Nornicotine-organocatalyzed aqueous reduction of α,β-unsaturated aldehydes†

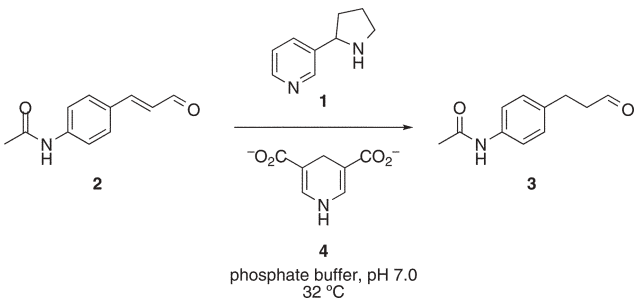
Andrew P. Brogan,[a] Tobin J. Dickerson*[b] and Kim D. Janda*[a]

Received (in Bloomington, IN, USA) 29th August 2007, Accepted 22nd September 2007
First published as an Advance Article on the web 9th October 2007
DOI: 10.1039/b713273e

Nornicotine, a native component of tobacco and minor nicotine metabolite, was found to catalyze the chemoselective reduction of α,β-unsaturated aldehydes under homogeneous aqueous conditions.

Organocatalysis has vast potential in synthetic organic chemistry, from the total synthesis of natural products to the manufacturing of fine chemicals and pharmaceuticals. For example, employing organocatalysts in place of transition metal catalysts eliminates the possibility of metal contamination in the purified product,[1] while also offering a less expensive and more environmentally friendly alternative. In order to improve the environmental compatibility of organocatalysis, the replacement of organic solvents with water has received considerable attention. Many early reports of organocatalysis "in water" reported aqueous reaction conditions;[2] however, upon closer inspection, most reactions actually occur in concentrated organic phases rather than under truly aqueous conditions. Furthermore, the reactants were often used in excess of water, providing no improvements from a "green" perspective. A discussion has been initiated recently in an attempt to clarify this area of research.[3]

Organocatalysis research in our laboratory has primarily focused on the chemical reactivity of abused and/or addictive drugs and their metabolites, providing inroads into the pathology of substance abuse. This work stems from the discovery that nornicotine (**1**), a natural product found in tobacco and a metabolic intermediate in humans, can catalyze the aldol reaction under buffered aqueous conditions.[4] We have since demonstrated that nornicotine enamine-based chemistry may play a role in metabolic diseases,[5] Alzheimer's disease,[6] macular degeneration,[7] and embryonic development.[7] While we have suggested several roles for nornicotine in disease progression, the relevance of this compound as a synthetically viable organocatalyst under aqueous conditions has not been realized due to limitations in substrate compatibility and low enantiospecificity. However, given that **1** is a small molecule natural product with aqueous organocatalytic activity, we believe this scaffold has future potential in "green" chemistry applications. In this vein, we now report that nornicotine can catalyze the chemoselective reduction of α,β-unsaturated aldehydes using a truncated, water-soluble mimic of the biological cofactor NADH as the hydride source, attaining the goal of true aqueous organocatalysis for this reaction.



Scheme 1 Nornicotine-catalyzed reduction of α,β-unsaturated cinnamaldehyde **2** in the presence of Hantzsch ester analog **4**.

Precedent for the nornicotine-catalyzed aqueous reduction of α,β-unsaturated aldehydes was established in two independent reports by the MacMillan[8] and List[9] laboratories. Unlike other organocatalysts, nornicotine functions particularly well under aqueous conditions,[4,10] therefore, we envisioned that nornicotine could catalyze the reduction of α,β-unsaturated aldehydes in aqueous buffer using NADH as the hydride source. Initial investigations began by treating **2** with nornicotine (50 mol%) and NADH (5 equiv.) in phosphate buffer (PB, pH 7.0) at 32 °C (Scheme 1; Table 1, entry 1). After 23 h, no starting material remained in these reactions, and **3** was formed in modest yield. Importantly, no reduced product was observed in the corresponding control reaction in the absence of catalyst (Table 1, entry 2).

Although these initial results validated our hypothesis, the reaction yields for the chemoselective reduction of **2** were synthetically unacceptable and required optimization. A pH study revealed that the reaction proceeded most efficiently under buffered conditions at pH 7.0, with a decrease in the reaction rate observed at pH 8.0 and the presence of additional side

Table 1 Screening results for optimal reaction conditions of the nornicotine-catalyzed reduction of **2**

Entry	Reductant (equiv.)	Catalyst (mol%)	DMSO (%)	Yield (%)	Time (h)
1	NADH (5)	50	0	25	23
2	NADH (5)	—	0	0	23
3	NADH (2)	50	0	Reaction incomplete	23
4	**4** (1.2)	50	0	30	16
5	**4** (1.2)	50	0	Reaction incomplete	6
6	**4** (1.2)	20	10	90	6
7	**4** (1.2)	—	10	13	6

[a]*Departments of Chemistry and Immunology, Skaggs Institute for Chemical Biology, & Worm Institute for Research and Medicine (WIRM), The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: kdjanda@scripps.edu*
[b]*Department of Chemistry & Worm Institute for Research and Medicine (WIRM), The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: tobin@scripps.edu*
† Electronic supplementary information (ESI) available: NMR spectra of starting materials and reduced products. See DOI: 10.1039/b713273e

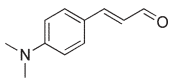
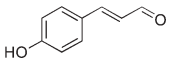
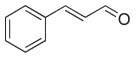
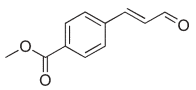
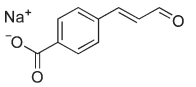
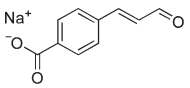
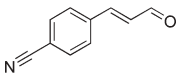
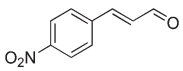
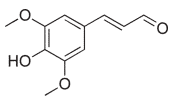
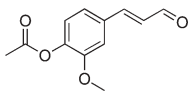
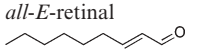
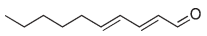
products as the pH was decreased to 6.2. Additionally, low conversion was observed in unbuffered water, presumably due to the basicity of nornicotine resulting in a sluggish reaction rate at high pH.

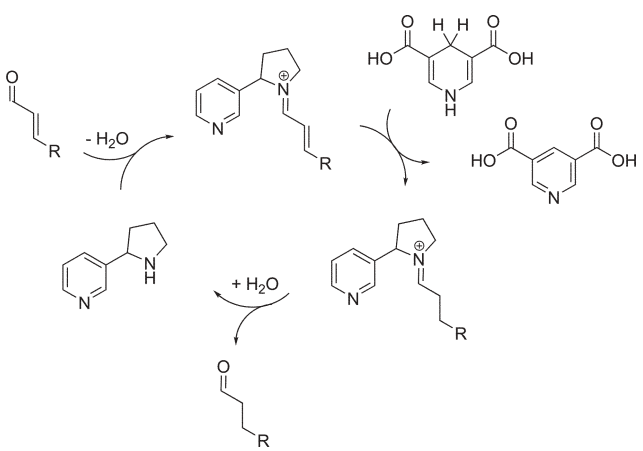
While NADH provided a reasonable starting point for a hydride source, this reductant is required in excess (Table 1, entry 3) and is neither cost effective nor atom efficient[11] given that the nicotinamide portion of NADH comprises less than 20% of the molecular weight of the biological cofactor. Previously, the MacMillan laboratory reported that the addition of electron-withdrawing groups to dihydropyridines, as is the case with the Hantzsch ester, led to much more efficient hydride transfer.[8] Unfortunately, the Hantzsch ester is insoluble in water and thus not a viable option as a reagent in homogeneous aqueous reactions. We envisioned that an analog of the Hantzsch ester, 1,4-dihydropyridine-3,5-dicarboxylic acid (**4**),[12] would possess suitable aqueous solubility and could function as an alternative hydride source. Indeed, reduction of **2** was accomplished with 1.2 equivalents of this reagent in greater yield than was accomplished using 5 equivalents of NADH (Table 1, entry 4).

Further optimization was accomplished by improving the solubility of the reactants in the aqueous media. Cinnamaldehyde **2** possessed modest aqueous solubility and the addition of a co-solvent increased product yield, decreased the reaction time, and enabled the catalyst load to be reduced (Table 1, entries 5 and 6). In fact, when 10% DMSO was employed to enhance substrate solubility, the reduced product **3** was obtained in 90% yield with 20 mol% nornicotine using **4** as the hydride source, whereas the corresponding control reaction without nornicotine provided the product in only 13% yield. While the inclusion of organic co-solvents decreases the "green" aspect of this reaction, this concentration of DMSO does not result in micellar aggregates and thus does not imply that catalysis occurs in concentrated organic phases. With regard to the catalyst loading, it should be noted that the concentration of active nornicotine catalyst is much lower than 20 mol% since the reaction is occurring under buffered conditions at pH 7.0. The pK_a of the nornicotine pyrrolidine nitrogen is 9.12;[13] therefore, most of the nornicotine in solution is protonated and unavailable for catalysis. According to the Henderson–Hasselbalch equation, 20 mol% total nornicotine corresponds to only 0.15 mol% of free base at pH 7.0, a significantly lower catalyst loading than is used in most organocatalytic reactions.

The substrate compatibility of the nornicotine-catalyzed aqueous reduction of α,β-unsaturated aldehydes was further explored after establishing optimal reaction conditions (Table 2). This organocatalytic transfer hydrogenation is thought to proceed through an iminium-ion LUMO-lowering intermediate using a conjugate addition-type mechanism that is dependent on the electrophilicity of the alkene (Scheme 2).[8,9] Accordingly, electron-withdrawing substituents should enhance the reaction rate while the reverse would occur with electron-donating substituents. In addition, since most organic small molecules have limited aqueous solubility, the yield and reaction rate are further dependent on substrate solubility. As a general trend, the electron-donating or -withdrawing character affected the reaction as expected. For example, the reaction of substrates with electron-withdrawing substituents proceeded in good yield under modest catalyst loading (Table 2, entries 4, 5, 7, 8), while substrates with electron-donating substituents required higher catalyst loads and provided the product in lower yields (Table 2, entries 2, 9, 10). Nornicotine was ineffective in catalyzing the reduction of non-aromatic

Table 2 Nornicotine-catalyzed reduction of α,β-unsaturated aldehydes

Entry	Substrate	Catalyst (mol%)	DMSO (%)	Yield (%)	Time (h)
1		20	10	0	23
2		200	5	20	7
3		50	5	48	6
4		50	10	39	7
5		20	0	66	0.5
6		—	0	5	0.5
7		20	5	60	5
8		30	20	75	6
9		200	5	23	7
10		100	5	42	7
11	*all-E*-retinal	100	20	0	8
12		100	10	0	8
13		100	10	0	8



Scheme 2 Proposed mechanism for nornicotine-catalyzed hydrogenation.[9]

α,β-unsaturated aldehydes or cinnamaldehydes with strongly donating substituents (Table 2, entries 1, 11–13), presumably as a consequence of the reduced electrophilicity of these substrates.

The solvent compatibility of this reaction was also studied in an effort to disprove the existence of concentrated organic phases. Analogous to our findings in the nornicotine-catalyzed aqueous aldol reaction,[4,10] no reduced product was formed when cinnamaldehyde was exposed to nornicotine (20 mol%) and the Hantzsch ester in THF or chloroform, while this reaction proceeded in acceptable yield under aqueous conditions utilizing **4** as a hydride source (Table 2, entry 3). Clearly, the catalytic mechanism of this reaction is unique since it requires an aqueous environment, possibly as the result of the involvement of explicit water molecules to achieve catalysis.[10]

The current debate over aqueous organocatalysis "in water" or "in the presence of water"[3] led us to pursue a synthetically viable, organocatalyzed reaction that occurs *dissolved* in an aqueous solution without any organic co-solvent. There is a fundamental distinction between an organocatalyst that functions *dissolved* in water *versus* an amphiphilic organocatalyst that catalyzes a reaction in the organic phase of a biphasic mixture. Towards this goal, aqueous soluble 4-carboxycinnamaldehyde could be reduced under the established reaction conditions in the absence of co-solvent in 66% yield (Table 2, entry 5), whereas the corresponding control reaction in the absence of nornicotine formed the product in only 5% yield (Table 2, entry 6). Interestingly, the reaction rate was much faster for 4-carboxycinnamaldehyde than the other substrates examined, most notably the methyl ester analog (Table 2, entry 4). Presumably, this is explained by the modest aqueous solubility of many of the other substrates, however, further study into the mechanism of this reaction is required before this difference can be conclusively explained.

As further evidence suggesting that nornicotine functions unlike other organocatalysts, dibenzylamine and proline, two recognized organocatalysts that are soluble in water,[9,14] were tested and found to provide minimal product formation over the corresponding control reaction using substrate 4-carboxycinnamaldehyde in the absence of organic co-solvent (19% yield for dibenzylamine and 14% yield for proline in 1 h *vs.* 66% yield for nornicotine in 30 min). In light of this disparity in catalytic efficiency between organocatalysts with closely related molecular structures, it is apparent that nornicotine operates by a unique mechanism allowing for efficient organocatalysis under completely aqueous conditions. Furthermore, the nornicotine-catalyzed reduction of α,β-unsaturated aldehydes is compatible with a range of cinnamaldehyde substrates and the addition of organic co-solvent is only needed in cases where the substrate possesses limited aqueous solubility.

Distinct from other organocatalysts, nornicotine, a natural product, functions only under aqueous conditions, providing a unique scaffold for the future development of "green" organocatalytic reactions. While the yields achieved using this methodology currently are not synthetically viable, the aqueous compatibility and low catalyst loading of nornicotine-catalyzed reactions relative to other organocatalysts justify further research endeavors.

We acknowledge The Skaggs Institute for Chemical Biology and the National Institutes of Health for financial support (DA 15700). A.P.B. was supported by an NIH Kirschstein NRSA postdoctoral fellowship (DA 18507).

Notes and references

1 P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138.
2 Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 958; Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 5527; N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 734; Y. Y. Peng, Q. P. Ding, Z. Li, P. G. Wang and J. P. Cheng, *Tetrahedron Lett.*, 2003, **44**, 3871; N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2006, **128**, 4966; A. Cordova, W. Notz and C. F. Barbas, III, *Chem. Commun.*, 2002, 3024; P. Dziedzic, W. Zou, J. Hafren and A. Cordova, *Org. Biomol. Chem.*, 2006, **4**, 38; H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983; Y. S. Wu, Y. Chen, D. S. Deng and J. Cai, *Synlett*, 2005, 1627; L. Cheng, X. Wu and Y. Lu, *Org. Biomol. Chem.*, 2007, **5**, 1018; V. Singh and V. K. Singh, *Org. Lett.*, 2007, **9**, 1117.
3 A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem., Int. Ed.*, 2006, **45**, 8100; Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 8103; D. G. Blackmond, A. Armstrong, V. Coombe and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798.
4 T. J. Dickerson and K. D. Janda, *J. Am. Chem. Soc.*, 2002, **124**, 3220.
5 T. J. Dickerson and K. D. Janda, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 15084.
6 T. J. Dickerson and K. D. Janda, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 8182.
7 A. P. Brogan, T. J. Dickerson, G. E. Boldt and K. D. Janda, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 10433.
8 S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 32.
9 J. W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660; J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2004, **44**, 108.
10 T. J. Dickerson, T. Lovell, M. M. Meijler, L. Noodleman and K. D. Janda, *J. Org. Chem.*, 2004, **69**, 6603; C. J. Rogers, T. J. Dickerson, A. P. Brogan and K. D. Janda, *J. Org. Chem.*, 2005, **70**, 3705; C. J. Rogers, T. J. Dickerson and K. D. Janda, *Tetrahedron*, 2006, **62**, 352.
11 B. M. Trost, *Science*, 1991, **254**, 1471.
12 E. Booker and U. Eisner, *J. Chem. Soc., Perkin Trans. 1*, 1975, 929.
13 T. Fujita, M. Nakajima, Y. Soeda and I. Yamamoto, *Pestic. Biochem. Physiol.*, 1971, **1**, 151.
14 B. List, R. A. Lerner and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.

