Sodium Triacetoxyborohydride[1]

[56553-60-7] $C_6H_{10}BNaO_6$ (MW 211.96)
InChI = 1/C6H10BO6.Na/c1-4(8)11-7(12-5(2)9)13-6(3)10;/h7H,1-3H3;/q-1;+1
InChIKey = HHYFEYBWNZJVFQ-UHFFFAOYAA

(the prototype of a class of $NaBH(OCOR)_3$ reagents that are selective reducing agents for a number of functional groups[1] and heterocycles;[1] alkylation of amines;[1–4] hydroboration[1])

Physical Data: mp 116–120 °C (dec); the related $NaBH_3OAc$ has not been fully characterized.

Solubility: $NaBH(OAc)_3$ and related acyloxyborohydrides are rapidly destroyed by H_2O and protic solvents; H_2 is liberated. Cosolvents that have been employed are benzene, toluene, THF, dioxane, CH_2Cl_2, $ClCH_2CH_2Cl$.

Form Supplied in: $NaBH(OAc)_3$ and the related ***Tetramethylammonium Triacetoxyborohydride*** are commercially available as colorless powders.

Preparative Method: $NaBH(OAc)_3$ and $NaBH_3OAc$ can be easily prepared in situ from the appropriate amount of acetic acid and $NaBH_4$.

Analysis of Reagent Purity: $NaBH(OAc)_3$ has been characterized by elemental analysis, IR, and ^1H, ^{13}C, and ^{11}B NMR.

Handling, Storage, and Precautions: because H_2 is liberated during the preparation of these reagents, all handling and storage of acyloxyborohydrides should take place under an inert atmosphere.

Original Commentary

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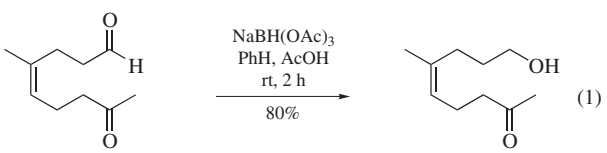
Functional Group Reductions. $NaBH(OAc)_3$ selectively reduces aldehydes but not ketones[5,6] (eqs 1 and 2),[7,8] even with excess reagent. However, α- and β-hydroxy ketones are reduced to the *anti*-diols by hydroxy-directed hydride delivery[6,9,10] (eqs 3 and 4).[11,12] Diastereoselectivities are generally excellent, although $Me_4NBH(OAc)_3$ seems to be a superior reagent in this regard.[9] Several recent examples of $NaBH(OAc)_3$ in the stereoselective reduction of hydroxy ketones attest to the power of this reagent.[13]



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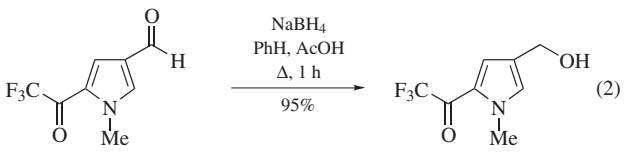

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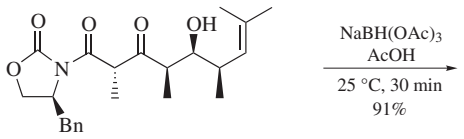

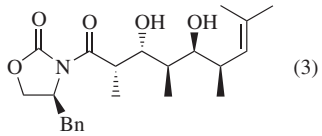

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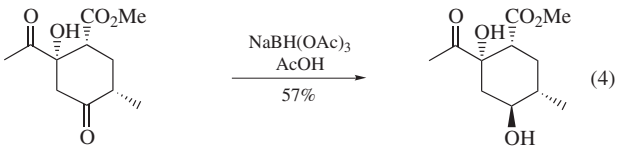
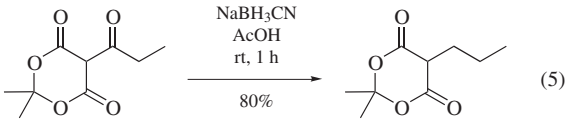


(4)

The hydroxy-directed $NaBH(OAc)_3$ reduction of an imide has been described.[14] The more reactive $NaBH_3OAc$ reduces enones to allylic alcohols,[15] and some ketones can be reduced to alcohols with ***Sodium Borohydride***–tartaric acid.[16] The combination of $NaBH_4$ or ***Sodium Cyanoborohydride–Acetic Acid*** serves to deoxygenate tricarbonyl systems (eq 5)[17] and tosylhydrazones of ketones and aldehydes (eq 6).[18] Primary and secondary amides are reduced to amines by the action of $NaBH_3OAc$ (eq 7),[19,20] while tertiary amides require ***Sodium Trifluoroacetoxyborohydride***.



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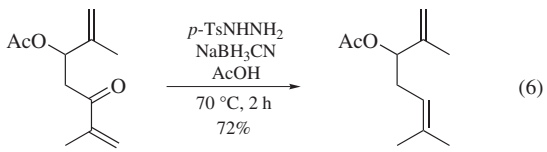

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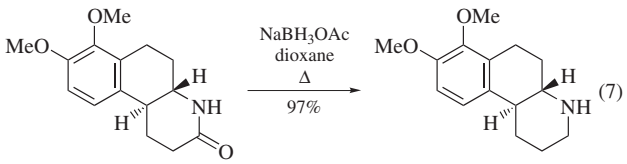
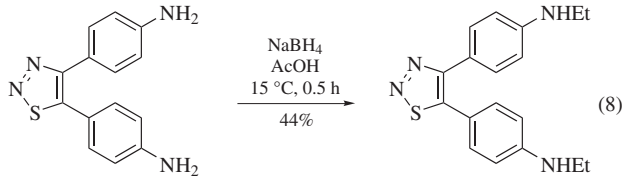


(7)

Amine Alkylation (Reductive Amination). By a pathway that may involve the generation of free aldehyde, the combination of $NaBH_4$ and carboxylic acids is capable of *N*-alkylation of amines.[1–4] Recent examples abound (eqs 8–11). At lower temperature, monoalkylation is generally observed (eq 8),[21] while at 50–55 °C, primary and secondary amines are converted into tertiary amines (eqs 9 and 10).[22,23] Neat carboxylic acid (eqs 8 and 9) or a cosolvent (eq 10) may be used. In the latter event, solid carboxylic acids function well (eq 11).[24] ***Formic Acid*** may be employed for *N*-methylation.[1,25] A useful variation is the reductive amination of aldehydes and ketones (eqs 12–14),[1,26–29] a method which is claimed to be superior to that using $NaBH_3CN$–MeOH.[26] ***Paraformaldehyde*** serves as a convenient source of HCHO for *N*-methylation in this protocol.[30,31]



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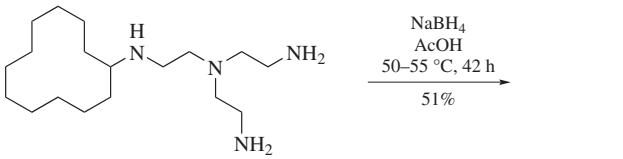

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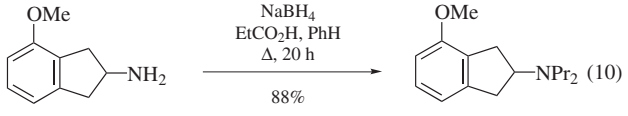

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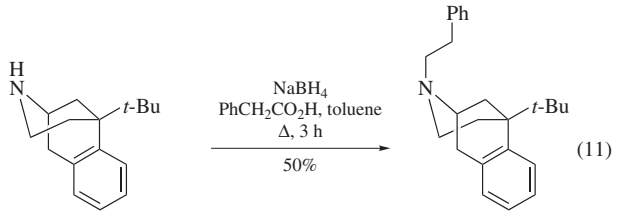

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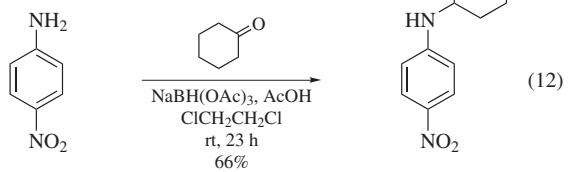

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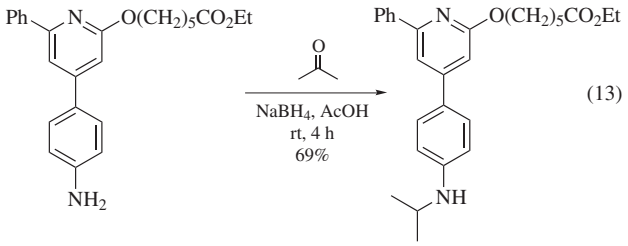

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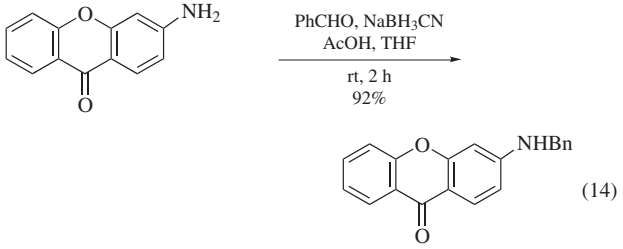
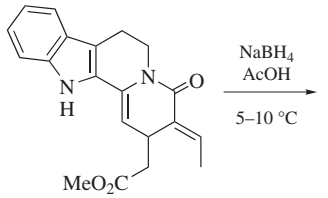
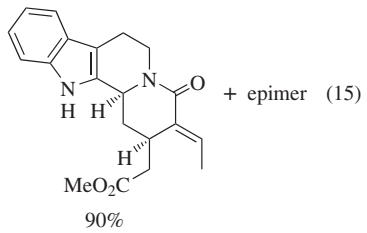


(14)

Carboxylic acids are reduced to alcohols with $NaBH_4$ in THF,[32] although the use of CF_3CO_2H in this regard is superior, and there is one report of an ester reduction to a primary alcohol with $NaBH_4$–HOAc.[33]

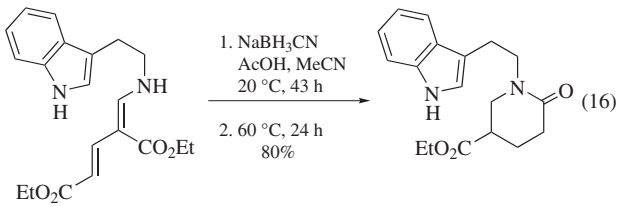
Enamine, Imine, Iminium Ion, and Enamide Reduction. The first reported use of $NaBH_4$–HOAc was in the reduction of dienamines,[34] and this application has found extensive use in synthesis[1] (eqs 15–19).[35–39]





+ epimer (15)

90%



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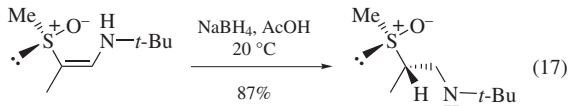
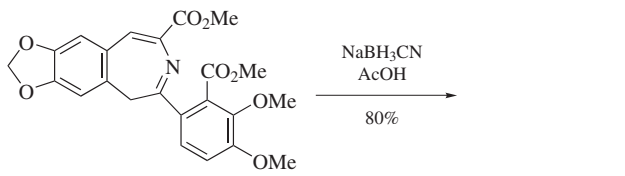
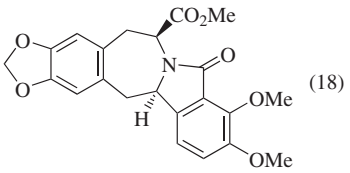


(17)

70% de





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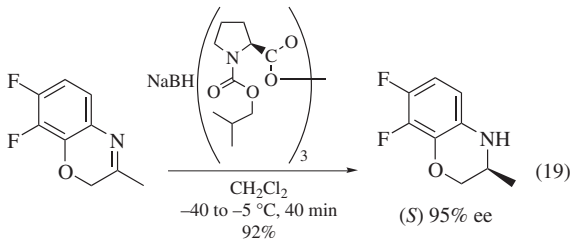
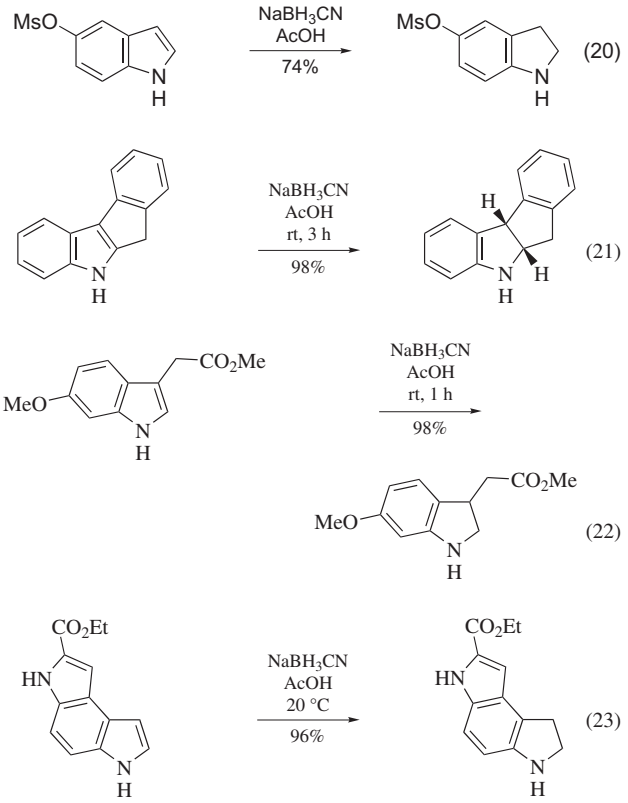


(19)

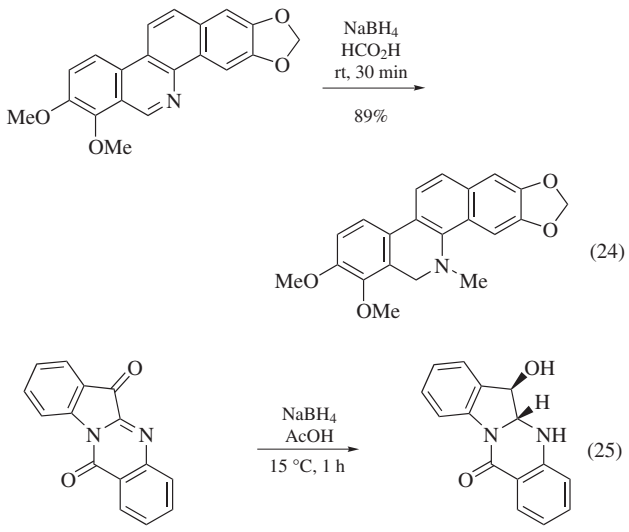
(*S*) 95% ee

Indole Reduction. Indole is smoothly reduced to indoline under the influence of $NaBH_3CN$–HOAc;[2] the reaction is quite general[1,40] and has been employed often (eqs 20–22),[41–43] especially in the synthesis of CC-1065, PDE, and analogs where only the more basic indole ring is reduced (eq 23).[44,45] *N*-Substituted

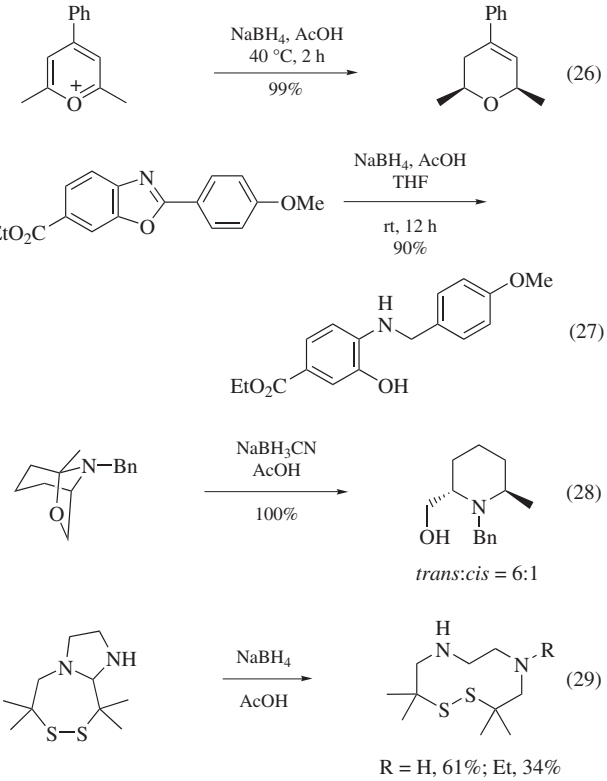
indoles are reduced to indolines with $NaBH_4$–HOAc,[1,2] and the action of $NaBH_4$–RCO_2H on *N*-unsubstituted indoles affords *N*-alkylindolines by *N*-alkylation of the initially formed indoline.[1,2]



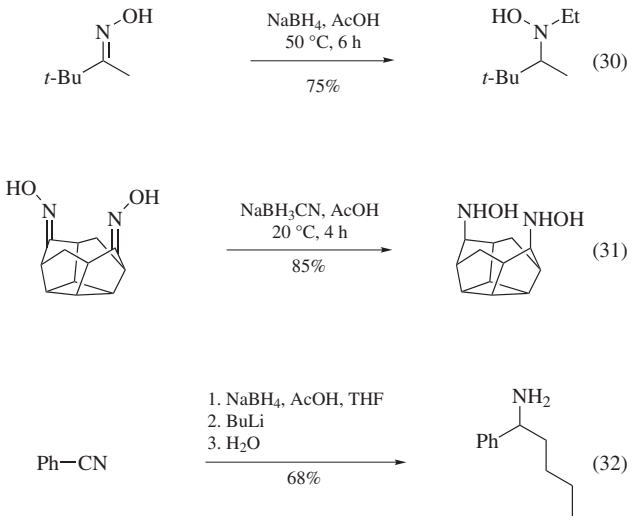
Reduction of Other Heterocycles. Quinolines and isoquinolines are reduced to the corresponding tetrahydro derivatives with $NaBH_3CN$ or $NaBH_4$–RCO_2H, the latter combination affording the *N*-alkylated compounds.[1,46] Related heterocycles have been subjected to this protocol (eqs 24 and 25).[47]



The reduction of pyrylium salts (eq 26),[48] the reductive cleavage of benzoxazoles (eq 27)[49] and of saturated nitrogen heterocycles (eqs 28 and 29),[1,50,51] and the reduction of other π-deficient nitrogen heterocycles[1] are known.



Reduction of Oximes. Oximes can be alkylated or reduced, depending on whether $NaBH_4$ or $NaBH_3CN$ is employed, to give hydroxylamines[1,52] (eqs 30 and 31).[52,53] Oxime ethers are also reduced under these conditions,[1,54] and the hydroxy-directed reduction of oxime ethers has been reported using $Me_4NBH(OAc)_3$.[55] Nitriles are converted into primary amines by the tandem action of acyloxyborohydrides and alkyllithium reagents (eq 32).[56]



Hydroboration of Alkenes. The second reported reaction of acyloxyborohydrides was the hydroboration of alkenes,[1,57] and this reaction has been further refined.[58] In a similar vein, the reduction of organomercurials by $NaBH(OAc)_3$ has been described.[59]

First Update

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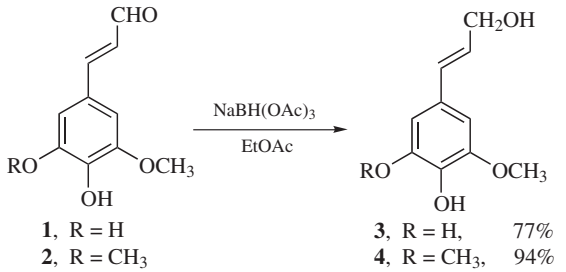
A Safe Process for Production of Sodium Triacetoxyborohydride (STAB-H). A detailed study of the process for in situ production of STAB-H from the reaction of solid $NaBH_4$ with glacial acetic acid in *N*,*N*-dimethylacetamide (DMAC) (eq 33) was reported by Lam et al.[60] The authors studied and identified several thermal hazards associated with the procedure and determined that the main hazard is the accumulation of a significant amount of unreacted solid $NaBH_4$ at the end of the addition. The late consumption of the accumulated $NaBH_4$ may result in a rapid heat release with the potential of decomposing STAB-H, the generation of a large amount of noncondensable gases, and a rapid and uncontrollable generation of hydrogen gas. The authors evaluated the reaction kinetics and obtained some fundamental information that allowed them to design a new procedure to minimize the hazards of the process.

$$NaBH_4 + 3\,CH_3COOH \longrightarrow NaBH(OOCCH_3)_3 + 3\,H_2 \quad (33)$$

The researchers developed a safer procedure that includes the use of a solution of $NaBH_4$ in DMAC instead of the solid. Thus, a slow addition of $NaBH_4$/DMAC solution to a solution of glacial acetic acid in DMAC at 15 °C resulted in a smoother reaction that practically eliminated the accumulation of $NaBH_4$. The heat release was uniformly distributed throughout the addition. A thermal conversion of 94% was achieved at the end of the addition compared to 63% in the original procedure. Following the addition, the reaction mixture is heated slowly to 22 °C and kept at this temperature for ∼3.5 h to achieve 99% conversion. The heat release during the temperature ramp from 15 to 22 °C was insignificant, thus eliminating the potential of decomposing STAB-H. Not only is this a safer and more efficient procedure, but also is economical as the cost of production of STAB-H was significantly reduced.

Functional Group Reductions.

Reduction of Unsaturated Aldehydes. STAB-H undergoes selective 1,2-reduction of α,β-unsaturated aldehydes to form allylic alcohols in excellent yields. For example, the reduction of α,β-unsaturated aldehydes coniferaldehyde (**1**) and sinapaldehyde (**2**) (eq 34) gave the corresponding allylic alcohols **3** and **4** in good yields with no trace of saturated alcohols.[61]

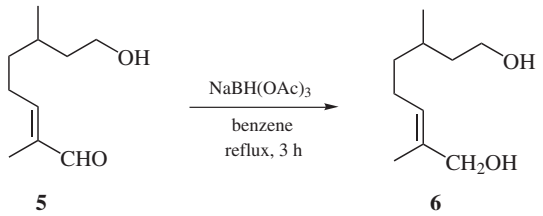


(34)

1, R = H
2, R = CH_3

3, R = H, 77%
4, R = CH_3, 94%

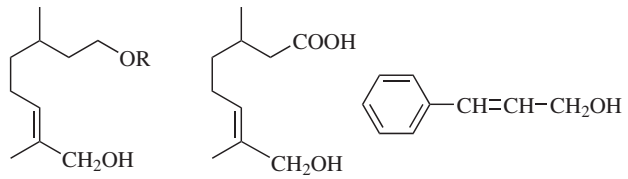
The reduction of 8-hydroxy-2,6-dimethyl-oct-2-enal (**5**) with STAB-H in benzene at reflux afforded 2,6-dimethyl-oct-2-ene-1,8-diol (**6**) in 84% yield (eq 35).[62]



(35)

5 **6**

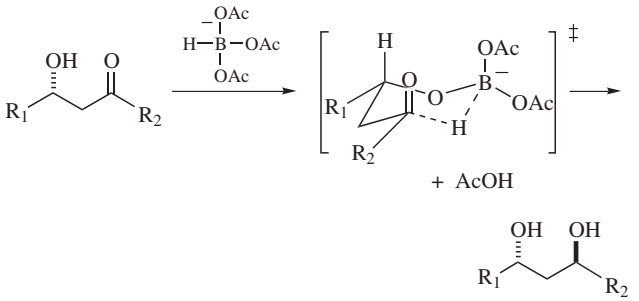
Other allylic alcohols prepared similarly are illustrated in Fig. 1 with reported yields.[62]



R = THP, 92% 83% 89%
R = $COCH_3$, 94%
R = C_2H_5, 94%

Figure 1 1,2-Reduction of α,β-unsaturated aldehydes

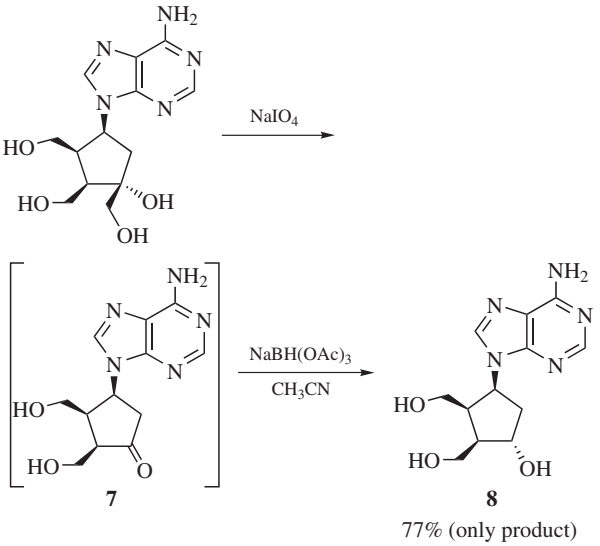
Reduction of Hydroxy Ketones. The diastereoselective reduction of β-hydroxy ketones is one of the most important applications of STAB-H. The hydroxy-directed reduction is believed to proceed via initial substitution of one of the acetoxy groups in STAB-H by the hydroxy group, followed by the intramolecular delivery of the hydride to form a *trans* (or *anti*)-diol (Scheme 1). The resulting hydride species is apparently more reactive since it reduces the keto group, which is not normally reducible by triacetoxyborohydride. In general, the reaction is better carried out with tetramethylammonium triacetoxyborohydride.[9]



Scheme 1 The major pathway for reduction of β-hydroxy ketones with triacetoxyborohydride

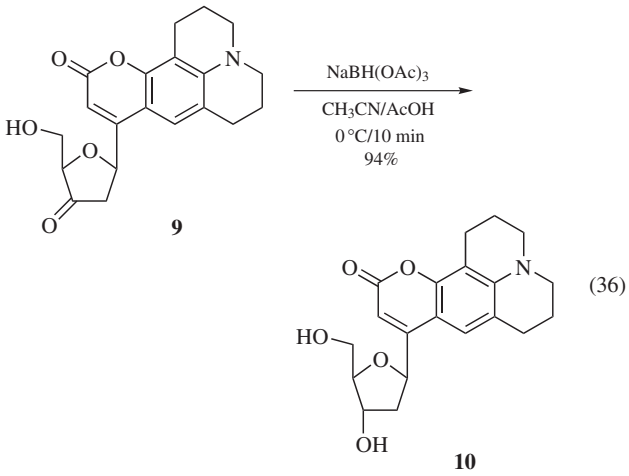
Another example of hydroxy-directed reduction of hydroxyl ketones is illustrated in the synthesis of the saturated nucleoside analog **8**, which was obtained from the β-hydroxy ketone **7** by reduction with STAB-H in acetonitrile. The reaction provided **8** as the only product in 77% yield (Scheme 2).[63]

The coumarin *C*-riboside (**10**) is obtained by the diastereoselective hydroxy-directed triacetoxyborohydride reduction of the ketone **9** in 94% yield (eq 36).[64]



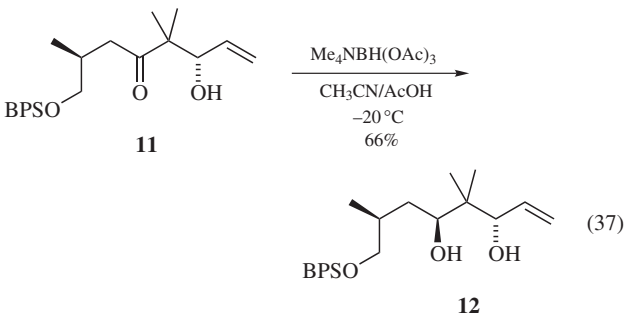
7 **8**

Scheme 2



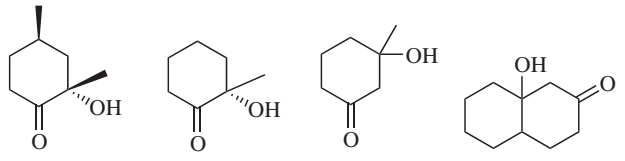
9 **10** (36)

In the synthesis of polycavernoside A, the *anti*-diol intermediate **12** was obtained in 66% yield by reduction of the hydroxy ketone **11** using tetramethylammonium triacetoxyborohydride (eq 37).[65]



11 **12** (37)

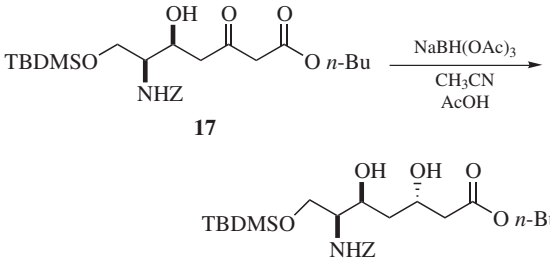
A comparative study of the reduction of the 2- and 3-hydroxy ketones **13–16** (Figure 2) showed that the use of STAB-H gave reduction products via the hydroxy-directed reduction to deliver the hydride from the same side of the hydroxy groups.[66]



13 **14** **15** **16**

Figure 2

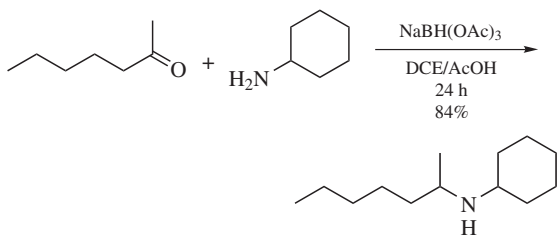
A recent synthesis of galantinic acid via intermediate **18** included a hydroxy-directed reduction of the β-hydroxy ketone **17** with STAB-H in CH_3CN/AcOH to give an 88:12 diastereomeric ratio of products favoring the *anti*-diol **18**. The ratio improved to 98:2 after purification (eq 38).[67]



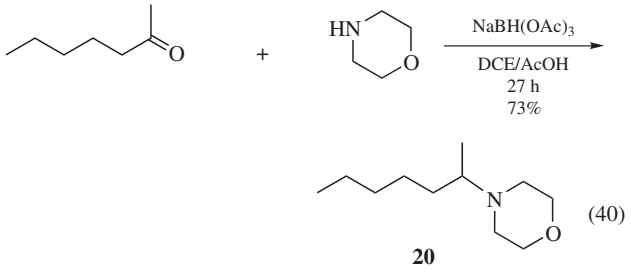
17 **18** (38)

Reductive Amination of Ketones and Aldehydes. The most reported use of STAB-H is in the reductive amination of ketones and aldehydes. This protocol has become the procedure of choice for these reactions.[26,27,68] The reagent has a wide scope of applications and fewer limitations than other reagents. It is applied successfully to all kinds of aldehydes, most ketones, and most primary and secondary amines.[68]

Reductive Amination of Ketones. Acyclic and cyclic ketones undergo direct reductive amination (i.e., without prior formation of intermediate imines, iminium ions, or enamines) with primary and secondary amines. Most reactions are carried out at rt in $ClCH_2CH_2Cl$, THF, CH_2Cl_2, or CH_3CN in the presence of AcOH with about 1.5 equiv of STAB-H. In most reactions, ketones are used as the limiting agents. The selected representative examples listed below show the synthesis of amines **19–28** (eqs 39–48)[68–72] from the appropriate ketones and amines via reductive amination with STAB-H. The reactions to prepare compounds **22** and **23** (eqs 42 and 43) are examples of diastereoselective reactions based on steric effects,[68,70] while the stereochemical outcome in synthesis of compound **25** (eq 45) is the result of a hydroxy-directed diastereoselective reaction.[72] Compound **27** (eq 47) is prepared using a unique reductive amination with phenylhydrazine.[68]



19 (39)



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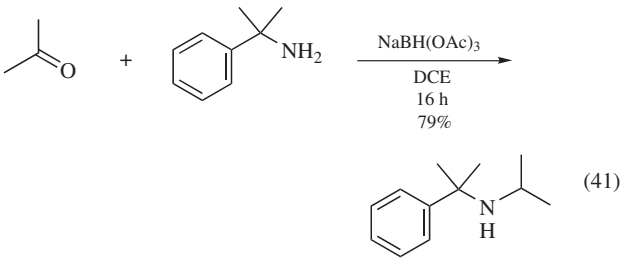

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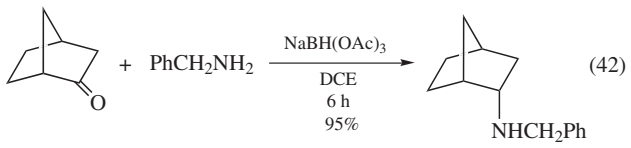

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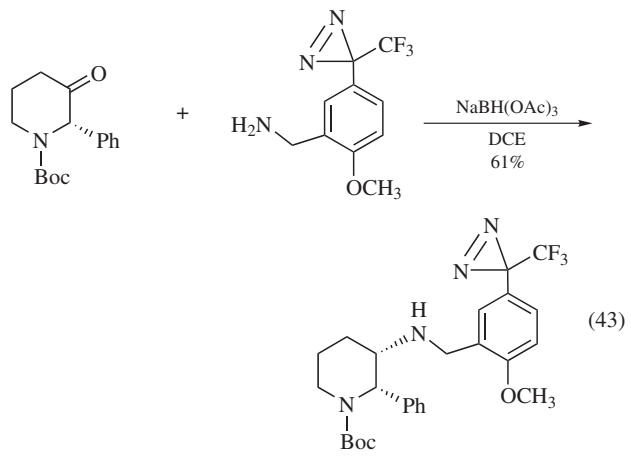

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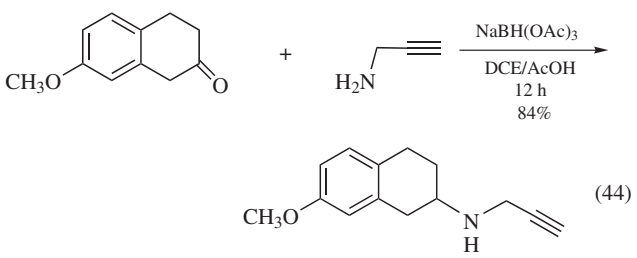

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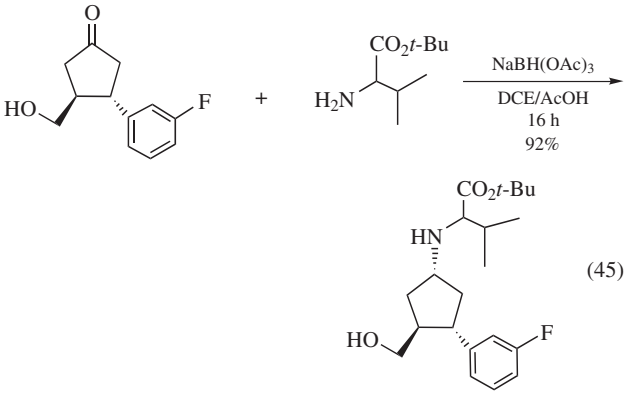

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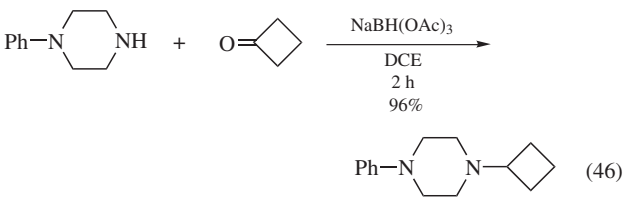

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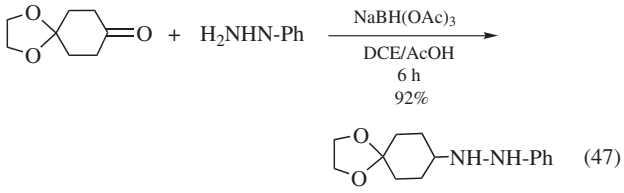

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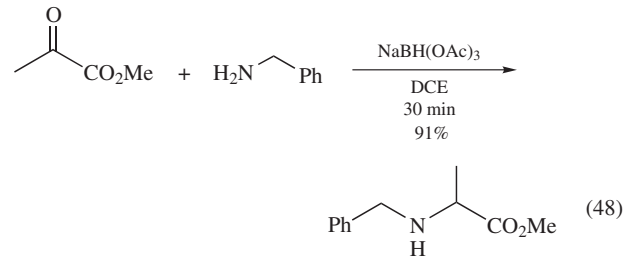
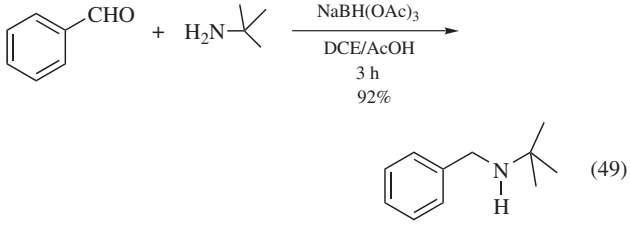


(48)

28

Reductive Amination of Aldehydes. Reductive aminations of aliphatic and aromatic aldehydes show very few limitations and are usually high yielding and faster reactions than those of ketones. Amines **29–35** (eq 49–55) obtained from reductive amination of various aldehydes with primary and secondary amines are selected to illustrate the utility and the scope of the reductive amination of aldehydes using STAB-H.[68,73–77]



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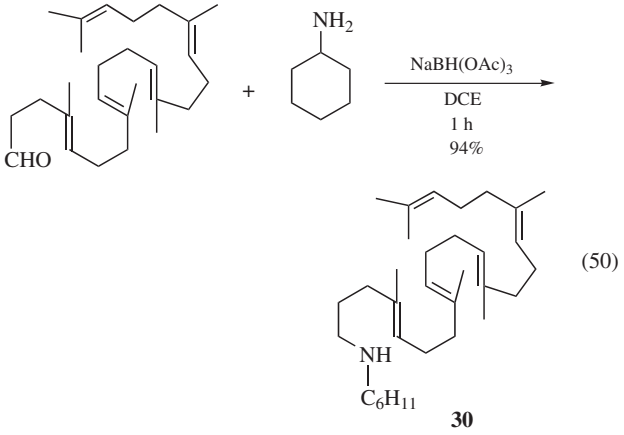

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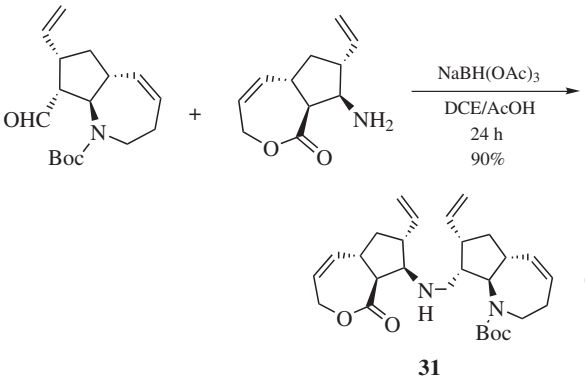

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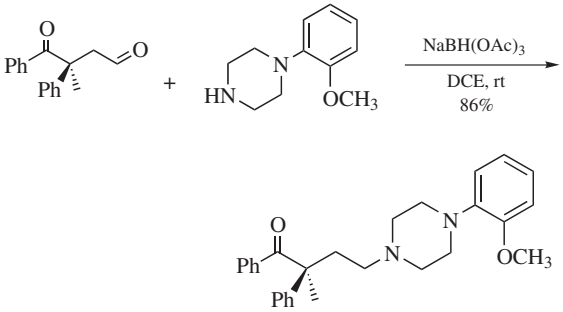

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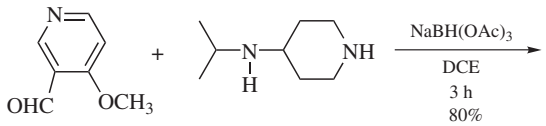

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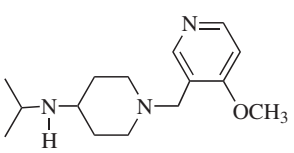

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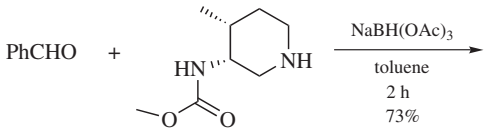

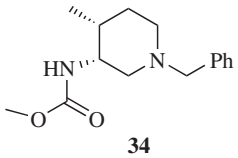

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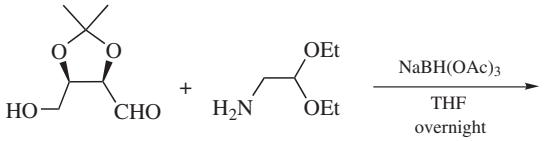
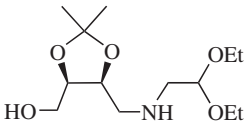
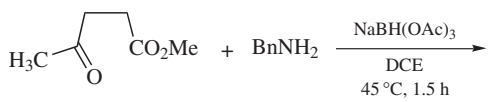


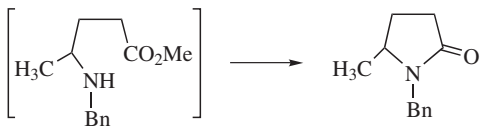


(55)

35

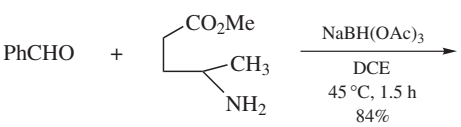
Reductive Amination/Lactamization. The reductive amination of methyl 4-oxopentanoate with primary amines such as benzylamine (eq 56) produces initially the *N*-benzylamino ester (**36**). This product is cyclized under the reaction conditions to produce the *N*-benzyl-γ-valerolactam (**37**) in excellent yield. Alternatively, lactam **37** is also obtained by the reductive amination of benzaldehyde with methyl 4-aminopentanoate via the same intermediate (eq 57). This is a convenient procedure to prepare γ-butyrolactams and δ-valerolactams via this tandem two-step procedure as exemplified by synthesis of lactams **38–40** (eqs 58–60). Many of these reactions are accelerated by increasing the reaction temperature to 45–55 °C.[78] While this is a convenient procedure to prepare lactams, it is limited to γ- and δ-lactams and does not apply to larger size lactams.

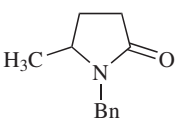




(56)

36 **37**





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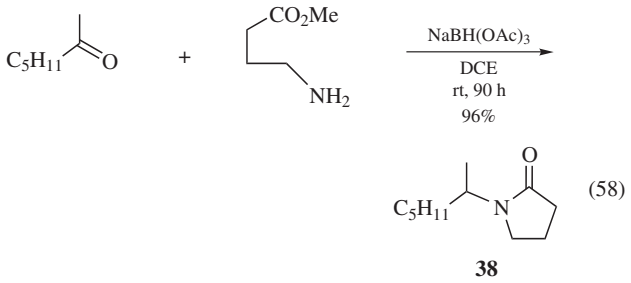

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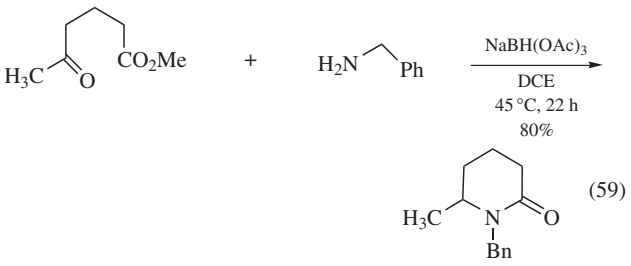

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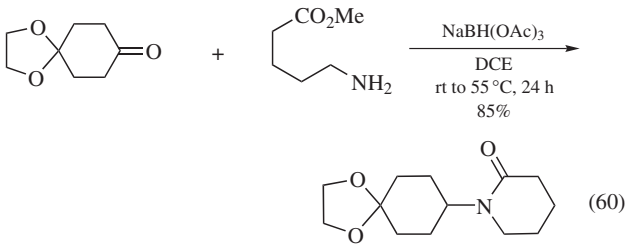
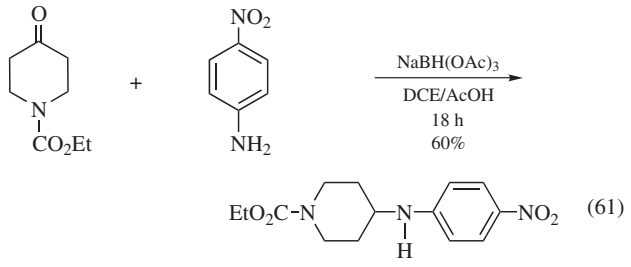


(60)

40

Reductive Amination with Weakly Basic Amines. Aromatic amines containing electron-withdrawing groups are weak bases and poor nucleophiles. The use of these amines in reductive amination of aldehydes and ketones is usually very limited due to their inactivity. STAB-H is a superior and a very efficient reducing agent in reductive amination reactions that utilize these amines with excellent results.[27,68] Several illustrative examples to prepare amines **41–45** are presented in eqs 61–65. As in the case with regular amines, aldehydes give better results than ketones. The reductive amination of cyclohexanone with *o*-nitroaniline and STAB-H produced **42** in only 31% yield after 144 h. Cyclohexanecarboxaldehyde required only 1.5 h to reach complete conversion and give 94% yield of **43**.



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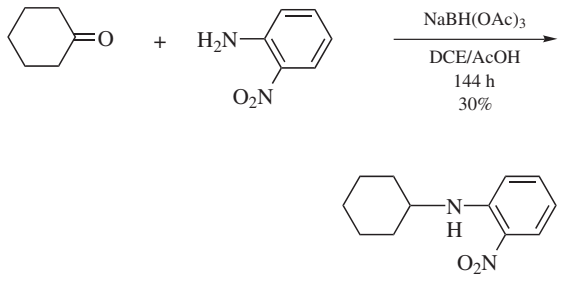

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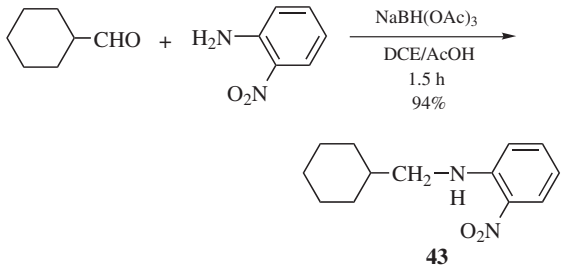

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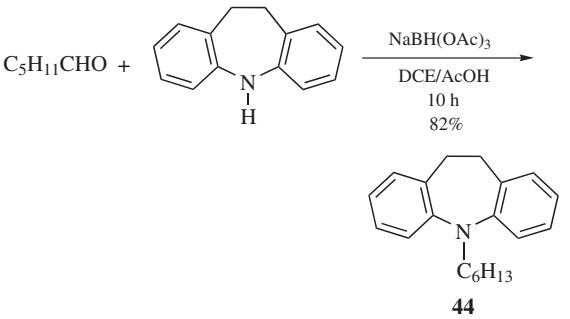

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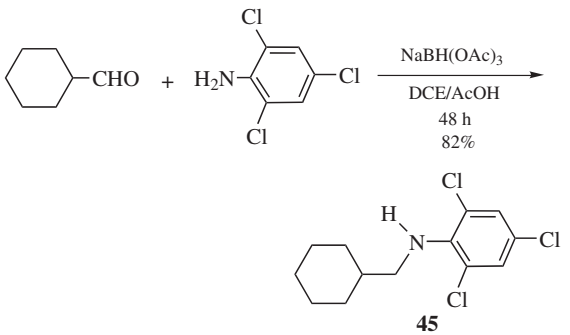
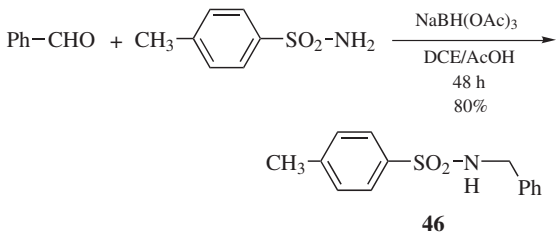


(65)

45

A remarkable reductive amination reaction is that of benzaldehyde with *p*-toluenesulfonamide using STAB-H to give the *N*-benzyl derivative **46** in excellent yield (eq 66).[68]

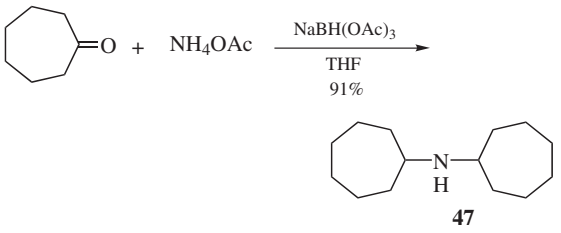


(66)

46

Reductive Amination with Ammonia. Ammonium acetate is usually used in reductive amination reactions as an ammonia equivalent. The reaction is limited in use because of the low solubility of ammonium acetate in the common solvents used

for STAB-H such as $ClCH_2CH_2Cl$, THF, CH_3CN, etc., which leads to formation of secondary amines since the initial primary amine product is more soluble and more reactive than ammonia. Reductive amination of cycloheptanone with excess NH_4OAc (10 equiv) and STAB-H gave dicycloheptylamine (**47**) as a major product (eq 67).[68] The use of ammonium trifluoroacetate, which is soluble in THF, was introduced[79a] as a better alternative. Thus, the reductive amination of cycloheptanone and cyclododecanone with NH_4OCOCF_3 and STAB-H in THF gives the primary amines **48** and **49**, respectively, as major products (eqs 68 and 69).[79]



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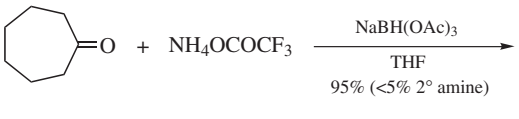
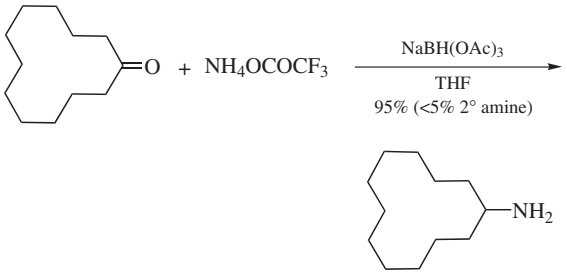


(68)

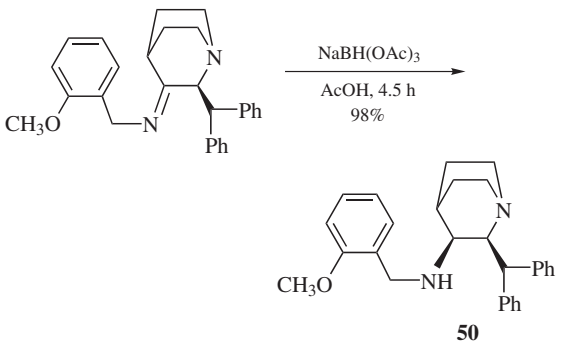
48



(69)

49

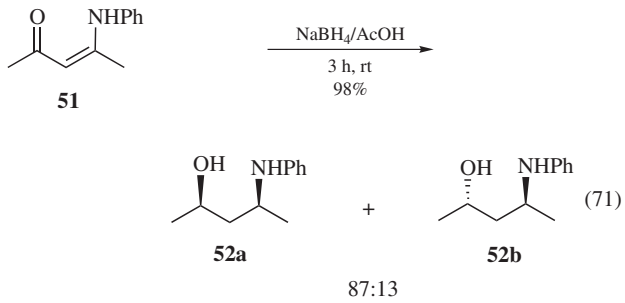
Reduction of Imines and Enamines. Reduction of imines and enamines continued to be one of the applications of STAB-H as an effective reducing agent. The 3-amino-1-azabicyclo[2.2.2] octane derivative (**50**) was prepared in 86% isolated yield by the reduction of the corresponding imine at 25 °C with STAB-H. The reported isolated product has *cis*-stereochemistry as illustrated in eq 70.[80]



(70)

50

The reduction of β-enamino ketones with $NaBH_4$ in glacial AcOH gives 3-amino alcohols in excellent yields. The *syn*-products were preferred in all reactions. An example is the reduction of enamino ketone **51** with $NaBH_4$/AcOH to give 98% yield of the amino alcohols **52a** and **52b** in an 87:13 ratio (eq 71). While the mixture of $NaBH_4$ in glacial AcOH usually produces triacetoxyborohydride, the nature of the reducing agent was not established.[81]



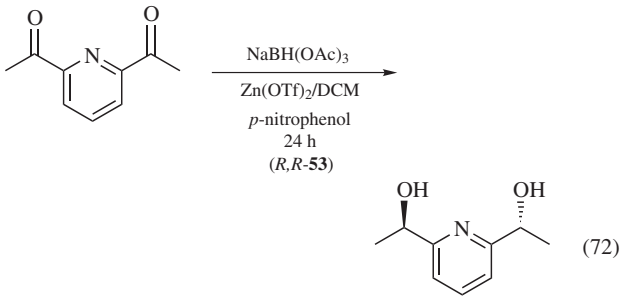
(71)

51

52a **52b**

87:13

Miscellaneous Reactions. The reduction of 2,6-diacetylpyridine was accomplished in about 90% conversion using STAB-H in combination with zinc triflate and *p*-nitrophenol to give the C_2-symmetric diol **53** (*R*,*R*- and *S*,*S*-pairs) as a major product. The initially formed diol seems to autocatalyze the reduction to favor the formation of the observed diastereomeric mixture. Addition of a catalytic amount of enantiomerically pure *R*,*R*-diol to the reaction mixture produced a product that is both enantiomerically and diastereomerically enriched as described in eq 72.[82]

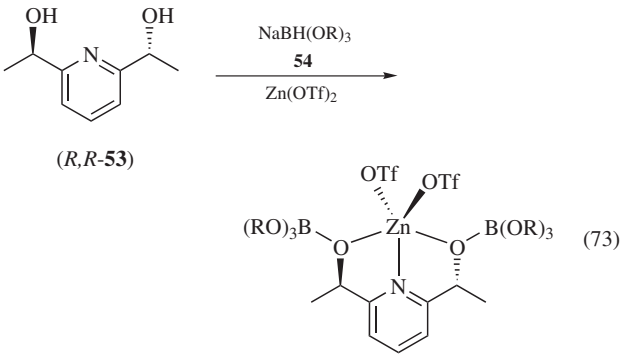


(72)

53

40% ee; 47% de

While STAB-H is used in this reduction, the actual reducing agent is tris-(*p*-nitrophenoxy) borohydride (**54**), resulting from substitution of the acetoxy groups of STAB-H with *p*-nitrophenol. The authors proposed enantiomeric catalyst **55** (eq 73) to explain the observed stereoselectivity.[82]



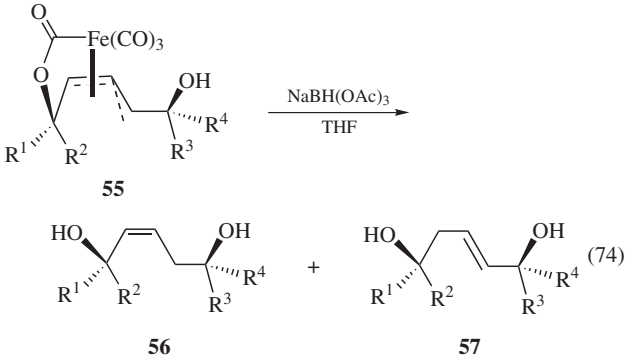
(73)

(*R*,*R*-**53**)

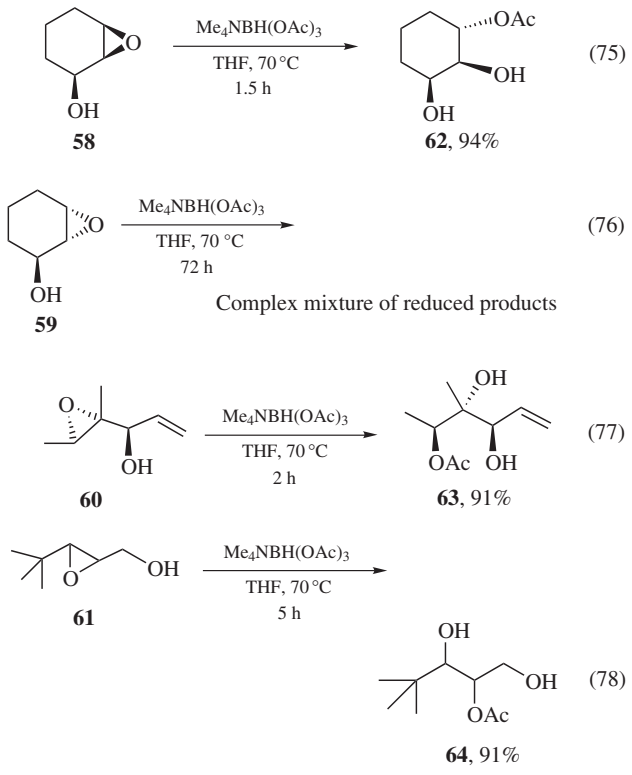
55

R = *p*-nitrophenyl

Reduction of π-allyltricarbonyliron lactone complexes (**55**) with STAB-H in THF resulted in the decomplexation to form the unsaturated alcohols **56** and **57** (eq 74), with retention of the stereochemistry of the hydroxy stereocenters. Other stronger reducing agents, such as $NaBH_4$, caused some loss of stereochemistry at this center and formation of some saturated alcohols. The presence of a hydroxy group in the side chain of the π-allyltricarbonyliron lactone is required for the success of the reduction with STAB-H; if the hydroxy group is absent or protected, no reduction occurs.[83]



Treatment of 2,3-epoxy alcohols with $Me_4NBH(OAc)_3$ afforded the ring-opened products at the C-3 position with high regioselectively. For example, the reduction of *syn*-2,3-epoxy cyclohexanol (**58**) with $Me_4NBH(OAc)_3$ in THF at 70 °C gave **62** as the sole product (eq 75). Similar reduction of the corresponding *anti*-epoxy alcohol **59** resulted in a sluggish reaction and a complex mixture of products (eq 76). The acyclic epoxy alcohol **60** gave the 3-acetoxy diol **63** in high yield and selectivity (eq 77) while the epoxy alcohol **61** bearing a *tert*-butyl group at the C-3 position afforded the C-2 opening product **64** with opposite regioselectivity (eq 78).[84]



Related Reagents. Sodium Borohydride; Sodium Cyanoborohydride; Sodium Trifluoroacetoxyborohydride; Sodium Tris (trifluoroacetoxy)borohydride, Tetramethylammonium Triacetoxyborohydride.

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