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Hydrogen Bond Catalyzed Direct Reductive Amination of Ketones

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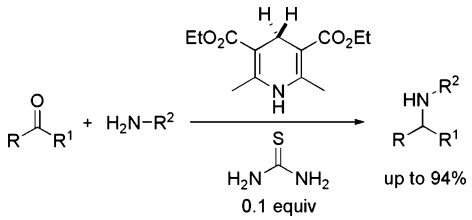
ABSTRACT



A novel, biomimetic concept for the direct reductive amination of ketones is described that relies on selective imine activation by hydrogen bond formation. The mild, acid- and metal-free process requires only catalytic amounts of thiourea as hydrogen bond donor and utilizes the Hantzsch ester for transfer hydrogenation. The method allows the efficient synthesis of structurally diverse amines.

Chiral amines are key structural elements in a multitude of biologically active natural products and pharmaceuticals rendering their synthesis an objective of high priority from the perspective of medicinal chemistry and organic synthesis.[1] Reductive amination of ketones, in which a mixture of a carbonyl compound and an amine is treated with a reductant in a "one-pot" fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds; thus, a number of methods have been developed to carry out this direct process.[2,3] Known methods such as the authentic procedure of Borch [$NaBH_3CN$, pH 3−4][4] rely on Brønsted and Lewis acids to facilitate formation of the intermediate imines and to activate these C═N intermediates for a preferential reduction in the presence of the carbonyl compound.[2−4]

Nevertheless, application of these protocols to sensitive, acid-labile or polyfunctional substrates is limited. Furthermore, many of these procedures seem not to be adaptable to asymmetric variants.[2d,5] This renders the development of novel catalytic concepts for a mild direct reductive amination a very important research goal.

Herein, we report the first direct reductive amination of ketones, which exclusively relies on hydrogen bonding for imine activation. This completely acid-free reaction is mediated by catalytic amounts of thiourea as a simple and readily modifiable organocatalyst and uses the Hantzsch ester for transfer hydrogenation. The general applicability of the method for the synthesis of a wide variety of diverse amines is demonstrated and the mechanistic background is studied.

(1) (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* 1999, *1*, 55. (b) Henkel, T.; Brunne, R. M.; Mueller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.

(2) For reviews, see: (a) Martens, J. *Methods of Organic Chemistry* (*Houben-Weyl*); G. Thieme: New York, 1995; Vol. E21d, p 4199. (b) Baxter, E. W.; Reitz, A. B. *Organic Reactions*; Wiley: New York, 2002; Vol. 59, p 1. (c) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037. (d) Tararov, V. I. Kadyrov, R.; Riermeier, T. H.; Fischer, C.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 561.

(3) More recent examples are described in the following: (a) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745. (b) Allegretti, M.; Berdini, V.; Candida Cesra, M.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257. (c) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055. (d) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. (e) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649.

(4) (a) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(5) (a) Blaser, H.-U.; Buser, H.-P.; Jalett, H. P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867. (b) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227. (c) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

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Living organisms employ organic dihydropyridine cofactors such as nicotinamide adenine dinucleotide (NADH, **1**, Figure 1) in combination with enzyme catalysts for the direct reductive amination of ketones.[6] A salient feature of this and the related vitamine B6 mediated amination is the activation of the imine nitrogen by hydrogen bonds, as schematically shown in **2**. To mimic key features of this biosynthetic pathway, assembly **3**/**4** was selected as a surrogate. Thus, in a similar fashion, a dihydropyridine unit would act as a reducing agent by hydride transfer and the imine should be activated by intermolecular hydrogen bonding (viz. **4**). The "Hantzsch ester" **3** was selected as a readily available replacement for NADH (**1**).

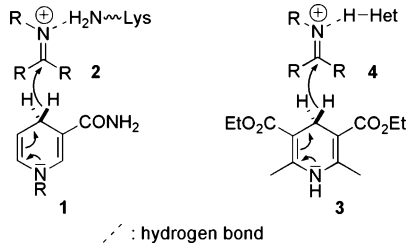
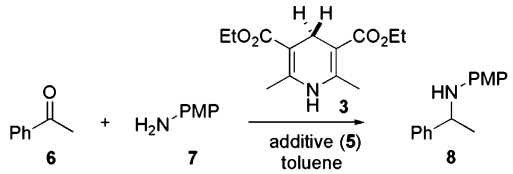


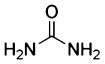
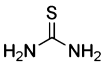
Figure 1. Delineation of a biomimetic concept.

While limited precedence in the literature has shown imines to be reduced by **3**, these reactions typically proceed in low yield and require extended reaction times. Lewis acid activation [$Mg^{(II)}$,[7a] SiO_2,[7b] Al_2O_3,[7b] and $Sc(OTf)_3$[7c]] of the imine significantly improves this result. Completely independent from our approach, the groups of Rueping[8] and List[9] have very recently reported on the organocatalytic, asymmetric hydrogenation of imines by **3** in the presence of chiral Brønsted acids. These procedures have not been adapted to a direct reductive amination.

To test our notion, whether a biomimetic H-bonding activation may be used to accelerate this process in vitro and in particular whether such an approach may be used for a direct process, the reductive amination of acetophenone (**6**) with equimolar amounts of *p*-anisidine (**7**)[10] and the Hantzsch ester was studied in the presence of mono- and bidentate hydrogen bond donors (Table 1). While under a variety of reaction conditions (solvent, temperature), no transformation to **8** was observed (entry 1), equimolar amounts of urea (**5a**, entry 2) and thiourea (**5b**, entry 3)[11,12] proved to be promising additives giving amine **8** as the main product. After optimizing conditions (number of equivalents, solvent,[13] temperature, drying agent, time), this reaction proceeded essentially quantitatively (entry 4).

Table 1. Development of the Hydrogen Bond Catalyzed Direct Reductive Amination



entry	additive **5**	**5** (equiv)	conditions	yield **8** [%]
1	-	-	rt, 4 Å MS, 24 h, 1 equiv **3**	< 5
2	 **5a**	1	rt, 4 Å MS, 24 h, 1 equiv **3**	36
3	 **5b**	1	rt, 4 Å MS, 24 h, 1 equiv **3**	45
4	**5b**	1	50 °C, 5 Å MS, 48 h, 1.5 equiv **3**	92
5	**5b**	0.5	50 °C, 5 Å MS, 48 h, 1.5 equiv **3**	83
6	**5b**	0.1	50 °C, 5 Å MS, 48 h, 1.5 equiv **3**	88
7	**5b**	-	50 °C, 5 Å MS, 48 h, 1.5 equiv **3**	< 5

With the same efficiency, this transformation may also be carried out with only catalytic quantities of thiourea.[14] Notably, the amount of additive appears to have no significant influence on the reaction rate (entries 5 and 6) indicating that **5b** is not participating in the rate determining step. Under the same reaction conditions but without thiourea, no formation of **8** was observed (entry 7), proving the crucial influence of **5b** as organocatalyst. This observation together with the finding that the corresponding, separately prepared ketimine (not shown) is only reduced in the presence of thiourea and no reduction of the ketone was observed under these conditions suggest a high selectivity of thiourea for imine activation. Notably, this one-pot process appears to

(6) (a) John, R. O. In *Comprehensive Biological Catalysis*; Sinnot, M., Ed.; Academic Press: London, UK, 1998; Vol. 2, p 173. (b) Silverman, R. B. *The Organic Chemistry of Enzyme-Catalyzed Reactions*; Academic Press: London, UK, 2002; p 428.

(7) (a) Steevens, J. B.; Pandit, U.K. *Tetrahedron* **1983**, *39*, 1395. (b) Fujii, M.; Aida, T.; Yoshihara, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3845. (c) Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105.

(8) Rueping, M.; Sugioni, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.

(9) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 47424.

(10) The PMP group is readily cleaved under oxidative conditions (CAN).

(11) For a review and more recent examples on the use of urea and analogues in organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2005. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (c) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. (d) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807.

(12) The higher yield with thiourea in comparison to **5a** may be rationalized by the stronger hydrogen bonds the former may form.

(13) Similar yields are obatined in benzene and dichloromethane, while ethyl acetate, THF, MeOH, and CH_3CN are less suitable.

(14) The amount of thiourea may be reduced to 3 mol % with only slight decrease in the chemical yield.

be the first nucleophilic amination process of carbonyls in general catalyzed by selective hydrogen bonding.[11a]

We then studied the general applicability of this procedure for the synthesis of sterically, electronically, and functionally diverse amines (**9**−**22**, Figure 2). In addition to *p*-anisidine (**7**, formation of **8**), also electron less rich and thus less reactive amines add with the same efficiency (formation of **9**−**11**). Electron deficient or hindered anilines are transformed with preparatively useful yields to give **12** and **13**. Both aromatic (**8**−**10**, **12**, **13**) and aliphatic ketones (**11**, **14**−**17**) are accepted as substrates allowing a direct and high-yielding access to substituted amines such as **8**−**17**. Moreover, this protocol is applicable to the preparation of substituted heteroaromatic amines, such as furans (**18**), thiophenes (**19**), or pyridines (**20**).[15] The broad applicability and chemoselectivity of our method is further demonstrated in the synthesis of amines **21** and **22**. In comparison to related, nondirect approaches, this tolerance of double bonds and free acids is noteworthy.[8,9]

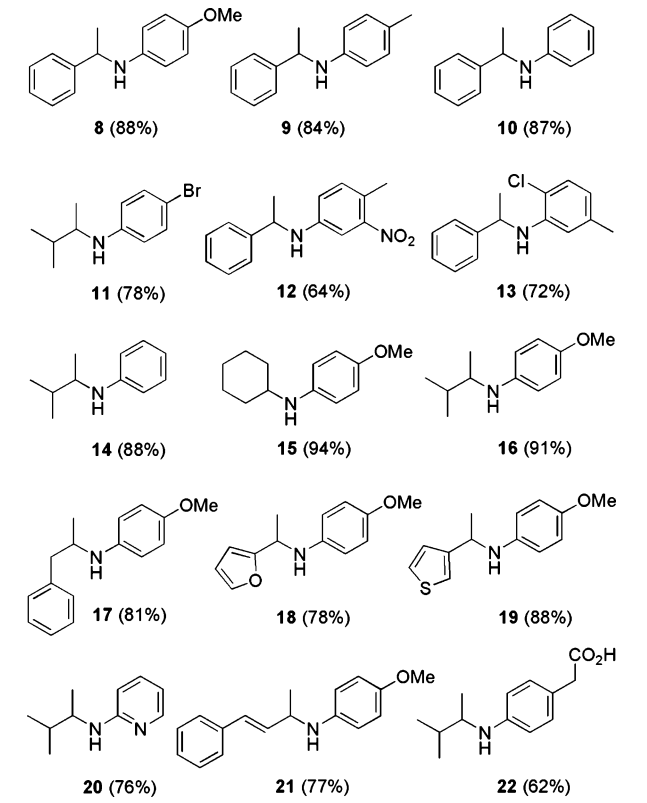


Figure 2. Scope of the hydrogen bond catalyzed reaction for the synthesis of diverse amines with the indicated yields.

Mechanistically, we assume that this reaction proceeds by the pathway shown in Figure 3. The first steps should involve an equilibrium of ketone **24** and amine **23** with ketimine **25**, which might be rate determining. Imine **25** is not reduced under the reaction conditions. It is only after hydrogen bond activation by thiourea (**5b**) to give intermediate **26** that the C═N moiety may be hydrogenated by the Hantzsch ester (**3**) to produce amine adduct **28**. For the catalytic cycle to proceed, a transfer of thiourea from **28** to **25** is required to give again complex **26** with concomitant liberation of the product amine **29**.

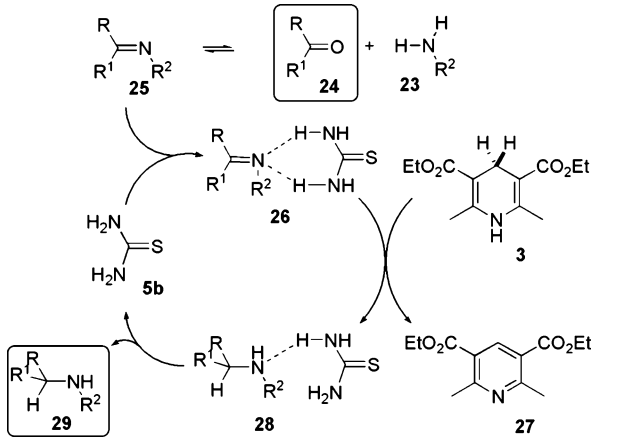


Figure 3. Proposed mechanism of the hydrogen bond catalyzed direct reductive amination.

This mechanistic proposal is supported by ab initio calculations (Gaussian 98, B3LYP: 6-31G* basis set)[16] of thiourea complexes of acetone (**24**, $R^1 = R^2 = Me$), methylisopropylamine (**29**, $R^1 = R^2 = Me$), and the respective ketimine (**25**, $R^1 = R^2 = Me$), which suggest that the interactions with the imine (8.2 kcal/mol) are stronger in comparison to the ones with the amine (4.3 kcal/mol) and the ketone (6.1 kcal/mol).[17,18]

In summary, based on a novel biomimetic approach, we have developed the first hydrogen bond catalyzed direct reductive amination of ketones, which allows the convergent and efficient synthesis of diverse amines. The mild and

(15) For complete conversion the reaction was stirred in this special case 24 h at 50 °C and 48 h at 85 °C.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(17) The calculations suggest that thiourea forms two hydrogen bonds to the ketimine and acetone, while only one such bond is formed to methylisopropylamine. The formation of two hydrogen bonds to the imine as depicted in **26** and only one such bond to the respective amine as presented in **28** is in agreement with related calculations on aldimines and amines by the group of Jacobsen.[18] Calculated bond lengths for the crucial hydrogen bonds of **26**, with $R^1 = R^2 = Me$ are 2.01 and 2.04 Å. NMR spectroscopic experiments of **5b** in [D_6]benzene support these calculations by showing downfield shifts of the thiourea N−H hydrogen atoms upon addition of separately prepared imine.

(18) Comparable calculations with aldimines and amines, however, without consideration of the carbonyls, are described by: Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

nonacidic conditions together with the high chemoselectivity of this protocol should enable applications to complex or acid-sensitive substrates. Furthermore, the underlying catalytic cycle and the modular structure of the organocatalyst should allow the development of asymmetric variants[19] and adaption of our approach also to other direct procedures with imines as reaction intermediates.

(19) Preliminary results show that thiourea derivatives with chiral, electron-withdrawing substituents on the nitrogens are particularly promising for such an endeavor.

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Supporting Information Available: Experimental details, spectral data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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