The Functional Group Selectivity of Complex Hydride Reducing Agents

By E. R. H. Walker
ICI LTD., PHARMACEUTICALS DIVISION, MERESIDE, ALDERLEY PARK, MACCLESFIELD, CHESHIRE, SK10 4TG

1 Introduction

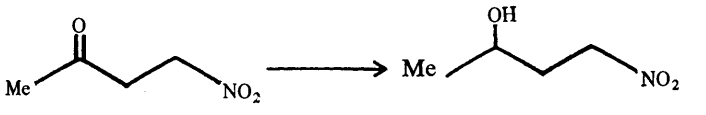
Sodium borohydride[1] and lithium aluminium hydride[2] have been known for over twenty years, and their use has revolutionized the procedures utilized for the reduction of functional groups in organic chemistry. However, despite their great convenience, these reagents suffer from certain deficiencies. As is well known, lithium aluminium hydride is an exceedingly powerful reagent, capable of reducing many functional groups, and is thus of little value for selective reductions, while sodium borohydride is a mild reducing agent, reacting readily only with aldehydes, ketones, and acid chlorides, and is thus only useful for the selective reduction of these relatively reactive groups. Much work has been conducted over the past few years to discover new reagents with reduction power intermediate between those of lithium aluminium hydride and sodium borohydride, and there is now available a wide range of reagents for selective reductions.

In this review the nucleophilic reducing agents sodium borohydride and lithium aluminium hydride are taken as starting points, and the effects on their reducing power of solvent, change of cation, and change of substituent are described. The electrophilic reducing agents diborane and aluminium hydride have, as expected, a quite different pattern of selectivity, and the effect of substituents on the reducing power of these reagents is examined. The majority of the reagents discussed are commercially available or are readily prepared from commercially available materials, and the review concentrates on the functional group selectivity of each reagent. The reactivity of each reagent towards twelve different functional groups is summarized in tabular form in Section 7 (p. 49), using a format introduced by H. C. Brown.[3a] The table indicates the reactivities of reagents towards sample representative groups and must be interpreted with caution, because the reactivity of many functional groups can be greatly modified by the molecular environment in which the group is placed. At the beginning

[1] H. I. Schlesinger, H. C. Brown, H. R. Hockstra, and L. R. Rapp, *J. Amer. Chem. Soc.*, 1953, **75**, 199.
[2] A. E. Finholt, A. C. Bond, and H. I. Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199.
[3] (*a*) H. C. Brown, 'Boranes in Organic Chemistry,' Cornell University Press, New York, 1972, p. 209; (*b*) G. M. L. Cragg, 'Organoboranes in Organic Synthesis,' Marcel Dekker, New York, 1973, p. 319; (*c*) E. Schenker, 'Newer Methods of Preparative Organic Chemistry', Vol. IV, ed. W. Forest, Academic Press, New York, 1968, p. 196; (*d*) H. O. House, 'Modern Synthetic Reactions,' 2nd. edn., Benjamin, Manto Park, California, 1972, p. 45.

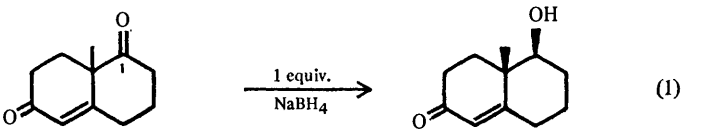
of each section is given a list of solvents in which each reagent has been used. Several recent books[3] have reviewed the subject of hydride reducing agents and have formed a source for some of the data given here.

2 Sodium Borohydride (Solvent: water, alcohols, or 2-methoxyethyl ether)
Sodium borohydride is a very mild reducing agent and can be used to reduce aldehydes, ketones, and acid chlorides in the presence of a wide variety of functional groups. For example, the nitro-ketone (1) can be readily reduced to the nitro-alcohol (2). In some systems saturated ketones can be selectively



(1) (2)

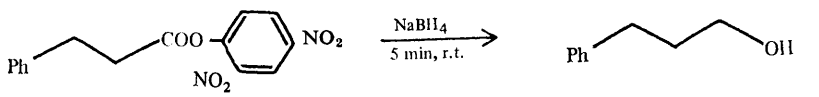
reduced[4] in the presence of $\alpha\beta$-unsaturated ketones [equation (1)]. Sodium borohydride is a nucleophilic reagent. Thus reduction occurs by attack at the centre of lowest electron density, which in the case of (3) is the carbon atom of the saturated ketone, C-1. Delocalization renders the unsaturated system less



(3) (1)

susceptible to nucleophilic attack. In the case of the electrophilic reducing agent diborane the reverse selectivity occurs (see Section 4).

Although esters are not usually reduced by sodium borohydride, 4-nitrophenyl and 2,4-dinitrophenyl esters, *e.g.* (4) (systems in which the electron-withdrawing effect of the nitro-groups has increased the susceptibility of the ester carbonyl



(4) (5)

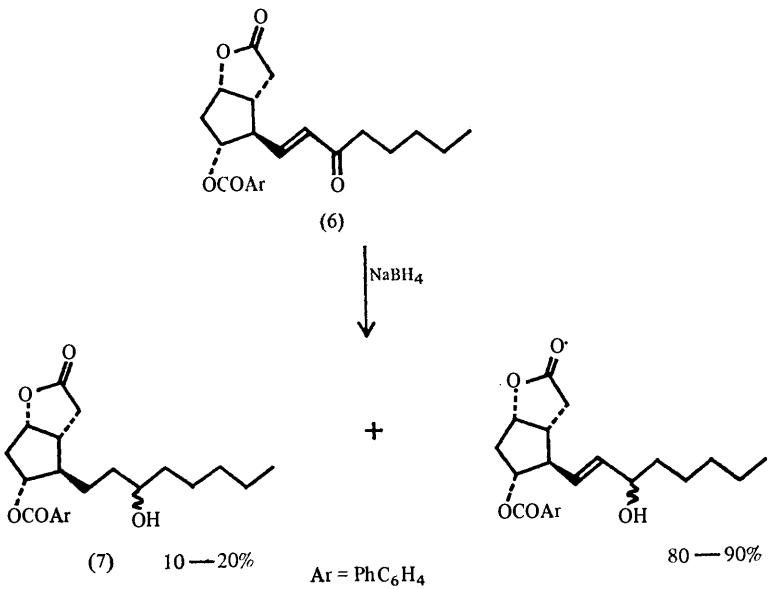
[4] J. D. Cocher and T. G. Halsall, *J. Chem. Soc.*, 1957, 3441.

to nucleophilic attack), are reduced[5] very rapidly at room temperature to give the corresponding alcohol, *e.g.* (5). Thus it should be possible to reduce a 2,4-dinitrophenyl ester selectively in the presence of a methyl ester.

Sodium borohydride has a number of disadvantages as a reducing agent. Thus, although alkyl esters are reduced only very slowly, because of the basicity of the reagent, transesterification can be rapid [equation (2)]. The reduction of

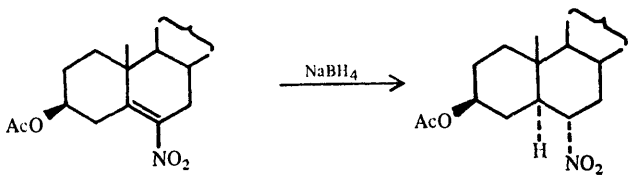
$$R^3CO_2R^1 + R^2OH \xrightarrow{NaBH_4} R^3CO_2R^2 + R^1OH \qquad (2)$$

enones is invariably accompanied by some double-bond reduction to yield the corresponding saturated alcohol. For example, sodium borohydride reduction[6] of the prostaglandin intermediate (6) yields 10—20% of the saturated alcohol (7). Double bonds conjugated to esters, nitriles, amides, aromatic rings, and nitro-groups can also be reduced[7] by sodium borohydride [equation (3)].



A. Effect of Solvent.—Sodium borohydride has a great advantage over lithium aluminium hydride in that it can be used in a wide range of solvents.

[5] S. Takahashi and L. A. Cohen, *J. Org. Chem.*, 1970, **35**, 1505.
[6] J. Bowler, K. B. Mallion, and R. A. Raphael, *Synth. Comm.*, 1974, **4**, 211.
[7] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1350.



(3)

(i) *Water.* Sodium borohydride is very soluble in water, reacting with it slowly to evolve hydrogen. These aqueous solutions can be stabilized by the addition of alkali.[1] Such aqueous solutions readily reduce aldehydes and ketones in two-phase systems even where the solubilities of the compounds in the aqueous phase are quite limited. The rate of reduction is increased in the presence of phase-transfer catalysts.[8]

(ii) *Alcohols.* Sodium borohydride is very soluble in methanol and ethanol. It reacts rapidly with methanol, but only slowly with ethanol, and therefore for most purposes ethanol is the preferred solvent, possessing the advantages of homogeneous solution together with little loss of reducing agent through side-reaction with the solvent.

(iii) *Ethers.* Sodium borohydride has a very low solubility in diethyl ether and THF, and is not used in these solvents. In 2-methoxyethyl ether[9] sodium borohydride is an exceptionally mild reducing agent, reducing aldehydes but not ketones. In this solvent it may be possible to reduce an aldehyde selectively in the presence of a ketone.*

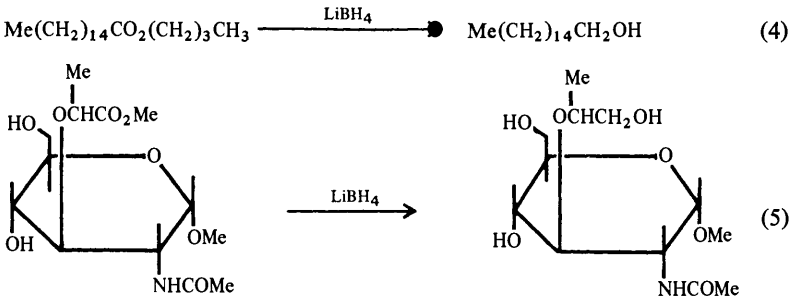
(iv) *Dimethyl Sulphoxide–Tetramethylene Sulphone.* Sodium borohydride has been used in dimethyl sulphoxide–tetramethylene sulphone mixtures to reduce alkyl halides[10] in the presence of acids, esters, lactones, and nitro-groups.

B. Effect of Cation.—(i) *Lithium Borohydride* (Solvent: tetrahydrofuran). Lithium borohydride is a stronger reducing agent than sodium borohydride and is ideal for the reduction of esters [equation (4)], particularly in the presence of functional groups that are readily reduced by lithium aluminium hydride, *e.g.* amides[11] [equation (5)].

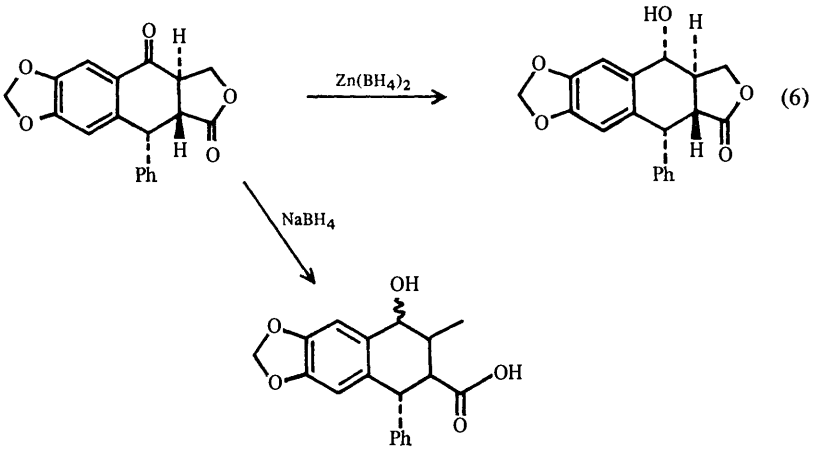
(ii) *Zinc Borohydride* (Solvent: dimethoxyethane). Zinc borohydride is readily prepared from sodium borohydride and zinc chloride in dimethoxyethane.[12] It has the same reducing power as sodium borohydride but is less basic, and is

*Sodium borohydride has been used in the presence of 3 equivalents of acetic acid for the selective reduction of aldehydes in the presence of ketones (G. W. Gribble and D. C. Ferguson, *J.C.S. Chem. Comm.*, 1975, 535).

[8] C. M. Starks, *J. Amer. Chem. Soc.*, 1971, **93**, 195.
[9] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209; ref. 3*a*, p. 216.
[10] R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Letters*, 1969, 3495.
[11] R. W. Jeanloz and E. Walker, *Carbohydrate Res.*, 1967, **4**, 504.
[12] W. J. Gensler, F. Johnson, and A. D. B. Sloan, *J. Amer. Chem. Soc.*, 1960, **82**, 6074.

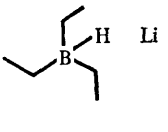


particularly suitable for the reduction of alkali-sensitive compounds[12] [equation (6)].



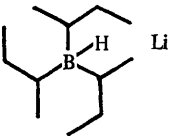
C. Effect of Substituent.—(i) *Alkyl and Aryl Borohydrides.* Many alkyl- and aryl-substituted borohydrides have been recently described in the literature, a few of which are shown here. Borohydrides (8),[13] (9),[14] and (10)[15] are commercially available, being named respectively Superhydride and L and K Selectride. Compounds (11),[16] (12),[17] and (13)[18] have been prepared for use as stereoselective reducing agents. The borohydrides (8)—(13) can be prepared from the corresponding boranes by reaction with either lithium hydride or t-butyl-lithium.[17]

[13] H. C. Brown, and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 1973, **95**, 1669.
[14] H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 1972, **94**, 7159.
[15] C. A. Brown, *J. Amer. Chem. Soc.*, 1973, **95**, 4100.
[16] H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, 1970, **92**, 709.
[17] E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaal, and R. K. Varma, *J. Amer. Chem. Soc.*, 1971, **93**, 1491.
[18] J. Hooz, S. Akiyama, F. J. Cedar, M. J. Bennett, and R. M. Tuggle, *J. Amer. Chem. Soc.*, 1974, **96**, 274.

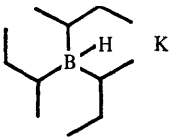


(8)

Superhydride

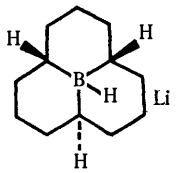


(9)

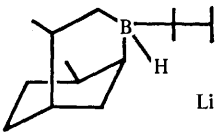


(10)

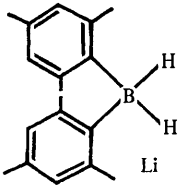
L and K Selectride



(11)

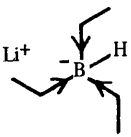


(12)

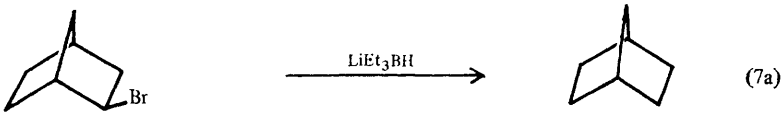


(13)

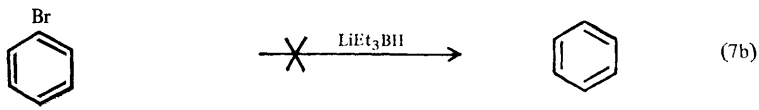
(*a*) *Lithium triethylborohydride* (*Superhydride*) (Solvent: tetrahydrofuran). Lithium triethylborohydride has a selectivity for functional groups (Section 7) that is similar to that of lithium borohydride. However, the inductive effect of



the alkyl substituents makes lithium triethylborohydride an extremely nucleophilic species,[13] being 20 times more nucleophilic than thiophenoxide ion and 10 000 times more nucleophilic than lithium borohydride. Lithium triethylborohydride readily reduces alkyl halides by an S_N2 process but does not reduce

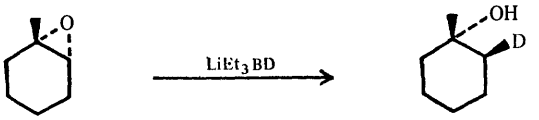


(7a)



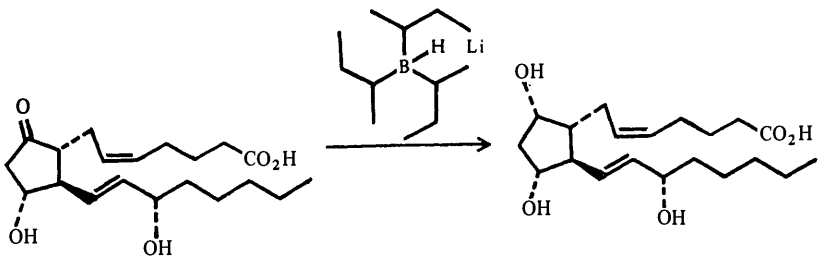
(7b)

aryl halides [equations (7a and b)]. Thus this reagent can be used for the selective removal of an alkyl halide in the presence of an aryl halide. Lithium aluminium hydride reduces both alkyl and aryl halides.[19] Epoxide (14) is readily opened in an S_N2 process by lithium triethylborodeuteride, also commercially available, to give the stereochemically pure deuterio-alcohol (15).

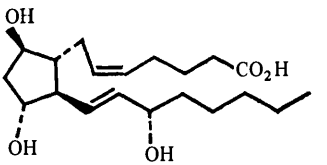


(14) (15)

(*b*) *Lithium and potassium tri-s-butylborohydride*[14,15] (*L and K Selectride*) (Solvent: tetrahydrofuran). Lithium tri-s-butylborohydride[14] has approximately the same functional group selectivity as lithium triethylborohydride. It is, however, an exceedingly stereoselective reducing agent, owing to the bulk of the s-butyl substituents. Thus the ketone function of PGE_2 (16) is stereoselectively reduced, the reagent approaching exclusively from the least hindered β-face of the cyclopentane ring to give $PGF_{2\alpha}$ (17); none of the epimeric $PGF_{2\beta}$ (18) is formed.[20] The substituted cyclohexanones (19) and (20) are also reduced[14]

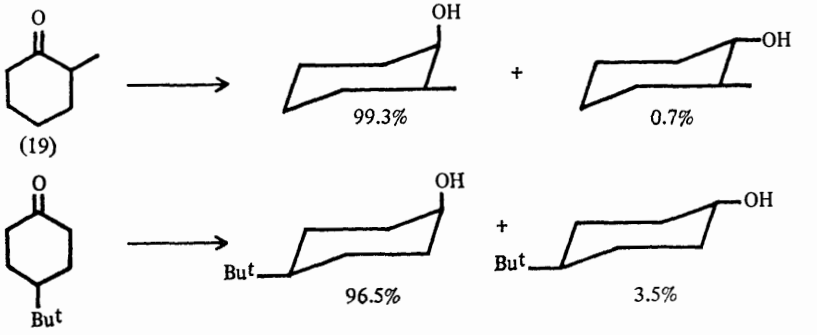


(16) (17)

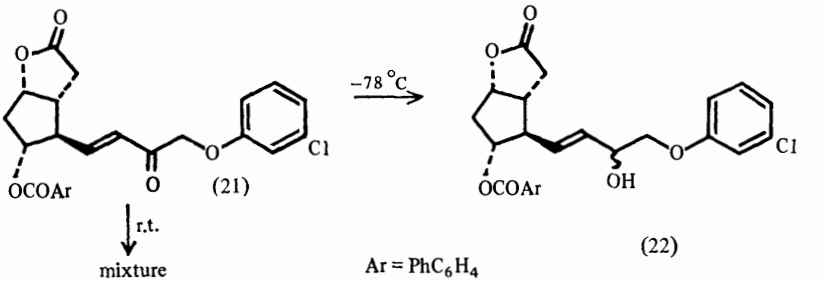


(18)

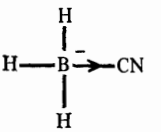
[19] H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, 1969, **34**, 3918.
[20] E. R. H. Walker, unpublished result.



with a very high degree of stereoselectivity. At -78 °C the ketone group of the enone (21) is selectively reduced[20] to the mixed epimers of the allylic alcohol (22). At ambient temperatures, however, reduction of the lactone and ester functionalities occurs to yield a complex mixture of products, showing that lithium tri-s-butylborohydride is a powerful reducing agent.*



(ii) *Cyanoborohydrides.* Sodium cyanoborohydride,[21] lithium cyanoborohydride,[22] and tetrabutylammonium cyanoborohydride[23] have been used as reducing agents. The electron-withdrawing effect of the cyano-group (23) makes these reducing agents weaker than their borohydride equivalents.

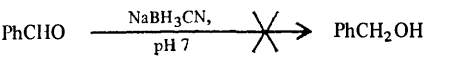


(23)

*It has recently been shown that L Selectride will convert $\alpha\beta$-unsaturated esters into saturated ester (B. Ganem and J. M. Fortunato, *J. Org. Chem.*, 1975, **40**, 2846).

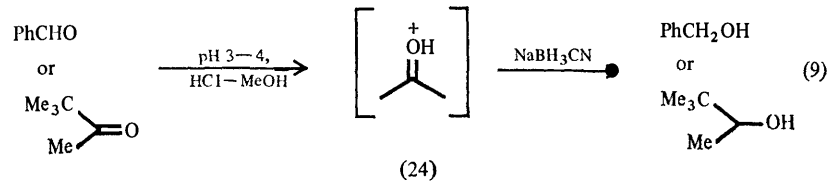
[21] R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, 1971, **93**, 2897.
[22] R. F. Borch and H. D. Durst, *J. Amer. Chem. Soc.*, 1969, **91**, 3996.
[23] R. O. Hutchins and D. Kandasamy, *J. Amer. Chem. Soc.*, 1973, **95**, 6131.

(*a*) *Sodium cyanoborohydride* (Solvent: water, methanol, hexamethylphosphoramide, or dimethyl sulphoxide). Sodium cyanoborohydride is an extremely selective reagent, reducing only aldehydes, ketones, alkyl halides, and iminium salts. By careful choice of the solvent media used, both alkyl halides and iminium salts can separately be reduced in the presence of aldehydes and ketones. Sodium cyanoborohydride is stable in aqueous acidic media. Under neutral conditions aldehydes and ketones are *not* reduced[21] by the reagent [equation (8)], and this



(8)

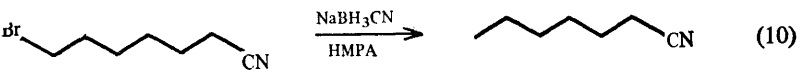
important property gives rise to its high degree of selectivity as a reducing species. Under acidic conditions (pH 3—4) aldehydes and ketones are readily reduced [equation (9)] *via* the corresponding protonated species (24). Under neutral



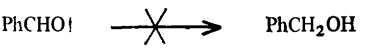
(24)

(9)

conditions in hexamethylphosphoramide sodium cyanoborohydride will reduce[24] primary alkyl halides in the presence of aldehydes [equations (10) and (11)].



(10)



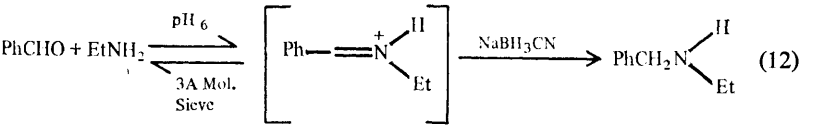
(11)

In principle, any double bond (25) which can be sufficiently polarized [*e.g.* that in (24)] should be reducible by sodium cyanoborohydride. When **A** and **B** are carbon and nitrogen respectively, (25) represents the iminium moiety (26),

(25) (26)

[24] R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *Chem. Comm.*, 1971, 1097.

which can readily be reduced by sodium cyanoborohydride. Since (26) can be generated from an aldehyde and amine at near neutral pH (conditions under which aldehydes and ketones are *not* reduced), the iminium intermediate can be reduced in the presence of the parent carbonyl group, leading to a facile method of reductive amination[21] [equation (12)]. This reaction is best carried out in the presence of 3A molecular sieve, and it can accommodate a wide range of functionality.



(12)

Replacement of the amine used above [*cf.* equation (12)] by toluene-*p*-sulphonyl hydrazide leads to a method of deoxygenation of ketones and aldehydes[25] [equation (13)] employing the same general principles outlined above. Again, a wide range of functionality can be accommodated.

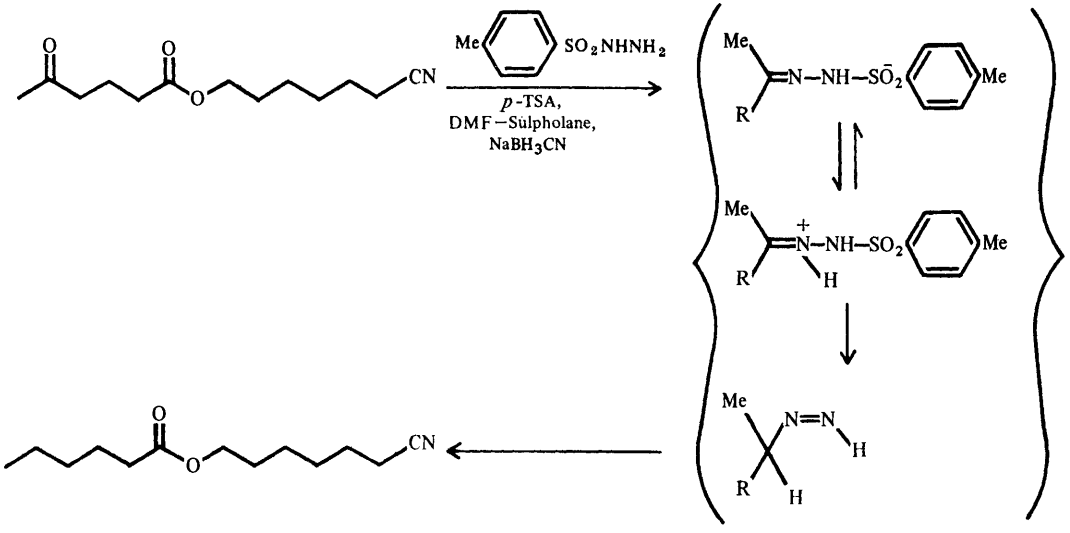
The generality of the reduction is demonstrated for the recently published[26] sulphoxide to sulphide transformation, where A and B in (25) are S and O, respectively. The sulphoxide is reduced after methylation with methyl fluorosulphonate [equation (14)], and the reaction can be carried out in the presence of a ketone.

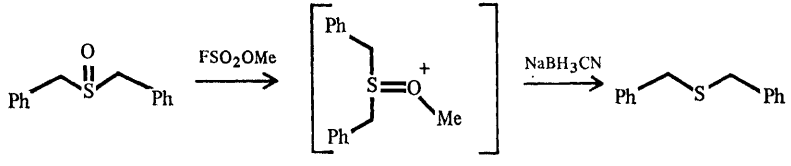
(*b*) *Lithium cyanoborohydride*.[22] For most purposes lithium cyanoborohydride and sodium cyanoborohydride are interchangeable.

(*c*) *Tetrabutylammonium cyanoborohydride*[23] (Solvent: hexamethylphosphoramide, methanol, or benzene). Tetrabutylammonium cyanoborohydride in 0.1N hydrochloric acid solution has been used for the selective reduction of an aldehyde in the presence of a ketone[23] [equation (15)].

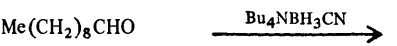
(iii) *Sulphurated Sodium Borohydride* (Solvent: tetrahydrofuran). When sodium borohydride and sulphur are allowed to react at room temperature in tetrahydrofuran there is a rapid evolution of hydrogen, and sulphurated sodium borohydride[27] is formed. Sulphurated sodium borohydride is a more powerful reducing agent than sodium borohydride, and reductions of functional groups containing nitrogen are particularly facile. Aromatic nitro-compounds are reduced in high yields to the corresponding amines,[27] and this reaction can be selectively carried out in the presence of *ortho*-, *meta*-, or *para*-substituted halogen, ester, nitrile, olefin, or ether groups [equation (16)]. In the case of aliphatic nitro-compounds the structure of the substrate governs the course of the

[25] R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Amer. Chem. Soc.*, 1971, **93**, 1793.
[26] H. D. Durst, J. W. Zubrick, and G. R. Kieczykowski, *Tetrahedron Letters*, 1974, 1777.
[27] J. M. Lalancette, A. Freche, J. R. Brindle, and M. Laliberte, *Synthesis*, 1972, 526.

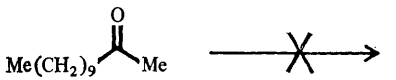

Me
SO2NHNH2
p-TSA,
DMF–Sulpholane,
NaBH3CN
CN
Me
N–NH–SO2
Me
R
H
N=N
(13)


Ph
S
Ph
FSO2OMe
O
Me
NaBH3CN

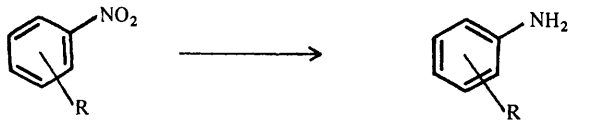
(14)



(15a)

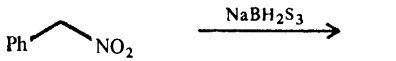


(15b)



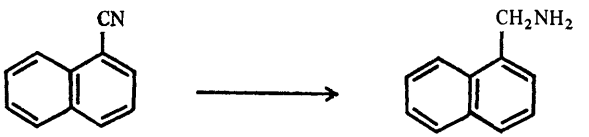
(16)

R = Hal, CO_2R', CN,  , or OR'



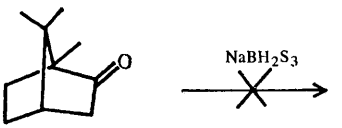
(17)

reaction. Primary nitro-derivatives, *e.g.* phenylnitromethane, are converted into the corresponding nitriles [equation (17)] and secondary nitro-compounds yield a mixture of the corresponding ketone and oxime, but tertiary nitro-compounds are inert. In the absence of the more reactive nitro-groups, aromatic nitriles are reduced to the corresponding amines [equation (18)].



(18)

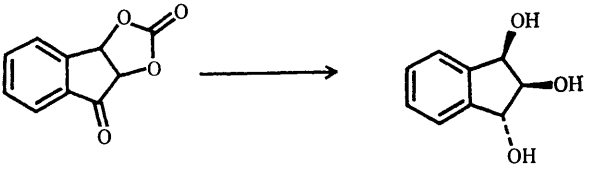
Although aldehydes and ketones are normally reduced by sulphurated sodium borohydride, sterically hindered ketones such as camphor are not reduced [equation (19)]. It should thus be possible with this reagent to reduce an aldehyde or unhindered ketone selectively in the presence of an hindered ketone.



(19)

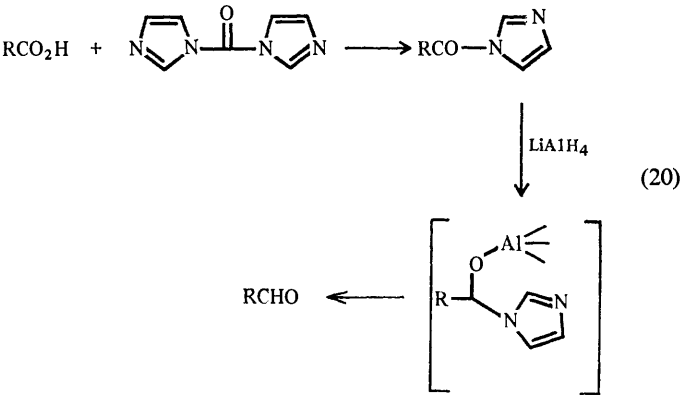
3 Lithium Aluminium Hydride (Solvent: tetrahydrofuran, diethyl ether, or methylene chloride)
Lithium aluminium hydride is a very powerful reducing agent, reducing a wide range of functional groups to their lowest oxidation state. Selective reductions of functional groups are rarely possible.

A. Effect of Solvent.—Lithium aluminium hydride must be used in aprotic solvents and is usually used in diethyl ether or tetrahydrofuran. In all the solvents used it is a very powerful reducing agent. The cyclic carbonate (27) has been reduced[28] by lithium aluminium hydride in a mixture of diethyl ether and methylene chloride to give the triol (28). The use of methylene chloride as solvent



(27) (28)

extends the range of lithium aluminium hydride as a reducing agent to those substrates that are insoluble in ether solvents. One partial reduction which can be achieved with lithium aluminium hydride is the reduction of an acid to the corresponding aldehyde *via* the imidazolide[29] [equation (20)].



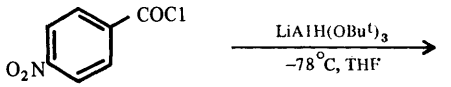
(20)

B. Effect of Cation.—Sodium aluminium hydride[30] has the same reducing power as lithium aluminium hydride and offers no major advantage as a reducing agent.

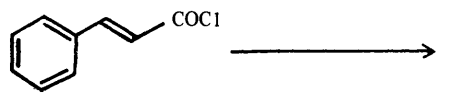
[28] D. Y. Curtin, J. A. Kampmeier, and M. L. Farmer, *J. Amer. Chem. Soc.*, 1965, **87**, 874.
[29] H. A. Staab and A. Mannschreck, *Chem. Ber.*, 1962, **95**, 1284.
[30] A. E. Finholt, E. C. Jacobson, A. E. Ogard, and P. Thompson, *J. Amer. Chem. Soc.*, 1955, **77**, 4163.

C. Effect of Substituent.—(i) *Alkoxy Substituents.* (*a*) *Lithium tri-t-butoxyaluminium hydride* (Solvent: tetrahydrofuran). The steric and electronic effects of the t-butoxy-groups render lithium tri-t-butoxyaluminium hydride a very mild reducing agent, and in terms of its selectivity for functional groups (Section 7) it resembles sodium borohydride much more than lithium aluminium hydride.

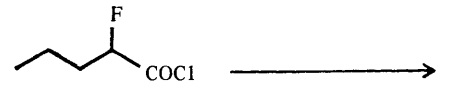
One of the key reactions of lithium tri-t-butoxyaluminium hydride is the reduction of acid chlorides to aldehydes,[31] which can be carried out in the presence of a wide range of different functional groups [equations (21), (22), and (23)[32]]. $\alpha\beta$-Unsaturated systems undergo 1,2- rather than 1,4-attack [equation (22)].



(21)



(22)

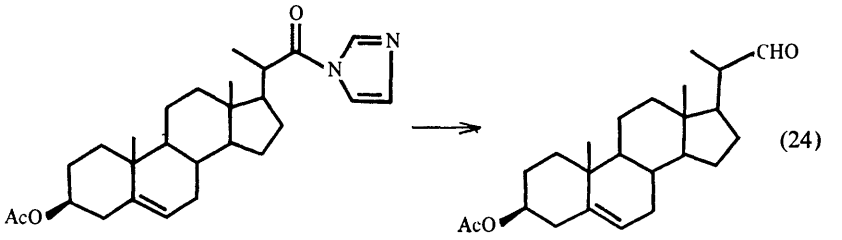


(23)

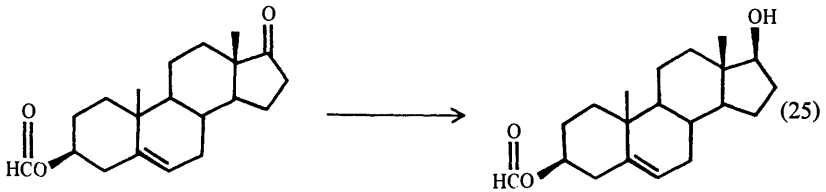
Lithium tri-t-butoxyaluminium hydride will also reduce imidazolides to aldehydes[33] and offers an advantage over lithium aluminium hydride in that a wide range of functionality can be accommodated [equation (24)]. The imidazolide is derived from the corresponding acid,[29] and equation (24) represents a selective method for the conversion of acids into aldehydes. To demonstrate the selectivity of the reagent, a ketone can be reduced[34] in the presence of a formate [equation (25)].

(*b*) *Sodium bis-*[*2-methoxyethoxy*]*aluminium hydride* (*RED-AL*) (Solvent: benzene, toluene, xylene, diethyl ether, or tetrahydrofuran). RED-AL[35] is commercially available as a 70% solution in benzene and has approximately the same reducing capability as lithium aluminium hydride. The reagent claims the following advantages over lithium aluminium hydride: (1) It is safer; it does not ignite in moist air or oxygen. (2) It is stable in dry air. (3) It is very soluble in aromatic solvents and ethers. (4) It is stable at 200 °C. RED-AL is therefore a safe, soluble reagent that is equivalent in reducing power to lithium aluminium hydride. It can rarely be used as a selective reagent because of its high reducing power.

[31] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1958, **80**, 5377.
[32] E. D. Bergmann and A. Cohen, *Tetrahedron Letters*, 1965, 1151.
[33] T. C. McMorris, *J. Org. Chem.*, 1970, **35**, 458.
[34] J. Fajkos, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2284.
[35] J. Malek and M. Cerny, *Synthesis*, 1972, 217.

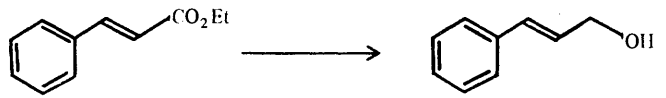


(24)



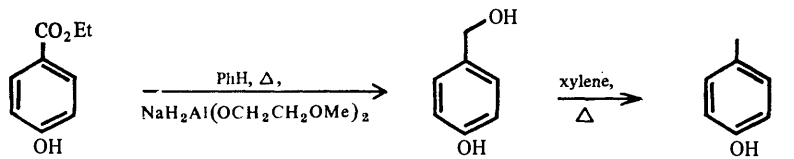
(25)

An $\alpha\beta$-Unsaturated system, *e.g.* (29), can be reduced by RED-AL to give the corresponding allylic alcohol, *e.g.* (30), in contrast to lithium aluminium hydride, which yields the corresponding saturated alcohol. Under forcing conditions



(29) (30)

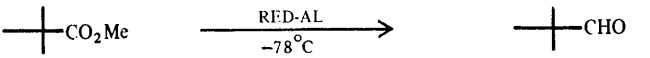
RED-AL can cause hydrogenolysis of benzyl alcohols. Thus the alcohol (32) formed by reduction of the ester (31) in refluxing benzene undergoes hydrogenolysis in refluxing xylene to give *p*-cresol (33). Because of its great solubility,



(31) (32) (33)

RED-AL can be used at low temperature, and some partial reductions can be achieved. For example, the ester (34) has been reduced in ether to the aldehyde (35)[36] by RED-AL at -78 °C.

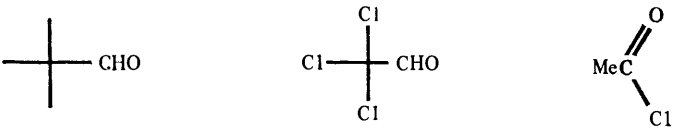
[36] J. Vit, *Org. Chem. Bull.*, 1970, **42**, (3), 1.



(34) (35)

(ii) *Alkyl Substituents.* (*a*) *Sodium diethylaluminium hydride* (Solvent: toluene). Sodium diethylaluminium hydride[37] is commercially available as a 25% solution in toluene. It has a similar reducing power to that of lithium aluminium hydride, and like RED-AL it is soluble in aromatic hydrocarbons.

4 Diborane (Solvent: tetrahydrofuran, methylene chloride, or dimethyl sulphide) Whereas the nucleophilic reducing agent sodium borohydride attacks a molecule at the centres of lowest electron density, the electrophilic reducing agent diborane initiates its reactions by attack at the centres of highest electron density. Excellent examples of the consequence of these differing modes of reaction are the reductions of trimethylacetaldehyde (36) and chloral (37). The electron-withdrawing effect of the halogen atoms of chloral (37) increases the susceptibility of the aldehyde to nucleophilic attack. Sodium borohydride therefore reduces chloral (37) far faster than trimethylacetaldehyde (36). This same electron-withdrawing effect results in a decreased susceptibility to electrophilic attack. Thus diborane reduces trimethylacetaldehyde (36) but does not reduce chloral (37). Similarly, acetyl chloride (38) is also not reduced by diborane.

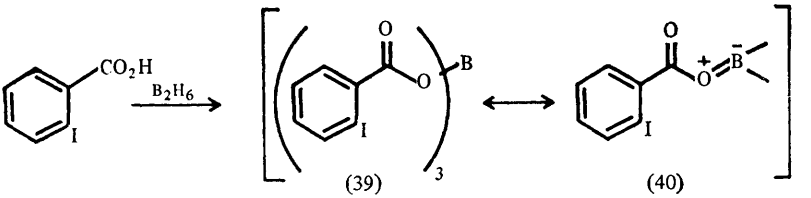


(36) (37) (38)

Diborane can be conveniently prepared in methylene chloride,[38] using sodium borohydride, a phase-transfer catalyst, sodium hydroxide, and an alkyl halide. Diborane is commercially available as a 1 molar solution in tetrahydrofuran or as a more stable 10 molar solution in dimethyl sulphide. While the tetrahydrofuran and methylene chloride solutions have equal reactivity in most reactions, the dimethyl sulphide solution is less reactive.

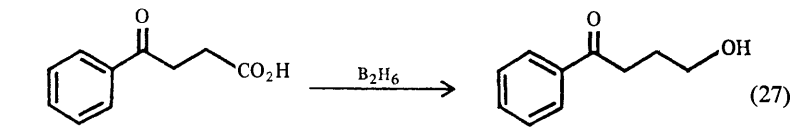
The spectrum of reducing activity (Section 7) of diborane is quite different to that of sodium borohydride. One of the key reactions is the reduction of carboxylic acids,[39] which can be carried out in the presence of a wide range of different functional groups [*e.g.* equations (26)—(28)]. Acids are reduced *via* the corresponding triacylboranes (39), in which the resonance interactions between the acyl oxygen and boron (40) render the carbonyl group much more susceptible

[37] H. J. Sanders, *Chem. Eng. News*, 1972, June 19, p. 29.
[38] A. Brandstrom, U. Junggren, and B. Lamm, *Tetrahedron Letters*, 1973, 3173.
[39] N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, 1973, **38**, 2786.

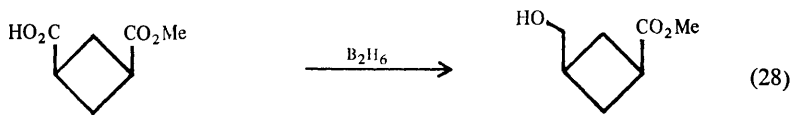


(39) (40)

(26)



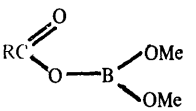
(27)



(28)

to reduction. An acid can be protected from diborane reduction by making an acid salt. Reduction of the salt is prevented because the triacylborane [*e.g.* (39)] can no longer form. The reduction of an acid with diborane in dimethyl sulphide occurs rather slowly, presumably because of the strength of the borane–dimethyl sulphide complex, but can be catalysed[40] by the addition of trimethyl borate, which reacts with the acid to form an acyl dimethyl borate (41), equivalent to the triacylborane (39). This derivative then undergoes rapid reduction to the required alcohol.

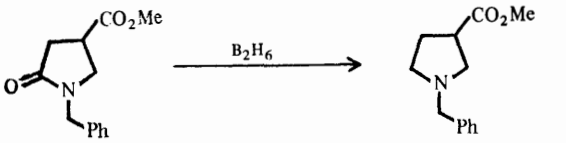
Diborane will reduce amides to amines[41] [equation (29)] and electron-rich



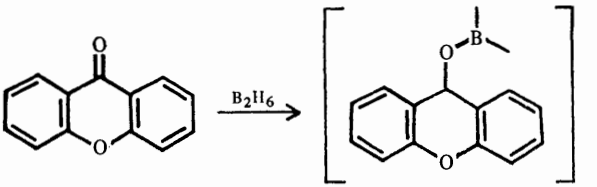
(41)

[40] C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, 1974, **39**, 3052.
[41] M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, 1968, **33**, 3637.

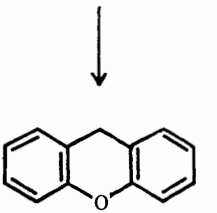
ketones to the corresponding methylene compounds[42] [equation (30)]. It is possible to reduce an enone selectively[43] in the presence of a ketone [equation (31)]. Sodium borohydride has the opposite selectivity (see Section 2).

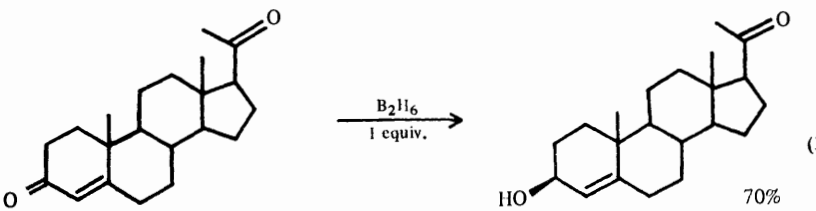


(29)



(30)



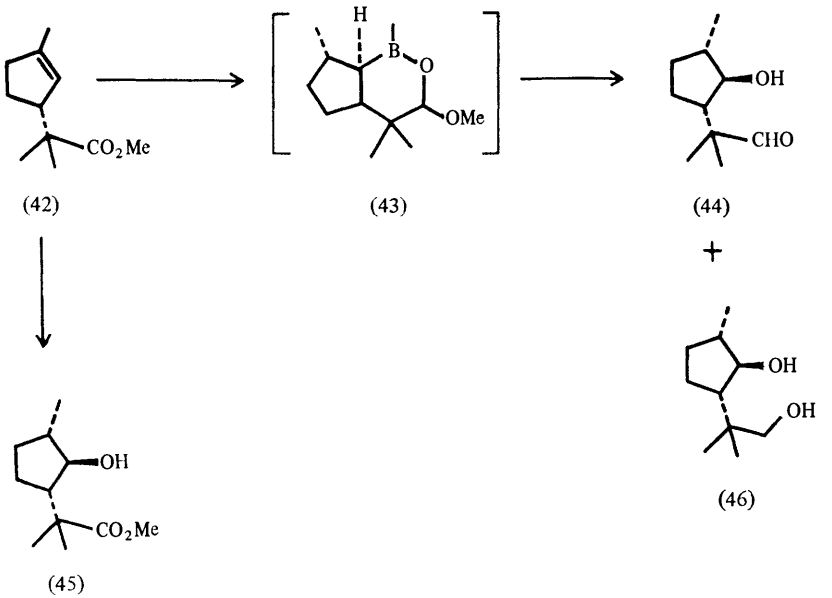


(31)

Esters are not usually reduced by diborane. However, hydroboration of olefinic esters often results in ester reduction,[44] indicating the important influence of chemical environment on the reactivity of a functional group. For example, hydroboration–oxidation[45] of the olefinic ester (42) gives the expected hydroxy-

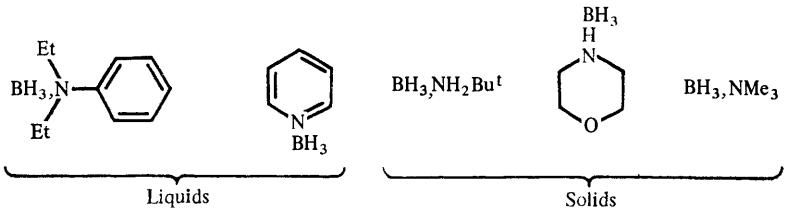
[42] W. J. Wechter, *J. Org. Chem.*, 1963, **28**, 2935.
[43] M. Stefanovic and S. Lajsic, *Tetrahedron Letters*, 1967, 1777.
[44] H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, 1964, **86**, 1795.
[45] D. Varech and J. Jacques, *Bull. Soc. chim. France*, 1969, 3505.

ester (45), together with the alcohols (44) and (46), in which the ester has been reduced *via* the cyclic intermediate (43).



(42) (43) (44) + (46) (45)

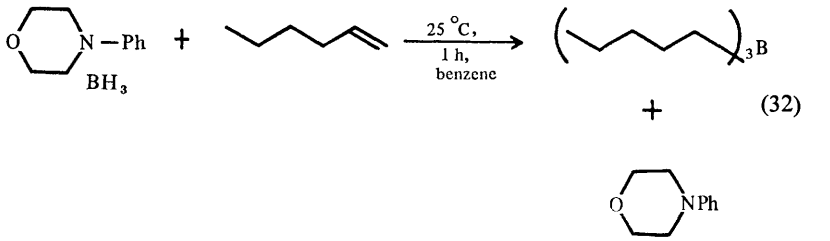
A. Borane–Amine Complexes.[46]—(Solvent: water, methanol, diethyl ether, hexane, methylene chloride, or toluene). The commercially available borane–amine complexes shown here have a wide range of physical properties and can



be used in many solvents, including water. The complexes have a very different reactivity to that of diborane (*e.g.* acids are not reduced) and are essentially very similar to sodium borohydride except for their reaction with carbon–carbon double bonds (see Section 7). Borane–amine complexes thus represent a 'safe' source of diborane for the hydroboration[47] of a carbon–carbon double bond [equation (32)].

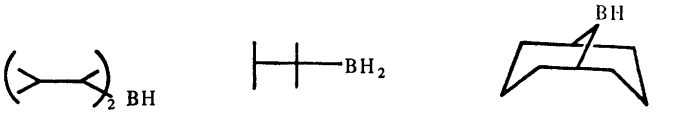
[46] C. F. Lane, 'The Borane–Amine Complexes,' Aldrich Chemical Company Reviews, Vol. 6, No. 3.

[47] L. T. Murray, Ph.D. Thesis, Purdue University, Lafayette, Indiana, 1963.



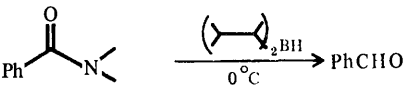
(32)

B. Effect of Substituent.—2-Methylbut-2-ene reacts with diborane to give the commercially available dialkyl-borane disiamylborane (47). Thexylborane (48) and 9-borabicyclo[3,3,1]nonane (9-BBN) (49), an air-stable white solid, are also commercially available.

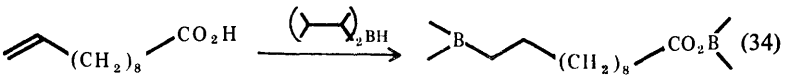


(47) (48) (49)

(i) *Bis-3-methyl-2-butylborane* (*Disiamylborane*) (Solvent: tetrahydrofuran). Dialkylboranes have a modified reduction power (see Section 7) compared with that of diborane, the most notable difference being that acids are not reduced by the reagents. The most useful reactions of dialkylboranes are the partial reduction of lactones to lactols[48] and of tertiary amides to aldehydes[49] [equation (33)] and the hydroboration[50] of a carbon–carbon double bond in the presence of an acid [equation (34)].*



(33)



(34)

*Brown has shown that 9-BBN can be used to convert $\alpha\beta$-unsaturated aldehydes and ketones into corresponding allylic alcohols in excellent yields. The transformations can be carried out selectively in the presence of an isolated carbon–carbon double bond, a nitro-group, or an ester group (S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, 1975, **40**, 1864).

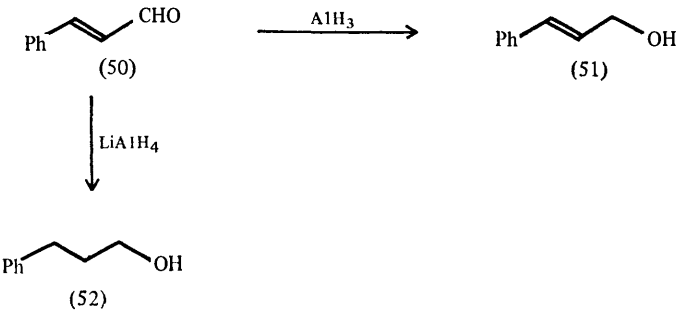
[48] R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, 1969, **34**, 3717.

[49] H. C. Brown, D. B. Bigley, and N. M. Yoon, *J. Amer. Chem. Soc.*, 1970, **92**, 7161.

[50] H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, 1961, **83**, 486.

5 Aluminium Hydride (Solvent: tetrahydrofuran or diethyl ether)
Aluminium hydride is a powerful reducing agent similar in activity to lithium aluminium hydride, and it is therefore of little value as a selective reducing agent. A recent report[51] gives details of the preparation of a stable ethereal solution of aluminium hydride.

Aluminium hydride has one major advantage over lithium aluminium hydride and diborane in that it reduces an $\alpha\beta$-unsaturated system, *e.g.* (50), to the corresponding allylic alcohol[52] (51); lithium aluminium hydride gives the saturated alcohol (52) while diborane hydroborates the double bond. The preferred

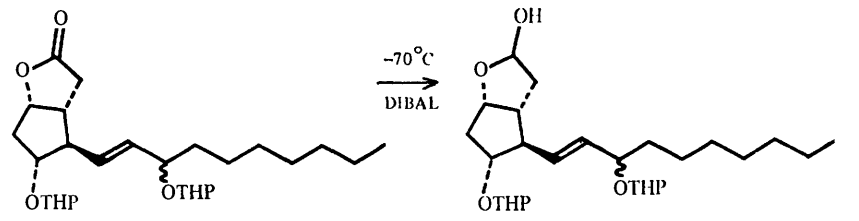


reagent for the transformation of (50) into (51) is, however, di-isobutylaluminium hydride (see below). Aluminium hydride can cause hydrogenolysis of acetals and ketals.

A. Effect of Substituent.—(i) *Di-isobutylaluminium Hydride* (Solvent: toluene or dimethoxyethane). Di-isobutylaluminium hydride (DIBAL) is commercially available either as the neat liquid or as a 20% solution in toluene. The reagent which can also be used in dimethoxyethane, is more selective than aluminium hydride (see Section 7) and is a very useful and versatile reagent.

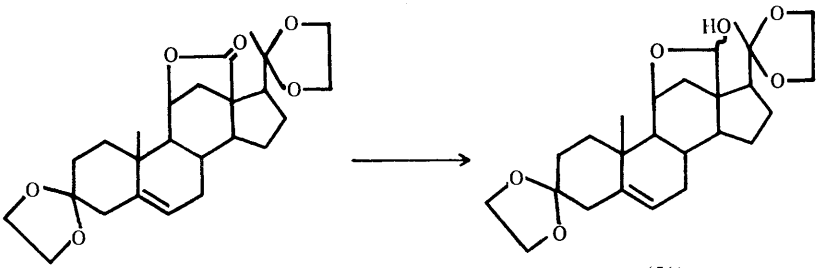
DIBAL is the preferred reagent for the reduction of lactones, esters, amides, and nitriles to the corresponding aldehydes. For example, the lactones (53)[53] and (55)[54] are reduced to the lactols (54) and (56), respectively, by DIBAL at −70 °C. The nitriles (57)[55] and (59)[56] are reduced to the corresponding aldehydes

[51] E. C. Ashby, J. R. Sanders, P. Clavely, and R. Schwartz, *J. Amer. Chem. Soc.*, 1973, **95**, 6485.
[52] M. J. Jorgenson, *Tetrahedron Letters*, 1962, 559.
[53] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[54] J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 2799.
[55] J. A. Marshall, N. H. Andersen, and J. W. Schlicher, *J. Org. Chem.*, 1970, **35**, 858; J. A. Marshall, N. H. Andersen, and P. C. Johnson, *ibid.*, p. 186.
[56] S. Trofimenko, *J. Org. Chem.*, 1964, **29**, 3046.



(53) (54)

THP = tetrahydropyran-2-yl ether



(55) (56)

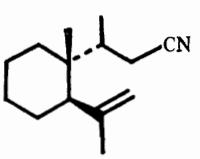
(58) and (60) by DIBAL at room temperature. The lactone (53) can be reduced to the lactol (54) in the presence of a nitrile[20] (61). Esters are also readily reduced[57] to the corresponding aldehydes by DIBAL at −70 °C, *e.g.* (62) to (63).

Another key reaction of DIBAL is the 1,2-reduction of $\alpha\beta$-unsaturated systems, Thus the enedione[58] (64) is cleanly reduced to the enediol (65) and the enone (66) reduced[58] to the allylic alcohol (67). DIBAL reacts with acetylenes to give on work-up a *cis*-substituted olefin[59] [equation (35)], but an ester can be selectively reduced[60] in the presence of an acetylene [equation (36)].

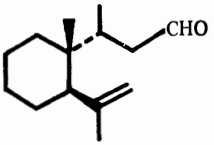
6 Miscellaneous Reagents

A. Lithium n-Butylcopperhydride.—(Solvent: diethyl ether). Masamune has recently described[61] the preparation and properties of the readily accessible lithium copper hydride reagent (68). Primary, secondary, and tertiary halides and mesylates are reduced with this reagent to the corresponding alkanes. The reduction can be carried out in the presence of esters and the reagent forms an attractive alternative to the use of sodium borohydride in dimethyl sulphoxide–

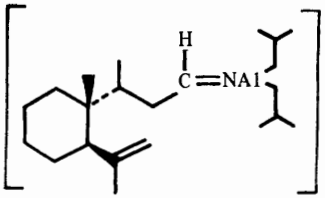
[57] C. Szantay, L. Toke, and P. Kolonits, *J. Org. Chem.*, 1966, **31**, 1447.
[58] K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Comm.*, 1970, 213.
[59] G. Wilke and H. Muller, *Chem. Ber.*, 1956, **89**, 444.
[60] E. J. Corey and R. A. Ruden, *Tetrahedron Letters*, 1973, 1495.
[61] S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Amer. Chem. Soc.*, 1974, **96**, 3686.

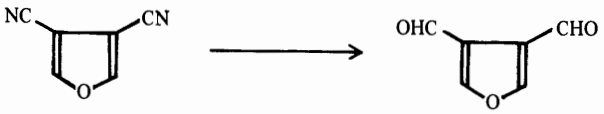


(57)



(58)

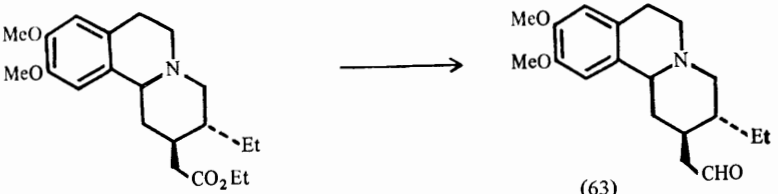




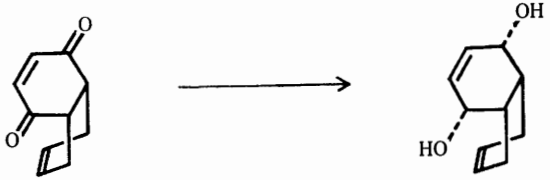
(59) (60)

$Me(CH_2)_5CN$

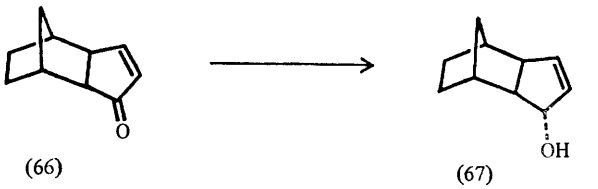
(61)



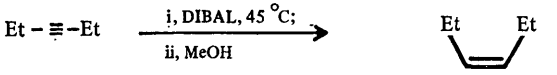
(62) (63)



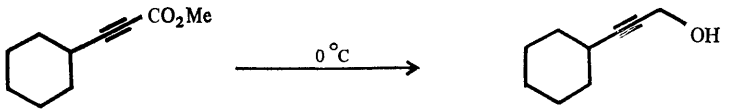
(64) (65)



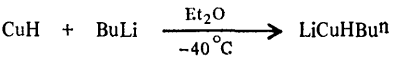
(66) (67)



(35)

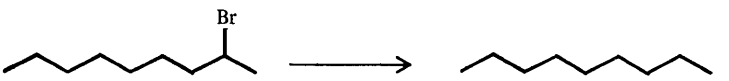


(36)



(68)

tetramethylene sulphone. For example, the halide (69) and mesylate (71) are conveniently reduced to the alkane (70) and ester (72), respectively, by lithium n-butylcopperhydride in diethyl ether. Aldehydes and ketones are reduced by lithium n-butylcopperhydride while an enone suffers 1,4-reduction to give the saturated ketone [equation (37)]. $(KCuH_2)_n$ has also recently been described.[62] It has approximately the same reducing specificity as lithium n-butylcopperhydride and appears to offer no significant advantage.



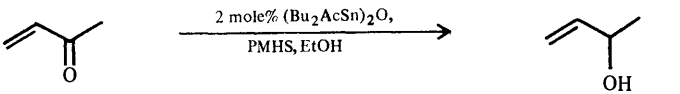
(69) (70)

[62] T. Yoshida and E. Negishi, *J.C.S. Chem. Comm.*, 1974, 762.

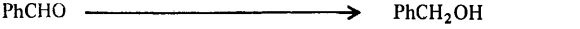
(71) (72)

(37)

B. Polymethylhydrosiloxane (PMHS).[63]—(Solvent: diethyl ether, toluene, ethanol, or dioxan). PMHS is a commercially available polymeric hydrosiloxane which can be used either for the selective reduction of aldehydes and ketones in the presence of all other functionality or as a source of hydrogen for the reduction of a double bond. The reduction of aldehydes and ketones is mediated by a catalytic amount of a tin oxide, which is converted into a tin hydride *in situ*. Thus, for example, the enone [equation (38)] and aldehyde [equation (39)] are reduced to the corresponding alcohols by PMHS in the presence of 2 mole% of dibutylacetyltin oxide. Under these conditions no other functional groups are reduced. If the quantity of the tin oxide is increased to 1 equivalent, nitro-groups, nitriles, and carbon–carbon double bonds are reduced.



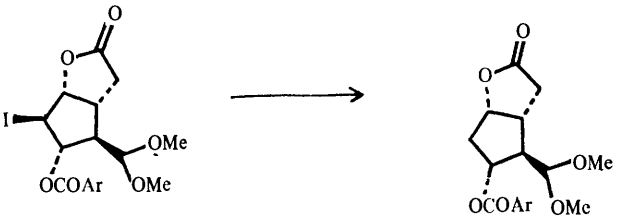
(38)



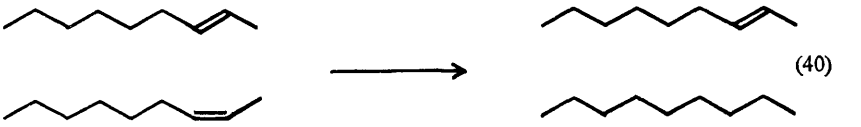
(39)

PMHS can be used for the *in situ* generation of tributyltin hydride from tributyltin oxide, and this has been used for the reduction[64] of the iodo-prostaglandin intermediate (73) to give the dimethyl acetal (74) in high yield. In the presence of palladium on charcoal PMHS will reduce[63] *cis*-carbon–carbon double bonds whereas *trans*-carbon–carbon double bonds are not reduced [equation (40)]. Under these conditions aromatic nitro-compounds are reduced to amines[63] [equation (41)].

[63] J. Lipowitz and S. A. Bowman, *J. Org. Chem.*, 1973, **38**, 162.
[64] G. Robinson, personal communication.



(73) Ar = PhC_6H_4 (74)



(40)

$$PhNO_2 \xrightarrow[\substack{Pd/C,\\ EtOH}]{PMHS,} PhNH_2 \qquad (41)$$

The author wishes to thank Dr N. S. Crossley for helpful discussions and Mrs K. Hurley for typing the manuscript.

7 Functional Group Selectivity Table*

Group affected	*Reducing agent*	$NaBH_4$	$LiBH_4$	$Zn(BH_4)_2$	$LiEt_3BH$	$LiBu^s_3BH$	$NaBH_3CN$	$NaBH_2S_3$	$Li(Bu^tO)_3AlH$	RED-AL	$LiAlH_4$	B_2H_6	BH_3,NR_3	$(\text{cyclohexyl})_2BH$	AlH_3	$(\text{cyclohexyl})_2AlH$
RCHO		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
>C=O		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RCOCl		✓	✓	✓	✓	✓		×	RCHO	✓	✓	×	✓	×	✓	
Lactone		V. slow	✓	×	✓	✓	×	✓	×	✓	✓	×		Lactol	✓	Lactol
		V. slow	✓	×	✓	✓	×	✓	×	✓	✓	✓		×	✓	
$R^1CO_2R^2$		V. slow	✓	×	✓	✓	×	×	R^2=Ph, →R^1CHO	✓	✓	×	×	×	✓	RCHO
RCO_2H		×	×	×			×	×	×	✓	✓	✓	×	×	✓	×
RCO_2M		×	×				×	×	×	✓	✓	×		×	✓	×
RCON<		×	×				×	✓	×		✓	✓		RCHO	✓	RCHO
RCN		×	×				×	✓	×	×	✓	✓	×	×	✓	RCHO
RNO_2		×	×				×	✓	×		✓	×		×	×	×
		×	×	×			×	×	×	×	×	✓	✓	✓	×	×
RHal		×	×		alkyl: ✓ aryl : ×		✓			✓	✓	×	×		×	×

* ✓ indicates that the functional group is reduced, while × indicates that it is resistant to reduction. Where appropriate the structure of the reduction product obtained is indicated in the Table.

8 Index of Reagents*

*The names of the reagents used in this review are those in common use among organic chemists, and are not necessarily correct inorganic nomenclature.