



Reductive amination using ammonia borane

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ABSTRACT

A variety of primary, secondary, and tertiary amines were prepared in 84–95% yields using ammonia borane for the reductive amination of aldehydes and ketones in the presence of titanium isopropoxide.

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Reductive amination of carbonyls or reductive alkylation of amines, the reaction of amines with aldehydes and ketones in the presence of a reducing agent, is one of the widely used and fundamental reactions in organic chemistry.^{1,2} Catalytic hydrogenation, sodium cyanoborohydride,³ sodium triacetoxyborohydride,⁴ sodium- or⁵ zinc borohydride⁶ in the presence of Brønsted or Lewis acids, and amine boranes, such as pyridine–BH₃,⁷ 2-picoline–BH₃,⁸ 2,6-diborane–methanol,⁹ dimethylamine–BH₃,¹⁰ *t*-BuMeⁱPrN–BH₃,¹¹ 5-ethyl-2-methylpyridine–BH₃,¹² and benzylamine–BH₃¹³ have been utilized to accomplish this transformation. However, most of these reagents suffer from drawbacks. For example, NaBH₃CN produces toxic by-products, such as NaCN and HCN.¹⁴ Catalytic hydrogenation is unselective since it can also reduce other functional groups such as alkenes, alkynes, and a nitro group.¹⁵ The amine boranes are relatively expensive and have to be stored under optimal conditions. For example, pyridine–borane¹⁶ undergoes an autocatalytic, highly exothermic hydroboration of the pyridine ring.¹⁷

The simplest amine borane, ammonia borane (AB), is a solid with remarkable thermal and hydrolytic stability. Although the use of AB for the reduction of carbonyls has been reported three decades ago,¹⁸ to the best of our knowledge, its application for reductive amination has not been reported, probably due to its relatively high cost.¹⁹ Ammonia borane has recently received a lot of attention as one of the promising materials for alternate energy.²⁰ As part of our project involving AB as a hydrogen storage material, we recently reported a large-scale synthesis of ammonia borane,²¹ which has been favorably received by the community.²² Our project required the handling of large quantities of AB and we observed that, indeed, AB is more convenient to handle in air than sodium borohydride. This prompted us to examine AB for reductive amination and the results are described herein.

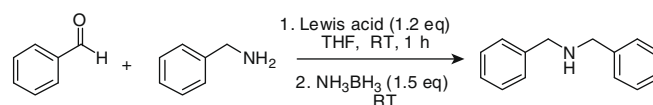
A successful reductive amination procedure relies on the rapid imine formation and selective reduction. Since imine formation is usually the rate-determining step for in situ reductive aminations, addition of mild Lewis acids as co-reactants is desirable. We,

therefore, examined a selected series of Lewis acids such as ZnCl₂, NiCl₂, SiO₂, and Ti(OⁱPr)₄ (Table 1) and carried out the reductive amination reaction in tetrahydrofuran (THF) using AB as the reducing reagent. In the absence of Lewis acids, imine formation does not occur and the aldehyde is reduced to benzyl alcohol.

In a typical reaction protocol, benzylamine (1.2 mmol) was added to the solution of benzaldehyde (1 mmol) in THF (5 mL) followed by the addition of the Lewis acid (1.2 mmol), and the reaction mixture was stirred for 1 h at room temperature (rt). Ammonia borane (1.5 mmol) was then added and stirring was continued at the same temperature until the completion of the reaction (disappearance of the carbonyl in thin layer chromatogram, 4 h). Utilization of ZnCl₂ provided 80% yield of dibenzylamine and increasing the equivalents of the amine had no beneficial effect. NiCl₂ failed to catalyze the reaction and the best result, 94% yield of the product amine, was obtained with Ti(OⁱPr)₄. Under the optimized condition,²³ the ratio of carbonyl/amine/Ti(OⁱPr)₄/AB is 1:1.2:1.2:1.5.

The reductive amination of a variety of aryl and alkyl aldehydes and ketones with aryl and 1°- and 2°-alkyl amines of varying steric

Table 1
Reductive amination using ammonia borane: examination of Lewis acids



| Entry | Lewis acids | Time (h) | Yield ^a (%) |
|-------|------------------------------------|----------|------------------------|
| 1 | ZnCl ₂ | 10 | 80 |
| 2 | ZnCl ₂ ^b | 8 | 78 |
| 3 | SiO ₂ | 11 | 75 |
| 4 | NiCl ₂ | 24 | Trace ^c |
| 5 | Ti(O ⁱ Pr) ₄ | 4 | 94 |

^a Isolated yield.


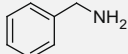
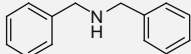


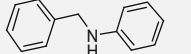

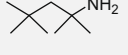
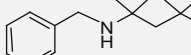


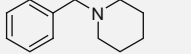


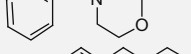
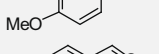
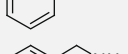
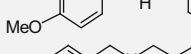
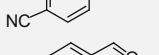
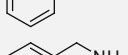
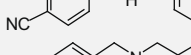
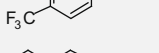
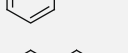
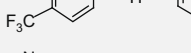

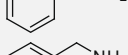
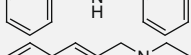
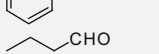
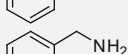
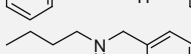

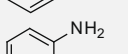
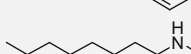
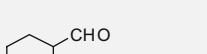

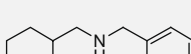
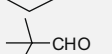
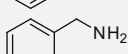
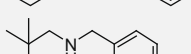

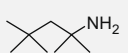
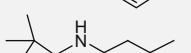

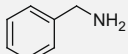
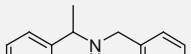

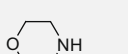
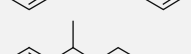


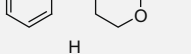


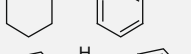

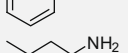
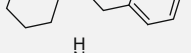

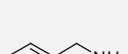
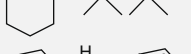

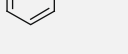
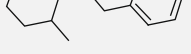

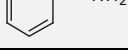
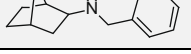
^b 1.5 equiv benzylamine was used.

^c Most of the starting material was recovered.

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Table 2
Preparation of 2°- and 3°-amines via reductive amination using AB^a

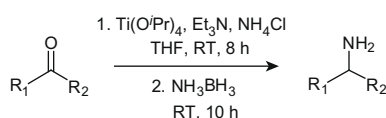
| Entry | R ₁ R ₂ CO | R ₃ R ₄ NH | Time (h) | Product | Yield ^b (%) |
|-------|---|---|----------|---|------------------------|
| 1 |  |  | 4 |  | 94 |
| 2 |  |  | 6 |  | 88 |
| 3 |  |  | 7 |  | 95 |
| 4 |  |  | 5 |  | 84 |
| 5 |  |  | 3 |  | 85 |
| 6 |  |  | 4 |  | 89 |
| 7 |  |  | 6 |  | 85 |
| 8 |  |  | 7 |  | 84 |
| 9 |  |  | 9 |  | 90 |
| 10 |  |  | 4 |  | 91 |
| 11 |  |  | 2 |  | 91 |
| 12 |  |  | 8 |  | 87 |
| 13 |  |  | 5 |  | 94 |
| 14 |  |  | 6 |  | 92 |
| 15 |  |  | 10 |  | 90 |
| 16 |  |  | 8 |  | 86 |
| 17 |  |  | 8 |  | 84 |
| 18 |  |  | 8 |  | 89 |
| 19 |  |  | 7 |  | 92 |
| 20 |  |  | 8 |  | 86 |
| 21 |  |  | 7 |  | 90 |
| 22 |  |  | 8 |  | 91 |

^a For the reaction conditions see footnote 23.

^b Isolated yields on the basis of the carbonyls.

Table 3

Preparation of 1°-amines via reductive amination using AB



| Entry | Ketone | R ₁ R ₂ CH ₂ NH ₂ | Yield ^a (%) |
|-------|--------|---|------------------------|
| 1 | | | 85 |
| 2 | | | 83 |
| 3 | | | 75 |
| 4 | | | 72 |
| 5 | | | 74 |

^a Isolated yield.

requirements using AB as the reductant was accomplished within 2–10 h to obtain the desired 2°- or 3°-amines, respectively, in 80–94% yields (Table 2). The reactions were slower with increasing steric requirements of the carbonyl or amine, and ketones were slower to react than aldehydes.

Following the successful application of AB for the preparation of 2°- and 3°-amines, we focused on the synthesis of 1°-amines, which remains a challenge due to over-alkylation reaction.²⁴ Triethylamine,²⁵ diallylamine,²⁶ and NH₄Cl²⁷ are often employed as surrogates to prepare primary amines and we chose NH₄Cl. In a typical reaction,²⁸ Ti(OⁱPr)₄ was added to the solution of acetophenone, NH₄Cl, and triethylamine in ethanol and stirred for 10 h at ambient temperature. Ammonia borane was then added and stirred for an additional 8 h to obtain the desired primary amine in 83–85% yield (Table 3). Aryl and alkyl ketones furnished the 1°-amine in 72–75% yields. However, the reaction of aldehydes resulted in 2°-amines.

In conclusion, we have shown that ammonia borane is a versatile and efficient reagent for the reductive amination of aldehydes and ketones providing 2°- and 3°-amines in good to excellent yields. The formation of primary amines was achieved in good yield from ketones using Ti(OⁱPr)₄/Et₃N and NH₄Cl as ammonia source. We believe that this reductive amination process will find applications in organic synthesis due to the stability and simple preparation of AB.²¹

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.014.

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