	1	1,11-Undecanediol	90
2	Dimethyl brassylate[b]	6	1,13-Tridecanediol	74
3	Methyl nonanoate	5	1-Nonanol	75
4	Methyl myristate	5	1-Tetradecanol	85
5	Methyl pivalate	6	2,2-Dimethyl-1-propanol	75
6	Methyl 3-bromopropionate	2	3-Bromo-1-propanol	79
7	Methyl phenylacetate	5	Phenethyl alcohol	75
8	Methyl myristate	6	1-Tetradecanal	80
9	Methyl phenylacetate	6	Phenylacetaldehyde	76

[a][ester]:[H^-]=1:2. [b][ester]:[H^-]=1:4

Table 3. Alkene-catalyzed reduction of esters with $Zn(BH_4)_2$.

			% reaction[a]					
Entry	Ester	Alkene[b]	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Methyl myristate	-	1.5	4.5	15	61	94	98
2	Methyl myristate	Cyclohexene	36	64	84	104[c]		
3	Methyl benzoate	-				4	9	
4	Methyl benzoate	Cyclohexene	9	16	34	60	87	101[c]
5	Methyl 2-chlorobenzoate	-			16	23	38	46
6	Methyl 2-chlorobenzoate	Cyclohexene			34	46	71	82
7	Methyl 2-chlorobenzoate	1-Decene			38	47	77	89
8	Methyl 2-chlorobenzoate	1,5-Cyclooctadiene			36	44	73	87

[a]Percent reaction is defined as in Table 1. [b]10 mol%. [c]These results include the hydride consumption for cyclohexene.



Scheme 1. Mechanism of alkene-catalyzed reduction of esters.

Table 4. Reduction of methyl esters, RCO_2Me, by $Zn(BH_4)_2$ in refluxing THF catalyzed by cyclohexene.

Entry	R	Time, h	Product, R	% Yield
1	C_6H_5	5	C_6H_5	72
2	2-ClC_6H_4	4	2-ClC_6H_4	83
3	3-$NO_2C_6H_4$	3	3-$NO_2C_6H_4$	80
4	4-$NO_2C_6H_4$	3	4-$NO_2C_6H_4$	75
5	4-HOC_6H_4	4	4-HOC_6H_4	72
6	2-HO-C_6H_4	4	2-HO-C_6H_4	70
7	4-$MeO_2CC_6H_4$	2	4-$HOCH_2C_6H_4$	70
8	$C_6H_5CH_2$	2	$C_6H_5CH_2$	75
9	$CH_3(CH_2)_{12}$	2	$CH_3(CH_2)_{12}$	76
10	$MeO_2C(CH_2)_{11}$	4	$HOCH_2(CH_2)_{11}$	76
11	CH_2=$CH(CH_2)_8$[a]	2	$HO(CH_2)_{10}$	80

[a] Cyclohexene was not used; [ester]:[H^-]=1:2

Table 5. Reactivity of $Zn(BH_4)_2$ towards various functional groups.

		% reaction					
Entry	Substrate	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Methyl myristate	1.5	4.5	15	61	94	98
2	Methyl benzoate				4	9	
3	Palmitic acid	35	65	74	84	92	94
4	Benzoic acid	46	51	56	61	85	92
5	1-Dodecene		72	80	96	98	99

Table 6. Competitive studies of the reduction of various substrates with zinc borohydride.

Entry	Substrate Pair	k_1/k_2[a]
1	Methyl myristate/Methyl benzoate	100
2	Methyl myristate/Methyl benzoate[b]	12
3	Palmitic acid/Benzoic acid	13
4	Palmitic acid/Methyl myristate	100
5	1-Dodecene/Methyl myristate	2.7
6	1-Dodecene/Palmitic acid	1.7

[a] k_1 and k_2 are calculated using the Ingold-Shaw equation. [b] The reduction was carried out in the presence of 10 mol % of cyclohexene as catalyst.

Table 7. Relative reactivity of functional groups towards $Zn(BH_4)_2$.

Entry	Functional Group	Relative Reactivity
1	Methyl benzoate	1
2	Methyl myristate	12
3	Benzoic acid	96
4	Palmitic acid	1200
5	1-Dodecene	2040

tendency of $Zn(BH_4)_2$ to hydroborate unsaturated systems in preference to reduction of carbonyl groups is in contrast to the behavior of other metal borohydrides. Indeed a study of the relative reactivity of $Zn(BH_4)_2$ towards various functional groups represented by methyl myristate, methyl benzoate, palmitic acid, benzoic acid and 1-dodecene indicated that hydroboration of the olefin is much faster than reduction (**Table 5**).[19]

To elucidate the spectrum of reactivity of $Zn(BH_4)_2$, competitive experiments were performed. In a typical procedure, to an equimolar mixture of methyl myristate and methyl benzoate was added just enough hydride to react with only one of the substrates. The products were analyzed by GLC and the relative reactivity obtained by using the Ingold-Shaw equation (**Table 6**).[20] The results indicated that the aliphatic ester was reduced much faster than the aromatic ester. Similarly, the aliphatic acid, palmitic acid, was reduced more rapidly than benzoic acid. This allowed us to determine the order of reactivity of the other substrates relative to that of methyl benzoate (**Table 7**): olefin > aliphatic CO_2H > aromatic CO_2H > aliphatic ester > aromatic ester. This spectrum of reactivity of $Zn(BH_4)_2$ indicates that it prefers to attack a nucleophilic carbon rather than an electrophilic one. This is contrary to the reactivity pattern of other metal borohydrides, which are nucleophilic species and prefer to attack an electrophilic carbon and seldom hydroborate olefins. This boranelike characteristic of $Zn(BH_4)_2$ offers an alternative to borane–methyl sulfide (BMS) in organic synthesis.

3.2. Reductions

3.2.1. Reduction of Carboxylic Acids

A number of carboxylic acids were reduced to the corresponding alcohols in good yields and using only stoichiometric quantities of zinc borohydride (**Table 8**).[21] These facile reductions are thought to take place as shown in **Scheme 2**.

3.2.2. Reduction Of Amino Acids

Chiral amino alcohols are useful in, among others, asymmetric synthesis,[22] peptide and pharmaceutical chemistry,[23] and the synthesis of insecticidal compounds.[24] Earlier preparative methods used reduction of esters of amino acids by sodium in ethanol.[25] Subsequently, $LiAlH_4$[26] and $NaBH_4$[27] were used for the reduction of esters. Moreover, reduction of amino acids directly to the amino alcohols was accomplished using $LiAlH_4$[28] or BMS in the presence of $BF_3 \cdot Et_2O$.[29] Metal borohydrides do not reduce amino acids; however, $LiBH_4$ with Me_3SiCl reduces amino acids to the corresponding alcohols.[30,31] Similarly, $NaBH_4$ in the presence of $BF_3 \cdot Et_2O$ also reduces amino acids.[32] The reduction in these cases is by borane which is generated in situ. Recently, $NaBH_4$–H_2SO_4 and $NaBH_4$–I_2 were used for the reduction of amino acids and derivatives.[33,34] Reductions of 1kg-scale quantities are effected with either BMS or $LiAlH_4$. However, the methods suffer from high cost, inflammability of the reagents used, and laborious isolation procedures. In the case of amino acids, it is necessary to use an excess of 1 molar equivalent of borane to compensate for complexation of the reducing agent with the amino group (**eq 1**).

Since $Zn(BH_4)_2$ had been shown to reduce carboxylic acids to the corresponding alcohols in excellent yields,[21] and in view of its basic nature, it was reasoned that such amine-borane complexation was not likely to occur and hence excess reagent might not be required. Thus, the reduction of amino acids to amino alcohols utilizing only stoichiometric quantities of zinc borohydride proceeded to completion (**Table 9**).[35] With excess hydride, no significant change in the reaction time or yield of the product was observed. Moreover, the excess hydride was liberated instantaneously during hydrolysis. These observations led to the conclusion that there was no strong coordination between boron and nitrogen, as is observed in the case of trivalent borane reagents. The intermediate obtained is presumably oxazaborolidine, which is highly useful in the enantioselective reduction of prochiral ketones.

The intermediate boroxazoles from chiral amino acids are optically active and are useful in asymmetric synthesis. The amino alcohols are obtained by simple hydrolysis of the boroxazoles. The method offers a simple and rapid conversion of amino acids to amino alcohols in excellent yields.

3.2.3. Reduction of Amides

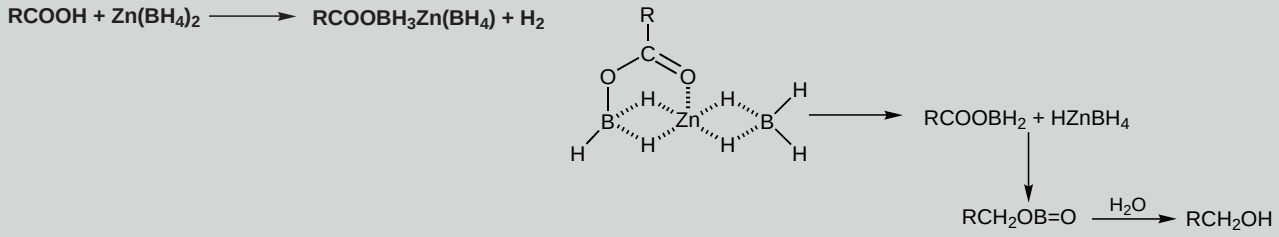
Reduction of carboxylic acid amides can lead to the formation of aldehydes or alcohols by cleavage of the C-N bond, or amines by cleavage of the C-O bond. All three product types have been observed when boron reagents were employed as reducing agents (**Table 10**).

Metal borohydrides do not reduce amides. However, the combination of metal borohydride and an electrophile has been used to effect this transformation. Thus, $NaBH_4$ reduces amides in the presence of carboxylic acids,[36] sulfonic acids,[37] and Lewis acids.[38] The mechanism of the reaction is believed to involve coordination of the metal with oxygen, rather than in situ generation of borane. Interestingly, $Zn(BH_4)_2$ can be used to reduce amides without the use of excess reagent. Thus, reduction of acetanilides by $Zn(BH_4)_2$ results in the evolution of one equivalent of hydrogen. Further reaction results in complete reduction to afford the amine.[39] A series of amides were reduced to yield the corresponding *N*-ethylanilines (**Table 11**). The products were isolated by simple hydrolysis of the reaction mixture (**eq 2**).

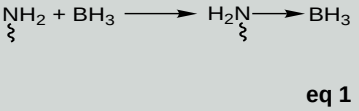
Table 8. Reduction of carboxylic acids with $Zn(BH_4)_2$.[a]

Entry	Substrate[b]	Time, h	Product	% Yield[c]
1	Benzoic acid	6	Benzyl alcohol	90
2	Palmitic acid	6	Cetyl alcohol	95
3	Palmitic acid[d]	6	Hexadecanal	90
4	Valeric acid	3	Amyl alcohol	95
5	2-Chlorobenzoic acid	6	2-Chlorobenzyl alcohol	90
6	4-Nitrobenzoic acid	4	4-Nitrobenzyl alcohol	90
7	3-Nitrobenzoic acid	4	3-Nitrobenzyl alcohol	90
8	3-Bromopropionic acid	6	3-Bromo-1-propanol	75
9	3,4,5-Trimethoxybenzoic acid	5	3,4,5-Trimethoxybenzyl alcohol	70
10	Pivalic acid	2	Neopentyl alcohol	70
11	Phenylacetic acid	3	Phenethyl alcohol	95
12	Phenylacetic acid	3	Phenylacetaldehyde	90
13	Cinnamic acid[e]	5	3-Phenylpropanediol[f]	90
14	2-Hydroxybenzoic acid[e]	4	no reaction	
15	Acetylsalicylic acid	3	2-Hydroxybenzyl alcohol	85
16	10-Undecenoic acid[e]	1	1,11-Undecanediol	90
17	Brassylic acid[g]	4	1,13-Tridecanediol	70
18	Terephthalic acid[g]	5	1,4-Benzenedimethanol	70

[a]All reactions were carried out at reflux in THF; no catalyst was used. [b][acid]:[H^-]=5:16.5. [c]Isolated crude product. [d]Oxidized using aqueous acidic sodium dichromate solution in $CHCl_3$. [e][acid]:[H^-]=5:22. [f]Mixture of 1,2-diol and 1,3-diol (3:2) by ^1H NMR. [g][acid]:[H^-]=5:33.



Scheme 2. Mechanism of the reduction of acids with zinc borohydride.



eq 1

Table 9. Reduction of amino acids by $Zn(BH_4)_2$.[a]

Entry	Substrate	Time (h)	Product	% Yield	Rotation of Amino Alcohol
1	Glycine	7	2-Aminoethanol	70	
2	L-Phenylalanine	5	L-Phenylalaninol	87	-21.7° (c = 1.7, EtOH)
3	L-Leucine	4	L-Leucinol[b]	85	+4.2° (c = 0.9, EtOH)
4	L-Isoleucine	3	L-Isoleucinol[b]	85	+6.7° (c = 1.0, EtOH)
5	L-Valine	4	L-Valinol	85	+8.7° (c = 1.1, EtOH)
6	L-Proline	3	L-Prolinol	85	+37.0° (c = 1.0, EtOH)

[a][substrate]:[H^-] = 1:3 ; in refluxing THF; no catalyst was used. [b]The reported values are: L-leucinol [+4° (c = 9, EtOH)] and L-isoleucinol[+5.4° (c = 1.6, EtOH)] . The *Aldrich Catalog/Handbook of Fine Chemicals*, 1996-1997 ed.; Aldrich Chemical Co.: Milwaukee, WI; pp 895 and 872.

Table 10. Reduction of carboxylic acid amides with various boron reagents.[a]

Entry	Substrate	Reagent	Product
1	$RCONH_2$	Borane-THF, BMS	RCH_2NH_2
2	RCONHR	Borane-THF, BMS	RCH_2NHR
3	$RCONR_2$	Borane-THF, BMS	RCH_2NR_2
4	$RCONR_2$	Sia_2BH[b]	RCHO
5	$RCONH_2$	Sia_2BH[b]	-
6	$RCONR_2$	9-BBN	RCH_2OH
7	$RCONH_2$	9-BBN	stops at deprotonation stage

[a]For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*; Academic Press: London, UK, 1988; pp 138-140. [b]Sia_2BH is disiamylborane.

3.3. Hydroborations

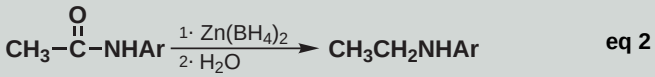
The electrophilic nature of the reagent shows potential for use in hydroboration reactions. The important features to be considered in hydroboration reactions are stoichiometry and regio- and stereoselectivity. Thus, while three equivalents of olefin are hydroborated by one molar equivalent of borane, controlled hydroboration to dialkyl or

monoalkyl species can be achieved with hindered alkenes. In the case of $LiBH_4$/ether[40] and $Ca(BH_4)_2$/THF in the presence of ethyl acetate,[41] tandem reduction-hydroboration results in the formation of dialkylborinate species indicating two equivalents of alkene uptake per BH_4^- ion. Such controlled hydroboration products are very useful as synthetic intermediates. Hence it is important to determine the number of alkenes that can be hydroborated with one molar equivalent of BH_4^- ion.

Table 11. Reduction of anilides by $Zn(BH_4)_2$.

Entry	Substrate	Time, h	Product	% Yield
1	Acetanilide	5	*N*-Ethylaniline	90
2	3'-Chloroacetanilide	4	*N*-Ethyl-3-chloroaniline	85
3	4'-Chloroacetanilide	4	*N*-Ethyl-4-chloroaniline	85
4	4'-Bromoacetanilide	4	*N*-Ethyl-4-bromoaniline	85
5	4'-Methoxyacetanilide	6	*N*-Ethyl-4-methoxyaniline	70
6	2'-Nitroacetanilide	8	*N*-Ethyl-2-nitroaniline	30[a]
7	3',4'-Dichloroacetanilide	5	*N*-Ethyl-3,4-dichloroaniline	80
8	4'-Bromo-3'-chloroacetanilide	5	*N*-Ethyl-4-bromo-3-chloroaniline	75
9	Benzanilide	7	*N*-Benzylaniline	70
10	2'-(Carbomethoxy)acetanilide	4	2-(Ethylamino)benzyl alcohol	80

[a]70% of unreacted anilide was recovered. [anilide]:[H^-]=5:11

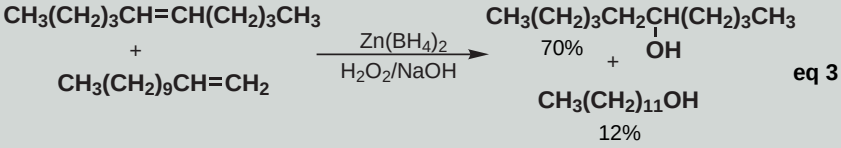


eq 2

Table 12. Hydroboration of alkenes: species and stoichiometry.[a]

Entry	Alkene/BH_4^- Ratio	^{11}B NMR δ(ppm)[b]	Alkene Consumed/BH_4^-
1	1	32 & 55	1
2	2	33 & 54	1.8
3	3	54 & 80	2.4
4	4	54 & 86	3.0

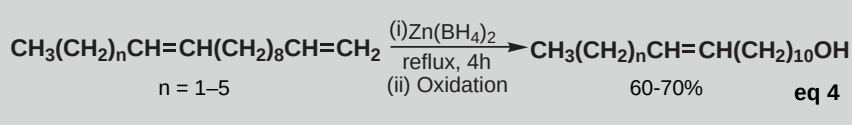
[a]Based on GC analysis, on a 2-m 3% OV-17 column, after 4 h of reflux. [b]With reference to BF_3•OEt_2.



eq 3

Table 13. Comparison of the relative reactivities of terminal and internal alkenes (k_t/k_i) towards hydroboration with various boron reagents.

Entry	Boron Reagent / Alkene	9-BBN	ThxBHCl .SMe_2	$HBBr_2$ .SMe_2	BMS	$Zn(BH_4)_2$	$Ca(BH_4)_2^-$ EtOAc
1	$CH_3(CH_2)_7$ ═	180	9.1	5.0	2.8	6.5	9.0
2	H, H; C=C; Bu^n, Bu^n	1.0	1.0	1.0	1.0	1.0	1.0



eq 4

3.3.1. Hydroboration of Simple Olefins

It is well-known that hydroboration of simple, linear, terminal alkenes using borane leads to the formation of trialkylboron species. However, it should be noted that mono- and dialkylboranes would also be present in the reaction mixture depending on the structure of the alkene and its concentration. The nature of the organoborane species formed and hence the stoichiometry of the reaction can be determined by ^{11}B NMR and hydride analysis studies. The results are presented in **Table 12**.

$Zn(BH_4)_2$ is able to hydroborate a terminal olefin leading to the formation of a trialkylboron species (which is evident from the peak at δ = 83) with excess alkene. This reduction may be utilized for the conversion of alkenes to alcohols whereby maximum use is made of the reagent. Interestingly, dialkylborinate is the major product when a starting ratio of two equivalents of alkene per borohydride ion is used. The dialkylborinate species is very valuable in the preparation of symmetrical ketones.

3.3.2. Hydroboration of Dienes

Regioselectivity is one of the major interests in hydroboration reactions. While a number of reagents are known to be more selective towards the terminal carbon atom, it was felt that if $Zn(BH_4)_2$ were to exhibit even marginal regioselectivity it might be very useful synthetically in view of the simplicity of its workup procedure. Accordingly, to elucidate the regioselectivity of the reagent, a competitive experiment was performed between a terminal olefin, 1-dodecene, and an internal olefin, 5-decene, with just enough hydride to hydroborate one of them (**eq 3**). From the Ingold-Shaw equation, the relative reactivity of the terminal versus internal double bond towards hydroboration was calculated as $k_t/k_i = 5.9$. This result indicates that $Zn(BH_4)_2$ exhibits a selectivity comparable to that of dibromoborane (**Table 13**).[41] This improved selectivity, as compared with that of BH_3•THF or BMS, can be taken advantage of in the hydroboration of dienes containing both terminal and internal double bonds.

An immediate synthetic application of this result was realized in the regioselective hydroboration of 1,11-dienes to produce (*Z*)-11-alken-1-ols, which are pheromone components for many species (**eq 4**).[42] The results are comparable to those of other hydroboration methods. Although 9-BBN, a dialkylborane species, shows excellent terminal carbon selectivity, its use yields only 68% of the required alkenol and suffers from contamination by cyclooctanediol. On the other hand,

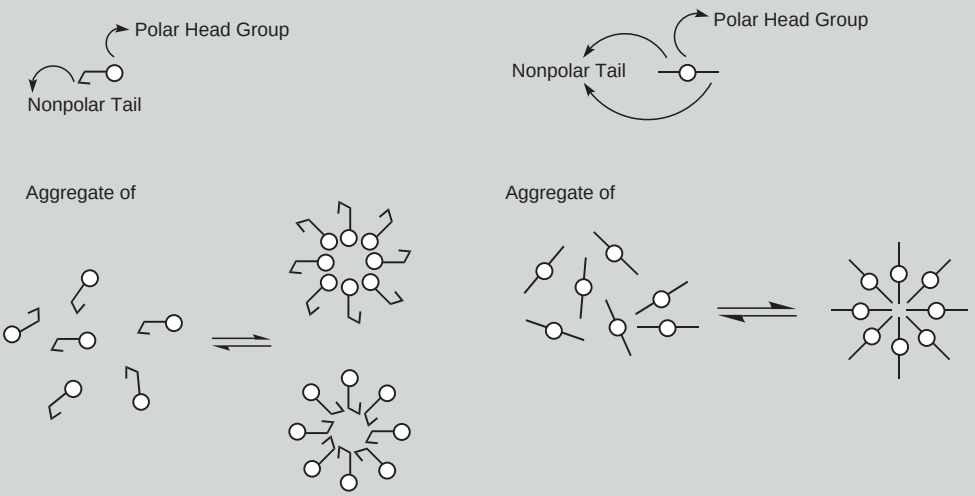
use of $Zn(BH_4)_2$ produces the terminal alcohol in good yield without the complication of side products. Interestingly, the organoboron intermediate was oxidized with sodium dichromate directly to (*Z*)-11-hexadecenal (**eq 5**). 9-BBN and the other selective reagents produce additional side products.

$$CH_3(CH_2)_3CH{=}CH(CH_2)_8CH{=}CH_2 \xrightarrow[\text{reflux, 4h}]{\text{(i) } Zn(BH_4)_2 \quad \text{(ii) } Na_2Cr_2O_7} CH_3(CH_2)_3CH{=}CH(CH_2)_9CHO$$

60%

eq 5

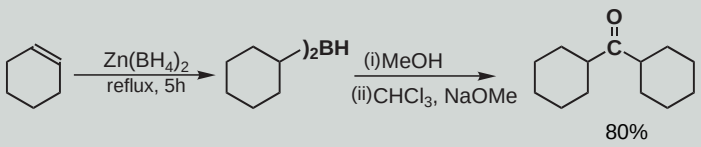
As indicated earlier, in order to derive the maximum utility from the reagent, two equivalents of diene were reacted with 1 equivalent of BH_4^-. Interestingly, ^{11}B NMR analysis of the quenched reaction mixture indicated the formation of monoalkyl boronates in major quantities. A possible in situ micellization of the intermediate could explain this observation. When hydroborated, a simple hydrocarbon diene would become bipolar in nature and hence result in aggregation of monomers (**Scheme 3**). Consequently, the rate of further hydroboration by the monohydroborated species would be very much reduced.



Scheme 3. In situ micellization during the hydroboration of long-chain dienes.

3.3.3. Hydroboration of Cyclic Olefins

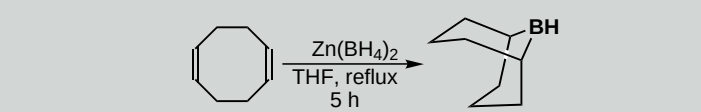
Cyclic olefins such as cyclohexene possess an internal double bond. Thus, hydroboration of these systems should stop at the dialkylboron stage due to steric hindrance. Indeed, hydroboration of cyclohexene by $Zn(BH_4)_2$ stops at the dialkylboron stage ($\delta = 53$, using $BF_3{\bullet}Et_2O$ as external standard). This dialkylboron intermediate can be converted to symmetrical ketones by treatment with $CHCl_3$ and NaOMe (**eq 6**).[43]



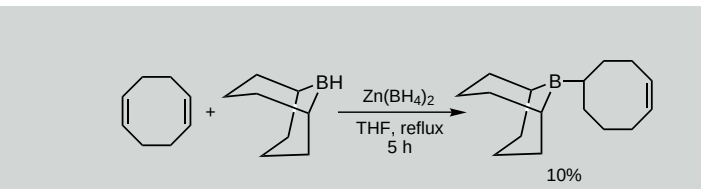
80%

eq 6

Hydroboration of 1,5-cyclooctadiene by simple borane reagents leads to the formation 9-borabicyclo[3.3.1]nonane (9-BBN), a highly selective hydroborating and reducing agent. Under the present reaction conditions, 1,5-cyclooctadiene is hydroborated intramolecularly and isomerizes to the stable 9-borabicyclo[3.3.1]nonane product (**eq 7**). This should be quite useful in the in situ generation of 9-BBN. A considerable amount of trialkylboron species is also observed by ^{11}B NMR, indicating further hydroboration of the cyclooctadiene by 9-BBN (**eq 8**).[44]



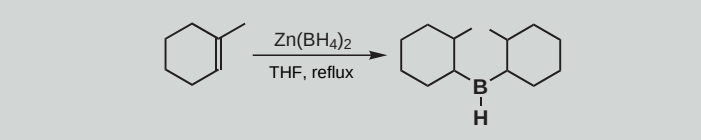
eq 7



10%

eq 8

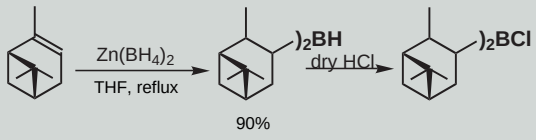
Substituted cyclic olefins such as 1-methylcyclohexene and α-pinene are easily hydroborated to the corresponding dialkylborinate species (**eq 9**).



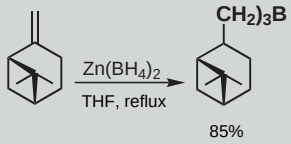
90%

eq 9

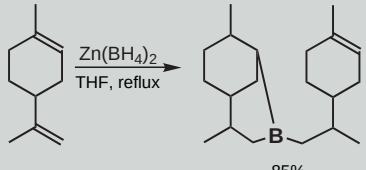
It should be pointed out that, in the case of α-pinene, the dialkylborinate intermediates can react with prochiral substrates such as



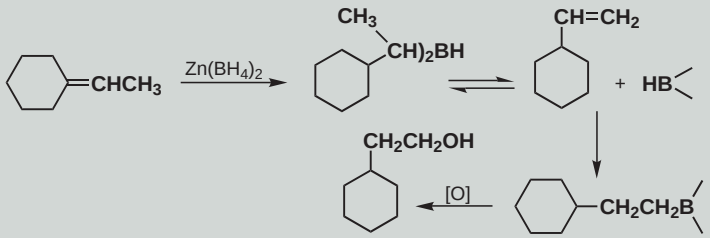
eq 10



eq 11



eq 12

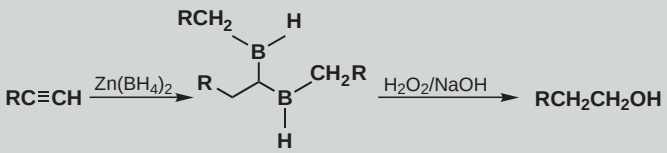


Scheme 4

Table 14. Alcohols obtained by hydroboration of olefins with $Zn(BH_4)_2$.

Entry	Substrate[a]	Time, h	Product	% Yield[b]
1	1-Dodecene	3	1-Dodecanol	90
2	1-Decene	3	1-Decanol	92
3	5-Decene	4	5-Decanol	85
4	Cyclohexene	4	Cyclohexanol	90
5	1,5-Cyclooctadiene	4	1,5-Cyclooctanediol 4-Cycloocten-1-ol (90:10)	85[c]
6	1,7-Octadiene	3	1,8-Octanediol	90
7	Ethylidenecyclohexane	4	1-Cyclohexylethanol 2-Cyclohexylethanol (90:10)	85[c]
8	1-Methylcyclohexene	4	2-Methylcyclohexanol cis:trans=85:15	90[c]
9	α-Pinene	4	Isopinocampheol	90
10	β-Pinene	4	Myrtanol	85
11	Limonene	4	Limonene-2,9-diol	85

[a][alkene]:[H^-]=1:2; in refluxing THF. The oxidations were carried out with H_2O_2/NaOH. [b]Isolated yield based on reacted olefin. [c]Yield of the mixture.



eq 13

activated ketones to produce optically active reduction products as reported in the literature using diisopinocampheylborane[45] or diisopinocampheylchloroborane (DIP-Chloride™)[46] (**eq 10**). Thus, this approach can offer a one-pot process for asymmetric synthesis.

Recently, *B*-hydroxydiisopinocampheylborane (Ipc_2BOH), prepared by the hydrolysis of the hydrido compound, has been employed as a chemoselective reducing agent for aldehydes over ketones.[47] Oxidation of the organoboron afforded isopinocampheol in excellent yield. Curiously, β-pinene produces a triorganoborane with $Zn(BH_4)_2$ as indicated by the ^{11}B NMR spectra of the reaction mixture (**eq 11**). Oxidation of the triorganoborane intermediate affords myrtanol.

Hydroboration of limonene also produced a significant amount of the corresponding trialkylborane. Presumably, the cyclic dihydroboration took place first resulting in a R_2BH species, which then hydroborated one more equivalent of limonene selectively at the terminal position (**eq 12**). On oxidation, the intermediate trialkylborane yields limonene-2,9-diol and minor amounts of *p*-menth-1-en-9-ol.

Interestingly, ethylidenecyclohexane, a sterically hindered substrate, also produced a significant amount of the trialkylboron intermediate. Upon oxidation, a small amount (10%) of the rearranged alcohol, 2-cyclohexylethanol, was also observed spectroscopically. It is likely that the initial organoboron intermediate underwent partial isomerization to the terminal position and yielded the isomerized trialkylborane as a minor product (**Scheme 4**). At high temperature such isomerism—to the terminal position thereby relieving the steric strain—has been observed with disiamylborane. These intermediates can be utilized in several synthetic transformations following the methods given in the literature. The simple application of the present method is summarized in **Table 14**.

3.3.4. Hydroboration of Alkynes

Alkynes undergo dihydroboration with $Zn(BH_4)_2$ giving rise to dibora adducts. Oxidation with alkaline hydrogen peroxide produces the corresponding alcohols in 40-90% yields (**eq 13** & **Table 15**).[19]

Generally, in the presence of excess alkyne, monohydroboration results. Unlike other metal borohydrides, and although $Zn(BH_4)_2$ is a basic reagent, it is still able to hydroborate without the addition of any Lewis acid or ester. Presumably, the soft Lewis acid nature of Zn^{2+} ion polarizes the borohydride ion and generates an electrophilic species which then reacts with the double bond.

Table 15. Hydroboration of alkynes with $Zn(BH_4)_2$.[a]

Entry	Alkyne	Time (h)	Product	Yield[b] (%)
1	1-Hexyne	3	1-Hexanol	80
2	1-Octyne	3	1-Octanol	80
3	1-Hexadecyne	4	1-Hexadecanol	90
4	1-Octadecyne	4	1-Octadecanol	90
5	3-Hexyne	4	3-Hexanone	75
6	1-Octyne[c]	3	1-Octanol	40
			Octanal	60

[a][alkyne]:[H^-]=1:2; refluxing THF. [b]Isolated yield. [c][alkyne]:[H^-]=10:1

4. Conclusion

In conclusion, $Zn(BH_4)_2$ can be used for the selective reduction of functional groups under various conditions. The reagent also offers an alternative to BMS in hydroboration reactions. Its remarkable regioselectivity, coupled with a simple workup procedure, makes it more advantageous to use than other selective reagents such as 9-BBN in the synthesis of several pheromones.

5. Acknowledgments

It is a pleasure to thank Professor T.R. Govindachari, our advisor, and earlier coworkers—Drs. K. Ganeshwar Prasad and S. Madhavan and Mr. Prem Palmer. We also thank all those who have contributed to the chemistry reviewed here and whose names appear in the cited references.

6. References

(1) James, B.D.; Wallbridge, M.G.M. *Progr. Inorg. Chem.* **1970**, *11*, 99.

(2) An excellent review is available on hydride reduction by Brown, H.C.; Krishnamurthy,S. *Tetrahedron* **1979**, *35*, 567, and references therein.

(3) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

(4) Ranu, B.C. *Synlett* **1993**, 885.

(5) Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* **1990**, *31*, 7663.

(6) Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* **1990**, *55*, 5779.

(7) Ranu, B.C.; Das, A.R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1561.

(8) Ranu, B.C.; Basu, M.K. *Tetrahedron Lett.* **1991**, *32*, 3243.

(9) Ranu, B.C.; Das, A.R. *J. Org. Chem.* **1991**, *56*, 4796.

(10) Ranu, B.C; Das, A.R. *J. Chem. Soc., Chem. Commun.* **1990**, 1334.

(11) Brown, H.C.; Narasimhan, S. *J. Org. Chem.* **1984**, *49*, 3891.

(12) Brown, H.C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.

(13) Gensler,W.J.; Johnson, F.; Sloan, A.D.B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

(14) Crabbe, P.; Garcia, G.A; Rius, C. *J. Chem. Soc., Perkin Trans. I* **1973**, 810.

(15) Yoon, N.M.; Lee, H.J.; Kim, H.K.; Kang, J. *J. Korean Chem. Soc.* **1976**, *20*, 59.

(16) Narasimhan,S.; Madhavan, S.; Ganeshwar Prasad, K. *Synth. Commun.* **1997**, *27*, 385.

(17) Narasimhan, S.; Palmer, P. *Ind. J. Chem.* **1992**, *31*, 701.

(18) Narasimhan, S.; Palmer, P.; Ganeshwar Prasad, K. *Ind. J. Chem.* **1991**, *30B*, 1150.

(19) Narasimhan, S.; Madhavan, S.; unpublished results.

(20) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918.

(21) Narasimhan, S.; Madhavan, S.; Ganeshwar Prasad, K. *J. Org. Chem.* **1995**, *60*, 5314.

(22) Zhang, Y.-W.; Shen, Z.-X.; Liu, C.-L.; Chen, W.-Y. *Synth. Commun*. **1995**, *25*, 3407.

(23) TenBrink, R.E. *J. Org. Chem.* **1987**, *52*, 418.

(24) Wu, S.; Takeya, R.; Ito, M.; Tomizawa, C.J. *J. Pestic. Sci.* **1987**, *12*, 221.

(25) Karrer, P.; Karrer, W.; Thomann, H.; Horlacher, F.; Mader, W. *Helv. Chim. Acta* **1921**, *4*, 76.

(26) Karrer, P.; Portmann, P.; Suter, M. *Helv. Chim. Acta* **1948**, *31*, 1617.

(27) Seki, H.; Koga, K.; Matsuo, H.; Ohiki, S.; Mutsuo, I.; Yamada, S. *Chem. Pharm. Bull.* **1965**, *13*, 995.

(28) Dickman, D.A.; Meyers, A.I.; Smith, G.A.; Gawley, R.E. In *Organic Syntheses*; Freeman, J.P., Ed.; Wiley: New York, 1990; Coll. Vol. 7, p 530.

(29) Smith, G.A.; Gawley, R.E. *Org. Synth.* **1985**, *63*, 136.

(30) Giannis, A.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 218.

(31) Dharanipragada, R.; Alarcon, A.; Hruby,V.J. *Org. Prep. Proc. Int.* **1991**, *23*, 396.

(32) Boesten, W.H.J.; Schepers, C.H.N.; Roberts, M.J.A. Eur. Pat. EPO322982, 1989; *Chem. Abstr.* **1989**, *111*, 233669a.

(33) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.

(34) McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.

(35) Narasimhan, S.; Madhavan, S.; Ganeshwar Prasad, K. *Synth. Commun.* **1996**, *26*, 703.

(36) Umino, N.; Iwakuma,T.; Itoh, N. *Tetrahedron Lett.* **1976**, 763.

(37) Wann, S.R.; Thorsen, P.T.; Kreevoy, M.M. *J. Org. Chem.* **1981**, *46*, 2579.

(38) Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* **1956**, *78*, 2582.

(39) Narasimhan, S.; Madhavan, S.; Balakumar, R.; Swarnalakshmi, S. *Synth. Commun.* **1997**, *27*, 391.

(40) Brown, H.C. Narasimhan, S. *Organometallics* **1982**, *1*, 762.

(41) Narasimhan, S.; Ganeshwar Prasad, K.; Madhavan, S. *Tetrahedron. Lett.* **1995**, *36*, 1141.

(42) Narasimhan, S.; Ganeshwar Prasad, K. *Org. Prep. Proced. Intl.* **1993**, *25*, 108.

(43) Periasamy, M.; Satyanarayana, M. *Tetrahedron Lett.* **1984,** *25*, 2501.

(44) Liotta, R.; Brown, H.C. *J. Org. Chem.* **1977**, *42*, 2836.

(45) Brown, H.C.; Mandal, A.K. *J. Org. Chem.* **1977**, *42*, 2996.

(46) Brown, H.C.; Chandrasekharan, J.; Ramachandran, P.V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

(47) Cha, J.S.; Kim, E.J.; Kwon, O.O.; Kwon, S.Y.; Seo, W.W.; Chang, S.W. *Org. Prep. Proc. Intl.* **1995**, *27*, 541.

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Mr. R. Balakumar received his M.Sc. and M.Phil. in Chemistry from Madras Christian College. He joined Dr. S. Narasimhan's group in February 1995 and is currently working towards his Ph.D. His research project involves the synthesis of oxazaborolidines using novel synthetic routes and studying their utility as chiral reagents in imparting enantioselectivity in reductions, Diels-Alder, and other reactions. Another project involves the study of zinc and zirconium borohydride as potential reducing agents.