



# Novel diacid accelerated borane reducing agent for imines

Zhi-Hui Lu,\* Nandkumar Bhongle, Xiping Su, Seth Ribe and Chris H. Senanayake\*

Sepracor, Inc., Chemical Process R&D, 84 Waterford Drive, Marlborough, MA 01752, USA

Received 3 July 2002; accepted 5 September 2002

**Abstract**—A remarkable effect of diacids in modulating the reactivity of borane has been discovered. This novel process provides a rapid and excellent access for reduction of a variety of imines with different functionalities. © 2002 Elsevier Science Ltd. All rights reserved.

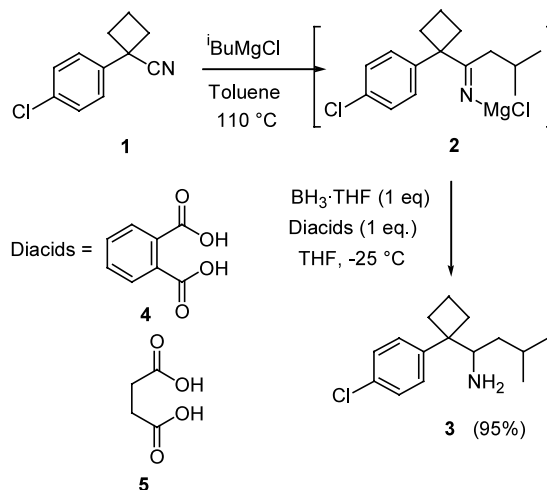
Reduction of imines is one of the most fundamental reactions in organic chemistry that is of continuous interest for more efficient and practical method.<sup>1</sup> Conventional reagents including  $\text{NaBH}_4\text{-CF}_3\text{CO}_2\text{H}$ ,<sup>2</sup>  $\text{NaBH}_3\text{CN}$ <sup>3</sup> and  $\text{NaBH(OAc)}_3$ <sup>4</sup> represent the primary choice for such a transformation. However, these reducing agents are less successful in cases when THF, toluene or *tert*-butyl methyl ether (TBME) etc., other than toxic  $\text{CH}_2\text{Cl}_2$ , is the choice of solvent due to their poor solubilities in these solvents.  $\text{NaBCNH}_3$  not only has high toxicity entailing special disposal procedure in industry,<sup>5</sup> but also prefers low pH reaction condition that is not feasible in cases when the imine intermediates are not stable in acidic media. Borane reagents such as 9-BBN or  $\text{BH}_3\cdot\text{Me}_2\text{S}$  would form stable complex with imines, thus show sluggish reactivity toward the reduction of imines.<sup>6</sup>

In our ongoing process development for preparation of didesmethylsibutramine (**3**), a major active metabolite of the anti-obesity drug Meridia<sup>®</sup> for treatment of CNS disorders,<sup>7</sup> we discovered a novel, homogeneous process which overcame the aforementioned drawbacks that had otherwise occurred. Herein, we would like to disclose a remarkable effect of diacids in modulating the reactivity of borane complexes for facile reduction of a variety of imines under very mild conditions.

The process, as exemplified in the preparation of **3**, involved reduction of the imine intermediate **2** derived from the addition of the Grignard reagent to nitrile **1**, with 1 equiv. of  $\text{BH}_3\cdot\text{THF}$  in the presence of 1 equiv. of diacids, such as **4**, or **5** (Scheme 1). A solution of nitrile

**1** in toluene was treated with isobutylmagnesium chloride in *tert*-butylmethyl ether (MTBE). After distillation of MTBE, the reaction mixture was warmed to 110°C to ensure complete conversion of the nitrile **1**. Upon cooling to below 0°C, the imine magnesium species was treated with 1 equiv. of phthalic acid (**4**), or succinic acid (**5**) in THF, followed by the addition of one equiv. of  $\text{BH}_3\cdot\text{THF}$  at below -25°C. The reaction completed within 30 min to give **3** in 95% overall yield.

For comparison, reduction of the imine magnesium intermediate **2** with  $\text{BH}_3\cdot\text{THF}$  in THF, or toluene, was performed. Not unexpectedly, the reduction without phthalic acid was slow even at ambient temperature and many by-products were observed. Only 75% of the product **3** was isolated after purification by chromatography. Other conventional reducing reagents, such as



Scheme 1.

**Keywords:** reduction; imines; borane; diacids.

\* Corresponding authors. E-mail: [zhihui\\_lu2002@yahoo.com](mailto:zhihui_lu2002@yahoo.com); [cseanayake@townisp.com](mailto:cseanayake@townisp.com)

**Table 1.** Reduction of imine **2** with various reducing agents

Entry	Reducing agent <sup>a</sup>	Solvent	Temp. (°C)	Time (h)	Yield <sup>b</sup> (%)
1	BH <sub>3</sub> ·THF	THF	22	14	75
2	NaBH <sub>4</sub>	IPA	Reflux	6	76
3	NaBH(OAc) <sub>3</sub>	THF	22	8	0
4	NaBH <sub>3</sub> CN	THF	22	8	0
5	BH <sub>3</sub> ·THF + <b>4</b>	THF	−25	0.5	96
6	BH <sub>3</sub> ·THF + <b>4</b>	THF	−78	0.5	98
7	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	THF	22	3	33

<sup>a</sup> All the reactions were run with 1 equiv. of reducing agents.

<sup>b</sup> Yield referred to the isolated yield.

NaBH<sub>4</sub>, NaBH(OAc)<sub>3</sub>, NaBH<sub>3</sub>CN etc., were examined on imine **2** for comparison, and the results are summarized in Table 1. From these results, it is obvious that this novel method features high reactivity, excellent yield, mild homogeneous reaction conditions (−78~−25°C), and an easy work-up procedure that is highly desirable in large-scale production of compound **3**.

In an independent experiment in which BH<sub>3</sub>·THF was mixed with phthalic acid in THF at below −25°C, no hydrogen evolution was observed indicating that no obvious reaction occurred between the two reagents at this temperature.<sup>8</sup>

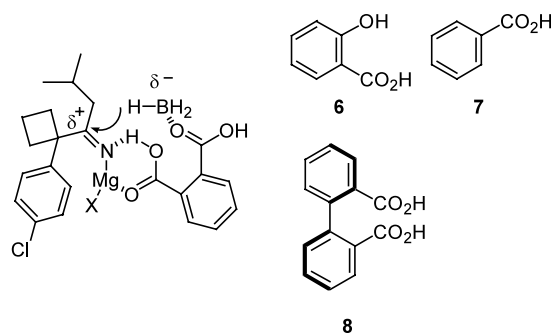
The mechanism of the reaction is not clear. It is postulated that the double functionalities of the diacid are acting as a Brønsted acid to protonate the nitrogen of imine, as well a Lewis base by coordinating the carbonyl oxygen with electron deficient reducing agent BH<sub>3</sub>·THF, thus, facilitating the reduction (Fig. 1).

Experiments using monoacids, such as benzoic acid (**7**), were examined (Table 2). When 1 equiv. of BH<sub>3</sub>·THF and benzoic acid was used, only 45% of the imine **2** was converted into **3** at −78°C over 3 h. Similarly, the reduction using two equiv. of benzoic acid and 1 equiv. of BH<sub>3</sub>·THF at −78°C gave only 51% of DDMS (**3**) in 3 h. This indicated that simple activation of the imine **2** with mono-carboxylic acid was not as effective as that of diacid. We propose that the diacid might play a ‘platform’ role in coordinating with both the reagent, as well as the substrate. This organization may lead to intramolecular delivery of the hydride to the substrate.<sup>9</sup>

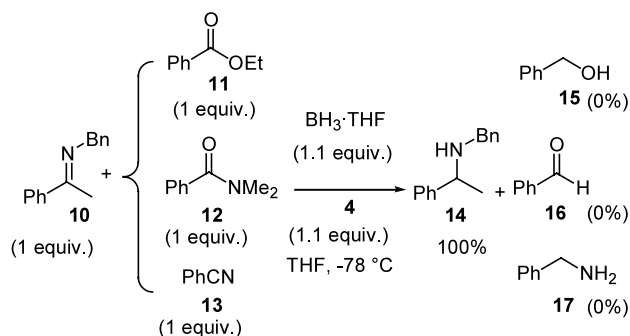
Other bifunctional molecules such as salicylic acid (**6**) and 2,2'-diphenylacetic acid (**8**) were examined. As expected, the reduction using **6** proceeded at −30°C with the same effectiveness.<sup>10</sup> However, a sluggish reaction was observed when using **8** as the additive. This implies that the conformation of the diacid had to be flexible to allow the construction of an ‘intramolecular’ transition state as depicted in Fig. 1.

The chemoselectivity of this reducing system (phthalic acid/BH<sub>3</sub> at −78°C) was exhibited in the intermolecular competitive reduction between ketimine **10** and molecules with other functionalities (Scheme 2). The method was effective in reducing ketimine **10** to provide *N*-benzyl phenethylamine in 80% isolated yield after purification. Other functional groups such as ester, tertiary amide and nitrile, are well tolerated in the system.

To examine the generality of this method, the process was expanded on a variety of substrates with multiple functionalities. The results are summarized in Table 3. The high reactivity of these novel reducing agents is

**Figure 1.****Table 2.** Reduction of the imine **2** with borane catalyzed by diacids

Entry	Acid (equiv.)	BH <sub>3</sub> ·THF (equiv.)	Temp. (°C)	Time (h)	Conv. (%)
1	<b>4</b> (1.0)	1.0	−78	0.5	99
2	<b>6</b> (2.0)	2.0	−25	1.5	96
3	<b>7</b> (1.0)	1.0	−78	3	43
4	<b>7</b> (2.0)	1.0	−78	3	51



Scheme 2.

exemplified by reduction of di-*tert*-butyl imine at  $-30^\circ\text{C}$  in 30 min (Table 3, entry 1). In the case of pyridine-containing imines (Table 3, entry 2), it is reduced in 30 min with 2 equiv. of the reducing agent. It is worthy to note that functionalities such as

substituted olefin, carboxyl ester, and nitrile, which are highly susceptible to borane reduction,<sup>11</sup> remain intact under these mild conditions (Table 3, entries 5a, 5b, 6). In the case of  $\alpha,\beta$ -unsaturated ketimine (Table 3, entry 7), only the 1,2-reduction product was observed. It is important to note that sulfinyl ketimine can be reduced without any complication with d.r. of 60:40 (Table 3, entry 8). The selectivity is increased to 90:10 with addition of  $\text{Ti}(\text{O}i\text{Pr})_4$  to this new reagent.

In summary, a mild homogeneous, chemoselective procedure for the reduction of imines has been developed by combination of  $\text{BH}_3 \cdot \text{THF}$  and diacids. This novel process allows the reaction to be conducted in environmentally benign solvent THF rapidly and at low temperature. Based on these preliminary achiral reduction results,<sup>12</sup> it is potential to design an asymmetric reduction protocol for imines by employing appropriate chiral diacids.

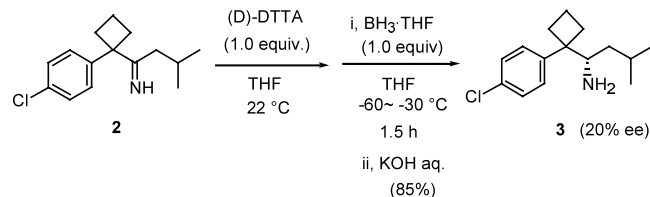
Table 3. Diacids-mediated borane reduction of imines<sup>a</sup>

Entry	Substrate	Temp ( $^\circ\text{C}$ )	Time (min)	Product	Yield (%)
1		-30	30		79
2	 a R = H; b R = Me	-30-0	60	 a R = H; b R = Me	86 (R=H) 88 (R=Me)
3	 a, R <sup>1</sup> = H, R <sup>2</sup> = Ph b, R <sup>1</sup> = Me, R <sup>2</sup> = Ph c, R <sup>1</sup> = Me, R <sup>2</sup> = Bn d, R <sup>1</sup> = n-Bu, R <sup>2</sup> = MgCl	-30	30	 a, R <sup>1</sup> = H, R <sup>2</sup> = Ph b, R <sup>1</sup> = Me, R <sup>2</sup> = Ph c, R <sup>1</sup> = Me, R <sup>2</sup> = Bn d, R <sup>1</sup> = n-Bu, R <sup>2</sup> = MgCl	a, 93 b, 90 c, 85 d, 81
4		-30	60		89
5	 a, R = CN b, R = CO <sub>2</sub> Me	-78	30	 a, R = CN b, R = CO <sub>2</sub> Me	a, 87 <sup>13</sup> b, 92 <sup>14</sup>
6		-78	30		90 <sup>15</sup>
7		-25	6		95 <sup>16</sup>
8		-30	15		92

<sup>a</sup> All reactions were conducted with substrates in THF (0.2 M) with 1.1 equiv. of  $\text{BH}_3 \cdot \text{THF}$  and 1.1 equiv. of phthalic acid at the specified temperature unless otherwise noted.

## References

- For recently reported reducing systems, see: (a) Shibata, I.; Kawakami, T. M.; Tanizawa, D.; Suwa, T.; (b) Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383; Shimizu, M.; Sahara, T.; Hayakawa, R. *Chem. Lett.* **2001**, 792; (c) Knettle, B. W.; Flowers, R. A., II *Org. Lett.* **2001**, *3*, 2321.
- Reductions in Organic Synthesis: Recent Advances and Practical Applications*; Abdel-Magid, Ahmed F., Ed.; Chapter 11 and references cited therein.
- For a review of the chemistry of sodium cyanoborohydride, see: *Synthesis* **1975**, 135.
- Reductions in Organic Synthesis: Recent advances and practical applications*; Abdel-Magid, Ahmed F., Ed.; Chapter 12 and references cited therein.
- The Sigma-Aldrich Library of Chemical Safety Data*, 1st ed.; Lenga, R. E., Ed.; Sigma-Aldrich Corp., 1985; p. 1609.
- Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2002**, *122*, 4217.
- (a) Buckett, W. R.; Thomas, P. C.; Luscomb, G. P. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1988**, *12*, 575; (b) Jerussi, T. P.; Senanayake, C. H.; Fang, Q. K. (Sepracor, Inc.) PCT Appl. 20020010198, 29 January, 2001.
- Acyloxyborane species were reported previously, see: Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052; Brown, H. C.; Stocky, T. P. *J. Am. Chem. Soc.* **1977**, *99*, 8218.
- For protocols of bifunctional catalysts, see: Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477; Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339 and references cited therein; Fields, L. B.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1993**, *4*, 2229; Ward, J.; Borner, A.; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, *3*, 849; Borner, A.; Ward, J.; Kortus, K.; Kagan, H. B. *Tetrahedron: Asymmetry* **1993**, *4*, 2219; Hola, J.; Quirnbach, M.; Borner, A. *Synthesis* **1997**, 983; Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523.
- No reduction was observed with mandelic acid as the additive. The readiness of reaction between borane and hydroxyl group to form alkoxy borane species might account for the inactivity of mandelic acid as catalyst.
- For hydroboration of olefins, see: Brwon, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; John Wiley & Sons, 1975; Chapter 1. For reduction of esters and nitriles, see: Brwon, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.
- Preliminary experiment showed that treatment of the imine **2** with 1 equiv. of (D)-ditoluoyl tartaric acid (DTTA) in THF at 22°C, followed by 1 equiv. of borane at -60~-30°C, provided the amine **3** in 20% ee.



- General procedure for the reduction of imines by borane and phthalic acid.** The preparation of 4-(benzylamino-methyl)-benzonitrile (entry 6, Table 3) was described as an example. Phthalic acid (365.5 mg, 2.2 mmol) in 8 mL THF at 25°C. After cooling the solution to -78°C, BH<sub>3</sub>·THF (2.2 mL, 1 M in THF, 2.2 mmol) was added below -70°C or at the specified temperature. Reaction was stirred for 30 min and quenched with methanol (2 mL). It was then allowed to warm to room temperature. Isopropyl acetate (25 mL) was added and the reaction was washed with 1 M KOH (3×20 mL), water (2×25 mL) and dried. Solvents were evaporated in vacuo to give the secondary amines. The crude was purified by passing through a short pad of silica gel to give the amine as colorless oil (387 mg, 87% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.80 (br s, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 7.20–7.48 (m, 5H), 7.50 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.1 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 52.6, 53.2, 110.7, 119.1, 127.2, 128.2, 128.6, 128.7, 132.2, 139.9, 146.1; HRMS: calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub> (M+H) 223.1233, found 223.1235.
- 4-(Benzylamino-methyl)-benzoic acid methyl ester was prepared according to the general procedure in 92% yield as colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.70 (br s, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 7.25–7.40 (m, 5H), 7.50 (d, *J*=7.2 Hz, 2H), 8.0 (d, *J*=7.0 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 52.1, 52.8, 53.2, 126.4, 127.2, 128.1, 128.2, 128.5, 128.9, 129.8, 140.1, 145.8, 167.1; HRMS: calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub> (M+H) 256.1326, found 256.1337.
- Benzyl-(4-styryl-benzyl) amine was prepared according to the general procedure in 90% yield as colorless crystalline, mp 42–44°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.70 (br s, 1H), 3.80 (s, 4H), 7.1–7.6 (m, 16H), <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 52.9, 53.2, 126.6, 126.7, 127.1, 127.3, 127.6, 128.3, 128.4, 128.5, 128.6, 128.8, 136.1, 137.4, 139.9, 140.3; HRMS: calcd for C<sub>22</sub>H<sub>21</sub>N (M+H) 300.1749, found 300.1752.
- (1,3-Diphenyl-but-2-enyl)-phenylamine was prepared according to the general procedure by adding BH<sub>3</sub>·THF (3.85 mL, 1 M in THF, 3.85 mmol) to a pre-mixed solution of the imine (500 mg, 1.68 mmol) and phthalic acid (639 mg, 3.85 mmol) in 10 mL THF at below -25°C. Reaction completed in 6 min. The amine was obtained as a white solid (480 mg, 95% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.29–7.54 (m, 10H), 7.20 (t, *J*=7.5 Hz, 2H), 6.76 (t, *J*=7.3 Hz, 1H), 6.66 (d, *J*=7.6 Hz, 2H), 6.01 (dd, *J*=8.5 Hz, *J'*=1.2 Hz, 1H), 5.33 (dd, *J*=8.49 Hz, *J'*=8.43 Hz, 1H), 4.15 (d, *J*=4.15 Hz, 1H), 2.26 (d, *J*=1.3 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 147.56, 143.25, 142.76, 137.04, 130.52, 129.29, 128.93, 128.38, 127.45, 127.35, 126.87, 125.98, 117.73, 113.58, 57.10, 16.74; MS: 298.09 (M<sup>+</sup>-1).