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Cleaving Amines by Water

Direct Deamination of Primary Amines by Water To Produce Alcohols**

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Chemical transformations involving primary amines are of great importance in biology and chemistry because the amino functionality is present in the vast majority of biomolecules, pharmaceuticals, and chemical precursors used in the manufacture of dyes and polymers.[1] Various methods for the preparation of primary amines by amination of alcohols, aldehydes, or halogenated hydrocarbons have been introduced in organic chemistry.[1,2] At the same time, the reverse reaction, a simple formal substitution of the amino group with a different nucleophile remains a challenging transformation.[3] For example, the deceivingly simple, direct conversion of aliphatic amines to alcohols using water as the only reagent [Eq. (1)] is exceedingly rare.[4,5] The only reported example of

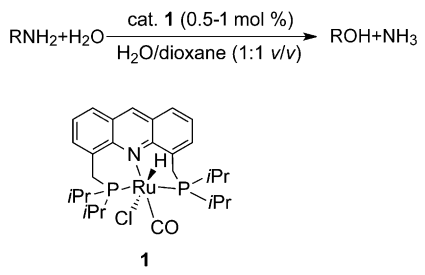
$$RNH_2 + H_2O \rightarrow ROH + NH_3 \quad (1)$$

direct conversion of amines to alcohols uses excess KOH and harsh conditions (210 °C in diethyleneglycol).[4,5]

A simple S_N2-type displacement is not favorable for the reaction in Equation (1) as NH_3 is a poor leaving group, while an S_N1 displacement requires strongly acidic conditions and is typically low yielding and non-selective.[3] The classical method for selective aliphatic deamination involves oxidation of amines with HNO_2 to form unstable diazonium salts, which can be then reacted with various nucleophiles, the reaction being driven by the release of N_2.[3,6] Owing to the low stability of diazonium salts and the formation of a carbocation intermediate, such reactions typically show low selectivity.[3,6] The oxidative deamination of amines to aldehydes or ketones requires stoichiometric amounts of strong oxidants, such as permanganate, dichromate, or others,[7] which are incompatible with the reductive conditions needed for the subsequent hydrogenation of carbonyls to alcohols.

While enzymatic oxidative deamination of aliphatic amines to generate aldehydes and ketones is a common transformation involved in the metabolism of amino acids[8] and neurotransmitters,[9] examples of biocatalytic conversion of amines to alcohols are more complex and involve a series of reactions catalyzed by several different enzymes in the presence of oxidizing and reducing equivalents.[9,10] For example, metabolic degradation of dopamine and norepinephrine involves the initial conversion of a primary amine to an aldehyde by a monoamine oxidase, followed by the reduction of an aldehyde to an alcohol by aldehyde reductase and NADPH in one of the metabolic pathways, or oxidized to a carboxylic acid in another pathway.[9]

We have previously reported selective amination of primary alcohols to form primary amines under NH_3 pressure catalyzed by (the now commercially available) acridine-based pincer complex (AcrPNP)RuH(CO)Cl (**1**).[11a] Reported herein is the reverse reaction, deamination of aliphatic amines to alcohols by water catalyzed by **1** (Scheme 1). This



1

Scheme 1. Deamination of amines catalyzed by **1**.

reaction occurs by way of a reversible dehydrogenation/hydrogenation sequence, and the formation of a hemiaminal is proposed as a key intermediate leading to the release of ammonia. Overall, the system described herein effectively mimics the function of natural enzymes in deamination reactions, while using the same catalyst for both dehydrogenation and alcohol formation; it uses water as the only reagent, with no added bases, oxidants, or reductants, thus establishing a green method of direct deamination of aliphatic amines in water.

During the course of investigation of the reactivity of amines with water in the presence of Ru pincer complexes, we found that heating an amine solution in water or water/dioxane mixture in the presence of catalytic amounts of **1** leads to the formation of alcohol as the major product (Table 1). While the reaction can be performed in water alone, the conversions are typically low owing to the low solubility of the catalyst and substrates in water (for example, Table 1, entry 1). Therefore, a dioxane/water mixture (1:1 *v*/*v*) was used for further experiments to ensure complete solubility of all the reaction components. The products were analyzed by GC–MS and NMR spectroscopy and identified by comparison with authentic samples. Control experiments

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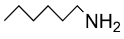
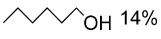
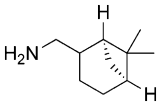
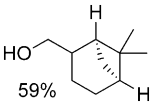
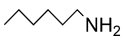
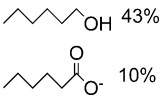
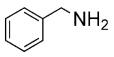
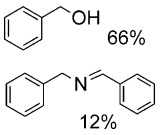
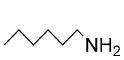
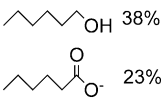
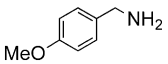
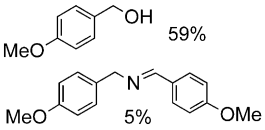
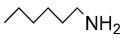
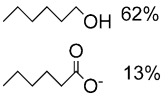
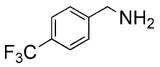
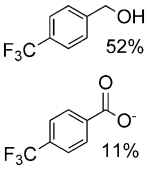
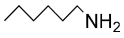
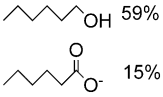
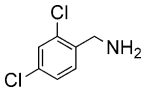
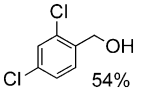
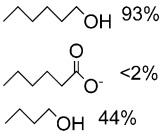
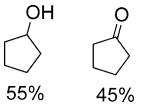
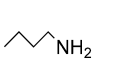
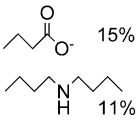
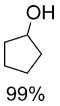
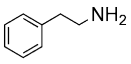
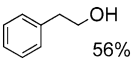
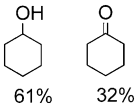
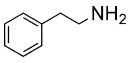
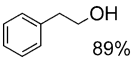
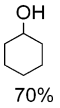
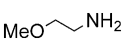
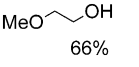
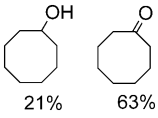
Table 1: Deamination of primary amines catalyzed by **1**.

Entry	Substrate	*t* [h]	Conv. [%][d]	Product [% yield][d]	Entry	Substrate	*t* [h]	Conv. [%][d]	Product [% yield][d]
1[a,c]		24	18	 14%	12[a,g]		48	>99[h]	 59%
2[b]		24	58	 43% 10%	13[b]		24	90	 66% 12%
3[b]		72	64	 38% 23%	14[a]		48	82	 59% 5%
4[a]		24	78	 62% 13%	15[a]		48	69	 52% 11%
5[a]		48	78	 59% 15%	16[a]		48	55	 54%
6[a,e]		48	96	 93% <2% 44%	17[a,g]		48	>99	 55% 45%
7[a]		48	81	 15% 11%	18[a,e,g]		48	≥99	 99%
8[a]		24	66	 56%	19[a,g]		48	>99	 61% 32%
9[a,e]		48	89	 89%	20[a,e,g]		48	71	 70%
10[a]		48	71	 66%	21[a,f]		48	>99	 21% 63%
11[a,f]		48	80	62%					

[a] Substrate (1 mmol), **1** (0.01 mmol), H_2O (3 mL), and dioxane (3 mL) were heated in a closed system at 135 °C or [b] in an open system at reflux at 100 °C under Ar flow. [c] In neat water. [d] Conversion and product yields were determined by GC or NMR spectroscopy and shown as an average of 2–3 runs. [e] Under H_2 (5 bars). [f] 4 mol % **1**; yield of the isolated product. [g] 0.5 mol % **1**. [h] The side product is likely di-*cis*-myrtanylamine (18 %) based on GC–MS and ESI-MS.

showed that no reaction took place under these conditions in the absence of the catalyst.

Thus, a *n*-hexylamine solution was heated to reflux under a N_2 atmosphere in a degassed water/dioxane mixture in the presence of **1** (1 mol %) at 100 °C. This resulted in deamination to form *n*-hexanol as the major product in 43 % yield after 24 h (Table 1, entry 2). Interestingly, another product of the reaction obtained under these conditions was identified as a hexanoate salt based on NMR spectroscopy and mass spectrometry. This salt likely forms through dehydrogenation of hexanol under anaerobic conditions, while NH_4^+ and/or hexylammonium serve as a counter cation. In accordance with this result, we recently showed dehydrogenation of primary alcohols in strongly basic aqueous solutions under anaerobic

conditions to form carboxylate salts catalyzed by a bipyridyl-based pincer Ru complex.[12] Longer reflux times resulted in a decrease of the yield of hexanol and an increase of the yield of the hexanoate salt at higher conversions of amine (entry 3). To prevent dehydrogenation of alcohol product to hexanoate, the reaction of hexylamine in water/dioxane was performed in a closed system at 135 °C. After 24 hours, hexanol was formed more selectively, in 62 % yield and 80 % overall selectivity (entry 4). However, at longer reaction times the amine conversion slowed down, while the yield of hexanol slightly decreased owing to the irreversible formation of carboxylate (entry 5). To stabilize the alcohol product against dehydrogenative oxidation to carboxylate, the reaction was performed under H_2 (5 bars) leading to the selective formation of hexanol in 93 % yield (entry 6). Overall, although H_2 is not required by the reaction, deamination under an atmosphere of H_2 improved the reaction by increasing the selectivity and the yield of the desired alcohol product and also suppressed the formation of carboxylates.

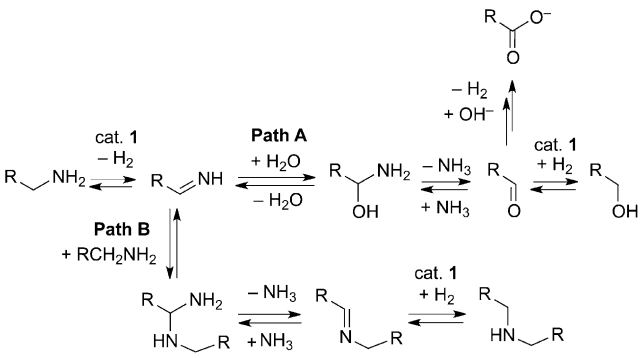
Similarly, heating solutions of phenethylamine, 2-methoxyethylamine, tryptamine, *cis*-myrtanylamine, and benzylamine in water/dioxane in a closed system resulted in formation of the corresponding alcohol product in 56–66 % yield (entries 8, 10–13). Substituted benzylamines with electron-donating and electron-withdrawing substituents were well-tolerated under the reaction conditions (entries 14–16). Substrates that can act as chelating ligands, such as ethylenediamine, diethylenetriamine, 2-(aminomethyl)pyridine, and the Na salt of phenylalanine, were not reactive towards deamination, likely owing to strong coordination to the metal center, while furfurylamine underwent non-selective reactions to give a mixture of products. Deamination of allylamine generated *n*-propanol in 17 % yield, which indicated the hydrogenation a C=C bond under these conditions.

Deamination of phenethylamine under H_2 (5 bars) lead to the more selective formation of phenethyl alcohol in 89 % yield (entry 9). The deamination of tryptamine and phenethylamine resembles the metabolism of these and analogous substrates in biological systems.[9,10]

By analogy with the reported reactivity of complex **1** in alcohol amination by NH_3,[11a] the deamination reaction likely proceeds by way of an initial dehydrogenation of the primary amine to an imine and H_2 (Scheme 2). The imine then undergoes a nucleophilic attack by water to form a hemiaminal intermediate, from which ammonia can be liberated to produce an aldehyde. Eventually, the resulting aldehyde intermediate is reduced to an alcohol using an H_2 molecule from the imine formation.

Interestingly, formation of dialkylamines (Path B in Scheme 2)[11a] is only a minor side reaction, and dihexylamine is formed in less than 4 % yield from hexylamine. Therefore, water successfully competes as a nucleophile with both the primary amine and NH_3 under the conditions of this reaction (Path A versus Path B in Scheme 2).

In accordance with the proposed mechanism, the presence of a β-hydrogen atom is necessary for deamination; no reactivity was observed in the reaction of *t*BuNH$_2$ under analogous conditions. Deamination of cycloalkylamines gave a complete conversion after 48 hours, with a mixture of



Scheme 2. Proposed mechanisms of deamination.

ketone and alcohol products (Table 1, entries 17, 19, and 21). Although oxidation of cycloalkylamines to ketones has been reported, it typically requires the use of a stoichiometric amount of oxidant.[7,13] Examples of amine-to-ketone transformations in the absence of oxidants are exceedingly rare.[14] The cycloalkyl alcohol products were obtained with high selectivity in good yields when the reaction was carried out under H_2 pressure (entries 18 and 20).

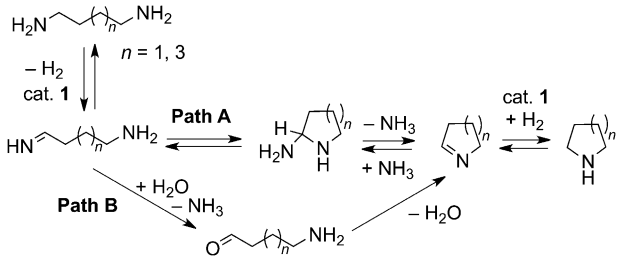
This deamination reaction can be used for facile and selective, entropy-driven cyclization of diamines to cyclic secondary amines at 100 °C in water/dioxane with 70–88 % yield (Table 2, entries 1–4). Although such catalytic reactivity is not unique, it typically requires harsh conditions: high temperatures (150–180 °C) and/or the presence of a reductant.[15]

Table 2: Cyclization of diamines catalyzed by **1**.

Entry	Substrate	*t* [h]	Conv. [%][c]	Product [% yield][c]
1[a]	H_2N⌇⌇NH_2	22	88	NH 88%
2[b]	H_2N⌇⌇NH_2	22	78	NH 77%
3[a]	H_2N–$(CH_2)_6$–NH_2	23	88	NH 63% HO–$(CH_2)_6$–NH_2 22%
4[a]	H_2N–$(CH_2)_6$–NH_2	40	93	NH 70% HO–$(CH_2)_6$–NH_2 10%

[a] Substrate (1 mmol), **1** (0.01 mmol), H_2O (3 mL), and dioxane (3 mL) were heated in a closed system at 100 °C or [b] in an open system at reflux at 100 °C. [c] Conversion and product yields were determined by NMR spectroscopy or GC and shown as an average of 2–3 runs.

The mechanism for the cyclic imine formation likely occurs by way of dehydrogenation of one of the amino functional groups (catalyzed by **1**) followed by the entropy-driven intramolecular attack of another amine group (Path A, Scheme 3) or via the formation of an aldehyde intermediate (Path B, Scheme 3).



Scheme 3. Proposed mechanisms of cyclic amine formation.

Following an analogy with the enzymatic deaminations, formation of pyrrolidine is functionally analogous to the synthetic route used in the biosynthesis of proline through the cyclodeamination of L-ornithine mediated by NAD^+/NADH.[16] Overall, the deamination mediated by complex **1** and described herein functionally resembles the deamination observed in enzymatic reactions, whereas the reversible liberation and addition of dihydrogen serves as an analogue of the $NAD(P)^+$/NAD(P)H mediated redox transformations. We previously demonstrated that the reactivity of complex **1** with H_2 in the presence of a base involves hydride transfer to the C(9)-position of an acridine,[11c] and our future efforts will be directed toward elucidation of the effect of metal-ligand cooperation in these transformations.

In summary, we have achieved direct conversion of primary amines to primary alcohols [Eq. (1)] using water, catalyzed by complex **1**, in the absence of added oxidants, reductants, or bases. While the enzymatic conversion of amines to alcohols is a multistep process involving several different enzymes and requiring the presence of reducing and oxidizing equivalents, a one-step deamination to alcohols in water using a relatively simple low molecular weight catalyst **1** is novel. The unique reversible reactivity of the acridine-based pincer complex **1** for the amination of alcohols and deamination of amines is due to its ability to mediate both dehydrogenation of amines and alcohols as well as hydrogenation of imines and aldehydes within the same system.[11a,b] The major side reaction observed in this system is an irreversible dehydrogenative oxidation to carboxylates, which can be suppressed by carrying out the reaction in the presence of H_2. We hope that if optimized for each particular application, the catalytic reaction described herein could find use in the synthesis of various primary alcohols,[4,17] the preparation of isotopically labeled compounds,[18] and the treatment of amine-containing waste water.[19]

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[1] S. A. Lawrence, *Amines: Synthesis Properties and Applications*, Cambridge University Press, Oxford, **2004**.
[2] a) M. J. Pouy, L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11312; b) S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 8303; *Angew. Chem. Int. Ed.* **2010**, *49*, 8126; c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 4705; d) C. Gunanathan, M. Hölscher, W. Leitner, *Eur. J. Inorg. Chem.* **2011**, 3381; e) K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima, *Angew. Chem.* **2012**, *124*, 154; *Angew. Chem. Int. Ed.* **2012**, *51*, 150; f) P. A. Dub, T. Ikariya, *ACS Catal.* **2012**, *2*, 1718.
[3] R. J. Baumgarten, *J. Chem. Educ.* **1966**, *43*, 398.
[4] a) S. M. A. Rahman, H. Ohno, N. Maezaki, C. Iwata, T. Tanaka, *Org. Lett.* **2000**, *2*, 2893; b) S. M. A. Rahman, H. Ohno, T. Murata, H. Yoshino, N. Satoh, K. Murakami, D. Patra, C. Iwata, N. Maezaki, T. Tanaka, *J. Org. Chem.* **2001**, *66*, 4831; c) S. M. A. Rahman, H. Ohno, T. Tanaka, *Tetrahedron Lett.* **2001**, *42*, 8007.
[5] In the previously reported direct conversion of amines to alcohols using KOH in diethylene glycol at 210 °C (Ref. [4c]), the H/D exchange experiments suggested possible participation of the solvent in the redox reaction.
[6] a) M. P. Doyle, R. J. Bosch, P. G. Seites, *J. Org. Chem.* **1978**, *43*, 4120; b) I. Shin, M.-r. Lee, J. Lee, M. Jung, W. Lee, J. Yoon, *J. Org. Chem.* **2000**, *65*, 7667; c) S. Deechongkit, S.-L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 497; d) T. Cupido, J. Spengler, K. Burger, F. Albericio, *Tetrahedron Lett.* **2005**, *46*, 6733.
[7] a) W. E. Bachmann, M. P. Cava, A. S. Dreiding, *J. Am. Chem. Soc.* **1954**, *76*, 5554; b) S. S. Rawalay, H. Shechter, *J. Org. Chem.* **1967**, *32*, 3129; c) R. M. Moriarty, R. K. Vaid, M. P. Duncan, M. Ochiai, M. Inenaga, Y. Nagao, *Tetrahedron Lett.* **1988**, *29*, 6913; d) N. A. Noureldin, J. W. Bellegarde, *Synthesis* **1999**, 939; e) M. Largeron, M.-B. Fleury, *J. Org. Chem.* **2000**, *65*, 8874; f) D. C. Barman, P. Saikia, D. Prajapati, J. S. Sandhu, *Synth. Commun.* **2002**, *32*, 3407; g) S. Sobhani, S. Aryanejad, M. F. Maleki, *Helv. Chim. Acta* **2012**, *95*, 613.
[8] D. A. Bender, *Amino Acid Metabolism*, 3rd ed., Wiley, Hoboken, **2012**.
[9] a) J. D. Elsworth, R. H. Roth, *Exp. Neurol.* **1997**, *144*, 4; b) A. A. Boulton, G. Eisenhofer, *Adv. Pharmacol.* **1998**, *42*, 273.
[10] a) E. A. Borman, N. M. Ol'gina, K. A. Koshcheenko, I. B. Romanova, *Prikl. Biokhim. Mikrobiol.* **1979**, *15*, 240; b) A.-M. Yu, C. P. Granvil, R. L. Haining, K. W. Krausz, J. Corchero, A. Küpfer, J. R. Idle, F. J. Gonzalez, *J. Pharmacol. Exp. Ther.* **2003**, *304*, 539.
[11] a) C. Gunanathan, D. Milstein, *Angew. Chem.* **2008**, *120*, 8789; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; b) C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146; c) C. Gunanathan, B. Gnanaprakasam, M. A. Iron, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 14763.
[12] E. Balaraman, E. Khaskin, G. Leitus, D. Milstein, *Nat. Chem.* **2013**, DOI: 10.1038/nchem.1536.
[13] a) E. J. Corey, K. Achiwa, *J. Am. Chem. Soc.* **1969**, *91*, 1429; b) T. F. Buckley, H. Rapoport, *J. Am. Chem. Soc.* **1982**, *104*, 4446; c) R. Neumann, M. Levin, *J. Org. Chem.* **1991**, *56*, 5707; d) H. Iwaki, M. Shimizu, T. Tokuyama, Y. Hasegawa, *Appl. Environ. Microbiol.* **1999**, *65*, 2232; e) J. Srogl, S. Voltrova, *Org. Lett.* **2009**, *11*, 843.
[14] A. Miyazawa, K. Tanaka, T. Sakakura, M. Tashiro, H. Tashiro, G. K. S. Prakash, G. A. Olah, *Chem. Commun.* **2005**, 2104.
[15] a) K. Kindler, D. Matthies, *Chem. Ber.* **1962**, *95*, 1992; b) K. Bui The, C. Concilio, G. Porzi, *J. Org. Chem.* **1981**, *46*, 1759; c) W. T. Reichle, *J. Catal.* **1993**, *144*, 556; d) T. M. Gädda, X.-Y. Yu, A. Miyazawa, *Tetrahedron* **2010**, *66*, 1249.
[16] J. L. Goodman, S. Wang, S. Alam, F. J. Ruzicka, P. A. Frey, J. E. Wedekind, *Biochemistry* **2004**, *43*, 13883.
[17] C. R. Nevill, Jr., P. T. Angell, *Tetrahedron Lett.* **1998**, *39*, 5671.
[18] a) H. Schlenk, B. W. DeHaas, *J. Am. Chem. Soc.* **1951**, *73*, 3921; b) B. Gold, A. Deshpande, W. Linder, L. Hines, *J. Am. Chem. Soc.* **1984**, *106*, 2072.
[19] D. Botheju, Y. Li, J. Hovland, H. A. Haugen, R. Bakke, *Energy Procedia* **2011**, *4*, 496.

