Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures[1]

Ahmed F. Abdel-Magid,* Kenneth G. Carson, Bruce D. Harris, Cynthia A. Maryanoff, and Rekha D. Shah

The R. W. Johnson Pharmaceutical Research Institute, Department of Chemical Development, Spring House, Pennsylvania 19477

Received January 8, 1996[⊗]

Sodium triacetoxyborohydride is presented as a general reducing agent for the reductive amination of aldehydes and ketones. Procedures for using this mild and selective reagent have been developed for a wide variety of substrates. The scope of the reaction includes aliphatic acyclic and cyclic ketones, aliphatic and aromatic aldehydes, and primary and secondary amines including a variety of weakly basic and nonbasic amines. Limitations include reactions with aromatic and unsaturated ketones and some sterically hindered ketones and amines. 1,2-Dichloroethane (DCE) is the preferred reaction solvent, but reactions can also be carried out in tetrahydrofuran (THF) and occasionally in acetonitrile. Acetic acid may be used as catalyst with ketone reactions, but it is generally not needed with aldehydes. The procedure is carried out effectively in the presence of acid sensitive functional groups such as acetals and ketals; it can also be carried out in the presence of reducible functional groups such as C−C multiple bonds and cyano and nitro groups. Reactions are generally faster in DCE than in THF, and in both solvents, reactions are faster in the presence of AcOH. In comparison with other reductive amination procedures such as $NaBH_3CN$/MeOH, borane−pyridine, and catalytic hydrogenation, $NaBH(OAc)_3$ gave consistently higher yields and fewer side products. In the reductive amination of some aldehydes with primary amines where dialkylation is a problem we adopted a stepwise procedure involving imine formation in MeOH followed by reduction with $NaBH_4$.

Introduction

The reactions of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively, known as reductive aminations (of the carbonyl compounds) or reductive alkylations (of the amines) are among the most useful and important tools in the synthesis of different kinds of amines. The reaction involves the initial formation of the intermediate carbinol amine **3** (Scheme 1) which dehydrates to form an imine. Under the reaction conditions, which are usually weakly acidic to neutral, the imine is protonated to form an iminium ion **4**.[2] Subsequent reduction of this iminium ion produces the alkylated amine product **5.** However, there are some reports that provide evidence suggesting a direct reduction of the carbinol amine **3** as a possible pathway leading to **5**.[3] The choice of the reducing agent is very critical to the success of the reaction, since the reducing agent must reduce imines (or iminium ions) selectively over aldehydes or ketones under the reaction conditions.

The reductive amination reaction is described as a *direct* reaction when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. A *stepwise* or *indirect* reaction involves the preformation of the intermediate imine followed by reduction in a separate step.

The two most commonly used direct reductive amination methods differ in the nature of the reducing agent. The first method is catalytic hydrogenation with platinum, palladium, or nickel catalysts.[2a,4] This is an economical and effective reductive amination method, particularly in large scale reactions. However, the reaction may give a mixture of products and low yields depending on the molar ratio and the structure of the reactants.[5] Hydrogenation has limited use with compounds containing carbon−carbon multiple bonds and in the presence of reducible functional groups such as nitro[6,7] and cyano[7] groups. The catalyst may be inhibited by compounds containing divalent sulfur.[8] The second method utilizes hydride reducing agents particularly sodium cyanoborohydride ($NaBH_3CN$) for reduction.[9] The successful use of sodium cyanoborohydride is due to its stability in relatively strong acid solutions (∼pH 3), its solubility in hydroxylic solvents such as methanol, and its different selectivities at different pH values.[10] At pH

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) Presented in part at the 33rd ACS National Organic Symposium, Bozeman, Mo, June 1993, Paper A-4. Preliminary communications: (a) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. (b) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537.

(2) The formation of imines or iminium ions was reported as possible intermediates in reductive amination reactions in catalytic hydrogenation methods, see (a) Emerson, W. S. *Org. React.* **1948**, *4*, 174 and references therein. It was also proposed in hydride methods, see (b) Schellenberg, K. A. *J. Org. Chem.* **1963**, *28*, 3259.

(3) Tadanier, J.; Hallas, R.; Martin, J. R.; Stanaszek, R. S. *Tetrahedron* **1981**, *37*, 1309

(4) (a) Emerson, W. S.; Uraneck, C. A. *J. Am. Chem. Soc.* **1941**, *63*, 749. (b) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1962**, *27*, 2205. (c) Klyuev, M. V.; Khidekel, M. L. *Russ. Chem. Rev.* **1980**, *49*, 14.

(5) Skita, A.; Keil, F. *Chem. Ber.* **1928**, *61B*, 1452.

(6) Roe, A.; Montgomery, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 910.

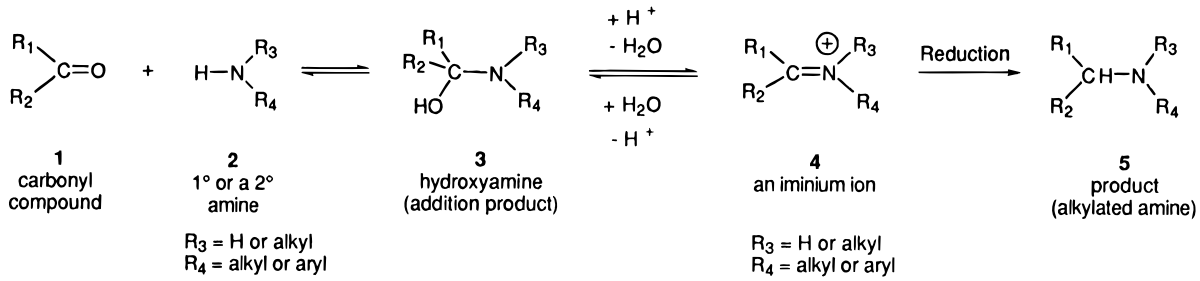
(7) Rylander, P. N. In *Catalytic Hydrogenation over Platinum Metals*; Academic Press, New York, 1967; p 128.

(8) Rylander, P. N. In *Catalytic Hydrogenation over Platinum Metals*; Academic Press, New York, 1967; p 21.

(9) For a recent review on reduction of C=N compounds with hydride reagents see: Hutchins, R. O., Hutchins, M. K. Reduction of C=N to CHNH by Metal Hydrides. In *Comprehensive Organic Synthesis*; Trost, B. N., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8.

S0022-3263(96)00057-6 CCC: $12.00

Scheme 1



3−4 it reduces aldehydes and ketones effectively, but this reduction becomes very slow at higher pH values.[11] At pH 6−8, the more basic imines are protonated preferentially and reduced faster than aldehydes or ketones.[10] This selectivity allows for a convenient direct reductive amination procedure. The literature is replete with publications that document the use of sodium cyanoborohydride in reductive amination reactions.[12] Limitations are that the reaction may require up to a fivefold excess of the amine,[10] is usually slow and sluggish with aromatic ketones[10] and with weakly basic amines,[13] and may result in the contamination of the product with cyanide.[14] The reagent is highly toxic[15] and produces toxic byproducts such as HCN and NaCN upon workup.

Other reported reductive amination reagents include borane-pyridine,[13a] $Ti(OiPr)_4/NaBH_3CN$,[13b] borohydride exchange resin,[16a] Zn/AcOH,[16b] $NaBH_4/Mg(ClO_4)_2$,[16c] and $Zn(BH_4)_2/ZnCl_2$.[16d] In addition, there are some reports of electrochemical reductive amination reactions.[17]

In our work on hydride-induced reductive aminations of aldehydes and ketones, we sought an alternative to the toxic sodium cyanoborohydride to eliminate the risk of residual cyanide in the product and in the workup waste stream, particularly for large scale reactions. After surveying many of the commercially available hydride reagents, we selected sodium triacetoxyborohydride [$NaBH(OAc)_3$].[18] This borohydride reagent is mild and exhibits remarkable selectivity as a reducing agent. It reduces aldehydes selectively over ketones,[18] except for β-hydroxy ketones which can be reduced selectively to give 1,3-*trans* diols.[19] The steric and the electron-withdrawing effects of the three acetoxy groups stabilize the boron−hydrogen bond and are responsible for its mild reducing properties.[20] Our selection was also based on the results of reductive alkylation of amines using sodium borohydride in neat liquid carboxylic acids reported earlier by Gribble *et al.*[21]

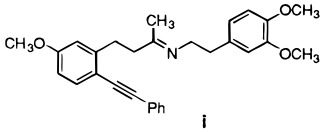
In this paper we report the results of our comprehensive investigation of the scope and limitations of sodium triacetoxyborohydride in a procedure for *direct* reductive amination of aldehydes and ketones with a variety of aliphatic and aromatic amines. This report also includes an alternative stepwise route for the reductive amination of aldehydes with primary amines which involves the preformation of imines and their subsequent reduction with $NaBH_4$ in one-pot reactions.

Results and Discussions

The direct reductive amination reactions were carried out in 1,2-dichloroethane (DCE), tetrahydrofuran (THF), or acetonitrile. The standard reaction conditions are as follows: a mixture of the carbonyl compound and the amine (0−5% molar excess) in the desired solvent is stirred with 1.3−1.6 equiv of sodium triacetoxyborohydride under a nitrogen atmosphere at room temperature. In some reactions, acetic acid (1−2 mol equiv) is added to the mixture. The progress of the reaction is followed by GC and GC/MS analysis. The results from various reductive amination reactions of ketones and aldehydes are listed in Tables 1 and 2, respectively. Solvents such as water or methanol are not recommended. Reactions in methanol resulted in a fast reduction of the carbonyl compound, and the reagent decomposed in water.

(a) Reductive Amination of Ketones. The results in Table 1 show that the reductive amination of a wide variety of cyclic and acyclic ketones with primary and

(10) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(11) Borch, R. F., Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996.
(12) (a) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*(5), 201. (b) Lane, C. F. *Synthesis* **1975**, 135.
(13) Occasional use of weakly basic or nonbasic amines was reported, see for example: (a) Pelter, A., Rosser, R. M., Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717. (b) Mattson, R. J., Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552. (c) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673. (d) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 3453.
(14) (a) The product from large scale reduction of the imine (i) with sodium cyanoborohydride was contaminated with cyanide. (b) A similar result was reported recently: Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789.



i

(15) For information on the safety data and health hazards associated with sodium cyanoborohydride see: The *Sigma-Aldrich Library of Chemical Safety Data*, 1st ed.; Lenga, R. E., Ed., Sigma-Aldrich Corp.: Milwaukee, 1985, p 1609.
(16) (a) Yoon, N. M.; Kim, E. G.; Son, H. S.; Choi, J. *Synth. Commun.* **1993**, *23*, 1595. (b) Micovic, I. V.; Ivanovic, M. D.; Piatak, D. M.; Bojic, V. Dj. *Synthesis* **1991**, 1043. (c) Brussee, J.; van Benthem, R. A. T. M.; Kruse, C. G.; van der Gen, A. *Tetrahedron: Asymmetry* **1990**, *1*, 163. (d) Bhattacharyya, S.; Chatterjee, A.; Duttachowdhhury, S. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1.
(17) (a) Pienemann, T.; Schafer, H.-J. *Synthesis* **1987**, 1005. (b) Smirnov, Yu. D.; Tomilov, A. P. *J. Org. Chem. U.S.S.R.* **1992**, *28(1)*, 42. (c) Smirnov, Yu. D.; Pavlichenko, V. F.; Tomilov, A. P. *J. Org. Chem. U.S.S.R.* **1992**, *28(3)*, 374.
(18) (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (b) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287. (c) Gribble, G. W. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed., John Wiley and Sons: New York, 1995; Vol. 7, p 4649.
(19) See for example: (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (c) Evans, D. A., Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(20) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317.
(21) Earlier work by Gribble *et al.* demonstrated the potential of triacyloxyborohydrides generated from $NaBH_4$ in neat liquid carboxylic acids in reductive alkylation of amines: (a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766.

secondary amines was successful under the standard conditions and gave the desired products in good to excellent yields. The scope of the reaction includes different alicyclic ketones, from cyclobutanone to cyclododecanone (Table 1: entries 1−23), bicyclic ketones such as norcamphor and tropinone (Table 1: entries 24−30), saturated acyclic ketones (Table 1: entries 31−39), and keto esters (Table 1: entries 47−49). Nearly all primary and nonhindered secondary amines were used successfully in these reactions. For the same ketone, the rate of the reaction was dependent on the steric and electronic factors associated with the amines. In general, primary aliphatic amines reacted faster than primary aromatic and secondary aliphatic amines (Table 1: entries 10 vs 11; 14 and 15 vs 16 and 17; 24 vs 26 and 27). Cyclic secondary amines such as morpholine reacted faster than acyclic secondary amines such as diethylamine (Table 1: entry 33 vs 36) while the sterically hindered diisopropylamine did not react even after days (Table 1: entry 45). In some slow reactions (e.g., Table 1: entries 11, 27, 32, 34, and 36), small amounts of side products were formed (1−5% by GC area % analysis) from *N*-ethylation and *N*-acetylation of the starting amines.[22] These impurities were easily removed in the workup or during the recrystallization of the salts.

The reaction conditions are very mild and can tolerate the presence of acid sensitive functional groups such as acetals and ketals. For example, the reductive amination of cyclohexanedione monoethylene ketal with primary and secondary amines afforded good to excellent isolated yields of the corresponding amines (Table 1: entries 14−18). Another example is the reductive alkylation of aminoacetaldehyde diethyl acetal with cyclododecanone (Table 1: entry 9). A particularly useful example is the reaction involving cyclohexanedione monoethylene ketal and aminoacetaldehyde diethyl acetal (Table 1: entry 18) which provides a secondary amine product containing protected aldehyde and ketone functionalities in a nearly quantitative yield.

Of all the ketones used in this study, small aliphatic cyclic ketones, ranging from cyclobutanone to cyclohexanone, were most reactive. Larger cyclic ketones such as cyclooctanone and cyclododecanone and acyclic ketones such as 2-heptanone reacted somewhat slower. Reactivity of cyclobutanone was so high that its reaction with benzylamine gave a mixture of mono- and dicyclobutylbenzylamines even with the use of excess amine (Table 1: entry 2). Clean formation of *N*,*N*-dicyclobutylbenzylamine resulted with the use of a 1:2 molar ratio of amine to ketone (Table 1: entry 1). The reactions with secondary amines were very effective since there was no dialkylation product (Table 1: entry 3).

The least reactive ketones were aromatic, α,β-unsaturated, and sterically hindered ketones. Aromatic and α,β-unsaturated ketones reacted very slowly (Table 1: entries 40, 41, and 43). Experimentally, a saturated aliphatic ketone was reductively aminated, selectively, and quantitatively in the presence of an aromatic or α,β-unsaturated ketone (Table 1: entries 42 and 44). The unreacted ketones were recovered unchanged except for the formation of trace amounts of their imines (as determined by GC/MS analysis of the reaction mixture). Sterically hindered ketones were even less reactive than aromatic and α,β-unsaturated ketones, e.g., camphor showed no reaction with benzylamine after four days (Table 1: entry 46). The steric factors associated with both ketones and amines seem to be very important in determining the outcome of the reaction.

In reactions where the formation of diastereomers was possible, we observed varying degrees of selectivity. Reductive amination of 4-*tert*-butylcyclohexanone with pyrrolidine and cyclohexylamine occurred with a moderate diastereoselectivity to give the thermodynamically less favored *cis* products. This results from equatorial attack by the hydride reagent on the intermediate imine, to form the axial amine (Table 1: entries 19 and 20).[23] The reductive amination of androstanolone with isopropylamine gave a mixture of 3α- and 3β-(isopropylamino)-androstan-17β-ol in about 25:75 ratio (Table 1: entry 21). The reactions involving bicyclic ketones showed higher degrees of diastereoselectivity. For example, the reductive aminations of norcamphor led to the exclusive formation of the *endo* products, from *exo* attack by the hydride reagent. The reductive amination of norcamphor with benzylamine (Table 1: entry 24) produced a single product. This product was identical to that obtained from the reductive amination of benzaldehyde with *endo*-2-aminonorbornane (Table 2: entry 13), thus confirming the *endo* stereochemistry of the product.

Reductive amination of tropinone with primary amines such as benzylamine and aniline (Table 1: entries 28 and 29) was accomplished in good yield and high diastereoselectivity giving the *endo* isomer as the major product (determined by ^{1}H NMR).[24] The reaction with benzylamine gave the *endo* and *exo* products in approximately 20:1 ratio while the reaction with aniline showed no detectable *exo* product. The reaction of tropinone with piperidine was extremely sluggish giving low conversion to about a 1:1 mixture of the *exo*- and *endo*-products after four days of reaction (Table 1: entry 30).

The poor solubility of ammonium acetate in DCE, THF, or CH_3CN limits its use in the reductive amination of ketones to prepare primary amines. The initial primary amine product is much more soluble than ammonium acetate and reacts faster with the ketone to generate dialkylamines, so this reaction can be used for the preparation of symmetrical dialkylamines. The amination reaction is relatively slow and some ketone reduction may occur if AcOH is added. Even the use of a large excess (10 equiv) of ammonium acetate in THF, DCE, or CH_3CN, in the presence of Et_3N, did not favor the formation of the monoalkylamine, the only product formed was dicycloheptylamine (Table 1: entries 22 and 23).

N-Substituted α-amino esters were prepared by the reductive amination of α-keto esters with primary and

(22) The *N*-ethylation of amines is a major process in reaction of amines with sodium borohydride in neat acetic acid and is believed to proceed through an acetaldehyde formation.[21a]

(23) This result is consistent with literature reports on the reduction of 4-substituted cyclohexanone imines or iminium salts which concluded that bulky hydride reagents such as L-Selectride attack preferentially from the less hindered equatorial side to give the *cis*-products, while less bulky hydride reagents such as $NaBH_4$ and $NaBH_3CN$ slightly favor the axial approach, see: (a) Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447. (b) Hutchins, R. O.; Markowitz, M. *J. Org. Chem.* **1981**, *46*, 3571. (c) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412. (d) Hutchins, R. O.; Adams, J.; Rutledge, M. C. *J. Org. Chem.* **1995**, *60*, 7396.

(24) Chemical shift assignments of individual protons were arrived at by COSY, HETCOR, and Inverse HMBC NMR experiments. The stereochemistry of *N*-phenyl-3-aminotropane and *N*-benzyl-3-aminotropane was assigned based on 1D NOE and coupling experiments. The assignments were in line with other literature reports; *cf.* Bagley, J. R.; Riley, T. N. *J. Hetrocycl. Chem.* **1977**, *14*, 599 and references therein.

Table 1. Reductive Amination of Ketones

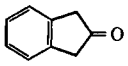
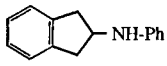
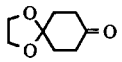
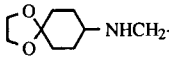
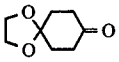
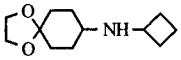
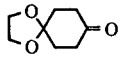
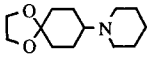
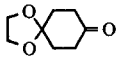
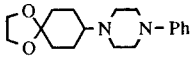
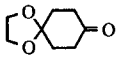
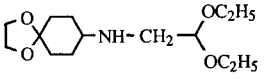
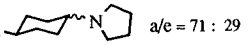
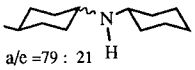
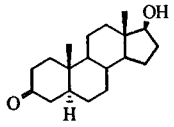
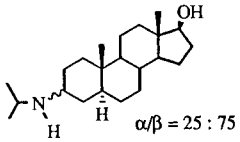
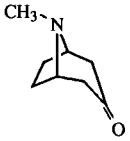
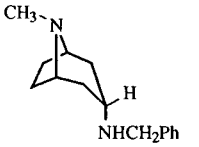
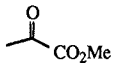
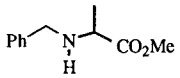
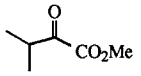
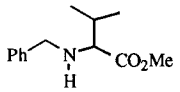
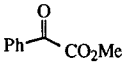
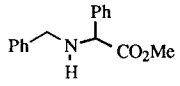
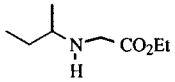
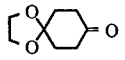
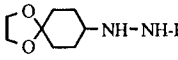
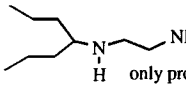
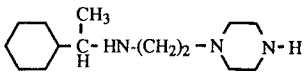
Entry	KETONE	AMINE	Method[a]	Time	PRODUCT	YIELD(%) Base[b]	Salt[c]
1.	Cyclobutanone (2 mol)	Benzylamine (1 mol)	I	2 h	*N,N*-Dicyclobutylbenzylamine	98	90 (HCl)
2.	Cyclobutanone (1 mol)	Benzylamine (1 mol)	II	2 h	*N,N*-Dicyclobutylbenzylamine + *N*-Cyclobutylbenzylamine (1 : 1)	88	---
3.	Cyclobutanone	1-Phenylpiperazine	II	2 h	1-Cyclobutyl-4-phenylpiperazine	96	86 (ox)
4.	Cyclopentanone	Hexamethyleneimine	I	24 h	*N*-Cyclopentylhexamethyleneimine	96	86 (ox)
5.	Cyclohexanone	Morpholine	I	2 h	*N*-Cyclohexylmorpholine	96	86 (HCl) 76 (pic)
6.	Cycloheptanone	1-Propylamine	IV	23 h	*N*- (1-propyl)aminocycloheptane	96	69 (HCl)
7.	Cycloheptanone	1-Propylamine	I	3 h	*N*- (1-propyl)aminocycloheptane	-	88 (HCl)
8.	Cyclooctanone	*m*-Methoxybenzylamine	I	36 h	*N*-Cyclooctyl-*m*-methoxybenzylamine	95	87 (HCl)
9.	Cyclododecanone	$H_2NCH_2CH(OC_2H_5)_2$	II	24 h	c-$C_{12}H_{23}$ - NH- $CH_2CH(OC_2H_5)_2$	88	77 (ox)
10.	β- Tetralone	Cyclohexylamine	IV	24 h	*N*-Cyclohexyl-1,2,3,4-tetrahydro-2-aminonaphthalene	-	85 (HCl)
11.	β- Tetralone	Morpholine	III	120 h	2-(Morpholin-4-yl)-1,2,3,4-tetrahydronaphthalene	58	54 (HCl)
12.	β- Tetralone	Aniline	I	24 h	*N*-Phenyl-1,2,3,4-tetrahydro-2-aminonaphthalene	--	87 (HCl)
13.		H_2N-Ph	I	6 h		--	85 (HCl)
14.		Benzylamine	I	20 m		98	92 (ox)
15.		Cyclobutylamine	I	25 m		98	82 (HCl)
16.		Piperidine	I	75 m		85	66 (HCl)
17.		1-Phenylpiperazine	I	4 h		78	---
18.		$H_2NCH_2CH(OC_2H_5)_2$	II	4 h		--	99 (ox)
19.	4-*t*-Butylcyclohexanone	Pyrrolidine	II	10 m	 a/e = 71 : 29	98	---
20.	4-*t*-Butylcyclohexanone	Cyclohexylamine	II	30 m	 a/e =79 : 21	91	---
21.		Isopropylamine	I	24 h	 α/β = 25 : 75	91	---
22.	Cycloheptanone	NH4OAc (10 eq.)	II,[d] IV[d]	48 h	Dicycloheptylamine	–	80 (HCl)
23.	Cycloheptanone	NH4OAc (10 eq.)	V[d]	30 h	Dicycloheptylamine	–	70 (HCl)
24.	Norcamphor	Benzylamine	IV	6 h	*endo-N*-Benzyl-2-aminonorbornane	95	82 (pic)
25.	Norcamphor	Aniline	III	48 h	*N*-Phenyl-2-aminonorbornane	80	75 (HCl)
26.	Norcamphor	Aniline	I	24 h	*N*-Phenyl-2-aminonorbornane	---	76 (HCl)
27.	Norcamphor	Diethylamine	I	96 h	*N,N*-Diethyl-2-aminonorbornane	---	79 (HCl)
28.		H_2N-CH_2-Ph	I	18 h		99	80 (ox)
29.	"	Aniline	I	72 h	*endo*-3-(*N*-Phenylamino)tropane	96	65 (ox)
30.	"	Piperidine	I	4 d	about 1:1 mixture of *endo* + *exo* products	60[e]	---

Table 1. (Continued)

Entry	KETONE	AMINE	Method[a]	Time	PRODUCT	YIELD(%) Base[b]	Salt[c]
31.	2- Heptanone	Cyclohexylamine	IV	24 h	*N*-Cyclohexyl-2-aminoheptane	99	84 (ox)
32.	2- Heptanone	Aniline	IV	96 h	*N*-Phenyl-2-aminoheptane	90	89 (ox)
33.	2- Heptanone	Morpholine	III	27 h	*N*-(2-Heptyl) morpholine	-	73 (HCl)
34.	2- Heptanone	Piperidine	IV	48 h	*N*-(2-Heptyl)piperidine	67	35 (HCl)
35.	2- Heptanone	Piperidine	I	48 h	*N*-(2-Heptyl)piperidine	–	65 (HCl)
36.	2- Heptanone	Diethylamine	III	192 h	*N,N*-Diethyl-2-aminoheptane	–	44 (HCl)
37.	Acetylcyclohexane	Benzylamine	II	24 h	*N*-(1-(Cyclohexyl)ethyl)benzylamine	91	71 (HCl)
38.	1-Phenyl-2-propanone	Aniline	II	30 h	*N*-(3-Phenyl-2-propyl)aniline	–	80 (HCl)
39.	4-Heptanone	Propargylamine	II	12 h	*N*-(4-Heptyl)propargylamine	99	84 (HCl)
40.	Acetophenone	Benzylamine	I	10 d	*N*-Benzyl-1-phenylethylamine	55[e]	–
41.	Acetophenone	Cyclohexylamine	I, III	1 d	*N*-Cyclohexyl-1-phenylethylamine	15[e]	–
42.	Acetophenone Cyclohexanone	Benzylamine	I	1 h	*N*-Benzylcyclohexylamine Acetophenone (92 %)	98	97 (HCl)
43.	1-Acetylcyclohexene	Morpholine	II	4 d	*N*-[1-(I-Cyclohexenyl)ethyl]morpholine	10[e]	–
44.	1-Acetylcyclohexane 1-Acetylcyclohexene	Benzylamine	I	4 h	*N*-[1-(Cyclohexyl)ethyl]benzylamine 1-Acetylcyclohexene	–	85 (HCl)
45.	Cycloheptanone	Diisopropylamine	IV	4 d	no reaction	–	–
46.	Camphor	Benzylamine	I	4 d	no reaction	–	–
47.		H_2N-CH_2-Ph	II	0.5 h		90	61 (HCl)
48.		H_2N-CH_2-Ph	VI	42 h		--	80 (HCl)
49.		H_2N-CH_2-Ph	VI	5 h		--	58 (HCl)
50.		H_2N-CH_2-CO_2Et	I	4 h		--	88 (HCl)
51.		H_2N-NH-Ph	I	4 h		98	71 (ox)
52.	Cyclohexanone	H_2N-NH-Ph	I	1 h	N^2-Cyclohexyl-N^1-phenylhydrazine	96[f]	–
53.	2-Heptanone	H_2N-NH-Ph	I	8 h	N^2-2-Heptyl-N^1-phenylhydrazine	98[f]	37 (ox)
54.	Cyclooctanone	H_2N-OH	I	72 h	Oxime formation, no reduction.	--	--
55.	4-Heptanone	H_2N-CH_2-CH_2-NH-Ph	II	30 h	 only product	99	79 (HCl)
56.	Acetylcyclohexane	H_2N-$(CH_2)_2$- 	II	12 h	 + diaddition product 94 : 6	98	83 (ox)

a) Methods: I: DCE, AcOH (1-2 eq.), $NaBH(OAc)_3$ (1.3-1.6 eq.); II: DCE, $NaBH(OAc)_3$ (1.3-1.6 eq.); III: THF, AcOH (1-2 eq.), $NaBH(OAc)_3$ (1.3-1.6 eq.); IV: THF, $NaBH(OAc)_3$ (1.3-1.6 eq.); V: CH_3CN, $NaBH(OAc)_3$ (1.3 - 1.6 eq.); VI : DCE, amine (1 eq.), AcOH (2-4 eq.), $NaBH(OAc)_3$ (2-5 eq.), ketone (2-5 eq.)

b) Salts: pic = picrate, ox = oxalate c) Yield of crude product determined to be > 96% pure by GC.

d) Reaction was carried out in presence of 1.5-2 equiv of Et_3N.

e) Yields were determined by GC and products were only characterized by GC/MS.

f) crude product contained about 15-31% byproduct(s), determined by area% GC analysis.

secondary amines. The reductive amination of methyl pyruvate with benzylamine was a fast and efficient reaction under the standard conditions that gave *N*-benzylalanine methyl ester in an excellent yield (Table 1: entry 47). The reaction was slower with hindered keto esters such as methyl 3-methyl-2-oxobutanoate (Table 1: entry 48), and the competing ketone reduction was a major reaction. The aromatic keto ester, methyl benzoyl formate reacted even slower with benzylamine and was also accompanied by considerable ketone reduction (Table 1: entry 49). Reactions involving other less reactive amines such as aniline or morpholine were much slower

and gave increasing amounts of ketone reductions. Whenever ketone reduction was a problem, the conditions were modified to use the amines as limiting reagents. The excess ketones were completely reduced to the corresponding alcohols which required the occasional addition of excess reducing agent. *N*-Substituted α-amino esters were also prepared by the reductive amination of α-amino esters with ketones, e.g., *N*-(2-butyl)glycine ethyl ester was prepared in very good yield from ethyl glycinate and 2-butanone (Table 1: entry 50).

The reductive amination of cyclohexanedione monoethylene ketal with phenylhydrazine gave cleanly the *N*-substituted phenylhydrazine (Table 1: entry 51) in nearly quantitative yield. Other ketones such as cyclohexanone and 2-heptanone reacted to give similar products (Table 1: entries 52 and 53); however, there were some competing side reactions. The crude products showed the formation of byproducts, about 15% with cyclohexanone and 31% with 2-heptanone. Attempted reductive amination of cyclooctanone with hydroxylamine was not successful and resulted in the oxime formation (Table 1: entry 54).

Reductive aminations in which diamines containing both primary and secondary amino groups were studied and in general, primary amines reacted faster. In the case where the primary amino group was aliphatic and the secondary group was aromatic, e.g., *N*-phenylethylenediamine, there was a clear difference in reactivity between the two amines. The reaction with 4-heptanone gave a quantitative yield of the product resulting from exclusive reaction with the primary amine (Table 1: entry 55). In the case where both amino groups were aliphatic, such as 1-(2-aminoethyl)piperazine, there was a high selectivity (94:6) for the primary group in reaction with acetylcyclohexane (Table 1: entry 56).

(b) Reductive Amination of Aldehydes. Unlike ketones, aldehydes can be reduced with sodium triacetoxyborohydride.[18] Thus, the possibility exists that the reduction of the aldehyde would compete with the reductive amination process under the standard conditions. However, these conditions were so selective that the reductive aminations with aldehydes occurred very effectively and resulted in fast reactions with no aldehyde reductions in most cases studied (Table 2). One case in which aldehyde reduction was detected involved a reaction with the very sterically hindered diisopropylamine (Table 2: entry 6). All other examples in Table 2 resulted in fast and efficient reductive aminations with a variety of aliphatic primary and secondary amines as well as aniline with no detectable aldehyde reductions. Both aliphatic and aromatic aldehydes were very reactive and gave reductive amination products with a broad variety of primary and secondary amines. The reaction times ranged from 20 min to 24 h. The mildness of the reaction conditions is well illustrated in the reductive amination of 1,1′,2-tris-nor-squalene aldehyde with diethylamine and diisopropylamine (Table 2: entries 19 and 20). The aldehyde was cleanly converted to the corresponding amines in high yields with no detectable side reactions.

In the reductive amination of aldehydes with primary amines, formation of dialkylated amines is a common side reaction.[5] This side reaction was rarely a problem in most reactions reported in Table 2. In the few cases when it was detected, it was suppressed by the addition of up to 5% molar excess of the primary amine. However, the dialkylation of amines remained a problem with certain substrates.[25] An alternative stepwise procedure for such systems is discussed later in this paper.

Some aldehydes, such as formaldehyde and glutaraldehyde are only available commercially as aqueous solutions which may restrict their use under the above reaction conditions because of the decomposition of the hydride reagent with water. However, the reaction may be carried out in DCE with excess hydride reagent, e.g., the reductive amination of either aqueous glutaraldehyde or formaldehyde with 1-phenylpiperazine and about 4 hydride equivalents was carried out on 10 mmol scale (Table 2: entries 21 and 22) and gave nearly quantitative yields of the corresponding amines. This, however, may not be suitable for large scale reactions.

The use of phenylhydrazine in reductive amination of benzaldehyde was not successful, resulting only in hydrazone formation.

Generally, with either ketones or aldehydes, reactions in DCE were noticeably faster than those carried out in THF (e.g., Table 1: entries 6 vs 7; 25 vs 26 and Table 2: entries 3 vs 4; 9 vs 10). Also, in the same solvent, reactions were consistently faster in the presence of 1 (or more) mol equiv of acetic acid. For most ketones, reactions were improved in the presence of acetic acid. However, the addition of acetic acid is not always advantageous to the reaction. Most reactions with aldehydes are fast and do not require addition of AcOH. Addition of AcOH to a slow reaction, e.g., cyclohexanecarboxaldehyde with diisopropylamine, resulted in a fast reaction accompanied with about 25% aldehyde reduction, and the yield of the isolated desired product was only 41%. When the reaction was carried out in the absence of AcOH, the reaction was slower; however, the aldehyde reduction was only about 5%, and the isolated yield of the purified reductive amination product increased to 75% (Table 2: entries 6 and 7). Direct comparisons were made between reactions in DCE and THF and with or without added acetic acid in representative reactions. The rate of product formation was determined quantitatively[26] in each case. The results of these comparisons were in agreement with the above observations.

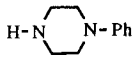
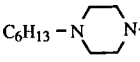
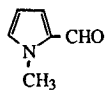
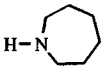
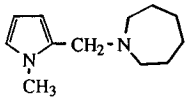
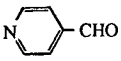
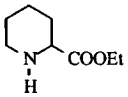
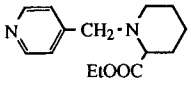
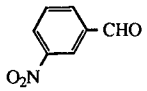
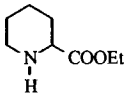
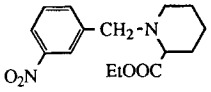
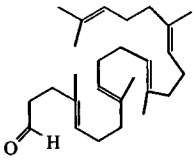
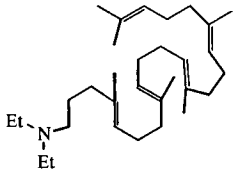
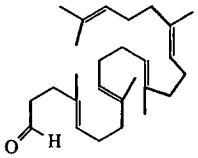
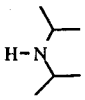
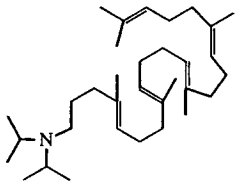
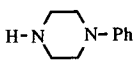
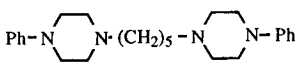
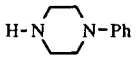
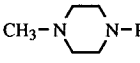
(c) Reductive Amination with Weakly Basic and Nonbasic Amines. Few literature references have dealt with aromatic amines containing electron withdrawing substituents in reductive amination reactions.[13,21a] Catalytic hydrogenation conditions do not allow the presence of many of the easily reduced electron-withdrawing substituents such as cyano and nitro groups, since these substituents are often reduced under catalytic hydrogenation conditions.[6,7] On the other hand, we and others[13a,b] have found the most used hydride reagent, sodium cyanoborohydride [$NaBH_3CN$], to be sluggish and inefficient when used with these weak bases in reductive amination reactions.

As a consequence of substitution by electron-withdrawing substituents, these amines are both poor nucleophiles and weak bases (e.g., pK_a 3.98 for 4-chloroaniline, 1.02 for 4-nitroaniline, −0.29 for 2-nitroaniline, −4.26 for 2,4-dinitroaniline).[27] This slows the initial nucleophilic at-

(25) For a discussion of the dialkylation side reactions involving γ- and δ-amino esters with aldehydes and a mechanistic explanation, see: Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.

(26) The progress of these reactions was followed by GC. Linear standard curves of the response factors by GC areas of starting materials and expected products were determined to allow the quantitative measurements of their concentrations in the reaction mixtures.

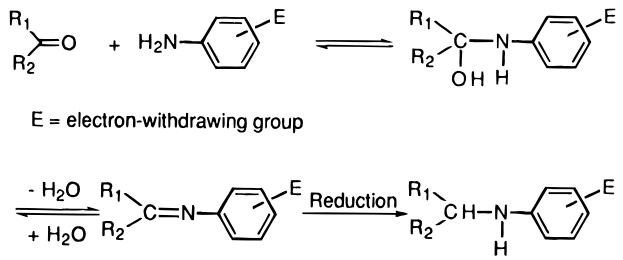
Table 2. Reductive Amination of Aldehydes

Entry	ALDEHYDE	AMINE	Method[a]	Time	PRODUCT	YIELD (%) Base[b]	Salt[c]
1.		Benzylamine	II	1 h		98	80 (HCl)
2.	"	Aniline	II	24 h	*N*-(Cyclohexylmethyl)aniline	95	85 (HCl)
3.	"	Morpholine	IV	2 h	*N*-(Cyclohexylmethyl)morpholine	74	63 (HCl)
4.	"	Morpholine	II	1 h	*N*- (Cyclohexylmethyl)morpholine	86	80 (HCl)
5.	"	Et_2NH	II	30 min	*N*-(Cyclohexylmethyl)diethylamine	95	84 (HCl)
6.	"	$(i\text{-Pr})_2NH$	I	3 h	$c\text{-}C_6H_{11}\text{-}CH_2\text{-}N(iPr)_2$	68	41 (HCl)
7.	"	$(i\text{-Pr})_2NH$	II	8 h	$c\text{-}C_6H_{11}\text{-}CH_2\text{-}N(iPr)_2$	88	75 (HCl)
8.	Hexanal		I	1 h		95	85 (ox)
9.	*m*-Anisaldehyde	Aniline	III	24 h	$m\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2\text{-}NH\text{-}Ph$	88	88 (HCl)
10.	*m*-Anisaldehyde	Aniline	I	20 min	$m\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2\text{-}NH\text{-}Ph$	-	95 (HCl)
11.	m-Anisaldehyde	Morpholine	IV	6 h	4-(3-Methoxybenzyl)morpholine	88	74 (HCl)
12.	Benzaldehyde	*tert*-Bu NH_2	I	3 h	*N*-(*tert*-Butyl) Benzylamine	95	92 (HCl)
13.	Benzaldehyde	*endo*-2-Aminonorbornane	II[d]	0.5 h	*endo*-*N*-Benzyl-2-aminonorbornane	97	85 (HCl)
14.	Benzaldehyde	*exo*-2-Aminonorbornane	I	3 h	*exo*-*N*-Benzyl-2-aminonorbornane	92	84 (HCl)
15.	Benzaldehyde	1-Adamantanamine	I	24 h	*N*-Benzyl-1-adamantanamine	—	66 (HCl)
16.			III	1.5 h		---	91 (ox)
17.			II	1.5 h		95	---
18.			II	1.5 h		96	---
19.		Et_2NH_2	II	1.5 h		98	---
20.			II	1.5 h		91	--
21.	 25% in H_2O		II	1 h		98	85 (ox)
22.	HCHO 30% in H_2O		II	1 h		98	82 (ox.)
23.	Benzaldehyde	Phenyl hydrazine	I	96 h	Hydrazone formation, No reduction	–	–

a) Methods: I: DCE, AcOH (1-2 eq.), $NaBH(OAc)_3$ (1.3-1.6 eq.); II: DCE, $NaBH(OAc)_3$ (1.3-1.6 eq.); III: THF, AcOH (1-2 eq.), $NaBH(OAc)_3$ (1.3-1.6 eq.); IV: THF, $NaBH(OAc)_3$ (1.3-1.6 eq.).
b) Yield of crude product determined to be > 96% pure by GC, c) ox = oxalate.
d) Reaction was carried out in presence of 1.5-2 equiv of Et_3N.

tack on the carbonyl carbon and leads to slower overall reaction rates (Scheme 2). In addition, the carbonyl group now competes effectively with the less basic intermediate imine for protonation and subsequently for the hydride in the reduction step.[2b] This may lead to a significant carbonyl reduction, consumption of both the carbonyl compound and the reducing agent and low yields of the reductive amination products. The reducing agent and reaction conditions should be chosen carefully to minimize such side reactions.

Scheme 2



Sodium triacetoxyborohydride is very efficient in reductive amination reactions with such unreactive amines. The results from several reactions are listed in Table 3. In several cases such as monosubstituted anilines (e.g., *p*-nitro-*p*-carbethoxy-, and *p*-cyanoanilines), the standard reaction conditions described previously (about 1:1 ratio of carbonyl compound to amine, 1.4 equiv of $NaBH(OAc)_3$ with 1 equiv of acetic acid) were adequate. However, with less basic amines such as *o*-nitroaniline, 2,4-dichloroaniline, or 2-aminothiazole, the reaction conditions were modified to compensate for the aforementioned effects and to maximize the yields of the reductive amination products. The optimum conditions included the use of the amine as the limiting reagent with 1.5−2 mol equiv of the carbonyl compound, 2−3 equiv of $NaBH(OAc)_3$, and 2−5 equiv of AcOH in 1,2-dichloroethane. Under these conditions, a variety of weakly basic amines were successfully employed in the reductive aminations of ketones and aldehydes in isolated yields ranging from 60% to 96%. The reaction is convenient and the conditions are mild and show a high degree of tolerance for a variety of functional groups including nitro, cyano, halo, carboxy, and carbethoxy groups.

Ketones reacted effectively with *p*-monosubstituted anilines to give good yields of the reductive amination products (Table 3: entries 1−8). The reaction was slightly slower with 2,4-dichloroaniline and gave a high yield of the desired reductive amination product in addition to some ketone reduction and the formation of about 3% of *N*-ethyl-2,4-dichloroaniline (Table 3: entry 9). The reaction became very slow with *o*-nitroaniline which progressed only to about 30% conversion to the reductive amination product and 17% of *N*-ethyl-2-nitroaniline after 6 days (Table 3: entry 10). The reaction stopped completely when both *ortho* positions were substituted as in 2,6-dibromo- and 2,4,6-trichloroanilines (Table 3: entries 11 and 12).

The reactions with aldehydes were faster than those with ketones and gave higher yields from similar reactions. Aldehyde reductions occurred only with the least reactive amines. In the reductive amination of aldehydes with *p*-carboxyaniline and *p*-nitroaniline (Table 3: entries 13, 14, and 18), no competing aldehyde reduction was observed. In these cases, the standard conditions were used. With weaker amines such as 2,4-dichloroaniline and *o*-nitroaniline (Table 3: entries 15 and 16), the conditions were modified to use the amine as a limiting reagent since aldehyde reduction occurred to the extent of 10−30%. This procedure was applied to other weakly basic primary amines such as 2-aminothiazole (Table 3: entries 22 and 23) and secondary amines such as iminostilbene (Table 3: entry 24). While iminostilbene reacted with hexanal to give a high yield of the *N*-hexyl product, the dihydro analogue iminodibenzyl gave no reaction under the same conditions (Table 3: entry 25).

One of the most unique reactions, however, was the reductive alkylation of *p*-toluenesulfonamide with benzaldehyde to give the *N*-benzyl derivative (Table 3: entry 26). The reaction is carried out initially under the standard conditions in the presence of Et_3N (2 equiv). The aldehyde is usually consumed in about 24 h to give a mixture of *N*-benzyl *p*-toluenesulfonamide and *N*-benzal *p*-toluenesulfonamide. The reaction mixture is then treated with AcOH (2.5 equiv) and additional $NaBH(OAc)_3$ (1 equiv) to finish the reduction. The reaction, however, was not successful with ketones or carboxamides.

The least reactive amines, 2,4-dinitroaniline and 2,4,6-trichloroaniline failed to undergo reductive amination with benzaldehyde (Table 3: entries 20 and 21). Cyclohexanecarboxaldehyde, on the other hand, reacted slowly with these two amines to give the corresponding reductive amination products. In these two reactions, the aldehyde reduction became a major reaction process. To assure the presence of enough aldehyde to react with the amine, the reaction required occasional additions of aldehyde and reducing agent, up to 5 equiv each and over a two to four day period (Scheme 3). The reactions progressed to reach 90−92% conversion (as determined by GC) and gave 61% and 58% isolated yields, respectively, after chromatography. It is possible that these reactions proceed via initial formation of intermediate enamines rather than imines which may explain the lack of reactivity of aromatic aldehydes which cannot form enamines.

(d) Comparison with Other Reducing Agents. In general, the results of reductive amination employing sodium triacetoxyborohydride were as good as or better than most comparable reported results whether done using hydrogenation or hydride reagents. However, in many cases, our results were far superior to others. For example, we compared the reductive amination of cyclohexanone with morpholine using $NaBH_3CN$ vs $NaBH(OAc)_3$. The reaction with $NaBH_3CN$ (6 hydride equiv) in methanol and in the absence of AcOH was only 34% complete after 23 h with the formation of about 10% of the corresponding enamine. The conversion improved to 50% in 23 h with AcOH (1 equiv) with no enamine formation. The reaction using the standard $NaBH(OAc)_3$ conditions was 99.8% complete in 3 h without a trace of enamine formation (Table 1: entry 5). In another comparison, the reductive amination of 1-carbethoxy-4-piperidinone with *p*-chloroaniline was only 45% complete with $NaBH_3CN$ after 22 h but was >96% with $NaBH(OAc)_3$ in 2.5 h (Table 3: entry 4).

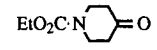
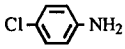
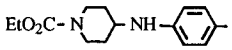
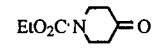
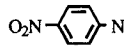
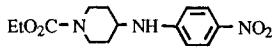
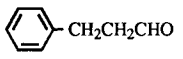
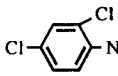
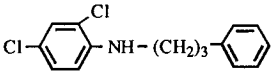
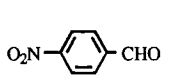
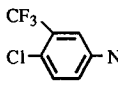
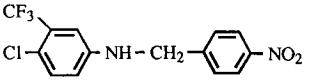
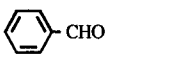
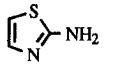
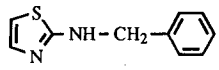
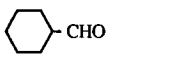
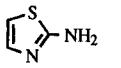
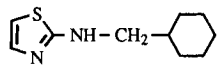
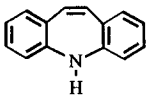
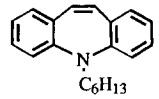
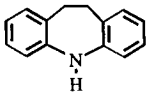
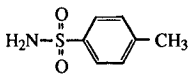
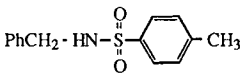
An impressive result was obtained in the reductive amination of 1,1′,2-tris-nor-squalene aldehyde with diethylamine and isopropylamine. These reactions were reported to give about 5% yield under regular Borch conditions.[28] The yields were improved to 46 and 42%, respectively, when the reactions were carried out with $NaBH_3CN$ in anhydrous THF in the presence of HCl (pH 3).[29] Under our standard conditions, these reactions gave

(27) (a) Albert, A.; Serjeant, E. P. In *The Determination of Ionization Constants*; Chapman and Hall: London, 1971; p 91. (b) Yates, K; Wai, H. *J. Am. Chem. Soc.* **1964**, *86*, 5408.

(28) Duriatti, A.; Bouvier-Nave, P.; Benveniste, P.; Schuber, F.; Delprino, L.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34*, 2765.

(29) Ceruti, M.; Balliano, G.; Viola, F.; Cattel; L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199.

Table 3. Reductive Amination with Weakly Basic Amines

Entry	CARBONYL COMPOUND	AMINE	Method[a]	Time	PRODUCT	YIELD[b](%)
1.	Cyclopentanone	*p*-Bromoaniline	I	48 h	*N*-(Cyclopentyl)-*p*-bromoaniline	89 (HCl)
2.	Cyclohexanone	*p*-Nitroaniline	VI	23 h	*N*-(Cyclohexyl)-*p*-nitroaniline	66
3.	Cyclohexanone	*p*-Chloroaniline	I	3.3 h	*N*-(Cyclohexyl)-*p*-chloroaniline	90 (HCl)
4.			I	3.5 h		85
5.			VI	18 h		60
6.	Cycloheptanone	*p*-Carboxyaniline	VI	22 h	*p*-Carboxy-*N*-cycloheptylaniline	79
7.	Cycloheptanone	*p*-Cyanoaniline	VI	24 h	*p*-Cyano-*N*-cycloheptylaniline	71
8.	2-Heptanone	*p*-Carbethoxyaniline	I	14 h	*p*-Carbethoxy-*N*-(2-heptyl)aniline	66
9.	Cyclohexanone	2,4-Dichloroaniline	VI	37 h	*N*-Cyclohexyl-2,4-dichloroaniline	95
10.	Cyclohexanone	*o*-Nitroaniline	VI	144 h	*N*-Cyclohexyl-2-nitroaniline	30[c]
11.	4-Heptanone	2,6-Dibromoaniline	VI	24 h	No Reaction	
12.	Cycloheptanone	2,4,6-Trichloroaniline	VI	24 h	No Reaction	
13.	c-C_6H_{11}-CHO	*p*-Nitroaniline	I	1.5 h	*p*-Nitro-*N*-(cyclohexylmethyl)aniline	95
14.	c-C_6H_{11}-CHO	*p*-Carboxyaniline	I	0.5 h	*p*-Carboxy-*N*-(cyclohexylmethyl)aniline	85
15.	c-C_6H_{11}-CHO	2,4-Dichloroaniline	VI	0.6 h	2,4-Dichloro-N-cyclohexylmethylaniline	96
16.	c-C_6H_{11}-CHO	*o*-Nitroaniline	VI	1.5 h	*o*-Nitro-*N*-cyclohexylmethylaniline	95
17.			VI	1.5 h		70[d] (HCl)
18.	Benzaldehyde	*p*-Nitroaniline	I	1.5 h	*p*-Nitro-*N*-benzylaniline	85
19.			I	1.5 h		75
20.	Benzaldehyde	2,4-Dinitroaniline	VI	24 h	No Reaction	
21.	Benzaldehyde	2,4,6-Trichloroaniline	VI	24 h	No Reaction	
22.			VI	72h		60
23.			VI	16h		85
24.	C_5H_{11}-CHO		VI	10 h		82
25.	C_5H_{11}-CHO		VI	24 h	No Reaction	
26.	Benzaldehyde		VI[e]	48 h		80
27.	Benzaldehyde	Benzamide	I	24 h	No reaction	

a) Methods: I: DCE, AcOH (1 eq.), $NaBH(OAc)_3$ (1.4 eq.); VI : DCE, amine (1 eq.), AcOH (2 - 5 eq.), $NaBH(OAc)_3$ (2 - 2.8 eq.), carbonyl compound (1.5 - 2 eq.)
b) Yield of isolated product, > 96% by GC area % analysis. Except for the cases indicated, all isolated as free bases.
c) Yield was determined by GC and the product was only characterized by GC/MS.
d) Crude product contained about 5% dialkylated amine.
e) Reaction was carried out in presence of 2 equiv of Et_3N.

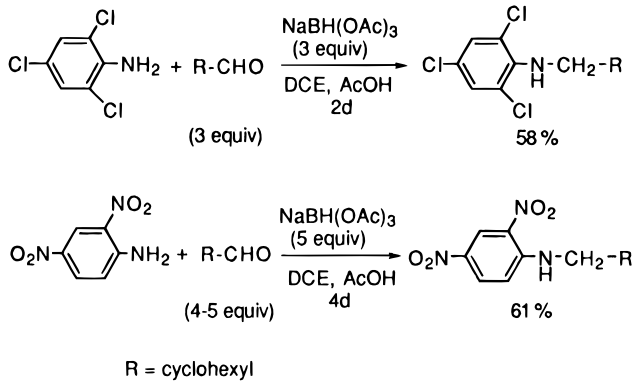
98 and 90% yield of products in high purity without chromatography (Table 2: entries 19 and 20).

The reductive amination of either 2-indanone, β-tetralone, or phenylacetone with aniline was reported to work when aniline was used as solvent under catalytic hydrogenation conditions and gave 72%, 54%, and 21% yield of products, respectively.[30] We obtained 85%, 87%, and 80% yield of these products using stoichiometric amounts of reagents under the standard conditions (Table 1: entries 12, 13, and 38).

Borane−pyridine is another reducing agent used for reductive amination reactions.[13a] Its use in the reductive amination of either pyridine-4-carboxaldehyde or *m*-nitrobenzaldehyde with ethyl piperidine-2-carboxylate

(30) Campbell, J. B.; Lavagnino, E. P. In *Catalysis in Organic Syntheses*; Jones, W. H., Ed.; Academic Press: New York, 1980; p 43.

Scheme 3



gave 12% and 13% yield of isolated reductive amination products, respectively, and considerable aldehyde reduction.[14b] Under our standard conditions, we did not observe any aldehyde reduction, and the isolated yields were nearly quantitative (Table 2: entries 17 and 18).

(e) Stepwise (*Indirect*) Reductive Amination of Aldehydes. Occasionally, some reactions of aldehydes and primary amines gave considerable amounts of dialkylation or other side products. As we mentioned previously, the addition of a slight excess of the primary amine may suppress this side reaction. However, the dialkylation of certain primary amines such as γ- or δ-amino esters and cyclobutylamine, remained a problem. This also occurred when certain aldehydes were used, such as cinnamaldehyde, hydrocinnamaldehyde, and some straight chain aldehydes. Those particular cases gave mixtures of monoalkylated and dialkylated amines in ratios ranging from 5:1 and up to 1:1 under the standard reaction conditions. Surprisingly, in some reactions, the dialkylation side reaction happened even when excess amine was used or when the reaction was carried out with a "preformed imine" and no excess aldehyde present. A discussion and a possible explanation of some of these results in case of γ- and δ-amino esters was reported.[25] We developed an alternative procedure for such reactions which involves the fast reduction of *preformed imines*. Imine formation, however, is a reversible reaction and requires long reaction times and the use of a dehydrating agent such as molecular sieves or azeotropic removal of water to drive the reaction to completion. We studied the relative rates of imine formation from aldehydes and primary amines in different solvents, namely THF, DCE, and methanol without added catalysts or dehydrating agents. A comparison of the relative rates of imine formation in the three solvents is listed in Table 4. The relative ratio of product imine to reactant aldehyde was determined by GC analysis of the reaction mixture and confirmed in some cases by ^{1}H NMR in CD_3OD, THF-d_8, or $CDCl_3$. In all the cases listed in Table 4, reactions in methanol were consistently faster and gave nearly quantitative conversions relative to those carried out in THF or DCE. The imine formation was slower for ketones in all three solvents; however, the reaction was still faster in methanol (Table 4: entry 7).

The reduction of the aldimines was carried out directly in methanol with sodium borohydride to give the corresponding secondary amines in very high yields and very short reaction times. Thus, this stepwise (or indirect) one-pot procedure involving imine formation in methanol followed by *in situ* reduction with sodium borohydride is a very convenient and efficient alternative for carrying out reductive aminations on substrates which tend to give significant amounts of dialkylated products using the direct procedure.

A similar transformation along the lines of prior formation of the imine is prior formation and then reduction of the enamine. We have found that sodium triacetoxyborohydride reduces enamines quickly and efficiently in DCE to give products in high yields (Table 5: entries 6 and 7), making it a useful reagent for this stepwise procedure.

Another very efficient stepwise reductive amination procedure was developed by Mattson *et al.*[13b] In this procedure, the amine and the carbonyl compound are mixed in neat titanium(IV) isopropoxide and the resulting intermediate is reduced with $NaBH_3CN$ in ethanol. The authors reported the formation of a carbinol amine intermediate (see Table 5: entries 8−10) rather than the usual iminium ion. The method is applicable to primary and secondary amines. We modified this procedure to reduce the intermediate with $NaBH_4$ in methanol (instead of $NaBH_3CN$/ethanol).[31] This modified reduction is very fast and gives the desired amine in very good yield and high purity, e.g., the reductive amination of the unsaturated ketone 1-acetylcyclohexene with benzylamine, which was very slow under our standard conditions, proceeded very fast under these modified conditions to give a quantitative yield of the reductive amination product (Table 5: entry 8). Of particular interest, the reductive amination of tropinone with benzylamine using this procedure which gave a near quantitative yield of a 3:2 mixture of the *endo*- and *exo* products (Table 5: entry 10). As reported earlier, this reaction gave approximately 20:1 ratio of the *endo* and *exo* products using $NaBH(OAc)_3$ (Table 1: entry 28). Attempts to achieve a reaction between tropinone and aniline using this modified system resulted in incomplete reactions. In regards to secondary amines, Mattson *et al.*[13b] reported a successful reductive amination of tropinone with piperidine in 58% yield; however, the stereochemistry of the product was not disclosed. Our modified conditions gave the product in a 90% crude yield as a mixture of the *endo*- and *exo*-products in about 1:7 ratio. The pure oxalate salt of the *exo* product was isolated in 66% yield (Table 5: entry 9). The *exo*-stereoselectivity of this reaction is opposite to that obtained from the primary amines. We are examining these systems to better understand their mechanistic pathway.

Summary and Conclusions

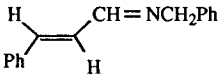
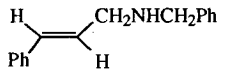
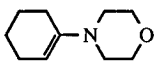
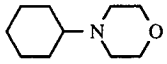
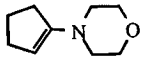
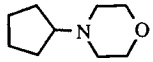
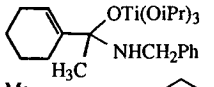
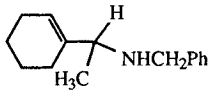
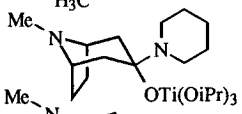
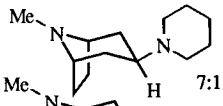
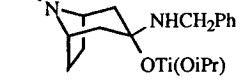
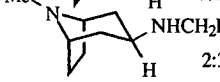
The results presented here indicate that sodium triacetoxyborohydride is a synthetically useful reagent for reductive aminations of aldehydes and ketones. It is a mild, commercially available reagent, and it is a reagent of choice for reductive amination of carbonyl compounds. The scope of the reaction covers all aldehydes and unhindered aliphatic ketones. Aliphatic ketones (and aldehydes) can be selectively reductively aminated in the

(31) (a) We reported the use of this modification of Mattson's procedure ($Ti(OiPr)_4$−$NaBH_4$/MeOH, rt) at the 198th ACS National Meeting, Miami Beach, FL, September 1989; paper ORGN 154 and at The International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December 1989; paper ORGN 409, Abdel-Magid, A. F.; Maryanoff, C. A.; Sorgi, K. L.; Carson, K. G. A similar modification [$Ti(OiPr)_4$−$NaBH_4$ in diglyme at 60 °C or in ethanol at 25 °C)] was reported recently: (b) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401. (c) Bhattacharyya, S. *Synlett* **1994**, 1029; (d) Bhattacharyya, S. *Synth. Commun.* **1995**, *25*, 9.

Table 4. Imine Formation from Aldehydes and Primary Amines

Entry	Aldehyde	Amine	Time (h)	Yield (%) by GC (solvent)	Yield (%) by ^{1}H NMR (solvent)
1	benzaldehyde	*tert*-$BuNH_2$	22	84 (DCE)	80 ($CDCl_3$)
			22	95 (THF)	98 (THF-d_8)
			4	97 (MeOH)	97 (CD_3OD)
2	benzaldehyde	aniline	4.2	81 (DCE)	90 ($CDCl_3$)
			4.3	74 (THF)	75 (THF-d_8)
			1.5	99 (MeOH)	97 (CD_3OD)
3	*m*-anisaldehyde	aniline	24	92 (DCE)	
			26	84 (THF)	
			2.4	99 (MeOH)	
4	*m*-anisaldehyde	2-(3,4-dimethoxyphenyl)ethylamine	2	97 (DCE)	100 ($CDCl_3$)
			0.24	95 (THF)	100 (THF-d_8)
			0.25	98 (MeOH)	100 (CD_3OD)
5	c-$C_6H_{11}CHO$	aniline	5.4	89 (DCE)	
			5.3	90 (THF)	
			2.7	96 (MeOH)	
6	c-$C_6H_{11}CHO$	*tert*-$BuNH_2$	4.6	89 (DCE)	
			5.3	90 (THF)	
			2.7	94 (MeOH)	
7	cycloheptanone	benzylamine	23	53 (DCE)	
			23	75 (THF)	
			23	85 (MeOH)	

Table 5. Stepwise Reductive Amination Reactions

Entry	SUBSTRATE	Time	Method[a]	PRODUCT	Yield (%) base	Yield (%) salt[b]
1	c-C_6H_{11} – CH = NPh	10 min	A	c-C_6H_{11} – CH_2 – NHPh	95	90 (HCl)
2	*m*-CH_3O-C_6H_4 – CH = N-Ph	10 min	A	*m*-CH_3O-C_6H_4 – CH_2 – NH-Ph	-	84 (HCl)
3	c-C_6H_{11} – CH = N-*t*-Bu	10 min	A	c-C_6H_{11} – CH_2 – NH-*t*-Bu	-	83 (HCl)
4	*p*-Cl-C_6H_5 - CH = N- 	10 min	A	*p*-Cl-C_6H_5 – CH_2 – N(H)- 	98	89 (HCl)
5		15 min	A		-	85 (HCl)
6		10 min	B		99	91 (HCl)
7		20 min	B		99	80 (HCl)
8		5 min	C		qu	83 (HCl)
9		20 min	C	 7:1 *exo/endo*	90	66 (ox)
10		10 min	C	 2:3 *exo/endo*	93	--

a) Methods A: Imine formation followed by $NaBH_4$ reduction in methanol.
B: Reduction of enamine with $NaBH(OAc)_3$ in DCE, 1 equiv of AcOH.
C: Mixing of carbonyl compound and amine in neat $Ti(OiPr)_4$ for 2 - 3 h, dilution with methanol and reduction with $NaBH_4$. The nature of the intermediates is uncertain, structures in entries 8 - 10 are proposed in reference 14b.
b) ox = oxalate, qu = quantitative

presence of aromatic and α,β-unsaturated ketones. Aliphatic and aromatic primary and sterically unhindered secondary amines can be used in these reactions. The procedure was superior with weakly basic and nonbasic amines. In representative comparisons with other commonly used reducing reductive amination reagents, sodium triacetoxyborohydride reacted consistently faster, gave better yields, and produced fewer side products. Methanol allows a rapid formation of imines from aldehydes and primary amines. Aldimines formed in methanol were efficiently reduced to their corresponding amines using $NaBH_4$.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz. The chemical shifts are expressed as δ units with Me_4Si as the internal standard. IR spectra were recorded on an FT-IR spectrometer and absorptions are reported in wave numbers (cm^{-1}). GC-MS (EI) were recorded on a GC/MSD instrument using a cross linked methyl

silicone 12 m × 0.2 mm × 0.33 mm capillary column. Mass spectra were recorded as CI or FAB. Accurate mass measurements were carried out using a double-focusing instrument of EB configuration (where E is an electric sector and B is a magnet). The reported accurate mass (mass-to-charge ratio) measurement values (mean ± 3σ) are for the $[MH]^+$ ions of the analytes of interest and are the average of nine individual determinations. The deviation of the experimental determinations from the theoretical values are expressed in parts-per-million (ppm). GC analyses were carried out on a cross linked methyl silicone 12 m × 0.2 mm × 0.33 μm capillary column or DB-17; 15 m × 0.2 mm × 0.25 μm. Sodium triacetoxyborohydride was purchased from Aldrich Chemical Company, Inc. Most reagents were commercially available reagent grade chemicals and used without further purification.

Procedures. 1. Direct Reductive Amination Methods. General Notes. (a) The amine and the carbonyl compound are mixed in 1,2-dichloroethane and treated with $NaBH(OAc)_3$. THF, CH_2Cl_2, or CH_3CN may also be used as solvents.

(b) Acetic acid (1−2 mol equiv) may be used in reactions of ketones but is not necessary with most aldehydes.

(c) Reactions are normally carried out using the free amines; however, the amine salt may be used. In this case, 1−2 equiv of Et_3N is added to the reaction mixture. The Et_3N must be removed from basified product prior to salt formation.

(d) The progress of the reaction is followed by GC analysis in most cases. A small aliquot is withdrawn from the reaction mixture, quenched with aqueous NaOH or aqueous $NaHCO_3$ and extracted with ether or any other suitable solvent and injected into the GC. In case of high MW or heat-sensitive compounds HPLC or TLC could be used.

(e) The reactions are usually quenched with aqueous 1 N NaOH. In the presence of esters, or other alkali hydroxide sensitive functional groups, aqueous $NaHCO_3$ is used for quench. Reactive amines such as benzylamine may dissolve in aqueous $NaHCO_3$ and that may give a false indication of their consumption.

(f) Most amines form HCl salts cleanly in ether with ethereal HCl, and most of these salts are recrystallized from EtOAc/MeOH. Some aromatic HCl salts may turn dark and a few aliphatic amine salts may be difficult to crystallize or may be hygroscopic; in these cases the oxalate salts are prepared, usually in MeOH. Picrate salts are prepared in ethanol.

Method I. This procedure is used for most ketone reactions. A representative example is the reductive amination of cyclopentanone with hexamethyleneimine (Table 1: entry 4): Hexamethyleneimine (1.0 g, 10 mmol) and cyclopentanone (0.84 g, 10 mmol) were mixed in 1,2-dichloroethane (35 mL) and then treated with sodium triacetoxyborohydride (3.0 g, 14 mmol) and AcOH (0.6 g, 10 mmol). The mixture was stirred at rt under a N_2 atmosphere for 24 h until the reactants were consumed as determined by GC analysis. The reaction mixture was quenched by adding 1 N NaOH, and the product was extracted with ether. The ether extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the crude free base (1.60 g, 96%). The oxalate salt was prepared in EtOAc/MeOH as shiny white crystals (2.2 g, 85.5%): mp 171−172 °C; FT-IR (KBr) 3435 (w), 2934 (s), 2872 (m), 2683 (m), 2648 (m), 2585 (m), 2524 (m), 1720 (m), 1623 (m), 1455 (m), 1404 (m), 1204 (m), 1116 (m), 717 (m), 499 (m), 466 (m) cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 2.94−2.83 (m, 1H), 2.68−2.65 (m, 4H), 1.87−1.25 (m, 16H); ^{13}C NMR (free base, $CDCl_3$) δ 65.9 (CH), 53.6 (CH_2), 30.2 (CH_2), 27.9 (CH_2), 26.9 (CH_2), 24.1 (CH_2); EI MS *m*/*z* (relative intensity) 167 (M^+, 15), 138 (100), 124 (17), 110 (24), 96 (9), 82 (7), 55 (16). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.69; H, 9.03; N, 5.44.

Method II. The above procedure is followed without the addition of glacial acetic acid. The reaction mixture remains cloudy throughout the reaction. This procedure is more appropriate with most aldehydes and unhindered aliphatic ketones. A representative example is the reductive amination of 4-pyridinecarboxaldehyde with ethyl 2-piperidinecarboxylate (Table 2: entry 17): Ethyl-2-piperidinecarboxylate (1.57 g, 10 mmol) and 4-pyridinecarboxaldehyde (1.07 g, 10 mmol) were mixed in 1,2-dichloroethane (35 mL) and then treated with sodium triacetoxyborohydride (3.0 g, 14 mmol). The mixture was stirred at rt under a N_2 atmosphere for 1.5 h. The GC analysis showed >90% conversion in 30 min, but the remainder of the time was needed for the complete conversion. The reaction mixture was quenched by adding aqueous saturated $NaHCO_3$, and the product was extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$), and the solvent was evaporated to give the crude free base (2.40 g, 96.7%), >98% pure by area % GC analysis. A small portion was converted to the dioxalate salt: an off-white solid, mp 109−111 °C (EtOAc/MeOH); FT-IR (KBr) 3076 (w), 2968 (w), 2870 (w), 2521 (m), 1738 (s), 1603 (s), 1504 (m), 1460 (w), 1372 (w), 1204 (s), 999 (w), 714 (m) cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 8.52 (d, J = 5.2 Hz, 2H), 7.29 (d, J = 5.2 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.80 (d, J = 14.4 Hz, 1H), 3.43 (d, J = 14.4 Hz, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.20 (m, 1H), 1.85 (m, 2H), 1.55 (m, 3H), 1.45 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (free base, $CDCl_3$) δ 174.1 (C), 153.3 (C), 149.7 (CH), 125.8 (CH), 64.8 (CH), 61.8 (CH_2), 59.9 (CH_2), 51.0 (CH_2), 30.5 (CH_2), 26.4 (CH_2), 23.1 (CH_2), 15.8 (CH_3); EI MS *m*/*z* (relative intensity) 175 ($M^+ - CO_2Et$, 100), 147 (4), 93 (5), 92 (25), 82 (5), 65 (15). Anal. Calcd for $C_{18}H_{24}N_2O_{10}$: C, 50.47; H, 5.65; N, 6.54. Found: C, 50.26; H, 5.74; N, 6.44.

Method III. Same as Method I except for using THF as a solvent. An example is the reductive amination of 2-heptanone with morpholine (Table 1: entry 33): 2-Heptanone (2.28 g, 20 mmol) and morpholine (1.92 g, 22 mmol) were mixed in THF (80 mL) at rt under N_2. Sodium triacetoxyborohydride (6.36 g, 30 mmol) and glacial AcOH (1.20 g, 20 mmol) were added, and the mixture was stirred at rt for 27 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution, and the product was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and cooled in an ice bath and then treated with ethereal HCl. The product precipitated as a white solid. The solid was collected by filtration and dried; yield: 3.24 g, 73% (>98% by GC area % analysis) mp 150−151 °C. The analytical sample was obtained as a white crystalline solid by recrystallization from EtOAc/MeOH: mp 151−153 °C; FT-IR (KBr) 3410 (m), 2924 (s), 2863 (s), 2656 (s), 2604 (s), 2462 (m), 1434 (m), 1266 (m), 1114 (s), 1073 (m), 928 (m), 881 (m); ^1H NMR ($CDCl_3$) δ 12.60 (bs, 1H), 4.43 (dt, J = 12.8, 2.1 Hz, 2H), 3.98 (dd, J = 12.8, 3.0 Hz, 2H), 3.30−3.16 (m, 3H), 3.09−2.95 (m, 2H), 2.15−2.06 (m, 1H), 1.64−1.10 (m, 10H), 1.44 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 63.43 (CH_2), 63.37 (CH_2), 62.5 (CH), 47.9 (CH_2), 47.4 (CH_2), 31.2 (CH_2), 30.0 (CH_2), 25.8 (CH_2), 22.2 (CH_2), 13.7 (CH_3), 13.4 (CH_3); EI MS *m*/*z* (relative intensity) 185 (M^+, 5), 170 (28), 115 (31), 114 (100), 86 (7), 84 (7), 70 (28). Anal. Calcd for $C_{11}H_{24}ClNO$: C, 59.58; H, 10.91; N, 6.32; Cl, 15.99. Found: C, 59.66; H, 11.00; N, 6.42; Cl, 16.09.

Method IV. Same as method II except for using THF as a solvent. An example is the reductive amination of β-tetralone with cyclohexylamine (Table 1: entry 10): Cyclohexylamine (1.09 g, 11 mmol) and β-tetralone (1.46 g, 10 mmol) were mixed in THF (50 mL) at rt under N_2. The mixture changed in about 1 min from yellow to dark blue in color. Sodium triacetoxyborohydride (3.18 g, 15 mmol) was added and the mixture stirred at rt under a N_2 atmosphere for 24 h. The color of the reaction mixture became light pink at the end of the reaction time. The reaction mixture was quenched by adding aqueous 3 N NaOH (the color changed to dark green), and the product was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and cooled in an ice bath and then treated with ethereal HCl. The product precipitated as a white solid with a light pink shade. The solid was collected by filtration and dried; yield: 2.27 g, 85% (>98% by GC area % analysis). The analytical sample was obtained as a white solid by recrystallization from EtOAc/MeOH: mp 230−233 °C; FT-IR (KBr) 3415 (s), 2941 (s), 2819 (s), 2679 (m), 2506 (w), 2430 (w), 1452 (m), 742 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.60 (bs, 2H), 7.16−7.02 (m, 4H), 3.62−3.45 (m, 1H), 3.43−3.12 (m, 3H), 2.91−2.80 (m, 2H), 2.61−2.50 (m, 1H), 2.40−2.17 (m, 3H), 1.91−1.60 (m, 6H), 1.39−1.18 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 134.6 (C), 132.4 (C), 129.2 (CH), 128.6 (CH), 126.5 (CH), 126.1 (CH), 54.2 (CH), 51.0 (CH), 32.3 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 24.7 (CH_2); EI MS *m*/*z* (relative intensity) 229 (M^+, 46), 187

(13), 186 (85), 158 (12), 132 (11), 131 (77), 130 (100), 129 (34), 128 (20), 116 (14), 115 (26), 104 (23), 100 (17), 91 (35), 78 (11), 77 (12), 56 (28), 55 (31). Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.27; Cl, 13.34. Found: C, 72.41; H, 9.27; N, 5.17; Cl, 13.53.

Method V. This method is similar to methods I and II except for the use of acetonitrile as a solvent.

Method VI. This method was used with those reactions involving hindered α-keto esters or weakly basic amines in which a competitive reduction of the carbonyl compounds occur. The amine is used as a limiting reagent. A representative example of the α-keto esters is the reductive amination of methyl 3-methyl-2-oxobutanoate with benzylamine (Table 1: entry 48): methyl-3-methyl-2-oxobutanate (1.8 g, 12.48 mmol) and benzylamine (0.446 g, 4.16 mmol) in DCE (14 mL) was treated with sodium triacetoxyborohydride (1.76 g, 8.32 mmol) at 0 °C. After stirring 21 h, GC analysis showed total consumption of the benzylamine with the presence of the product amine and the intermediate imine in an 8:1 relative ratio. The reaction was then treated with additional sodium triacetoxyborohydride (0.88 g, 4.16 mmol). After stirring an additional 21 h, GC analysis showed completion of the reaction. The reaction mixture was diluted with EtOAc (20 mL) and quenched with distilled water (10 mL). After further dilution with EtOAc (20 mL), the pH of the water layer was adjusted to 7 with saturated aqueous $NaHCO_3$. The EtOAc layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product (2.45 g). The crude product was dissolved in ether and treated with ethereal HCl to give the HCl salt, 0.92 g, 81% yield, as a white solid: mp 190−191 °C; FT-IR (KBr) 2966 (m), 2806 (m), 2696 (m), 1742 (s), 1565 (m), 1469 (m), 1424 (m), 1249 (s), 1030 (m), 753 (m), 704 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.65 (bs, 1H), 10.00 (bs 1H), 7.66−7.63 (m, 2H), 7.41−7.38 (m, 3H), 4.40 (d, J = 13.3 Hz, 1H), 4.25 (d, J = 13.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.45−3.35 (m, 1H), 2.75−2.60 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7 (C), 130.9 (CH), 129.5 (CH), 129.0 (CH), 63.1 (CH_2), 62.2 (CH_2), 50.3 (CH_2), 29.4 (CH), 19.5 (CH_3), 17.6 (CH_3), 14.0 (CH_3); CI MS m/z (rel intensity) 236 (MH^+, 100), 162 (38), 91 (20). Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16: N, 5.15. Found: C, 61.94; H, 8.21: N, 5.05.

An example of the use of weakly basic amines is the reductive amination of 1-Carbethoxy-4-piperidone with *p*-nitroaniline (Table 3: entry 5): 1-Carbethoxy-4-piperidone (3.2 g, 19 mmol), *p*-nitroaniline (1.4 g, 10 mmol), and glacial AcOH (3.6 g, 60 mmol) were mixed in 1,2-dichloroethane (45 mL). Sodium triacetoxyborohydride (6.0 g, 28 mmol) was added to the above solution and the reaction mixture stirred at room temperature under N_2 for 18 h (GC analysis indicated a complete reaction in addition to ca 20% ketone reduction). The reaction was quenched with saturated aqueous $NaHCO_3$, and the product was extracted with EtOAc (3 × 75 mL). The EtOAc extract was dried ($MgSO_4$), and the solvent was evaporated to give a yellow semisolid (4.7 g). The semisolid was triturated with ether/hexane (7:3) to disolve the excess piperidone and the piperidol byproduct. The yellow solid was collected by filtration and dried (1.75 g, 60%), >99% pure by GC area % analysis. The analytical sample was obtained by recrystallization from EtOAc/hexane: mp 172−174 °C; FT-IR (KBr) 3327 (s), 3182 (w), 3097 (w), 2929 (w), 2870 (m), 2398 (m), 1679 (s), 1600 (s), 1546 (m), 1460 (s), 1387 (m), 1296 (s), 1234 (m), 1184 (m), 1144 (m), 1105 (s), 1033 (m), 937 (m); ^1H NMR ($CDCl_3/d_6$−DMSO) δ 8.03 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.14 (d, J = 7.5 Hz, 1H), 4.16−4.10 (m, 4H), 3.58−3.50 (m, 1H), 3.02 (m, 2H), 2.04−2.00 (m, 2H), 1.51−1.42 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3/d_6$−DMSO) δ 154.9 (C), 152.5 (C), 136.4 (C), 125.9 (CH), 110.6 (CH), 60.8 (CH_2), 49.0 (CH), 41.9 (CH_2), 31.0 (CH_2), 14.2 (CH_3); MS (EI), 293 (95), 277 (15), 276 (76), 264 (9), 248 (12), 220 (23), 177 (19), 156 (29), 155 (100), 154 (9), 131 (10), 130 (23), 129 (16), 128 (13), 127 (37), 126 (41), 117 (14), 100 (21), 96 (19), 82 (28), 57 (18), 56 (57). Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.27; H, 6.54; N, 14.21.

2. Stepwise Procedures. Aldimine Formation/Reduction in Methanol. An example is the preparation of *N*-cyclobutyl-4-chlorobenzylamine (Table 5: entry 4): *p*-Chlorobenzaldehyde (1.40 g, 10 mmol) and cyclobutylamine (0.75 g, 10.6 mmol) were mixed in MeOH (40 mL) at rt under a N_2 atmosphere. The mixture was stirred at rt for 3 h, until the aldimine formation was completed (determined by GC). The aldimine in MeOH was carefully treated with solid $NaBH_4$ (0.6 g, 16 mmol). The reaction mixture was stirred for 10 min and quenched with 1 M NaOH. The product was extracted with ether. The ether extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was evaporated to give the crude product as a nearly colorless oil (1.92 g, 98%) which was >97% pure by area % GC analysis. The oil was dissolved in ether and treated with ethereal HCl to give the HCl salt which was recrystallized from EtOAc/MeOH as white crystals, 2.07 g, 89%, mp 237−238 °C; FT-IR (KBr) 2917 (s), 2804 (s), 2762 (s), 2435 (m), 1497 (m), 1432 (m), 1092 (m), 808 (m), 520 (m) cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 7.25−7.22 (m, 4H), 3.64 (s, 2H), 3.28−3.21 (m, 1H), 2.23−2.16 (m, 2H), 1.71−1.63 (m, 4H), 1.38 (bs, 1H); ^1H NMR (HCl salt, $CDCl_3$ + CD_3OD) δ 9.70 (bs, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 3.94 (s, 2H), 3.52 (q, J = 8.15 Hz, 1H), 2.95 (bs, 2H), 2.41−2.35 (m, 2H), 2.22−2.13 (m, 2H), 1.99−1.89 (m, 1H), 1.83−1.73 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) δ 138.9 (C), 132.4 (C), 130.1 (CH), 129.4 (CH), 50.2 (CH), 53.4 (CH_2), 30.9 (2 CH_2), 14.6 (CH_2); EI MS m/z (relative intensity) 196 (M^+), 167 (48), 125 (100), 89 (26), 39, (18). Anal. Calcd for $C_{11}H_{15}Cl_2N$: C, 56.91; H, 6.51; N, 6.03; Cl, 30.54. Found: C, 56.89; H, 6.45; N, 5.87; Cl, 30.82.

Reduction of Enamines. An example is the reduction of 1-morpholino-1-cyclohexene (Table 5, entry 6 and Table 1, entry 5): 1-Morpholino-1-cyclohexene (1.67 g, 10 mmol) in DCE (30 mL) and AcOH (0.61 g, 10 mmol) was treated with sodium triacetoxyborohydride (3.0 g, 14 mmol) and stirred under argon. The GC analysis determined that the reduction was complete after 10 min. The reaction was quenched by adding 1 M NaOH, and the product was extracted with ether. The ether extract was dried (MgSO4), and the solvent was evaporated under reduced pressure to give the crude product as a colorless oil (1.70 g). The oil was dissolved in ether (50 mL), cooled in an ice bath, and treated with ethereal HCl to give the HCl salt as a white solid. The solid was collected by filtration air-dried, and then recrystallized from EtOAc/MeOH to give the purified product (1.88 g, 91.4%): mp 260-262 °C. Picrate salt: a yellow solid, mp 174−175 °C (ethanol) (lit.[11] 176−177 °C); FT-IR (HCl salt, KBr) 3425 (s), 2937 (s), 2861 (m), 2672 (s), 2606 (s), 2478 (m), 1448 (m), 1399 (w), 1267 (w), 1110 (s), 1070 (w), 950 (w) cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 3.74 (t, J = 5.0 Hz, 4H), 2.43 (t, J = 5.0 Hz, 4H), 2.29 (m, 1H), 1.88 (d, J = 10.0 Hz, 4H), 1.61 (d, J = 13.0 Hz, 1H), 1.28 (m, 5H); ^{13}CNMR (free base, $CDCl_3$) δ 66.9 (CH_2), 63.4 (CH), 49.3 (CH_2), 28.4 (CH_2), 25.9 (CH_2), 25.4 (CH_2); EI MS m/z (relative intensity) 169 (M^+, 16), 127 (11), 126 (100), 98 (7), 83 (10), 82 (12), 68 (10), 56 (19), 55 (36). Anal. Calcd for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; N, 6.81; Cl, 17.23. Found: C, 58.22; H, 9.69; N, 6.72; Cl, 17.25.

The Use of Titanium(IV) Isopropoxide. An example is the synthesis of *N*-[1-(1-cyclohexenyl)ethyl]benzylamine (Table 5, entry 8): 1-Acetylcyclohexene (1.24 g, 10 mmol) and benzylamine (1.2 g, 11.2 mmol) were mixed in neat titanium-(IV) isopropoxide (4.78 g, 16.8 mmol) and stirred under nitrogen for 3 h. Methanol (45 mL) was added followed by careful addition of $NaBH_4$ (0.6 g, 16 mmol). Analysis of the reaction mixture after 5 min by GC indicated a complete reduction to the amine. The reaction was quenched by adding 0.1 N NaOH. The resulting mixture was filtered through Celite, and the residue was washed with ether (2 × 50 mL) and with CH_2Cl_2 (50 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product (2.2 g). The crude product was dissolved in ether and treated with ethereal HCl to give the HCl salt as a white solid. The solid was purified by recrystallization from EtOAc/MeOH to give 2.1 g, 83%, of white crystals: mp 215−217 °C; FT-IR (KBr) 3417 (m), 2932 (vs), 2835 (m), 2782 (s), 2732 (s), 2481 (w), 2422 (w), 1581 (m), 1454 (m), 1381 (w), 748 (m), 680 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.65 (bs, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H),

7.29 (d, $J = 7.0$ Hz, 1H), 5.73 (s, 1H), 3.95−3.92 (m, 1H), 3.78−3.72 (m, 1H), 3.44 (bs, 1H), 2.25−2.21 (m, 1H), 2.05−1.95 (m, 3H), 1.72−1.51 (m, 4H), 1.52 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 132.6 (C), 130.6 (CH), 130.5 (C), 129.9 (CH), 128.9 (CH), 128.7 (CH), 59.0 (CH), 48.3 (CH_2), 25.1 (CH_2), 23.8 (CH_2), 22.2 (CH_2), 21.9 (CH_2), 17.4 (CH_3); EI MS m/z (relative intensity) 215 (M^+, 4), 201 (16), 200 (83), 134 (17), 109 (4), 108 (4), 105 (10), 93 (5), 92 (13), 91 (100), 79 (13), 77 (11). Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.55; H, 8.81; N, 5.56; Cl, 14.08. Found: C, 71.73; H, 8.92; N, 5.40; Cl, 13.96.

Acknowledgment. We are grateful to the PRI spectroscopy group for their help and assistance: D. Gauthier, G. Leo, and P. McDonnell for NMR spectra, J. Masucci and W. Jones for the FT-IR and mass spectra, and X. Xiang, D. Burinsky, and R. Dunphy for the high resolution mass spectra. We also thank Dr. Norman Santora, the chemical information specialist, for his valuable help with the library search. We thank professor Robert O. Hutchins (Drexel University) for helpful discussions and for supplying some authentic samples.

Supporting Information Available: Supporting data for nearly all products are available including mp, FT-IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960057X