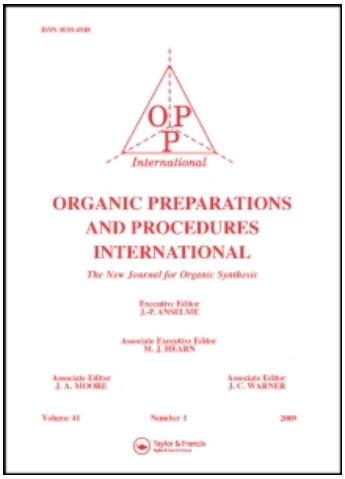

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CYANOBOROHYDRIDE. UTILITY AND APPLICATIONS IN ORGANIC SYNTHESIS. A REVIEW

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CYANOBOROHYDRIDE. UTILITY AND APPLICATIONS IN ORGANIC SYNTHESIS. A REVIEW

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INTRODUCTION

Substituted boron hydrides are well entrenched as effective and valuable reagents for a great variety of reductive transformations. The main reason for their utility stems from the ability to modify the reducing potency by changing substituents on the central boron. Such alterations have vastly augmented the versatility and chemoselectivity of boron hydride reagents and have led to their wide acceptance and use for a variety of reductions.[1]

One of the newer members of this group is trihydridocyanoborate (cyanoborohydride) which, although discovered[2] and briefly explored[3] before 1960, remained unexploited until 1969 when Borch and Durst[4a] introduced lithium cyanoborohydride as a highly selective reagent for a variety of useful conversions. This was immediately followed by the synthesis and commercial offering of the more convenient sodium salt by Ventron Corporation.[4b] Since then, exploration has mushroomed; a review[5] covering the literature through mid-1974 appeared in 1975 and increasing applications to specific synthetic problems have been developed. Since the majority of such applications has occurred during the past three years, it seems timely to review the period from mid-1974 through most of 1978; coverage will emphasize the chemoselective synthetic scope of cyanoborohydride and specific applications where the use of the reagent has been advantageous.

The utility of cyanoborohydride derives from several unique and

useful properties.

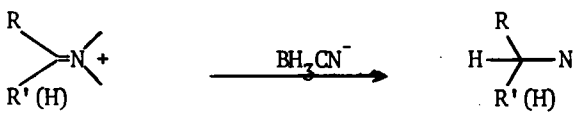
1. The electron-withdrawing cyano group markedly increases the Lewis acidity of cyanoborane (over borane) thereby increasing the reluctance of cyanoborohydride to deliver a hydride; the result is a greatly moderated reducing ability (and enhanced stability) which allows a substantially more discriminate selection among functional groups.

2. The reagent is remarkably stable toward protic solvents and acidic media (to pH 2-3) while the reducing capabilities are exceptionally pH dependent, often permitting pH controlled chemoselectivity.

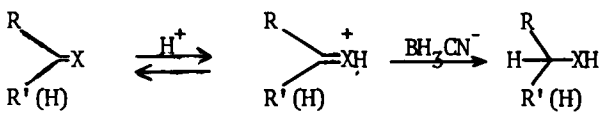
3. Acid-catalyzed proton exchange is considerably more rapid than hydrolysis which provides facile procurement of isotopically labeled (D or T) reagents via exchange in D_2O or T_2O.

The reductions available with cyanoborohydride may be divided into two general types.

1. Reduction of Polar π-Bonds. With the exception of iminium ions, π bonds are nearly inert toward cyanoborohydride unless activated for nucleophilic attack by complexation as illustrated below.



(1)

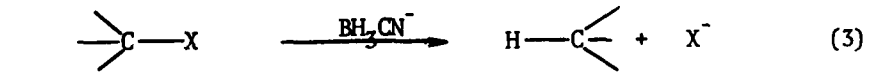


(2)

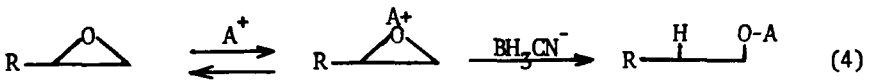
X = N, O, S, CYZ (Y, Z = electron withdrawing groups)

2. Reductive Displacement of σ-Bonded Leaving Groups by Hydride via SN_2 or SN_1 Reactions. Substitution reactions require the enhancement of the hydride delivering ability of cyanoborohydride by polar, aprotic

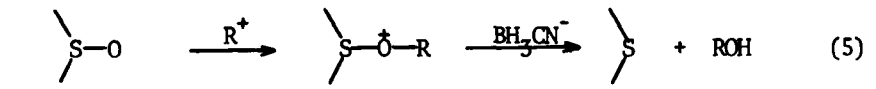
solvents (DMSO, HMPA, DMF, sulfolane) or activation toward nucleophilic attack by complexation as presented below.



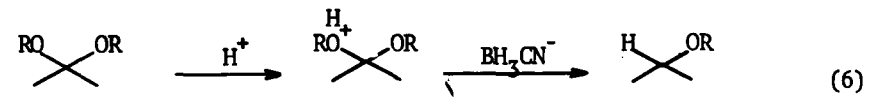
X = I, Br, OSO_2R (3)



(4)



(5)



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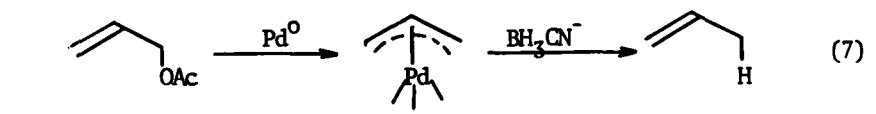


(7)

Virtually all other functional groups are unaffected by cyanoborohydride, including amides, esters, lactones, acids, nitriles, nitros, alkenes and alkynes. Furthermore, the pH and media dependence of many of the above type transformations (1-7) allows a wide variance in chemoselectivity by judicious choice of reaction conditions. Each type of reduction of a functional group reported to date (late 1978) is presented separately below along with specific applications and any noted limitations.

I. REDUCTION OF POLAR π-BONDS

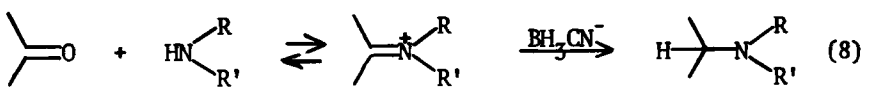
1. Reduction of Aldehydes and Ketones[6-16,162]

In basic media, aldehydes and ketones are nearly inert toward cyanoborohydride.[5] However, at pH values below 7, reduction occurs and the reagent has found significant synthetic usefullness, particularily in complex molecules harboring other reducible groups. The usual solvent is methanol although other media (THF, THF/HOAc, HMPA) have also been employed.

Competitive[9a] and mechanistic[9b] studies confirm that aldehydes are reduced preferentially over ketones[5,9] and that the transition state for carbonyl reduction is late.[9b] A list of representative examples are presented in Table I including cases where the chemoselectivity is evident (i.e. entries 5,7,8,10) and one example of the conversion of a thioketone to a thiol, albeit in low yield (entry 3). One study[14] noted the cleavage of a trifluoromethyl ketone in acidic media (see entry 13, Table III). Reduction of α,β-unsaturated carbonyls in methanol,[16] HMPA[16] or THF/HOAc[13] appears to be useful for preparing allylic alcohols from alicyclic carbonyl compounds with methyl ethers produced as side-products in methanol. Further conjugation often results in reduction to hydrocarbons, presumably via acid-induced ionization and hydride trapping. Cyclic enones give mixtures of allylic and saturated alcohols.[16]

2. Reductive Amination of Aldehydes and Ketones[17-67,152,154-56,163-66]

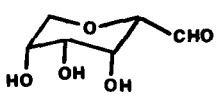
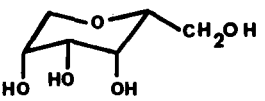
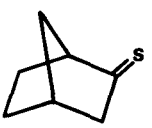
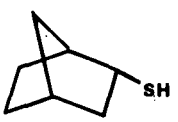
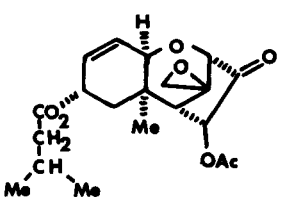
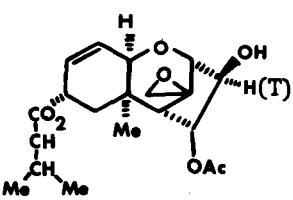
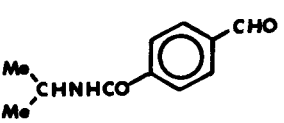
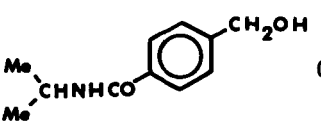
Since its introduction in 1969,[4] the reductive amination of carbonyl compounds with amines and cyanoborohydride has found considerable application and is firmly established as a method of choice on the laboratory scale, especially in complex molecules which require the gentleness and chemoselectivity of cyanoborohydride. The method relies on the rapid rate of reduction of iminium ions compared to carbonyl groups at pH 6-8; this alows the in situ reaction of amines with carbonyl compounds in the presence of cyanoborohydride followed by subsequent reduction (eq. 8). This

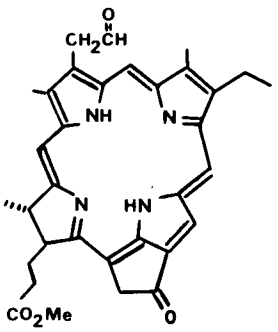
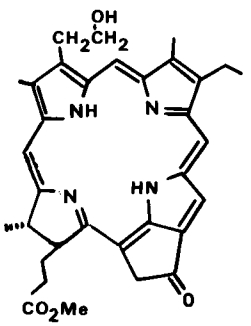
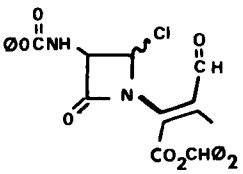
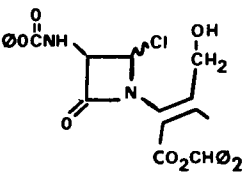
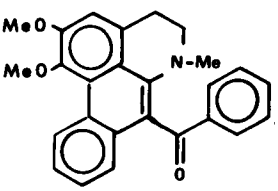
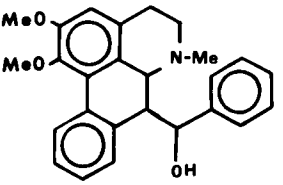
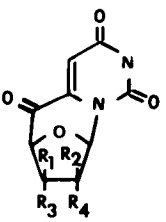
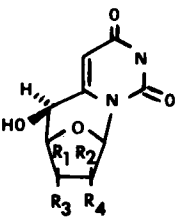


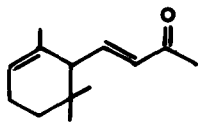
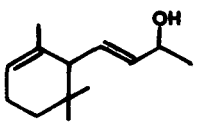
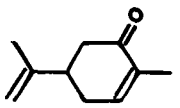
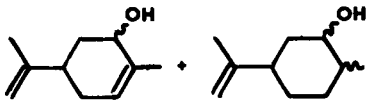
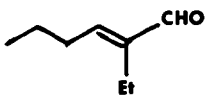
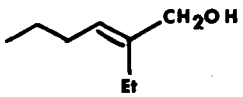
(8)

usefulness is increased by the facile methylation of amines with formaldehyde, providing a convenient, mild alternative to the Clark-Eshwieler and other procedures. The versatility and scope of the procedures are readily

TABLE I. REDUCTION OF ALDEHYDES AND KETONES

Entry	Compound	Product	Comments (%Yield)	Ref.
1			pH 4, CH_3OH	6
2	$HOCCH_2C(OH)(CH_3)CH_2CO_2Et$	$HO(CH_2)_2C(OH)(CH_3)CH_2CO_2Et$	pH 2.7 citrate buf. (100)	7
3			pH 3-4, CH_3OH	8
	$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_3OH$	(62)	
	$CH_3CH_2COCH_3$	$CH_3CH_2CHOHCH_3$	(38)	9
	C_6H_5CHO	$C_6H_5CH_2OH$	(91)	
	$C_6H_5COCH_3$	$C_6H_5CHOHCH_3$	(9)	
5			4:1 ratio of isomers; BH_3CN and BT_3CN used (60)	10
6			pH 4, CH_3OH	11

Entry	Compound	Product	Comments (%Yield)	Ref.
7			0.2 M H^+ HMPA, Bu_4NBH_3CN (51)	12
8			HOAc/THF (90)	13
9			(75)	14
10			HOAc R_1, R_2 = H R_2, R_4 = OH (96) R_1, R_4 = OH R_2, R_3 = H (55)	15
11	$C_6H_5CH{=}CHCOCH_3$	$C_6H_5CH{=}CHCHOHCH_3$ (77) $C_6H_5CH{=}CHCH(OCH_3)CH_3$ (11)	CH_3OH	16
12	$C_6H_5CH{=}CHCHO$	$C_6H_5CH{=}CHCH_2OH$ (80) $C_6H_5CH{=}CHCH_2OCH_3$ (8)	CH_3OH	16

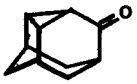
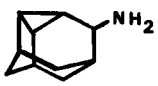
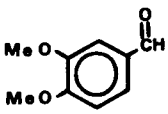
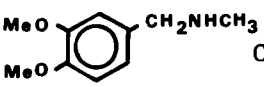
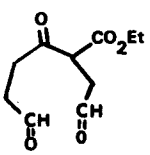
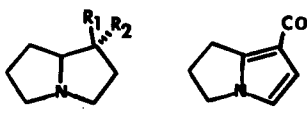
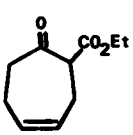
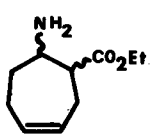
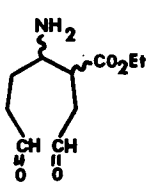
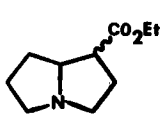
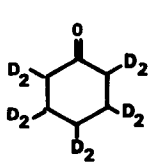
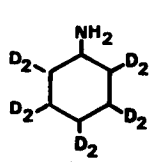
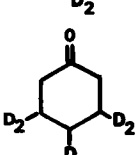
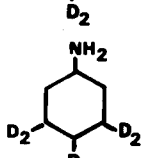
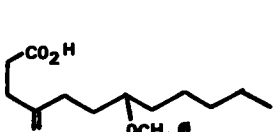
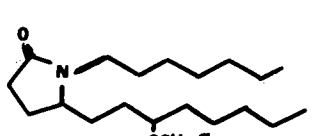
Entry	Compound	Product	Comments (%Yield)	Ref.
13			CH_3OH (88)	16
14		 (64) (31)	CH_3OH	16
15	$C_6H_5CH{=}CHCOCH_3$	$C_6H_5CH{=}CHCHOHCH_3$	HMPA (65)	16
16	$p\text{-}CH_3OC_6H_4CH{=}CHCOCH_3$	$p\text{-}CH_3OC_6H_4CH{=}CHCH_2CH_3$	HMPA (82)	16
17			HMPA (82)	16
18	cholest-4-en-3-one	cholest-4-en-3-ol (14) cholestane-3-ol (80)	HMPA, Bu_4NBH_3CN	16

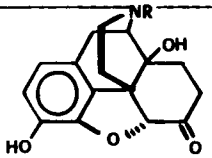
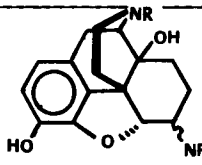
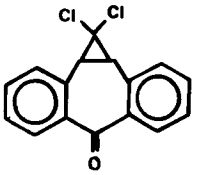
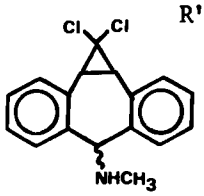
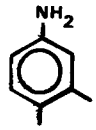
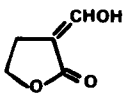
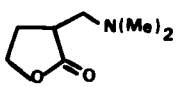
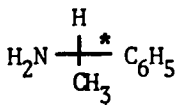
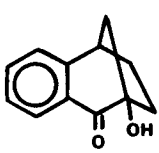
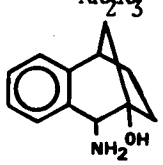
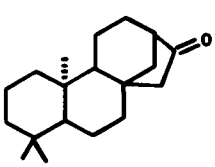
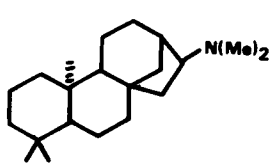
apparent from the results presented in Table II. The only limitations appear to involve diaryl ketones, which react very slowly with amines, (entry 19) highly hindered amines (entry 19) and molecules containing highly reactive groups (entry 21). A modified procedure involves the use of $TiCl_4$ as a Lewis acid catalyst.[23] Conjugated carbonyls lead to 1,3-diamino derivatives via a combination of Michael addition and reductive amination.[25] Certain dicarbonyl compounds provide nitrogen heterocycles by successive reductive aminations[19,34,46] or reductive amination and subsequent amination of an ester[38,39] or an acid.[33] A Japanese group (Takeda Chemical) has utilized the reaction extensively for the preparation of a large number of substituted cyclohexylamines as possible β-adrenoceptor agonists; a selection is presented in Table II.[61-66] A conceptually related process involves the N-methylation of amines by cyanoborohydride-trifluoroacetic acid reduction of methylols which are prepared from amides and formaldehyde (entry 55).[67b]

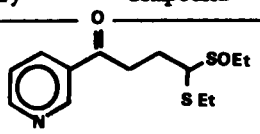
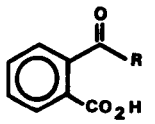
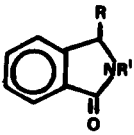
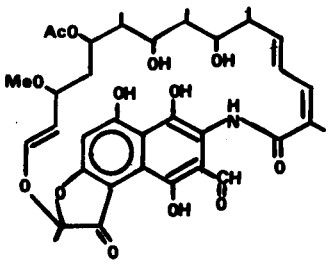
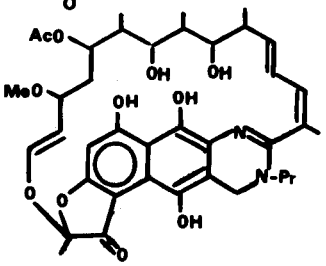
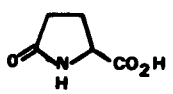
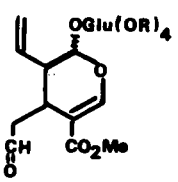
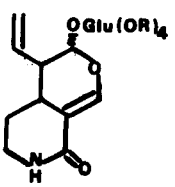
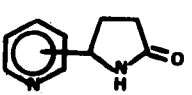
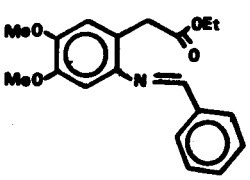
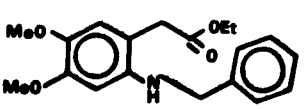
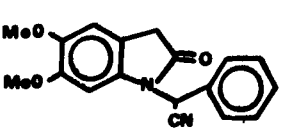
3. Reduction of Oximes, Enamines, Nitrones and Imines[14,60,68-84,157,167]

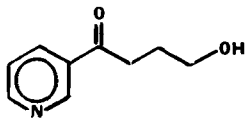
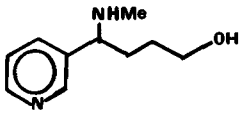
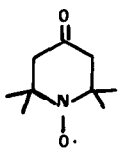
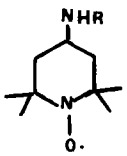
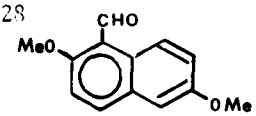
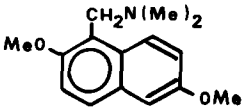
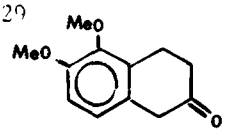
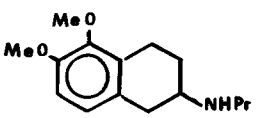
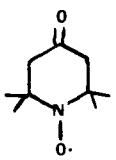
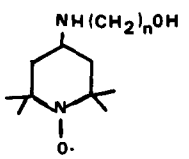
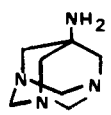
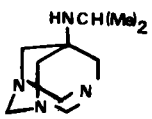
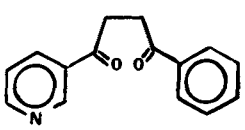
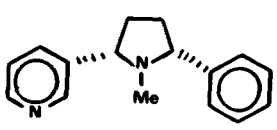
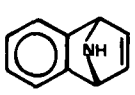
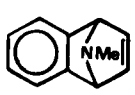
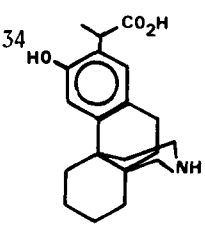
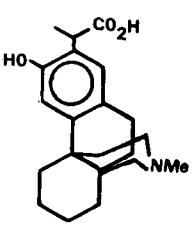
Oximes are reduced by cyanoborohydride in acidic media to either monoalkyl (pH 3) or dialkyl (pH 4) hydroxylamines.[5] The process is related to reductive amination and may be conducted without isolation of the oxime (reductive hydroxylamination). Likewise, N-alkylhydroxylamines may be further alkylated with carbonyl compounds.[59] The reduction of oximes has been utilized for the preparation of N-(4-pentenyl) and N-(5-hexenyl)-hydroxylamines which in turn are cyclized to 2-methylpyrrolidine and 2-methylpiperidine, respectively.[69] Table III lists several examples. Nitrones are also reduced (at pH 4) to the corresponding hydroxylamines (Table III, entry 9).[59] Enamines in acidic media are reduced to amines by way of rearrangement to intermediate iminium ions.[72-80] Such reductions have been utilized for the reduction of indoles to indolines in acetic[76-78,80] or trifluoroacetic acid.[75,79] Imines, including certain substituted

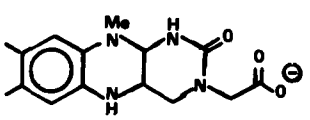
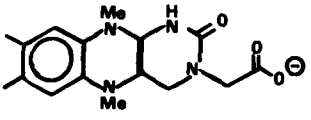
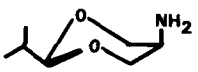
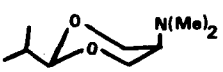
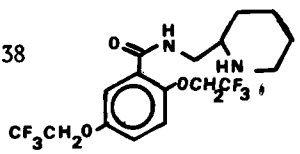
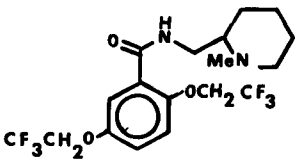
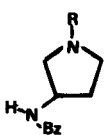
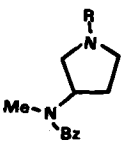
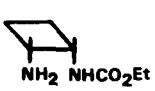
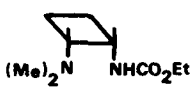
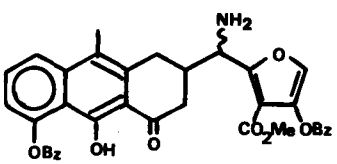
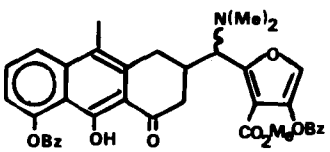
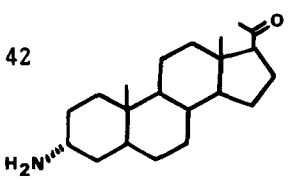
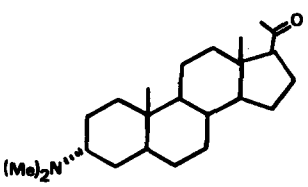
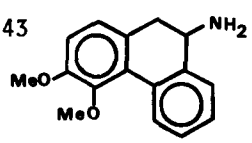
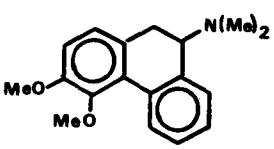
TABLE II. REDUCTIVE AMINATION OF ALDEHYDES AND KETONES

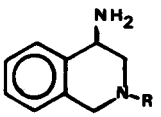
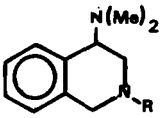
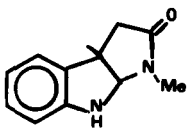
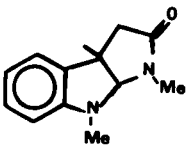
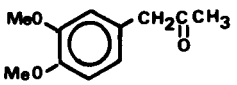
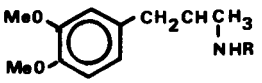
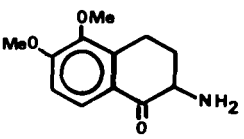
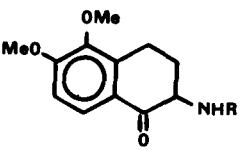
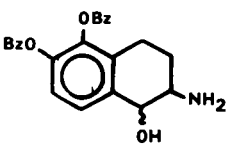
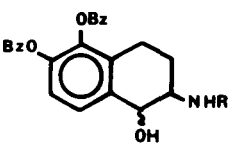
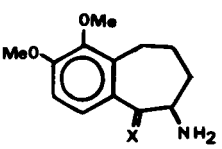
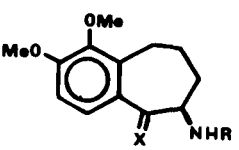
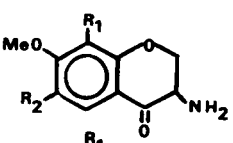
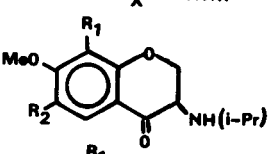
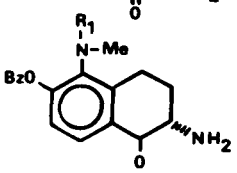
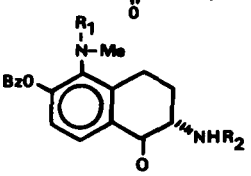
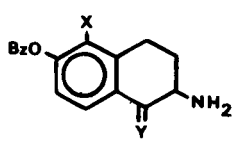
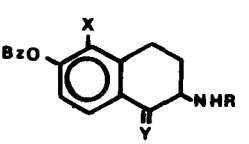
Entry	Compound	Product	Comments (%Yield)	Ref.
1			(40) NH_4OAc	17
2			CH_3NH_2	18
3		 (7) (14)	NH_4OAc	19
4			(48) NH_4OAc	19
5			(35)	19
6			NH_4OAc molecular sieves purified $NaCNBH_3$ necessary	20
7			(70)	
8			(74)	21

Entry	Compound	Product	Comments (%Yield)	Ref.
9			NH_4OAc ca. 2:1 ax:eq R'=H, R=$CH_2CH=CH_2$ (79) R'=H, R=CH_2-  (72) R'=CH_2CH_2OH, R=CH_2-  (44)	22 22 28
10			CH_3NH_2 (53) 1. $TiCl_4$ 2. BH_3CN^-	23
11	D-(1-^{14}C)ribose	N-(D-(1-^{14}C)ribityl)-3,4-dimethyl aniline		24
12	RCH=CHCR' ‖ O	R-CHCH$_2$CH-R' CH_3NH $NHCH_3$ R=CH_3, R'=H (40) R=H, R'=CH_3 (15) R=CH_3, R'=CH_3 (20)	CH_3NH_2	25
13			(42-81) several other examples given	26
14	$C_6H_5COCF_3$	C_6H_5CH-NHCHC_6H_5 F_3C CH_3	 83:17 to 96:4 ratio	27
15	(EtO)$_2$P-CH-C-R' ‖ ‖ O O	(EtO)$_2$P-CH-CH-R' ‖ ‖ O NR_2R_3	(31-91) several examples	29
16			NH_4OAc	30
17			(89)	31

Entry	Compound	Product	Comments (%Yield)	Ref.
18		.....	no reductive amination with NH_4Br, over-reduction of pyridine	32
19			(46-88) failed with R=C_6H_5 Failed with R'=i-Pr, t-Bu	33
20				34
21	$EtOCNH\text{-}N{=}CH(CH_2)_2NHCO_2Bz$ (O)	.....	Reductive amination unsucessful, hydrolysis of benzyloxycarbonyl	35
22	$H_2N\text{-}CO\text{-}(CH_2)_2\text{-}CO\text{-}CO_2^{\ominus}$		(70)	36
23			NH_4OAc	37
24			2-pyr (15) 4-pyr (11)	38
25			(86)	39
			(10)	

Entry	Compound	Product	Comments (%Yield)	Ref.
26			CH_3NH_2 (39-91)	40
27			$R\text{-}NH_2$ molecular sieves several examples	41
28			$(CH_3)_2NH$ (90)	42
29			(19) $Pr\text{-}NH_2$	43
30			$H_2N(CH_2)_nOH$ n=2-6(ca. 60) other examples	44, 163
31			CH_3COCH_3 ("low yield")	45
32			CH_3NH_2 other examples (52)	46
33			(50-75) several examples CH_2O	47
34			(ca. 50) CH_2O	48

Entry	Compound	Product	Comments (%Yield)	Ref.
35			CH_2O pH 4-7	49
36	$(CH_3)_3CCH_2NH_2$	$(CH_3)_3CCH_2N(CH_3)_2$	(84) CH_2O	50
37			(75) CH_2O	51
38			(61) CH_2O	52
39			$R=CH_3$ (100) $R=CON(Et)_2$ (78)	53
40			(35) CH_2O	54
41			(40) CH_2O	55
42			CH_2O	56
43			(71) CH_2O	57

Entry	Compound	Product	Comments (%Yield)	Ref.
44			R=C_6H_5 (36) R=$C_6H_5CH_2$ (57)	58
45			(63) CH_2O	59
46			R=H (95) R=CH_3 (92)	60
47			(53-81) several examples with ketones $LiCNBH_3$ used	61
48			(43-65) several examples	61a
49			(70-80) X=O X= OH,H several examples	62
50			R_1=OCH_3, R_2=H (68) R_1=H, R_2=OCH_3 (70)	63
51			(45-85) several examples	64
52			(50-89) X= CO_2Et, CN Y= O or OH,H several examples	65

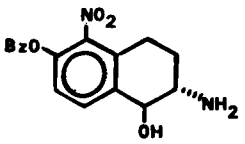
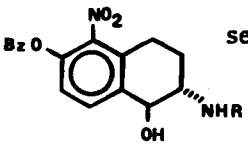
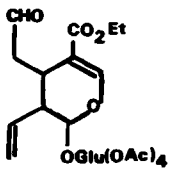
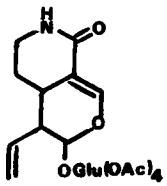
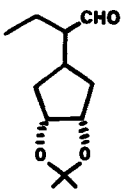
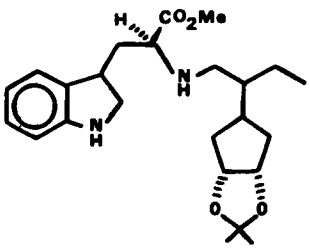
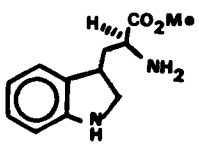
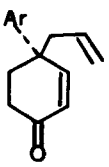
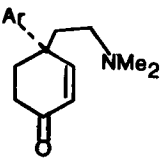
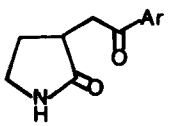
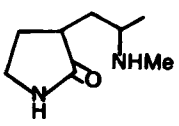
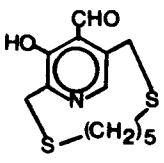
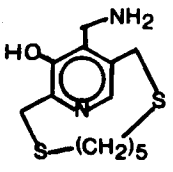
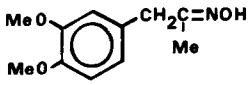
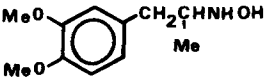
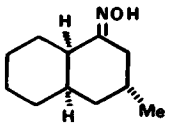
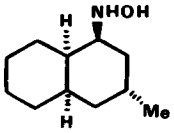
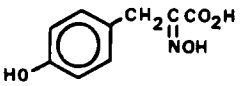
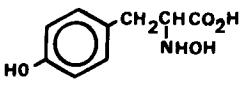
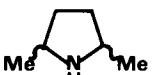
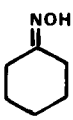
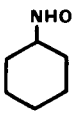
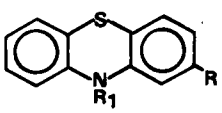
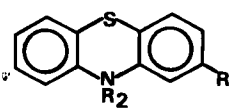
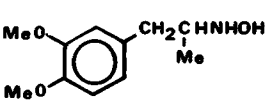
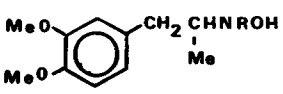
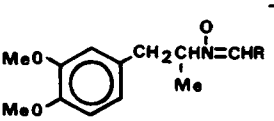
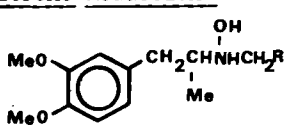
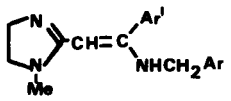
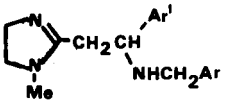
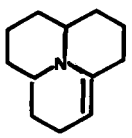
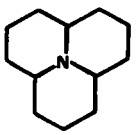
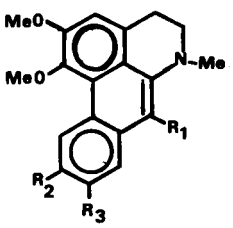
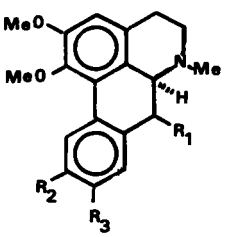
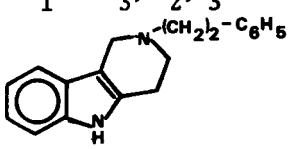
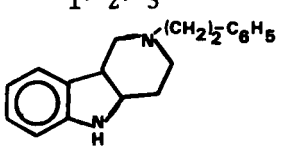
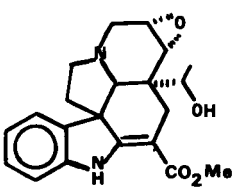
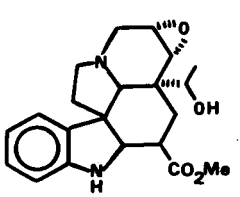
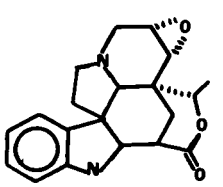
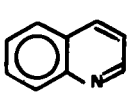
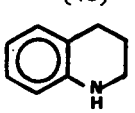
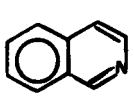
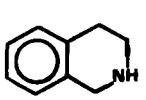
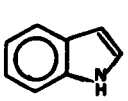
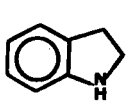
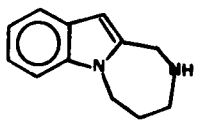
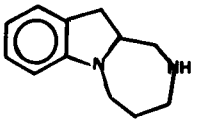
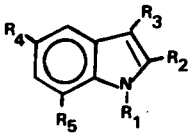
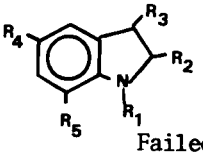
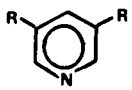
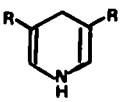
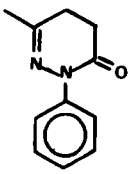
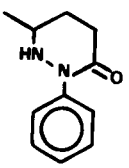
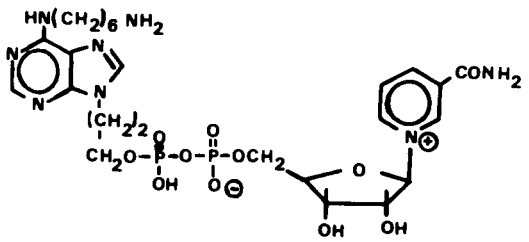
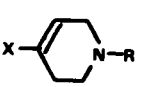
Entry	Compound	Product	Comments(%Yield)	Ref.
53			(35-88) several examples	66
54			NH_4OAc	67a
55	$C_6H_5CONHCH_2OH$	$C_6H_5CONHCH_3$	(97)	67b
	$CH_3CON(CH_3)CH_2OH$	$CH_3CON(CH_3)_2$	(79)	
56				152
57			Me_2NH_2Cl (60) t-BuOH	154
58			$MeNH_3OAc$ (91)	155
59			NH_4Cl + considerable amount of the alcohol	156
60	$CH_3COCOOH$	$CH_3C(CO_2H)NHCH(CO_2H)(CH_2)_3NHC(=NH)NH_2$		164

TABLE III. REDUCTION OF OXIMES, NITRONES, ENAMINES, IMINES AND IMMONIUM SALTS

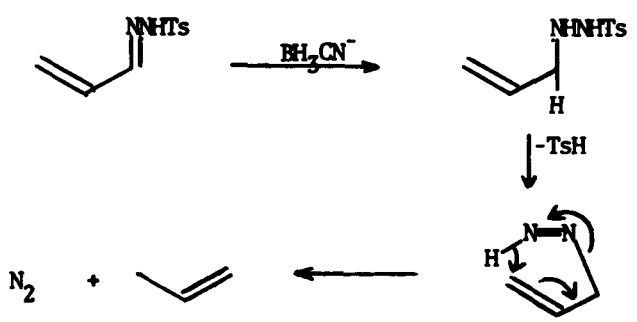
Entry	Compound	Product	Comments (%Yield)	Ref.
		Oximes		
1			(62)	60
2			(100)	68
3				69
4	$H_2C{=}CH(CH_2)_2C{=}NOH$ CH_3		(83-95) hydroxylamine intermediates, other examples; see also 161	70
5	$H_2C{=}CH(CH_2)_3CH{=}NOH$	$H_2C{=}CH(CH_2)_3CH_2NHOH$	(93) other examples	70
6			(81) $NaBH_3CN$, HOAc	71
7			R = H, Cl $R_1 = (CH_2)_2N{=}OH$ $R_2 = (CH_2)_2NHOH$	167
8			R=$C_6H_5CH_2$ (84) R=CH_3 (51) C_6H_5CHO or CH_2O, pH 6	60
		Nitrone Reductions		
9			R=H (85) R=C_6H_5 (60) pH 4	60

Entry	Compound	Product	Comments (%Yield)	Ref.
		Enamine Reduction		
10			(70-77)	72
11			pH 4-5	73
12			R_1=H, R_2,R_3=OCH_3	74
13	R_1=$COCF_3$, R_2,R_3=H	R_1,R_2,R_3=H		14
14			(58) $NaBH_3CN$, TFA	75
15		 (43)	 (30)	76
16			(71) $NaBH_3CN$, HOAc	77
17			(71)	77
18			(88)	78

Entry	Compound	Product	Comments(%Yield)	Ref.
19			$NaBH_3CN$,TFA (81) $NaBH_3CN$,HOAc(<5)	79
20			(61-97) $NaBH_3CN$,HOAc several examples Failed with R_4=NO_2,R_2,R_3=C_6H_5	80
	Imine and Iminium Ion Reduction			
21			(60-97) R=H,Et,CN, CO_2Et $NaBH_3CN$,HOAc	81
22			pH 3-4	82
23			"dihydro form" produced	83
24			X=CN, R=p-$O_2NC_6H_4$ (75-91) X=$CONH_2$,R=P-$BrC_6H_4COCH_2$ (50) X=CH=NOH,R= -$O_2NC_6H_4$ (79)	84
25	$C_6H_5{}^{15}CH{=}NH{\cdot}HCl$	$C_6H_5{}^{15}CH_2NH_2{\cdot}HCl$	(69)	157

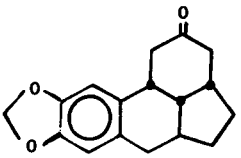
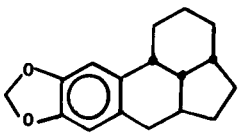
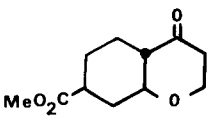
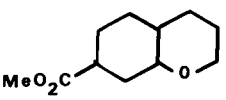
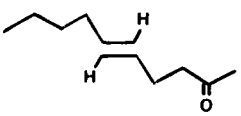
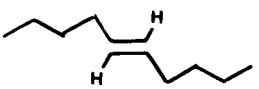
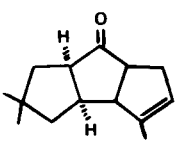
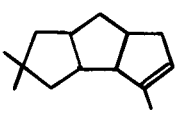
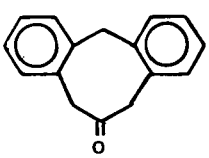
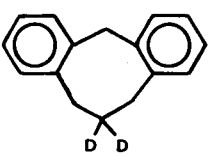
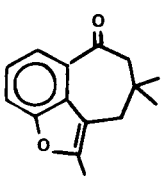
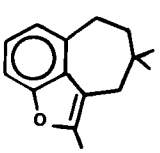
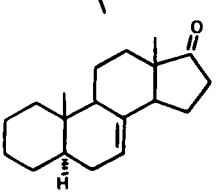
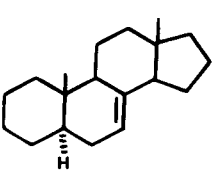
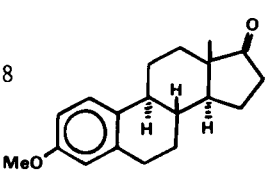
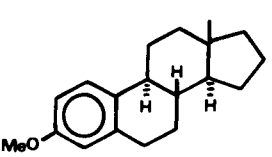
pyridines[81] are reduced in acidic solution; these latter derivatives afford 1,4-dihydropyridines (Table III, entry 21). Pyridinium ions are likewise reduced in neutral or basic protic media;[83,84] 4-substituted cases afford 1,2,5,6-tetrahydro derivatives (entry 24)[84] while unsubstituted systems give products arising from both 1,2 and 1,4 attack.[85]

4. Reductive Deoxygenation of Carbonyls via Tosylhydrazones[86-107,153,168-69] The reductive deoxygenation of tosylhydrazones to hydrocarbons with cyanoborohydride provides a mild and chemoselective alternative to the standard Wolf-Kishner and other procedures.[5] Since its introduction,[86] the method has been utilized in a number of synthetic schemes including several requiring functional group selectivity (i.e. Table IV, entries 10-14,29). The procedure avoids epimerization of α-positions (entries 2,4) and has been used to introduce deuterium (entries 5,24,25,28). A modified procedure using mercury (II) complexes of tosylhydrazones overcomes the reluctance toward reduction of aryl carbonyl tosylhydrazones[86] (i.e. entry 16, Table IV). The reductive deoxygenation of α,β-unsaturated carbonyls is accompanied by migration of the double bond to the position formerly occupied by the carbonyl.[5,86] The mechanism of this "alkene walk" reaction relies on transfer of a hydrogen from an intermediate diazene stereospecifically to the β-carbon with concomitant electron reorganization and N_2 elimination (eq. 9).[102,104] The process is general except for cyclohexenone systems where geometric constraints limit intramolecular migration; in



(9)

TABLE IV. REDUCTIVE DEOXYGENATION OF CARBONYL TOSYLHYDRAZONES.

Entry	Compound	Product	Comments (%Yield)	Ref.
1			(80)	87
2			no epimerization at adjacent position	88
3				89
4			no epimerization at adjacent position	90
5			Na BD_3CN entensive scrambling	91
6			(85)	92,93
7			(46)	94
8				95

Entry	Compound	Product	Comments (%Yield)	Ref.
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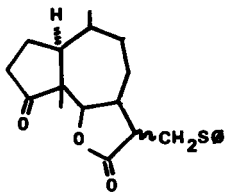
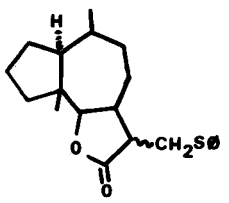
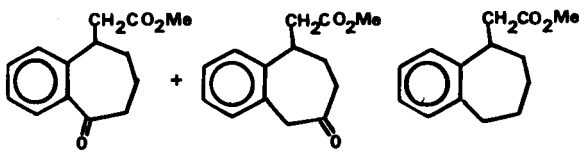
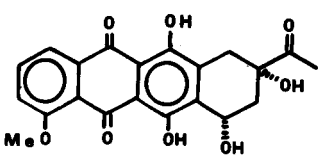
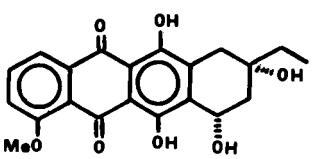
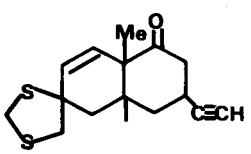
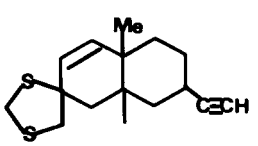
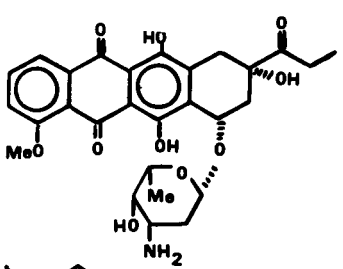
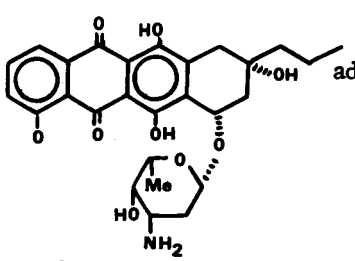
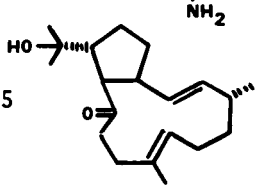
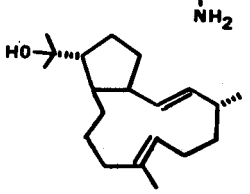
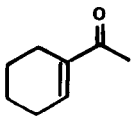
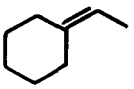
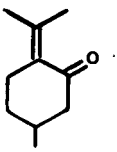
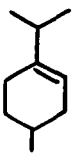
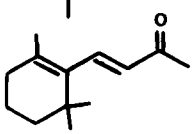
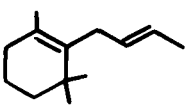
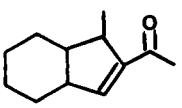
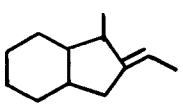
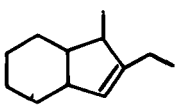
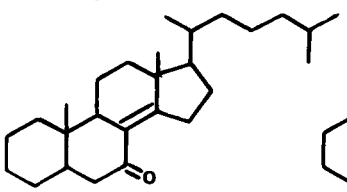
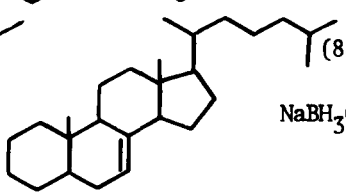
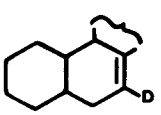
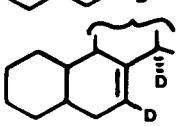
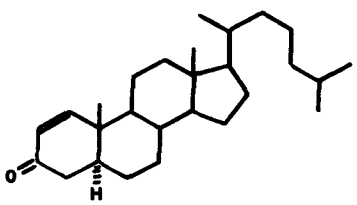
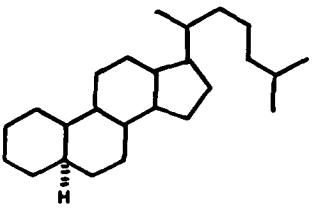
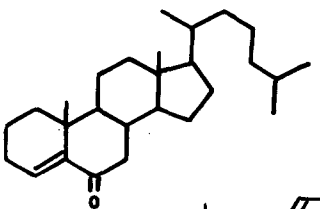
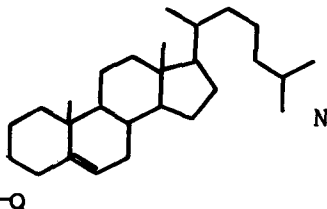
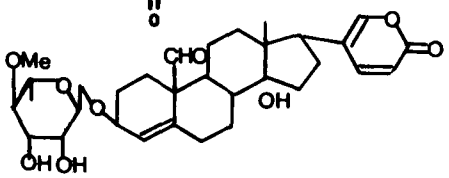
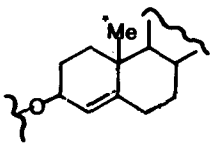
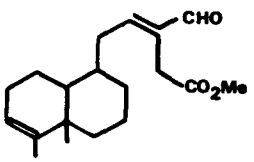
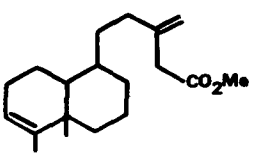
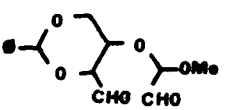
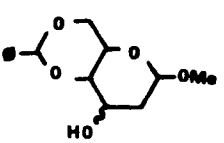
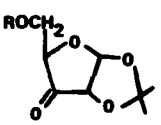
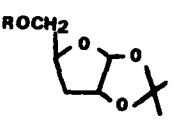
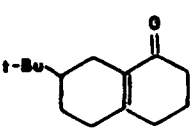
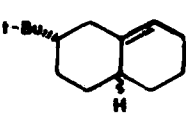
10			(ca. 50)	97
11				98
12			(18) daunomycinone	99
13				168
14			(33) adriamycin	99
15				100

Entry	Compound	Product	Comments(%Yield)	Ref.
16			1.p-TsNHNH$_2$ Hg(OAc)$_2$ 2.NaCNBH$_3$,THF	101
17	C_6H_5CH=CH-CHO	$C_6H_5CH_2CH$=CH_2	(98)	102
18			(84)	102
19			(70)	102
20			(65-70)	102
21		 90% + 1.4% Z	 8.6% (75.5)	153
22			 1:9 ratio	103
23		 NaBH$_3$CN	(88)	104
24			NaBD$_3$CN	104
25			NaBD$_3$CN DCl,DOAc	104

Entry	Compound	Product	Comments (%Yield)	Ref.
26			(70)	104
27			(79) $NaBH_3CN$	104
28			$NaBT_3CN$, Me labeled	169
29				105
30			(50) $NaBH_3CN, H_2O$:EtOH	107a
31			(96) MeOH, pH 3.8 25°, 16 hours	107b
32			4aα (62) 4aβ (19)	107c

such systems, conjugate attack competes leading to saturated hydrocarbons.[102,104] This problem is avoided by using either catecholborane[106a] or $NaBH_4$ in acetic acid.[106b]

An interesting divergent reaction path accompanied the attempted reductive deoxygenation of the ditosylhydrazone depicted in entry 30 of Table IV in neutral aqueous ethanol.[107a] With an acidic catalyst (Amberlite IR-120), reduction stopped at the ditosylhydrazine stage. The original literature[107a] should be consulted for mechanistic postulations. A modification of the standard procedure was found to be advantageous with certain carbohydrate derivatives;[107b] this method involves initial reduction by cyanoborohydride to the tosylhydrazine in acidic methanol followed by subsequent conversion to the hydrocarbon using NaOAc (entry 31). The reaction of the sugar tosylhydrazones with NaOAc in hot DMF gave Bamford-Stevens elimination products in good yields.[107b]

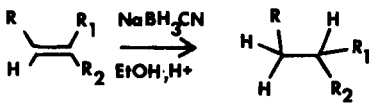
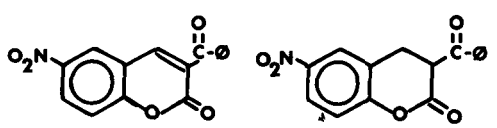
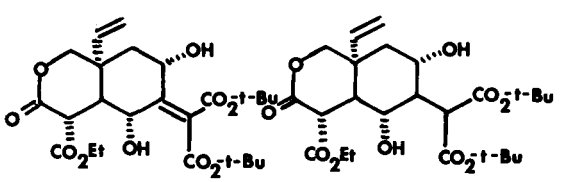
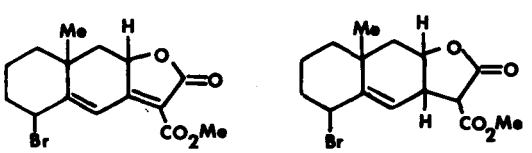
5. Reduction of Polarized Alkenes[108,109]

Although alkenes are normally inert toward cyanoborohydride, systems containing a nitro or two other electron withdrawing groups are cleanly reduced to the hydrocarbon in acidic ethanol and many other functional groups including lactones and aryl ketones remain intact as shown in Table V. An interesting example is provided by entry 9, conducted in wet HMPA. The stereoselective conversions indicated in entry 10 suggest that the procedure may be generally useful for the preparation of cis-fused γ-butyrolactones from fused ring α- carboalkoxy-α,β-butenolides.[109b]

6. Reduction of Iron Carbonyl-Alkene Complexes[110-112]

The reduction of $[(h^5\text{-}C_5H_5)Fe(CO)_2(h^2\text{-alkene})]^+ BF_4^-$ complexes to the corresponding $[(h^5\text{-}C_5H_5)Fe(CO)_2(h^1\text{-alkyl})]$ complexes occurs readily in acetonitrile with cyanoborohydride. The reaction provides a general synthesis for the latter compounds except with certain ring systems (Table

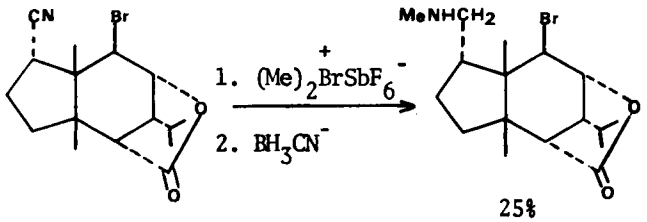
TABLE V. REDUCTION OF POLAR ALKENES

Entry	Compound	Product	Comments(%Yield)	Ref.
				
	R	R_1	R_2	
1	C_6H_5	$CO_2C_2H_5$	$CO_2C_2H_5$	(90) 108
2	p-$CH_3CONHC_6H_4$	$CO_2C_2H_5$	$CO_2C_2H_5$	(80) 108
3	m-NCC_6H_4	$CO_2C_2H_5$	$CO_2C_2H_5$	(84) 108
4	m-$O_2NC_6H_4$	$CO_2C_2H_5$	CN	(82) 108
5	o-BrC_6H_4	$CO_2C_2H_5$	CN	(88) 108
6	C_6H_5	$CONH_2$	CN	(72) 108
7	C_6H_5	NO_2	CH_3	(67) 108
8				(86) 108
9				wet HMPA 109a
10				(97) 109b

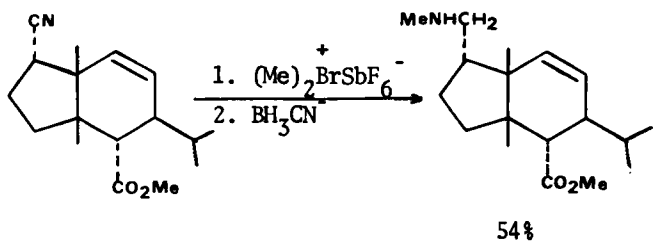
VI).[110,111] Likewise, cyclic and acyclic diene iron tricarbonyl cation complexes are reduced to the corresponding diene complexes (entries 2-4).[112]

7. Reduction of Nitriles to Alkylamines[113,114]

Although nitriles are not reduced to amines by cyanoborohydride, even under strongly acidic conditions, the transformation is accomplished by initial methylation with dimethylbrominium hexafluoroantimonate and subsequent reduction with cyanoborohydride as shown below (eqs. 10, 11).[113,114]



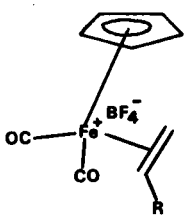
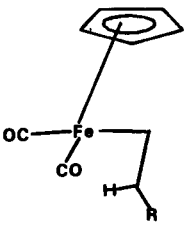
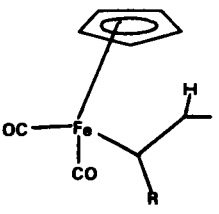
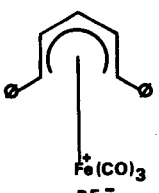
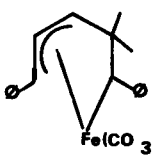
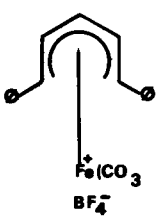
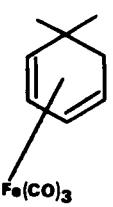
(10)



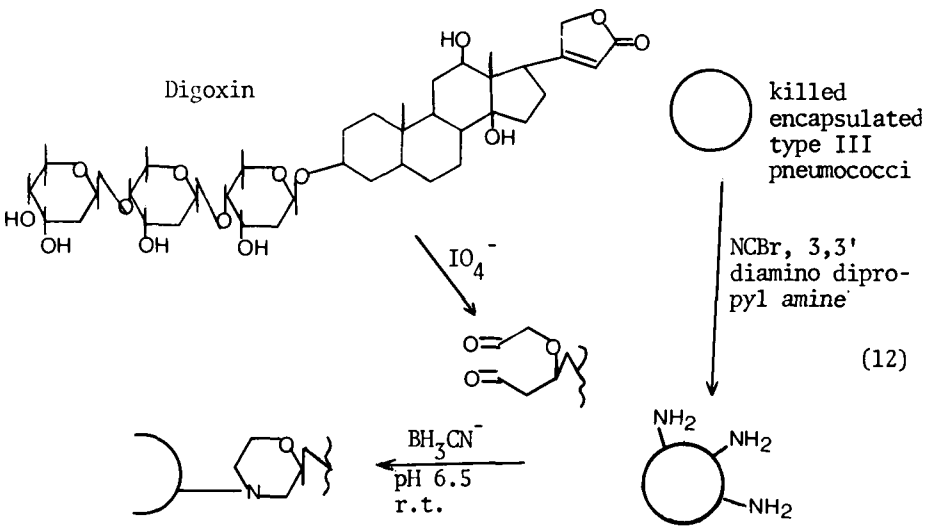
(11)

8. Applications of Reductive Amination to Biochemical Problems[115-33,157-171-72] Predictably, an area where cyanoborohydride has found fruitful and increasing applications involves biochemical investigations where maximum chemoselectivity is required with sensitive molecules such as enzymes. In particular, reductive amination of imine linkages has been utilized in mechanistic studies to trap (or attempts to trap),[115-117] Schiff-base intermediates,[118-120] to prepare modified enzymes[121] (i.e. α-bugarotoxin-horseradish peroxidase),[121a] to inhibit head-tail separation of spermatozoa,[122] to

TABLE VI. REDUCTION OF IRON CARBONYL-ALKENE COMPLEXES

Entry	Compound	Product(s)	Comments(%Yield)	Ref.
1		 	several examples 0 yield for cycloheptene, cyclooctene and norbornadiene (56-95)	110, 111
2		  (38) (40)	THF, -22°	112
3		 	$NaBD_3CN$	112
4				112

link proteins (including enzymes) with various substrates including MRNA,[123] steroids,[124] carbohydrates[125-129] or polyacrylamide.[130] A particularly illustrative example of the potential value of cyanoborohydride in this area is provided by the successful attachment of digoxin to an amine derivative of type III pneumonococcal vaccine by reductive amination as given in eq. 12.[129] In addition, various affinity column materials have been prepared via reductive amination[131] and retinal biochemistry has been explored.[132-3] The procedure has also found utility in the preparation of labeled compounds of biological importance.[157-159]



Digoxin-S3 Vaccine

III. REDUCTIVE DISPLACEMENT OF σ-BONDED LEAVING GROUPS BY HYDRIDE VIA SN_2 OR SN_1 REACTIONS

1. Reduction of Alkyl Halides and Sulfonate Esters[134-44,160,170]

Although cyanoborohydride is unreactive toward σ-bonds in the usual media (CH_3OH, THF, H_2O), in polar aprotic solvents the reagent can functior as a potent sourse of nucleophilic hydride for displacements.[5] An

extensive study of the scope and limitations of such substitutions (with 136 examples)[134] demonstrates that cyanoborohydride in HMPA (or DMSO) furnishes a convenient, efficient and chemoselective system for the reduction of alkyl halides and sulfonate esters. The displacement by hydride occurs predominantely with inversion of configuration and the leaving ability pattern follows the order I> Br≈ OSO_2R>> F, as expected for an SN_2 process.[134] Alcohols may be converted to hydrocarbons in a convenient procedure involving in situ transformation to the iodide with methyltriphenoxyphosphonium iodide and subsequent reduction.[134] Several representative examples are presented in Table VII along with synthetic applications.[134-144] A particularly interesting case is illustrated in entry 16 in which a tertiary mesylate is reduced to the methine hydrocarbon, presumably by initial elimination to a strained α,β-unsaturated ketone and subsequent conjugate reduction.[142] Benzylic quaternary ammonium salts are also reduced.[144]

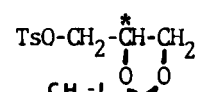
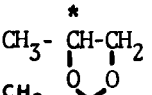
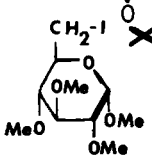
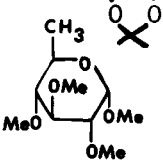
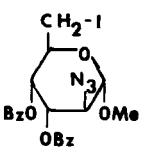
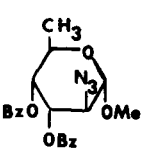
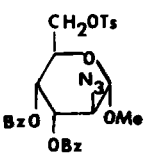
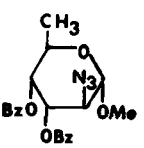
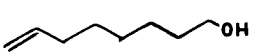
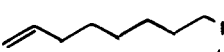
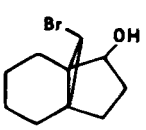
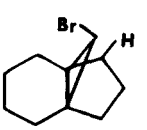
2. Reduction of Epoxides[109,146]

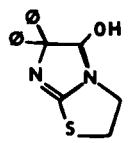
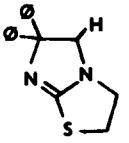
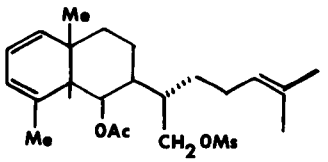
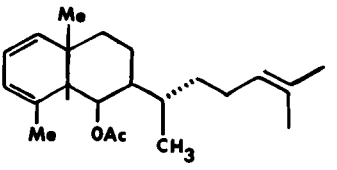
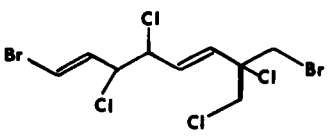
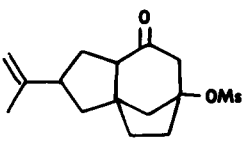
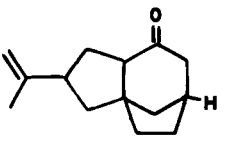
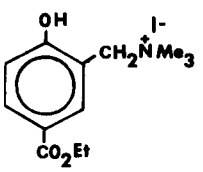
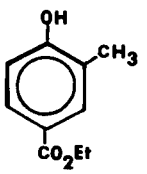
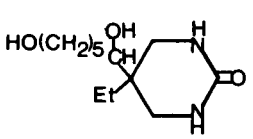
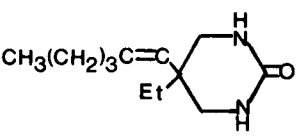
Although epoxides are resistant to attack by cyanoborohydride under basic conditions,[134] preliminary results indicate that coordination with Lewis acids in the presence of cyanoborohydride leads to ring opening and trapping of hydride at the site best able to accommodate a carbonium ion. This affords the less substituted alcohols as opposed to results with most nucleophilic hydride reagents (which attack at the less substituted carbon).[145] Representative examples are illustrated below.[146] An unusual epoxide ring opening accompanied by proton abstraction was observed with cyanoborohydride in dry HMPA (eq. 16).[109] In wet HMPA, the double bond was also reduced (entry 9, Table V).[109]

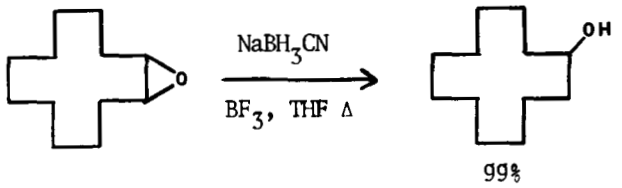
3. Reduction of Acetals and Ketals to Ethers[147]

A related reaction, involving the trapping of a carbonium ion by cyanoborohydride, is the reduction of acetals and ketals in methanolic HCl to

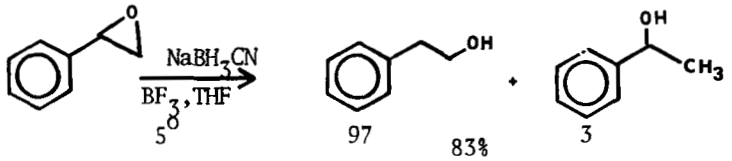
TABLE VII. REDUCTION OF ALKYL HALIDES AND SULFONATE ESTERS.

Entry	Compound	Product	Comments (% Yield)	Ref.
	R-X	R-H	BH_3CN^-, HMPA, 136 examples	134
1	$CH_3(CH_2)_9I$	$CH_3(CH_2)_8CH_3$	Na or Bu_4NBH_3CN (81-90)	134
2	3β-(3-iodopropionoxy) pregn-5-en-20-one	3β-propionoxy-5-pregnen-20-one	$NaBH_3CN$,HMPA (89)	134
3	$CH_3CO(CH_2)_3CO_2(CH_2)_3Br$	$CH_3CO(CH_2)_3CO_2(CH_2)_2CH_3$	$NaBH_3CN$,HMPA (63)	134
4	$C_6H_5CH{=}CH{-}CH_2Br$	$C_6H_5CH{=}CH{-}CH_3$	Na9-BBNCN,HMPA (80)	134
5	$p\text{-}NO_2C_6H_4CH_2Br$	$p\text{-}NO_2C_6H_4CH_3$	$NaBH_3CN$,HMPA (85)	134
6	1-iodonaphthalene	naphthalene	$NaBH_3CN$,HMPA (88)	134
7				135
8			$NaBH_3CN$,HMPA (31)	136
9			$NaBH_3CN$, HMPA	136
10			$NaBH_3CN$, HMPA, NaI	136
11			1.MTPI 2.BH_3CN (BD_3CN^-)	137
12			1. TsCl 2. $NaBH_3CN$	138

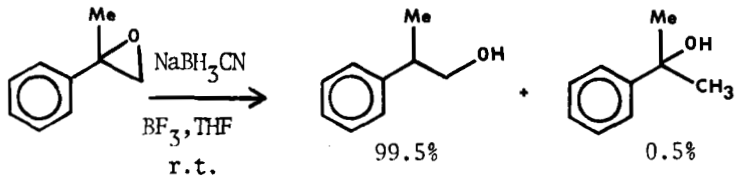
Entry	Compound	Product	Comments (%Yield)	Ref.
13			1. MTPI 2. $NaBH_3CN$ (33)	139
14			HMPA	140
15	$C_6H_5CBr(CH_3)CH_2Br$	$C_6H_5CH(CH_3)_2$	HMPA (83)	141
16		no reduction	HMPA	141
17			HMPA	142
18	$CH_3OCH_2O(CH_2)_{15}CD_2OH$	$CH_3OCH_2O(CH_2)_{15}CD_3$	1. MTPI, HMPA 2. $NaBD_3CN$ (95)	143
19			HMPA (91) several examples	144
20	$C_6H_5(CH_2)_{13}CH_2OH$	$C_6H_5(CH_2)_{13}CH_3$	1. MTPI, HMPA 2. $NaBH_3CN$	160
21			1. MTPI, HMPA 2. $NaBH_3CN$	170



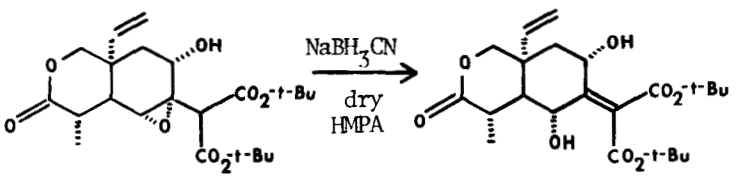
(13)



(14)



(15)



(16)

give ethers (eq. 6);[147] the previously mentioned conversion of certain conjugated carbonyls to ethers and/or hydrocarbons (Table I, entries 11,12) is probably related to this process.

4. Reduction of Allylic Acetates via Activation by Pd^0 [149]

Carboxylate anions are normally very poor leaving groups and thus esters are not very susceptible to displacement by hydride reagents under usual substitution conditions. However, net reductive replacement may be accomplished via initial activation by Pd^0 complexation[148] followed by acetate expulsion and hydride attack on the resulting π-allyl complex (eq. 7). The process is catalytic in Pd^0 and preliminary results indicate that the regioselectivity of the hydride attack is dependent upon steric and electronic effects. Representative conversions are illustrated below (eqs 17,

18).[149]

$$CH_3(CH_2)_6CH{=}CHCH_2OAc \xrightarrow[NaBH_3CN,\ THF,\ \Delta,\ 4\ h.]{Pd(Ph_3P)_4,\ Ph_3P} \begin{matrix} CH_3(CH_2)_6CH{=}CHCH_3 \\ 58\% \\ CH_3(CH_2)_7CH{=}CH_2 \\ 29\% \end{matrix} \quad (17)$$

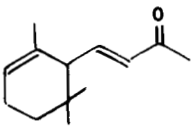
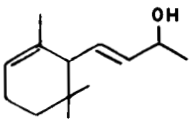
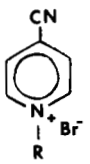
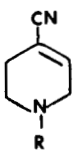
$$o\text{-}O_2NC_6H_4CH{=}CHCH_2OAc \xrightarrow[NaBH_3CN,\ THF,\ \Delta,\ 3\ h.]{Pd(Ph_3P)_4,\ Ph_3P} \begin{matrix} o\text{-}O_2NC_6H_4CH{=}CHCH_3 \\ 80\% \end{matrix} \quad (18)$$

IV. ION-EXCHANGE RESIN SUPPORTED CYANOBOROHYDRIDE[150,151]

The immobilization of cyanoborohydride on ion-exchange resin provides a convenient and easily handled modification of the reagent[150] which provides the added advantages of work-up ease and retention of spent reagent, including cyanide, on the resin. Preliminary investigation indicates the resin cyanoborohydride to be equally effective as the sodium salt for reductive amination, amine methylation, enone reductions to allylic alcohols, dehalogenations and pyridinium ion reductions as shown in Table VIII.[151]

TABLE VIII. REDUCTIONS WITH RESIN-SUPPORTED CYANOBOROHYDRIDE

Entry	Compound	Product	Comments(%Yield)	Ref.
1	$C_6H_5COCH_3$	$C_6H_5CH(NH_2)CH_3$	NH_4OAc, 78° (53-66)	151
2	cyclooctanone	cyclooctylamine	NH_4OAc, 78° (49)	151
3	$C_6H_5CH(CH_3)NH_2$	$C_6H_5CH(CH_3)N(CH_3)_2$	CH_2O (84)	151

Entry	Compound	Product	Comments(%yield)	Ref.
4			(70)	151
5			R = p-$BrC_6H_4COCH_2$(50) R = p-$O_2NC_6H_4CH_2$ (71)	151
6	$CH_3(CH_2)_{11}I$	$CH_3(CH_2)_{10}CH_3$	HMPA, 90°(89)	151

ACKNOWLEDGEMENT.- We wish to thank Ventron Corporation for their encouragement and continued support.

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