Chapter 12

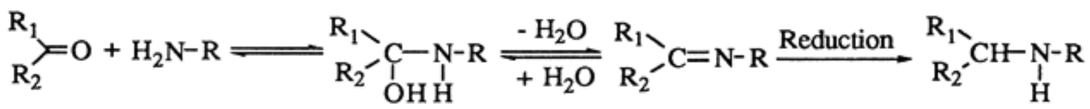
Use of Sodium Triacetoxyborohydride in Reductive Amination of Ketones and Aldehydes

Ahmed F. Abdel-Magid and Cynthia A. Maryanoff

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

Herein we present an overview of the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes, with an emphasis on scope. In general, this is an extremely useful reagent and experimental conditions are convenient and simple. Alicyclic and cyclic ketones furnish excellent yields of secondary and tertiary amines. Where diastereomer formation is possible, this reagent is more sterically demanding than sodium cyanoborohydride, and higher selectivity is often observed, especially from bicyclic ketones. Acid sensitive groups in the molecule are unaffected under normal reaction conditions. Hydrazines are reductively alkylated with ketones to furnish monalkyated products. Ketoesters are reductively aminated with primary and secondary amines. The initial products from γ- and δ-ketoesters or acids cyclize to the lactams in a tandem reductive cyclization procedure. The combination of $NaBH(OAc)_3$ /$CF_3CO_2NH_4$ furnishes primary amines in high yields. Weakly basic amines demonstrate the clear advantage of this reagent, as they undergo reductive alkylation in high yields with ketones and aldehydes. Non-basic amines and sulfonamides furnish high yields of monoalkyl products with most aldehydes.

Amines occupy an important position in organic synthesis as target molecules of biological interest and as synthetic intermediates. Reductive amination of ketones and aldehydes is a cornerstone reaction for the synthesis of different kinds of amines. This reaction is also described in the literature as reductive alkylation of amines (*1*). In this chapter we limit our discussion to *direct* reductive amination reactions in which the carbonyl compound and the amine are mixed in the presence of the reducing agent. The reaction involves the initial formation of an intermediate carbinol amine which dehydrates to form an imine (with ammonia and primary amines) or an iminium ion (with secondary amines) (Scheme I). Reduction of any of these intermediates produces the amine product (*2*). The choice of the reducing agent is very critical to the success of the reaction, since it must reduce imines (or iminium ions) selectively over aldehydes or ketones under the reaction conditions.



Scheme I

The reducing conditions utilized in this reaction may be catalytic hydrogenation or borohydride reagents. Catalytic hydrogenation has the advantage of being economical and easy to scale up (*1*). The borohydride reagents are more selective and can be used in the presence of C-C multiple bonds, divalent sulfur-containing compounds and in the presence of nitro and cyano groups (*2*). Sodium cyanoborohydride ($NaBH_3CN$) is the most commonly used borohydride reagent in reductive amination reactions (*3*). It is stable in hydroxylic solvents and has different selectivities at different pH values. At pH 1-3 it reduces aldehydes and ketones effectively. At pH 6-8, imines and iminium ions are reduced faster than aldehydes or ketones (*4*). On the other hand, it is highly toxic, (*5*) slow and sluggish with aromatic ketones and with weakly basic amines (*5a*) and its use may result in the contamination of the product with cyanide (*6*).

Over the past few years, we developed the use of the commercially available sodium triacetoxyborohydride [$NaBH(OAc)_3$] in the reductive amination of aldehydes and ketones (*7*). This borohydride is mild and exhibits remarkable selectivity as a reducing agent. It is very convenient and safe to handle. The use of this reagent, formed *in-situ* from sodium borohydride and glacial acetic acid, in reductive alkylation of aromatic amines was pioneered by Gribble et al (*8*). Our study of the scope and limitations of this reagent in the *direct* reductive amination of aldehydes and ketones with primary and secondary aliphatic and aromatic amines showed clearly that it is the reagent of choice in most cases (*9*). Since our earlier communication (*7*), we and other research groups have found it advantageous to use this procedure over other literature methods. The reactions are very easy to conduct and the isolated yields are good to excellent. This chapter will provide an overview of the utility of sodium triacetoxyborohydride as a reducing agent in reductive amination reactions.

DISCUSSION

(a) Reductive Amination of Ketones:

Early reports on the use of sodium triacetoxyborohydride in reduction indicated its inertness towards ketones (*10*). We expected it to be ideal to use in reductive amination of ketones. A ketone would interact faster with an amine to form an imine or iminium ion without interference from the reducing agent. Under the reaction conditions, the more basic imine would be protonated and reduced faster than a ketone. This expectation was realized in the results obtained in our systematic study (*9*) which clearly showed the utility and wide scope of this reagent in reductive amination of different kinds of ketones. The ketone and amine are used in stoichiometric amounts or with a slight excess of the amine. The reducing agent is used in some excess, 1.5 - 2 equivalents. Most reactions were carried out in 1,2-dichloroethane (DCE) or in tetrahydrofuran (THF) in the presence of one equivalent of AcOH. These conditions are referred to herein as the standard conditions. In some cases they are modified to optimize the yield of a particular class of compounds.

Alicyclic ketones, ranging in size from cyclobutanone to cyclododecanone, give excellent yields in reductive amination reactions with primary and secondary amines. The small ring ketones are usually more reactive than the larger ones and all react efficiently under the standard conditions. Figure 1 features some amines obtained from representative reductive amination reactions of alicyclic ketones (*9*).

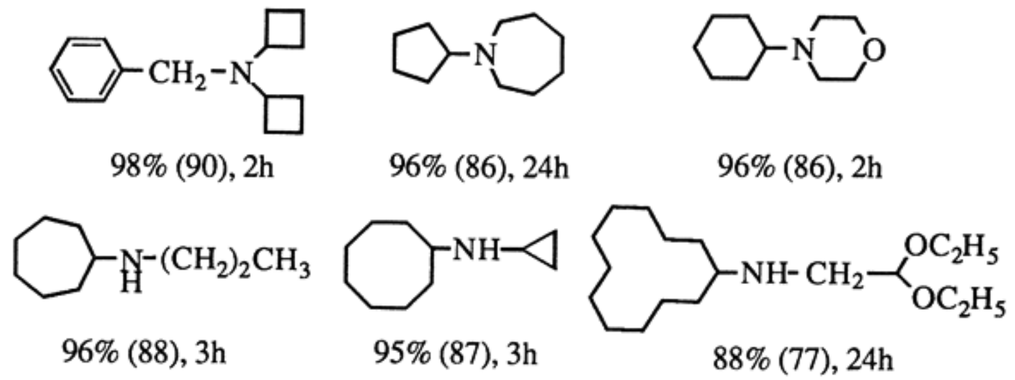
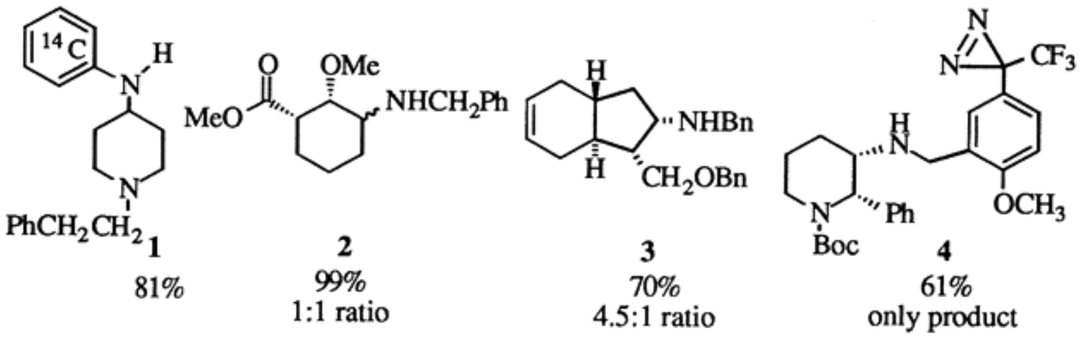


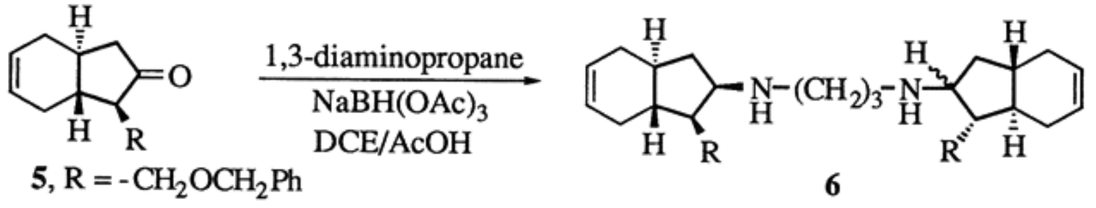
Figure 1: Reductive Amination of Alicyclic Ketones.
Values in parentheses are yields of recrystallized isolated salts.

The reductive amination of cyclic ketones such as β-tetralone and 2-indanone with aniline and $NaBH(OAc)_3$ (*9*) gives high isolated of the corresponding products and is superior to hydrogenation methods (*11*).

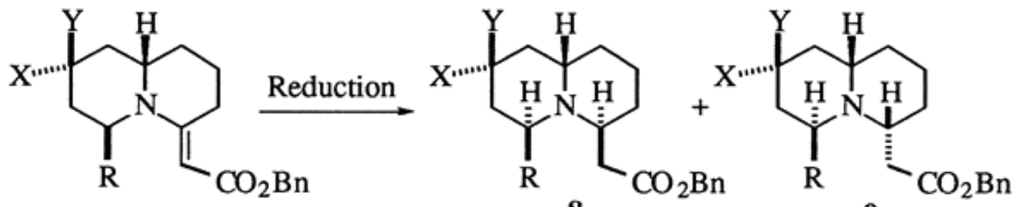
Other examples of forming carbon-nitrogen bonds by reductive amination of cyclic ketones with $NaBH(OAc)_3$ are reported in literature such as the preparation of the ^{14}C-labeled amine **1** (*12*), the fused ring didemnin analogue intermediate **2** (*13*), the (+)-papuamine intermediate **3** (*14*) and the intermediate for photoactivatable analogues of substance P non-peptidic antagonist **4** (*15*).



In the total synthesis of the marine alkaloids (-)-papuamine and (-)-Haliclonadiamine, the intermediate **6** was obtained in 58% (92% based on recovered starting material) as a 3.4:1 mixture of diastereomers from the reductive amination of the ketone **5** with 1,3-diaminopropane using $NaBH(OAc)_3$ (*16*).



In the synthesis of compounds such as **2, 3, 4** and **6**, where diastereomer formation is possible, variable degrees of diastereoselectivity occur, from non-selective formation of **2** to exclusive formation of one diastereomer in **4**. A comparison between $NaBH_3CN$ and $NaBH(OAc)_3$ in reduction of vinylogous urethanes such as **7** to the diastereomeric tertiary amines **8** and **9** showed that *cis*-selectivity (formation of **8**) was dramatically enhanced with sodium triacetoxyborohydride (*17*). This reagent appears to be sterically more demanding in reducing the intermediate iminium ion than sodium cyanoborohydride (Scheme II). This finding agrees with earlier studies on reduction of 4-*tert*-butylcyclohexanone imines (*18*) and direct reductive amination of 4-*tert*-butylcyclohexanone (*9*).



	$NaBH(OAc)_3$	$NaBH_3CN$
a: R = *m*-OMe-C_6H_4-; X = Y = H	92% (>50 : 1)	70% (5 : 1)
b: R = (*E*)-TMS-CH=CH-, X = H, Y = OCOPh	72% (10 : 1)	77% (1 : 2)

Scheme II

Saturated acyclic ketones also undergo clean reductive amination with both primary and secondary amines, however, the reactions may be slower and the isolated yields may be lower than the alicyclic ketones, particularly with hindered secondary amines. Some of the slow reactions are accelerated by adding 1-2 equivalents of AcOH, the use of about 5 - 10% excess of the amine and up to 2 equivalents of sodium triacetoxyborohydride. Several products obtained by reductive amination of saturated ketones are shown in Figure 2 (*9*).

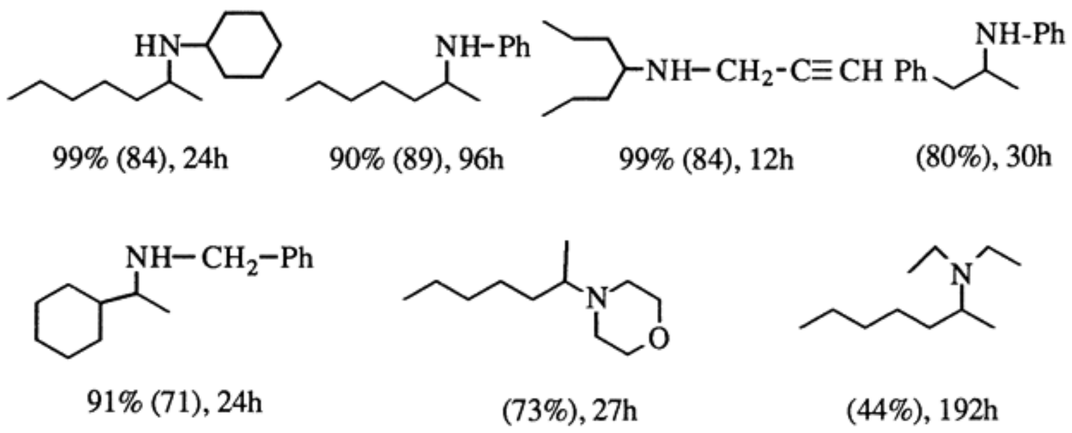


Figure 2: Reductive Amination of Acyclic Aliphatic Ketones.
Values in parentheses are yields of recrystallized isolated salts.

Bicyclic ketones such as norcamphor and tropinone are successfully reductively aminated with primary and secondary amines in good to excellent yields. The reactions involving these systems usually show high levels of diastereoselectivity

towards the *endo*- products. Products from norcamphor and both primary and secondary amines are exclusively *endo*- while those obtained from tropinone and primary amines show at least a 20 : 1 ratio of the *endo*- to *exo*- products. The exception is the reaction of tropinone with piperidine which is very slow and gives a 1 : 1 ratio of the *endo*- and *exo*- products (Figure 3) (*9*). A related example is the reductive amination of the diketone **10** to give the symmetric diamine **11** in 96% yield with slight contamination of two diastereomers (*19*).

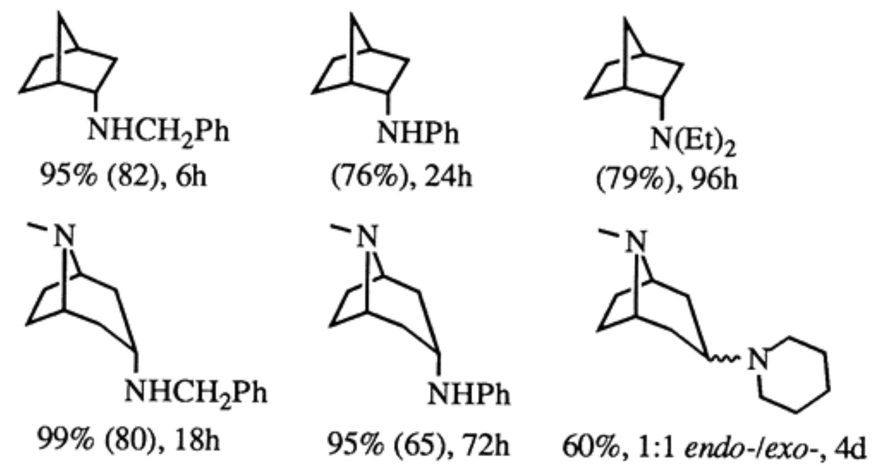
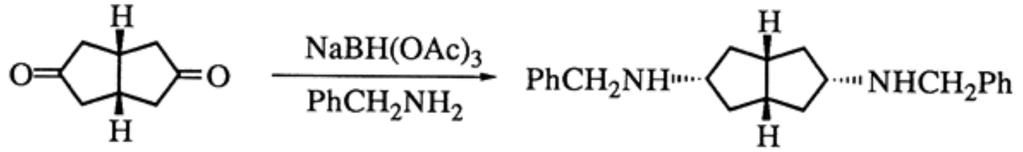
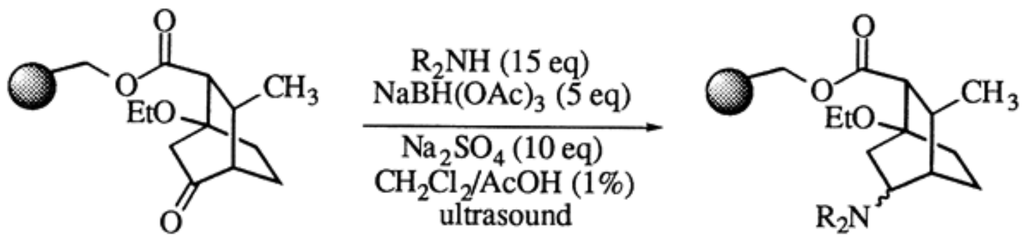


Figure 3: Reductive Amination of Bicyclic Ketones.
Values in parentheses are yields of recrystallized isolated salts.



The reaction conditions are modified in another study to use $NaBH(OAc)_3$ in reductive amination of polymer bound bicyclo[2,2,2]octanones (**12**). While the standard conditions give only a trace of product (**13**), the use of excess amine, addition of Na_2SO_4, and application of ultrasound effects efficient reductive amination with various amines (*20*).



The reaction conditions have been applied to substrates containing acid sensitive functionalities such as acetals and ketals on either reactant. With the use of AcOH or no acid, the products are stable to aqueous work up conditions. The reductive amination of cyclohexanedione monoethylene ketal with primary and secondary

amines affords good to excellent isolated yields of the corresponding amines. Similar results are obtained from reactions of aminoacetaldehyde diethyl acetal with ketones (Figure 4) (*9*).

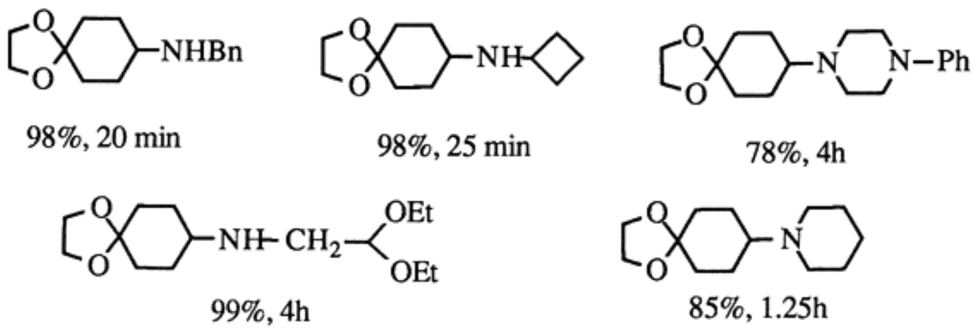
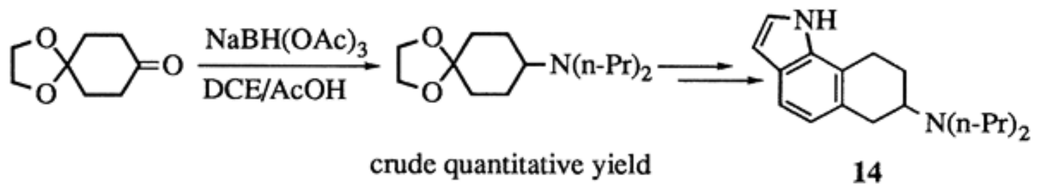


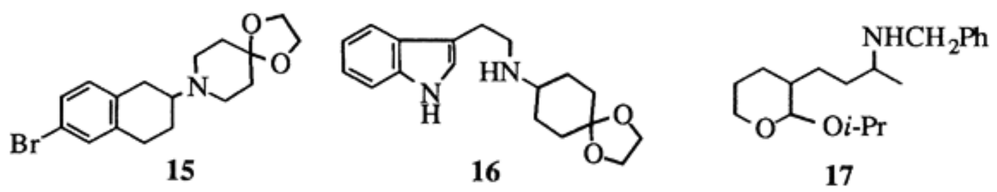
Figure 4: Reductive Amination in The Presence of Ketals and Acetals.

This reaction has found an application in the synthesis of the potential dopamine receptor agonist **14** in a recent publication (*21*). In this case, $NaBH(OAc)_3$ gives a better result than $NaBH_3CN$ or the $Ti(OiPr)_4/NaBH_3CN$ combination.



crude quantitative yield — **14**

Other related examples showing the use of $NaBH(OAc)_3$ in reductive amination in the presence of ketals are reported for the synthesis of compounds **15** - **17** (*22-24*).



15 — 85% — intermediate in synthesis of MK-0499 (ref. 22)

16 — 87% — intermediate in synthesis of Melinonine-E (ref. 23)

17 — mixture of diastereomers (ref. 24)

Substituted hydrazines such as phenylhydrazine and 1-aminopiperidine are reductively alkylated with ketones giving rise to monoalkylation products. The reaction of phenylhydrazine with cyclohexanedione monoethylene ketal is a very clean reaction, however, those with cyclohexanone and 2-heptanone show variable ratios of byproducts and give lower yields (*9*). The reactions of 1-aminopiperidine with either 2-heptanone or cycloheptanone are very clean giving exclusively the expected *N*-monoalkyl products (Figure 5) in nearly quantitative yields (unpublished results).

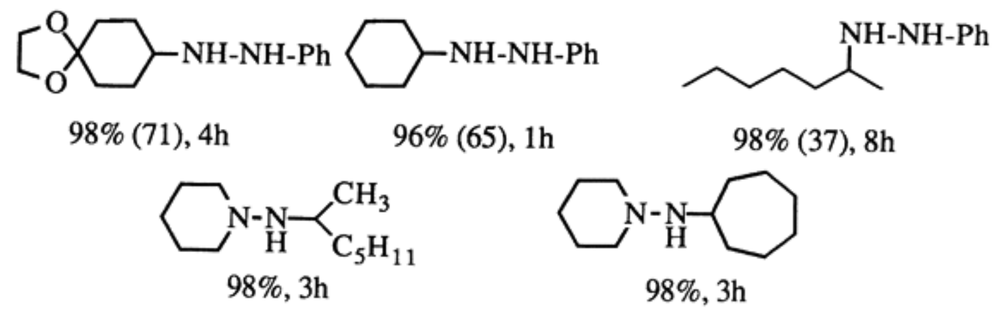


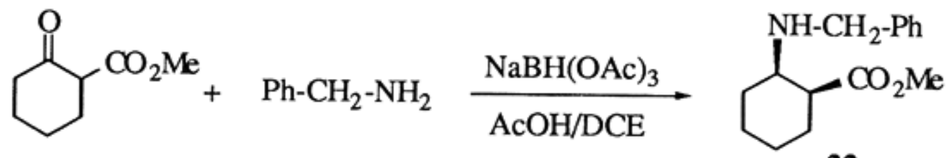
Figure 5: Reductive Amination with Hydrazines.
Values in parentheses are yields of recrystallized isolated salts.

Ketoesters are a special class of ketones. The relative position of the keto group to the ester may effect the outcome of the reaction chemically or stereochemically or may result in a secondary reaction. The reductive amination of α-ketoesters with primary and secondary amines gives the corresponding *N*-substituted α-aminoesters. The reductive amination of various α-ketoesters with benzylamine affords the α-benzylamino esters (**18 - 20**) in good to excellent yields (*9*). Reactions involving other amines, such as aniline or morpholine, are not as efficient and give variable amounts of ketone reductions. Alternatively, *N*-substituted α-aminoesters may be prepared by the reductive alkylation of α-aminoesters with aldehydes and ketones. This is demonstrated in the reductive amination of 2-butanone with methyl glycinate (*9*) which results in the clean formation of methyl *N*-(2-butyl)glycinate (**21**).

18 R = Me, 90%
19 R = i-Pr, 82%
20 R = Ph, 58%

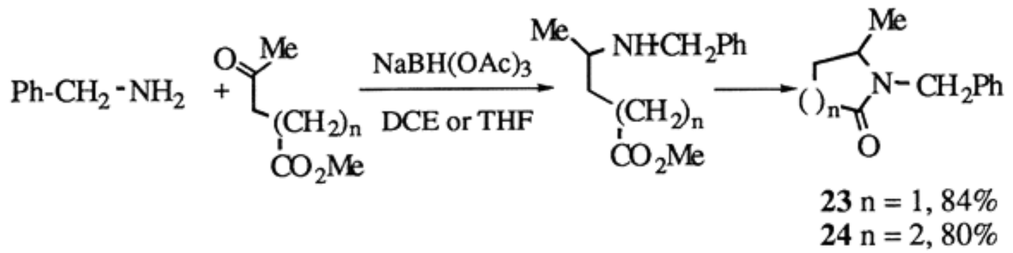
21
88%

The reductive amination of cyclic β-ketoesters such as methyl cyclohexanone-2-carboxylate gives almost exclusively the *cis*-product (**22**) (*25*). There is evidence that the intermediate is an enamine rather than an imine. This reaction is currently under further investigation to evaluate its generality in different systems and its mechanistic pathway.



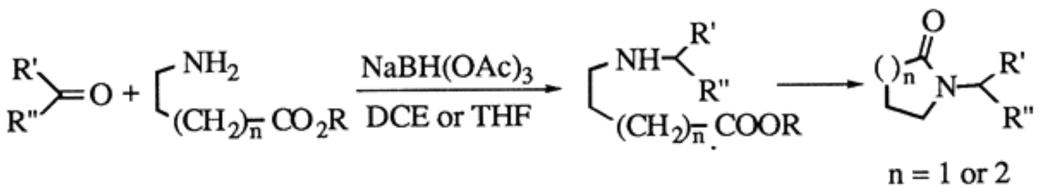
22

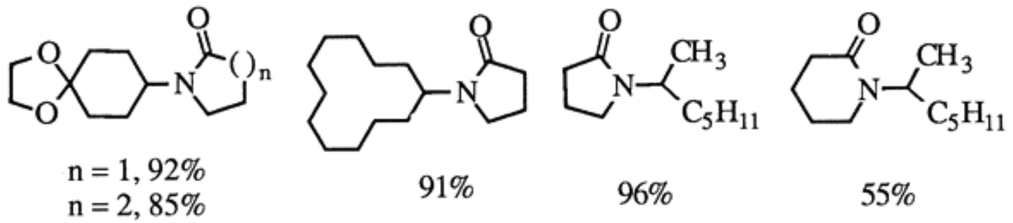
The reductive amination of γ- and δ-ketoesters or acids with primary amines is a special case (*26*). The initial product, an *N*-substituted γ- or δ-aminoester or acid cyclizes to the corresponding lactam (such as **23** and **24**) under the reaction conditions (Scheme III). This tandem two-step procedure, which we termed "reductive lactamization" is a convenient method for the synthesis of *N*-substituted butyro- and valerolactams under mild conditions.



Scheme III

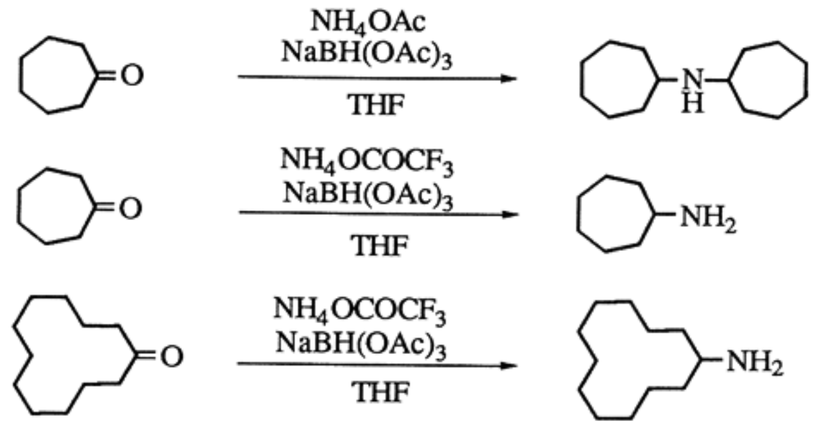
The same products are obtained from reductive alkylation of γ- or δ-aminoacids or esters with carbonyl compounds. As in the above case, the initial reductive amination product, cyclizes to the corresponding lactam under the reaction conditions (*26*). Some representative examples are shown in Scheme IV. The reaction could not be applied to ε-aminoesters or larger homologues to obtain lactams; these reactions result only in reductive amination but no cyclization.





Scheme IV

Our attempts to develop a practical procedure for the synthesis of primary amines by reductive amination of ketones with $NaBH(OAc)_3$ were hindered by the poor solubility of ammonium acetate, the most common and convenient source of ammonia, in THF or DCE. The reaction gives dialkylamines exclusively. Even the use of a large excess, up to 10 equivalents, of ammonium acetate in DCE, THF or CH_3CN, still gives the dialkylamines. This reaction can thus be used for the effective preparation of symmetric dialkylamines, such as dicycloheptylamine (*9*). Our search for better conditions that may be used in preparation of primary amines via reductive amination in aprotic solvents led to ammonium trifluoroacetate. This salt is soluble in THF and can be used effectively in reductive amination reactions. The reaction with cycloheptanone and cyclododecanone (Scheme V) gives the corresponding primary amines as the major products with 7% or less of the dialkylamines (unpublished results). This reaction is currently under further investigation and will be the subject of a future report.



Scheme V

Perhaps, the results that best demonstrate the superior advantage of using $NaBH(OAc)_3$ over other reagents are those obtained from reactions with weakly basic amines. These amines are weak bases as well as poor nucleophiles. The pK_a values for the amines used in this study range from 3.98 for *p*-chloroaniline to -4.26 for 2,4-dinitroaniline (*27*). The reductive amination of ketones with anilines substituted with electron withdrawing groups is usually sluggish and slow and the ketone may be reduced preferentially with most reagents. The use of sodium triacetoxyborohydride in reductive amination with several of the monosubstituted anilines in stoichiometric quantities or in the presence of excess ketones gives the corresponding *N*-alkyl products in very good isolated yields. However, the efficiency of these reactions decreases considerably with less basic amines such as *o*-nitroaniline, 2,6-dibromoaniline and 2,4,6-trichloroaniline which react slow or result in no reaction. Some of the products obtained from reductive amination of ketones with some weakly basic amines are listed in Figure 6 with their isolated yields and reaction times.

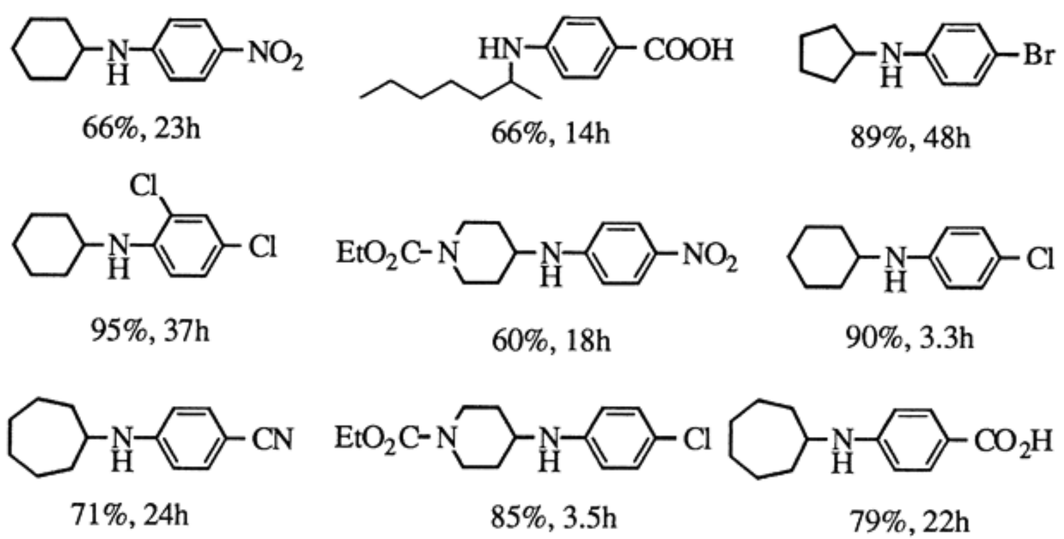
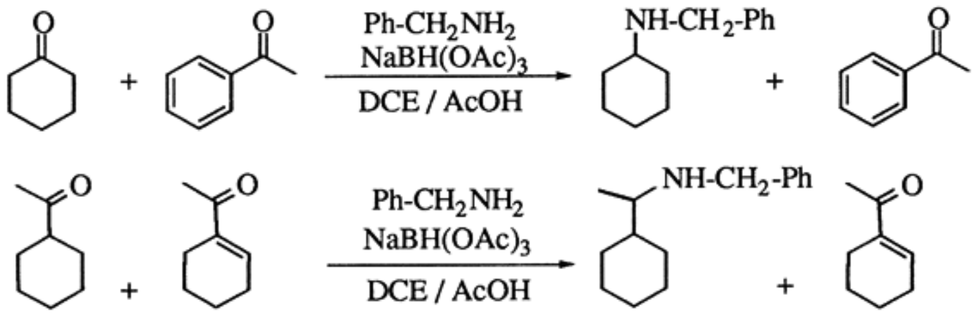


Figure 6: Reductive Amination of Ketones with Weakly Basic Amines.

Aromatic, α,β-unsaturated, and sterically hindered saturated ketones react very slowly or show no reaction under the standard reaction conditions (*9*). In competition studies, featuring cyclohexanone *vs.* acetophenone and acetylcyclohexane *vs.* 1-acetylcyclohexene, the saturated ketones reacted faster and were selectively reductively aminated in the presence of the slow reacting aromatic and α,β-unsaturated ketones (Scheme VI) (*9*).



Scheme VI

(b) Reductive Amination of Aldehydes:

Unlike ketones, aldehydes can be reduced with sodium triacetoxyborohydride (*28*). However, under the standard reaction conditions the reductive aminations with aldehydes occur very effectively and result in fast reactions with no aldehyde reductions in most cases. Both aliphatic and aromatic aldehydes are very reactive and give reductive amination products with nearly all kinds of primary and secondary amines. In most reactions, the aldehyde and amine are mixed in stoichiometric amounts in DCE or THF with about 1.4 - 1.5 equivalents of $NaBH(OAc)_3$. The reaction times range from 20 minutes to 24 hours. These conditions are mild and allow for a convenient reaction and an easy work up and isolation of products. Some representative examples from our work (*9*) are illustrated in Figure 7.

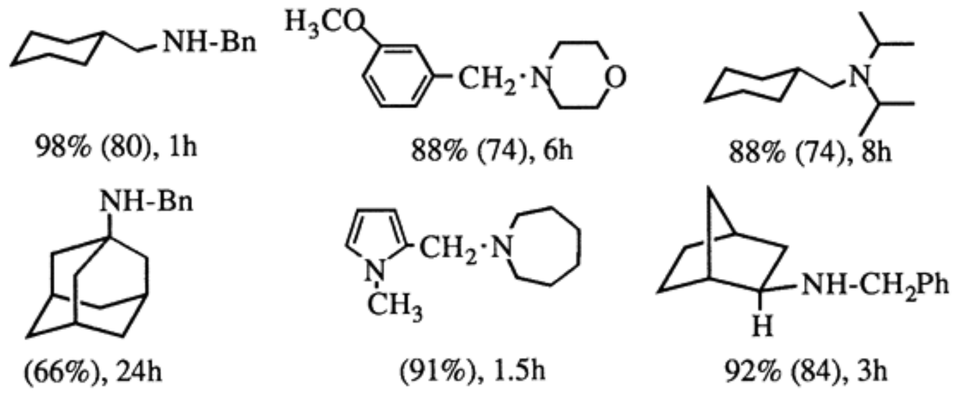
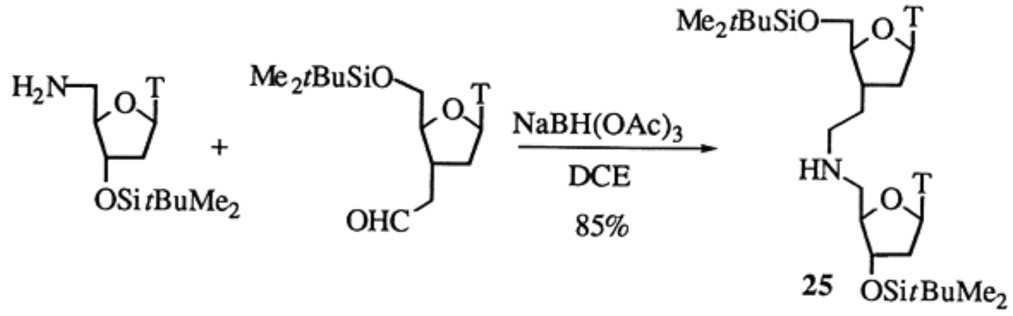


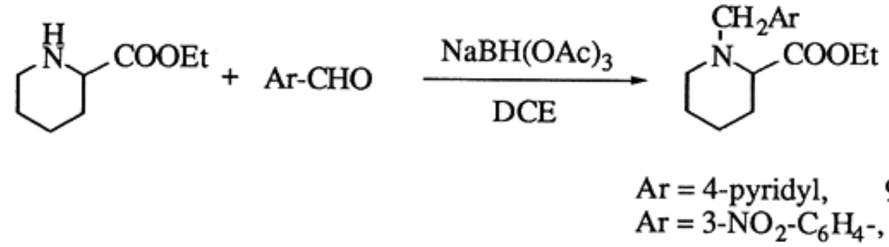
Figure 7: Reductive Amination of Aldehydes.
Values in parentheses are yields of recrystallized isolated salts.

When compared to most other reducing agents, $NaBH(OAc)_3$ does not cause significant aldehyde reduction when used in reductive amination reactions. Most aldehyde reactions do not require the use of acid activation as is the case with ketones. This seems to minimize the chance of aldehyde reduction. For example, the formation of *N,N*-diisopropylcyclohexylmethylamine (Figure 7) from cyclohexane

carboxaldehyde and diisopropylamine is accompanied by about 25% aldehyde reduction in the presence of AcOH, but only 5% in its absence. A literature example has shown, in the construction of the internucleoside -CH_2-CH_2-NH- linkage in the thymidine dimer (**25**), that the use of $NaBH(OAc)_3$ gives a high yield of product and very little reduction of aldehyde. The use of $NaBH_3CN$ causes significant aldehyde reduction and gives a lower yield (*29*).

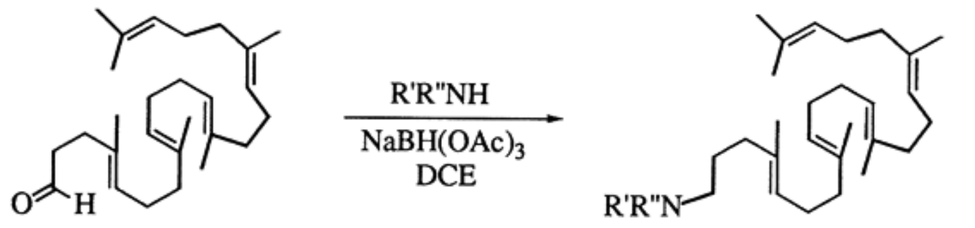


The reductive amination of aromatic aldehydes with ethyl 2-carboxypiperidine under the standard conditions (*9*) shows no aldehyde reduction and is superior to other literature procedures (*6b*).



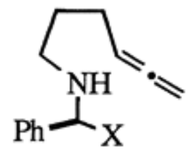
Ar = 4-pyridyl, 95%
Ar = 3-NO_2-C_6H_4-, 96%

The mild nature of this reducing agent is well represented in the reductive amination of the 1,1',2'-tris-nor-squalene aldehyde. The aldehyde was cleanly converted to the corresponding amines in high yields with no detectable aldehyde reduction or other side reactions (*9*). This is a significant improvement over results obtained from $NaBH_3CN$ (*30*).

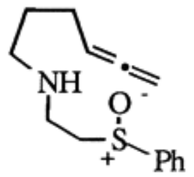


R' = H, R" = cyclohexyl, 94%
R' = R" = i-Pr, 91%
R' = R" = Et, 98%

The mildness of the reaction conditions is also demonstrated in the synthesis of the allenic amines **26a-c** and **27** from hexa-4,5-dienal and the appropriate amine (*31*).

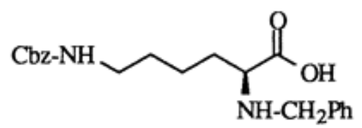


26a X = CH_2Ph
26b X = CH_2Sph
26c X = CH_2SePh



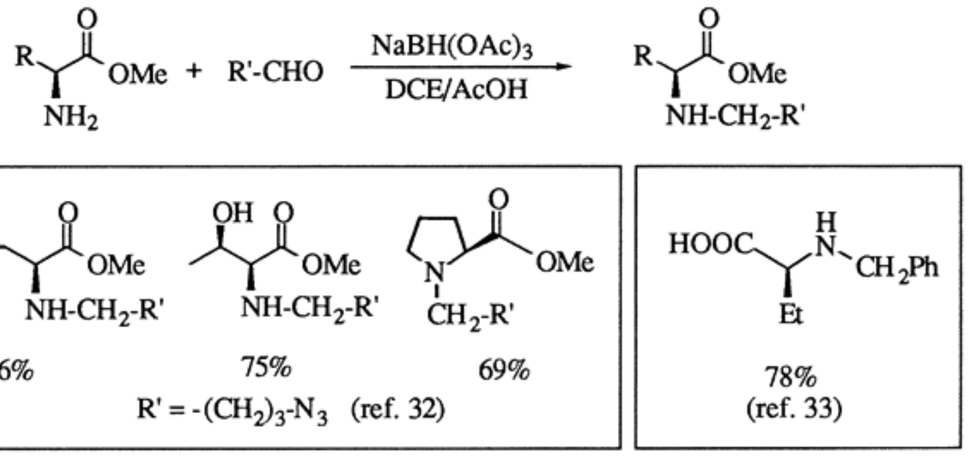
27

The reductive alkylation of aminoacids or esters with aldehydes is achieved effectively by using $NaBH(OAc)_3$. The *N*-benzylation of *N*-ε-Cbz-L-lysine with benzaldehyde and $NaBH(OAc)_3$ in DCE at 50 °C gives the desired product (**28**) in 82% isolated yield (unpublished result).



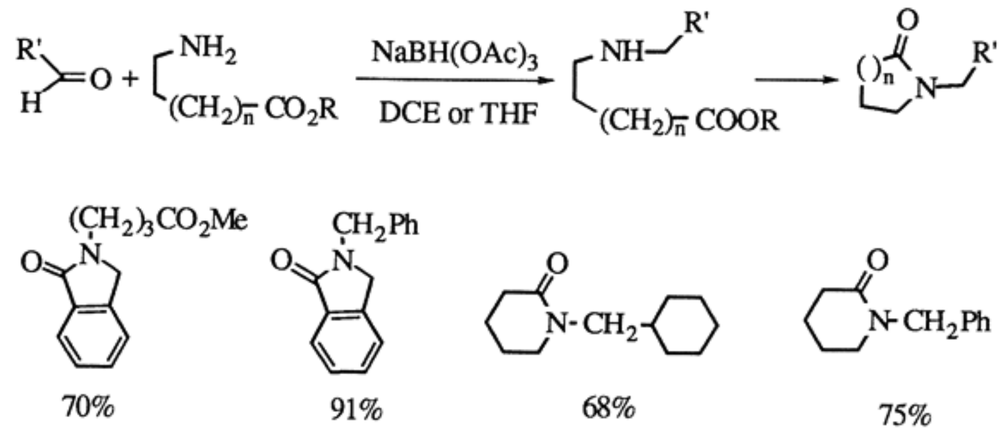
28

The reductive amination of aldehydes with aminoesters and $NaBH(OAc)_3$ under the standard conditions was found to be more convenient than other methods in the preparation of *N*-alkyl aminoesters (*33*). Various *N*-alkylated amino acid esters were prepared according to our standard procedure in good isolated yields as shown in Scheme VII (*32, 33*.



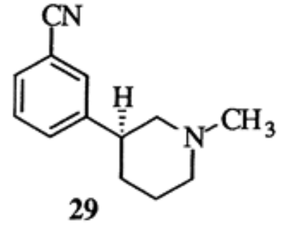
Scheme VII

Similar to ketones , aldehydes react with primary γ- and δ-aminoacids or esters, to give the initial *N*-alkyl products which cyclize to the corresponding lactams under the reaction conditions. A particularly interesting aldehyde is *o*-carboxybenzaldehyde which gives the benzolactams with either simple amines or aminoesters. The cyclization occurs preferentially on the *o*-carboxyl group even in the presence of a δ-ester group on the chain (Scheme VIII) (*26*).



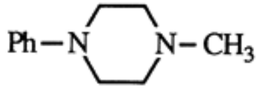
Scheme VIII

The *N*-methylation of amines can be carried out using formaldehyde under the standard conditions. This reaction, however, is not selective with primary amines; it gives only the *N,N*-dimethyl derivative. Paraformaldehyde may be used as a source of formaldehyde as in the synthesis of compound **29** (*34*) which was isolated in 89% yield.

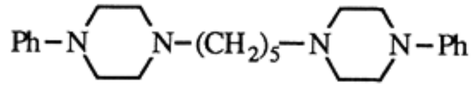


29

Formalin may also be used in reductive amination reactions on a small scale (10 - 20 mmol) with excess sodium triacetoxyborohydride. The restriction on the scale results from the exothermic decomposition of the hydride reagent by water. About 5 equivalents of the hydride reagent are used in the reaction which may be impractical in larger scale reactions. Aqueous glutaraldehyde may similarly be used in these reactions. Reactions of formalin and glutaraldehyde with 1-phenylpiperazine give nearly quantitative yields of the corresponding amines **30** and **31** (*9*).



30 (98%)



31 (98%)

The reductive amination of aldehydes with weakly basic amines is faster and has wider scope than ketones. Most reactions with anilines monosubstituted by electron-withdrawing groups are carried out under the standard conditions with undetectable aldehyde reduction. The products are obtained effectively and in high yields, such as the synthesis of the compounds listed in Figure 8 (*9*).

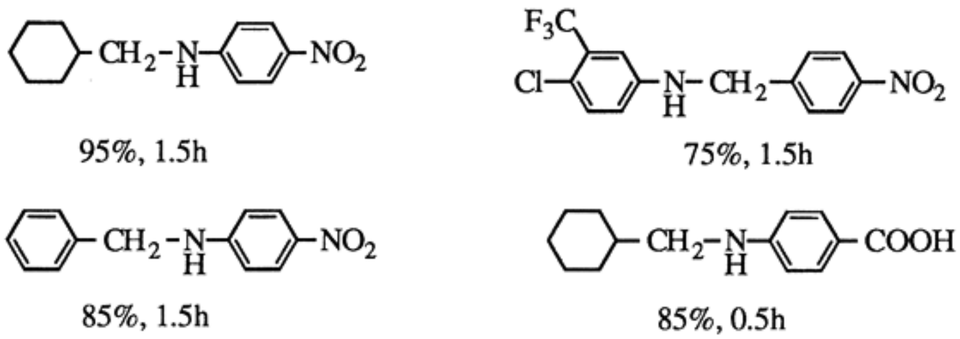


Figure 8: Reductive Amination of Aldehydes with Weakly Basic Amines

As the basicity and nucleophilicity of the amines decrease, the reductive amination becomes slow and aldehyde reduction becomes a competing reaction. The reductive amination of aldehydes with amines such as *o*-nitroaniline, 2,4-dichloroaniline, 2-aminothiazole and iminostilbene are accompanied by about 10 - 30% aldehyde reduction. The reactions are modified to use the amines as limiting agents and up to 1.5 equivalents of aldehyde to compensate for this side reaction. These reductive aminations are very efficient and give isolated yields ranging from 60 to 96% (Figure 9) (*9*). These reactions expand the scope of reductive amination reactions to limits never before achieved with any of the commonly used reducing agents.

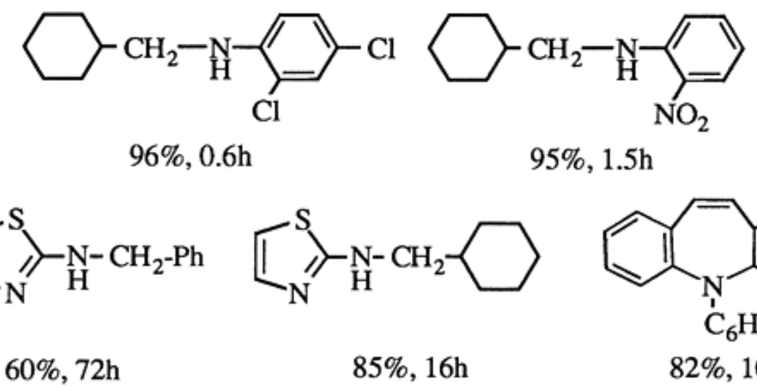
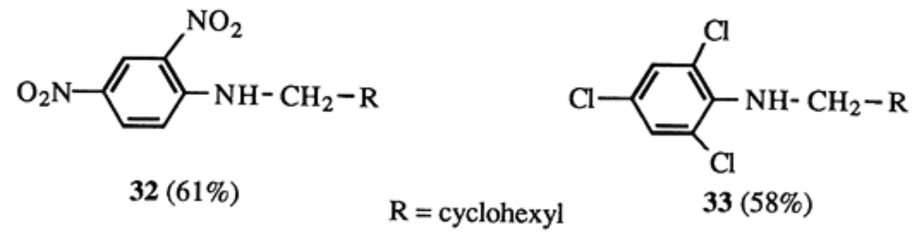


Figure 9: Reductive Amination of Aldehydes with More Weakly Basic Amines.

The non-basic amines such as 2,4-dinitroaniline and 2,4,6-trichloroaniline are the least reactive. There is no detectable reaction with aromatic aldehydes such as benzaldehyde. However, the reductive amination of cyclohexane carboxaldehyde with either amine progresses slowly and is accompanied by considerable aldehyde reduction. The reaction is carried out in the presence of 3 - 5 equivalents of AcOH and requires the occasional addition of excess aldehyde and reducing agent up to 5 equivalents each over 2 - 4 days to effect complete reaction of the amines. The products (**32** and **33**) are isolated by chromatography in 61% and 58% yield respectively (*9*). We believe that these reactions proceed via initial formation of enamines which will be reduced under the reaction conditions. This also explains the lack of reactivity toward aromatic aldehydes which can not form enamines.



This procedure has been extended to substrates that never before used in reductive amination reactions, namely, sulfonamides. The reaction of *p*-toluenesulfonamide with aldehydes affords the corresponding *N*-alkyl sulfonamides, e.g., **34** and **35** in good isolated yields (*9*).

Conclusion:

This overview shows clearly that sodium triacetoxyborohydride is a synthetically useful reagent that can be used effectively in reductive amination of ketones and aldehydes with most amines. While the wide applications mentioned here make it an attractive choice for reductive amination, the most attractive features of this reagent are the convenience of use, the ease of work up and the simplicity of product isolation.

References

1. Emerson, W. S. *Organic Reactions* **1948**, *4*, 174 and references therein.
2. Schellenberg, K. A. *J. Org. Chem.* , **1963**, *28*, 3259.
3. (a) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*(5), 201; (b) Lane, C. F. *Synthesis,* **1975**, 135.
4. (a) Borch, R. F., Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Borch, R. F., Durst, H. D. *J. Am. Chem. Soc*. **1969**, *91*, 3996.
5. The *Sigma-Aldrich Library of Chemical Safety Data*, Edition I, p 1609, Lenga, R. E., Ed., Sigma-Aldrich Corp. **1985**.
6. (a) We detected cyanide contamination in large scale reduction of imines with sodium cyanoborohydride. (b) A similar result was reported: Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789.
7. (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.
8. (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.
9. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* , **1996**, *61,* 3849.
10. (a) Gribble, G. W. and Ferguson, D. C. *J. C. S. Chem. Commun.* **1975**, 535; (b) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287.
11. Campbell, J. B.; Lavagnino, E. P. In *Catalysis in Organic Syntheses*; Jones, W. H. Ed.; Academic Press, New York, 1980; p 43.

12. Bagley, J. R.; Wilhelm, J. A. *J. Labelled Comp. Radiopharm.* **1992**, *31*, 945.
13. Mayer, S. C., Pfizenmayer, A. J.; Cordova, R.; Li, W-R; Joullié, M. M. *Tetrahedron: Asymm.* **1994**, *5*, 519.
14. Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881.
15. Kersey, I. D.; Fishwick, C. W. G.; Findlay, J. B. C.; Ward, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1271.
16. McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.* , **1996**, *61*, 700.
17. Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757.
18. (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.
19. Camps, P.; Muñoz-Torrero, D.; Pérez, F. *J. Chem. Res. (S)* **1995**, 232.
20. Ley, S. V.; Mynett, D. M.; Koot, W-J. *Synlett* **1995**, 1017.
21. Demopoulos, V. J.; Gavalas, A.; Rekatas, G.; Tani, E. *J. Heterocyclic Chem.* **1995**, *32*, 1145.
22. Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U-H.; Frey, L.; Karady, S.; Shi, Y-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.
23. Quirante, J.; Escolano, C.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2141.
24. Duhamel, P.; Deyine, A.; Dujardin, G.; Plé, G.; Poirier, J-M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2103.
25. (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A. The 33rd ACS National Organic Symposium, Bozeman, Mo, June **1993**, Paper A-4. (b) Vanderplas, B.; Murtiashaw, C. W.; Sinay, T.; Urban, F. J. *Org. Prep. Proced. Int.* **1992**, *24*, 685.
26. Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.
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. (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, vol. 7, p 4649, **1995**.
29. Caulfield, T. J.; Prasad, C. V. C.; Prouty, C. P.; Saha, A. K.; Sardaro, M. P.; Schairer, W. C.; Yawman, A.; Upson, D. A.; Kruse, L. I. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2771.
30. (a) Duriatti, A.; Bouvier-Nave, P.; Benveniste, P.; Schuber, F.; Delprino, L.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34*, 2765. (b) Ceruti, M.; Balliano, G.; Viola, F.; Cattel; L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199.
31. Davies, I. W.; Gallagher, T.; Lamont, R. B.; Scopes, D. I. C. *J. Chem. Soc., Chem. Commun.* **1992**, 335.
32. Ramanjulu, J. M.; Joullié, M. M. *Synthetic Commun.* **1995**, *26*,
33. Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem.* **1995**, *60*, 6776.
34. Sonesson, C.; Lin, C-H.; Hansson, L.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Wikstrom, H. *J. Med. Chem.* **1994**, *37*, 2735.