Thiourea Catalyzed Direct Reductive Amination of Aldehydes

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Abstract: A hydrogen bond catalyzed direct reductive amination of aldehydes is reported. The acid- and metal-free process uses thiourea as organocatalyst and the Hantzsch ester for transfer hydrogenation and allows the high-yielding synthesis of diverse amines.

Key words: amines, aminations, reductions, organocatalysis, hydrogen bonds

The reductive amination presents one of the most powerful and widely utilized methods for the synthesis of amines.[1] The versatile coupling reaction enables a rapid and general access to C-N bonds, a key structural feature in natural products and pharmaceuticals.[2] Particularly important are direct procedures, where the carbonyl component is treated in a 'one-pot' fashion with the amine and a reducing agent.[1,3] Known procedures to carry out this transformation rely on Brønsted and Lewis acids to facilitate the formation and selective reduction of the intermediate imines in the presence of the carbonyl.[1,3] However, application of these protocols to sensitive or polyfunctional substrates is limited, which renders the development of mild and acid-free protocols an important research goal.

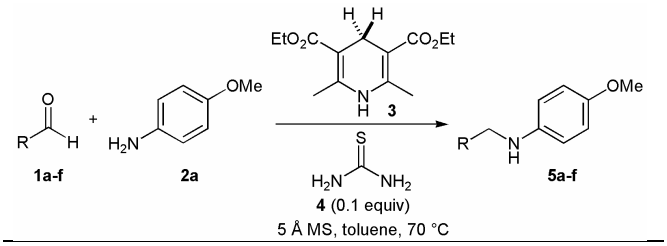
Herein, we report a novel method for the direct reductive amination of aldehydes which exclusively relies on hydrogen bond catalysis. The completely acid-free method utilizes thiourea as hydrogen bond donor and the Hantzsch ester as hydride source. The procedure is of broad applicability for the synthesis of diverse amines and characterized by a high degree of functional group tolerance.

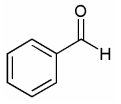
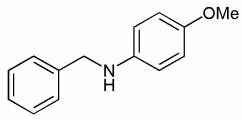
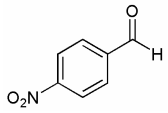
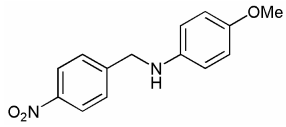
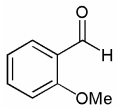
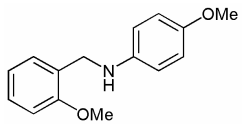
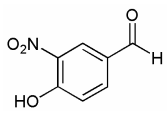
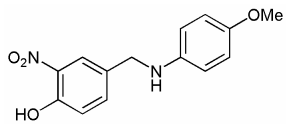
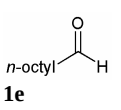
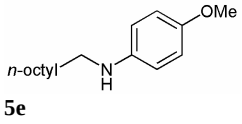
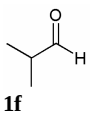
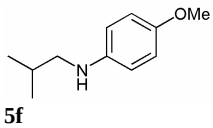
Biosynthetically, amines may be derived by reductive amination of carbonyls by NADH-dependent transferases or the vitamin B_6 pathway.[4] These pathways rely on hydrogen bonding to activate imines towards the hydride delivery. This prompted us to investigate, whether such hydrogen bonding may also be used for a related process in vitro.

In our biomimetic approach, the Hantzsch ester **3** (Table 1) was selected as a readily available mimic to the enzymatic dihydropyridine cofactors. It has been shown that the Hantzsch ester is not suitable for the direct reduction of imines.[5] However, this reduction proceeds smoothly in the presence of Lewis acids, such as $Mg^{(II)}$,[5] SiO_2,[6] Al_2O_3[6] or $Sc(OTf)_3$.[7] In the course of our studies, the groups of Rueping,[8] List[9] and MacMillan[10] have very recently reported that this imine-reduction by the Hantzsch ester may also be catalyzed by phosphoric acids.

To test our notion, whether such a biomimetic amination may also be accelerated by hydrogen bonds, we studied the reaction of benzaldehyde (**1a**, Table 1) with *p*-anisidine (**2a**) and the Hantzsch ester in the presence of non-acidic hydrogen bond donors. Best results were obtained with thiourea (**4**).[11] After optimizing reaction conditions,[12] the desired substituted amine **5a** was obtained in an essentially quantitative manner.[13] This reaction requires only catalytic amounts of the organocatalyst to proceed,[14] which suggests a selective complexation of thiourea to the imine in the

Table 1 Thiourea Catalyzed Direct Reductive Amination of Diverse Aldehydes



Entry	Aldehyde **1a-f**	Productamine **5a-f**	Yield (%)
1	 **1a**	 **5a**	93
2	 **1b**	 **5b**	93
3	 **1c**	 **5c**	93
4	 **1d**	 **5d**	73
5	 **1e**	 **5e**	82
6	 **1f**	 **5f**	83

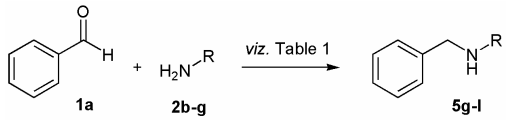
presence of free amine and aldehyde.[15] In addition, no reduction of the aldehyde was observed under the reaction conditions, which further corroborates a high degree of selectivity of the organocatalyst and adds to the efficiency of the protocol.

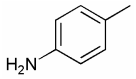
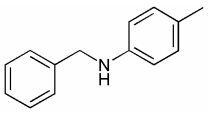
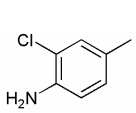
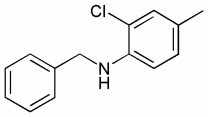
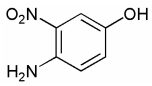
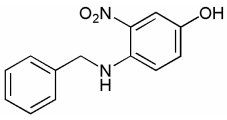
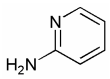
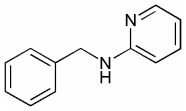
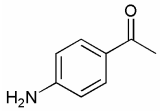
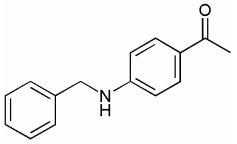
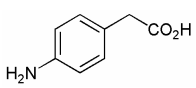
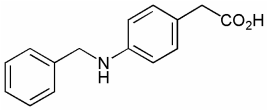
To evaluate the general applicability of this protocol, various aromatic (**1b-d**) and aliphatic (**1e-f**) aldehydes were submitted to the reaction conditions. In all cases, the desired product amines (**5b-f**) were obtained in high yields, without the need for further adaption of the reaction conditions for specific substrates.[16] Both electron-deficient (entry 2) as well as electron-rich aromatic aldehydes (entry 3) are readily aminated. No reduction of the nitro-group (entry 2) was observed and free hydroxyls are tolerated (entry 4). Aliphatic aldehydes react with the same effectiveness (entries 5 and 6), regardless whether they are linear (**1d**) and α-branched (**1e**).

As shown in Table 2, the method is also applicable to various aromatic and heterocyclic amines (**2b-g**) allowing an efficient access to the substituted products **5g-l** (Table 2).[16] A broad spectrum of electronically and sterically diverse amines is accepted. Furthermore, hydroxyls (entry 3), nitro groups (entry 3) as well as ketones (entry 5) and carboxylic acids (entry 6) are tolerated, demonstrating a high degree of functional group tolerance of our protocol.

In summary, we have developed an organocatalytic direct reductive amination of aldehydes which relies on hydrogen bonding for imine activation. A mild and operationally simple fragment coupling has been accomplished with a wide range of aldehydes in combination with aryl and heterocyclic amines. Expansion of the catalytic principle to related procedures is underway.

Table 2 Scope of Amines



Entry	Amine **2b-g**	Productamine **5g-l**	Yield (%)
1	 **2b**	 **5g**	93
2	 **2c**	 **5h**	73
3	 **2d**	 **5i**	68
4	 **2e**	 **5j**	91
5	 **2f**	 **5k**	72
6	 **2g**	 **5l**	75

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References and Notes

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(12) (a) Benzene and dichloromethane are as suitable as toluene, while more polar solvents such as dioxane or THF are less efficient. Protic solvents (e.g. MeOH) are of limited applicability. (b) Upon extended reaction times, the transformation may also be carried out at r.t.

(13) **General Procedure**: A solution of the aldehyde (**1a-f**, 2.20 mmol) and the amine (**2a-g**, 2.00 mmol) in toluene (5 mL) is treated with the Hantzsch ester (**3**, 608 mg, 2.40 mmol), thiourea (**4**, 15.2 mg, 0.200 mmol) and MS 5 Å (2.0 g) and the mixture is stirred 24 h at 70 °C under nitrogen. After filtration over celite, the solvent is evaporated and the residue purified by flash chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluants to give the product amines (**5a-l**) in pure form.

(14) (a) The catalysts loading may be reduced to 1 mol% upon extended reaction times (> 48 h). (b) Under the same reaction conditions but in the absence of thiourea, the product amine is only obtained in low yields proving the vital influence of the organocatalyst.

(15) This assumption is supported by previous calculations on related thiourea complexes with aldimines and amines: Vachal, P.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

(16) All new compounds had spectroscopic data in support of the assigned structures, e.g.:
5d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 4.27 (s, 2H), 6.56 (d, *J* = 9.04 Hz, 2H), 6.76 (d, *J* = 9.04 Hz, 2H), 7.12 (d, *J* = 8.48 Hz, 1H), 7.60 (d, *J* = 10.74 Hz, 1H) 8.10 (d, *J*= 2.26 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 47.95, 55.80, 114.37, 115.02, 120.26, 123.37, 132.45, 133.56, 136.76, 141.58, 152.66, 154.27. HRMS (ESI): *m*/*z*:calcd for $C_{14}H_{15}N_2O_4$ $[M+H]^+$: 275,1032. Found: 275,1034.
5k: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.54 (s, 3H), 4.21 (s, 1H), 4.37 (s, 2H), 6.71 (d, *J* = 4.14 Hz, 2H), 6.82 (d, *J* = 3.96 Hz 2H), 7.26-7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.73, 48.31, 111.82, 118.01, 127.55, 128.77, 129.40, 138.27, 139.89, 148.29, 198.57. HRMS (ESI): *m*/*z*:calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226,1232. Found: 226,1233.
5l: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.52 (s, 2H), 4.31 (s, 2H), 6.60 (d, *J* = 8.65 Hz, 2H), 7.07 (d, *J* = 8.65 Hz, 2H), 7.26–7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.00, 48.47, 113.12, 122.18, 127.54, 128.69, 130.24, 139.24, 139.35, 147.43, 176.85. HRMS (ESI): *m*/*z*:calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242,1181. Found: 242,1178.

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