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A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes

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Introduction

Amines occupy a very special place in organic chemistry. They exist in many natural biologically important molecules such as amino acids, nucleic acids, alkaloids, and many others. They are also common features in many of the synthetic compounds used as medicines and commercial drugs. Amines are used as bases in many synthetic transformations, serve as key intermediates in organic synthesis, and are important building blocks in many of the common polymers such as nylons. Due to their importance, there are numerous methods for the preparation of amines. Some of the general methods include the reduction of nitrogen-containing functional groups such as nitro, cyano, azide, and carboxamide derivatives. Another general method is the alkylation of ammonia, primary amines, or secondary amines. Alkyl halides or sulfonates may be used as alkylating agents in these reactions; however, overalkylation of ammonia and primary amines is a common side reaction. A superior method of alkylating ammonia and amines is the reaction 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. The reaction is referred to as either reductive alkylation (of amines) or reductive amination (of carbonyl compounds). In this review we use the term reductive amination in reference to this reaction. The reductive amination of aldehydes and ketones is a cornerstone reaction and is one of the most useful and important tools in the synthesis of different kinds of amines. Generally, the reaction proceeds via the initial formation of an intermediate carbinolamine **3** (Scheme 1), which dehydrates to form an imine (Schiff base) or iminium ion **4**.[1,2] Reduction of **4** produces the amine product **5**. Some reports provided evidence suggesting a direct reduction of the carbinolamine **3** as a possible pathway leading to **5**.[3]

We describe the reductive amination reaction as *direct* when the carbonyl compound and the amine are mixed with the proper reducing agent without prior formation of the intermediate imine or iminium salt. In this case, the choice of reducing agent is very critical to the success of the reaction. The reducing agent must reduce imines (or iminium ions) selectively over aldehydes and ketones under the same reaction conditions. *Indirect* or *stepwise* reductive amination reactions involve the preformation of intermediate imines (from ammonia or a primary amine and an aldehyde or a ketone) or sometimes enamine or iminum species (from secondary amines and aldehydes or ketones) followed by reduction in a separate step. The choice of reducing agent is not as critical as in the direct reactions since there will be no competition or interference from a carbonyl compound. Several reducing agents, including strong and nonselective ones, may be used based on the structure.

The direct reductive amination is most convenient, and it is usually the method of choice. The two most commonly used direct reductive amination methods differ in the nature of the reducing agent. The first and older method is catalytic hydrogenation.[1,4,5] The success of this procedure requires the reduction of the carbonyl compound to be relatively slow. Catalytic hydrogenation is economical, convenient, and a very effective reductive amination method, particularly in large-scale reactions. On the other hand, in many cases, the reaction may give a mixture of products and low yields depending on the molar ratios and the structure of the reactants.[6] It has seen limited use with compounds containing carbon−carbon (and other) multiple bonds and in the presence of reducible functional groups such as nitro[7,8] and cyano[8] groups. Another limitation is associated with compounds containing divalent sulfur that may inhibit and deactivate the catalyst.[8] The second method utilizes hydride reducing agents. The use of hydride reagents in reduction of Schiff bases appeared in scattered reports in the 1950s.[9−11] The first study of a direct reductive amination procedure using a hydride reagent was reported by Schellenberg in 1963, in which he used sodium borohydride ($NaBH_4$) as the reducing agent.[2] The reactions were carried out by mixing amine salts and carbonyl compounds in buffered aqueous solutions at 0 °C followed by addition of $NaBH_4$. In spite of the fast rate of ketone and aldehyde reduction with $NaBH_4$, the reductive amination occurred rapidly "*even in some instances where the equilibrium for the formation of the Schiff base is too unfavorable to permit its ready isolation*." Yields of 50% (acetone + lysine), 63% (isobutylamine +

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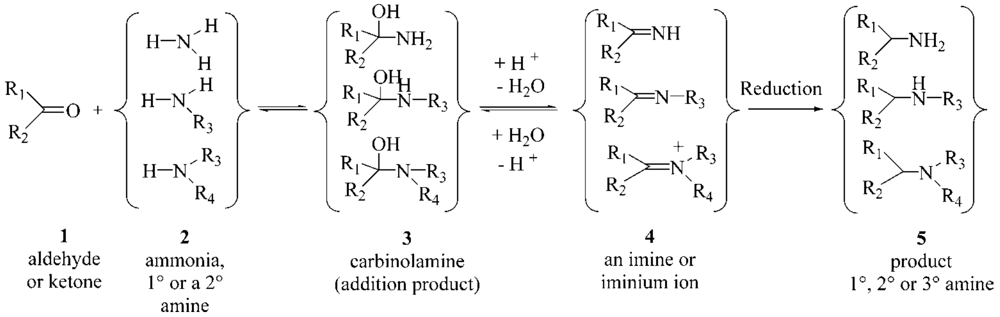
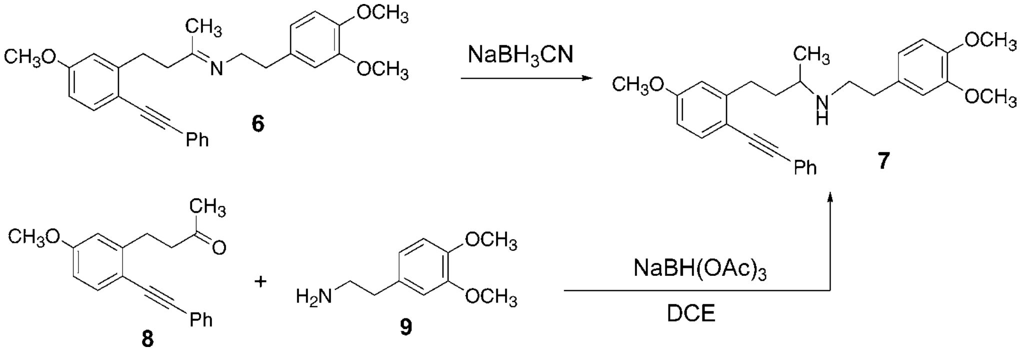
Scheme 1. General reductive amination pathway



Scheme 2. First direct reductive amination using $NaBH(OAc)_3$



acetone), 91% (isobutyraldehyde + aniline), and 83% (benzaldehyde + aniline) were reported. The study also reported failed reactions with acetophenone and benzophenone and failed reactions between piperidine and ketones although a successful reaction between piperidine and acetaldehyde. This study was significant and opened new possibilities for reductive amination reactions. The major limitations of this procedure were originated from the use of $NaBH_4$, a nonselective reducing agent. In 1971 Borch[12] reported the first practical hydride procedure for direct reductive amination in which he used the more selective sodium cyanoborohydride ($NaBH_3CN$) as the reducing agent.[13] The successful use of $NaBH_3CN$ is due to its different selectivities at different pH values[12] and its stability in relatively strong acid solutions (~pH 3) as well as its good solubility in hydroxylic solvents such as methanol. At pH 3−4 it reduces aldehydes and ketones effectively.[14] At pH 6−8, imines are preferentially protonated and reduced faster than aldehydes or ketones.[12] Therefore, by carrying out the reductive amination reaction under neutral to weakly acidic conditions, the reactants have the chance to form imines or iminium ions without consumption of aldehydes or ketones via reduction. This selectivity permits a very convenient and high yielding direct reductive amination procedure. The literature is replete with publications that document the very successful use of sodium cyanoborohydride in a wide scope of applications in reductive amination reactions.[15,16] Some reported limitations are the requirement of a large excess of the amine,[12] the sluggish reactions with aromatic ketones[12] and with weakly basic amines,[17−20] and the possibility of contamination of the product with cyanide.[21] The reagent is also highly toxic[22] and produces toxic byproducts such as HCN and NaCN upon workup.

Following the introduction of sodium cyanoborohydride for reductive amination reactions, some modifications and other reductive amination procedures were introduced in the 1980s and early 1990s but had much limited applications. Examples include borane−pyridine,[20] $Ti(OiPr)_4/NaBH_3CN$,[19] borohydride exchange resin,[23] Zn/AcOH,[24] $NaBH_4/Mg(ClO_4)_2$,[25] $Zn(BH_4)_2/ZnCl_2$,[26] electrochemical reductive amination,[27−29] and many others.

The next major advancement came in 1989 when we introduced a new procedure for reductive amination of aldehydes and ketones using sodium triacetoxyborohydride

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as reducing agent[30] that has become one of the most used in carrying out reductive amination reactions with a large number of applications and literature reports. It is noteworthy to mention that the procedure was conceived from one of our process chemistry projects in early 1988, during the development of a large-scale synthesis of amine **7** (Scheme 2), a key precursor in the synthesis of a drug candidate. The synthesis included the formation of imine **6** from ketone **8** and amine **9** followed by reduction with sodium cyanoborohydride.[31] While the reduction was successful, the isolated product was always contaminated with cyanide and could not be purified by simple means. As a result, we sought an alternative to sodium cyanoborohydride to eliminate the risk of residual cyanide, not only in the product but also in the workup waste stream, which is an environmental concern. Because of the presence of the alkyne functionality, the use of catalytic hydrogenation methods was not an option. Our efforts to solve the problem resulted in the identification of sodium triacetoxyborohydride [$NaBH(OAc)_3$] abbreviated here as STAB-H[32−34] as a superior, convenient, and effective reducing agent for reductive amination reactions. Thus, the direct reductive amination of the ketone **8** with the amine **9** in the presence of sodium triacetoxyborohydride in 1,2-dichloroethane or THF gave nearly quantitative yield of product **7** in high purity. This eliminated the separate step of forming the imine and solved the problem of contamination with cyanide. Our selection of sodium triacetoxyborohydride was based on the studies of Gribble on reductive alkylation of amines using sodium borohydride in neat liquid carboxylic acids.[35,36]

Following this remarkable result, we initiated a comprehensive study on the scope and limitations of this reagent in the *direct* reductive amination of aldehydes and ketones with ammonia, primary amines, and secondary amines. Comparative studies on the use of sodium triacetoxyborohydride versus other literature methods clearly showed it to be the reagent of choice in most cases.[37] The reactions are convenient, easy to conduct, and easy to work up, and the isolated yields are usually good to excellent. In our study, most products were isolated by simple extraction and salt formation without the need for chromatographic purification. Since the introduction of this procedure, it has been applied to the synthesis of a large number of amine substrates and continues to be an outstanding reagent for reductive amination reactions. In this review, we provide an outline and an update of the utility of sodium triacetoxyborohydride as a reducing agent in reductive amination reactions with an emphasis on the scope. The majority of the reactions compiled in this review were carried out on a small scale of milligrams to a few grams. Our purpose is to emphasize the scope of the reaction; therefore while we list most of the known reactions, we highlight and comment mostly on reactions that were carried out on a large scale or provide a unique application or both.

Discussion

1. Reaction Conditions. 1.a: The Reagent: STAB-H. Sodium triacetoxyborohydride (STAB-H) is a mild reagent that exhibits remarkable selectivity as a reducing agent. It reduces aldehydes but not ketones;[32−34] however, β-hydroxyketones can be reduced selectively to give 1,3-*trans* diols.[38−40] 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.[41] It is commercially available as a hygroscopic white powder with a melting point of 116−120 °C.[34] It is also easily prepared by the reaction of $NaBH_4$ with excess acetic acid in benzene or toluene.[39] In large-scale reactions, it may be economical to prepare the reagent in the appropriate solvent rather than using the commercial product. However this introduces a safety concern because of the exothermic nature of the reaction and the hydrogen evolution. A recent report[42] identified and discussed the possible thermal and chemical hazards associated with the preparation of STAB-H. The reference concluded that the use of solid $NaBH_4$ causes many of the hazards because of the accumulation of the solid and the late initiation that may result in a sudden increase in temperature, hydrogen evolution, and decomposition of product. The report described a modified safer procedure for the *in situ* production of STAB-H by the reaction of a *solution* of $NaBH_4$ in *N*,*N*-dimethylacetamide (DMAC) with glacial acetic acid that minimized the hazards of using solid $NaBH_4$.

1.b: Solvents. In our initial evaluation, 1,2-dichloroethane emerged as the better choice for a reaction solvent based on isolated yields and reaction times.[37] However, other solvents such as THF, acetonitrile, and DMF were also used with successful results. In general many polar aprotic solvents were suitable solvents for this reaction. We avoided the use of dichloromethane despite its suitablity as a solvent, due to its tendency to react with amines.[43] It is also undesirable in large-scale reactions because of its toxicity and volatility which increase the chance of exposure. Water reacts with sodium triacetoxyborohydride, and it was avoided as a solvent or cosolvent. However, water may be present in small

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quantities without affecting the outcome of the reaction. In cases where one of the reagents contains water as in formalin and glyoxaldehyde, additional amounts of triacetoxyborohydride are used to compensate for decomposed hydride reagent. Reactions in methanol were not consistent, and in many cases, particularly with aldehydes, reduction of the carbonyl compound was competitive with reductive amination. Several groups have used methanol successfully as solvent in reductive amination reactions.[44−46] Higher alcohols such as ethanol and isopropanol react slower with $NaBH(OAc)_3$ than water and methanol and may be used as solvents. Another solvent that may be useful in reductive amination with STAB-H is *N*,*N*-dimethylacetamide (DMAC). It was successfully used in the synthesis of a substance P agonist via reductive amination (see Table 5, entry 25).[47]

1.c: Stoichiometry. In most reactions, the carbonyl compound is the limiting reagent and the amine is used in slight excess (1.05−1.1 equiv). Small amines, volatile amines, or easy to remove amines may be used in larger excess as needed. Larger nonvolatile or expensive amines are used in stoichiometric amounts. In many slow reductive amination reactions such as reactions of aldehydes and ketones with weakly basic amines, the amine is used as the limiting reagent. Sodium triacetoxyborohydride is commonly used in excess ranging from 1.4 to 4 or more equivalents. In most cases the entire amount of triacetoxyborohydride is added in one portion, but in some others, particularly on larger scale, it is added in small portions and/or with cooling to avoid sudden increases in the reaction temperature.

1.d: Effect of Acids. In general, addition of 1 equiv of a weak acid or using amine salts of weak acids increases the rate of reductive amination. Acetic acid is commonly used as the weak acid additive. Addition of strong acids or using their amine salts may completely stop the reaction. When using amine hydrochlorides, for example, an equivalent amount of a tertiary amine such as triethylamine is added to free the reactant amine. Most ketone reactions require the addition of 1 equiv of acetic acid to speed up the reaction. In many slow reactions (>24 h), we observed the formation of *N*-acetyl and *N*-ethyl derivatives of the starting and/or product amines (up to 5% by GC analysis) as side products. Many of these reactions may be suppressed by using trifluoroacetic acid in place of acetic acid. Most aldehyde reactions do not require activation with acids and are better carried out without addition of acids to eliminate (or minimize) any chance of aldehyde reduction.

1.e: Reaction Temperature. The majority of reactions are carried out at room temperature (20−25 °C). Addition of the hydride reagent may be exothermic in some cases; the temperature may rise by 5−10 °C. While that is not a concern in small reactions, during large-scale reactions, it may be a safety concern, and therefore cooling the reaction or addition of the hydride reagent in portions may be necessary to control the reaction temperature. Nearly all the reactions we studied were carried out at room temperature. In the case of reductive amination of *N*-ϵ-Cbz-L-lysine with benzaldehyde using $NaBH(OAc)_3$ in DCE, we did not obtain any significant reaction at room temperature, probably because of the low solubility of the amino acid. Heating the reaction to 50 °C gave the desired product in 82% isolated yield.[48]

1.f: Isolation. The most common method of isolating amine products is extraction after basification with aqueous 1 N NaOH. Basification of products containing esters or other base sensitive groups is done with aqueous solutions of Na_2CO_3 or $NaHCO_3$. Some highly basic amines such as benzylamines may dissolve in aqueous solutions of carbonate and bicarbonate and may be lost in extractions. In most reactions, the isolated crude product is purified by crystallization of their salts, such as hydrochloride salts (usually from EtOAc/MeOH) or oxalate salts (usually from MeOH). Other salts or solid free amines may also be purified by crystallization. Few cases require chromatographic purifications.

1.g: Standard Conditions. Based on the aforementioned observations, the following standard conditions are recommended for the reductive aminations:

For Ketones. Ketone (1 equiv), amine (1.05−1.1 equiv), AcOH (1 equiv), and $NaBH(OAc)_3$ (1.4 equiv) in DCE or THF as solvent at rt.

For Aldehydes. Aldehyde (1 equiv), amine (1.05−1.1 equiv), and $NaBH(OAc)_3$ (1.4 equiv) in DCE or THF as solvent at rt.

These conditions may be modified to optimize the yield of a particular compound or a class of compounds, for example, using the amines as limiting reagents; using a larger excess of $NaBH(OAc)_3$; using other solvents such as CH_3CN, DMF, or *i*-PrOH; and conducting the reaction at higher or lower temperatures.

2. Reductive Amination of Ketones: With a few exceptions,[38−40] sodium triacetoxyborohydride does not reduce ketones.[32,33] It is however capable of reducing ketimines under neutral to weakly acidic conditions. That made it ideal for reductive amination of ketones. Ketones would react with amines to form imines or iminium ions without interference from the reducing agent. Our systematic study[37] and the vast literature that followed clearly showed the utility and the wide scope of this reagent in reductive amination of different kinds of ketones with some few limitations.

In general, the scope of the reactions includes most alicyclic and heterocyclic ketones, bicyclic ketones, and saturated acyclic ketones. Limitations include most aromatic ketones, α,β-unsaturated ketones, and sterically hindered aliphatic ketones.

2.a: Alicyclic, Heterocyclic, and Bicyclic Ketones. Saturated cycloalkanones and hetercycloalkanones ranging

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in size from 4- to 12-membered rings give excellent yields in reductive amination reactions with primary and secondary amines. Small ring ketones are usually more reactive than the larger ones, and all react efficiently under the standard conditions. Six-membered ring ketones are the most common amongst the reported reductive amination reactions with cyclic ketones. Table 1 features several examples of amines obtained from reductive amination of this class of ketones. Entries 1−3 represent reactions with cyclobutanones, entries 4−12 are representative reactions of cyclopentanones, entries 13−46 represent six-membered ring ketones, and entries 47−49 are examples of larger ring ketones. While most of the literature reactions are carried out on a small scale, the structural diversity of the molecules used in these examples should be helpful in determining the scope of this procedure. The conditions are very tolerant to the presence of many functional groups, and the conditions vary to a large degree based on the solubility and reactivity of the individual ketones and amines.

The reactivity of cyclobutanone compares to that of aldehydes; for example, reductive amination of cyclobutanone with benzylamine gave a mixture of *N*-cyclobutyl and *N*,*N*-dicyclobutyl benzylamines even when using excess benzylamine. The only homogeneous reactions were achieved when using excess ketone to form *N*,*N*-dicyclobutyl benzylamine (Table 1, entry 1) or in reactions with secondary amines when only one product is possible (Table 1, entry 2).

Most other cyclic ketones react slower, and the dialkylation of primary amines is not a common occurrence. Reactions with cyclopentanones and cyclohexanones are usually complete in a few hours to 24 h. However, we noticed very fast reactions with 4-*tert*-butylcyclohexanone and other 4-substituted cyclohexanones such as cyclohexane-1,4-dione monoethylene ketal (see Tables 2 and 10). Some reactions are complete in only 10 min. The structural diversity and complexity of the substrates are illustrated in the listed examples.

2.b: Diastereoselection in Reductive Amination of Cyclic and Bicyclic Ketones. In substituted cyclic and bicyclic ketones, the formation of diastereomers is possible; in these cases we observe variable degrees of diastereoselectivity based on the location and the size of the substituent or other steric factors.[37,75−78] The examples listed in Table 2 are those with reported diastereoselectivity resulting from the reductive amination of cyclic and bicylic ketones. The degree of selectivity in cycloalkanones varies from completely nonselective (Table 2, entry 1)[79] to exclusive formation of one diastereomer (Table 2, entry 6).[80] Sodium triacetoxyborohydride is more sterically demanding than other "smaller" borohydrides such as sodium borohydride and cyanoborohydride.[75−78] As the hydride reagent favors the least hindered approach, the newly formed C−N bond(s) in the major product(s) is(are) usually *cis* (or *syn*) to the existing substituent. A very practical and efficient synthesis of *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (Table 2, entry 7) was developed by Ripin et al.[81] and was carried out on about a 25 kg scale. The sodium triacetoxyborohydride reagent was generated, *in situ*, from $NaBH_4$ and AcOH in THF. The imine intermediate was prepared by reacting *N*-benzyl-4-methylpiperidin-3-one with methylamine in toluene/THF/EtOH solvent mixture. The imine solution was added to the triacetoxyborohydride suspension to effect the reduction and provide an excellent yield (92%) of the product, in 86:14 ratio in favor of the desired *cis*-diastereomer.

Conlon et al. reported another case of practical and efficient diastereocontrol in the synthesis of an anti-HIV drug

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Table 1. **Reductive amination of saturated alicyclic and heterocyclic ketones**[a]

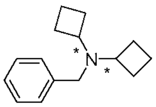
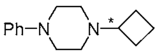
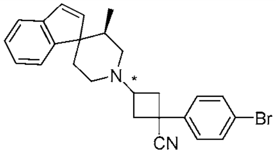
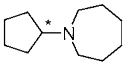
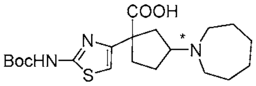
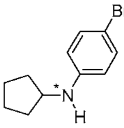
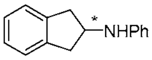
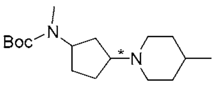
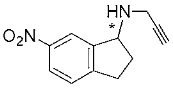
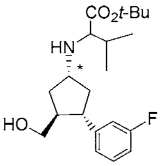
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE AcOH 1.5 h	98%	37
2		STAB-H DCE 2 h	96%	37
3		STAB-H DCM 4A MS 24 h	99%	49
4		STAB-H DCE AcOH 24 h	85%	37
5		STAB-H THF overnight	75%	50
6		STAB-H DCE AcOH 48 h	89%	37
7		STAB-H DCE AcOH 6 h	85%	37
8		STAB-H DCE AcOH 22h rt	35%	51
9		STAB-H DCE 50h	69%	52
10	 major isomer	STAB-H DCE AcOH 16 h rt	92%	53

Table 1 (Continued)

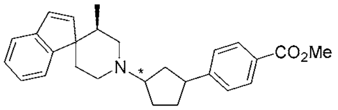
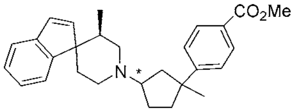
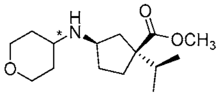
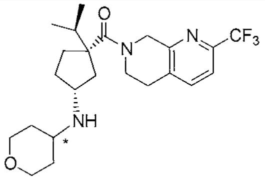
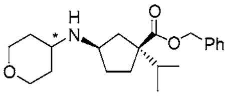
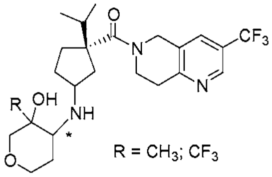
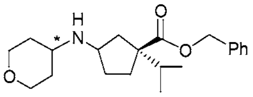
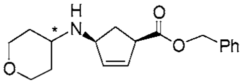
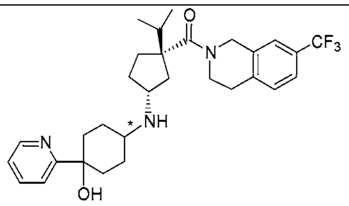
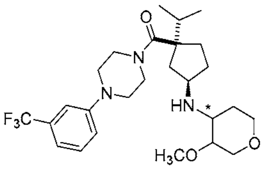
Entry	Reductive Amination Product	Conditions	Yield	Reference
11		STAB-H DCM 4A MS 2h	70%	49
12		STAB-H DCM 4A MS 24 h	29%	49
13		STAB-H DCM overnight		54
14		STAB-H DCM overnight		54
15		STAB-H DCM 2h	97%	55
16	 R = CH_3; CF_3	STAB-H DCM 4A MS overnight		56
17		STAB-H DCM 4A MS overnight	42% isolated as *N*-$COCF_3$ derivative	54
18		STAB-H DCM 4A MS overnight	84%	54
19		STAB-H DCM overnight		57
20		STAB-H DCM Overnight	92%	58

Table 1 (Continued)

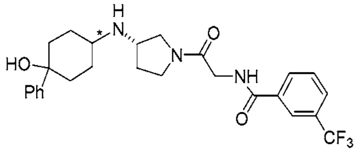
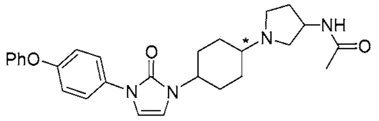
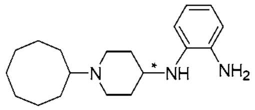
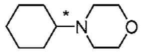
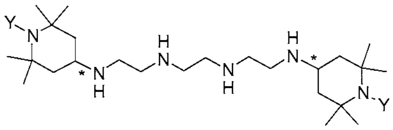
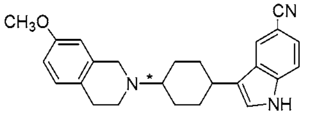
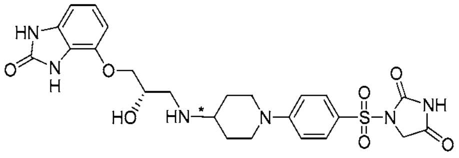
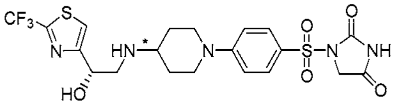
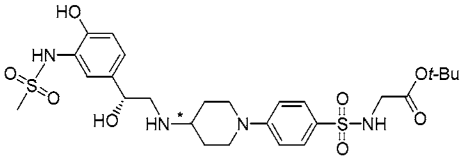
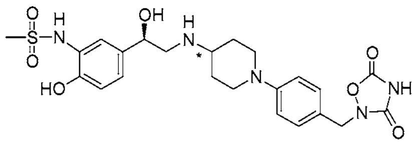
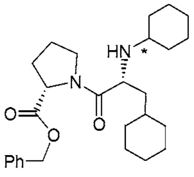
Entry	Reductive Amination Product	Conditions	Yield	Reference
21		STAB-H THF		59
22		STAB-H DCE 48h		60
23		STAB-H DCE overnight	81%	61
24		STAB-H DCE AcOH	96%	37
25		STAB-H DCM AcOH 2 h	Y= O, 43% Y = H, 36%	62
26		STAB-H DCE/AcOH overnight	40%	63
27		STAB-H DMF AcOH 24 h	40%	64
28		STAB-H DMF AcOH 24h	68%	64
29		STAB-H DMF AcOH 24h	80%	64
30		STAB-H DMF AcOH 24h	71%	65
31		STAB-H DMF AcOH 16h	80%	66

Table 1 (Continued)

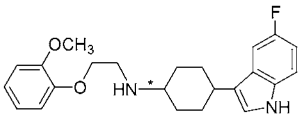
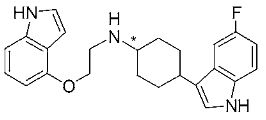
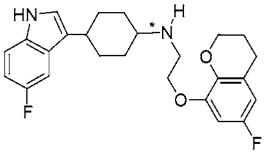
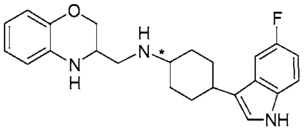
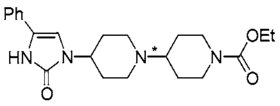
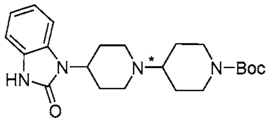
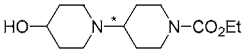
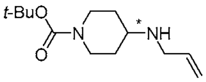
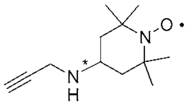
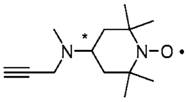
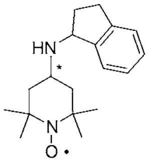
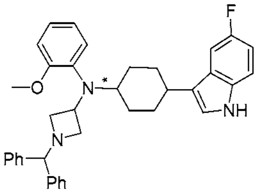
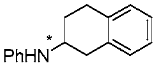
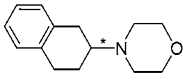
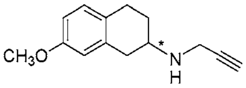
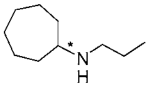
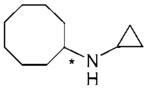
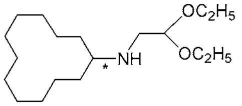
Entry	Reductive Amination Product	Conditions	Yield	Reference
32		STAB-H DCE AcOH 4 h	71%	67
33		STAB-H DCE AcOH 4 h	48%	67
34		STAB-H DCE AcOH 5 h	64%	67
35		STAB-H DCE AcOH 16 h	66%	68
36		STAB-H DCE AcOH 72 h	61%	69
37		STAB-H DCE AcOH 2 h	76%	69
38		STAB-H DCM AcOH 2d	17%	70
39		STAB-H DCE AcOH 3h	99% (crude)	71
40		STAB-H DCE 40h	84%	52,72
41		STAB-H DCE 32h	36%	52,72
42		STAB-H DCE 40h	71%	52,72

Table 1 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
43		STAB-H DCE AcOH 23 °C 12 h	54%	73
44		STAB-H DCE AcOH	97%	37
45		STAB-H THF AcOH	58%	37
46		STAB-H DCE AcOH rt 12h	84%	74
47		STAB-H DCE AcOH	96%	37
48		STAB-H DCE AcOH	95%	37
49		STAB-H DCE AcOH	88%	37

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; DMF = *N*,*N*-dimethylformamide; THF = tetrahydrofuran; AcOH = acetic acid; MS = molecular sieves; rt = room temperature.

candidate (compound **B**, Table 2, entry 8).[82] While other cases listed here are diastereoselective based on steric effects that produce *cis*-products, the key step in this synthesis is a unique hydroxy-directed reductive amination of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentanone with D-valine, *tert*-butyl ester, to prepare compound **A** in which the *trans*-product was favored. The researchers were able to improve the selectivity of the reductive amination with STAB-H from a 1.9:1 ratio in DCE at rt to about 7:1 in favor of the desired *trans*-diastereomer by carrying out the reaction in dry acetonitrile, by elevating the reaction temperature to 50 °C and by increasing the stoichiometric ratio of D-valine ester. Further improvement was obtained by using sodium tripropoxyborohydride (prepared *in situ* from propionic acid and $NaBH_4$ in dry acetonitrile). The increased bulk of this hydride reagent and higher reaction temperature (70 °C) gave a 10:1 ratio favoring the *trans*-isomer. The reaction was carried out on about a 4 mol scale, and the product was converted directly to the *N*-methyl derivative by a second reductive amination with formalin using STAB-H. This sequence provided compound **A** in 61% isolated yield for the two reductive amination steps. To finish the synthesis a third reductive amination was carried out on the corresponding aldehyde to prepare compound **B** in 99% yield.

In the preparation of the CCR2-inhibitor listed in Table 2, entry 9, the final step is a reductive amination of (3*R*)-3-methoxytetrahydro-4*H*-pyran-4-one with a cyclopentenamine derivative. The reaction was carried out in an

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(82) Conlon, D. A.; Jensen, M. S.; Palucki, M.; Yasuda, N.; Um, J. M.; Yang, C.; Hartner, F. W.; Tsay, F.-R.; Hsiao, Y.; Pye, P.; Rivera, N. R.; Hughes, D. L. *Chirality* **2005**, *17* (Suppl.), S149.

Table 2. **Diastereoselectivity in reductive amination of alicyclic ketones and bicyclic ketones**[a]

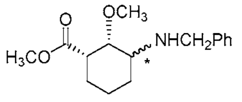
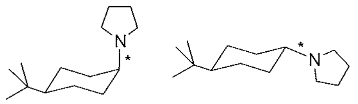
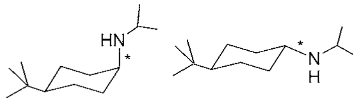
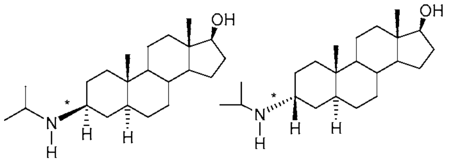
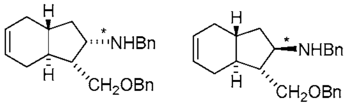
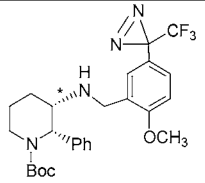
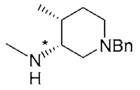
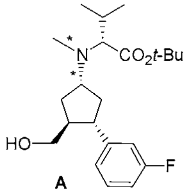
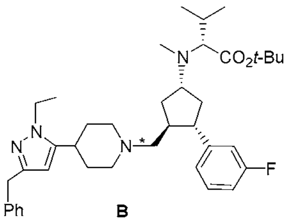
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCM AcOH	99% dr 1 : 1	79
2		STAB-H DCE AcOH 10 min	98% a/e = 71 : 29	37
3		STAB-H DCE AcOH 30 min	96% a/e = 79 : 21	37
4		STAB-H DCE AcOH 24 h	99% α/β = 75 : 25	37
5		STAB-H DCE	70% dr 82 : 18	87
6		STAB-H DCE	61% only product	80
7		STAB-H THF AcOH 2.5 h	92% dr 86:14	81
8	 A	**Step 1**: $NaBH(OCOEt)_3$ CH_3CN 70 °C 30 min	61% (dr 7 : 1)	82
	 B	**Step 2**: STAB-H CH_2O/H_2O Rt 30 min **Step 3:** STAB-H DCM	99%	82

Table 2 (Continued)

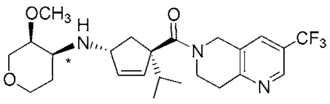
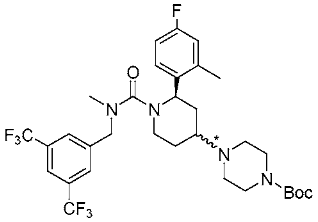
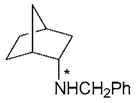
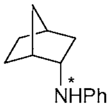
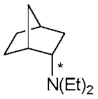
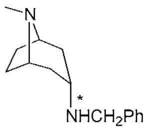
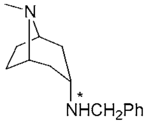
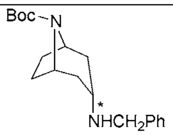
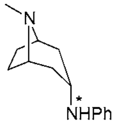
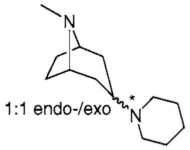
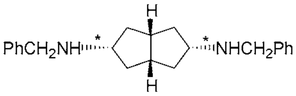
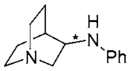
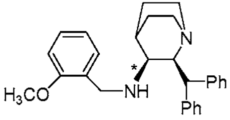
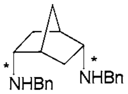
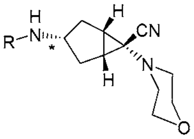
Entry	Reductive Amination Product	Conditions	Yield	Reference
9		STAB-H *i*-PrOAc/*i*-PrOH 1 °C – rt 6 h	90%	83
10		STAB-H DCE 24 h	4*R*: 34% 4*S*: 29%	88
11		STAB-H DCE AcOH 6 h	95%	37
12		STAB-H DCE AcOH 24 h	76%	37
13		STAB-H DCE AcOH 96 h	79%	37
14		STAB-H DCE AcOH 20 h	85%	37
15		NaBH(OCOR)$_3$ DCM	77-89%	84
16		STAB-H DCE 18 h	99%	89
17		STAB-H DCE AcOH 72 h	95%	37
18		STAB-H DCE AcOH 4 d	60%	37

Table 2 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
19	 + 2 minor diastereomers	STAB-H	96%	85
20		STAB-H THF overnight	30%	90
21		STAB-H AcOH 4.5_h	86%	86
22		STAB-H DCM 6_h	98%	91
23		STAB-H DCE AcOH 24 h rt	R = Ph 21% R = Bn 59%	92

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; AcOH = acetic acid; rt = room temperature.

i-PrOAc/*i*-PrOH solvent mixture on a relatively large scale of 0.5 kg. The reaction proceeded with the exclusive formation of the *cis*-product to give an excellent isolated yield of 90%.[83]

The kind of stereochemical control based on steric factors is also observed in bicyclic ketones. Bicyclic ketones such as norcamphor and tropinone are successfully reductively aminated with primary and secondary amines in good to excellent yields (Table 2, entries 11−17). The reactions involving these ketones usually show high levels of diastereoselectivity towards the *endo*-products. Products from norcamphor and primary or secondary amines are exclusively *endo*-, while those obtained from tropinone with primary amines show about a 15:1 ratio of the *endo*- to *exo*-products. An exception is the reaction of tropinone with secondary amines such as piperidine, which is very slow and gives a 1:1 ratio of the *endo*- and *exo*-products (Table 2, entry 18).[37] In the synthesis of zatosetron, an agonist of 5HT$_3$ receptor, the key intermediate is 3-*endo*-tropamine. McGill et al.[84] prepared this amine in a 12:1 ratio of *endo*/*exo* products by the reductive amination of tropinone with benzylamine using STAB-H and subsequent hydrogenolysis to cleave the benzyl group. In addition to about 7% of the undesired *exo*-product, the reaction was also accompanied by large amounts of *N*-benzylacetamide. A study carried out by the group showed that replacing the acetoxy groups in NaBH(OAc)$_3$ with larger acyloxy groups, increased the steric bulk of the reagent, and led to formation of a higher ratio of *endo*/*exo*-products. The best result came from using tri(2-ethylhexanoyl)borohydride which gave a >50:1 ratio of *endo*/*exo*-products and no amine acylation (Table 2, entry 15).

The reductive amination of *cis*-bicyclo[3.3.0]octane-3,7-dione (Table 2, entry 19) gives the symmetric diamine product in 96% yield with a slight contamination of two minor diastereomers.[85]

The 3-amino-1-azabicyclo[2.2.2]octane derivative listed in Table 2, entry 21, was prepared effectively on a 1 mol scale by the reduction of the corresponding imine at 25 °C with sodium triacetoxyborohydride to give the amine in 86% isolated yield.[86] The reported isolated product has *cis*-stereochemistry, but no ratio of products was given.

Thus, whenever structurally possible, STAB-H is a useful and very effective reagent in diastereoselctive formation of amines via reductive amination based on steric factors. In many reported cases, increasing the diastereoselectivity may be benefited from examining other bulkier triacyloxyborohydrides as seen in some of the above examples. The reductive amination of hydroxyketones is another effective

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(83) Cai, D.-W.; Fleitz, F.; Ge, M.; Hoerrner, S.; Javadi, G.; Jensen, M.; Larsen, R.; Li, W.; Nelson, D.; Szumigala, E.; Yang, L.; Zhou, C. WO Patent Application 05/044795A1, 2005.

(84) McGill, J. M.; LaBell, E. S.; Williams, M. *Tetrahedron Lett.* **1996**, *37* (23), 3977.

(85) Camps, P.; Munoz-Torrero, D.; Perez, F. J. *J. Chem. Res., Synop.* **1995**, 232.

(86) Godek, D. M.; Murtiashaw, C. W. U.S. Patent 95/5442068, 1995.

method for achieving diastereocontrol; however, it is not yet widely used.

2.c: Saturated Acyclic Ketones. Saturated acyclic ketones also undergo facile reductive amination with both primary and secondary amines. 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 equiv of AcOH, the use of about a 5−10% excess of the amine, and 2 or more equivalents of sodium triacetoxyborohydride. Examples of products obtained by reductive amination of several saturated acyclic ketones are shown in Table 3. In some of these slow reductive aminations, (e.g., Table 3, entries 2 and 7), some side reactions may occur. These include *N*-acetylation and *N*-ethylation of the starting amines and to a lesser extent the product amines. The *N*-acetylation is believed to be the result of nucleophilic attack by the amines on the triacetoxyborohydride.[18,36] The *N*-ethylation of amines is a well-known process in the reaction of amines with sodium borohydride in neat acetic acid and is believed to proceed through acetaldehyde formation under the reaction conditions.[35] As mentioned above, addition of acetic acid is a common practice to accelerate slow reactions. Sometimes, it is the addition of acetic acid that causes the increase in the amount of these side reactions. The use of trifluoroacetic acid instead of AcOH may eliminate or decrease the formation of these side products.

While the majority of the reactions listed here are carried out in DCE, DCM, or THF, the reductive amination of acetone with 1-benzyl-4-aminopiperidine (Table 3, entry 16)[44,93] was carried out in methanol. The reaction mixture was cooled to 5 °C for 30 min prior to addition of STAB-H; after stirring at rt for 2 h the reaction was worked up. The product was isolated in a very high yield of 95%. However, when the reaction was scaled up to a 2 kg scale, it was carried out in DCM (Table 3, entry 17). The mixture was cooled to 0−5 °C before adding STAB-H, and the reaction was worked up after stirring for 3 h at 25 °C. This reductive amination reaction performed equally well on the larger scale to give an isolated yield of 96% of 1-benzyl-4-isopropylaminopiperidine.

3. Reductive Amination of Aldehydes. Sodium triacetoxyborohydride was introduced by Gribble et al. as a selective reducing agent that reduces aldehydes but not ketones.[32−34] However, under the standard reaction conditions the reductive aminations with aldehydes occur very effectively and result in fast reactions with no aldehyde reduction 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, THF, or any other solvent of choice with 1.4−1.5 equiv of $NaBH(OAc)_3$. The reaction times are usually much shorter than those with ketones, and nearly all reactions are complete within 20 min to 24 h. The mild reaction conditions, the convenient procedure, and the easy workup and isolation of products can tolerate the presence of different functionalities and allow the application of the reaction to a wide range of aldehydes with variable degrees of structural complexities.

3.a: Reductive Amination of Aldehydes with Primary Amines. These reactions are typically the easiest, fastest, and highest yielding reactions. This type of reductive amination is carried out using the standard conditions, and most do not require the use of acid activation. There are only very few limitations with highly unreactive primary amines such as 2,4-dinitroaniline, particularly with aromatic aldehydes. Aldehydes and primary amines condense readily (completely or partially) to form imines in most solvents, particularly in methanol, THF, and DCE.[37] It may be possible to use this property to carry out indirect stepwise reductive amination effectively as an alternative to the direct procedure. Representative examples of reductive amination of aldehydes with primary amines are illustrated in Table 4.

The mild nature of sodium triacetoxyborohydride is well demonstrated in the reductive amination of aldehydes such as 1,1′,2′-tris-nor-squalene aldehyde (Table 4, entry 43)[37] and hexa-4,5-dienal (Table 4, entries 44−47).[99] These aldehydes were converted to the corresponding amines in good yields under STAB-H reductive amination standard conditions with no detectable aldehyde reduction or other side reactions. This is a significant improvement over other literature procedures.[100,101]

A testimony to the convenient and safe use of STAB-H comes from the use of the reductive amination procedure as an undergraduate lab experiment. The procedure for reductive amination of piperonal with *p*-toluidine to form *N*-(*p*-tolyl)-piperonylamine (Table 4, entry 53) was introduced as an experiment for a second-semester organic chemistry class.[102]

An interesting reaction is that involving the reductive amination of a stable ozonide aldehyde with several primary

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(87) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, *16*, 1881.
(88) Alvaro, G.; Di Fabio, R.; Maragni, P.; Tampieri, M.; Tranquillini, M. E. WO Patent Application 02/032867A1, 2002.
(89) Kazmierski, W. M.; Aquino, C. J.; Bifulco, N.; Boros, E. E.; Chauder, B. A.; Chong, P. Y.; Duan, M.; Deanda, F. J.; Koble, C. S.; McLean, E. W.; Peckham, J. P.; Perkins, A. C.; Thompson, J. B.; Vanderwall, D. WO Patent Application 04/054974A2, 2004.
(90) Boyd, R. E.; Reitz, A. B. WO Patent Application 04/035574A2, 2004.
(91) Berkessel, A.; Schröeder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudöerfl, J. M. *J. Org. Chem.* **2004**, *69* (9), 3050.
(92) Vilsmaier, E.; Roth, W.; Bergsträsser, U. *J. Mol. Struct.* **1999**, *513* (1−3), 21.
(93) Wilson, R. D.; Congdon, J.; Mammen, M.; Zhang, W.; Chao, R. WO Patent Application 05/042514A2, 2005.
(94) Lim, M.-I.; Pan, Y.-G.; Popp, M. WO Patent Application 02/047635A1, 2002.
(95) Mantell, S. J.; Monaghan, S. M.; Stephenson, P. T. WO Patent Application 02/000676A1, 2002.
(96) Mahmoud, A. E.; Waseem, G. WO Patent Application 06/002105A1, 2006.
(97) Cherney, R. J.; Carter, P.; Duncia, J. V.; Gardner, D. S.; Santella, J. B. WO Patent Application 04/071460A2, 2004.
(98) Al-awar, R. S.; Ray, J. E.; Hecker, K. A.; Joseph, S.; Huang, J.; Shih, C.; Brooks, H. B.; Spencer, C. D.; Watkins, S. A.; Schultz, R. M.; Considine, E. L.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Carr, M. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2004**, *14* (15), 3925.
(99) Davies, I. W.; Gallagher, T.; Lamont, R. B.; Scopes, D. I. C. *J. Chem. Soc., Chem. Commun.* **1992**, 335.
(100) Ceruti, M.; Balliano, G.; Viola, F.; Cattel, L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22* (3), 199.
(101) Duriatti, A.; Bouvier-Nave, P.; Benveniste, P.; Schuber, F.; Delprino, L.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34* (15), 2765.
(102) Carlson, M. W.; Ciszewski, J. T.; Bhatti, M. M.; Swanson, W. F.; Wilson, A. M. *J. Chem. Educ.* **2000**, *77* (2), 270.

Table 3. **Reductive amination of saturated alicyclic ketones**[a]

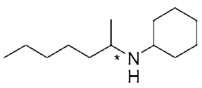
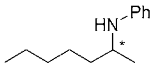
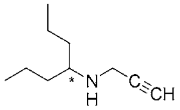
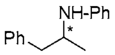
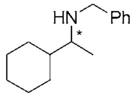
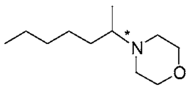
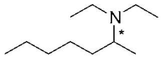
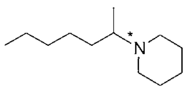
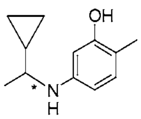
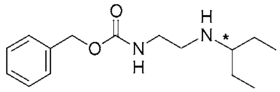
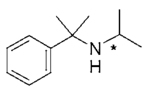
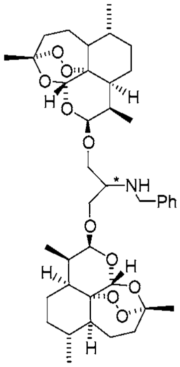
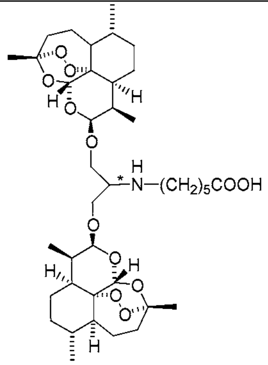
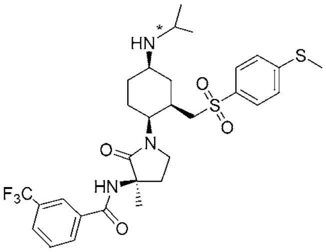
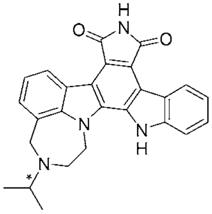
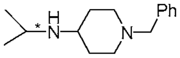
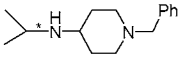
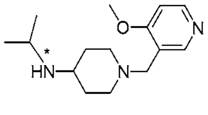
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE AcOH 24 h	84%	37
2		STAB-H DCE AcOH 96 h	90%	37
3		STAB-H DCE AcOH 12 h	84%	37
4		STAB-H DCE AcOH 30 h	80%	37
5		STAB-H THF AcOH 24 h	71%	37
6		STAB-H THF AcOH 27 h	73%	37
7		STAB-H THF AcOH 192 h	44%	37
8		STAB-H THF 48 h	37%	37
9		STAB-H DCE AcOH		94
10		STAB-H DCM 16 h	79%	95
11		STAB-H DCM 16 h	79%	95

Table 3 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
12		STAB-H DCE 72 h		96
13		STAB-H DCE AcOH 4h		96
14		STAB-H DCE 20h	75%	97
15		STAB-H AcOH DCE	90%	98
16		STAB-H MeOH 0°C - rt 3 h	95%	44,93
17		STAB-H DCM 0°C – 25°C 3 h	96%	93
18		STAB-H DCM 0 °C rt 3 h	80%	93

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; DMF = *N*,*N*-dimethylformamide; THF = tetrahydrofuran; AcOH = acetic acid; rt = room temperature.

Table 4. **Reductive amination of aldehydes with primary amines**[a]

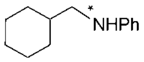
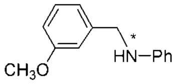
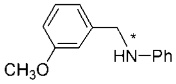
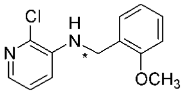
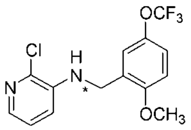
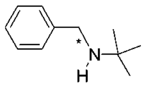
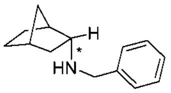
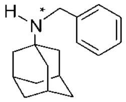
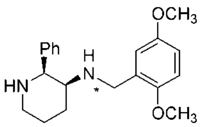
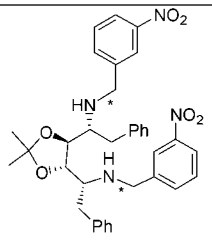
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE 24 h	83%	37
2		STAB-H THF AcOH 24 h	88%	37
3		STAB-H DCE AcOH 20 min	95%	37
4		STAB-H AcOH 20 °C 12-18 h	86%	107
5		STAB-H AcOH 25 °C 23 h	92%	107
6		STAB-H DCE AcOH 3 h	92%	37
7		STAB-H DCE 20 min	85%	37
8		STAB-H DCE 24 h	66%	37
9		STAB-H AcOH rt overnight	83%	108
10		STAB-H AcOH	83%	109

Table 4 (Continued)

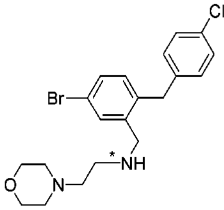
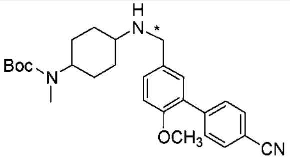
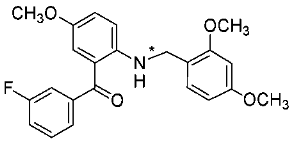
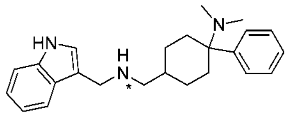
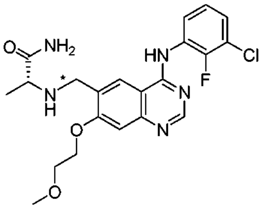
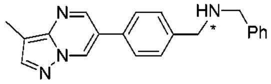
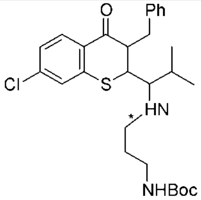
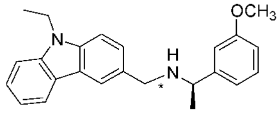
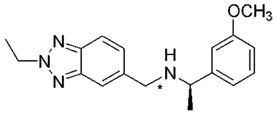
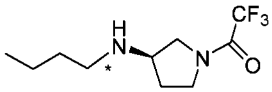
Entry	Reductive Amination Product	Conditions	Yield	Reference
11		STAB-H DCE 18 h		110
12		1. HC(OMe)$_3$ 16 h 2. STAB-H	69%	111
13		STAB-H DCE 4A MS 3 h	100% (Crude)	112
14		STAB-H DCE 4 d rt	41%	113
15		STAB-H MeOH 20 min	84%	114
16		STAB-H DCE AcOH overnight		115
17		STAB-H DCM 3 h	75%	116
18		STAB-H DCE AcOH		117
19		STAB-H DCE AcOH		117
20		STAB-H TEA DCE 18 h	94%	118

Table 4 (Continued)

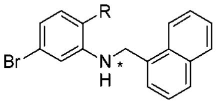
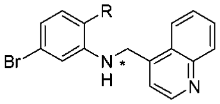
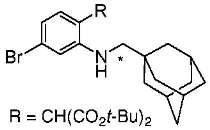
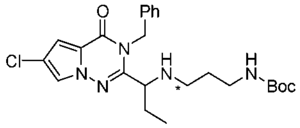
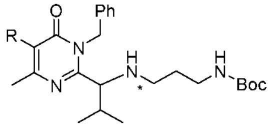
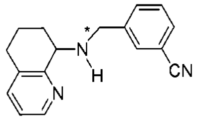
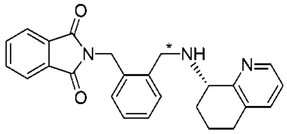
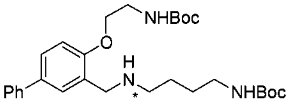
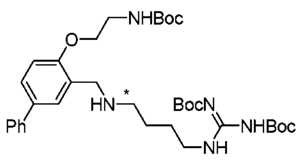
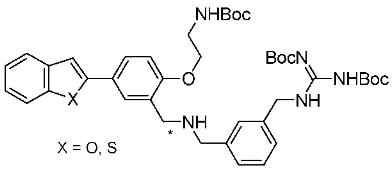
Entry	Reductive Amination Product	Conditions	Yield	Reference
21	 R = CH(CO_2t-Bu)$_2$	STAB-H AcOH 45 min	>90%	119
22	 R = CH(CO_2t-Bu)$_2$	STAB-H AcOH	>90%	119
23	 R = CH(CO_2t-Bu)$_2$	STAB-H AcOH	>97%	119
24		STAB-H THF AcOH Overnight	92%	120
25		STAB-H DCM 3 h	R = H, 65% R = Me, --	121
26		STAB-H DCM 16 h	81%	122
27		STAB-H DCM	84%	122
28		STAB-H DCE 16 h rt		123
29		STAB-H DCE 16 h		123
30	 X = O, S	STAB-H DCE 16 h		123

Table 4 (Continued)

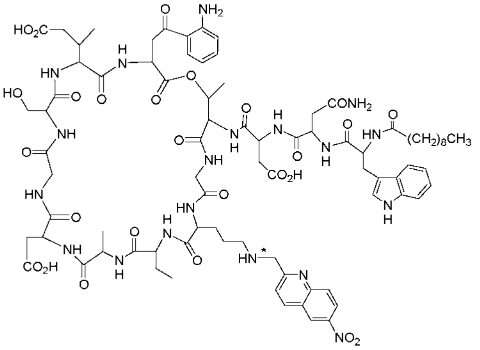
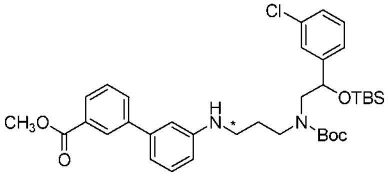
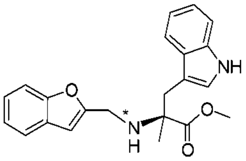
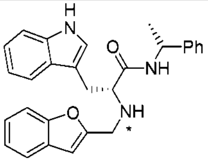
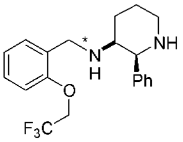
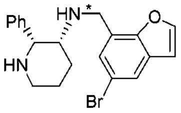
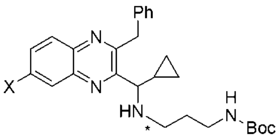
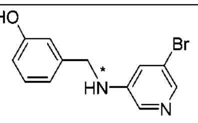
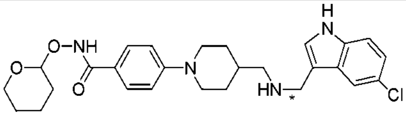
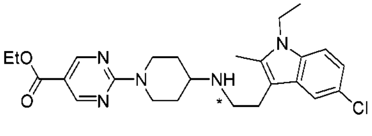
Entry	Reductive Amination Product	Conditions	Yield	Reference
31		STAB-H DMF 24 h		124
32		STAB-H DCM AcOH 3 d	75%	125
33		STAB-H DCM 2 h	82%	126
34		STAB-H DCM 2 h	68%	126
35		STAB-H AcOH overnight	20%	127
36		STAB-H DCM AcOH 18 h	53%	128
37		STAB-H MeOH AcOH 2 h	X = H, 80% X = Cl, 20%	129
38		STAB-H DCM 18 h	48%	130
39		STAB-H DCE 4 h	16%	131
40		STAB-H Ti(OEt)$_4$ DCE 18 h	21%	131

Table 4 (Continued)

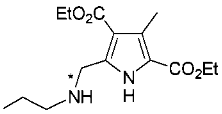
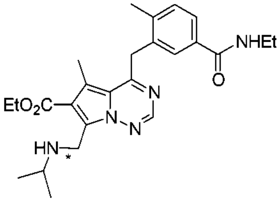
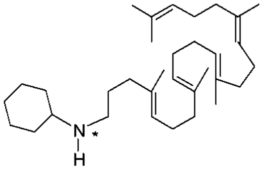
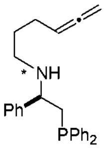
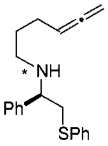
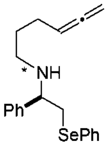
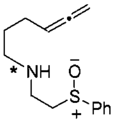
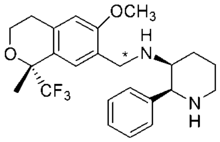
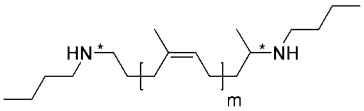
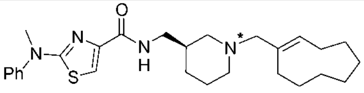
Entry	Reductive Amination Product	Conditions	Yield	Reference
41		STAB-H THF overnight	66%	132
42		STAB-H THF 2 h	44%	132
43		STAB-H DCE 1 h	94%	37
44		STAB-H DCE AcOH rt		99
45		STAB-H DCE AcOH Rt		99
46		STAB-H DCE AcOH Rt		99
47		STAB-H DCE AcOH rt	47%	99
48		STAB-H DCM 2.5 h	93% crude 32% as (+)-mandlate 4:1 ratio of diast.	133
49		STAB-H DCE rt 24 h	86%	134
50		STAB-H THF, AcOH	76%	135

Table 4 (Continued)

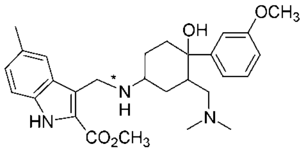
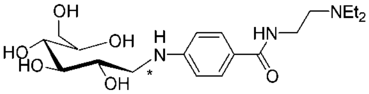
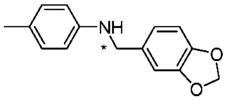
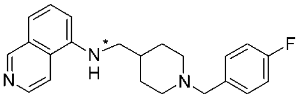
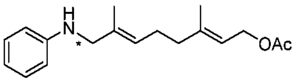
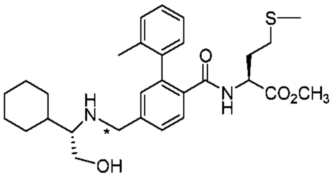
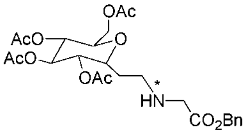
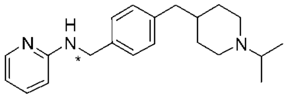
Entry	Reductive Amination Product	Conditions	Yield	Reference
51		STAB-H THF/DCE	82%	137
52		Glycan, AcOH, 60 °C STAB-H 2.5 h		138
53		STAB-H DCM rt 1.5 h		102
54		STAB-H MeOH 0°C rt 18 h	>44%	139
55		STAB-H DCE AcOH 5h 25°C	85% 97:3 (*trans* : *cis*)	140
56		STAB-H DCE rt 3h	49%	141
57		STAB-H THF AcOH pH 5 0 °C	85%	142
58		STAB-H THF 16 h rt	71%	143

Table 4 (Continued)

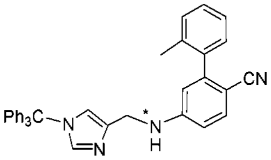
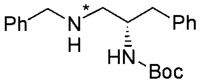
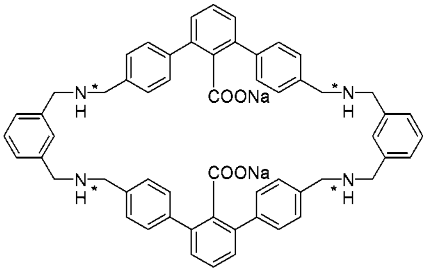
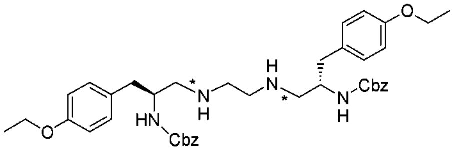
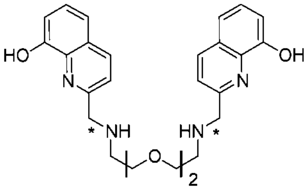
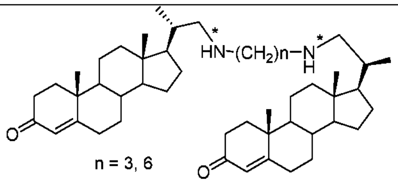
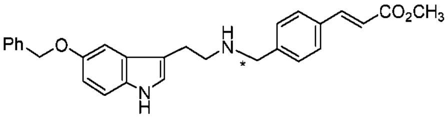
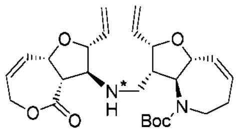
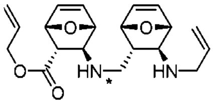
Entry	Reductive Amination Product	Conditions	Yield	Reference
59		STAB-H AcOH DCE	74%	144
60		STAB-H DCM Overnight rt	62%	145
61		STAB-H MeOH/DCM Overnight stepwise	70%	146
62		STAB-H DCE AcOH rt 2.5 h	73%	147
63		STAB-H DCE rt 8 h	27%	148
64		STAB-H DCE AcOH 72 h	60-53%	149
65		STAB-H DCE	82%	150
66		STAB-H DCM AcOH 24 h rt	90%	151
67		STAB-H DCM rt 24 h	36%	151

Table 4 (Continued)

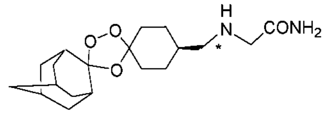
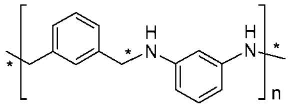
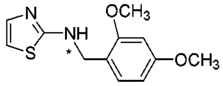
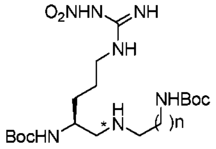
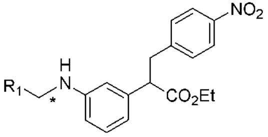
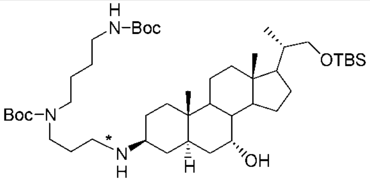
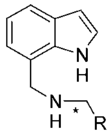
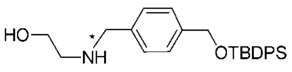
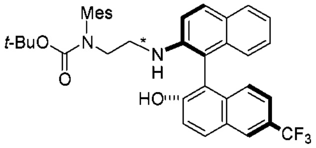
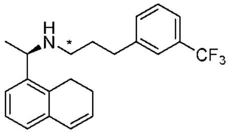
Entry	Reductive Amination Product	Conditions	Yield	Reference
68		STAB-H DCE AcOH	51%	103
69		STAB-H DCE LiCl 25 °C 48 h	79%	104
70		STAB-H TiCl(OiPr)$_3$ DCM 16 h	73%	152
71	 n = 1, 2, 3	STAB-H MeOH 3A MS rt 1 h	45%	153
72		STAB-H MeOH R1 = alkyl		154
73		STAB-H DCM	56%	155
74		STABH AcOH DCE	R = CH$_2$OH 95% R = CH=CH$_2$ 82%	98
75		STAB-H THF AcOH rt 20 h	33%	156
76		STAB-H 22 °C 2 h	81% (after 2 more steps)	157
77		STAB-H, AcOH	90%	158

Table 4 (Continued)

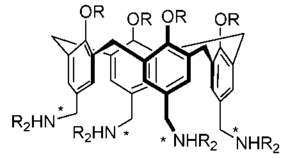
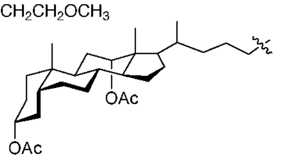
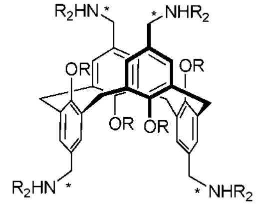
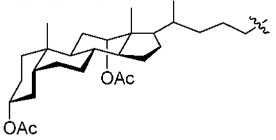
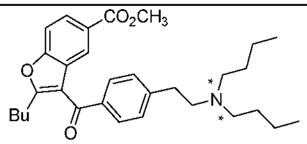
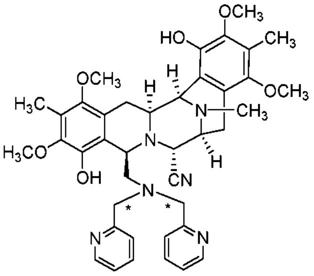
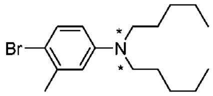
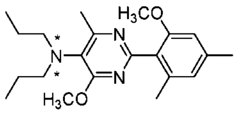
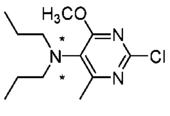
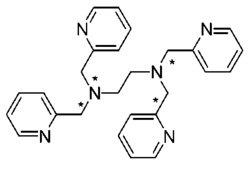
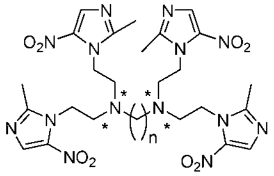
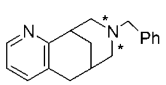
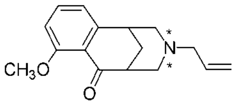
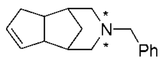
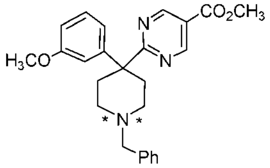
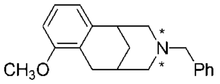
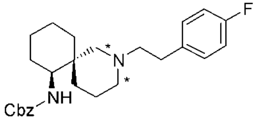
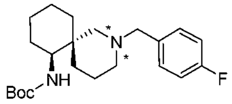
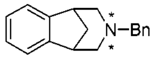
Entry	Reductive Amination Product	Conditions	Yield	Reference
78	 R = -CH$_2$CH$_2$OCH$_3$ R$_2$ = 	STAB-H DCE AcOH rt overnight	63%	105
79	 R = -CH$_2$CH$_2$OCH$_3$ R$_2$ = 	STAB-H DCE AcOH rt overnight	78%	105
80		STAB-H DCE 18 h	69%	159
81		STAB-H CH$_3$CN 1.5 h	85%	160
82		STAB-H MeOH 3 h	95%	45
83		STAB-H DCE AcOH 3 h		161
84		STAB-H DCE AcOH 3 h	95%	162

Table 4 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
85		STAB-H DCE, 24 h rt	46%	163,164
86	 n = 2 - 8	STAB-H DCE AcOH	75-94%	165
87		STAB-H DCM 7 h	50%	166
88		STAB-H DCM 18 h	29%	166
89		STAB-H DCE 2 h	66%	166
90		STAB-H DCM AcOH 24 h	35%	167,168
91		STAB-H DCE AcOH 18 h	45%	169
92		STAB-H DCM 2h	74%	170
93		STAB-H DCM 24h	100%	170
94		STAB-H DCE 0 °C to rt up to 2h	82-85%	171

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; DMF = *N,N*-dimethylformamide; THF = tetrahydrofuran; AcOH = acetic acid; MS = molecular sieves; rt = room temperature.

and secondary amines. The example shown here (Table 4, entry 68) gave the amine product in 51% yield.[103]

An oligomeric compound, "carbonyl telechelic *cis*-1,4-oligoisoprene," obtained by oxidative cleavage of high molecular weight polyisoprene, was subjected to reductive amination with *n*-butylamine using STAB-H as the reducing agent in DCE. The compound bearing an aldehyde on one end and a methyl ketone on the other was converted effectively to the diamine in an excellent yield (Table 4, entry 49; another example is listed in Table 13).

In one of the unusual applications, STAB-H was used in the reductive polycondensation of dialdehydes with diamines to produce a variety of polyamines under mild conditions.[104] Reaction times were typically 24−48 h to produce the polyamines in moderate yields (28−79%). The reactions were improved by the addition of LiCl. The authors speculated that LiCl is probably cleaving the H-bonding in intermediate hydroxyamines to facilitate the formation of the iminium ions.[104] The reactions were not improved by adding acetic acid, while heating to 70 °C or cooling to 5 °C decreased the yields. The highest yield was reported for the reductive polycondensations of isophthalaldehyde with *m*-phenylenediamine (Table 4, entry 69), which provided the polymer product in good yield. In general, electron-rich aromatic dialdehydes such as 2,5-thiophene dicarbaldehyde and cyclic secondary amines such as 4,4′-trimethylenedipiperidine (see Table 5, entry 109) gave better results than electron-poor dialdehydes and acyclic secondary amines, respectively. Other reducing conditions such as a $Ti(Oi\text{-}Pr)_4$/$NaBH_4$, Cl_3SiH/DMF, and borane−pyridine complex were used but gave little or no polycondensation products.

The synthesis of chiral Ru-based metathesis catalysts included initial reductive amination of *N*-Boc-(methanesulfonylamino)acetaldehyde with 2′-amino-6-trifluoromethyl-[1,1′]binaphthalenyl-2-ol to give the product in high yield (Table 4, entry 76).

Another interesting application is the synthesis of a new class of amphiphilic calyx[4]arene-based ionophores via reductive amination with STAB-H as a key step.[105] To this end, two analogous tetraaldehydes were prepared and used in the reductive amination reactions to introduce four steroidal amine units simultaneously. The 1,3-*cone* calix[4]arene scaffold (Table 4, entry 78) was obtained in 63% yield, while the 1,3-*alternate* calix[4]arene scaffold (Table 4, entry 79) was obtained in 78% yield. In total, five analogues were prepared and evaluated for their H^+ and Na^+ transporting properties.

In the reductive amination of aldehydes with primary amines, dialkylation of amines may occur as a side reaction. This side reaction is rarely a problem in most reported reactions. In the cases when dialkylation is detected, it is usually suppressed by the addition of a 5% or more molar excess of the primary amine. If the dialkylation of primary amines remains a problem, an alternative stepwise procedure is a possible solution for such a reaction. Most aldehydes form imines with primary amines relatively fast in solvents such as methanol, THF, and DCE.[37] It is recommended to carry out the imine formation in methanol since it is the preferred solvent for faster imine formation, and the resulting solution of the imine may be reduced directly with sodium borohydride to the amine. The faster the reduction, the less chance of formation of dialkylamines.[106]

Occasionally, however, the dialkylation of primary amines may be the desired outcome; in this case, the amine is used as the limiting reagent with two (or more) aldehyde equivalents. Representative examples of dialkylation of primary amines are listed in Table 4, entries 80−94. In some of these listings, the reaction of 1,5-dialdehydes with primary amines was used to form piperidine rings in good yields (Table 4, entries 87−94).

3.b: Reductive Amination of Aldehydes with Secondary Amines. The results from reductive amination of aldehydes with secondary amines vary considerably based on the structural features of the amines. Table 5 contains a large number of applications to illustrate the versatility of this class of reductive amination. The reaction time may be as short as 30 min or as long as 24 h. As the reaction becomes slower, it may suffer from some competing side reactions, namely, aldehyde reduction and the aforementioned *N*-acetylation and *N*-ethylation. Generally, the slower the reductive amination reaction, the larger the chance of aldehyde reduction. When compared to most other reducing agents, $NaBH(OAc)_3$ does not cause significant aldehyde reduction when used in reductive amination reactions. For example, the preparation of a thymidine dimer (Table 5, entry 10) via reductive amination shows that the use of $NaBH(OAc)_3$ resulted in a higher yield of product and very little reduction of aldehyde and was superior to the use of $NaBH_3CN$ which gave a lower yield and caused significant aldehyde reduction.[172]

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(103) Tang, Y.; Dong, Y.; Karle, J. M.; DiTusa, C. A.; Vennerstrom, J. L. *J. Org. Chem.* **2004**, *69* (19), 6470.

(104) Sakano, T.; Kawai, Y.; Kanbara, T.; Hasegawa, K. *Polym. J. (Tokyo)* **1998**, *30* (10), 857.

(105) Maulucci, N.; De Riccardis, F.; Botta, C. B.; Casapullo, A.; Cressina, E.; Fregonese, M.; Tecilla, P.; Izzo, I. *Chem. Commun.* **2005**, (*10*), 1354.

(106) For a discussion of these dialkylation side reactions involving γ- and δ-aminoesters with aldehydes and a mechanistic explanation, see reference 255.

(107) Rosen, T. J.; Godek, D. M.; Gut, S.; Wint, L. U.S. Patent 97/5663349, 1997.

(108) Rosen, T. J. U.S. Patent 97/5686615, 1997.

(109) Smyser, T. E.; Confalone, P. N. U.S. Patent 96/5532356, 1996.

(110) Davey, D.; Lee, W.; Lu, S.-F.; Phillips, G.; Wei, G. P.; Ye, B. U.S. Patent Application 05/0101644A1, 2005.

(111) Baxter, A. D.; Boyd, E. A.; Frank-Kamenetsky, M.; Porter, J.; Price, S.; Rubin, L. L.; Stibbard, J. H. A. U.S. Patent Application 05/0070578A1, 2005.

(112) Dinsmore, C. J.; Bergman, J. M. WO Patent Application 05/030792A2, 2005.

(113) Sundermann, B.; Schick, H. WO Patent Application 04/043899A1, 2004.

(114) Harris, C. S.; Hennequin, L. F. A.; Halsall, C. T.; Pease, J. E.; Smith, P. M. WO Patent Application 05/075439A1, 2005.

(115) Fraley, M. E.; Hambaugh, S. R.; Rubino, R. S.; Hungate, R. W. WO Patent Application 04/052286A2, 2004.

(116) McDonald, A.; Zhou, H.-J. WO Patent Application 04/024086A2, 2004.

(117) Kelly, M. G.; Xu, S.; Xi, N.; Townsend, R.; Semin, D. J.; Ghiron, C.; Coutler, T. WO Patent Application 03/099814A1, 2003.

(118) Andrews, M. D.; Brown, A. D.; Fradet, D. S.; Gordon, D. W.; Lansdell, M. I.; MacKenny, M. C. US Patent Application 05/0014789A1, 2005.

(119) Lyssikatos, J. P.; Yang, B. V. US Patent 03/6586447B1, 2003.

(120) Lombardo, L. J.; Bhide, R. S.; Kim, K. S.; Lu, S. WO Patent Application 03/099286A1, 2003.

(121) Morgans, D. J. C. J.; Knight, S. D.; Newlander, K. A.; Dhanak, D.; Zhou, H.-J.; Adams, N. D. WO Patent Application 03/094839A2, 2003.

Table 5. **Reductive amination of aldehydes with secondary amines**[a]

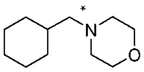
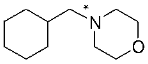
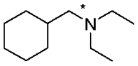
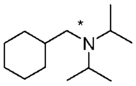
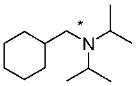
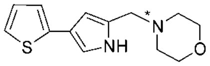
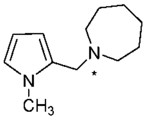
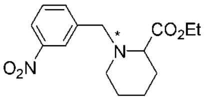
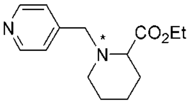
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H THF 2 h	63%	37
2		STAB-H DCE 1 h	80%	37
3		STAB-H DCE 0.5 h	84%	37
4		STAB-H DCE AcOH 3 h	41%	37
5		STAB-H DCE 8 h	74%	37
6		STAB-H DCE 2 h rt	88%	175
		STAB-H THF 2 h rt	65%	
		STAB-H CH_3CN 2 h rt	79%	
7		STAB-H DCE AcOH 1.5 h	91%	37
8		STAB-H DCE 1.5 h	96%	37
9		STAB-H DCE 1.5 h	95%	37

Table 5 (Continued)

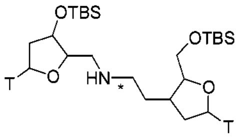
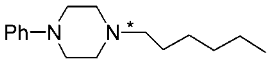
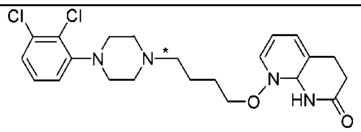
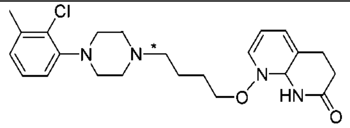
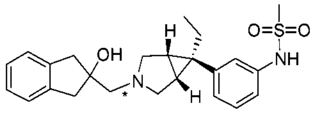
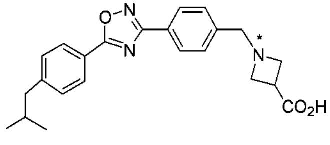
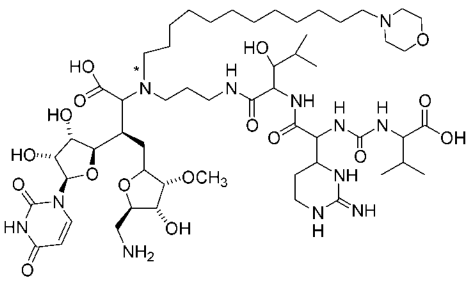
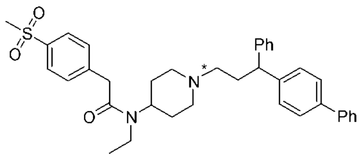
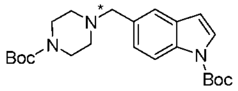
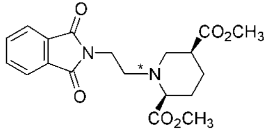
Entry	Reductive Amination Product	Conditions	Yield	Reference
10		STAB-H DCE	85%	172
11		STAB-H DCE 1 h	85%	37
12		STAB-H DCE 3 h	61%	176
13		STAB-H DCE 3 h	53%	176
14		STAB-H NMP or Me-THF rt	53% (from bisulfite adduct) 71% (from aldehyde)	177
15		STAB-H DCE 1 h	74%	178
16		1. $CH_3COCH_2COCH_3$ Pyridine/MeOH 2. STAB-H DMF AcOH 48 h 3. TFA/H_2O/dioxane	22%	173
17		STAB-H THF/EtOH AcOH 2 h	44%	179
18		STAB-H THF	85%	174
19		STAB-H AcOH	79%	180

Table 5 (Continued)

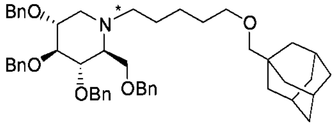
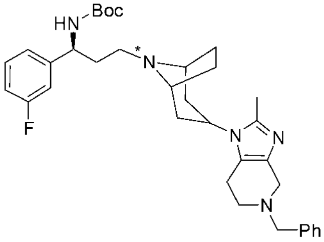
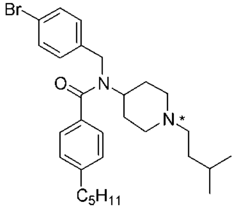
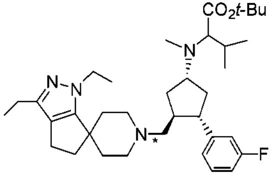
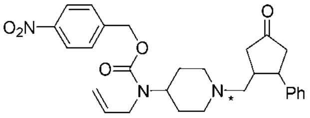
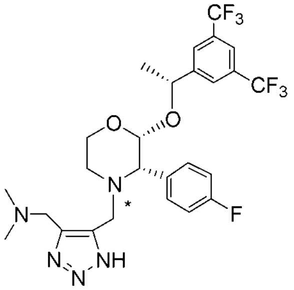
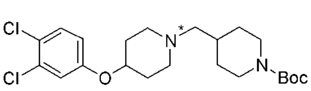
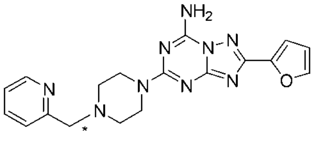
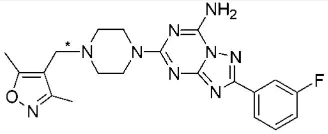
Entry	Reductive Amination Product	Conditions	Yield	Reference
20		STAB-H DCE	59%	181
21		STAB-H DCE 2 h	68%	182
22		STAB-H DCM	83%	136
23		STAB-H DIPEA DCE 16 h		53
24		STAB-H DCE rt 4 h	43%	71
25		STAB-H DMAC 0 °C to –5 °C 2 h	95% (as HCl salt)	47
26		STAB-H THF overnight	69%	183
27		STAB-H DCM AcOH 18 h		114
28		STAB-H DCM 18 h		114

Table 5 (Continued)

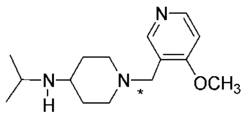
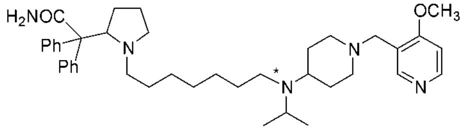
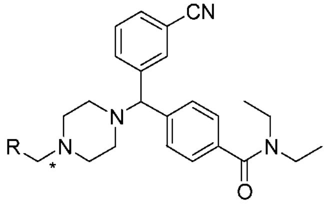
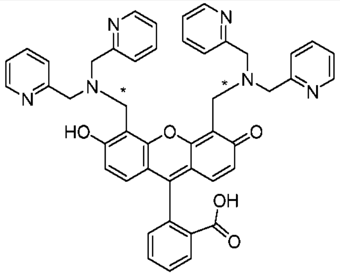
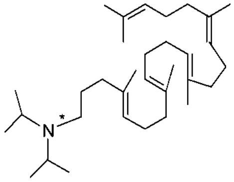
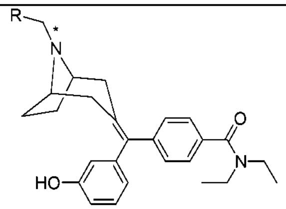
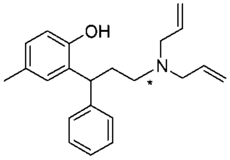
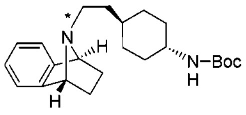
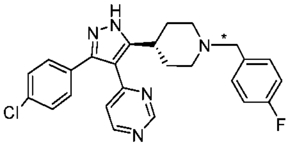
Entry	Reductive Amination Product	Conditions	Yield	Reference
29		STAB-H DCM 0°C – 10°C 3 h	80%	93
30		STAB-H DCM 20 h	63%	44,93
31		STAB-H DCE 3 d	R = Ph, 57% R = furyl, 53%	32
32		STAB-H DCE AcOH 24h	28%	183
33		STAB-H DCE 1.5 h	90%	37
34		STAB-H DCM AcOH 16 h	60-95%	184
35		STAB-H DCE Overnight rt		185
36		STAB-H DCE overnight	85%	186
37		STAB-H THF/DMF AcOH 16 h	97%	187

Table 5 (Continued)

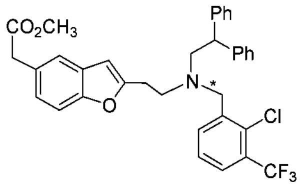
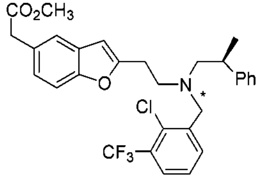
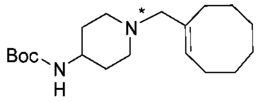
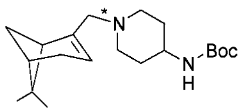
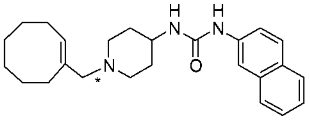
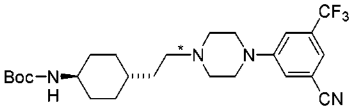
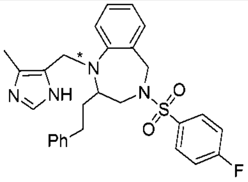
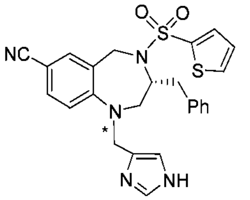
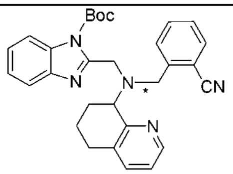
Entry	Reductive Amination Product	Conditions	Yield	Reference
38		STAB-H DCM AcOH	100%	188
39		STAB-H DCM AcOH	65%	188
40		STAB-H DCM HC(OEt)$_3$ overnight	80%	189
41		STAB-H DCM HC(OEt)$_3$ overnight	64%	189
42		STAB-H DCM HC(OEt)$_3$ overnight		189
43		STAB-H DCE 20h	85.8%	190
44		STAB-H DCE AcOH 30 min	90%	191
45		1. TFA/TCAA 2. STAB-H DCE 2.5 h (TFA/TCAA act as water scavenger)	91%	192
46		STAB-H DCM overnight	65%	122

Table 5 (Continued)

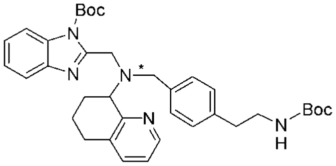
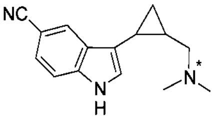
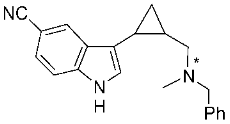
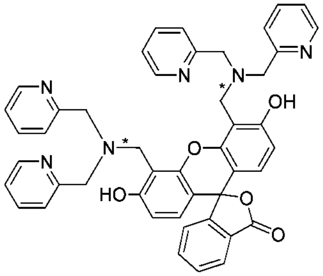
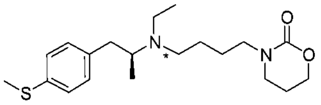
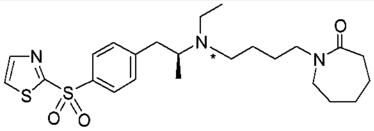
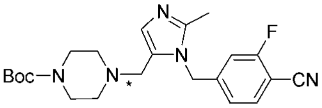
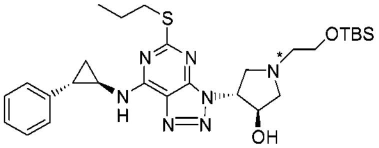
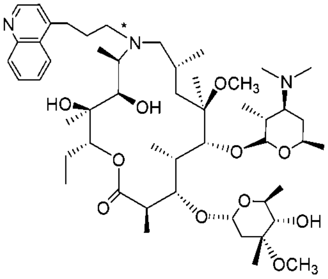
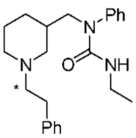
Entry	Reductive Amination Product	Conditions	Yield	Reference
47		STAB-H THF AcOH 46 h		122
48		STAB-H THF 30 min	77%	46
49		STAB-H MeOH 30 min	55%	46
50		STAB-H DCE AcOH 12 h	28%	193
51		STAB-H DCE 15 h	86%	194
52		STAB-H DCE 15 h		194
53		STAB-H DCE AcOH 4 h		195,196
54		STAB-H THF 16 h	36%	197
55		STAB-H DCE AcOH 1 h	16%	198
56		STAB-H DCE AcOH 3 h	56%	199

Table 5 (Continued)

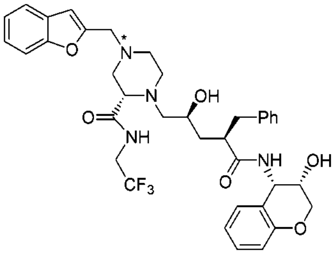
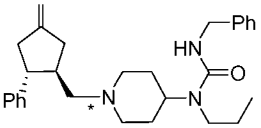
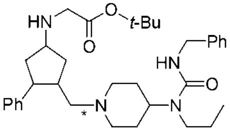
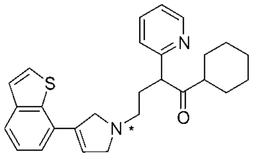
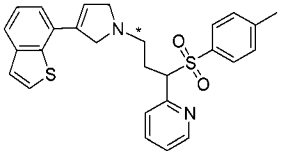
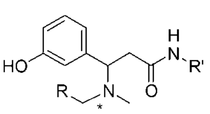
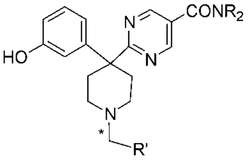
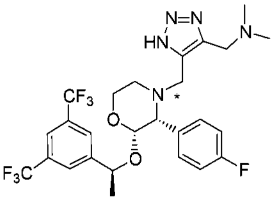
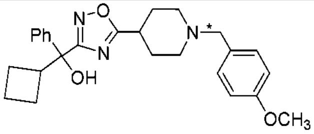
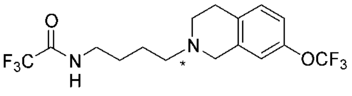
Entry	Reductive Amination Product	Conditions	Yield	Reference
57		STAB-H DCE AcOH 4 h		200
58		STAB-H DCE AcOH 3 h	86%	71
59		STAB-H DCE 3 h		71
60		STAB-H DCM 1.3 h	24%	201
61		STAB-H DCM 2 h		201
62		STAB-H DCM AcOH 16 h	60-95% Several examples	202
63		STAB-H DCM AcOH 24 h	50-90% Several examples	167,168
64		STAB-H Tol/DMF 5 h or dimethylacetamide 1 h		203
65		STAB-H THF 6 h	56%	204
66		STAB-H DCE 18 h	57%	205

Table 5 (Continued)

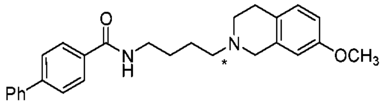
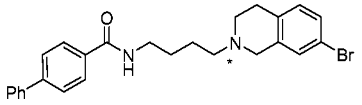
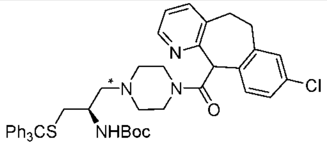
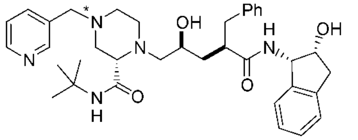
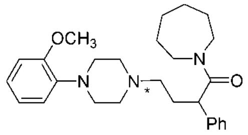
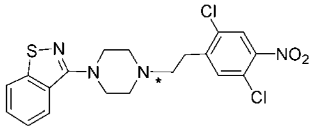
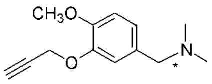
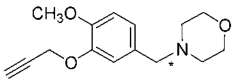
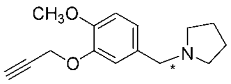
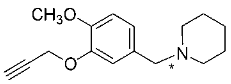
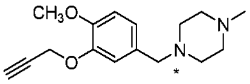
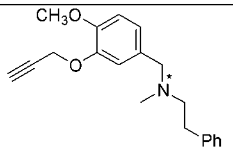
Entry	Reductive Amination Product	Conditions	Yield	Reference
67		STAB-H DCE 16 h	83%	205
68		STAB-H DCE 16 h	68%	205
69		STAB-H DMF 2.5 h		206
70		STAB-H DCE 1.25 h	88%	207
71		STAB-H DCE AcOH 3 h		208
72		STAB-H DCE AcOH overnight	71%	209
73		STAB-H DCE 0.5 h	93%	210
74		STAB-H DCE 1 h	100%	210
75		STAB-H DCE 1 h	86%	210
76		STAB-H DCE 1 h	80%	210
77		STAB-H DCE 2 h	52%	210
78		STAB-H DCE 1 h	47%	210

Table 5 (Continued)

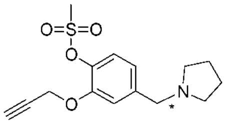
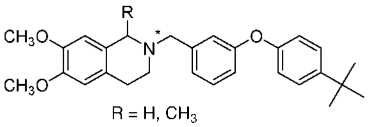
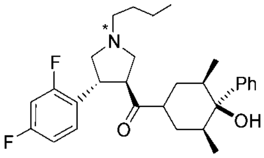
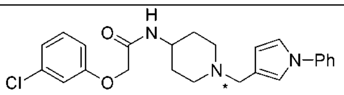
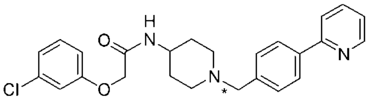
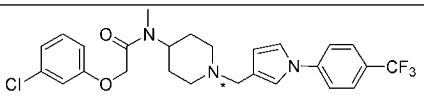
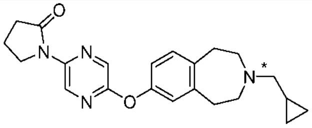
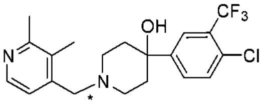
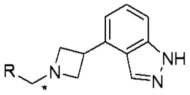
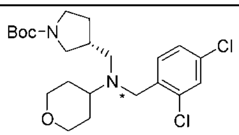
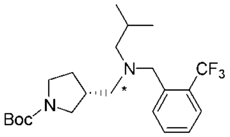
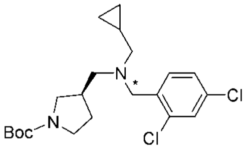
Entry	Reductive Amination Product	Conditions	Yield	Reference
79		STAB-H DCE 1.5 h	95%	210
80	 R = H, CH$_3$	STAB-H DCE AcOH 16 h		211
81		STAB-H DCM 24 h	32%	212
82		STAB-H DCM	21%	213
83		STAB-H DCM	51%	213
84		STAB-H DCM	79%	213
85		STAB-H DCM		214
86		STAB-H DCM 70 °C overnight		215
87		STAB-H DCM 18 h	21-41%	216
88		STAB-H DCE 18 h		217
89		STAB-H DCE 18 h		217
90		STAB-H DCE 18 h		217

Table 5 (Continued)

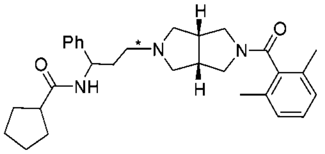
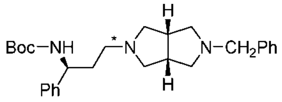
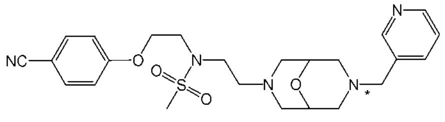
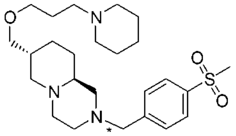
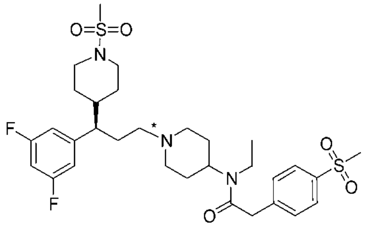
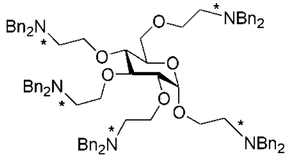
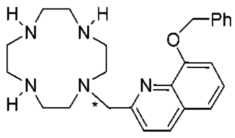
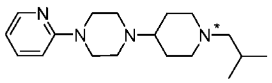
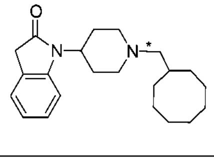
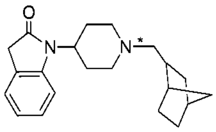
Entry	Reductive Amination Product	Conditions	Yield	Reference
91		STAB-H DCM/Toluene AcOH 18 h	29%	218
92		STAB-H DCM 18 h	46%	218
93		STAB-H DCM overnight	68%	219
94		STAB-H AcOH overnight		220
95		STAB-H DCM 2 h	68%	221
96		STAB-H THF AcOH 3 h, 10 °C	74%	222
97		240mg DCM STABH 2eq 15 h	61%	223
98		STABH, DCM AcOH rt 12-15 h	99%	224
99		STAB-H DCE AcOH rt 2h	10-70%	225
100		STAB-H DCE AcOH rt 2 h	10-70%	225

Table 5 (Continued)

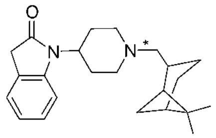
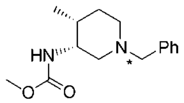
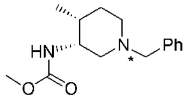
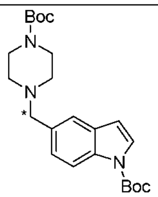
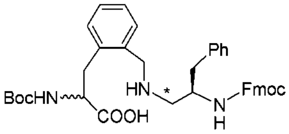
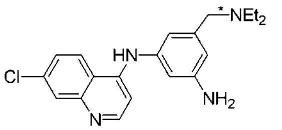
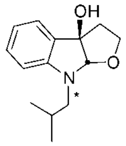
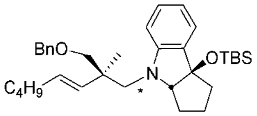
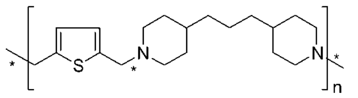
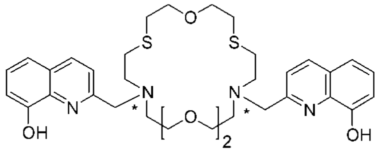
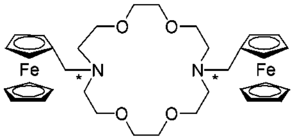
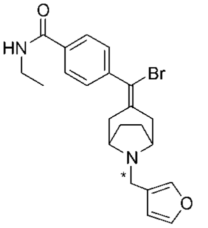
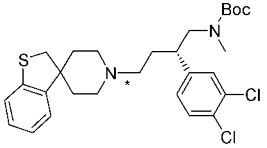
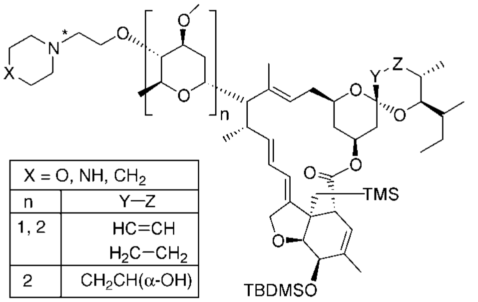
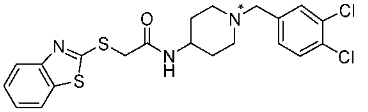
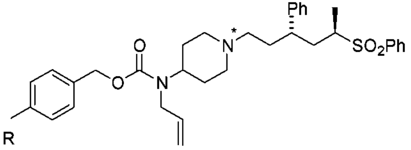
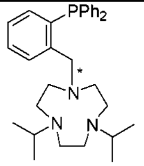
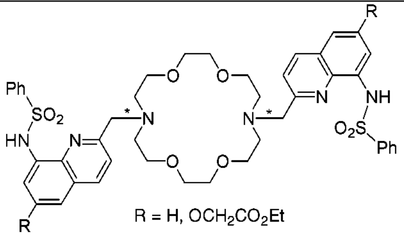
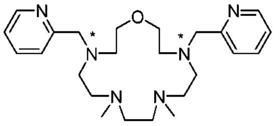
Entry	Reductive Amination Product	Conditions	Yield	Reference
101		STAB-H DCE AcOH rt 2 h	10-70%	225
102		STAB-H DCM AcOH	68%	226
103		STAB-H PhMe 2 h 20-30 °C	73%	226
104		STAB-H PhMe/THF 23-27 °C, 1.5 h	80%	227
105		STAB-H DCE $MgSO_4$	>49%	228
106		STAB-H DCM rt 18 h	30%	229
107		STAB-H DCE AcOH 0 °C	82%	230
108		STAB-H $Sn(OTf)_2$ DCE 0 °C 4A MS	66%	230
109		STAB-H DCE LiCl 25 °C 48 h	65%	104
110		STAB-H DCE rt 8 h	48%	148

Table 5 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
111		STAB-H DCE 12 h	86%	231
112		STAB-H DCE, DMF Microwave 120 °C 6 min		232
113		STAB-H DCE		233
114		STAB-H $ZnCl_2$ DCM 0 °C	66-91%	234
115		STAB-H DCM	90+%	235
116		STAB-H DCM		236
117		STAB-H, DCE	72%	237
118		STAB-H DCE	85%	238
119		STAB-H DCE	87%	239

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; DMAC = *N*,*N*-dimethylacetamide; NMP = *N*-methyl pyrrolidinone; AcOH = acetic acid; DMF = *N*,*N*-dimethylformamide; THF = tetrahydrofuran; Me-THE = 2-methyltetrahydrofuran; DIPEA = *N*,*N*-diisopropylethylamine; MS = molecular sieves; rt = room temperature.

As mentioned before, most aldehyde reductive aminations do not require the use of acid activation. All aldehydes are reactive, and their only limitations to undergo reductive amination reactions arise primarily from the use of unreactive or sterically hindered amines. The absence of acids minimizes the chance of aldehyde reduction in some slow reactions. For example, the reductive amination of cyclohexane carboxaldehyde with the sterically hindered diisopropylamine in the presence of AcOH forms *N*,*N*-diisopropylcyclohexylmethylamine in only 41% yield accompanied by about 25% aldehyde reduction. In the absence of AcOH, the reaction is slower but the isolated yield is higher and only 5% aldehyde reduction is observed (Table 5, entries 4 and 5). A better result was obtained from the reductive amination of 1,1′,2′-tris-nor-squalene aldehyde with diisopropylamine (Table 5, entry 33) which needed 15 h to be completed with no acid added but gave the product in 90% isolated yield and no aldehyde reduction. This is a much improved result as compared to standard Borch reduction with cyanoborohydride giving only 4% of product in the absence of acetic acid and 45% in its presence.[100,101]

The reductive aminations of aromatic aldehydes with ethyl 2-carboxypiperidine (Table 5, entries 8 and 9) using STAB-H under the standard conditions[37] are high yielding reactions that show no aldehyde reduction. The results were superior to those obtained by other literature procedures.[21]

We have found DCE to be the preferred solvent for most reactions. A similar finding was observed in the reductive amination of 4-(2-thienyl)-1*H*-pyrrole-2-carbaldehyde with morpholine in which the highest yield was obtained in DCE (Table 5, entry 6).

The synthesis of the compound listed in Table 5, entry 16 features a one-pot procedure for the reductive amination of a secondary amine in the presence of a primary amine.[173] The primary amine is protected, *in situ*, with pentane-2,4-

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dione in pyridine/methanol. The secondary amine was reductively alkylated with 12-(4-morpholinyl)dodecanal using STAB-H in DMF/AcOH followed by removal of the protective group with aqueous TFA to recover the primary amine and give the product in a modest 22% yield.

The reductive amination of Boc-indole-5-carboxaldehyde with Boc-piperazine using STAB-H gives aminoalkyl indole intermediate (Table 5, entry 18). The indole derivative was utilized in the synthesis of potentially useful compounds that treat cancer and other diseases by inhibiting, regulating and/or modulating tyrosine kinase signal transduction.[174] This reductive amination reaction was scaled up effectively at 25−27 °C to about a 14 mol scale to produce about 5 kg of the indole derivative in 85% yield.

A selective reductive amination of a ketoaldehyde resulted in the exclusive reaction with the aldehyde in the presence of the ketone (Table 5, entry 24). Thus the reductive amination of (±)-*trans*-4-oxo-2-phenylcyclopentanecarbaldehyde with 4-[(*N*-allyl-*N*-(4-nitrobenzyloxycarbonyl))amino]piperidine gave the product in 43% yield.

The final step in the convergent synthesis of a substance P antagonist (Table 5, entry 25) was a reductive amination using STAB-H in *N*,*N*-dimethylacetamide (DMAC) as a solvent. The reaction was carried out on a 4.4 mol scale to give the product in 95% isolated yield. The use of DMAC was superior to that of DMF which caused formylation of the secondary amine as a side reaction.[47]

3.c: Reductive Amination of Formaldehyde: *N*-Methylation of Amines. The *N*-methylation of amines can be carried out using formaldehyde under the standard conditions for reductive amination (Table 6). Either paraformaldehyde or formalin may be used as a source of formaldehyde. This reaction, however, is not selective with primary amines; it gives only the *N*,*N*-dimethyl derivatives (Table 6, entry 1) in good yields. The reaction is ideal for methylation of secondary amines as there is only a possibility of monomethylation. Since water reacts with STAB-H, paraformaldehyde has an advantage of being anhydrous and may be used as a source of formaldehyde as in the *N*-methylation of 3-(3-cyanophenyl)piperidine to give the product in 89% isolated yield (Table 6, entry 2).

Formalin was also used in reductive amination reactions mostly on a small scale (10−20 mmol) with excess sodium triacetoxyborohydride. For example, *N*-methylation of 1-phenylpiperazine with formalin and STAB-H in DCE gives nearly a quantitative yield of the 4-methyl-1-phenylpiperazine (Table 6, entry 3). Other reported reactions show a diversity of structures in which formalin was used in the *N*-methylation of several amines (Table 6, entries 4−10). The restriction on the scale results from the decomposition of the triacetoxyborohydride reagent by water. We typically used about 5 equiv of the hydride reagent in the reaction, which may appear impractical in larger scale reactions. Apparently, this was not a restriction in at least one case mentioned earlier in which the reaction was carried out successfully on a 4 mol scale (see Table 2, entry 8).

4. Reductive Amination of Keto Acids/Keto Esters. The study of the reductive amination of keto esters and keto acids is a subject of special interest. The relative position of the two functional groups may effect the outcome of the reaction chemically or stereochemically or may result in a secondary reaction.

4.a: α- and β-Keto Acids/Esters. The reductive amination of α-keto esters with primary and secondary amines gives the corresponding *N*-substituted α-aminoesters. The reductive amination of various α-keto esters with benzylamine (Table 7, entries 1−3) proceeds in good to excellent yields to afford the α-benzylamino esters.[37] Reactions involving other amines, such as aniline or morpholine, are not as efficient and are accompanied by variable amounts of ketone reductions. The electron-withdrawing effect of the α-esters activates the ketones towards nucleophilic additions compared to those with corresponding alkyl or aryl groups. This effect explains the relative reactivity of methyl benzoylformate (Table 7, entry 3) compared to acetophenone, which is very unreactive in most reductive aminations. However, this activation makes these ketones prone to reduction by sodium triacetoxyborohydride, which becomes a competing process in slow reductive amination reactions of this class of ketones. An alternative method for the preparation of these *N*-substituted α-aminoesters is the reductive amination of aldehydes or simple ketones with α-aminoesters. Several examples representing the reductive amination of ketones and aldehydes with amino esters are listed in Table 7 (entries 6−13). These reactions are faster and produce the corresponding *N*-substituted amino esters in high yields. In the examples listed in Table 7, entries 7−10, the methyl esters of leucine, proline, threonine, and phenylalanine were reductively alkylated with 4-azidobutanal and STAB-H in DCE in good yields. These results were much improved over those obtained using $NaBH_3CN$ or via alkylation with alkyl halides. A novel one pot procedure was developed to reduce *S*-ethyl thioesters to aldehydes with Et_3SiH in the presence of Pd-C followed by subsequent reductive amination with amino esters using STAB-H. The compound listed in Table 7, entry 12 was prepared using this sequence in 93% yield.

The reductive amination of β-keto esters is a very unique reaction that warrants further investigation. We studied many of these reactions particularly the reactions of α-substituted-β-keto esters.[48] The reductive amination of these substrates exhibits apparent control of the stereochemistry at both the α- and β-positions. By monitoring these reactions and isolating the initial reaction intermediates, we see structural evidence of formation of enamines rather than imines as intermediates. As the reduction proceeds, it usually favors formation of one major diastereomer. The effect is most pronounced in reductive amination of cyclic β-keto esters such as methyl cyclohexanone-2-carboxylate, which gives almost exclusively the *cis*-product with benzylamine (Table

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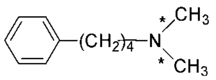
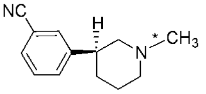
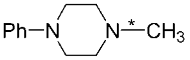
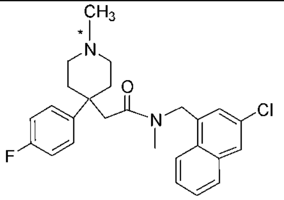
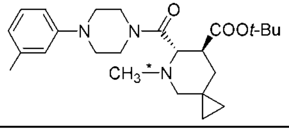
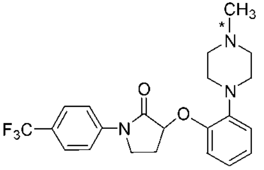
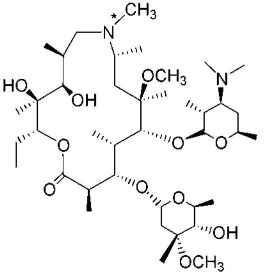
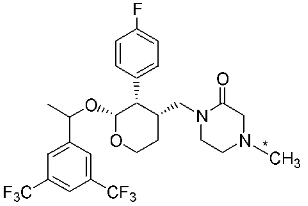
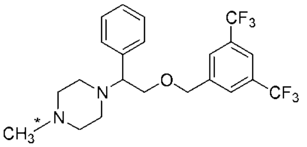
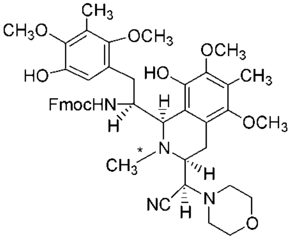
Table 6. **Use of formaldehyde in reductive amination**[a]

Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE 1 h	90%	37
2		STAB-H DCE 1 h	89%	240
3		STAB-H DCE 1 h	95%	37
4		STAB-H CH_3CN 2 h	85%	241
5		STAB-H CH_3CN/THF overnight		242
6		STAB-H THE AcOH overnight	13%	243
7		STAB-H DCE AcOH 1 h	96%	198
8		STAB-H DCE	75%	244
9		STABH DCE	77%	245
10		STAB-H CH_3CN	94%	246

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[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; AcOH = acetic acid.

Table 7. **Reductive amination of α- and *β*-keto acids/keto esters**[a]

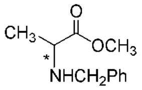
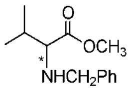
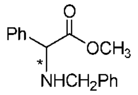
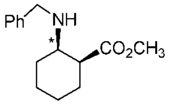
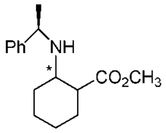
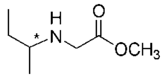
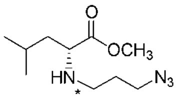
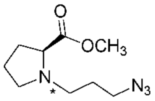
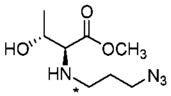
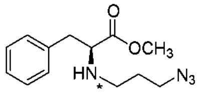
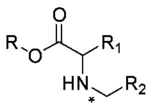
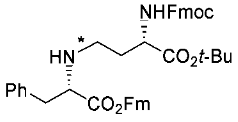
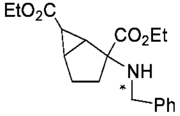
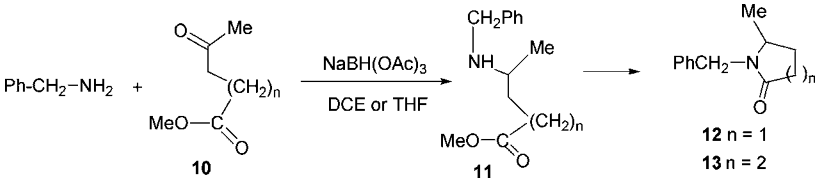
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE 30 min	90%	37,250
2		STAB-H DCE 16 h	82%	37
3		STAB-H DCE 54 h	58%	37
4		STAB-H THF AcOH 24 h	85%	247,248
5		STAB-H THF AcOH 24 h	85%	48
6		STAB-H DCE AcOH 4 h	88%	37
7		STAB-H DCE AcOH	83%	251
8		STAB-H DCE AcOH	69%	251
9		STAB-H DCE AcOH	75%	251
10		STAB-H DCE AcOH	76%	251
11	 R_2 = Ar	STAB-H DCM rt overnight	96%	252

Table 7 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
12	 Fm = 9-fluorenemethyl	STAB-H DMF 30 min	93%	253
13		STAB-H DCM		254

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; DMF = dimethylformamide; AcOH = acetic acid; rt = room temperature.

Scheme 3. **Reductive amination of γ- and δ-keto esters**



7, entry 4).[247,248] Furthermore, the reductive amination of the same β-keto ester with (R)-α-methyl benzylamine produces a major enantiomer with a *cis* stereochemistry at the cyclohexane ring (Table 7, entry 5).[48] A similar finding was reported using NaBH$_4$ with different carboxylic acids.[249] We see a similar trend with acyclic β-keto esters. A more detailed study will be reported on this class of compounds shortly.

4.b: The Reductive Amination of γ- and δ-Keto Esters. The reductive amination of γ- and δ-keto esters or acids with primary amines is another special case.[255] The initial products, *N*-substituted γ- or δ-amino esters or acids, cyclize to the corresponding lactams (such as **12** and **13**, Scheme 3) under the reaction conditions. This tandem two-step procedure which we termed "reductive lactamization" is a convenient method for the synthesis of *N*-substituted γ-butyro- and δ-valerolactams under mild conditions. Examples of these reactions are listed in Table 8. The reductive amination of ethyl levulinate and ethyl-5-oxohexanoate with

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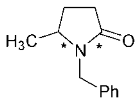
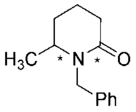
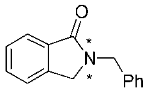
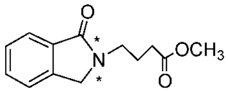
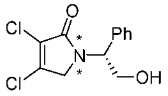
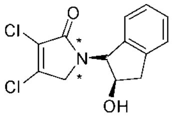
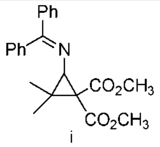
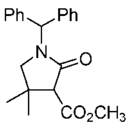
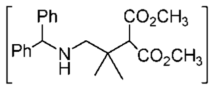
Table 8. **Reductive amination of γ- and δ-keto acids/keto esters**[a]

Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE 1.5 h 45 °C	84%	255
2		STAB-H DCE 22 h 45 °C	80%	255
3		STAB-H DCE AcOH 48 h, rt	91%	255
4		STAB-H DCE AcOH 48 h, rt	70%	255
5		STAB-H $CHCl_3$ AcOH 4A MS 24 h, rt	92%	256
6		STAB-H $CHCl_3$ AcOH 4A MS 24 h, rt	79%	256
7	 i  iii  ii	STAB-H THF AcOH -78°C to rt 22 h	62%	257

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; AcOH = acetic acid; MS = molecular sieves; rt = room temperature.

benzylamine gave 1-benzyl-5-methyl-pyrrolidin-2-one (Table 8, entry 1) and 1-benzyl-6-methyl-piperidin-2-one (Table 8, entry 2), respectively, in very good yields. The cyclization was accelerated by warming the reaction to 40−45 °C. The reductive amination of *o*-carboxybenzaldehyde with 4-aminobutyrate gives an intermediate that may cyclize to two different products; only a single product was obtained from cyclization with the carboxy group (Table 8, entry 4). Similar results were obtained from the reductive amination of mucochloric acid with different primary amines (Table 7,

Scheme 4. **Reductive amination of aldehydes and ketones with amino acids/esters**

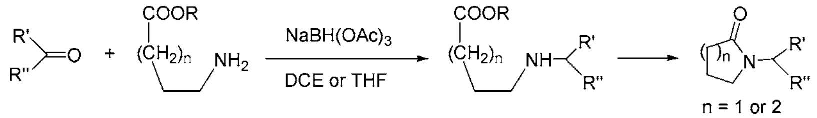
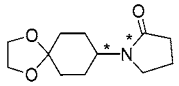
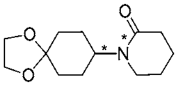
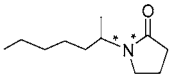
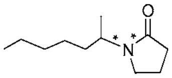
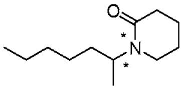
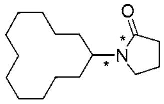


Table 9. **Reductive amination of γ- and δ-amino acids/amino esters**[a]

Entry	Reductive Amination Product	Conditions	Yield
1		STAB-H DCE 45 h rt	92%
2		STAB-H DCE rt, 4 h 55 °C, 24 h	85%
3		STAB-H DCE 90 h rt	96%
4		STAB-H THF 75 h rt	50%
5		STAB-H THF rt, 24 h; 55°C, 10 h	55%
6		STAB-H DCE 100 h rt	91%

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; AcOH = acetic acid; rt = room temperature. All the examples in this table from reference 255.

entries 5 and 6). The example in Table 8, entry 7, features the reduction of dimethyl 3,3-dimethyl-2-(diphenylmethylidenamino)-cyclopropane-1,1-dicarboxylate (**i**) with STAB-H (and other hydride reagents). The reaction gives the γ-lactam **iii** in 62% yield together with 38% of unreacted starting material. A possible explanation for the formation of **iii** is the initial formation of the ring opened aminoester **ii** which cyclizes under the reaction conditions to form product **iii**.

The same products may alternatively be obtained from reductive alkylation of γ- or δ-amino acids or esters with ketones and aldehydes (Scheme 4). As in the above case, the initial reductive amination products cyclize to the corresponding lactams under the reaction conditions.[255] Some representative examples are listed in Table 9. In either case, these reactions are limited to formation of γ-butyrolactams and δ-valerolactams. When applied to ϵ-amino esters or larger homologues, these reactions result only in reductive amination and no lactam formation.

5. Compounds Containing Ketals and Acetals. The standard reaction conditions of reductive amination with STAB-H are sufficiently mild to tolerate the presence of 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 workup conditions and are isolated in high yields. For example, the reductive amination of cyclohexanedione monoethylene ketal with a variety of primary and secondary amines affords very good isolated yields of the corresponding amines and provides a means for further elaboration of the reductive amination products. Several structurally diverse examples are listed in Table 10. The products may be isolated either as free amines or as the corresponding salts including salts of strong acids provided that the salt formation is carried out under anhydrous conditions to avoid acid hydrolysis of the acetals or ketals.

6. Reductive Amination of Aldehydes and Ketones with Weakly Basic Amines. What we describe as weakly basic amines are mostly aromatic amines that are both weak bases and poor nucleophiles. The pK_a values for represented amines range from 3.98 for *p*-chloroaniline to −4.26 for 2,4-dinitroaniline (measured for the protonated amines).[269,270] The reductive amination of aldehydes and ketones with these amines is usually sluggish. As a consequence, aldehydes and ketones may be reduced preferentially with most reducing agents. 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. Representative examples are listed in Table 11. The use of sodium triacetoxyborohydride in the reductive amination of ketones with several of the monosubstituted anilines in stoichiometric quantities or in the presence of excess ketone gives the corresponding reductive amination products in very good isolated yields (Table 11, entries 1−8). 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 slowly or result in no reaction (Table 11, entry 9; see also Table 15, entries 8 and 9).

The reductive amination of aldehydes with weakly basic amines is faster and has a wider scope than that of ketones.

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Table 10. **Reductive amination of substrates containing ketals and acetals**[a]

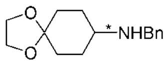
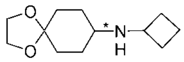
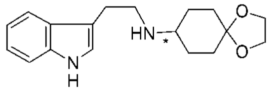
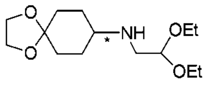
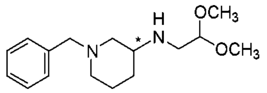
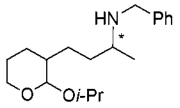
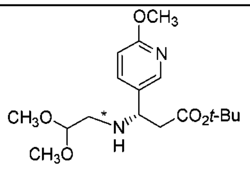
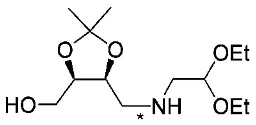
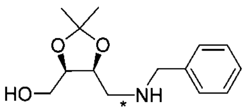
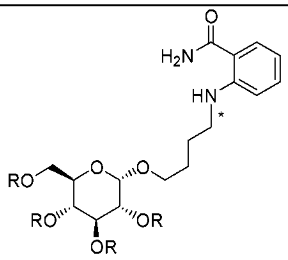
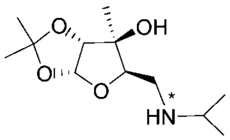
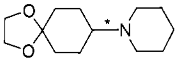
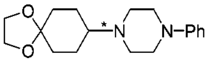
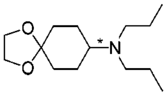
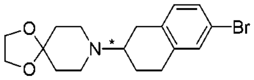
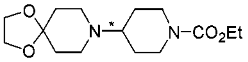
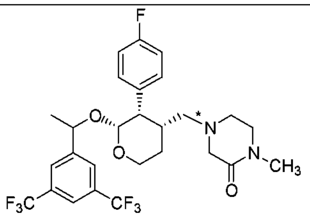
Entry	Reductive Amination Product	Conditions	Yield	Reference
1		STAB-H DCE AcOH 20 min	98%	37
2		STAB-H DCE AcOH 25 min	98%	37
3		STAB-H THF overnight	87%	258
4		STAB-H DCE AcOH 4 h	99%	37
5		STAB-H THF AcOH 1 h	98%	259
6		STAB-H DCE 20 h	75% mixture of diastereomers	260
7		STAB-H THF 10°C 30 min	92%	261
8		STABH THF rt overnight	60%	262
9		STAB-H THF rt 16 h	41%	262
10		STAB-H DCE rt 4 h	R = Ac: 80% R = Bn: 87%	263

Table 10 (Continued)

Entry	Reductive Amination Product	Conditions	Yield	Reference
11		STAB-H DCE rt overnight	95%	264
12		STAB-H DCE AcOH 75 min	85%	37
13		STAB-H DCE AcOH 4 h	78%	37
14		STAB-H DCE AcOH	quant	265
15		STAB-H THF AcOH 45°C 16 h	88%	266,267
16		STAB-H DCM/AcOH overnight	47%	268
17		STAB-H DCE rt 40 h	74%	244

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; AcOH = acetic acid; rt = room temperature.

Most reactions with monosubstituted anilines are carried out under the standard conditions with undetectable aldehyde reduction. The products are obtained effectively and in high yields, (Table 11, entries 10−12). As the basicity and nucleophilicity of the amines decrease, the reductive amination becomes slow and aldehyde reduction becomes a competing reaction. The reductive aminations of aldehydes with amines such as *o*-nitroaniline (Table 11, entry 13), 2,4-dichloroaniline (Table 11, entries 14 and 15), 2-aminothiazole (Table 11, entries 16 and 17), and iminostilbene (Table 11, entry 18) are accompanied by about 10−30% aldehyde reduction. The reactions are modified to use the amines as limiting agents and up to 1.5 equiv of aldehyde to compensate for this side reaction. These reductive aminations are very efficient and give isolated yields ranging from 60 to 96%. These reactions expanded the scope of reductive amination reactions to limits that are not achievable by any of the commonly used reducing agents.

The non-basic amines such as 2,4,6-trichloroaniline and 2,4-dinitroaniline are the least reactive. Aromatic aldehydes such as benzaldehyde could not be reductively aminated with these amines (see Table 15). However, the reductive ami-

Table 11. **Reductive amination of ketones and aldehydes with weakly basic amines**[a]

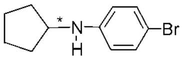
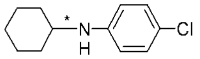
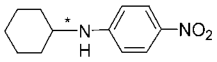
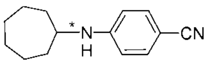
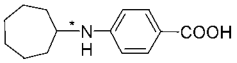
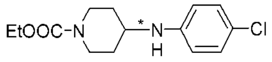
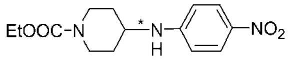
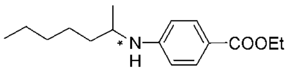
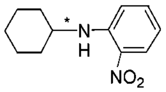
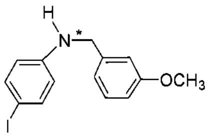
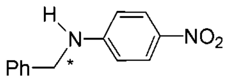
Entry	Reductive Amination Product	Conditions	Yield
1		STAB-H DCE AcOH 48 h	89%
2		STAB-H DCE AcOH 3.5 h	90%
3		STAB-H DCE 23 h	66%
4		STAB-H DCE 24 h	71%
5		STAB-H DCE 22 h	79%
6		STAB-H DCE AcOH 3.5 h	85%
7		STAB-H DCE 18 h	60%
8		STAB-H DCE AcOH 14 h	94%
9		STAB-H DCE 144 h	30%
10		STAB-H DCE AcOH 0.5 h	90%
11		STAB-H DCE AcOH 1.5 h	85%

Table 11 (Continued)

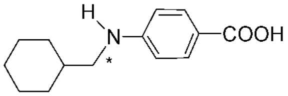
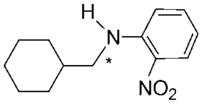
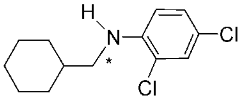
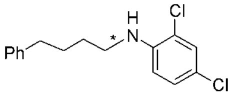
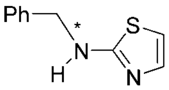
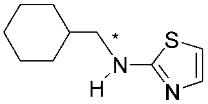
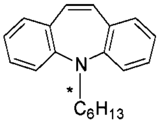
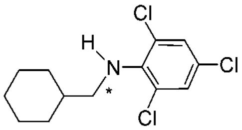
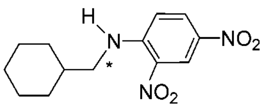
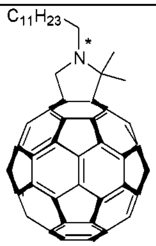
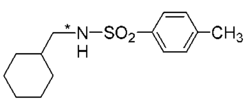
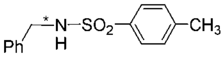
Entry	Reductive Amination Product	Conditions	Yield
12		STAB-H DCE AcOH 0.5 h	86%
13		STAB-H DCE AcOH 1.5 h	66%
14		STAB-H DCE AcOH 0.6 h	96%
15		STAB-H DCE AcOH 1.5 h	70%
16		STAB-H DCE AcOH 72 h	60%
17		STAB-H DCE AcOH 16 h	85%
18		STAB-H DCE AcOH 10 h	82%
19		STAB-H DCE AcOH 48 h	58%
20		STAB-H DCE AcOH 96 h	61%
21		STAB-H AcOH DCM 2h rt	95%

Table 11 (Continued)

Entry	Reductive Amination Product	Conditions	Yield
22		STAB-H DCE AcOH 28 h	85%
23		STAB-H DCE AcOH 48 h	80%

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; AcOH = acetic acid; rt = room temperature. All examples (except entry 21) from reference 37; entry 21 from reference 271.

nation of cyclohexane carboxaldehyde with either amine progressed slowly and was accompanied by considerable aldehyde reduction. The reaction was carried out in the presence of 3−5 equiv of AcOH and required an occasional addition of excess aldehyde and reducing agent up to 5 equiv each over 2−4 days to effect complete consumption of the amines. The amine products are not basic enough to form salts and could only be isolated by chromatography to give a 61% and 58% yield, respectively (Table 11, entries 19 and 20). Based on GC/mass spectrometric analysis of these reactions we hypothesize that these reactions probably proceed via initial formation of enamines, rather than imines. This may also explain the lack of reactivity toward aromatic aldehydes, which cannot form enamines.

[60]Fulleropyrrolidines are very weakly basic; however, they were used in reductive amination of aldehydes to synthesize *N*-alkylated derivatives. An example is the reductive amination with dodecanal, which provided the *n*-dodecyl derivative in 95% yield (Table 11, entry 21). Aromatic and unsaturated aldehydes reacted much slower, while attempts to apply the reaction for ketones failed (see Table 15).

This procedure is exceptional not only with weakly and nonbasic amines but also with substrates that never before were used in reductive amination reactions, namely, sulfonamides. The reaction of *p*-toluenesulfonamide with both aliphatic and aromatic aldehydes afforded the corresponding *N*-alkyl sulfonamides in good isolated yields (Table 11, entries 22 and 23). However, this reaction is limited to aldehydes; ketones did not react.

7. Reductive Aminations Using Solid Supports. A variety of solid supports have been utilized to perform reductive amination reactions using STAB-H as a reducing agent. In most cases, ketones or aldehydes are attached to the solid support and then reacted with excess amines to drive the reactions to completion. Due to the mild nature of STAB-H, it is an ideal choice to perform reductive amination on a solid support. Often libraries of compounds are created with this technique, which utilizes a wide range of aldehydes, ketones and/or amines where STAB-H will not leave residual CN as can be the case with $NaBH_3CN$, and a wide range of functional groups are tolerant to its mild nature.

The BAL (backbone amide linker) resin bearing aldehyde groups has been utilized to perform reductive amination with a variety of aromatic amines (Table 12, entries 1, 2). A FMPB solid-supported secondary amine was subjected to reductive amination conditions with a variety of aromatic aldehydes to generate a library of *mu* and *delta* opioid agonists (Table 12, entry 3). Substituted aniline derivatives were attached to a formyldimethoxyphenyl (FDMP) resin using reductive amination with STAB-H to form a series of a resin-bound arylamines (step 1, Table 12, entry 4). The amines were further functionalized with nitrobenzoyl chlorides to the corresponding nitroamides, reduced to aminobenzanilides and the amines were reductively alkylated with a diverse collection of aromatic aldehydes using STAB-H to build a library of alkylaminobenzanilides for biological testing (step 4, Table 12, entry 4). A HMBA-POEPOP900-supported peptide−aldehyde was treated with a variety of amines (e.g., cyclohexyl amine) and STAB-H to give the product in high purity (Table 12, entry 5). The Merrifield resin has been used as a solid support for both ketones and aldehydes to perform reductive amination with aliphatic and aromatic amines to give products in high yields. For example, Merrifield-supported enol-ethers were hydrolyzed and subjected to direct reductive amination with amines and STAB-H to give the amine products in yields ranging from 13% to 89% (Table 12, entry 6). Arylsulfonate ester resin bearing an aldehyde group was reductively aminated with STAB-H in high yield and purity (Table 14, entry 7). Triacetoxyborohydride was attached to an MP resin and utilized to perform reductive amination on a variety of solution phase aldehydes and amines with encouraging results (Table 12, entry 8). A PEG-OMe supported aldehyde was treated with a variety of amino esters to give excellent yields of isolated reductive amination products (Table 12, entry 9). A very diverse carbohydrate mimetic library was created using solid supported sugar ketones and aldehydes. Upon reaction with amines and/or ammonia good to excellent yields were obtained with high purity (Table 12, entries 10, 11). A

Table 12. **Reductive aminations using solid supports**[a]

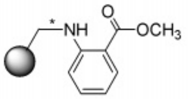
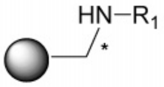
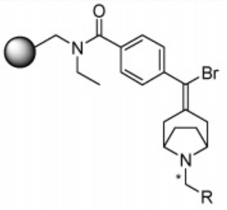
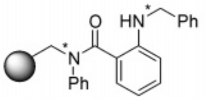
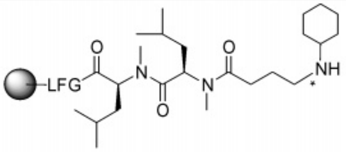
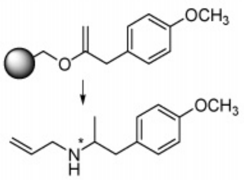
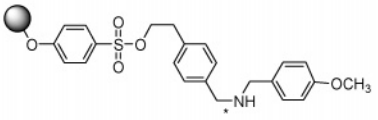
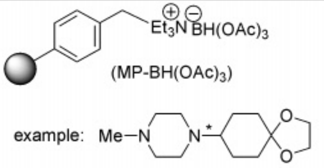
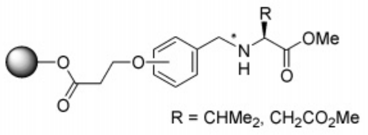
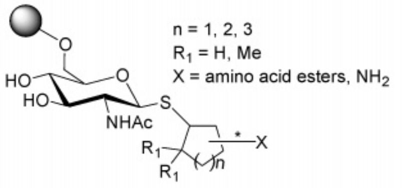
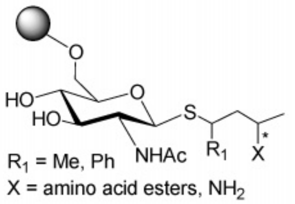
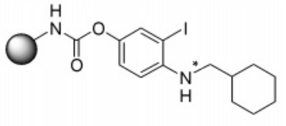
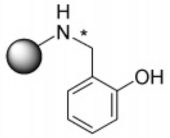
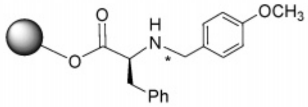
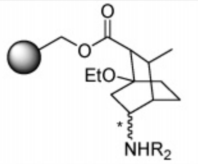
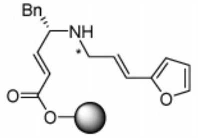
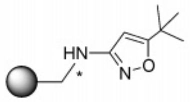
Entry	Structure	Conditions	Resin	Yield	Ref
1		STAB-H AcOH NMP	BAL		272
2		STAB-H DMF-MeOH or DCE AcOH	BAL-PEG-PS	41-63% (including 3-additional steps)	273
3		STAB-H DCE/DMF Microwave irradiation 120 °C	FMPB		232
4		Step 1: STAB-H DMF AcOH overnight Step 4: STAB-H DCE AcOH overnight	FDMP	13-94%	274
5		STAB-H DMSO:DCM (1:1) 1%AcOH	HMBA-POEPOP900	31% (>90% by hplc)	275
6		1. 1M H_2SO_4 DMF 2. STAB-H rt DMF	Merrifield	89%	276
7		STAB-H DCM AcOH 24 h rt	Merrifield	>95% (85% purity)	277,278
8		MP-BH(OAc)$_3$ THF 16 h	MP-BH(OAc)$_3$	39-93%	279

Table 12 (Continued)

Entry	Structure	Conditions	Resin	Yield	Ref
9		STAB-H DCM NaOAc 0 °C to rt 5 h	PEG-OMe	91-99%	280
10		STABH DCM / MeOH Na_2SO_4 AcOH 18 h rt	PS-Trityl-Cl	80-99% purity >90% When X = NH_2	281
11		STABH DCM / MeOH Na_2SO_4 AcOH 18 h rt	Rink	80-99%	281
12		STAB-H DCM rt 16 h	Rink Amide	95%	282
13		STAB-H $HC(OMe)_3$ DMF 12 h + 12 h, rt	Rink Amide	55-87%	283
14		STAB-H DCM sonicate	Wang	85-95%	284
15		STAB-H DCM AcOH Na_2SO_4 ultrasound	Wang		285
16		STAB-H AcOH (10%)	Wang		286
17		STAB-H AcOH DMF	4-(4-formyl-3-methoxy-phenoxy) butyryl resin	53%	152
		TiCl(O*i*-Pr)$_3$ STAB-H		66%	

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[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide; DMSO = dimethylsulfoxide; AcOH = acetic acid; NMP = *N*-methylpyrrolidinone; rt = room temperature.

functionalized aniline derivative bound to a rink amide resin was treated with cyclohexylcarboxaldehyde and STAB-H in DCM to give a 95% yield of the product (Table 12, entry 12). The rink amide resin was reacted with salicylaldehyde under standard reductive amination conditions with STAB-H utilizing trimethyl orthoformate as a solvent to provide the supported phenol derivative (Table 12, entry 13) which was used in the synthesis of substituted dibenzazocines. A modified Wang resin has been used to support amino acid derivatives and upon treatment with aldehydes and STAB-H in DCM provided excellent yields of isolated products (Table 12, entry 14). Wang resin supported bicyclo[2,2,2]octanones were reductively aminated using excess amine, Na_2SO_4 and ultrasound to drive the reactions to completion (Table 12, entry 15). Another Wang-resin-supported amine was treated with 2-acrolein furan performs intramolecular Diels−Alder reactions (Table 12, entry 16). A solid supported aldehyde was found to react with an isoxazole using a combination of TiCl(O*i*-Pr)$_3$/STAB-H. It was determined the use of Ti(O*i*-Pr)$_4$ was not sufficiently Lewis acidic to activate the aldehyde for imine formation (Table 12, entry 17).

8. Synthesis of Primary Amines. The reductive amination of aldehydes and ketones with ammonia is a known way for the preparation of primary amines; however, most of the existing reductive amination procedures are not effective in achieving this task. The reaction usually requires the use of a large excess of ammonia (10 or more equivalents) to avoid formation of secondary amines. The use of sodium cyanoborohydride is advantageous since the reactions are carried out in methanol which can dissolve either ammonia or ammonium acetate, the most common and convenient source of ammonia. Our attempts to develop a practical procedure for the synthesis of primary amines by reductive amination of ketones or aldehydes with $NaBH(OAc)_3$ were hindered by the poor solubility of ammonium acetate in THF or DCE. The reaction gave exclusively dialkylamines. The use of a large excess, up to 10 equiv, 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 (Table 13, entry 1).[37] Our search for better conditions that may be used in preparation of primary amines via reductive amination in aprotic solvents led to the use of ammonium trifluoroacetate.[287−289] It has a clear advantage over ammonium acetate for being soluble in THF and can be used effectively in reductive amination reactions. The reactions with cycloheptanone and cyclododecanone (Table 13, entries 2−4) give the corresponding primary amines in excellent isolated yields as the major products with <5% of the dialkylamines.[288] We have reported some of these results with ketones and aldehydes previously,[287−289] but since then we expanded the study and applied the reaction to several ketone and aldehyde substrates and the results will be the subject of a future report. Other reported reactions included the formation of a cyclohexylamine derivative in 41% yield (Table 13, entry 5) and the preparation of a secondary amine (Table 13, entry 6). A very interesting result was obtained from the carbonyl *cis*-1,4-oligoisoprene mentioned earlier in Table 4, entry 49. The reductive amination of this ketoaldehyde with excess ammonium acetate and STAB-H resulted in the selective formation of the primary amine in reaction with aldehyde in 86% yield and no reaction with the ketone (Table 13, entry 7).

9. Miscellaneous Reactions. As can be seen throughout the tables of examples, a wide range of carbon−nitrogen bonds have been formed utilizing STAB-H as the reducing agent. Many examples fit into bimolecular aldehydes and ketones with primary or secondary amines. The examples below (Table 14) represent reactions that do not fall into

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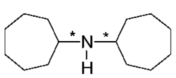
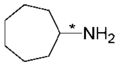
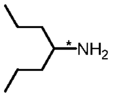
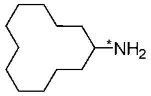
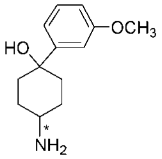
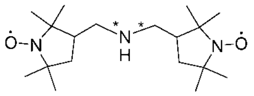
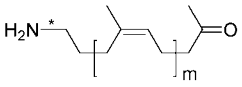
Table 13. **Preparation of primary amines**[a]

Entry	Product	Conditions	Yield	Reference
1		STAB-H NH_4OAc THF	91%	287
2		STAB-H NH_4OCOCF_3 THF 4 h	95% < 5% diamine	287
3		STAB-H NH_4OCOCF_3 THF 3h	95% < 5% diamine	287
4		STAB-H NH_4OCOCF_3 THF 1 h	95% < 5% diamine	287
5		STAB-H NH_4OCOCF_3 THF Overnight	41%	290
6		STAB-H NH_4OCOCF_3 THF 3A MS	65%	291
7		STAB-H NH_4OAc DCE AcOH rt 24 h	86%	134

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; AcOH = acetic acid; MS = molecular sieves; rt = room temperature.

this general class of reactions by being either intramolecular or unique substrates.

Manescalci et al. have examined the reductive amination of 5-phenyl-5-oxopentanal with (*S*)-valine methyl ester using STAB-H. The initial reductive amination is intermolecular with the aldehyde followed by a intramolecular reductive amination to provide the cyclized piperidine derivatives in good yield and moderate selectivity (Table 14, entry 1). It is evident from this result the intramolecular reductive amination of an aromatic ketone occurred much more readily than the intermolecular reductive amination of acetophenone with benzylamine (see Table 15, entry 1). Liu has demonstrated the synthesis of tetra-substituted pyrrolidine using an intramolecular cyclization of a 4-azido ketone. Using STAB-H, a 3:1 mixture of two isomers was obtained, whereas the use of sodium cyanoborohydride lead to the formation of a 10:1 ratio of the same mixture (Table 14, entry 2). It is interesting to note that using the epimer of the starting azidoketone lead to formation of one major product almost exclusively with either sodium cyanoborohydride or STAB-H

Table 14. **Miscellaneous reactions**[a]

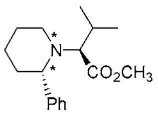
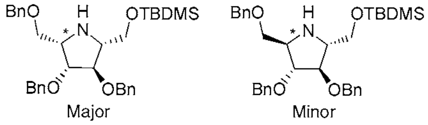
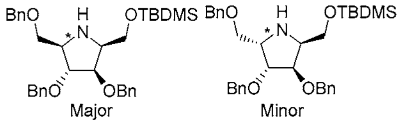
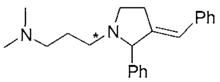
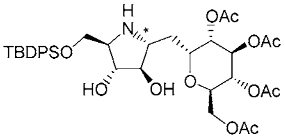
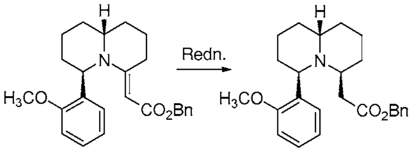
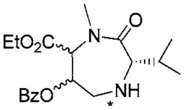
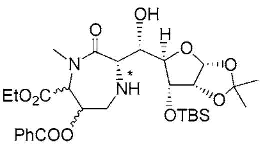
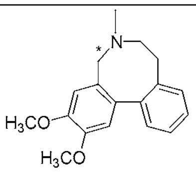
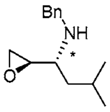
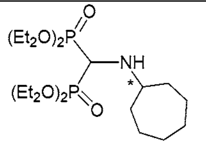
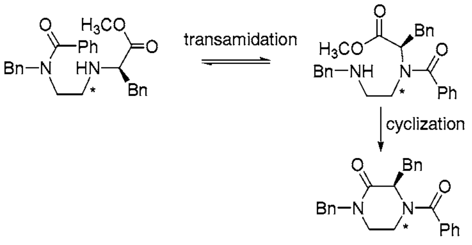
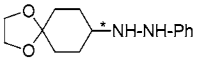
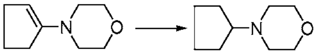
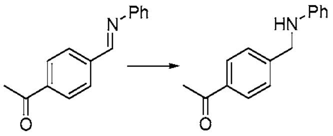
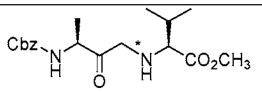
Entry	Structure	Conditions	Yield	Reference
1		STAB-H THF AcOH 24 h 0 °C to rt	84% (52% de) (better de ratio from NaCNBH$_3$)	292
2		STAB-H or NaCNBH$_3$ *p*-TsOH DCM		293
3		STAB-H or NaCNBH$_3$ *p*-TsOH DCM	72%	293
4		1. Et$_2$AlI, MeCN 2. STAB-H 6 h rt	63%	294
5		STAB-H DCM AcOH MgSO$_4$	54% 3:1 (*R*:*S*) mixture at new center	295
6		STAB-H AcOH rt 1 h	92% (50:1 ratio)	296
7		STAB-H DCE *i*-Pr$_2$EtN rt overnight	41%	297
8		STAB-H DCE 4A MS rt 15 h	28%	298
9		STAB-H DCE Et$_3$N 12 h	86%	299

Table 14 (Continued)

Entry	Structure	Conditions	Yield	Reference
10		Me_4N-BH(OAc)$_3$ DCE AcOH 4A MS 8 h rt	68% Anti / syn ratio (92:8)	300
11		STAB-H MeCN	71%	301
12		STAB-H MeCN AcOH 4A MS 4 h reflux,	86% (>99% ee)	302
13		STAB-H DCE AcOH 6 h	92%	37
14		STAB-H 10min	91%	37
15		STAB-H 1.5 h	80%	37
16		STAB-H DCE 19 h rt	94:6 product : starting material	303
17		STAB-H DCM		304

[a] Note: Newly formed C−N bonds are labeled by asterisks (*); a blank entry for yield indicates no yield was given; STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; AcOH = acetic acid; MS = molecular sieves; rt = room temperature.

(Table 14, entry 3). A variety of 1,2-disubstituted-3-alkylidenylpyrrolidines were synthesized via in situ formation of pyrrolium salts and subsequent reduction using STAB-H (Table 14, entry 4). Sucrose-related imino-C-disaccharides were synthesized utilizing an intramolecular reductive amination to form the tetra-substituted pyrrole in reasonable yield and fair selectivity. It was noted that the selectivity of the reduction was due to an intramolecular hydroxy-directed delivery of hydride via alcohol at the 3-position (Table 14, entry 5). In the synthesis of quinolizidine alkaloids, Hart et al. has conducted a comparison between $NaBH_3CN$ and $NaBH(OAc)_3$ in the reduction of vinylogous urethanes to the corresponding tertiary amines (Table 14, entry 6). STAB-H reduced the vinylogous urethane to give a 92% isolated yield of the indicated product in >50:1 selectivity. The use of sodium cyanoborohydride lead to a 70% yield as

Table 15. **Limitations**[a]

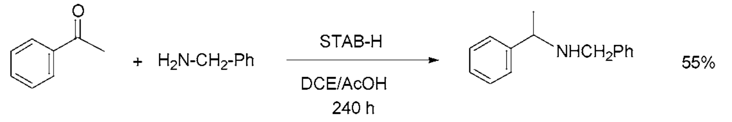
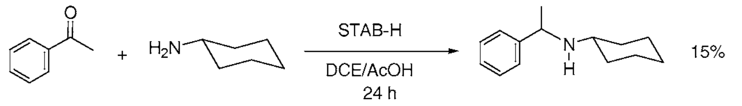
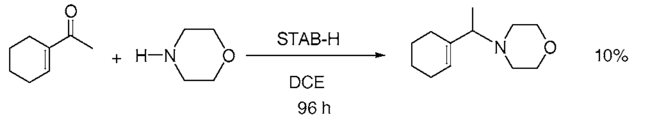
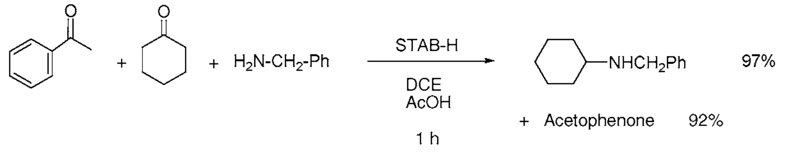
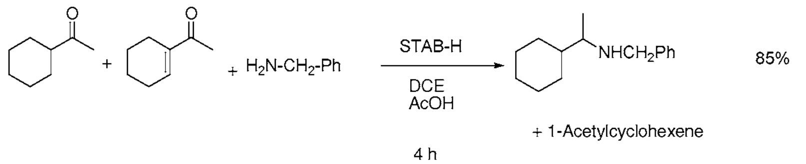
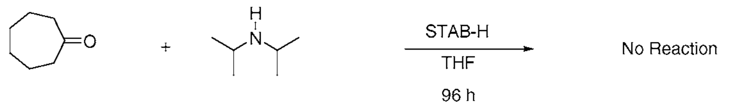
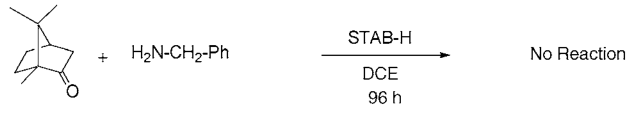
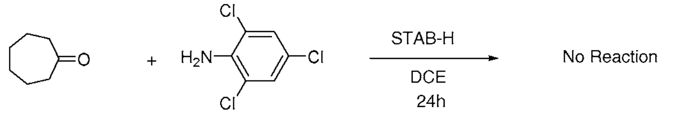
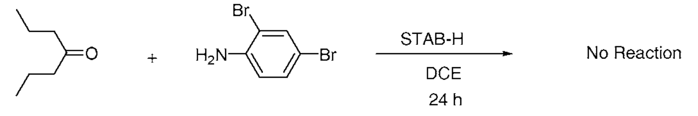
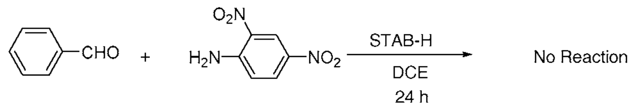
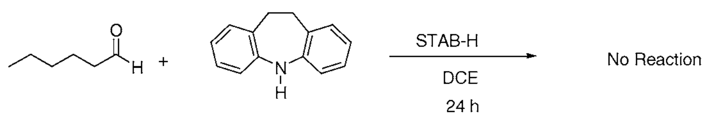
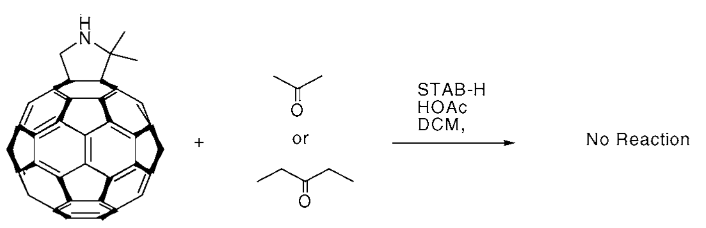
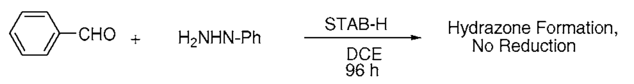
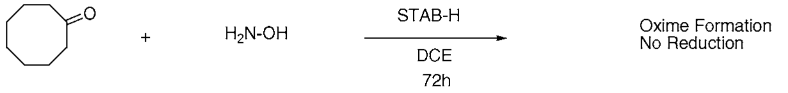
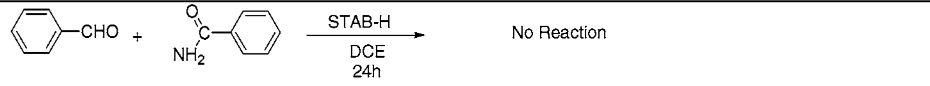
Entry	Reaction
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	

Table 15 (Continued)

Entry	Reaction
14	
15	

[a] Note: STAB-H = sodium triacetoxyborohydride; DCE = 1,2-dichloroethane; DCM = dichloromethane; THF = tetrahydrofuran; AcOH = acetic acid. Examples in entries 1−11 and 13−15 from reference 37; entry 12 from reference 271.

a 1:1 mixture. The enhanced selectivity of STAB-H was attributed to the steric bulk difference as compared to sodium cyanoborohydride.

Knapp et al. was able to assemble seven-membered rings utilizing an intramolecular reductive amination strategy (Table 14, entries 7, 8). In the synthesis of amaryllidaceae alkaloid, buflavine (Table 14, entry 9), the final key step was an intramolecular reductive amination of the appropriate aminoaldehyde with STAB-H to construct the tetrahydrodibenzo[*c*,*e*]azocine ring structure in an excellent isolated yield of 86%. The mild nature of STAB-H allows the reductive amination of α,β-epoxyketones with a range of amines using tetramethylammonium triacetoxyborohydride, without affecting the epoxide, to give reasonable yields (33−69%) and selectivities (72:28 to 95:5) of the *anti*-alkylamino epoxides (Table 14, entry 10). STAB-H was effectively used to reduce imines derived from the condensation of aminoalkylbisphosphonates with ketones or aldehydes to the corresponding amines (Table 14, entry 11). A variety of substituted piperazinones were prepared via a tandem three-reaction sequence of reductive amination of aldehydes with α-amino acids using STAB-H followed by heating to reflux to effect transamidation and finally cyclization to form the piperazinone rings (Table 14, entry 12). The example shown here required heating for 4 h, following the initial reductive amination, to give the piperazinone in 86% yield and >99% ee. Phenyl hydrazine is not usually a candidate for reductive amination reactions; however, it was successfully used to reductively aminate a cyclohexanone derivative in excellent yield using STAB-H (Table 14, entry 13). A variety of hydride reducing agents were examined to reduce the aldimine derived from 4-acetylbenzaldehyde. The result showed that STAB-H would selectively reduce the imine in the presence of the ketone, giving rise to a 94:6 ratio of product to starting material after 19 h of reaction time (Table 14, entry 16). While this study did not introduce any new findings for STAB-H, the reduction was carried out by mixing the reactants in the absence of any solvent. *N*-Protected aminoglyoxals were treated with α-amino acids, and the resulting imines were subjected to reduction with STAB-H to give peptide analogues (Table 14, entry 17). The use of STAB-H however caused some ketone reduction, the use of the Cl_3SiH/DMF reducing system gave a better result with no ketone reduction.

10. Limitations. The limitations of the reductive amination using sodium triacetoxyborohydride include many unreactive ketones either due to electronic factors such as aromatic and α,β-unsaturated ketones or because of stereochemical reasons as in camphor. These ketones react either very slowly or show no reaction under the standard reaction conditions. Examples of slow and failed reactions representing the limitations of this procedure are listed in Table 15. For example, the reductive amination of acetophenone with benzylamine proceeds at a very slow rate to reach 55% conversion over 10 days (Table 15, entry 1). A similar reaction rate was observed in the reductive amination of acetophenone with cyclohexylamine and 1-acetylcyclohexene with morpholine (Table 15, entries 2 and 3). In competition studies, saturated ketones such as cyclohexanone and acetyl cyclohexane were reductively aminated selectively in the presence of these slow reacting ketones to give the corresponding amines in excellent yields with full recovery of the unreacted ketones (Table 15, entries 4 and 5).[37] The reductive amination with sterically hindered amines or ketones proceeds slowly and may not result in any reaction. For example, the attempted reductive amination of cycloheptanone with diisopropylamine (Table 15, entry 6) or camphor with benzylamine (Table 15, entry 7) gave no detectable products even after 4 days of reaction. As mentioned before, aldehydes are reductively aminated with sterically hindered amines, however, at a slower rate and may be accompanied by some aldehyde reduction (see Table 5, entries 4 and 5).

Attempted reductive amination of cycloheptanone with the weakly basic 2,4,6-trichloroaniline or 4-heptanone with 2,4-dibromoaniline resulted in no reaction even after 24 h, and ketones such as acetone and 3-pentanone could not be reductively aminated with the very weakly basic [60]-fulleropyrrolidines. All these amines showed some reactivities in reductive amination with aldehydes (see Table 11). As stated before, benzaldehyde failed to react with 2,4-dinitroaniline. While iminostilbene reacted readily with aldehydes (Table 11, entry 18), the dihydro derivative, iminodibenzyl, showed no reactivity under the same conditions with aldehydes (Table 15, entry 11). Although, we mentioned earlier that some ketones were reductively aminated with phenylhydrazine (Table 14, entry 13), this was not the case with benzaldehyde, which gave a stable hydrazone that was not reduced (Table 15, entry 13). The same results were obtained from hydroxylamine with ketones (Table 15, entry 14). Also we presented examples of reductive amination of sulfonamides with aldehydes (Table 11, entries 22 and 23), but no similar reaction with carboxamides was observed (Table 15, entry 15).

Conclusion

Sodium triacetoxyborohydride is a mild, very effective, and synthetically useful reducing agent for the reductive amination of aldehydes and ketones. The examples presented here undoubtedly illustrate the reagent's wide scope, the diverse and numerous applications, and the high tolerance for many functional groups. It also shows fewer limitations than other reagents. In addition, the convenience of use, the ease of workup, and the simplicity of product isolation make it an attractive choice for reductive amination reactions.

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