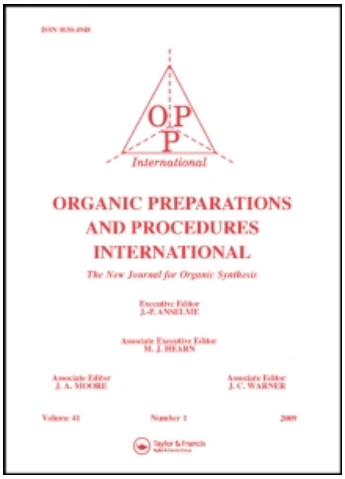

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SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA. A REVIEW OF THE SYNTHETIC UTILITY OF ACYLOXYBOROHYDRIDES

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SODIUM BOROHYDRIDE IN CARBOXYLIC ACID MEDIA.

A REVIEW OF THE SYNTHETIC UTILITY OF ACYLOXYBOROHYDRIDES

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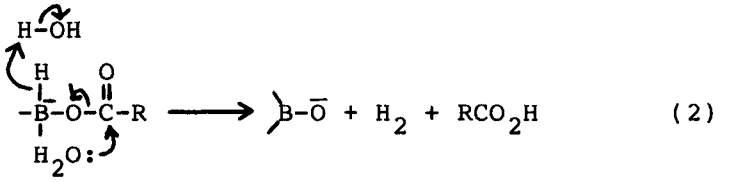
INTRODUCTION

Sodium borohydride ($NaBH_4$), alone or in conjunction with certain metals or solid supports, is one of the most useful reagents in chemistry.[1] Modified versions of $NaBH_4$, such as sodium cyanoborohydride ($NaBH_3CN$), also have widespread utility in synthesis.[2] A relatively new modified-$NaBH_4$ reagent is that produced when $NaBH_4$ is allowed to react with a carboxylic acid (RCO_2H) (Eq. 1). The resulting sodium acyloxyborohydrides and their use in organic synthesis are the subject of this review.[3]

$$NaBH_4 + x\ RCO_2H \longrightarrow NaBH_{4-x}(OCOR)_x + xH_2 \qquad (1)$$
$$x = 1\text{-}3$$

Unlike the reaction of $NaBH_4$ with mineral acids or aqueous acids,[4] which leads to diborane formation or complete hydrolysis, the reaction of $NaBH_4$ with neat carboxylic acids (RCO_2H) or solutions of RCO_2H in nonprotic solvents leads to the formation of acyloxyborohydrides. Depending on the relative concentration of RCO_2H, one, two, or three hydrides will be available for reaction. Indeed, as will be seen, even in the presence of excess RCO_2H the triacyloxyborohydride species ($x = 3$, Eq. 1) is relatively stable and only surrenders its

last hydride upon heating or prolonged exposure to RCO_2H. However, all three types of acyloxyborohydrides are rapidly hydrolyzed by water (Eq. 2).



$$\text{H-OH} \;\; \text{H}\!-\!\underset{\text{H}_2\text{O:}}{\underset{|}{\text{B}}}\!-\!\text{O}\!-\!\text{C}\!-\!\text{R} \longrightarrow \text{B-O}^- + \text{H}_2 + \text{RCO}_2\text{H} \qquad (2)$$

As will be apparent in this review, the fact that one can in principle control the number and kind of acyloxy groups on the boron atom leads to remarkable chemoselectivity. The data thus far accumulated indicate the following order of decreasing hydride-donating ability.

$$\overset{-}{\text{B}}\text{H}_3\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{R} \;>\; \overset{-}{\text{B}}\text{H}_2(\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{R})_2 \;>\; \overset{-}{\text{B}}\text{H}(\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{R})_3$$

This reactivity order is presumably a consequence of both the inductive electron-withdrawing ability of the acyloxy group (e.g., σ_I = 0.39 for $\overset{-}{\text{O}}\text{Ac}$)[5] which strengthens the B-H bond and the steric bulk surrounding the B-H bond.

I. HISTORICAL. DISCOVERY AND CHARACTERIZATION OF ACYLOXYBOROHYDRIDES

Interestingly, the first reported synthesis of an acyloxyborohydride, in 1955, did not involve carboxylic acids. Wartik and Pearson[6] prepared sodium triformyloxyborohydride by allowing $NaBH_4$ to react with carbon dioxide in dimethyl ether at room temperature (Eq. 3).

$$\text{NaBH}_4 + 3\text{CO}_2 \xrightarrow[25^0]{\text{Me}_2\text{O}} \text{NaBH}(\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{H})_3 \qquad (3)$$

These workers noted that $NaBH(OCHO)_3$ reacts rapidly with dilute aqueous acid to give dihydrogen, formic acid, and boric acid in the expected stoichiometry. Moreover, they made the important observation that $NaBH(OCHO)_3$ decomposes on standing, or more rapidly on melting, to give methyl formate. This result implicates the formation of methanol by the self-reduction of $NaBH(OCHO)_3$ to formaldehyde, thence to methanol, and finally to methyl formate; the ramifications of this observation will be seen later.

At about the same time, Nenitzescu and Badea[7] reported the synthesis of $NaBH(OAc)_3$, as "a white solid, insoluble in organic solvents," from the reaction of $B(OAc)_3$ and sodium hydride in boiling dioxane (Eq. 4). A small amount of $NaBH_2(OAc)_2$ was reported to be present in the filtrate from which $NaBH(OAc)_3$ precipitated. These workers also noted that $NaBH(OAc)_3$ decomposes in moist air and in water. Two years later Reetz[8] and Brown and Subba Rao[9]

$$NaH + B(OAc)_3 \xrightarrow[\Delta,\ 4\ hr]{dioxane} NaBH(OAc)_3 \qquad (4)$$

independently described the formation of acyloxyborohydrides from the reaction of $NaBH_4$ with RCO_2H (Eqs. 5 and 6).

Reetz[8] isolated $NaBH_3OAc$ from $NaBH_4$ and acetic acid in tetrahydrofuran (THF) (Eq. 5), and provided some analytical data in support of the structure. Thus, on reaction with water this substance liberates three moles of dihydrogen. Moreover, no diborane can be detected on heating $NaBH_3OCOCH_3$ at 55° for 10 min, although it does react with trialkylphosphites to form $(RO)_3PBH_3$ in good yield.

$$NaBH_4 + HOAc \xrightarrow[\substack{2.\ 30\text{-}40^0 \\ 1\ hr}]{\substack{1.\ THF \\ -30^0\ to\ -35^0}} NaBH_3OAc + H_2 \quad (5)$$

Brown and Subba Rao[9] proposed the formation of the related propionic acid derivative (Eq. 6) but no experimental evidence was advanced to support its structure. They also suggested that the reaction of diborane with sodium propionate led to the same material.

$$CH_3CH_2CO_2H \xrightarrow[diglyme]{NaBH_4} H_2 + NaBH_3OCOCH_2CH_3 \xleftarrow{B_2H_6} CH_3CH_2CO_2Na \quad (6)$$

Several years later, we[10,11] and Marchini et al.[12] observed that $NaBH_4$ reacts with excess glacial acetic acid to liberate 3 moles of dihydrogen (Eq. 7). The last hydride is released slowly at 20° or more rapidly on heating or in the presence of water.

$$NaBH_4 + CH_3CO_2H \xrightarrow{20^0} 3H_2 + NaBH(OAc)_3 \xrightarrow[80^0]{HOAc} H_2 + NaB(OAc)_4 \quad (7)$$

Marchini and coworkers[12] also reported the preparation and chemical, physical, and spectral properties of several acyloxyborohydrides (Table 1), prepared according to Eq. 8;

$$NaBH_4 + 3RCO_2H \xrightarrow[20^0]{PhH} NaBH(O_2CR)_3 + 3H_2 \quad (8)$$

they also observed that $NaBH(OCOC_6H_5)_3$ undergoes self-reduction in refluxing toluene to give benzyl alcohol.

Another Italian group[13] prepared sodium tris(trifluoroacetoxy)borohydride (Eq. 9) and observed a mp of 64-66° and bands at 1775 and 1680 cm^{-1} in the infrared spectrum.

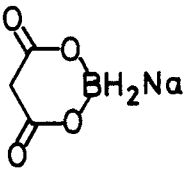
$$NaBH_4 + 3CF_3CO_2H \xrightarrow[75\%]{toluene} NaBH(OCOCF_3)_3 + 3H_2 \quad (9)$$

TABLE 1. Properties of Sodium Triacyloxyborohydrides[12]

Compound	mp (°C)	IR(cm^{-1}) B-H	C=O
$NaBH(OCHO)_3$	>300°	2480	1680
$NaBH(OAc)_3$	>300°	2480	1660
$NaBH(OCOPh)_3$	>300°	2490	1670, 1635
$NaBH(OCOCH_2Cl)_3$	120-5° (dec)	2530	1735, 1685

Egan and Morse[14] have recorded the IR spectrum of $NaBH_3OAc$ and observed 2500 and 1683 cm^{-1} for the B-H and C=O stretching absorptions, respectively. These workers also noted, as did Hui,[15] that $NaBH_2(OAc)_2$ could not be prepared cleanly.

However, Hui[15] was able to synthesize the malonic acid-derived acyloxyborohydride shown below, perhaps the only known stable diacyloxyborohydride species.



The remaining few cases of acyloxyborohydride isolation and study will be presented in the appropriate section to follow.

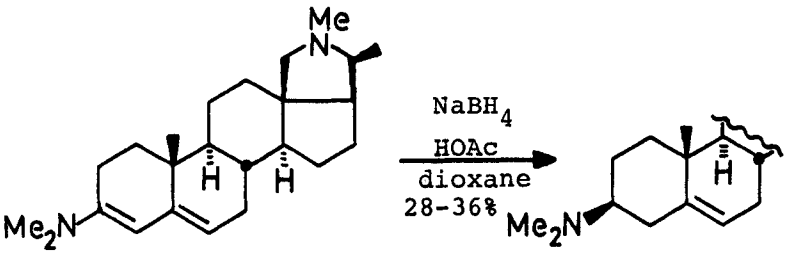
In most of the examples of the use of acyloxyborohydrides in synthesis (vide infra), the reagent is not isolated per se but, rather, is generated and utilized in situ. Therefore, in the ensuing discussion we have not specified the actual acyl-

oxyborohydride reagent, except where it has been isolated and employed as such.

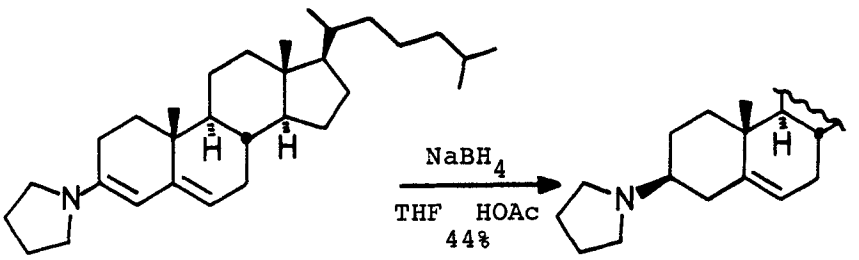
Finally, it will be noted that this review covers also $NaBH_3CN$, $LiBH_4$, KBH_4, and $\underline{n}$-Bu_4NBH_4 in combination with carboxylic acids.

II. REDUCTION OF ENAMINES

Apparently, the first reported use of $NaBH_4/RCO_2H$ in organic synthesis was the reduction of two steroidial dienamines by Marshall and Johnson[16] (Eq. 10 and 11) and, in fact, was the final step in their total synthesis of (±)-conessine[16c] (Eq. 10).



(10)



(11)

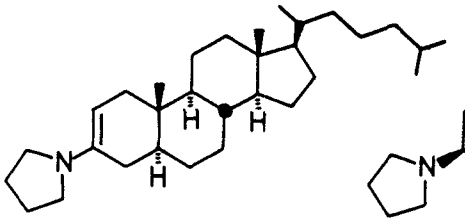
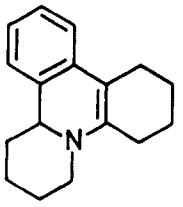
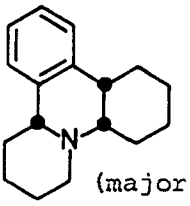
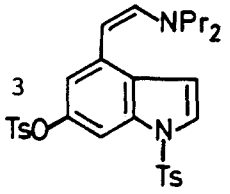
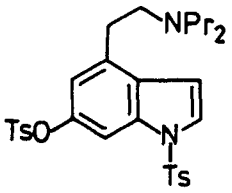
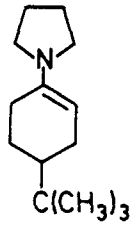
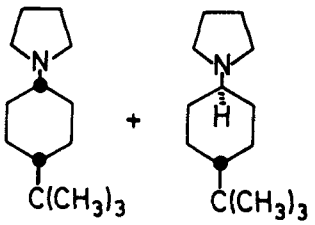
(60% in diglyme)

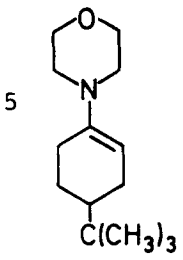
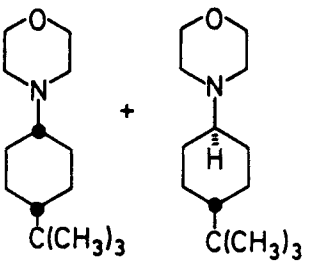
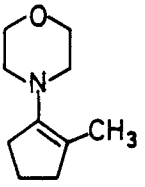
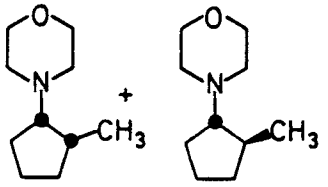
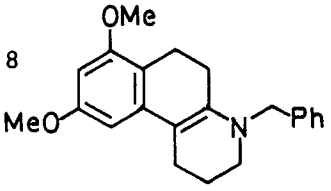
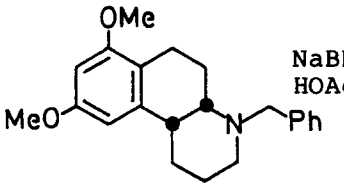
These workers also showed that simple enamines were reduced under these conditions, and since then a number of other enamine reductions have been described (Table 2). Noteworthy is the extensive study by Hutchins[19] (entries 4-7). Sodium cyanoborohydride can be substituted for $NaBH_4$

(entries 3, 6, 8), especially if amine alkylation is to be avoided (vide infra).

From these studies it is clear that reductions of enamines (via immonium ions) with sodium triacetoxyborohydride are reasonably (entries 2, 4-6) to highly (entry 7) stereoselective, with the preferred approach being from the less hindered side (equatorial attack) to give the axial product.

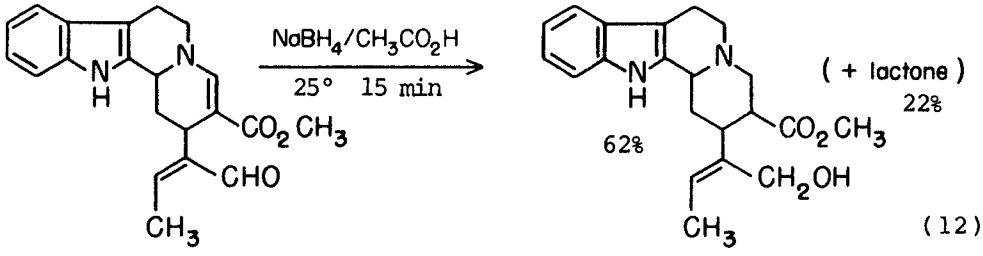
TABLE 2. Reduction of Enamines

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$, THF HOAc, Δ, 1 hr	70%	16a
2		 (major)	$NaBH_4$, THF HOAc, rt	80%	17
3			$NaBH_3CN$ MeCN HOAc rt, 10 min	78%	18
4		 72 : 28	$NaBH_4$ HOAc 25°, 24 hr	78%	19

5		 79 : 21	$NaBH_4$ HOAc 25°, 24 hr	84%	19
6	//	// 89 : 11	$NaBH_3CN$ HOAc 25°, 24 hr	--	19
7		 98 : 2	$NaBH_4$ HOAc 25°, 24 hr	93%	19
8		 2:1 cis/trans	$NaBH_3CN$ HOAc, MeCN	75%	20

III. REDUCTION OF VINYLOGOUS AMIDES, CARBAMATES, UREAS AND N-ACYLENAMINES

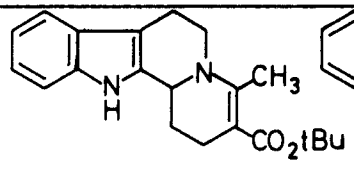
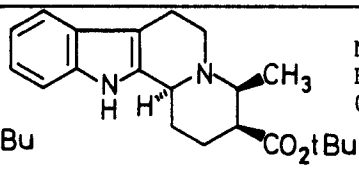
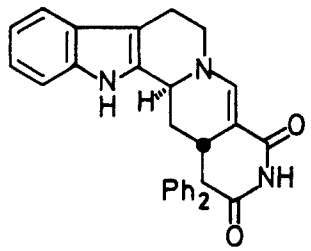
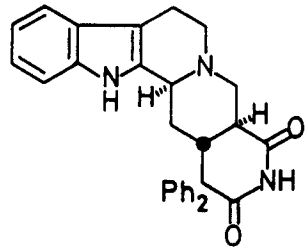
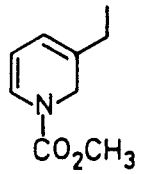
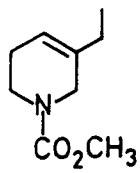
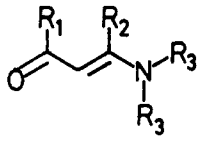
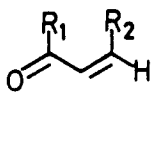
Another pioneering application of $NaBH_4/RCO_2H$ methodology was the chemoselective reduction of the vinylogous carbamate double bond in vallesiachotamine as reported in 1966 by Djerassi[21] (Eq. 12). The aldehyde functionality was also reduced, but, interestingly, the indole double bond was not reduced, in contrast to studies discussed later (Section V).



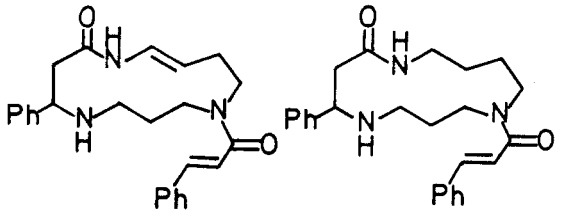
(12)

Several other examples of this particular reduction have been revealed (Table 3). Noteworthy is the fact that the stronger trifluoroacetic acid can be used (entry 3) and that acyclic systems may undergo β-elimination (entry 4).

TABLE 3. Reduction of Vinylogous Amides, Carbamates, Ureas and N-Acylenamines

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ HOAc 0°→rt	80%	22
2			$NaBH_3CN$ HOAc THF MeOH 45°, 4 h	75%	23
3			$NaBH_4$ CF_3CO_2H PhH	55%	24
4			$NaBH_4$ CF_3CO_2H i-PrOH	60-80%	25

R_1 = i-Pr, Ph, C_6H_{11}
R_2 = i-bu, Pr, neo-pentyl
R_3 = Et, $-CH_2CH_2OCH_2CH_2-$



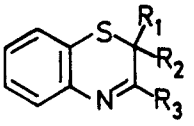
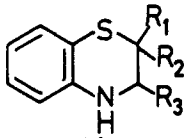
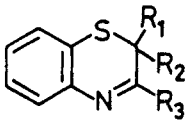
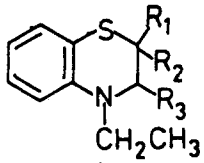
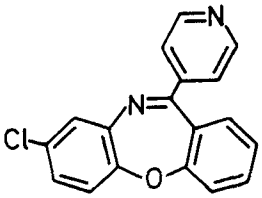
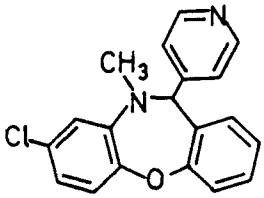
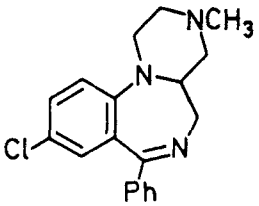
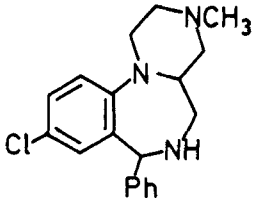
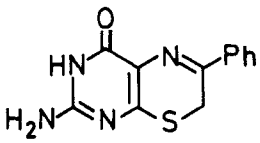
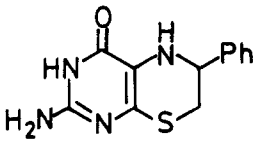
$NaBH_3CN$
HCO_2H -- 26

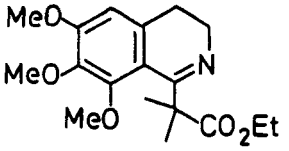
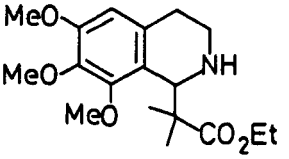
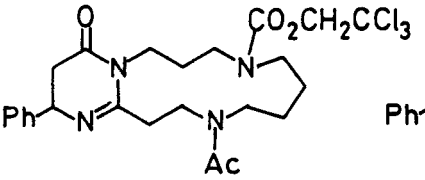
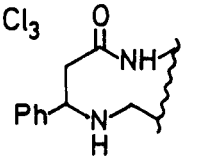
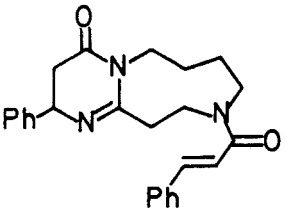
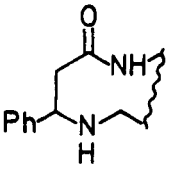
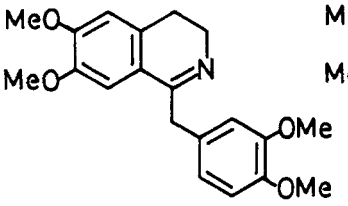
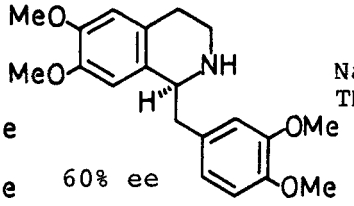
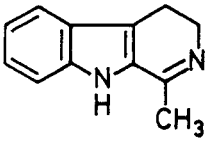
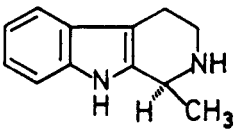
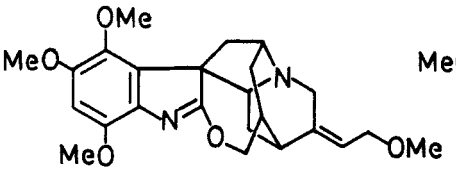
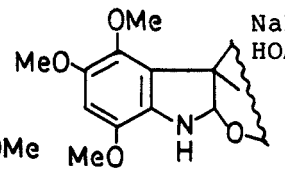
IV. REDUCTION OF IMINES, IMMONIUM SALTS, AND RELATED SYSTEMS

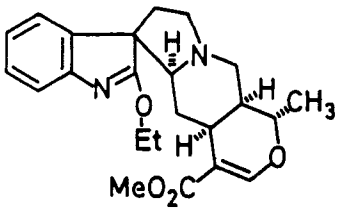
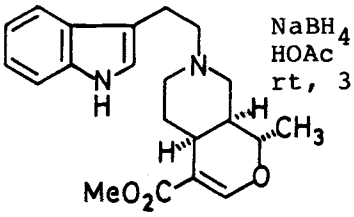
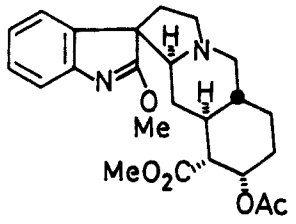
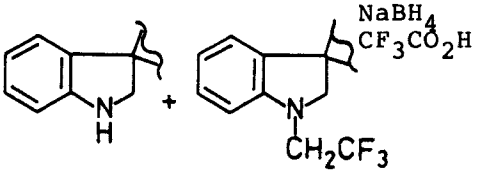
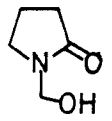
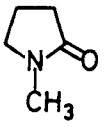
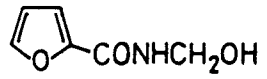
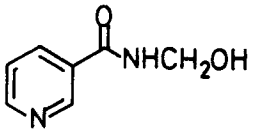
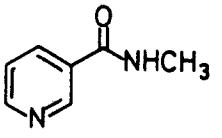
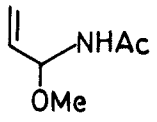
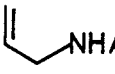
In view of the results described in the previous two sections, it is not surprising that imines and immonium salts are smoothly reduced to amines (Table 4). Depending on the system and reaction conditions, the initially-produced amine may be N-alkylated by the carboxylic acid (entries 2, 3, 13). This novel amine alkylation will be discussed in detail in Section VI. The $NaBH_4/RCO_2H$ reduction of imines is analogous to that utilizing $NaBH_3CN$/MeOH/pH 3.[27] Several points about Table 4 should be made. Pyridine, pyrimidine, and furan rings (entries 3, 5, 15, 16) are generally inert to the action of $NaBH_4$ (or $NaBH_3CN$)/ RCO_2H. In some cases very useful ring cleavage is observed (entries 7, 8, 12) and Wasserman has made extensive use of this reductive cleavage in his elegant syntheses of spermine/spermidine alkaloids.[26,32] The N-trifluoroethylation (entry 13) can be suppressed by using $NaBH_3CN/CF_3CO_2H$. It is interesting to note that the acetic acid-induced ring opening observed by Sakai[34] (entry 12) is not observed when trifluoroacetic acid is used (entry 13). Especially noteworthy is the high degree of asymmetric reduction observed with a $NaBH_4$/proline acyloxyborohydride complex (entries 9, 10). Several other imines and optically active amino acids were examined in this important study.[33] Finally, Weinreb has used this methodology ($NaBH_3CN$/ CF_3CO_2H) to effect a

convenient N-methylation of primary and secondary amides (entries 14-16), in a transformation that presumably involves the formation and subsequent reduction of acylimmonium ion intermediates (cf. Table 3, entry 5 for a related example).

TABLE 4. Reduction of Imines, Immonium Salts, and Related Systems

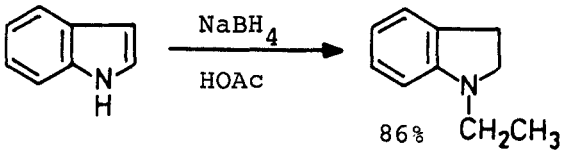
Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ (1 eq.) CH_3CO_2H 80°, 1 hr	60-95%	12
	a; $R_1 = R_2 = Me$, $R_3 = Ph$ b; $R_1 = H$, $R_2 = R_3 = Ph$				
2			$NaBH_4$ (5 eq.) HOAc 80°, 3 hr	75-95%	12
	a; $R_1 = R_2 = Me$, $R_3 = Ph$ b; $R_1 = H$, $R_2 = R_3 = -(CH_2)_5-$				
3	 (others)		$NaBH_4$ HCO_2H 10°÷25°	84%	28
4			$NaBH_3CN$ HOAc rt	95%	29
5			$NaBH_4$ CF_3CO_2H rt	51%	30

6			$NaBH_3CN$ HOAc rt, 3 hr; 50°, 1 hr	94%	31
7			$NaBH_3CN$ HOAc	88%	32
8			$NaBH_3CN$ HOAc 25°, 3 hr 50°, 1 hr	93%	26,32
9		 60% ee	$NaBH_4$ THF	68%	33
10		 79% ee	$NaBH_4$ THF	85%	33
11			$NaBH_4$ HOAc	77%	34

12			$NaBH_4$ HOAc rt, 3 hr	55%	34
13			$NaBH_4$ CF_3CO_2H	--	35
14			$NaBH_3CN$ CF_3CO_2H rt, 1-2 days	90%	36a
15			$NaBH_3CN$ CF_3CO_2H rt, 1-2 days	83%	36a
16			$NaBH_3CN$ CF_3CO_2H rt, 1-2 days	68%	36a
17			$NaBH_4$ CF_3CO_2H PhH rt, 10 min	--	36b

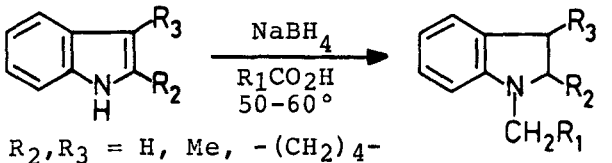
V. REDUCTION OF INDOLES

Our own research in the area of $NaBH_4/RCO_2H$ methodology began in 1973 when the senior author attempted to reduce indole to indoline with $NaBH_4$ in glacial acetic acid.[37] Much to our surprise, the product was not indoline but rather N-ethylindoline in 86% distilled yield! (Eq. 13).



(13)

Control experiments and other data show that indoline is formed rapidly and then undergoes N-alkylation to give product. Details of this N-alkylation will be described in Section VI. This synthesis of N-alkylindolines is general for a variety of indoles and carboxylic acids (Eq. 14).[11]

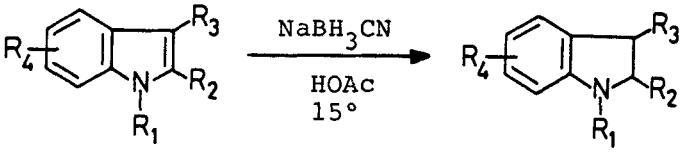


R_2, R_3 = H, Me, $-(CH_2)_4-$
R_1 = H, Me, Et, i-Pr

49-86%

(14)

By using $NaBH_3CN$ in place of $NaBH_4$, one can avoid N-alkylation and achieve a very simple and efficient synthesis of indolines (Eq. 15).[38] Only those indoles having electron-withdrawing groups fail to undergo reduction (e.g., 5-nitro- and 2,3-diphenylindole); this modification using $NaBH_3CN$/HOAc to reduce indoles to indolines was recently "rediscovered" by Kumar and Florvall.[39]



(15)

R_1 = H, Me, Et, n-Pr, CH_2Ph
R_2, R_3 = H, Me, $-(CH_2)_4-$
R_4 = H, 5-Br, 7-Me

79-97%

It is important to note that earlier workers did not observe reduction of the indole double bond because in these systems (e.g. Eq. 12; Table 3, entries 1, 2; Table 4, entry 12) a basic nitrogen atom is present which, when protonated, protects the indole ring from protonation and reduction. However, as can be seen in Table 5, the stronger trifluoroacetic acid overcomes this difficulty and reduction of the indole double bond can be achieved.

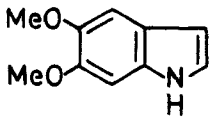
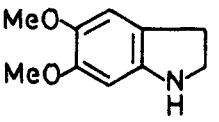
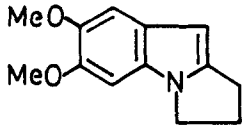
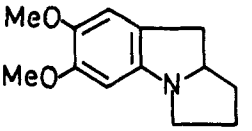
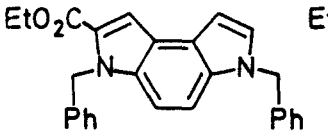
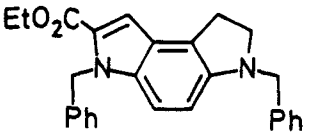
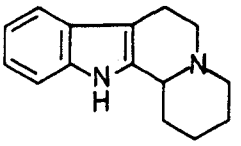
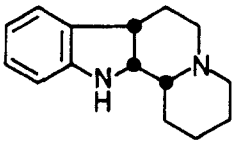
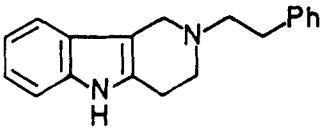
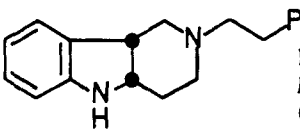
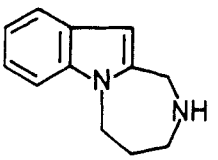
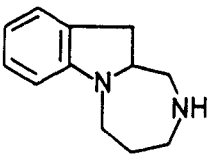
Several additional examples of the use of $NaBH_4$ (or $NaBH_3CN$)/ RCO_2H to reduce the indole ring are tabulated in Table 5. A striking example of the inherent chemoselectivity noted earlier is seen in the reduction of only the more basic indole double bond in the molecule shown in entry 3.

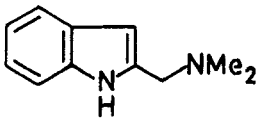
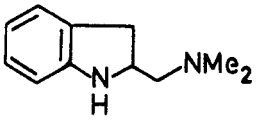
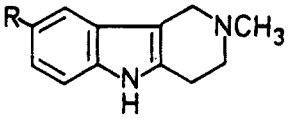
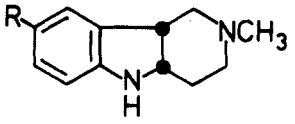
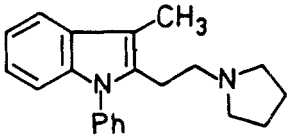
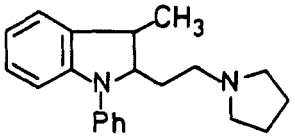
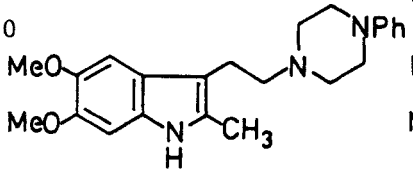
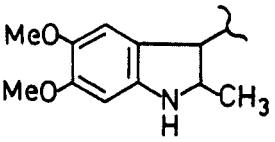
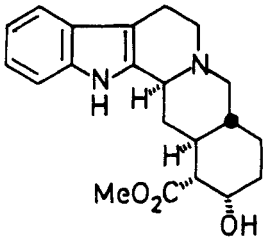
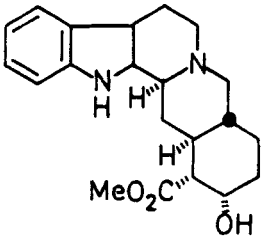
Generally, the use of trifluoroacetic acid does not give much N-trifluoroethylation; however, if this becomes a problem (entry 6), then $NaBH_3CN$ can be substituted for $NaBH_4$. Alternatively, lesser amounts of $NaBH_4$ (or KBH_4) may be used (entry 8).

As discussed in Section II, the reduction can be highly stereoselective giving product resulting from axial protonation and hydride delivery from an equatorial direction (entries 4, 5, 8). However, in simple indole systems there is virtually no stereoselectivity (entries 9, 10).

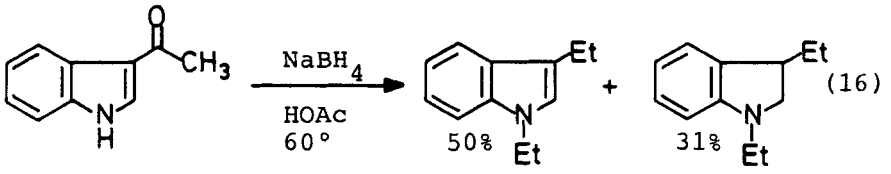
Indole itself undergoes an interesting reaction with $NaBH_4/CF_3CO_2H$, which will be discussed in Section XIX.

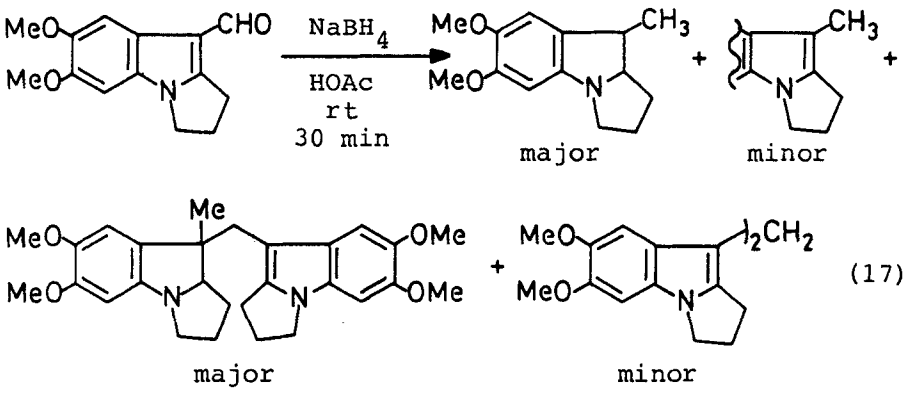
TABLE 5. Reduction of Indoles

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_3CN$ HOAc rt	86%	40
2			$NaBH_4$ HOAc rt, 30 min	100%	41
3			$NaBH_3CN$ HOAc rt	78%	42
4			$NaBH_4$ CF_3CO_2H 0°	90%	11,43
5			$NaBH_3CN$ MeOH CF_3CO_2H	82%	44
6			$NaBH_3CN$ CF_3CO_2H ($NaBH_4$ CF_3CO_2H)	81% (35%)	45

7			$NaBH_4$ CF_3CO_2H 0°-10°	67%	46
8	 R = Me, Cl, F, Br, CO_2Et		1-2 moles KBH_4 (or $NaBH_4$) CF_3CO_2H	80%	47
9		 60:40 trans/cis	$NaBH_4$ CF_3CO_2H	>95% (gc)	48
10		 56:44 trans/cis	$NaBH_3CN$ CF_3CO_2H	84%	49
11			$NaBH_4$ (or $NaBH_3CN$) CF_3CO_2H	80-100%	35,50

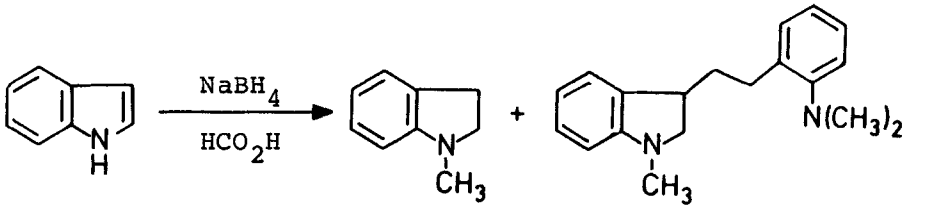
The reaction of 3-acylindoles with $NaBH_4/RCO_2H$ can take a complicated course (Eq. 16[51] and 17[41]).





(17)

Likewise, the reaction of indole with $NaBH_4/HCO_2H$ gives, in addition to the expected N-methylindoline (Eq. 14),[11] the dimeric product shown in Eq. 18.[52] This aberrant pathway has not been observed with other carboxylic acids.

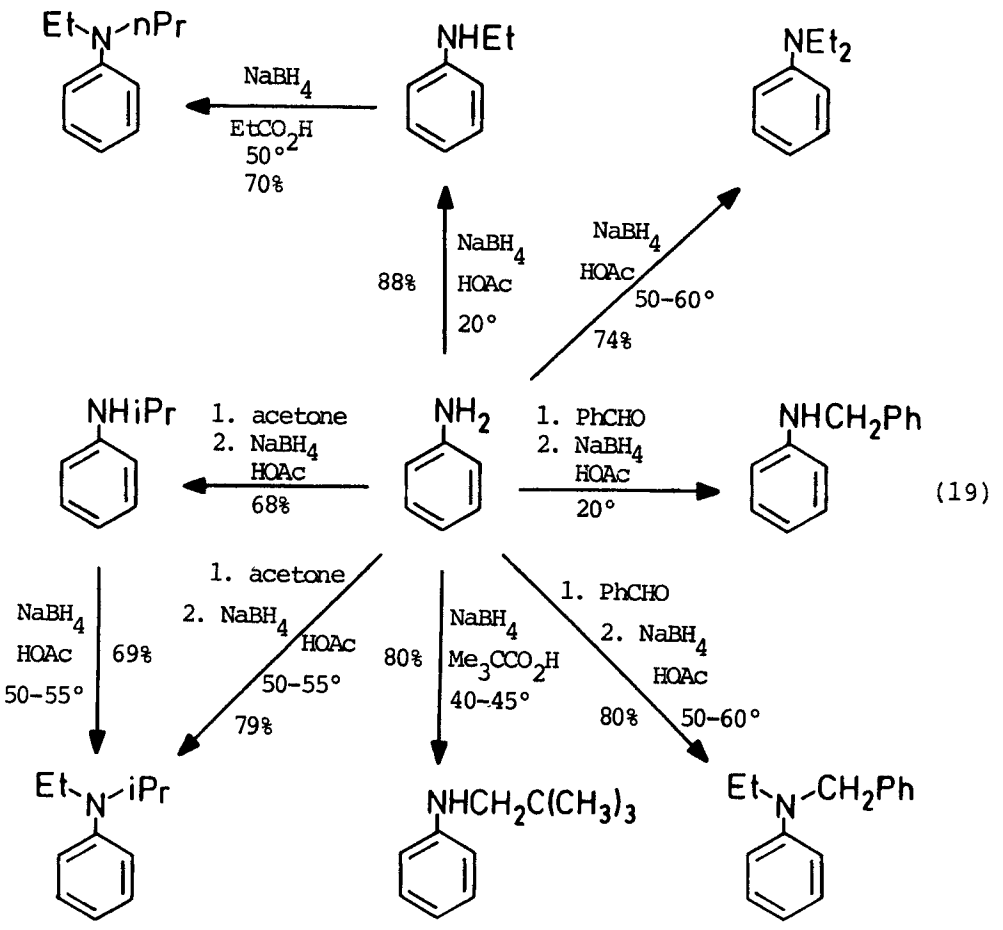


(18)

VI. N-ALKYLATION OF AMINES

Perhaps the most extraordinary property of the $NaBH_4/RCO_2H$ reagent is its ability to N-alkylate amines, alluded to several times earlier. We believe that the mechanism for this transformation involves self-reduction of the acyloxyborohydride species to give free aldehyde (or its synthetic equivalent) followed by condensation with the amine and reduction to the N-alkylated amine.[11]

The power and versatility of this amine alkylation methodology is illustrated in Eq. 19.[11,51]



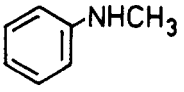
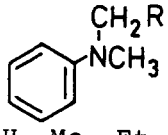
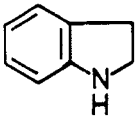
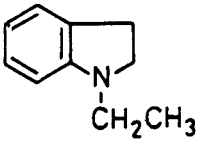
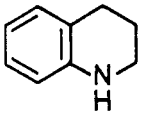
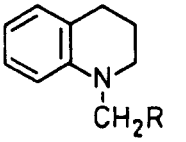
(19)

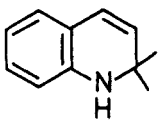
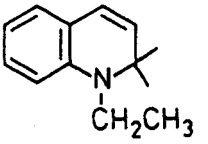
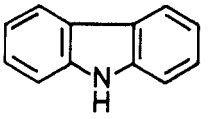
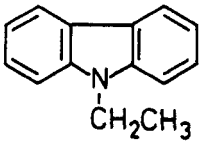
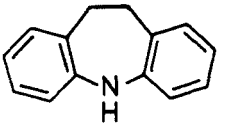
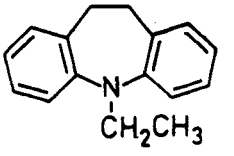
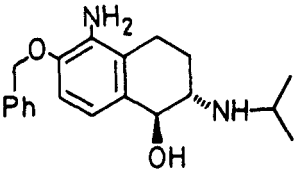
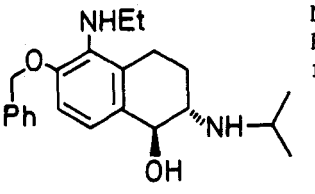
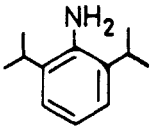
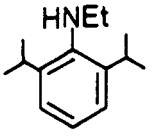
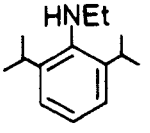
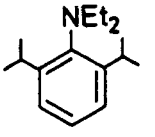
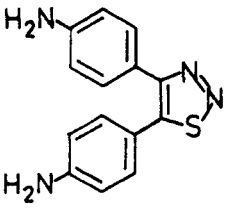
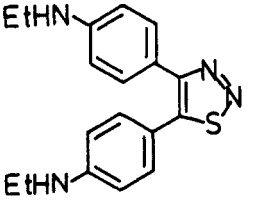
Thus, one can prepare unsymmetrical tertiary amines from primary amines in one pot, introduce the very bulky neopentyl group using pivalic acid, control the reaction (in some cases) so as to stop at the secondary amine stage, and use ketones so as to introduce secondary alkyl groups.

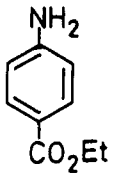
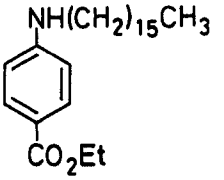
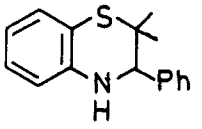
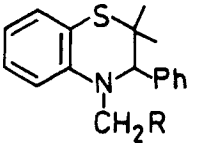
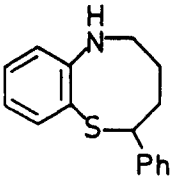
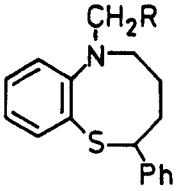
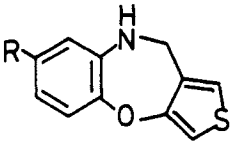
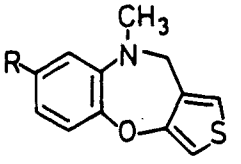
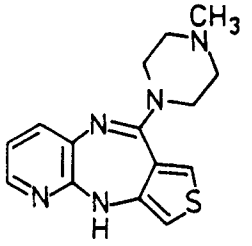
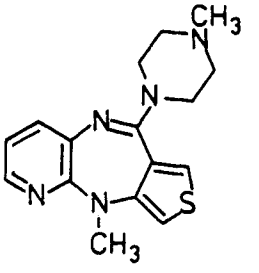
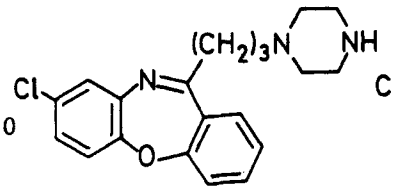
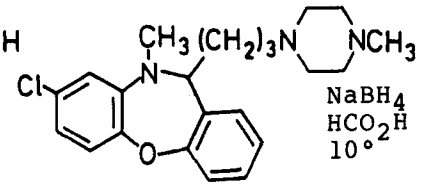
Simultaneously and independently of our own work,[11] Marchini and coworkers[12] also discovered this amine N-alkylation and extended it to the use of solid carboxylic acids in cosolvents. This important contribution as well as other examples of this amine N-alkylation are tabulated in Tables 6 (aromatic amines) and 7 (aliphatic amines).

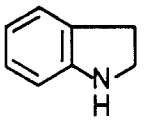
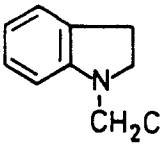
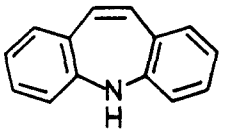
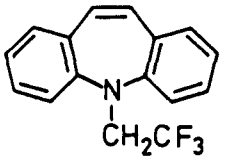
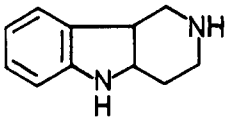
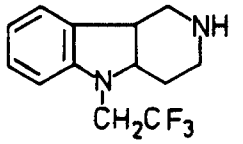
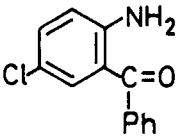
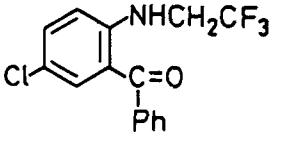
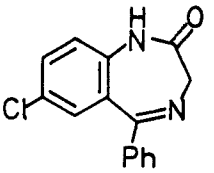
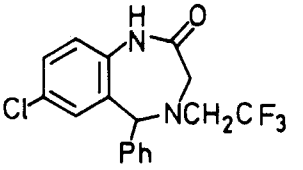
The N-alkylation of aromatic amines works equally well for nonbasic amines (entries 6-9), can be made chemoselective in the presence of an aliphatic amine (which requires higher temperatures for N-alkylation, cf., Table 7) (entries 10, 11, 23), and can be controlled so as to give mono- or dialkylation (entries 10-14). Moreover, a variety of functional groups (hydroxyl, alkene, carboethoxy, sulfur, amide, aryl ketone) and heterocyclic rings (pyridine, thiophene, thiadiazole) are unaffected by the appropriate $NaBH_4/RCO_2H$ conditions. In contrast to other carboxylic acids, trifluoroacetic acid gives lower yields of N-trifluoroethylation in most cases (entries 21-25).

TABLE 6. N-Alkylation of Aromatic Amines

Entry	Substrate	Product	Conditions	Yield	Ref.
1		 R = H, Me, Et	$NaBH_4$ RCO_2H	72-83%	11
2	"	" R=Ph	$NaBH_4$ toluene $PhCO_2H$ Δ	90%	12
3			$NaBH_4$ HOAc 50-60°	88%	11
4		 R = Me, Et	$NaBH_4$ RCO_2H THF	68-83%	53

5			$NaBH_4$ HOAc 50-55°	85%	51
6	Ph_2NH	$Ph_2NCH_2CH_3$	$NaBH_4$ HOAc 60°	80%	11
7	"	$Ph_2NCH_2CH_2Cl$	$NaBH_4$ $ClCH_2CO_2H$	90%	12
8			$NaBH_4$ HOAc	92%	11
9			$NaBH_4$ HOAc 60°	72%	11
10			$NaBH_4$ HOAc rt, 7 hr	63%	54
11	"		$NaBH_4$ HOAc rt, 5 days	71%	54
12			$NaBH_4$ HOAc 20°	89%	51
13			$NaBH_4$ HOAc 60°	81%	51
14			$NaBH_4$ HOAc 15°	44%	55

15			$NaBH_4$ $CH_3(CH_2)_{14}CO_2H$	"low yield"	56
16		 R = H, Me	$NaBH_4$ RCO_2H	70-95%	12
17		 R = H, Me	$NaBH_4$ RCO_2H	92%	57
18	 R = H, Me, Cl		$NaBH_4$ HCO_2H 0°	17-52%	58
19	 (others)		$NaBH_4$ HCO_2H	--	58
20			$NaBH_4$ HCO_2H 10°	58%	28

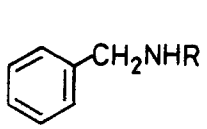
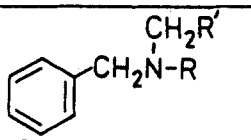
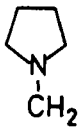
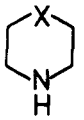
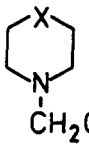
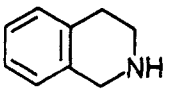
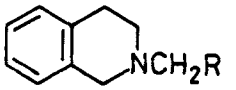
21			$NaBH_4$ CF_3CO_2H	7%	11,59
22			$NaBH_4$ CF_3CO_2H	61%	59
23			KBH_4 CF_3CO_2H	89%	47
24			$NaBH_4$ CF_3CO_2H toluene Δ	64%	13
25			$NaBH_4$ CF_3CO_2H 20°, 4 hr	25%	13

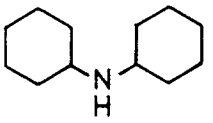
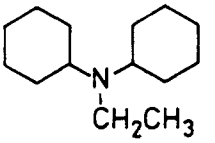
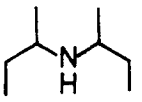
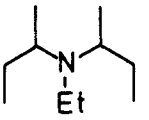
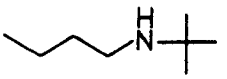
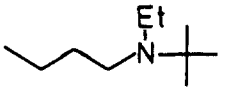
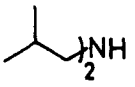
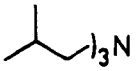
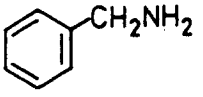
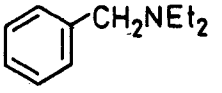
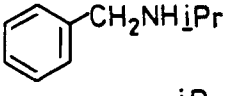
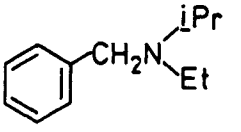
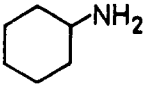
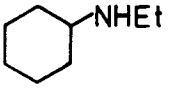
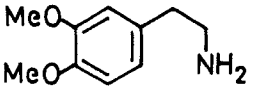
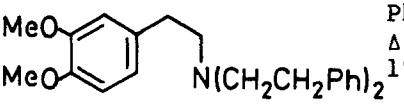
The N-alkylation of aliphatic amines using $NaBH_4/RCO_2H$ is tabulated in Table 7. It has proven to be a very general method with both primary and secondary amines and a variety of carboxylic acids (neat or in a cosolvent such as benzene). Hindered amines alkylate poorly (entries 8-10) or not at all (entry 28). The use of a ketone allows for the introduction of a secondary alkyl group (entry 13) or for the introduction of two different alkyl groups in converting a primary amine to a tertiary amine (entry 14). In some cases one can achieve N-monoalkylation of a primary amine (entries 15, 21).

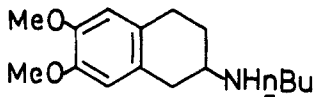
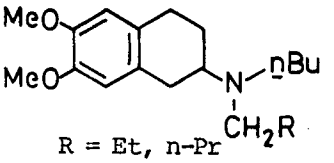
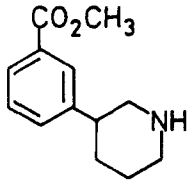
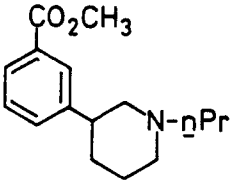
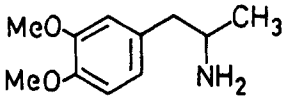
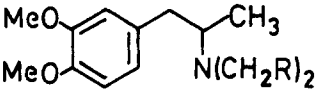
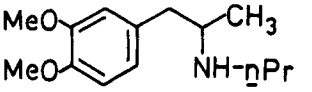
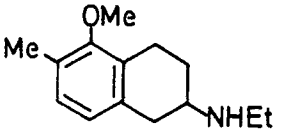
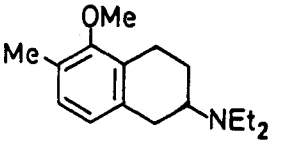
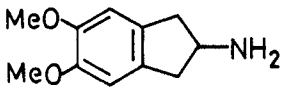
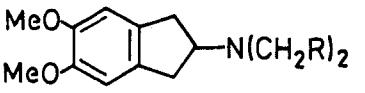
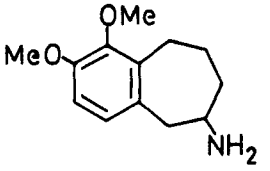
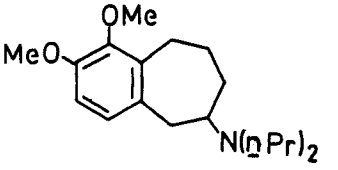
The Marchini modification[12] using benzene as a cosolvent has been widely used (entries 17-27) by three groups[62-72] to synthesize an array of dopamine analogues.

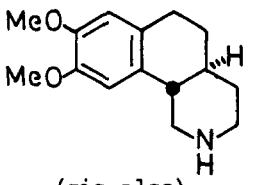
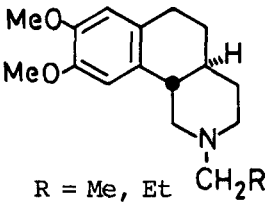
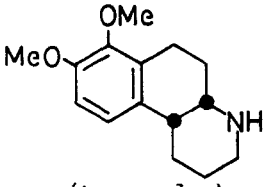
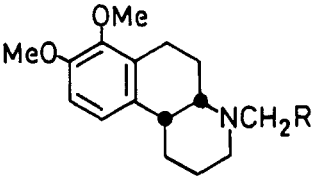
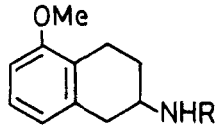
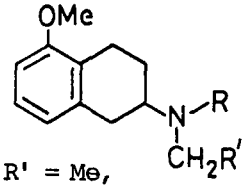
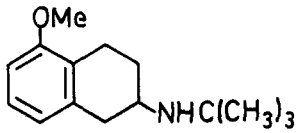
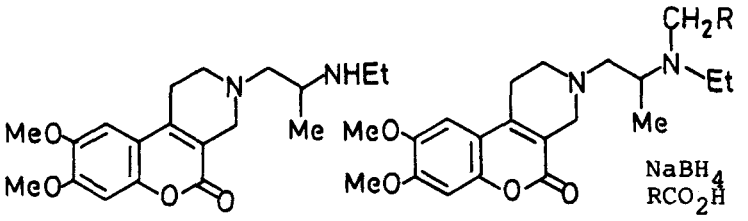
Fewer examples of N-methylation of aliphatic amines using $NaBH_4/HCO_2H$ have been reported (Table 6, entry 20), perhaps because alternative, well-established methods exist (e.g., $HCHO/NaBH_3CN$) and the reaction of $NaBH_4$ with neat formic acid is exceptionally vigorous and unpleasant to conduct.

TABLE 7. N-Alkylation of Aliphatic Amines

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 R = Me, Et, CH_2Ph, i-Pr, t-Bu	 R' = Me, Et, n-Pr, i-Pr, t-Bu	$NaBH_4$ $R'CO_2H$ 50-55°	62-84%	60
2			$NaBH_4$ HOAc 50-55°	74%	60
3	 X = CH_2, O, NMe		$NaBH_4$ HOAc 50-55°	69-84%	60
4	$(CH_3)_2NH_2Cl$	$(CH_3)_2N(CH_2)_8CH_3$	$NaBH_4$ $CH_3(CH_2)_7CO_2H$ THF NaOAc 50-55°	78%	60
5	$(CH_3CH_2)_2NH$	$(CH_3CH_2)_2N(CH_2)_7CH_3$	$NaBH_4$ $CH_3(CH_2)_6CO_2H$ 50-55°	70%	60
6		 R = Me, Et	$NaBH_4$ RCO_2H	58-65%	53

7	nBu$_2$NH	nBu$_2$NEt	$NaBH_4$ HOAc 80°, 3 hr	80%	12
8			$NaBH_4$ HOAc 50-55°	14%	60
9			$NaBH_4$ HOAc 50-55°	13%	60
10			$NaBH_4$ HOAc 50-55°	9%	60
11			$NaBH_4$ i-Pr-CO_2H	90%	51
12			$NaBH_4$ HOAc 50-55°	66%	60
13	"		$CH_3\overset{O}{\overset{\|}{C}}CH_3$ $NaBH_4$ HOAc 25°	84%	60
14	"		1. CH_3COCH_3 $NaBH_4$ HOAc, 25° 2. 50-55°	82%	60
15			$NaBH_4$ HOAc 45°, 4 hr	61%	51
16	$(CH_3)_2NH$	$(CH_3)_2N(CH_2)_{12}N(CH_3)_2$	$NaBH_4$ $HO_2C(CH_2)_{10}CO_2H$	21%	61
17			$NaBH_4$ $PhCH_2CO_2H$ PhH Δ 19 hr	51%	62

18		 R = Et, n-Pr	$NaBH_4$ RCO_2H PhH Δ 3 hr	80-86%	62
19			$NaBH_4$ $EtCO_2H$ PhH Δ	72%	63
20		 R = Me, Et, n-Pr	(15 molar equiv.) $NaBH_4$ RCO_2H PhH Δ, 16 hr	54-87%	64
21	"		(2 molar equiv.) $NaBH_4$ $EtCO_2H$ PhH Δ, 16 hr	38%	64
22			$NaBH_4$ HOAc PhH Δ	96%	65
23		 R = Me, Et	$NaBH_4$ RCO_2H PhH 20 hr, Δ	53-75%	66
24			$NaBH_4$ $EtCO_2H$ PhH CH_2Cl_2	43%	67

25	 (cis also)	 R = Me, Et	$NaBH_4$ RCO_2H PhH, Δ	83-86%	68
26	 (trans also)	 R = Me, Et	$NaBH_4$ RCO_2H PhH Δ	89-91%	69
27	 R = Me, Et, n-C_5H_{11}, n-Pr, i-Pr	 R' = Me, Et, CH_2Ph	$NaBH_4$ RCO_2H PhH Δ 5 hr	46-98%	70
28		—	$NaBH_4$ $EtCO_2H$	failed	70
29	 R = Me, Et, Pr, i-Bu		$NaBH_4$ RCO_2H	20-54%	132

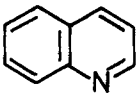
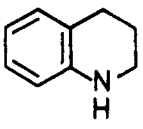
VII. REDUCTION AND REDUCTION/N-ALKYLATION OF π-DEFICIENT HETEROCYCLES

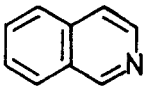
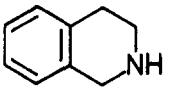
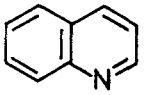
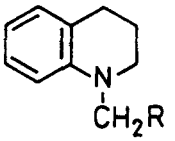
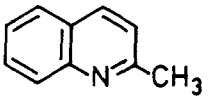
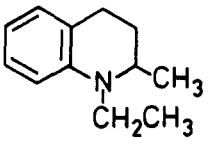
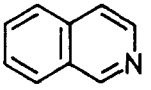
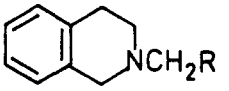
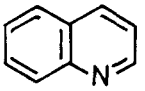
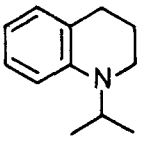
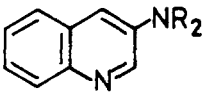
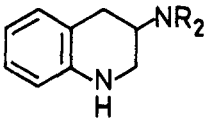
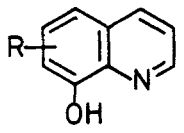
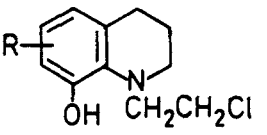
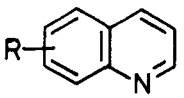
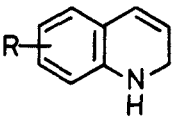
Following an early report by Rao and Jackman[73] on the reduction of nitroquinolines and related compounds with $NaBH_4$/ HOAc, numerous examples of the reduction of π-deficient

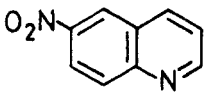
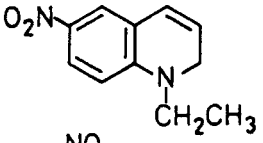
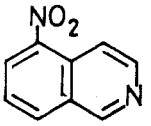
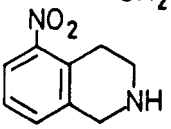
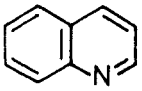
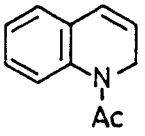
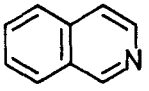
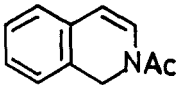
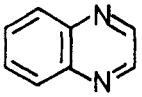
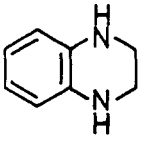
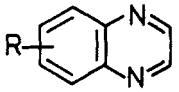
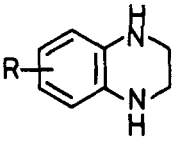
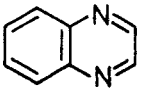
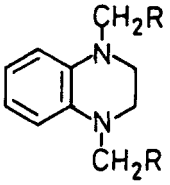
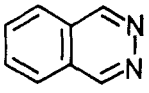
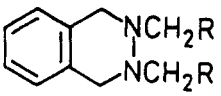
heterocycles using this methodology have been disclosed (Table 8). As has been seen earlier, the reaction can be controlled by changing either the borohydride reagent or the temperature to give reduction with or without N-alkylation (entries 1 and 3, 2 and 5, 9 and 10, 14 and 16, 19 and 20, 24 and 25). A ketone can be employed to give a secondary N-alkyl group (entry 6). Only in the case of nitroquinolines does the reduction stop at the 1,2-dihydroquinoline stage (entries 9, 10), although, in the presence of acetic anhydride, the 1,2-dihydro heterocycles can be trapped in the case of quinoline and isoquinoline (entries 12-13). The reduction of quinoline and isoquinoline with $NaBH_4/CF_3CO_2H$ (not shown in Table 8) gives a mixture of the corresponding 1,2,3,4-tetrahydro heterocycle and the N-trifluoroethylated derivative (17-21%).[53]

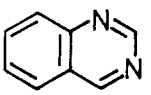
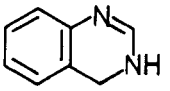
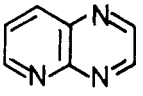
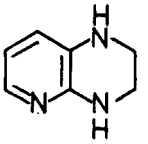
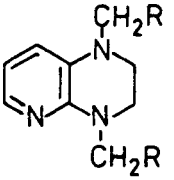
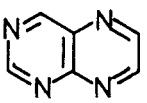
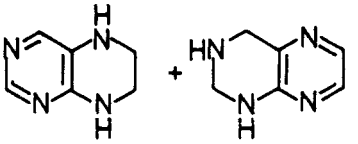
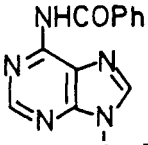
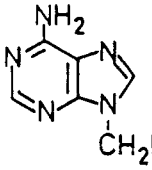
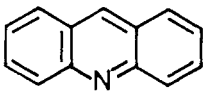
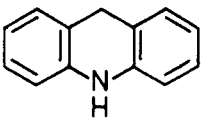
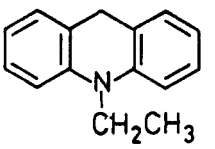
Although pyridine is not reduced with $NaBH_4/RCO_2H$, under conditions thus far investigated,[51] pyridines containing 3,5-electron-withdrawing groups are smoothly reduced to the 1,4-dihydro compounds with $NaBH_3CN$/HOAc (entries 27-29) but not with $NaBH_4$/HOAc (entry 26).

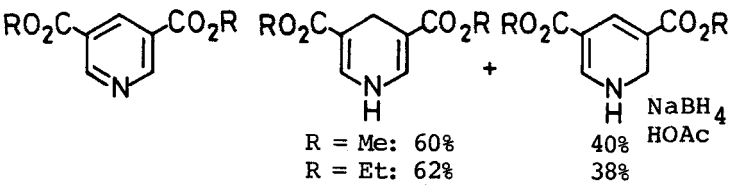
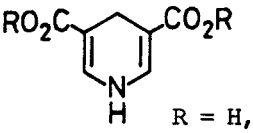
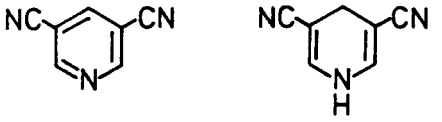
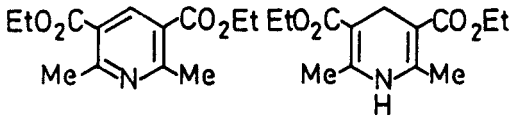
TABLE 8. Reduction and Reduction/N-Alkylation of π-Deficient Heterocycles

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_3CN$ HOAc 50°, 1 hr	71%	53

2			$NaBH_3CN$ HOAc 50°, 1 hr	71% 53
3		 R = H, Me, Et	$NaBH_4$ RCO_2H 50°	52-68% 53
4			$NaBH_4$ HOAc 50°, 2.5 hr	65% 53
5		 R = H, Me, Et	$NaBH_4$ RCO_2H 50°	76-79% 53
6			$NaBH_4$ HOAc CH_3COCH_3 50°, 1 hr	59% 53
7	 R = H, Me		$NaBH_3CN$ HOAc 55°, 1.5 hr	44-66% 74
8	 R = H, 6-Me, 5-Cl (2-Me failed)		$NaBH_4$ $ClCH_2CO_2H$ THF	45-68% 75
9	 R = 5, 6, 7, 8-NO_2		$NaBH_4$ HOAc 5°	67-90% 73

10			$NaBH_4$ HOAc 50°	44%	53
11			$NaBH_4$ HOAc 5°	65%	73
12			$NaBH_4$ HOAc Ac_2O 60°, 2 hr	72%	76
13			$NaBH_4$ HOAc Ac_2O 60°, 2 hr	80%	76
14			$NaBH_4$ CF_3CO_2H THF rt, 1 hr	90%	77
15	 R = 5-NO_2, 6-NO_2, 6-CN, 6-CF_3, 6-CO_2Et		$NaBH_4$ HOAc 5°	43-87%	73
16		 R = H, Me, Et	KBH_4 RCO_2H Δ, 6 hr	70-87%	78
17		 R = H, Me, Et	KBH_4 RCO_2H Δ, 6 hr	41-97%	78

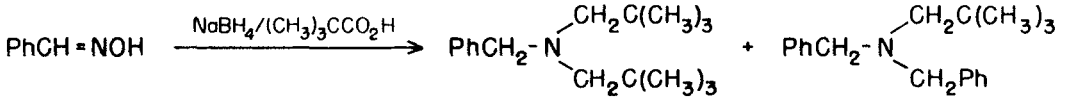
18			$NaBH_4$ CF_3CO_2H THF rt, 1 hr	85%	77
19			$NaBH_4$ CF_3CO_2H THF rt, 1 hr	75%	77
20	"	 R = H, Me, Et	KBH_4 RCO_2H Δ, 6 hr	43-66%	78
21		 58% 38%	$NaBH_4$ CF_3CO_2H THF rt, 1 hr	96%	77
22	 R = CH_2Ph, sugar		$NaBH_4$ HOAc rt, 20 min	58-75%	79
23		—	$NaBH_4$ HOAc rt, 20 min	failed	79
24			$NaBH_4$ HOAc 20°	96%	51
25	"		$NaBH_4$ HOAc 75°	82%	51

26	 R = Me: 60% 40% R = Et: 62% 38%	$NaBH_4$ HOAc	57-76%	80
27	 R = H, Me, Et	$NaBH_3CN$ HOAc	74-77%	80
28		$NaBH_3CN$ HOAc	98%	80
29		$NaBH_3CN$ HOAc	60%	80

VIII. REDUCTION AND REDUCTION/N-ALKYLATION OF OXIMES

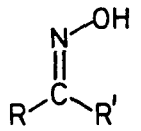
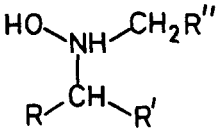
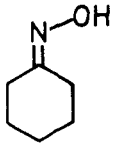
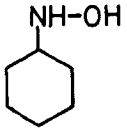
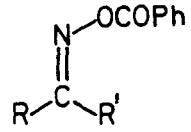
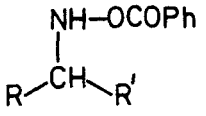
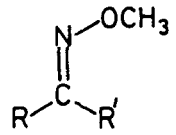
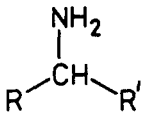
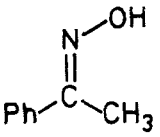
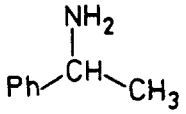
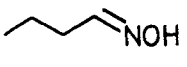
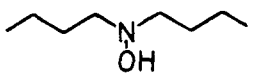
Depending on the reaction conditions, oximes can be reduced either to N-monoalkylhydroxylamines or N,N-dialkylhydroxylamines, and oxime ethers can be reduced to primary amines (Table 9). The unsymmetrical dialkylhydroxylamines so prepared would be very difficult to synthesize other ways.

In some cases, aberrant reaction products are obtained, especially with aldoximes, where the initially-formed monoalkylhydroxylamine condenses with the oxime leading, after reduction, to the symmetrical dialkylhydroxylamine where both alkyl groups derive from the oxime (entry 6). Another side reaction is overreduction and subsequent alkylation, an example of which is shown in Eq. 20.[81] Note that this particular reaction also gives a product of the type formed in entry 6.



(20)

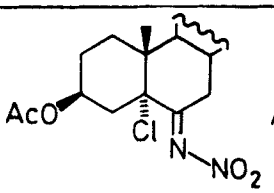
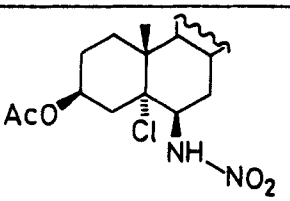
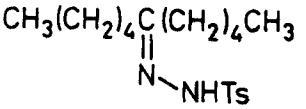
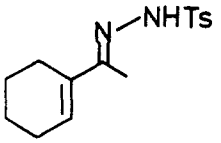
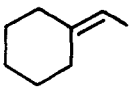
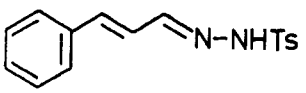
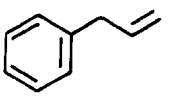
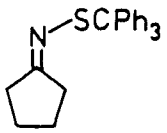
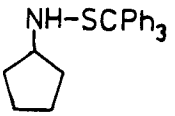
TABLE 9. Reduction and Reduction/N-Alkylation of Oximes, Oxime Ethers, and Oxime Esters

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ $R''CO_2H$ 40-50° 4-5 hr	36-87%	81
	R = H, Me R' = Me, Et, t-Bu, Ph, CH_2-Ph, n-Pr R,R' = $-(CH_2)_5-$ R" = Me, Et, i-Pr, n-Pr				
2			$NaBH_3CN$ HOAc 25°	81%	81
			($NaBH_4$ HOAc 25°)	(63%)	
3			$NaBH_3CN$ HOAc 20°	70-92%	82
	R = CH_2Ph, R' = Me R,R' = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_{11}-$				
4			$NaBH_4$ CF_3CO_2H THF Δ, 2 hr	81-91%	83
	R = Ph, n-C_9H_{19}, CH_2CH_2Ph R' = Me, H, Ph R,R' = $-(CH_2)_5$, $-(CH_2)_6-$				
5			$NaBH_4$ CF_3CO_2H diglyme Δ, 5 hr	51%	83
6			$NaBH_4$ HOAc 40-50° 2 hr	21%	81

IX. REDUCTION OF OTHER C=N COMPOUNDS

As might be anticipated from the results in the previous Section, a smattering of other C=N species have been reduced with $NaBH_4/RCO_2H$. These are tabulated in Table 10. Noteworthy is the convenient reductive deoxygenation of carbonyl compounds via their tosylhydrazones as developed by Hutchins and Natale[85] (entries 2-4).

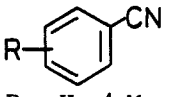
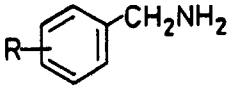
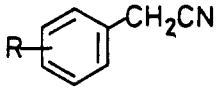
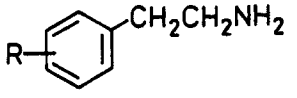
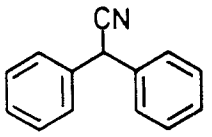
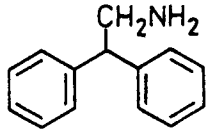
TABLE 10. Reduction of Other C=N Compounds

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 (others)		$NaBH_4$ HOAc dioxane EtOH rt	76%	84
2	 (others)	$CH_3(CH_2)_9CH_3$	$NaBH_4$ HOAc 70° 1-2 hr	84%	85
3	 (others)		$NaBH_4$ HOAc 70° 1-2 hr	72%	85
4			$NaBH_4$ HOAc 70°, 1-2 hr	56%	85
5	 (others)		$NaBH_3CN$ CF_3CO_2H THF	97%	86

X. REDUCTION OF NITRILES

Although nitriles are not reduced under conditions which produce $NaBH(OCOR)_3$ (Table 8, entries 15 and 28; Table 15, entry 1), Umino and coworkers[87] have shown that nitriles are smoothly reduced to primary amines with $NaBH_3OCOCF_3$ (*in situ*) in THF at rt (Table 11). The reduction is poor with $NaBH_3OAc$.

Table 11. Reduction of Nitriles

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 R = H, 4-Me, 4-CO_2Me, 3-NO_2		$NaBH_4$ CF_3CO_2H THF 20°, 4 hr	76-89%	87
2	 R = H, 4-NO_2, 4-Cl		$NaBH_4$ CF_3CO_2H THF 20°, 4 hr	70-71%	87
3			$NaBH_4$ CF_3CO_2H THF 20°, 4 hr	70%	87

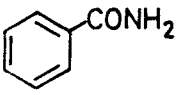
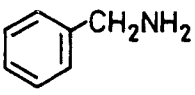
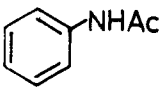
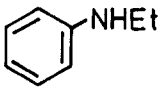
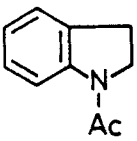
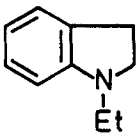
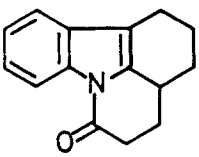
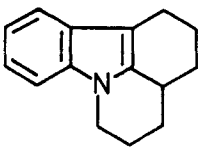
XI. REDUCTION OF AMIDES AND CARBAMATES

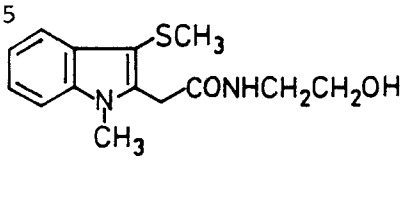
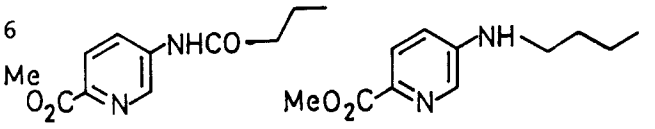
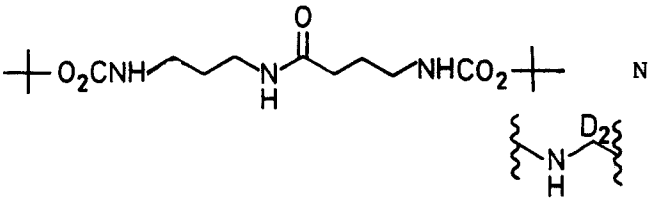
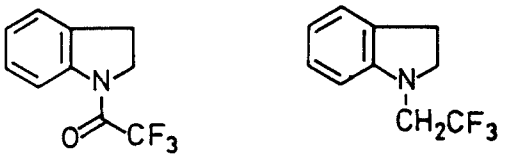
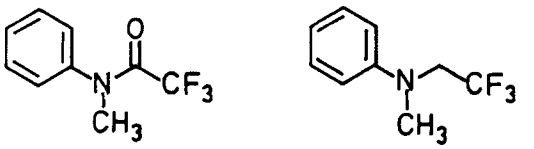
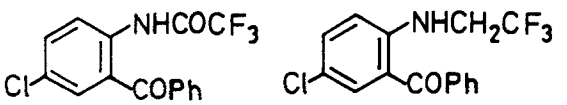
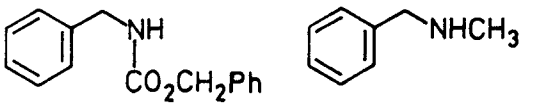
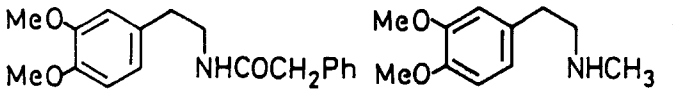
As is the case with nitriles (*vide supra*), amides are not reduced under conditions which produce $NaBH(OCOR)_3$. For example, we determined that 1-acetylindole and 1-acetylindoline were not reduced to 1-ethylindoline to any appreciable extent under conditions which convert indole to 1-ethylindoline in high yield ($NaBH_4$, excess HOAc).[11] For other examples of

amides (and similar carbonyls) that are not reduced under these conditions, see Table 3, entries 2, 3, 5; Table 4, entries 5, 7, 8, 14-16; Table 6, entry 25; Table 15, entries 1, 15.

However, Umino and coworkers[88] have shown that the more reactive $NaBH_3OCOR$ (R = CH_3, CF_3) are capable of reducing amides and carbamates to amines (Table 12). Tertiary amides require $NaBH_3OCOCF_3$ for reduction (entries 3, 4), whereas primary and secondary amides are reduced by $NaBH_3OAc$. Although carbamates can also be reduced under these conditions (entries 11, 12), the t-BOC protecting group survived intact in the reduction of an amide with $NaBD_3OCOCF_3$ (entry 7).

TABLE 12. Reduction of Amides

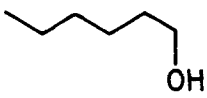
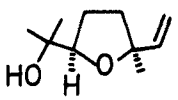
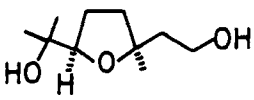
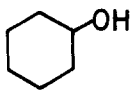
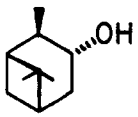
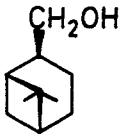
Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ CH_3CO_2H dioxane Δ, 4 hr	76%	88
2			$NaBH_4$ CH_3CO_2H dioxane Δ, 1 hr	88%	88
3			$NaBH_4$ CF_3CO_2H dioxane Δ, 5 hr	64% (28% with HOAc)	88
4			$NaBH_4$ CF_3CO_2H THF Δ, 4 hr	83%	89

5		$NaBH_4$ HOAc dioxane Δ, 2 hr	80%	90
6		$NaBH_4$ HOAc dioxane Δ, 30 min	69%	91
7		$NaBD_3O_2CCF_3$	--	92
8		$NaBH_4$ CF_3CO_2H THF	58%	59
9		$NaBH_4$ CF_3CO_2H THF	32%	59
10		$NaBH_4$ CF_3CO_2H tol, 6 hr 30-40°	76%	13
11		$NaBH_4$ HOAc dioxane Δ, 5 hr	66%	88
12		$NaBH_4$ HOAc dioxane Δ, 5 hr	82%	88

XII. HYDROBORATION OF ALKENES

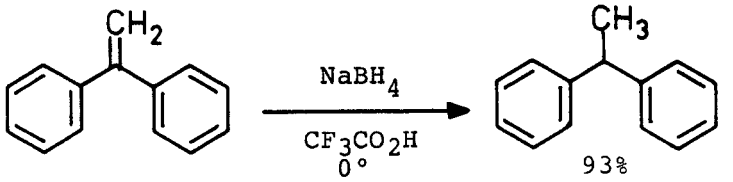
The second reported use of $NaBH_4/RCO_2H$ in synthesis--also described by Marshall and Johnson[93]--was the hydroboration of alkenes. Although this method has not been widely used as such, several examples are known (Table 13). It is presumed that the hydroborating agent is $NaBH_3OAc$ from the work of Hach[95] who optimized the reaction conditions. This would explain the apparent lack of hydroboration of alkenes under conditions that generate $NaBH(OCOR)_3$ (e.g., Table 6, entry 5; Table 10, entries 3, 4).

TABLE 13. Hydroboration of Alkenes

Entry	Substrate	Product	Conditions	Yield	Ref.
1			1. $NaBH_4$ HOAc THF 2. H_2O_2, OH^-	75%	93
2			1. $NaBH_4$ HOAc THF 2. H_2O_2, OH^-	79%	94
3	 (others)		1. $NaBH_4$ HOAc THF 10-20° 2. H_2O_2, OH^-	85%	95
4	 (others)		1. $NaBH_4$ THF HOAc, 20° 2. H_2O_2, OH^-	73%	96a
5			1. $LiBH_4$ THF, 20° HOAc 2. H_2O_2, OH^-	95%	96a

XIII. REDUCTION OF ALKENES

A second reaction of alkenes with $NaBH_4/RCO_2H$ that has been observed in one case is reduction (Eq. 21).[97] Thus far, this alkene reduction is restricted to alkenes that can form a resonance-stabilized carbocation (e.g., doubly benzylic) in trifluoroacetic acid (TFA).



(21)

The use of TFA in this regard is discussed further in the next two sections.

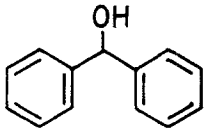
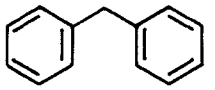
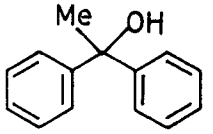
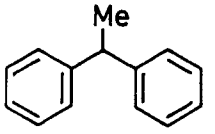
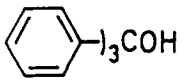
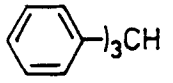
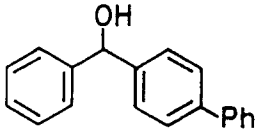
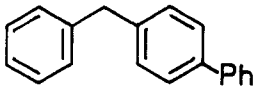
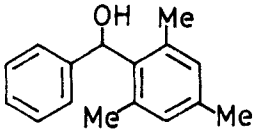
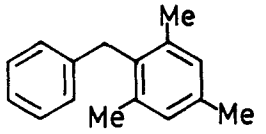
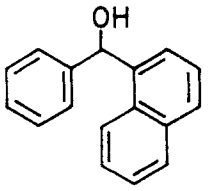
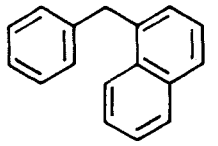
XIV. REDUCTION OF ALCOHOLS

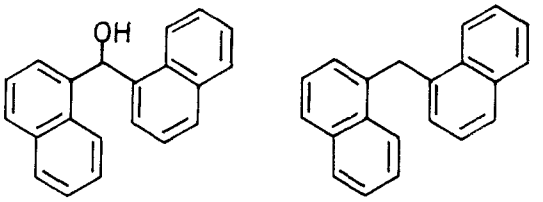
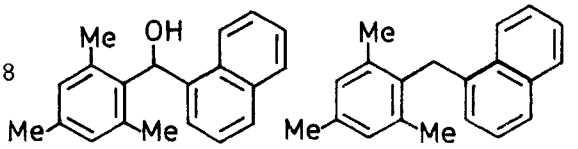
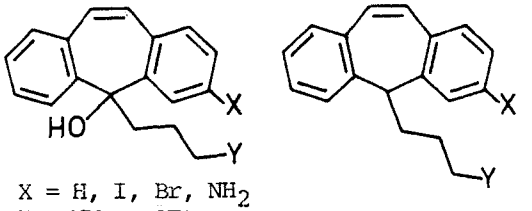
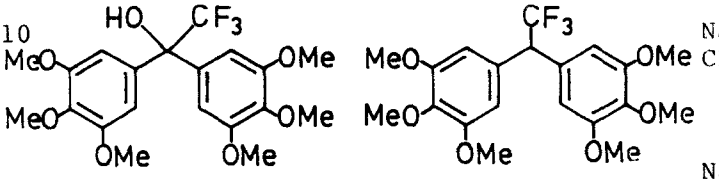
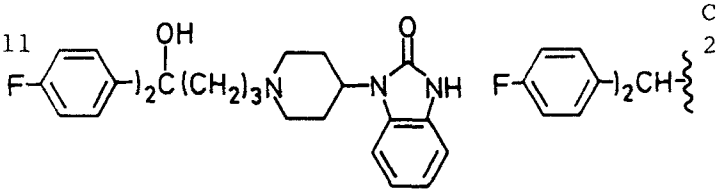
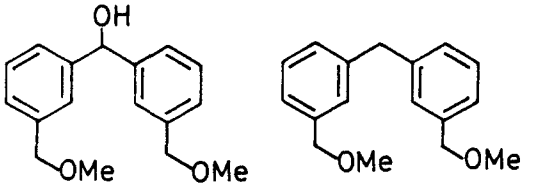
Trifluoroacetic acid, which is an excellent solvent for solvolysis and other S_N1 reactions (ionizing power Y value = 1.84[98]), proves to be an ideal solvent with which to reduce diarylmethanols and triarylmethanols to the corresponding hydrocarbons with $NaBH_4$.[97] This reduction method has proven to be exceedingly general and highly efficient (Table 14). Although yields are generally lower for monobenzylic alcohols (entries 20-22), in some cases it has been very successful (entries 17, 18). Reduction of benzyl alcohol, 1- and 2-octanol, and 1-methylcyclohexanol under these conditions is not observed.[97] The reduction is very slow or fails in glacial HOAc, at least with triphenylmethanol.[97]

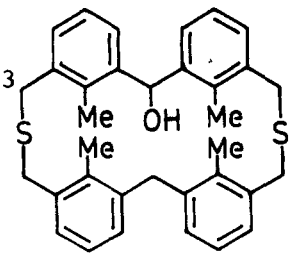
In most of the cases that we have studied,[97] the reaction is complete in seconds and can be monitored visually. Thus, the carbocation, which is usually highly colored, forms instantly as the alcohol is added to the suspension of $NaBH_4$

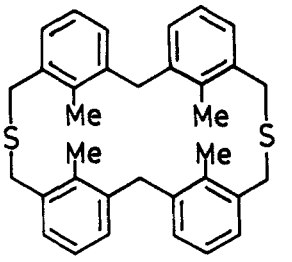
in TFA, but then is rapidly quenched (color disappears) to give product. In one case (entry 19), the intermediate carbocation cyclizes faster than it undergoes reduction. In the case of several monobenzylic alcohols (entries 20-22), other products, resulting from dehydration and dimerization (entries 20, 21) or alkylation of the product by the carbocation (entry 22), are observed.

TABLE 14. Reduction of Alcohols

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ CF_3CO_2H 15-20°	93%	97
2			$NaBH_4$ CF_3CO_2H 0° 5 min	97%	97
3			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	99%	97
4			$NaBH_4$ CF_3CO_2H 15-20° CH_2Cl_2	94%	97
5			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	90%	97
6			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	86%	97

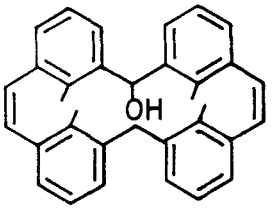
7		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	94%	97
8		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	77%	97
9	 X = H, I, Br, NH_2 Y = NMe_2, OEt	$NaBH_4$ CF_3CO_2H 0° 5 min	98-100%	97
10		$NaBH_4$ CF_3CO_2H	78%	99
		$NaBH_4$ CF_3CO_2H CH_2Cl_2 2 hr	--	100
11				
12		$NaBH_4$ CF_3CO_2H 0°	94%	101

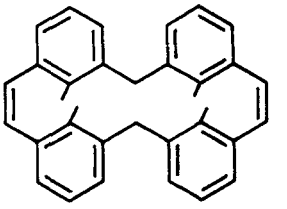
13 



$NaBH_4$
CF_3CO_2H
0°

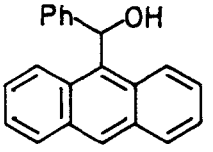
89% 102
(from ketone)

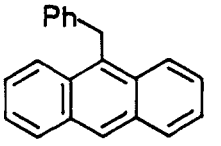
14 

(E,E isomer also)


$NaBH_4$
CF_3CO_2H
0°

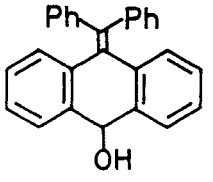
88% 102
(from ketone)

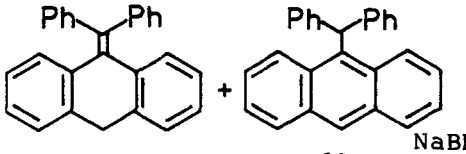
15 



$NaBH_4$
CF_3CO_2H
CH_2Cl_2
0°

95% 103

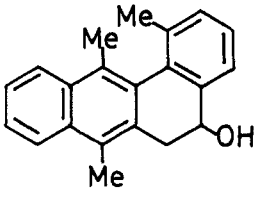
16 

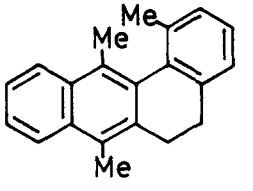


90 : 10

$NaBH_4$
CF_3CO_2H
2 hr
CH_2Cl_2

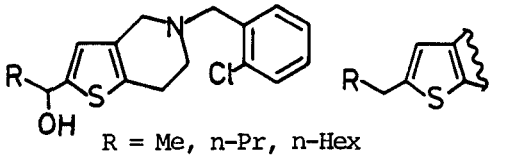
60% 103

17 



$NaBH_4$
CF_3CO_2H

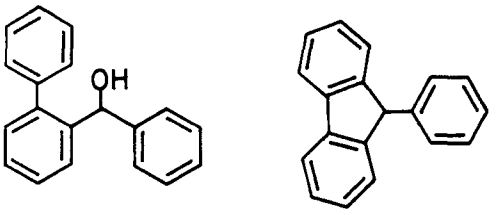
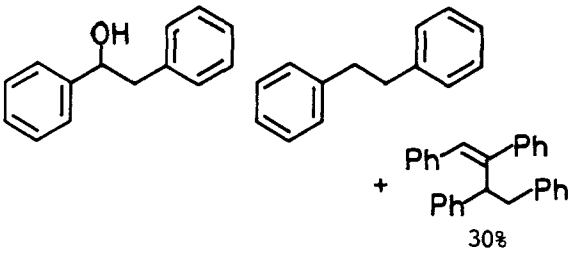
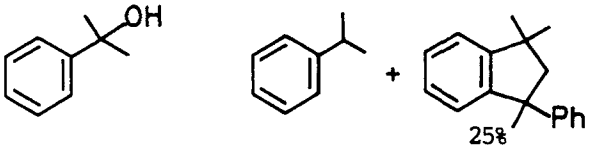
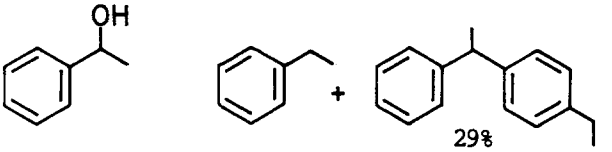
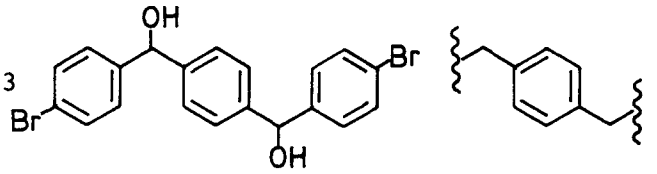
-- 104

18 

R = Me, n-Pr, n-Hex

$NaBH_4$
CF_3CO_2H
CH_2Cl_2
0°

75-82% 105

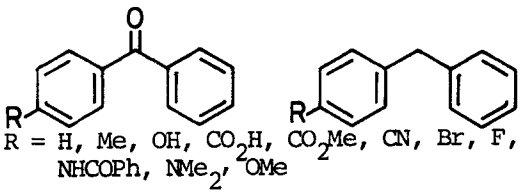
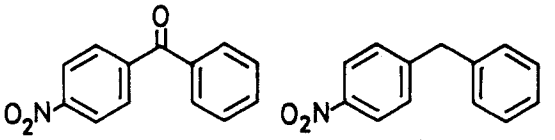
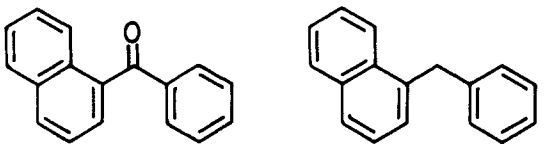
19		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	93%	97
20		$NaBH_4$ CF_3CO_2H 0°	70%	97
21		$NaBH_4$ CF_3CO_2H 15-20°	45%	97
22		$NaBH_4$ CF_3CO_2H 15-20°	9%	97
23		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	97%	51

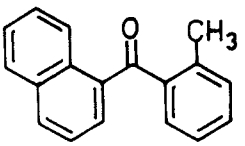
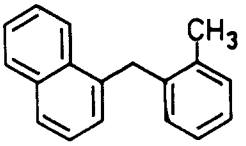
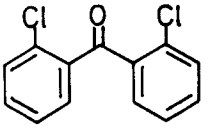
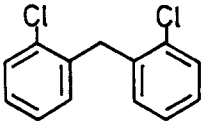
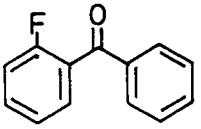
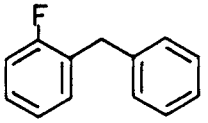
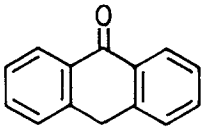
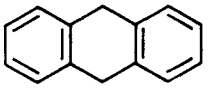
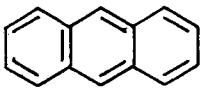
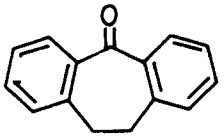
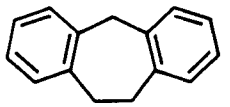
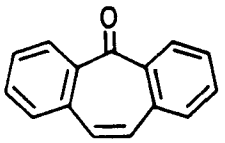
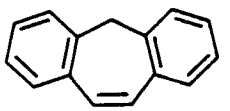
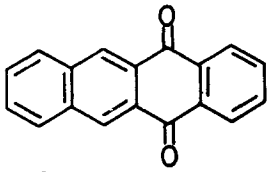
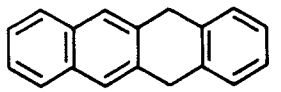
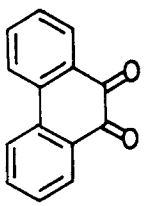
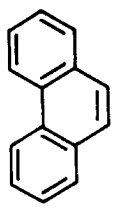
XV. REDUCTION OF KETONES TO HYDROCARBONS

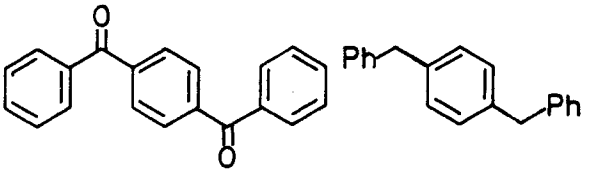
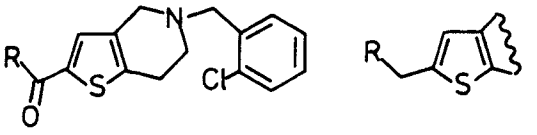
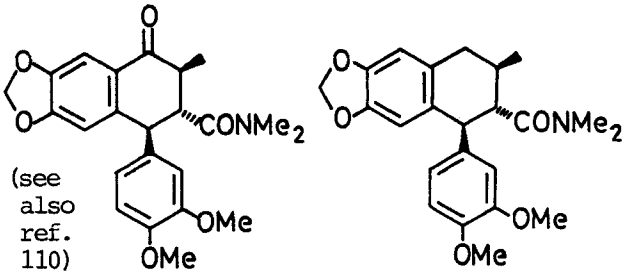
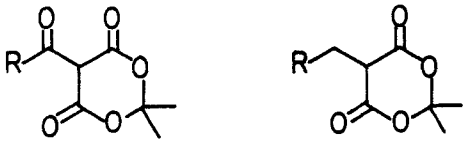
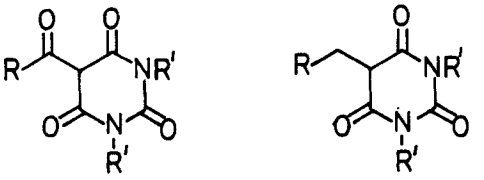
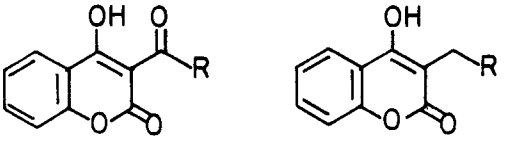
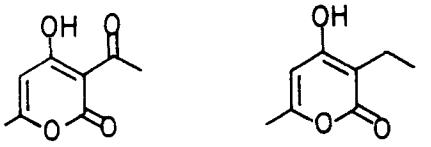
The companion reaction to the reduction of diarylmethanols to diarylmethanes with $NaBH_4$/TFA (Section XIV) is the reduction of diarylketones to diarylmethanes under the same conditions (Table 15). This reaction is very efficient and general, and in some cases works well for monoaryl ketones (entries 14, 15, 22). However, Michler's ketone (4,4'-bis-[dimethylamino]benzophenone) and decafluorobenzophenone fail to

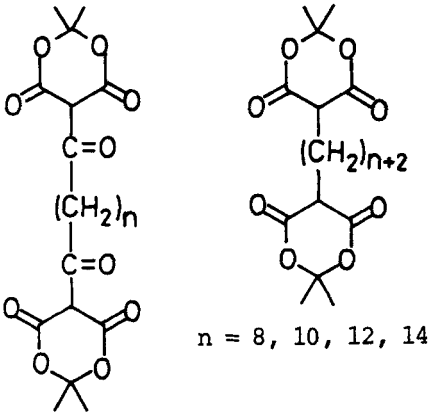
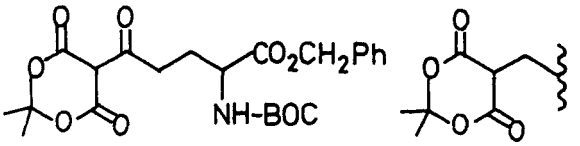
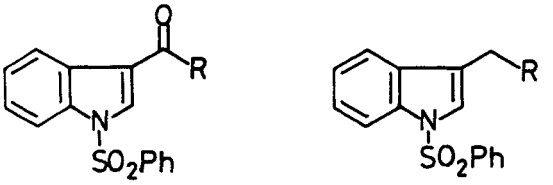
react with $NaBH_4/CF_3CO_2H$, and the reduction of 4-nitrobenzophenone (entry 2) is very slow. Likewise, the sterically hindered diarylketones mesityl phenyl ketone, dimesityl ketone, and mesityl α-naphthyl ketone give little or no reduction product.[106] Depending on the mode of addition, anthrone may be reduced either to dihydroanthracene (entry 7) or to anthracene (entry 8). In unpublished work, we have found that quinones are reduced either to a fully reduced compound (entry 11) or to the corresponding aromatic hydrocarbon (entry 12). 1,4-Naphthoquinone and 9,10-anthraquinone are also reduced to their respective aromatic hydrocarbons in variable yields.[51] Smith and coworkers[111-112] have developed a facile two-carbon homologation sequence using the $NaBH_3CN$/HOAc reduction of acylated Meldrum's acid and related derivatives (entries 16-21).

TABLE 15. Reduction of Ketones to Hydrocarbons

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 R = H, Me, OH, CO_2H, CO_2Me, CN, Br, F, NHCOPh, NMe_2, OMe		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	73-94%	106
2		(+ 53% alcohol)	$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	43%	106
3			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	91%	106

4			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	91%	106
5			$NaBH_4$ CF_3CO_2H	--	107
6			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	85%	106
7			$NaBH_4$ (added last) CF_3CO_2H 15-20°	91%	106
8	"		$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	78%	106
9			$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	88%	106
10			$NaBH_4$ CF_3CO_2H	85%	108
11			$NaBH_4$ CF_3CO_2H 15-25°	57%	51
12			$NaBH_4$ CF_3CO_2H 10-20°	23%	51

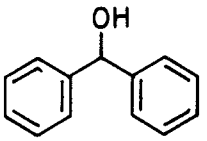
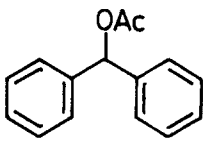
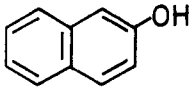
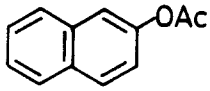
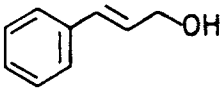
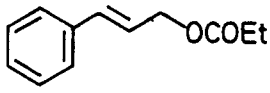
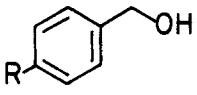
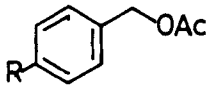
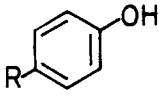
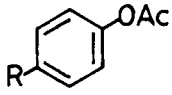
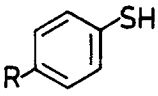
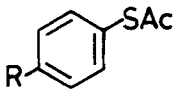
13		$NaBH_4$ CF_3CO_2H 15-20°	86%	51
14	 R = Me, n-Pr, n-Hex	$NaBH_4$ CF_3CO_2H CH_2Cl_2 0°	75-88%	105
15	 (see also ref. 110)	$NaBH_4$ CF_3CO_2H 0° → 25°	76%	109
16	 R = Et, i-Pr, CH_2Ph	$NaBH_3CN$ HOAc	50-85%	111
17	 R = n-Pr, i-Bu, n-Pen, $n\text{-}C_{15}H_{31}$ R' = H, Me	$NaBH_3CN$ HOAc	75-96%	111
18	 R = Et, n-Pr, n-Bu, $n\text{-}C_{15}H_{31}$	$NaBH_3CN$ HOAc	78-86%	111
19		$NaBH_3CN$ HOAc	70%	111

20	 n = 8, 10, 12, 14	$NaBH_3CN$ HOAc THF 65° 2 hr	74-84%	112
21		$NaBH_3CN$ HOAc	75%	113
22	 R = Ph, Me	$NaBH_4$ CF_3CO_2H CH_2Cl_2 15-20°	99%	51

XVI. ACYLATION OF ALCOHOLS AND AMINES

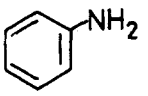
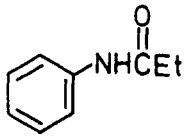
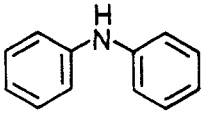
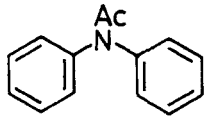
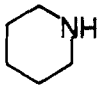
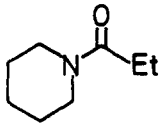
In what could be considered as a side-reaction in the chemistry of $NaBH_4/RCO_2H$, the acylation of suitable functional groups (e.g., alcohols, phenols, amines) is frequently encountered. Indeed, the isolation of methyl formate by Wartik and Pearson[6] (Section I) is an example of the acylation (formylation) of methanol by a formyloxyboron species. Apparently independently, two groups have developed this into a useful alcohol and phenol acylation method (Table 16). It is presumed that under the reaction conditions (excess RCO_2H, reflux, 3 hr)[12] the acylating agent is $NaB(OCOR)_4$ or even $B(OCOR)_3$ (plus NaO_2CR).

TABLE 16. Acylation of Alcohols, Phenols and Thiophenols

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ HOAc Δ, 3 hr	95%	12
2			$NaBH_4$ HOAc Δ, 3 hr	50%	12
3			$NaBH_4$ $EtCO_2H$ 85-90° 3 hr	80%	114
4	 R = H, OMe, NO_2		$NaBH_4$ HOAc 85-90° 3 hr	90-95%	114
5	 R = H, Me, Cl		$NaBH_4$ HOAc Δ, 12 hr	80-98%	114
6	 R = H, Me		$NaBH_4$ HOAc Δ, 12 hr	75-95%	114

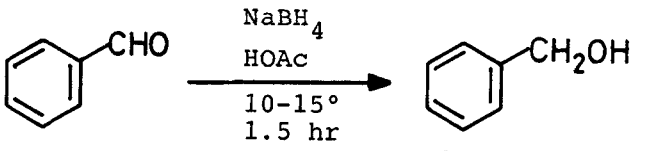
Amines can be similarly acylated to form amides (Table 17).

TABLE 17. Acylation of Amines

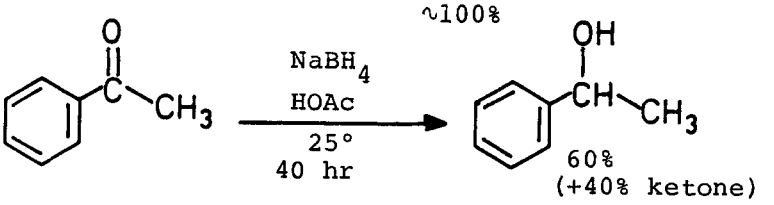
Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ $EtCO_2H$ Δ, 3 hr	95%	12
2			$NaBH_4$ HOAc Δ, 3 hr	40%	12
3			$NaBH_4$ $EtCO_2H$ Δ, 3 hr	60%	12

XVII. REDUCTION OF ALDEHYDES AND KETONES TO ALCOHOLS

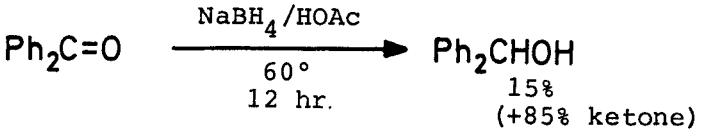
Early in our exploration of the chemistry of $NaBH_4/RCO_2H$, we observed that aldehydes and, especially, ketones are reduced more slowly to alcohols by $NaBH_4$ in glacial acetic acid than in alcoholic solution. For example, although benzaldehyde is completely reduced to benzyl alcohol, acetophenone and benzophenone are incompletely reduced to their alcohols with a large excess of $NaBH_4$ in glacial acetic acid (Eqs. 22-24).[51] Even after these long reaction periods active borohydride reagent is present at the end of the reaction. In contrast, both of these ketones are rapidly and completely reduced to their respective alcohols with $NaBH_4$ in ethanol.



(22)



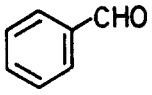
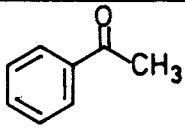
(23)

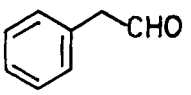
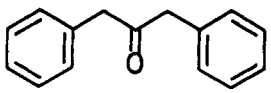
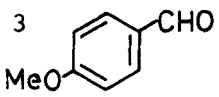
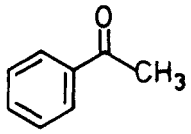
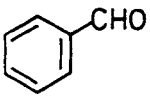
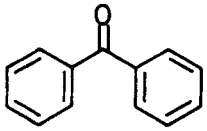
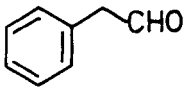
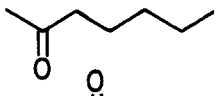
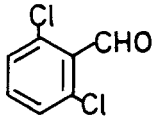
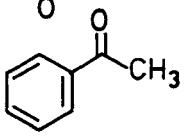
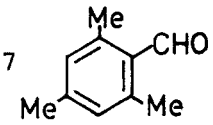


(24)

These observations paved the way for the chemoselective reduction of aldehydes, in the presence of ketones, using $NaBH(OAc)_3$ in benzene[115] or, even better, $\underline{n}$-$Bu_4NBH(OAc)_3$ in benzene.[116] In both cases excess hydride reagent can be used. Examples of this chemoselective reduction of aldehydes to primary alcohols, in the presence of ketones, are tabulated in Table 18.

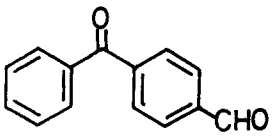
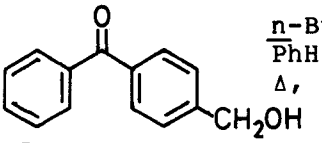
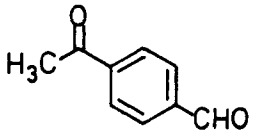
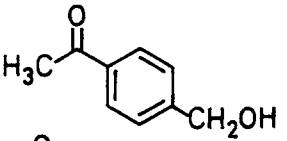
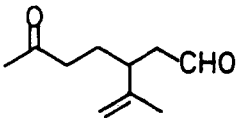
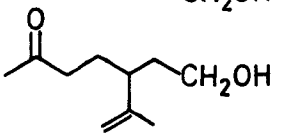
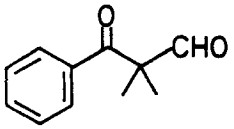
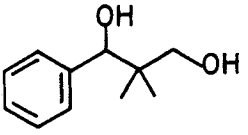
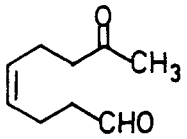
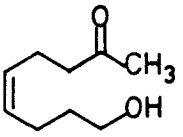
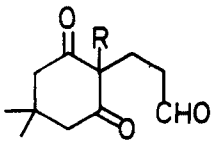
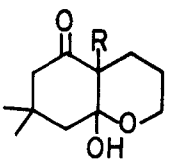
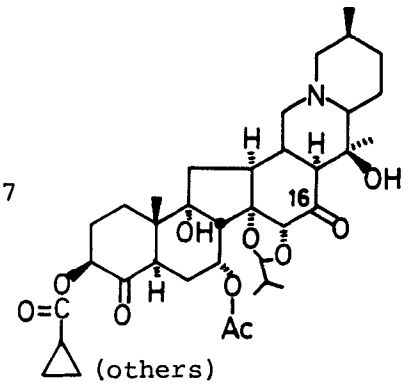
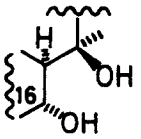
TABLE 18. Reduction of a 1:1 Mixture of Aldehyde and Ketone With $\underline{n}Bu_4NBH(OAc)_3$ in Benzene (24 hr, reflux)[116]

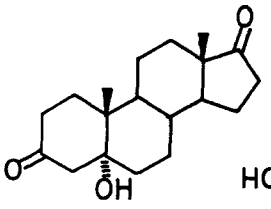
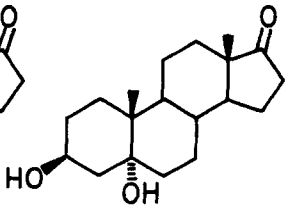
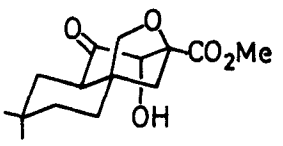
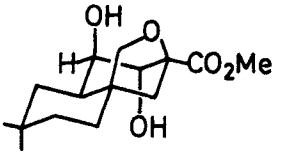
Entry	Aldehyde	Ketone	Yield of Primary Alcohol	Yield of Recovered Ketone
1			95%	96%

2			96%	94%
3			95%	99%
4			90%	94%
5			92%	96%
6			80%	92%
7		"	87%	96%

Moreover, as shown in Table 19, several ketoaldehydes have been reduced selectively to ketoalcohols or, in those cases where the hydroxyl group can complex with the borohydride species, to 1,3-diols (entry 4). Indeed, this method has been used by Saksena[119] to reduce β-hydroxyketones to 1,3-diols with complete stereoselectivity (OH-assisted hydride delivery) (entries 7, 8). A related reduction has been described by Fuchs,[120] involving an α-hydroxyketone (entry 9).

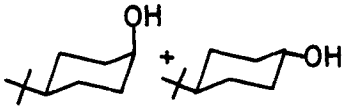
TABLE 19. Reduction of Ketoaldehydes and Related Systems

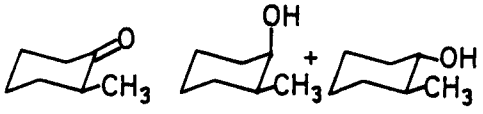
Entry	Substrate	Product	Conditions	Yield	Ref.
1			n-$Bu_4NBH(OAc)_3$ PhH Δ, 24 hr	88%	116
2			n-$Bu_4NBH(OAc)_3$ PhH Δ, 24 hr	72%	116
3			n-$Bu_4NBH(OAc)_3$ PhH Δ, 24 hr	77%	116
4			n-$Bu_4NBH(OAc)_3$ PhH Δ, 24 hr	80%	116
5			$KBH(OAc)_3$ PhH	60%	117
6	 R = Me, CH_2Ph, allyl		$NaBH_3CN$ HCO_2H t-BuOH	--	118
7	 (others)		$NaBH(OAc)_3$ HOAc rt	96%	119

8	 (others)		$NaBH(OAc)_3$ HOAc THF (or CH_2Cl_2) 5 min	90%	119
9			$NaBH_3CN$ CF_3CO_2H 3 hr 0-5°	92-96%	120

Several groups have examined the stereochemistry of cyclic ketone reduction using $NaBH_4/RCO_2H$ (Table 20). Although the reduction of cyclohexanones is only moderately stereoselective with $NaBH_4$/HOAc, generally favoring the equatorial alcohol (entries 2, 3, 6), the stereoselectivity can be greatly enhanced by using acyloxyborohydride reagents derived from mandelic acid (entries 1, 5) or tartaric acid (entries 4, 7).

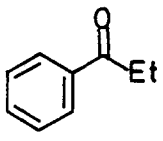
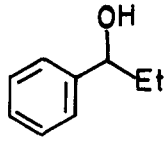
TABLE 20. Reduction of Cyclic Ketones

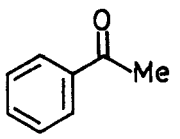
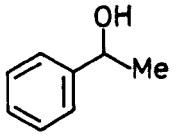
Entry	Substrate	Product			Conditions	Yield	Ref.
1	 (others)		8	92	$NaBH_4$ PhCH-OH CO_2H i-PrOH, Δ 2 hr	--	121
2	"		26	74	$NaBH_4$ HOAc	90%	19
3	"		23	77	$NaBH_3CN$ HOAc	95%	19

4	"	6 : 94	$NaBH_4$ tartaric acid THF	122
5		25 : 75	$NaBH_4$ PhCH(OH)CO_2H i-PrOH, Δ, 2 hr	121
6	"	55 : 45	$NaBH_4$ HOAc	19
7	"	20 : 80	$NaBH_4$ tartaric acid THF	122

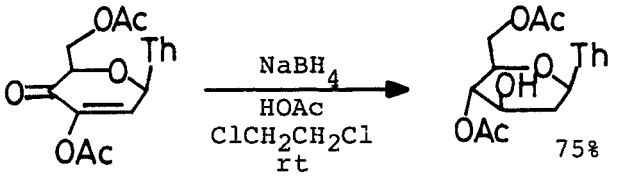
Several groups have examined the asymmetric reduction of ketones with optically active acyloxyborohydrides (Table 21), in some cases achieving good enantioselectivity. For each study, only the best of several systems examined is shown in Table 21.

TABLE 21. Asymmetric Reduction of Ketones

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 (others)	 63% ee (R)	$NaBH_4$ i-$PrCO_2H$ THF, 25° sugar	56%	123
2	"	" 51% ee (R)	$NaBH_4$ PhCH(Et)CO_2H, THF 2 hr, rt sugar	68%	124
3	"	" 50% ee (S)	$NaBH_4$ THF, rt 10 days proline	92%	125

4		 11.5% ee (R)	$NaBH_4$ dioxane Δ, 4 hr $Ph-CH(OH)CO_2H$	94%	121

Finally, the interesting double reduction of the ketone and enol acetate functionalities in a nucleoside has been reported, accompanied by an acetyl transposition (Eq. 25).[126]

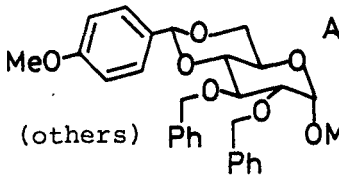
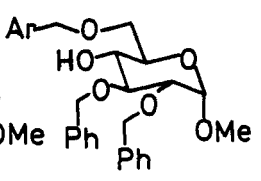


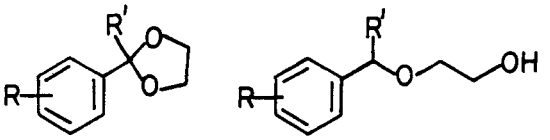
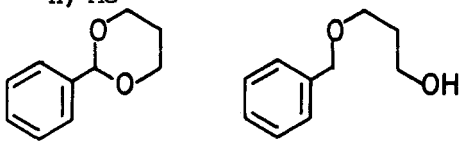
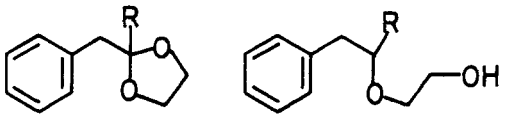
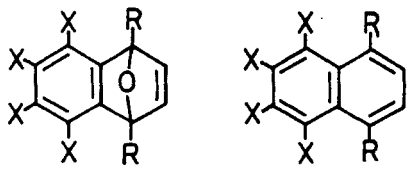
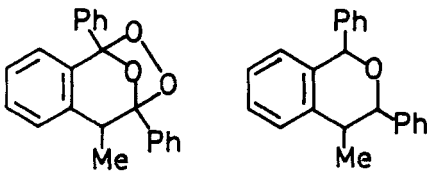
(25)

XVIII. REDUCTIVE CLEAVAGE OF ACETALS, KETALS, AND ETHERS

As might be expected, the use of trifluoroacetic acid in combination with $NaBH_4$ can effect the reductive cleavage of acetals, ketals, and ethers. A few examples have been reported (Table 22). The yields are higher for those systems giving rise to phenyl-stabilized oxonium ions (entries 1-3, 5 vs. entry 4). Recently, the deoxygenation of an ozonide was reported (entry 6).[133]

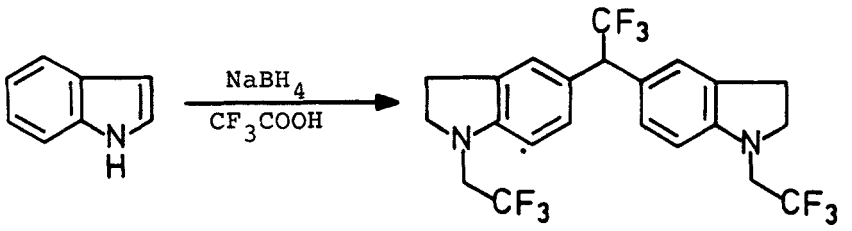
TABLE 22. Reductive Cleavage of Acetals, Ketals, and Ethers

Entry	Substrate	Product	Conditions	Yield	Ref.
1	 (others)		$NaBH_3CN$ CF_3CO_2H DMF	85%	127

2	 R = H, 4-OMe, 4-Me, 4-Cl, 2-NO_2, 3-NO_2; R' = H, Me	$NaBH_4$ CF_3CO_2H THF 20°, 5 hr	11-83%	128
3		$NaBH_4$ CF_3CO_2H THF 20°, 5 hr	78%	128
4	 R = H, CH_2Ph	$NaBH_4$ CF_3CO_2H THF Δ, 24 hr	33-40%	128
5	 X = H, F, Cl; R = H, Me	$NaBH_4$ CF_3CO_2H	57-97%	129
6	 (others)	$NaBH_4$ CF_3CO_2H 20°, 30 min	40%	133

XIX. FRIEDEL-CRAFTS ALKYLATION OF ARENES

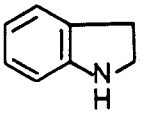
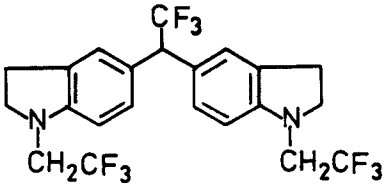
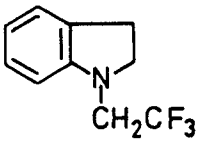
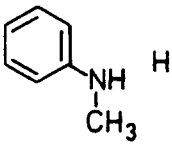
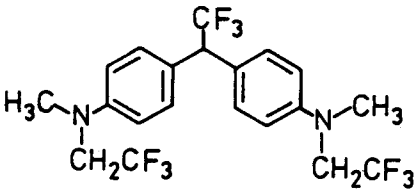
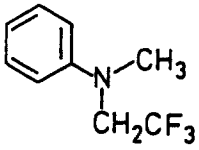
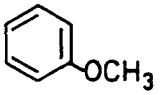
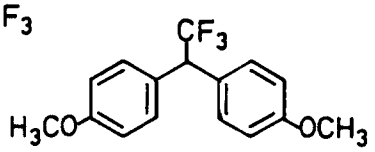
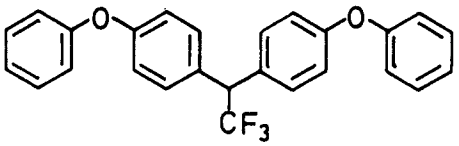
During our studies[11,59] of the reaction of indole (or indoline) with $NaBH_4/CF_3CO_2H$, we observed the formation of an interesting bis-indole product (Eq. 26).

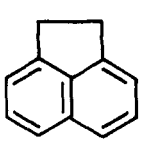
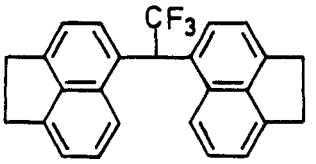
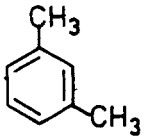
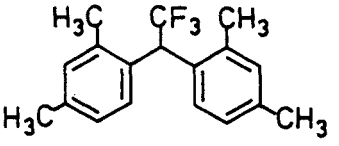
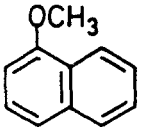
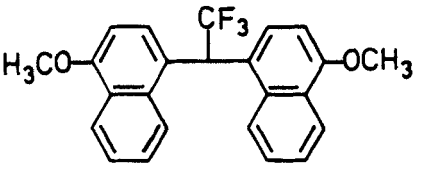


(26)

More recently, we have found[130] that this "Baeyer condensation"[131] is general for activated arenes and generally furnishes the p,p'-isomer in fair to good yield (Table 23). The reaction fails with benzene, toluene, and p-xylene.

TABLE 23. Reaction of Arenes With $NaBH_4/CF_3CO_2H$ to Give 1,1,1-Trifluoro-2,2-diarylethanes

Entry	Substrate	Product	Conditions	Yield	Ref.
1			$NaBH_4$ CF_3CO_2H 60°	34%	59
2		"	$NaBH_4$ CF_3CO_2H Δ	52%	59
3			$NaBH_4$ CF_3CO_2H Δ	22%	59
4		"	$NaBH_4$ CF_3CO_2H Δ	46%	59
5			$NaBH_4$ CF_3CO_2H Δ	47%	59
6	Ph_2O		$NaBH_4$ CF_3CO_2H Δ, 3 hr	53%	130

7			$NaBH_4$ CF_3CO_2H Δ, 3 hr	65%	130
8			$NaBH_4$ CF_3CO_2H Δ, 3 hr	48%	130
9			$NaBH_4$ CF_3CO_2H 25°	78%	130

XX. SUMMARY

In this review we have tried to illustrate the versatility of the relatively new acyloxyborohydride class of reducing agents. We have shown how, by changing carboxylic acid, solvent, stoichiometry, temperature, time, and hydride reagent itself, one can achieve remarkable chemoselectivity in an array of different types of reactions.

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