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Methods of enhancement of reactivity and selectivity of sodium borohydride for applications in organic synthesis

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Abstract

$NaBH_4$ does not reduce carboxylic acids, esters, amides and nitriles under ambient conditions. However, the reactivity of $NaBH_4$ can be enhanced by the addition of certain additives. For example, addition of iodine to $NaBH_4$ in THF provides H_3B–THF that is useful for hydroborations and reductions of various functional groups. The aldehydes and ketones are reduced in a fast manner by the $NaBH_4$ reagent. Even so, the selectivities realised in such reductions can be enhanced using $NaBH_4$ along with another additive. In this article, various methods used for the enhancement of reactivity and selectivity of $NaBH_4$ in organic synthesis are described. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Sodium borohydride; Enhancement of reactivity; Additives; Reduction of organics

1. Introduction

Metal hydrides are valuable reagents in modern organic chemistry. The most frequently used hydride is the $NaBH_4$ reagent. It is a mild, inexpensive and invaluable reagent for applications in a wide range of reduction processes. It is the reagent of choice for the reduction of aldehydes and ketones to alcohols [1] and imines [2] or iminium salts [3] to amines with protic solvents [4]. The carboxylic acids, esters, amides and nitriles are more resistant towards $NaBH_4$ [1]. However, the reactivity of $NaBH_4$ can be enhanced by carrying out the reaction in the presence of certain additives. In this article, various methods of enhancement of reactivity and selectivity of $NaBH_4$ using additives for applications in organic synthesis are described.

2. Hydroboration of alkenes and alkynes

Hydroboration of carbon–carbon multiple bonds provides a method for the synthesis of the valuable organoborane intermediates with high regio- and stereospecificities [5]. Historically, Brown and Subba Rao discovered the hydroboration reaction during their investigation of the activation of $NaBH_4$ for the reduction of esters using $AlCl_3$ [6]. The use of BF_3 in the place of $AlCl_3$ led to more effective utilisation of the hydride for the generation of diborane, B_2H_6 and borane Lewis base complexes (Eqs. 1–3) [7].

$$9RCH{=}CH_2 + AlCl_3 \xrightarrow{\text{diglyme}} 3(RCH_2CH_2)_3B + AlH_3 + 3NaCl \quad (1)$$

$$12RCH{=}CH_2 + 3NaBH_4 + 4BF_3 \xrightarrow{\text{diglyme}} 4(RCH_2CH_2)_3B + 3NaBF_4 \quad (2)$$

$$(RCH_2CH_2)_3B + 3H_2O_2 + NaOH \rightarrow 3RCH_2CH_2OH + NaB(OH)_4 \quad (3)$$

Although several of these borane complexes are commercially available (e.g. H_3B–THF, H_3B–SMe_2 and H_3B–NR_3), there have been sustained efforts towards the development of alternative, simple and convenient methods of generation of boranes in situ for hydroboration. In 1963, it was reported that a 1:1 mixture of $NaBH_4$ and CH_3COOH hydroborates alkenes [8a]. Later, a modified procedure for hydroboranes using $NaBH_4$–CH_3COOH was reported (Eq. (4)) [8b].

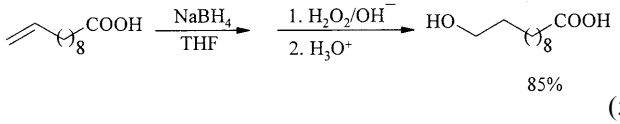
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$$NaBH_4 + CH_3COOH \rightarrow CH_3COOBH_3Na$$
$$\xrightarrow[2.\ H_2O_2\text{–}OH^-]{1.\ n\text{-}C_4H_9CH=CH_2} \underset{75\%}{n\text{-}C_4H_9CH_2CH_2OH} \quad (4)$$

Selective hydroboration of olefinic moiety in the presence of carboxylic acid group was reported from this laboratory (Eq. (5)) [9].

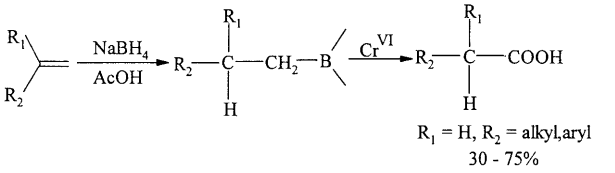


(5)

Also, a new method of conversion of olefins to dialkyl ketone was developed (Eq. (6)) [10].

$$NaBH_4 \xrightarrow[2.\ n\text{-}C_8H_{17}CH=CH_2,\ 25°C,\ 12\ h]{1.\ AcOH\text{–}THF} \xrightarrow[2.\ H_2O_2\text{–}OH^-]{1.\ CHCl_3\text{–}NaOMe} \underset{80\%}{(n\text{-}C_8H_{17}CH_2CH_2)_2C{=}O} \quad (6)$$

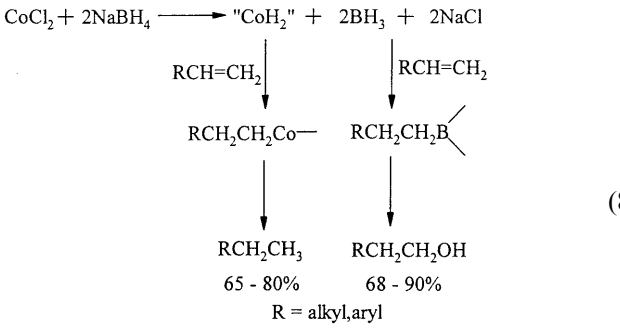
A method of conversion of terminal alkenes to carboxylic acids through hydroboration of olefins was also developed (Eq. (7)) [11]. This method provides a simple, one-pot synthesis of carboxylic acids from terminal alkenes.



(7)

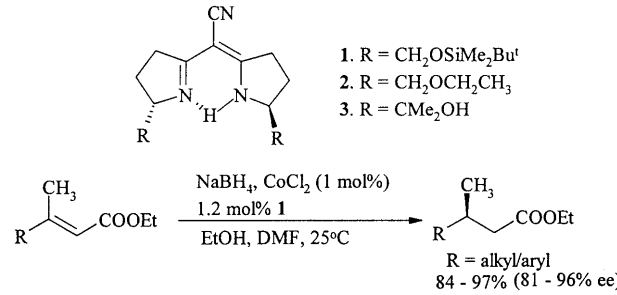
Also, various combinations of metal salts and borohydrides, such as $SnCl_4$–$NaBH_4$ [12], $TiCl_4$–$NaBH_4$ [13], $TiCl_4$–$PhCH_2N^+(Et)_3BH_4^-$ [14] and $CoCl_2$–$NaBH_4$ [15] have been reported to effect hydroboration of olefins.

Whereas the $CoCl_2$–$NaBH_4$ combination behaves as a hydroborating agent when the reaction is carried out with THF for 2 h at room temperature (r.t.) before the addition of alkene, it works as a hydrogenating agent [15] in methanol (Eq. (8)). This method has some advantages over the reported method using alcoholic medium [16].



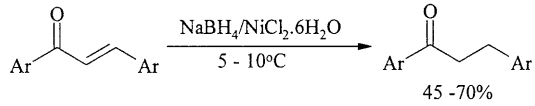
(8)

Chiral semicorrin **1**–**3** cobalt complexes can be prepared readily using $CoCl_2$ and the corresponding free ligands. These complexes are efficient enantioselective catalysts for the conjugate reduction of α,β-unsaturated carboxylates (Eq. (9)) [17] and α,β-unsaturated carboxamides [18] using $NaBH_4$.



(9)

Chalcones undergo facile reduction on reaction with $NiCl_2$–$NaBH_4$ system to afford dihydrochalcones (Eq. (10)) [19]. The use of copper or cobalt chloride in place of $NiCl_2$ is not as efficient for this application.



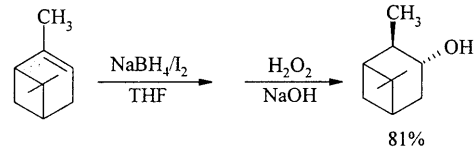
(10)

The $NaBH_4$ reacts with I_2 to give diborane (Eq. (11)) [20a].

$$2NaBH_4 + I_2 \rightarrow B_2H_6 + H_2 + 2NaI \quad (11)$$

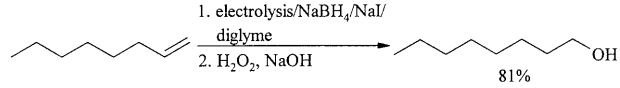
The reactive 'H_3B–THF' species can be easily generated in situ by mixing $NaBH_4$ and I_2 in THF [20b]. Hydroboration of alkenes using this $NaBH_4$–I_2 system in THF followed by oxidation gives the corresponding *anti*-Markovnikov alcohols (Eqs. (12) and (13)) in good yields [21,22].

$$n\text{-}C_8H_{17}CH=CH_2 \xrightarrow[THF]{NaBH_4\text{–}I_2} \xrightarrow[NaOH]{H_2O_2} \underset{92\%}{n\text{-}C_8H_{17}CH_2CH_2OH} \quad (12)$$



(13)

Later, it was reported that electrochemical oxidation of $NaBH_4$ using catalytic amounts of sodium iodide gives diborane that hydroborates olefins (Eq. (14)) [23].

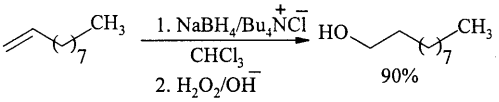


(14)

The Me_3SiCl–$PhCH_2N^+(Et)_3BH_4^-$ reagent system has been reported to effect hydroboration of olefins to give *anti*-Markovnikov alcohols after oxidation (Eq. (15)) [24].

$$CH_3(CH_2)_6CH=CH_2 \xrightarrow[Me_3SiCl,\ CH_2Cl_2]{1.\ PhCH_2N^+(Et)_3B^-H_4} \underset{72\%}{CH_3(CH_2)_7CH_2OH} \quad (15)$$

Very recently, it has been reported that the tetrabutylammonium borohydride liberates diborane in solvents such as CH_2Cl_2, $CHCl_3$ and CCl_4. A number of terminal, internal and cyclic alkenes were hydroborated using this borohydride (Eq. (16)) [25].



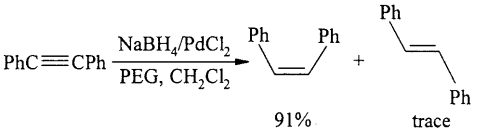
(16)

The 1-alkynes undergo dihydroboration to yield the corresponding terminal alcohols after oxidation. Generally, the disubstituted alkynes give vinyl boranes that on oxidation offord ketones as the major product (Eqs. (17) and (18)) [25,26]. However, the diphenyl acetylene yields 1,2-diphenylethanol as the major product through dihydroboration under these conditions.

$$C_6H_5C{\equiv}CC_6H_5 \xrightarrow[CHCl_3]{NaBH_4\text{–}Bu_4N^+Cl^-} \underset{83\%}{C_6H_5CH(OH)CH_2C_6H_5} \quad (17)$$

$$CH_3CH_2C{\equiv}CCH_2CH_3 \xrightarrow[CHCl_3]{NaBH_4\text{–}Bu_4N^+Cl^-} \underset{90\%}{CH_3CH_2CO(CH_2)_2CH_3} \quad (18)$$

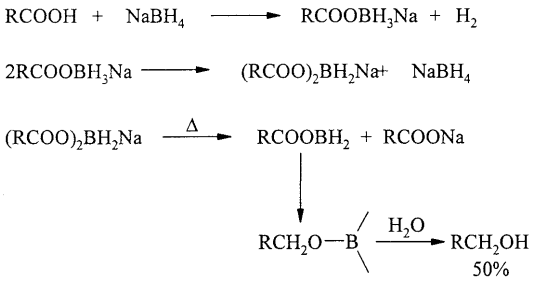
The $PdCl_2$–$NaBH_4$–polyethyleneglycol (PEG)–CH_2Cl_2 system is effective for hydrogenation of carbon–carbon triple bonds to the corresponding *cis*-alkenes (Eq. (19)) [27]. This reagent has advantages of faster rates and higher selectivity.



(19)

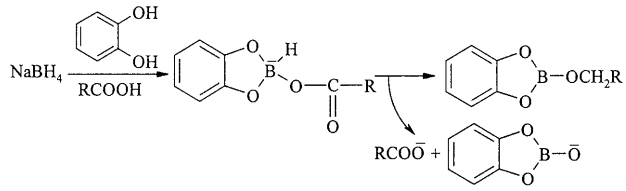
3. Reduction of carboxylic acids

The $NaBH_4$ gives acyloxyborohydride species on reaction with carboxylic acids in THF that hydroborate olefins. The acyloxy moieties in such acyloxyborohydrides remain unchanged under ambient conditions. However, one half of the acyloxy moiety undergoes reduction upon heating to give the corresponding alcohol (Eq. (20)) [28].



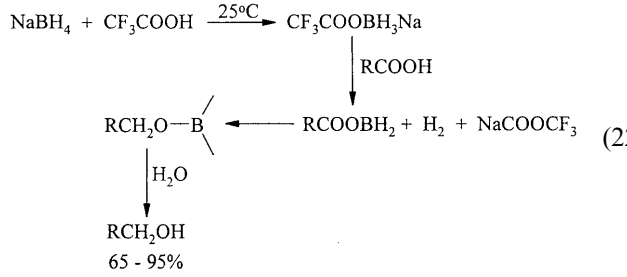
(20)

A similar reaction was also observed using $NaBH_4$, RCOOH and catechol at 25°C (Eq. (21)) [29].



(21)

Aliphatic carboxylic acids are reduced by $NaBH_4$ to the corresponding alcohols in good yields when RCOOH and CF_3COOH are used in 1:1 ratio under ambient conditions (Eq. (22)). However, the aromatic acids give poor yields (e.g. benzoic acid 20%). Also, the $NaBH_4$–CF_3COOH combination is good for the reduction of aliphatic carboxylic acids (65–95% yields). Again, aromatic acids give poor results under these conditions (30%).



(22)

The $ZnCl_2$–$NaBH_4$ reagent system readily reduces both aliphatic and aromatic acids to the corresponding alcohols in refluxing THF (Eq. (23)) [30]. The reaction requires only stoichiometric quantities of hydride for this conversion. Also, dicarboxylic acids are reduced to the corresponding diols under these conditions.

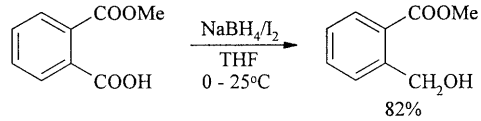
$$RCOOH \xrightarrow[THF,\ \Delta]{NaBH_4\text{–}ZnCl_2} \underset{\substack{R = alkyl/aryl \\ 70\text{–}95\%}}{RCH_2OH} \quad (23)$$

The reagent prepared using $ZrCl_4$ and $NaBH_4$ reduces the carboxylic acids in excellent yields under mild conditions (Eq. (24)) [31].

$$PhCOOH \xrightarrow[THF,\ rt,\ 5\ h]{NaBH_4\text{–}ZrCl_4} \underset{85\%}{PhCH_2OH} \quad (24)$$

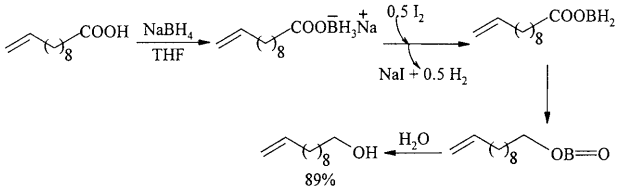
Carboxylic acids are reduced to the corresponding alcohols under ambient conditions by the $NaBH_4$–I_2 reagent system in very good yields with some selectivities (Eqs. (25) and (26)) [32].

$$CH_3(CH_2)_8COOH \xrightarrow[\substack{THF \\ 0\text{–}25°C}]{NaBH_4\text{–}I_2} \underset{95\%}{CH_3(CH_2)_8CH_2OH} \quad (25)$$



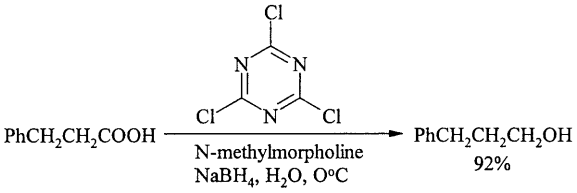
(26)

Further, selective reduction of the carboxylic acid group in an olefinic acid has also been achieved by forming the corresponding acyloxyborohydride before the addition of I_2 (Eq. (27)) [32].



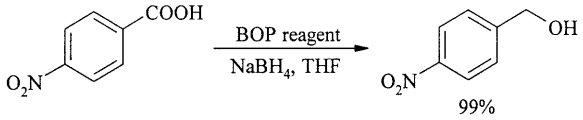
(27)

Cyanuric chloride–$NaBH_4$ reagent system has also been used to effect the reduction of carboxylic acids to alcohols under mild conditions (Eq. (28)) [33].

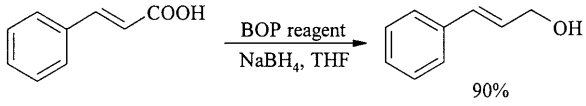


(28)

Facile, chemoselective reduction of carboxylic acids to alcohols using a phosphonium hexafluorophosphate (BOP reagent)–$NaBH_4$ reagent system has been reported (Eqs. (29) and (30)) [34]. Also, this method is convenient, rapid and chemoselective in several cases. For example, functional groups such as nitro, nitrile, azido and ester are unaffected under these conditions.



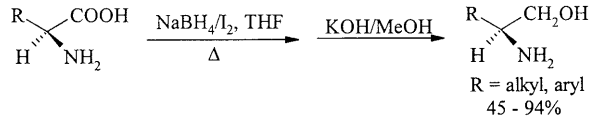
(29)



(30)

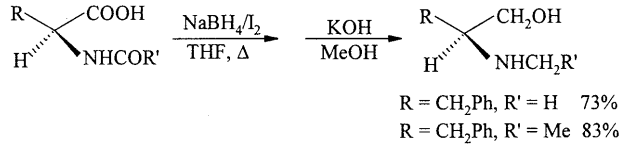
4. Reduction of amino acids and their derivatives

Chiral amino alcohols are important class of compounds. They are useful in asymmetric transformations, synthesis of pharmaceuticals [35], resolution of racemic mixtures [36] and in synthesis of insecticides [37]. Obviously, several reagents are available (e.g. $LiAlH_4$ [38], DIBAL [39], H_3B–THF [40]) for the reduction of free as well as protected amino acids to the corresponding amino alcohols. However, these reagents suffer from disadvantages of cost, inflammability and tedious isolation procedures. Meyers and coworkers examined the reduction of amino acids using the $NaBH_4$–I_2 reagent system. The results indicate that it is an excellent reagent system for the conversion of amino acids to amino alcohols (Eq. (31)) [41].



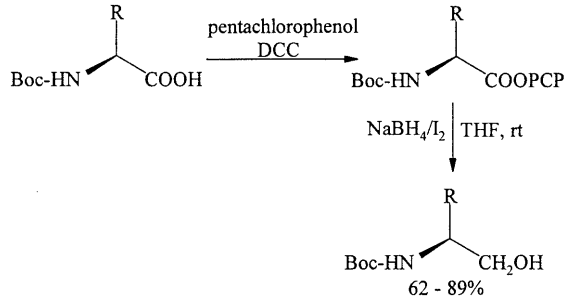
(31)

The *N*-acyl amino acids give the corresponding *N*-alkyl amino alcohols under these conditions (Eq. (32)) [41].



(32)

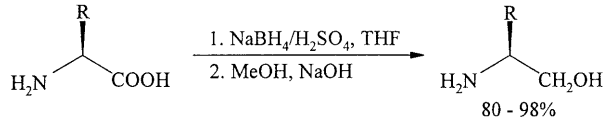
However, the *N*-carbamate protecting group is unaffected under these conditions [41]. Also, the reductions of pentachlorophenyl esters of the Boc protected amino acids and peptides to the corresponding alcohols have been reported (Eq. (33)) [42].



(33)

The $NaBH_4$–I_2 reagent system is safe, simple and inexpensive. Hence, it is useful, especially in the large scale synthesis of chiral amino alcohols.

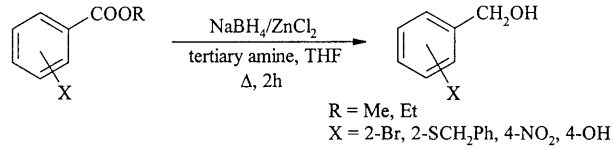
Amino acids are also reduced using the inexpensive $NaBH_4$–H_2SO_4 reagent system in THF (Eq. (34)) [43]. It is of interest to note that no racemization occurs in the reduction of amino acids using $NaBH_4$–I_2 or $NaBH_4$–H_2SO_4.



(34)

5. Reduction of carboxylic acid esters

The $NaBH_4$–$ZnCl_2$ reagent system exhibits powerful reducing properties in the presence of a tertiary amine. The carboxylic esters were smoothly reduced by this reagent to their corresponding alcohols (Eq. (35)) [44]. Further, the reduction does not take place without the amine under these conditions.



(35)

The $NaBH_4$–I_2 reagent system has also been used for this application. It readily reduces carboxylic acid esters under reflux conditions in good yields (Eq. (36)) [21].

$$PhCH_2COOEt \xrightarrow[70°C,\ 0.5\ h]{NaBH_4-I_2,\ THF} \xrightarrow{H_2O} \underset{85\%}{PhCH_2CH_2OH} \quad (36)$$

6. Reduction of carboxylic acid amides

Numerous chemicals of importance in medicinal chemistry have been prepared through reduction of amides [45]. It was found that the amides can be easily reduced to primary amines using $NaBH_4$–$CoCl_2$ system in good yields in hydroxylic as well as in non-hydroxylic solvents (Eq. (37)) [46].

$$n\text{-}C_3H_7CONH_2 \xrightarrow{NaBH_4-CoCl_2} \underset{70\%}{n\text{-}C_3H_7CH_2NH_2} \quad (37)$$

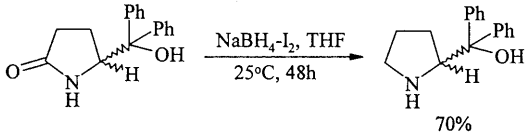
The $NaBH_4$–I_2 system is also useful for the reduction of amides (Eqs. (38)–(40)) [21].

$$PhCONH_2 \xrightarrow[THF,\ \Delta]{NaBH_4-I_2} \xrightarrow{NaOH} \underset{70\%}{PhCH_2NH_2} \quad (38)$$

$$PhNHCOCH_3 \rightarrow \underset{75\%}{PhNHCH_2CH_3} \quad (39)$$

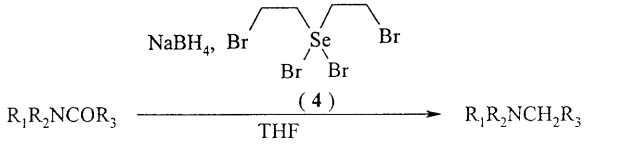
$$Ph(CH_3)NCOCH_3 \rightarrow \underset{74\%}{Ph(CH_3)NCH_2CH_3} \quad (40)$$

Further, reduction of amides containing sensitive functional groups can also be carried out using $NaBH_4$–I_2 reagent system under ambient conditions (Eq. (41)) [47].



70% (41)

A new procedure for the highly selective reduction of tertiary amides to amines using $NaBH_4$–bis(2-bromoethyl)selenium dibromide **4** has been reported (Eq. 42) [48a,b].



(42)

At a higher temperature, this reaction takes place smoothly in a shorter period. However, reduction of secondary and primary amides with this system in THF failed. Also, without the selenium compound, the reaction did not take place. It has been observed that the reaction of $NaBH_4$ with **4** produces borane (**5**) and bis(2-bromoethyl)selenide (**6**).

$(BrCH_2CH_2)_2Se$–BH_3 $(BrCH_2CH_2)_2Se$

5 **6**

7. Reduction of nitriles

The $CoCl_2$–$NaBH_4$ reagent system effectively reduces the nitriles in good yields [46] in hydroxylic as well as non-hydroxylic solvents (Eq. (43)).

$$C_6H_5CH(OH)CN \xrightarrow{NaBH_4-CoCl_2} \underset{80\%}{C_6H_5CH(OH)CH_2NH_2} \quad (43)$$

Mandelonitrile is smoothly reduced using the $NaBH_4$–$CoCl_2$ system [49]. It is of interest to note that reduction by $LiAlH_4$ gives the α-hydroxy-β-phenylethylamine in low yields. Cupric salts–$NaBH_4$ combinations are also effective for reduction of nitriles. The halogenides, sulfates, carboxylates of cobalt, nickel, iridium, rhodium, osmium and platinum were also used along with $NaBH_4$ in several applications. Also, $ZrCl_4$–$NaBH_4$ reagent system has been used for the reduction of nitriles in excellent yields (Eq. (44)) [31].

$$PhCH_2CN \xrightarrow[THF,\ r.t.]{NaBH_4-ZrCl_4} \underset{91\%}{PhCH_2CH_2NH_2} \quad (44)$$

Nitriles are also reduced by $NaBH_4$–I_2 system in THF under refluxing conditions (Eq. (45)) [21].

$$PhCN \xrightarrow[THF]{NaBH_4-I_2} \xrightarrow{NaOH} \underset{72\%}{PhCH_2NH_2} \quad (45)$$

Also, nitriles on reaction with a mixture of $NaBH_4$ and bis(2-bromoethyl)selenium dibromide (**4**), in boiling THF give the corresponding primary amines (Eq. (46)) [48].

$$RCN \xrightarrow[2.\ HCl]{1.\ NaBH_4-\mathbf{4},\ THF} \underset{\substack{R = alkyl/aryl \\ 35-73\%}}{RCH_2NH_2.HCl} \quad (46)$$

This reagent system does not affect many other substituents that are susceptible to H_3B–THF [48b].

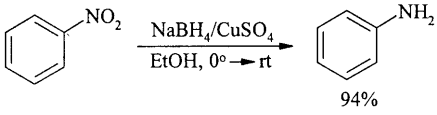
8. Reduction of acid chlorides

The acyl chlorides are efficiently reduced to the corresponding alcohols on reaction with $Zn(BH_4)_2$ in presence of TMEDA (Eq. (47)) [50]. Electron withdrawing group in the substrates enhances the rate of reduction. It is of interest to note that the selective reduction of acyl chlorides in the presence of other functional groups, such as chloro, nitro, ester and conjugated double bond can be achieved using this reagent system.

$$RCOCl \xrightarrow[TMEDA]{NaBH_4-ZnCl_2} \underset{\substack{R = alkyl/aryl \\ 86-98\%}}{RCH_2OH} \quad (47)$$

9. Reduction of nitro compounds

Nitro compounds are reduced to the corresponding amino compounds effectively using the $NaBH_4$–$CuSO_4$ system (Eq. (48)) [51]. It was reported that this system also reduces ketones, aliphatic esters, olefins and nitriles.

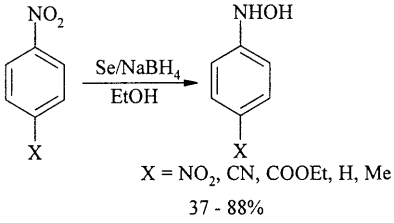


(48)

A novel reagent system, prepared using $BiCl_3$ and $NaBH_4$, reduces aromatic nitro compounds to the corresponding amines in good yields (Eq. (49)) [52]. The functional groups such as Me, OH, NH_2, OMe, Cl in the aromatic ring do not have any marked effect on the rate of the reaction. Moreover, these functional groups survive during the reduction, making this process fairly general and selective.

$$RNO_2 \xrightarrow[THF]{NaBH_4-BiCl_3} \underset{35-90\%}{RNH_2} \quad (49)$$

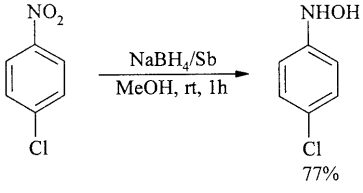
The aromatic nitro compounds are also reduced in good yields to the corresponding *N*-aryl hydroxylamines using $NaBH_4$ in the presence of catalytic amounts of metallic selenium (Eq. (50)) [53].



(50)

These selenium catalysed reductions were accelerated by electron withdrawing groups. The aliphatic nitro compounds gave the corresponding oximes under these conditions. The active species in this system is the hydrogen selenide anion [54]. Hence, this method opens up a new way to the use of selenium as a redox catalyst in organic synthesis.

The *N*-aryl hydroxylamines have been also prepared through antimony catalysed $NaBH_4$ reduction of nitroarenes (Eq. (51)) [55].



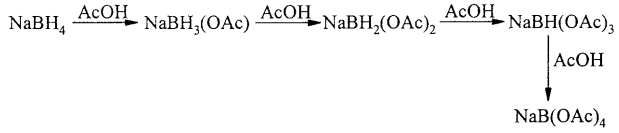
(51)

The novel $NaBH_4$–$(NH_4)_2SO_4$ reagent system has been used for the selective, rapid reduction of nitro compounds to the corresponding amino derivatives in good yields (Eq. (52)) [56].

$$RNO_2 \xrightarrow[EtOH,\ r.t.,\ 30-120\ min]{NaBH_4-(NH_4)_2SO_4} \underset{R = aryl\ (70-90\%)}{RNH_2} \quad (52)$$

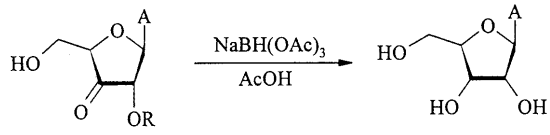
10. Reduction of aldehydes and ketones

The $NaBH_4$ is a reagent of choice for the reduction of aldehydes and ketones. The reactivity of $NaBH_4$ can be readily modified through its reaction with acetic acid (Eq. 53) [2,57]. With excess of acetic acid, triacyloxy borohydride is formed. The $NaBH_4$–CH_3COOH reagent system has been used for reductions of enamines, imines, vinylogous carbamates, aromatic and aliphatic α,β-unsaturated tosylhydrazones, pyrylium salts [58]. It has been also used for the reduction or reductive *N*-alkylation of amines, oximes [59] and nitrogen containing heterocycles [2].



(53)

The $NaBH(OAc)_3$ reagent has been used for the chemoselective reduction of aldehydes in the presence of ketones [2]. Also, selective reduction of ketones using $NaBH_4$ in glacial acetic acid solvent or $NaBH_4$ in THF using 3 equivalents of acetic acid were reported [60]. Further, highly stereoselective reduction of ketones was also achieved using $NaBH(OAc)_3$ in acetic acid (Eq. 54) [61].



A = adenin-9-yl; R = TBDMS

(54)

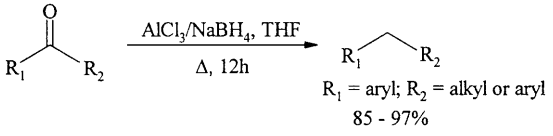
In the presence of $ZrCl_4$, $NaBH_4$ reduces the aldehydes selectively in high yields (Eq. (55)) [31].

$$PhCHO \xrightarrow[THF,\ r.t.,\ 5\ h]{NaBH_4-ZrCl_4} \underset{95\%}{PhCH_2OH} \quad (55)$$

Aromatic aldehydes are more selectively reduced than the related ketones by the reducing system consisting of $NaBH_4$ and $SnCl_2$ in THF (Eq. (56)) [62]. It may of interest to note that selective reduction of aldehydes in the presence of ketones is ordinarily impracticable using the reducing agents such as alkali metal borohydrides, aluminohydrides and diborane [63].

$$PhCHO \xrightarrow{NaBH_4-SnCl_2} \underset{96.8\%}{PhCH_2OH} + \underset{92\%}{PhCOPh} \quad (56)$$

The $NaBH_4$ in combination with anhydrous $AlCl_3$ conveniently reduces diaryl and aryl alkyl ketones to methylenic hydrocarbons (Eq. (57)) [64].



(57)

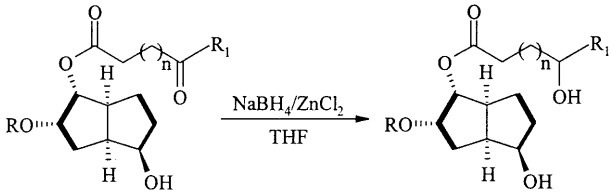
Although alkali metal borohydrides have received much attention in organic synthesis, the studies on the use of alkaline earth metals are limited. For example, α,β-unsaturated ketones more readily converted to allylic alcohols selectively using $NaBH_4$ in the presence of $CaCl_2$ (Eq. (58)) [65]. Among the alkaline earth metal chlorides examined, $CaCl_2$ gives the best combination of good yields and selectivities in the $NaBH_4$ reduction of 2-cyclohexen-1-one. Further, this method provides a simple, inexpensive alternative procedure for the selective 1,2-reduction of α,β-unsaturated ketones.



Additive	Yield(%)	Ratio of 1,2:1,4
None	-	51:49
$MgCl_2$	85	95:05
$CaCl_2$	92	97:03
$SrCl_2$	91	81:19
$BaCl_2$	86	93:07

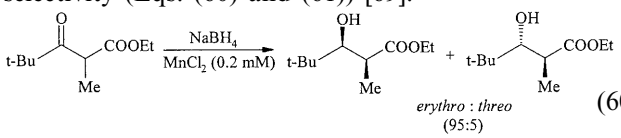
(58)

Metal salts mediated $NaBH_4$ reduction of α-alkyl-β-keto esters leads to different stereochemical control depending on the nature of the metal atom. For example, the strongly chelating $TiCl_4$ led to the *syn* isomer while non-chelating $CeCl_3$ [66] gave *anti* isomer [67]. The keto esters are also reduced using the $ZnCl_2$–$NaBH_4$ system to afford the corresponding hydroxy ester (Eq. (59)) [68].

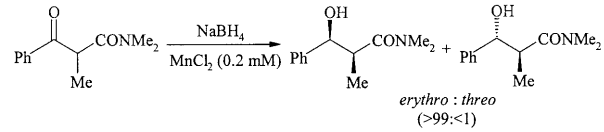


(59)

Stereoselective reduction of 3-keto-2-methyl esters and 3-keto-2-methyl amides with $NaBH_4$ and catalytic amount of $MnCl_2$ leads to the corresponding erythro-alcohols. Of the metal salts examined, $MnCl_2$ provides high selectivity (Eqs. (60) and (61)) [69].

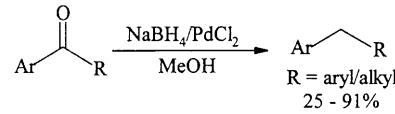


(60)



(61)

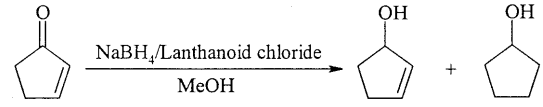
The $PdCl_2$–$NaBH_4$ reagent system [70] reduces aryl ketones, aryl chlorides and benzylic alcohols to the corresponding hydrocarbons (Eq. (62)). Also, certain hindered steroidal ketones are reduced to the corresponding alcohols in good yields.



(62)

Moreover, this reagent is useful for the preparation of alkylbenzenes from aryl alkyl ketones. This reduction proceeds under mild conditions at r.t. and neutral pH in a short time with high selectivity. Also, the chlorine atoms attached to aromatic rings are removed reductively by this reagent.

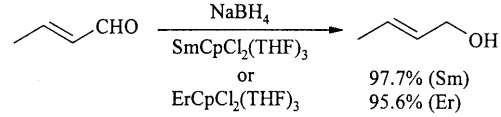
The lanthanoid ion-promoted $NaBH_4$ reduction of enones to allylic alcohols is a process of immense interest, since the regio- and chemoselectivity observed are in sharp contrast to the reduction promoted using other additives [71]. Among the lanthanoid chlorides examined, the $CeCl_3$ is the best reagent for selective 1,2-reduction of enones by $NaBH_4$ (Eq. (63)). Moreover, this reducing system does not affect carboxylic acids, esters, amides, halides, cyano and nitro groups.



Additive	Yield (%) (1,2:1,4 reduction)
La^{3+}	90:10
Ce^{3+}	97:03
Sm^{3+}	94:06
Eu^{3+}	93:07

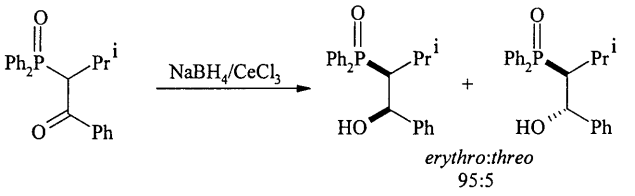
(63)

High chemo- and regioselective 1,2-reductions of unsaturated carbonyl compounds using $NaBH_4$ assisted by organolanthanide complexes, $LnCpCl_2(THF)_3$ (Ln = Sm and Er) in methanol have been reported (Eq. (64)) [72].



(64)

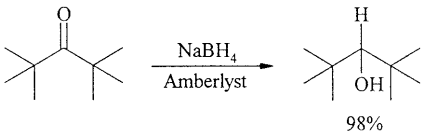
Finally, the $CeCl_3$–$NaBH_4$ system [66] reduces the α′-diphenylphosphinoyl enones and ketones stereoselectively in good yields (Eq. (65)) [73].



(65)

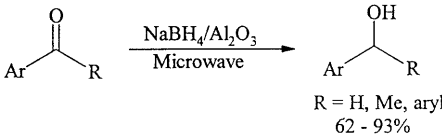
10.1. Reduction of ketones using $NaBH_4$ supported reagents

A novel reagent system consisting of $NaBH_4$ and amberlyst-15(H^+) in THF is a powerful reducing agent for the reduction of unreactive ketones (Eq. (66)) [74]. The reduction is fast, high yielding and the workup is very simple. Ketals, silyl ethers, acetates, allylic acetates, allylic γ-lactones, carboxylic esters, halides and isolated double bonds are not disturbed during the reduction.



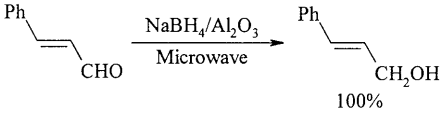
(66)

The $NaBH_4$ impregnated on neutral alumina reduces a wide variety of carbonyl compounds to the corresponding hydroxy derivatives in solution phase [75]. The solid state reduction has also been achieved by mixing ketones with $NaBH_4$ and storing the mixture in a dry box for 5 days [76]. The major disadvantage of these solid state methods is that they require long reaction time. Accordingly, a facile microwave assisted reduction of aldehydes and ketones by alumina supported $NaBH_4$ has been developed (Eq. (67)) [77].



(67)

Significant chemoselectivity is observed in the reduction of *trans*-cinnamaldehyde and the olefinic moiety remains intact under these conditions (Eq. (68)).



(68)

A novel solid state reduction of organic functional groups using $NaBH_4$ impregnated on Merrifield's resin has been reported [78]. Several aldehydes and ketones were also reduced using this reagent system.

10.2. Reduction of aldehydes and ketones under phase transfer catalysis

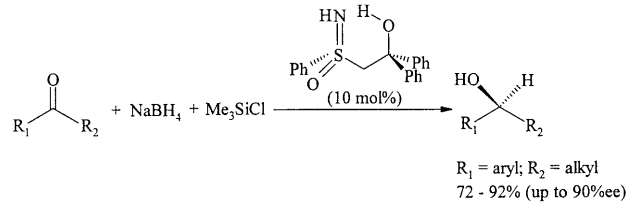
A simple, efficient and economical method for chemoselective reduction of aldehydes in the presence of ketones using stoichiometric amounts of $NaBH_4$ under phase-transfer catalysis was reported (Eq. (69)) [79]. Aliphatic, aromatic and unsaturated aldehydes are reduced rapidly in high yields while dialkyl, aralkyl, diaryl and cyclic ketones were not affected under these conditions. Toluene and CH_2Cl_2 have also been used as solvents while $PhCH_2NEt_3Cl$ and Aliquat-336 worked well as catalysts.



(69)

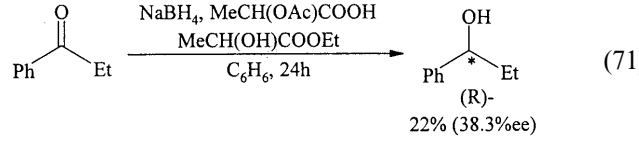
10.3. Asymmetric reduction of ketones using $NaBH_4$ and a chiral auxiliary

The use of $NaBH_4$–Me_3SiCl reagent system in the β-hydroxysulfoximine catalysed asymmetric reduction of ketones affords the corresponding secondary alcohols in high yields with good enantioselectivities (Eq. (70)) [80].



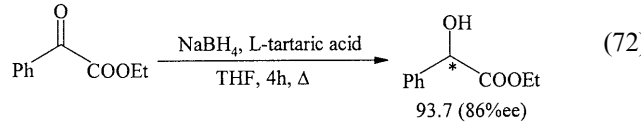
(70)

There are a few reports in the literature on asymmetric reduction in non-aqueous solutions using $NaBH_4$ modified by chiral ligands [81]. For example, asymmetric reduction of acetophenone, propiophenone and 2-acetylnaphthalene using $NaBH_4$ and optically active (*S*)-lactic acid derivatives produced the corresponding optically active (*R*)-alcohols in up to 38.3% ee (Eq. (71)) [82].



(71)

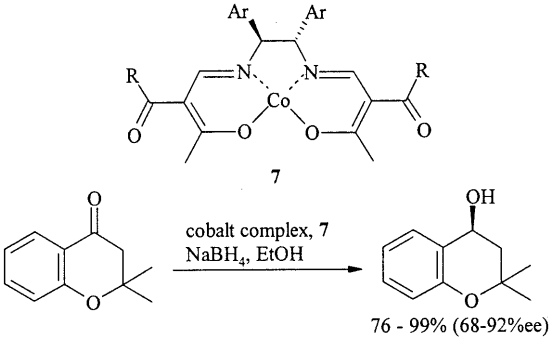
Also, successful asymmetric reduction of functionalized ketones using a $NaBH_4$–(*L*)-tartaric acid system was reported (Eq. (72)) [83]. This system is effective for the reduction of keto esters which are expected to chelate to a reductant through both the carbonyl and alkoxycarbonyl groups.



(72)

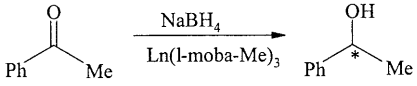
Unfortunately, lower reactivity was observed in the case of simple ketones and the products were almost

racemic in these cases. A catalytic enantioselective borohydride reduction of aromatic ketones using an optically active cobalt(II) complex catalyst **7** was reported (Eq. (73)) [84].



(73)

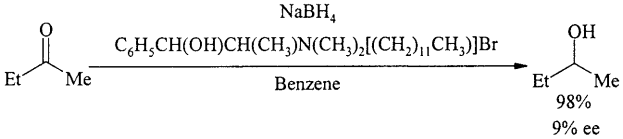
The lanthanoid complexes, tris{4-(l-menthyloxy)-1-(*p*-tolyl) butane-1,3-dionato}-lanthanoid(III), [Ln(l-moba-Me)$_3$] facilitate enantioselective borohydride reduction of ketones (Eq. (74)) [85]. The reaction is stoichiometric on the chiral lanthanoid complex. However, the host complexes are readily recovered in good yields for use again.



Additive	Yield(%)
None	00
La	52
Pr	44
Gd	64
Er	41

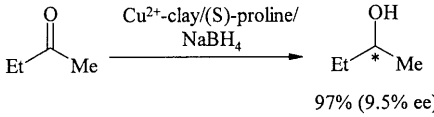
(74)

The use of montmorillonite clay in the asymmetric reduction of ketones using (-)-*N*-dodecyl-*N*-methyl ephedrenium borohydride was investigated (Eq. (75)) [86]. The rates of reductions are quite fast both in polar as well as in non-polar solvents. However, the asymmetric inductions realised were only poor.



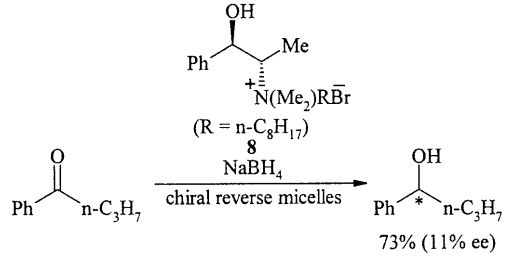
(75)

The chirally modified Cu^{2+}–montmorillonite has been prepared using (−)-2-amino-1-propanol and (*S*)-proline. The ketone pre-adsorbed on this clay was reduced by the addition of $NaBH_4$ in ethanol with low asymmetric inductions (Eq. (76)) [87]. The advantage of this system is the reusability of the chiral moiety.



(76)

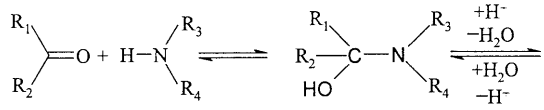
The chiral reverse micelles formed from chiral surfactants **8** are useful for the asymmetric reduction of prochiral ketones with $NaBH_4$ (Eq. (77)) [88]. It was noticed that the enantioselectivity of the reaction is affected by the structures of both surfactant and substrate. Also, the results depend on the composition of the micro environment. Further, it was reported that the presence of some sugars increases the enantiomeric excess of the products.



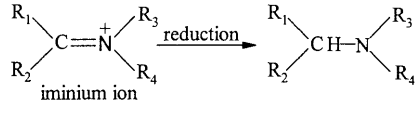
(77)

10.4. Reductive amination of aldehydes and ketones

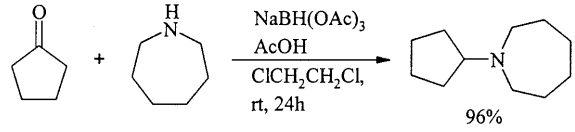
The reactions of aldehydes or ketones with NH_3, primary amines or secondary amines in the presence of reducing agents to obtain primary, secondary or tertiary amines, respectively are among the most useful and important processes for the synthesis of different amines. The choice of the reducing agent is very important for the success of the reaction since the reducing agent must reduce the imines (or iminium salts) intermediates selectively over aldehydes or ketones under the reaction conditions (Eq. (78)).



(78)



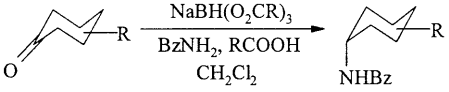
The $NaBH_4$ suits well for such applications. For example, reductive alkylation of amines were be readily carried out using $NaBH_4$ in neat liquid carboxylic acids (Eq. (79)) [89]. Also, reductive amination of aldehydes and ketones were reported using sodium triacetoxyborohydride [90].



(79)

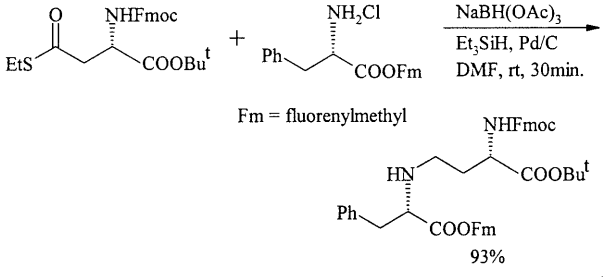
The scope of this transformation has been illustrated using aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, primary and secondary amines including a variety of weakly basic and non basic amines.

Further, highly diastereoselective reductive amination of substituted cyclohexanones give axial amines using sodium triacyloxyborohydrides derived from various carboxylic acids (Eq. (80)) [91].



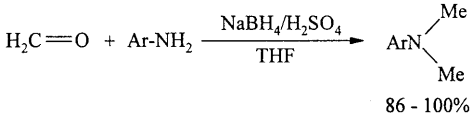
(80)

Very recently, a novel one-pot reductive alkylation of amines, by *S*-ethylthioesters mediated by triethyl silane and sodium triacetoxyborohydride in the presence of Pd on carbon, was reported (Eq. (81)) [92].



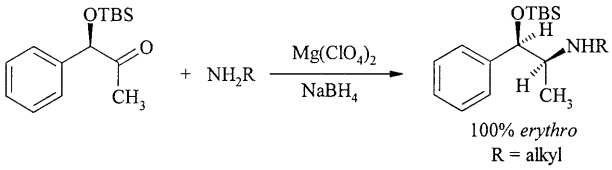
(81)

Also, the reaction of formaldehyde with primary and secondary aromatic amines using $NaBH_4$–H_2SO_4 in THF lead to reductive amination (Eq. (82)) [93].



(82)

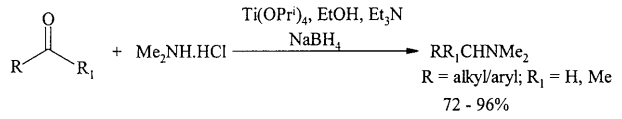
Also, the reaction of the chiral O-protected-α-hydroxyketone with primary amines by $NaBH_4$ in the presence of magnesium perchlorate, $Mg(ClO_4)_2$ led to the exclusive formation of erythro (1*R*,2*S*)-O-protected-*N*-substituted ethanolamines (Eq. (83)) [94].



(83)

Evidently, the intermediacy of magnesium bidendate complex leads to a more rigid conformation resulting in a higher percentage of the erythro diastereomer [95].

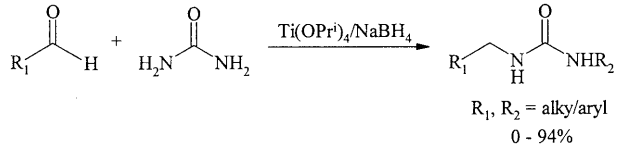
A simple, mild and efficient procedure for reductive alkylations of dimethylamine [96], methylamine hydrochloride, triethylamine [97] with carbonyl compounds using titanium(IV) isopropoxide and $NaBH_4$ has been reported (Eq. (84)).



(84)

The titanium(IV) isopropoxide [98] is a mild reagent compatible with a variety of potentially acid sensitive functional groups such as acetals, lactams, acetonide and *t*-butyldimethylsilyl ether.

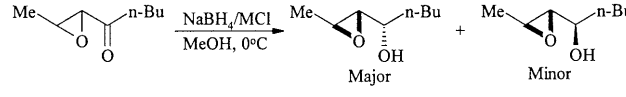
The $Ti(OPr^i)_4$–$NaBH_4$ has been also used in the synthesis of unsymmetrically disubstituted ureas by the reductive amidation of aldehydes and monosubstituted ureas (Eq. (85)) [99].



(85)

10.5. Reduction of epoxy ketones

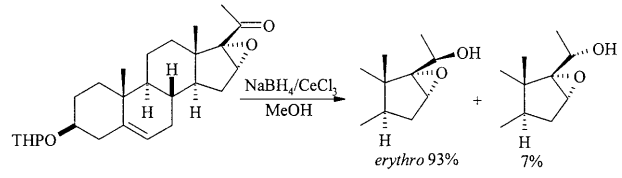
The α,β-epoxy alcohols serve as versatile synthetic intermediates that can be efficiently elaborated into poly hydroxy derivatives with multiple chiral centers [100]. A highly stereoselective reduction of α,β-epoxyketones using $NaBH_4$–$ZnCl_2$ reagent system has been reported [100]. Also, a very simple alternative procedure for the stereoselective reduction of α,β-epoxyketones into erythro-α,β-epoxy alcohols with $NaBH_4$ in the presence of $CaCl_2$–$LaCl_3$ in methanol was reported (Eq. (86)) [101].



(86)

In these cases, use of metal salt facilitates the formation of the erythro product. Also, the metal chlorides that have larger radii provided higher erythro-selectivity. For example, the lanthanum chloride gave the highest erythro-selectivity [102]. Further, the reductions proceeded very slowly in ether or benzene because of insolubility of $NaBH_4$ and metal chlorides in these solvents.

Reduction of α,β-epoxy ketones under the Luche conditions using $NaBH_4$–$CeCl_3$ in methanol provides *anti*- (or erythro-) α,β-epoxy alcohols in high yields and with extremely high stereoselectivity (Eq. (87)) [102].

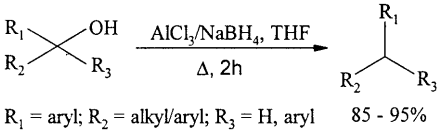


(87)

11. Miscellaneous

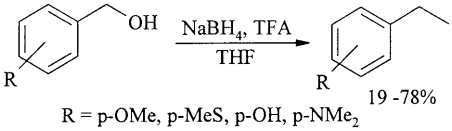
11.1. Reduction of carbinols and benzylic alcohols

The $NaBH_4$ in combination with anhydrous $AlCl_3$ conveniently reduces some diaryl–arylalkylcarbinols to methylenic hydrocarbons (Eq. (88)) [64].



R_1 = aryl; R_2 = alkyl/aryl; R_3 = H, aryl 85 - 95% (88)

The reduction of di- and triarylmethanols using $NaBH_4$ and TFA is ineffective in the case of non-benzylic and monobenzylic alcohols [103]. These methods lead to rapid formation of a very weak reducing agent i.e. trifluoroacetoxy borohydrides [2] which are slow in effecting hydride capture of the carbocation intermediate. It was found that dropwise addition of trifluoroacetic acid to a mixture of the substrate and $NaBH_4$ in THF provides a protonating medium rich in more reactive reducing species (Eq. (89)) [104]. This method was found to be highly effective for the reduction of monobenzylic alcohols to give the corresponding hydrocarbons in moderate to high yields.



R = p-OMe, p-MeS, p-OH, p-NMe_2 (89)

11.2. Reduction of azides

Aroyl azides are reduced predominantly to the corresponding benzyl alcohols using $NaBH_4$ in methanol [105]. However, they yield the corresponding amides using the $NiCl_2$–$NaBH_4$ system (Eq. (90)) [106].

$$p\text{-X-C}_6\text{H}_4\text{CON}_3 \xrightarrow[\text{MeOH, 0–10°C}]{\text{NaBH}_4\text{–NiCl}_2\cdot 6\text{H}_2\text{O}} p\text{-X-C}_6\text{H}_4\text{CONH}_2 \quad (90)$$

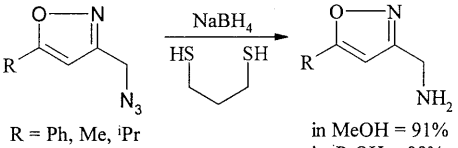
80–100%

A facile reduction of alkyl, aryl and aroyl azides using $NaBH_4$–$CuSO_4$ system has also been achieved (Eq. (91)) [107].

$$\text{PhCON}_3 \xrightarrow[\text{MeOH, 0–5°C}]{\text{NaBH}_4\text{–CuSO}_4} \text{PhCONH}_2 \quad (91)$$

90%

A series of isoxazole azides were reduced selectively to isoxazole amines in good yields by $NaBH_4$ in the presence of 1,3-propanedithiol (Eq. (92)) [108]. A solvent effect on this reaction was observed due to differences in the rate of decomposition of $NaBH_4$ in the alcoholic media. When the reduction was carried out in isopropanol under the same conditions, the azides were reduced to amines in quantitative yields.

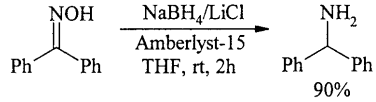


R = Ph, Me, ^{i}Pr in MeOH = 91%, in ^{i}PrOH = 98% (92)

It is of interest to note that the reducing power of $NaBH_4$ increases in THF (or *t*-butyl alcohol) when methanol is added dropwise during the reaction [109].

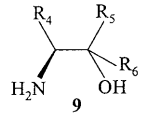
11.3. Reduction of oximes and oxime ethers

A reagent system consisting of $NaBH_4$–LiCl–amberlyst–15(H^+) in THF is powerful for the reduction of oximes (Eq. (93)) [110].



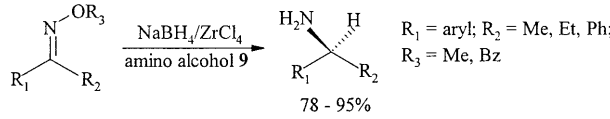
(93)

Reducing agents prepared using $ZrCl_4$–$NaBH_4$ and chiral amino alcohols **9** have been successfully applied to the enantioselective reduction of oxime ethers [111]. Optically active primary amines were obtained in high enantiomeric excess ($\geq$ 95% ee) with good chemical yields (Eq. (94)).



9

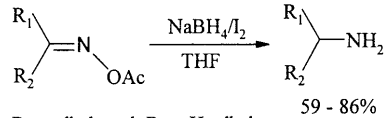
a. R_4 = ^{i}Pr, R_5, R_6 = H
b. R_4 = ^{i}Pr, R_5, R_6 = Ph
c. R_4 = ^{i}PrCH$_2$, R_5,R_6 = H



(94)

The reduction was examined using different Lewis acids. High enantioselectivity was observed using $ZnCl_2$ and $AlCl_3$ (1:1) mixture, but the removal of the mixed salts posed a difficulty leading to lowering of the chemical yield. Reductions using $ZrCl_4$–$NaBH_4$ system gave high chemical and optical yields. Removal of the metal salts after the reaction and isolation of the product are easy in the case of $ZrCl_4$.

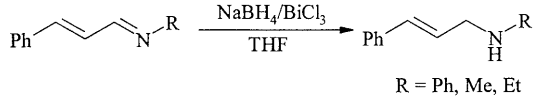
O-Acyl derivatives of aldoximes and ketoximes are reduced in good yields to the corresponding amines using the $NaBH_4$–I_2 system (Eq. (95)) [112].



R_1 = alkyl, aryl; R_2 = H, alkyl (95)

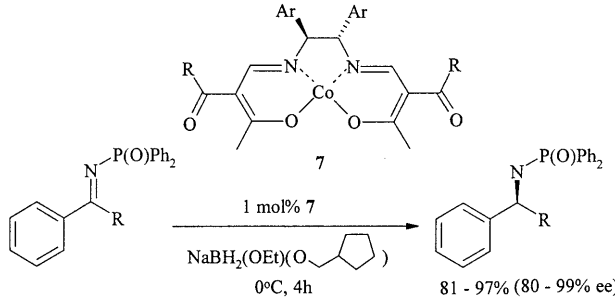
11.4. Reduction of C=N and N=N functional groups

The $BiCl_3$–$NaBH_4$ system can be used effectively for the reduction of azomethines to the corresponding amines (Eq. (96)) [52].



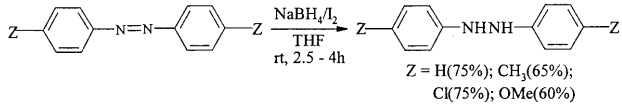
R = Ph, Me, Et 80 - 85% (96)

A catalytic enantioselective borohydride reduction of imines in the presence of optically active cobalt(II) catalyst **7** was achieved (Eq. (97)) [84].



(97)

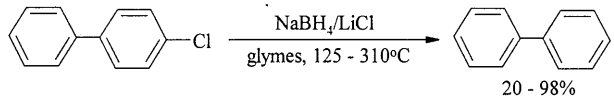
The $NaBH_4$–I_2 reducing system was successfully used for the reduction of azoarenes and azoxyarenes to the corresponding hydrazobenzenes in good yields (Eq. (98)) [113]. The reaction did not take place in the absence of iodine.



(98)

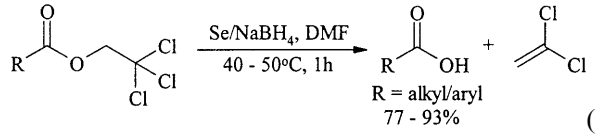
11.5. Reduction of alkyl and aryl halides

Dechlorination of 4-chlorobiphenyl with $NaBH_4$ was promoted by LiCl in high boiling inert solvents (Eq. (99)) [114].



(99)

The 2,2,2-trichloroethoxy moiety is widely used as a protective group in organic synthesis. It can be easily deprotected by $NaBH_4$ under the catalysis of selenium in DMF (Eq. (100)) [115].



(100)

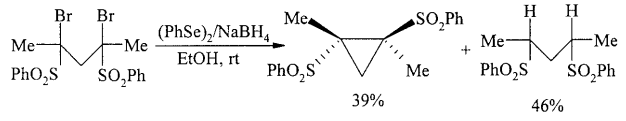
The $(PhSe)_2$–$NaBH_4$ system has been used as a reducing agent for the reduction of α-bromosulfones [116]. This reduction did not proceed without $(PhSe)_2$. Whereas iodomethyl sulfone also undergoes this reduction, the corresponding chloro derivative was not affected (Eqs. (101)–(103)).

$$PhSO_2CH_2Br \xrightarrow[EtOH,\ r.t.]{(PhSe)_2-NaBH_4} \underset{(quantitative)}{PhSO_2CH_3} \quad (101)$$

$$PhSO_2CH_2I \xrightarrow[95\%]{} PhSO_2CH_3 \quad (102)$$

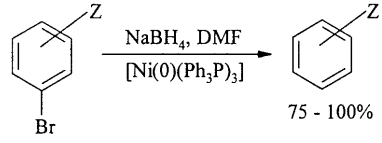
$$PhSO_2CH_2Cl \rightarrow \text{No reaction} \quad (103)$$

This reagent system was also applied for the radical cyclization and intramolecular coupling reactions (Eq. (104)).



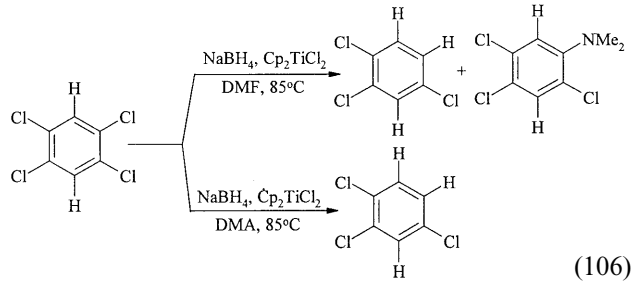
(104)

There is no appreciable reaction between $NaBH_4$ and aryl halides under most conditions. It was discovered that in the presence of catalytic amount of tris-(triphenylphosphine)nickel(0), $[Ni(0)(Ph_3P)_3]$, $NaBH_4$ serves as a powerful nucleophilic reagent in the reduction of aryl bromides (Eq. (105)) [117]. Use of DMF gives good results and ethanol, methanol and THF were proved to be ineffective. The aromatic chlorides also react, but much more slowly.



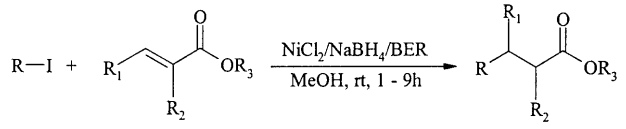
(105)

The reduction of aryl halides by $NaBH_4$ catalysed by titanocene dichloride is highly effective [118]. The adduct of DMF and $NaBH_4$ reduces simple aryl halides to give dechlorinated and dimethylamino-substituted products. In dimethyl–acetamide or in ether solvents only dechlorinated products are obtained (Eq. (106)).



(106)

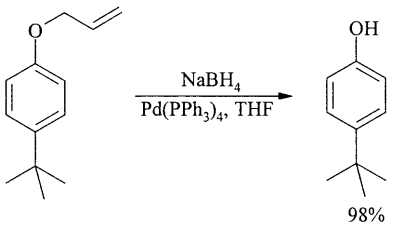
Nickel boride on borohydride exchange resin (BER) [119] is a good alternative reagent to tributyltin hydride [120] for the coupling of alkyl iodides with the electron deficient alkenes in methanol (Eq. (107)).



(107)

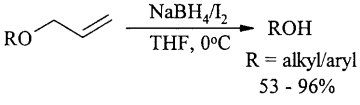
11.6. Cleavage of ethers using $NaBH_4$ and additives

A facile cleavage of allylic ethers has been achieved by $NaBH_4$ using catalytic amount of $Pd(PPh_3)_4$ (Eq. (108)) [121]. The $Pd(PPh_3)_2Cl_2$ could also be used as a catalyst in this reaction.



(108)

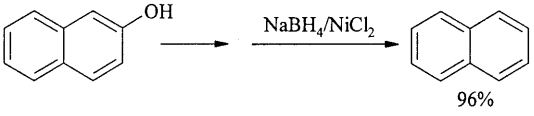
Also, a facile cleavage of allyl ethers has been achieved using the $NaBH_4$–I_2 reagent system (Eq. (109)) [122].



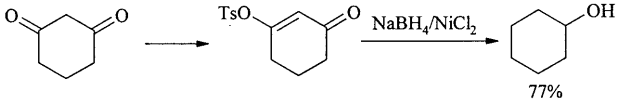
(109)

11.7. Deoxygenation of phenols and enols using $NaBH_4$ and additives

Deoxygenation reaction of phenol and 1,3-dicarbonyl compounds was investigated [123]. Phenols, enolizable 1,3-diketones and 3-keto esters are converted to the toluene–*p*-sulfonates that are reduced by the $NiCl_2$–$NaBH_4$ system to obtain the deoxygenated aromatic compounds, alcohols and esters, respectively (Eqs. (110) and (111)).



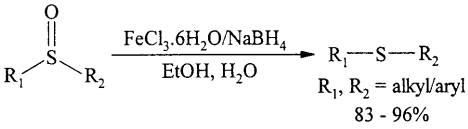
(110)



(111)

11.8. Reduction of sulfides using $NaBH_4$ and additives

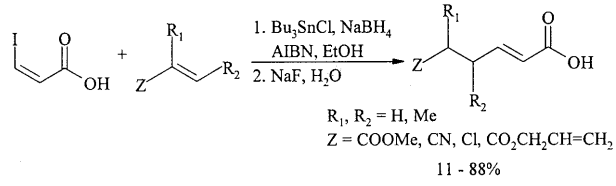
It was found that the arylalkyl, diaryl and dialkyl sulfoxides were reduced to the corresponding sulfides by $FeCl_3$–$NaBH_4$ in excellent yield under mild conditions (Eq. (112)) [124]. The sulfur–oxygen bond is weakened by the coordination of the sulfoxide oxygen with the metal ion, rendering it more liable to borohydride reduction [125].



(112)

11.9. Reactions using Bu_3SnCl–AIBN in combination with $NaBH_4$

The reaction of (*Z*)-3-iodoacrylic acid with electrophilic alkenes using tributyltin hydride, $NaBH_4$ and a catalytic amount of AIBN followed by NaF treatment produced the (*E*)-α,β-unsaturated carboxylic acids in a stereoselective manner (Eq. (113)) [126].



(113)

Also, it has been reported that replacement of hydride in borohydride by an electron donating alkylamino group greatly enhances the reducing ability of the resulting reagents. Thus, sodium(dimethylamino)borohydride (NaDMAB) and (tert-butylamino)-borohydride (NaTBAB) are more effective for the conversion of aldehydes, ketones and esters to alcohols (Eqs. (114) and (115)) and primary amides to amines in good yields [127]. Aryl halides are slowly converted to arenes, but alkyl halides and epoxides undergo unusual reactions with the amino portion of the reagents.

$$\mathrm{PhCHO} \xrightarrow{\text{NaDMAB–THF}} \underset{90\%}{\mathrm{PhCH_2OH}} \quad (114)$$

$$\mathrm{PhCOPh} \xrightarrow{\text{NaDMAB–THF}} \underset{99\%}{\mathrm{PhCH(OH)Ph}} \quad (115)$$

Besides the use of Lewis acids and other additives for enhancing the reaction and selectivity of $NaBH_4$, different solvents can be also used to realise similar objectives. For example, the rate of reduction of a ketone is solvent dependent with the order of reactivity among alcohols being, MeOH > EtOH > *i*-PrOH > *t*-BuOH. Thus, the $NaBH_4$ reactivity may be attenuated by the nature of the hydroxylic solvent and its concentration [128].

12. Conclusions

There have been sustained efforts on the development of methods of activation of $NaBH_4$ using Lewis acids, carboxylic acids, metal salts and some other additives for synthetic applications. Metal halides, Lewis and protic acids and oxidising agents enhance the reactivity of $NaBH_4$ towards the reduction of various functional groups, including carbon–carbon double bonds, carbon–carbon triple bonds, carboxylic acids, acyl chlorides, carboxamides, oximes, sulfoxides, nitriles and nitro compounds. Also, certain additives enhance the selectivities in the reduction of aldehydes and ketones. Further, several recipes were reported for

enantioselective reductions using $NaBH_4$. Since it is easy to handle $NaBH_4$ in large scale syntheses, it is anticipated that this area of research will continue to expand.

Acknowledgements

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