Brønsted Acid Catalyzed Reductive Amination with Benzothiazoline as a Highly Efficient Hydrogen Donor

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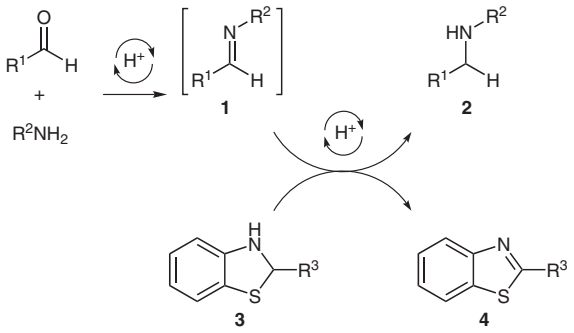
Abstract: Reductive amination of aldehyde and amine proceeded smoothly in the presence of benzothiazoline as efficient hydrogen source by means of 20 mol% trifluoroacetic acid to give the corresponding amines in excellent yields. Hydrogen-donor abilities of benzothiazoline, benzimidazoline, and benzoxazoline were compared.

Key words: reduction, reductive amination, benzothiazoline, transfer hydrogenation, phosphoric acid

The preparation of amines by constructing a novel carbon–nitrogen bond is one of the most fundamental synthetic methods. The reductive amination, in which carbonyl compounds and amines are treated with hydrogen source in the presence of catalyst, is an expedient method for the preparation of amines, enabling the rapid access to primary and secondary amines.[1–3] It has been successfully employed both in academia and industry. A biomimetic approach that relies on the utilization of a hydrogen source has been developed, inspired by naturally occurring hydrogenation processes. As the most prevalent analogue of NADH, Hantzsch esters[4,5] are efficiently employed in the reductive amination as well as reduction of imines under the catalysis of Lewis acid[6] and Brønsted acid.[7] A highly enantioselective version of the Brønsted acid catalyzed reductive amination has been reported lately.[8,9] Furthermore, Hantzsch ester has been broadly applied to other hydrogenation reactions.[10–12] One weakness of Hantzsch esters, however, is difficulties in the structural modification and/or introduction of additional substituents. Thus, the search for novel biomimetic hydrogen source remains to be elusive.

We focused on benzothiazolines, which have been recognized to be efficient antioxidants[13] with potent reducing ability,[14] and envisioned that they might be employed as hydrogen source in the Brønsted acid catalyzed reductive amination with concurrent generation of benzothiazole. Based on the consideration, we reported chiral phosphoric acid catalyzed enantioselective transfer hydrogenation of ketimines by use of benzothiazoline as a novel hydrogen donor.[15] We wish to report herein Brønsted acid catalyzed reductive amination using benzothiazoline as a hydrogen donor. The strategy is shown in Scheme 1. Exposure of aldehyde, amine, and benzothiazoline with acid catalyst, aldimine **1** is generated in situ and reduced by benzothiazoline to give amine **2**. Aromatization of benzothiazoline proceeded concurrently to give benzothiazole **4**. Brønsted acid worked twofold: generation of aldimine and transfer hydrogenation.



Scheme 1 Reductive amination with benzothiazoline

At the outset, we studied the reductive amination of *p*-nitrobenzaldehyde (**5a**) and *p*-anisidine (**6a**) with 1.2 equivalents of benzothiazoline **3a** as hydrogen source (Table 1). Although the reduction did not proceed in the absence of acid (Table 1, entry 1), the addition of Brønsted acid (10 mol%) promoted the reductive amination to give **2**. Biphenyl phosphoric acid (BPP), acetic acid, and *p*-toluenesulfonic acid were less efficient (Table 1, entries 2–4), whereas use of trifluoroacetic acid (TFA) significantly improved the chemical yield (Table 1, entry 5). Increasing the amount of TFA to 20 mol% furnished **2a** in an excellent yield (Table 1, entry 6). Further screening of solvents revealed that use of CH_2Cl_2 as a solvent furnished **2a** quantitatively (Table 1, entry 7). Moreover, increasing the concentration of **5a** to 0.2 M significantly accelerated the reaction (Table 1, entry 8).

We examined the scope of the reductive amination of aldehydes and amines under the optimal reaction conditions [**5** (0.2 M, 1.0 equiv), **6** (1.2 equiv), TFA (20 mol%), CH_2Cl_2, r.t.], and the results are shown in Table 2. A range of aromatic aldehydes, bearing electron-withdrawing, electron-donating, and steric groups proved to be suitable substrates (Table 2, entries 1–6). An aldimine derived from cinnamaldehyde exclusively underwent 1,2-reduction (Table 2, entry 7). In addition, heteroaromatic aldehyde and aliphatic aldehyde also gave **2** in good chemical yield by prolonging the reaction time (Table 2, entries 8

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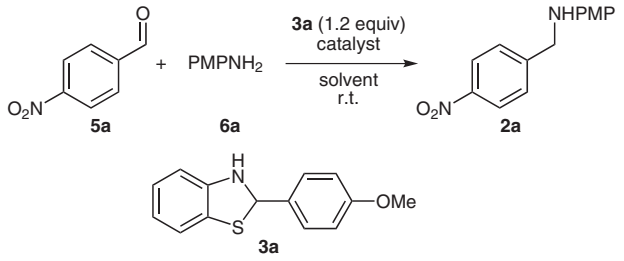
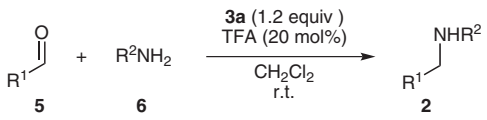
Table 1 Examination of Brønsted Acids and Solvents for the Reductive Amination



Entry[a]	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	–	toluene	20	0
2	BPP (10)	toluene	24	47
3	AcOH (10)	toluene	24	30
4	TsOH (10)	toluene	24	29
5	TFA (10)	toluene	24	70
6	TFA (20)	toluene	24	93
7	TFA (20)	CH_2Cl_2	14	99
8[c]	TFA (20)	CH_2Cl_2	5	99

[a] Reactions were performed with aldehyde **5a** and *p*-$MeOC_6H_4NH_2$ (1.2 equiv) at 0.07 M concentration.
[b] Isolated yield.
[c] Concentration was 0.2 M.

Table 2 Substrate Scope of the Reductive Amination



Entry[a]	R^1	R^2	Time (h)	Yield (%)[b]
1	Ph	PMP	5	93
2	2-naphthyl	PMP	4	91
3	4-$O_2NC_6H_4$	PMP	5	99
4	4-$MeOC_6H_4$	PMP	6	95
5	3-ClC_6H_4	PMP	5	90
6	4-ClC_6H_4	PMP	5	93
7	C_6H_5CH=CH	PMP	9	82
8	4-pyridyl	PMP	48	87
9	*c*-Hex	PMP	40	66
10	4-$O_2NC_6H_4$	Ph	14	87
11	4-$O_2NC_6H_4$	4-ClC_6H_4	15	84
12	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	24	77

[a] Reactions were performed with aldehyde **5** and amine **6** (1.2 equiv) at 0.2 M concentration.
[b] Isolated yield.

and 9). Other aniline derivatives also participated in the reductive amination,[16] giving the corresponding amines in good yields (Table 2, entries 10–12).

One of the advantages of benzothiazoline resides in its ease of tuning of the 2-substituents on the backbone of benzothiazoline. Thus, we investigated the effect of the 2-substituents on the reactivity in the reductive amination of **5a** and **6a** with **3a**, **3b**, and **3c** under the standard conditions, and the results are shown in Figure 1.[17] It was found that reductive amination proceeded smoothly even when benzothiazolines, bearing electron-rich or electron-deficient substituent, were employed to give **2a** in excellent yields with slight difference of reaction rate.

Because the 2-substituents on the benzothiazolines did not influence the reactivity in the reductive amination, we supposed a novel one-pot reduction process in which both benzothiazoline and imine were generated in situ to participate in the transfer hydrogenation. We tried the three-component reaction starting from aldehyde **5**, aniline **6**, and *ortho*-substituted aniline **7**, in which aldehyde **5** played two roles under the standard reaction conditions: CH_2Cl_2 as solvent and 20 mol% TFA as a catalyst (Table 3).

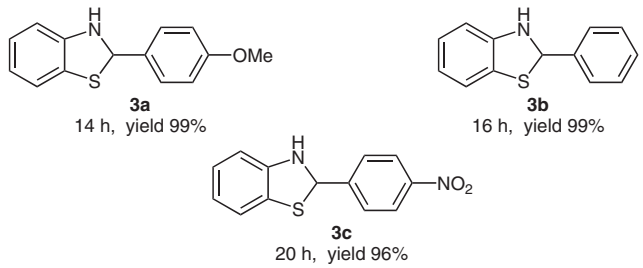
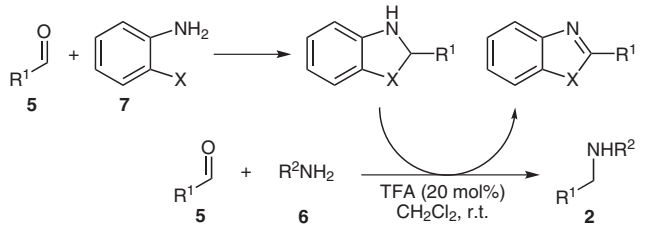


Figure 1 Comparison of the hydrogen donor ability

Initially, we examined different *ortho*-substituted anilines, which could be converted to the corresponding benzoxazoline, benzimidazoline, and benzothiazoline. While *o*-aminophenol and *o*-phenylenediamine did not give satisfactory results (Table 3, entries 1 and 2), *o*-aminothiophenol furnished **2** in an excellent yield (Table 3, entry 3). Benzothiazoline proved to be more efficient hydrogen donor in this reductive amination than other analogous heterocycles. Using *o*-aminothiophenol as the precursor of reducing agent, a variety of aromatic aldehydes were surveyed and furnished the corresponding amines **2** in high yields (Table 3, entries 4–8). It is noted that aliphatic aldehydes also gave the corresponding amines in good yields (Table 3, entry 9 and 10). Practicably, extending the one-pot approach to gramscale, the reaction proceeded smoothly without compromising the excellent chemical yield (Table 3, entry 11). These results clearly show the order of the reactivity to be as follows: benzothiazoline > benzimidazoline >> benzoxazoline (Figure 2). Because benzimidazolines automatically generate hydrogen to form benzimidazole on standing, benzothiazoline is the most efficient and useful hydrogen donor from a practical point of view.

Table 3 One-Pot Reductive Amination with Generation of Reducing Agents in situ



Entry[a]	X	R^1	R^2	Time (h)	Yield(%)[b]
1	OH	4-$O_2NC_6H_4$	PMP	24	trace
2	NH_2	4-$O_2NC_6H_4$	PMP	24	56
3	SH	4-$O_2NC_6H_4$	PMP	20	96
4	SH	4-$O_2NC_6H_4$	4-ClC_6H_4	15	99
5	SH	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	19	99
6	SH	Ph	PMP	17	97
7	SH	4-$O_2NC_6H_4$	PMP	19	86
8	SH	C_6H_5CH=CH	PMP	20	78
9	SH	*c*-Hex	PMP	22	83
10	SH	*i*-Pr	PMP	43	64
11[c]	SH	Ph	PMP	17	94

[a] The one-pot reactions were performed with aldehyde **5** (2.2 equiv), amine **6** (1.0 equiv), and **7** (1.2 equiv) at 0.2 M concentration.
[b] Isolated yield.
[c] Aldehyde **5** (2.33 g), amine **6** (1.23 g), and **7** (1.50 g) at 0.2 M concentration.

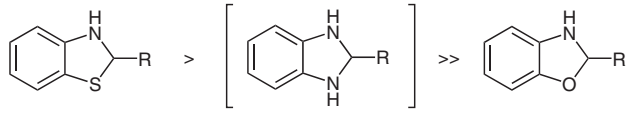


Figure 2 The order of reactivity of the hydrogen donor

In summary, we have described an efficient and novel approach of utilizing benzothiazolines as reducing agents for the reductive amination of aldehydes. A range of aldehydes, including aromatic aldehyde, heteroaromatic aldehyde, cinnamaldehyde, and aliphatic aldehyde, participated in the reductive amination to give the corresponding amines in high yields. Several functional groups such as nitro, halide survived under the mild conditions. Benzothiazoline possesses many advantages, including: 1) one-step or in situ preparation from inexpensive materials in excellent yield; 2) convenient structural modification. It is believed that the development of benzothiazolines would find wide applications also in asymmetric transfer hydrogenation.

Typical Experimental Procedure for the Reductive Amination
Under nitrogen, a mixture of aldehyde, amine (0.24 mmol), benzothiazole (0.24 mmol) in CH_2Cl_2 (1 mL), was added TFA (0.04 mmol). The reaction was stirred at r.t. until the aldehyde was consumed monitoring by TLC. The product was purified by flash column chromatography on SiO_2.

Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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