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# Selective reduction of aldehydes and ketones to alcohols with ammonia borane in neat water<sup>†</sup>

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Chemoselective reduction of various carbonyl compounds to alcohols with ammonia borane (AB), a nontoxic, environmentally benign, and easily handled reagent, in neat water was achieved in quantitative conversions and high isolated yields. Interestingly,  $\alpha$ - and  $\beta$ -keto esters were selectively reduced to corresponding hydroxyl esters by AB, while diols were obtained when sodium borohydride was used as a reducing agent. The procedure is also compatible with the presence of a variety of base-labile protecting groups, such as tosyl, acetyl, benzoyl, ester groups, and acid-labile protecting groups such as trityl and TBDMS groups, and others, such as the unsaturated double bond, nitro and cyano groups. Finally, a kilo scale reaction of methyl benzoylformate with AB was conducted in water and gave methyl mandelate in 94% yield.

#### Introduction

The reduction of carbonyl compounds to alcohols is one of the most widely used and fundamental reactions in organic chemistry.1 Catalytic hydrogenation,2 transition metal catalyzed hydrogenation,<sup>3</sup> biocatalytic reductions with bakers' yeast reductase<sup>4</sup> and chemical reductions by LiAlH<sub>4</sub>, nickel-aluminum alloy,<sup>5</sup> tri-*n*-butyltin hydride,<sup>6</sup> sodium formate,<sup>7</sup> alkyl phosphines,<sup>8</sup> poly(methylhydrosiloxane),<sup>9</sup> or borane reagents such as zinc borohydride, <sup>10</sup> NaBH<sub>4</sub>,<sup>11</sup> NaBH<sub>3</sub>CN,<sup>12</sup> BH<sub>3</sub>-THF,<sup>13</sup> and amine boranes14 have been utilized to accomplish the reduction of the carbonyl group. However, the reductive activity and selectivity of catalytic hydrogenation greatly depend on the catalysts and conditions used. Biocatalytic reductions usually require a specific temperature, pH value and reductase. The use of NaBH<sub>3</sub>CN may result in the contamination of products with toxic materials.<sup>15</sup> The traditional methods for the reduction of a carbonyl group often involve long reaction times,<sup>7</sup> harsh conditions (under nitrogen; in acid or alkaline condition<sup>5</sup>), toxic solvents (such as toluene,<sup>6</sup> benzene,<sup>14a</sup> ether,<sup>14b</sup> THF) and complicated operation. NaBH<sub>4</sub> is the most common reductant in the chemical conversion due to its relatively cheap cost, ease of handling, and possibility of being used in aqueous alcohol solvent.14

Ammonia borane (AB), the simplest amine borane, has recently received a lot of attention as one of the promising materials for alternate energy.<sup>16</sup> AB is a solid with remarkable

thermal and hydrolytic stability. AB is not only a nontoxic, environmentally benign, and stable material that can be safely transported without hydrogen loss, but also equally important for various applications in synthetic organic chemistry.<sup>17</sup> Recently S. G. Shore et al. and P. V. Ramachandran et al. have reported large-scale methods for the preparation of AB,<sup>18</sup> which make it very readily available. Reactions in aqueous media have attracted much attention in synthetic organic chemistry, because water is one of the most abundant, cheap, and environmentally friendly solvents.<sup>19</sup> Since AB is water-soluble, nontoxic and environmentally benign, it is a good combination to conduct green organic reactions in water using AB as a reductant. Although the use of AB for the reduction of carbonyls was reported three decades ago,<sup>14b,c</sup> to the best of our knowledge, its application in neat water for reduction of various carbonyl compounds has not been reported. Thus, we report herein a detailed investigation on the reduction of carbonyl compounds using AB as a green reductant in neat water (Scheme 1).

#### **Results and discussion**

The reduction of various carbonyl compounds with AB to alcohols in neat water was shown in Scheme 1. In a typical reaction protocol, AB (0.5 mmol) was added to the solution of carbonyl compound (0.5 mmol) in neat water (2 mL), and the reaction mixture was stirred at room temperature until the completion of





Scheme 1 Reduction of carbonyl compounds with AB in neat water.

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Yield <sup>b</sup> (%)
88
94
90
91
91
95
93
92
85
88
87
91
85
82
97
90
93
86
85
89

Reduction of aldehydes and ketones to alcohols with AB in Table 1



21 22

23

24

25

26

27

28

29

30

31



24 h<sup>c</sup>

 $12 h^d$ 

1 h

2.5 h

85

86

91

87

<sup>a</sup> All reactions were carried out with AB (0.5 mmol), aldehyde or ketone (0.5 mmol) in H<sub>2</sub>O (2 mL) at room temperature, unless otherwise indicated. <sup>b</sup> Isolated yields. <sup>c</sup> Reactions were conducted at 50 °C. <sup>d</sup> Reactions were conducted at 80 °C.

2x

2y

the reaction. Aldehydes and ketones were reduced rapidly in quantitative conversions and excellent isolated yields (82-97%) (Tables 1 and 2). The procedure is perfectly compatible with the presence of a variety of base-labile protecting groups, such as tosyl, acetyl, benzoyl, ester groups, and acid-labile protecting groups such as trityl and TBDMS groups. Unsaturated double bond, nitro and cyano groups also remain intact in the process.

As shown in Table 1, aliphatic aldehyde (entry 1),  $\alpha$ ,  $\beta$ -unsaturated aldehyde (entry 2), heterocyclic aldehydes (entries 3-5), benzaldehyde (entry 6), and aromatic aldehydes with electron donating groups (EDG) or electron withdrawing groups (EWG) (entries 7–17) were reduced to alcohols 2a-q in excellent yields at rt in 1 h. Diverse substituents on the aryl, whether EDG or EWG, did not show significant effect on the yield. It is noteworthy that the heterocyclic aldehyde 1e, a nucleoside analogue, was reduced with AB in 10 min in 91% yield (entry 5) and no deacetylated product was obtained, while the use of NaBH<sub>4</sub> gave 10% deacetylated product. Reductions of ketones also underwent smoothly and gave corresponding secondary alcohols in excellent yields, but required longer time. The slow reaction rate and lower reactivity of ketones are due to their steric hindrance and poor water-solubility (entries 18-31). The solubility is important to the reaction rate. The reductions of substrates 1t-w, which are poorly soluble in water, needed over 10 h at rt, while higher temperatures improved the solubility and thus, accelerated the reaction (entries 20–29).

α-Hydroxyl or β-hydroxyl esters are important synthetic intermediates which are commonly prepared by reducing corresponding keto esters.<sup>20</sup> Reduction of ketoesters to diols was observed with most chemical reductants, such as LiAlH<sub>4</sub> and NaBH<sub>4</sub>. For example, aromatic and aliphatic keto esters were reduced to diols





Entry	Substrate	Reductant	Time/product/yield (%) <sup>b</sup>
32 33 34	OMe	$\begin{array}{c} AB\\ NaBH_4\\ NaBH_4 \end{array}$	0.5 h/ <b>2A</b> /91 10 min/ <b>2A,3A</b> /22,39 <sup>c</sup> 1.0 h/ <b>3A</b> /92
35	OBn	$\begin{array}{c} AB\\ NaBH_4 \end{array}$	8 h/ <b>2B</b> /86
36	OBn		15 h/ <b>3A</b> /92
37	CI O	$egin{array}{c} AB \ NaBH_4 \end{array}$	1.5 h/ <b>2C</b> /92
38	OMe		2.0 h/ <b>3C</b> /85
39	CI O	$\begin{array}{c} AB\\ NaBH_4 \end{array}$	10 h/ <b>2D</b> /90
40	OBn		17 h/ <b>3C</b> /80
41	OEt	AB	1.0 h/ <b>2E</b> /90
42		NaBH4	2.0 h/ <b>3E</b> /88
43 44	NC 0	$f AB NaBH_4$	3.0 h/ <b>2F</b> /89 3.0 h/ <b>3F</b> /80

<sup>*a*</sup> All reactions were carried out with AB (0.5 mmol), aldehyde or ketone (0.5 mmol) in H<sub>2</sub>O (2 mL) at room temperature, unless otherwise indicated. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> Recovered 20% methyl mandelate.

in methanol by NaBH<sub>4</sub>,<sup>11b</sup> and the diol was also obtained when using ethanol and water as solvent, whereas hydroxyl ester was the major product when using THF as solvent.<sup>11b</sup> To further evaluate the generality and selectivity of our procedure using AB as a green reductant, the reactions of aromatic keto esters (**1A– E**) and aliphatic keto ester **1F** with AB were conducted in water (Table 2). As shown in Table 2, these keto esters were selectively reduced to corresponding hydroxyl esters **2A–F** in isolated yields of 86–92% and no diols were observed. In our parallel experiments with NaBH<sub>4</sub>, we observed that diols are exclusive products (Table 2) or major product (Table 2, entry 33) if the reaction was quenched in short time.

To demonstrate the easy use of the reductant, a kilo scale reduction of methyl benzoylformate with AB was conducted in water. After vigorously stirring the mixture containing methyl benzoylformate **1A** (1.0 kg, 6.1 mol), AB (189.1 g, 6.1 mol) in water (3 L) for 2 h, the completion of the reaction was monitored by TLC. Thereafter, the reaction mixture was thoroughly extracted with EtOAc, and the combined organic layers were then washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was distilled under reduced pressure to give mandelate **2A** (951 g, 94% yield) as a white solid.

#### Conclusions

In conclusion, the present work describes a selective and convenient green procedure for the reduction of a variety of aldehydes and ketones to corresponding alcohols using AB as reductant. This method is applicable to a broad range of carbonyl substrates including aliphatic, aromatic,  $\alpha$ ,  $\beta$ -unsaturated, and heterocyclic aldehydes, and keto esters to give excellent yields in neat water. It is noteworthy that AB showed better selectivity than NaBH<sub>4</sub> in the reduction of  $\alpha$ - and  $\beta$ -keto esters to hydroxyl esters in water. The procedure is also compatible with the presence of a variety of base-labile protecting groups, such as tosyl, acetyl, benzoyl, ester groups, and acid-labile protecting groups such as trityl and TBDMS groups, and the unsaturated double bond, nitro and cyano groups are intact in the process. AB is a convenient reagent with remarkable thermal and hydrolytic stability, and easily handled, especially in large-scale manufacturing in neat water solvent. The advantages of the present method, including green and convenient reaction processes, excellent yields, mild conditions and simple operation, readily available and stable reagent, applicability to a wide range of substrates and large-scale manufacturing, and the nontoxic and environmentally friendly nature of the reductant, make this new method a valuable addition to existing options.

#### Experimental

## General procedure for the reduction of carbonyl compounds to alcohols

A mixture of carbonyl compound 1 (0.5 mmol), AB (0.5 mmol) in neat water (2 mL) was stirred at rt for an appropriate time. The reaction was monitored by TLC. Upon completion, the reaction mixture was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated by rotary evaporation, the residue was

purified by silica gel column chromatography to obtain the product.

## General large-scale procedure for the reduction of carbonyl compounds to alcohols

AB (189.1 g, 6.1 mol) was added to a 10 L flask containing a mixture of methyl benzoylformate **1A** (1.0 kg, 6.1 mol) in water (3 L) and vigorously stirred for 2 h. TLC showed the reaction was completed. The reaction mixture was thoroughly extracted with EtOAc. The combined organic extracts were then washed with saturated brine and dried over anhydrous magnesium sulfate, and thereafter concentrated to recover EtOAc. The residue was distilled under reduced pressure (11 mmHg) to collect the fraction at 133–135 °C. The pure product mandelate **2A** (951 g, 94% yield) was obtained in the form of a white solid (m.p. 53–55 °C).

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