Organocatalysis

A Metal-Free Transfer Hydrogenation: Organocatalytic Conjugate Reduction of α,β-Unsaturated Aldehydes**

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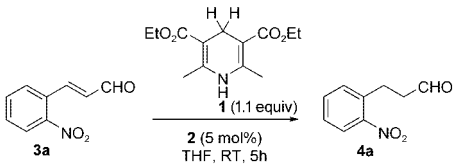
Hydrogenations of double-bond-containing compounds such as carbonyls, imines, and olefins are crucial for living organisms as well as for the industrial production of chemicals. While chemical hydrogenations require metal catalysts or the use of stoichiometric amounts of metal hydrides, nature typically relies on organic cofactors such as nicotinamide adenine dinucleotide (NADH) in combination with metalloenzymes. Metal-free catalytic hydrogenations of olefins have been unknown both in nature and in chemical synthesis.[1] Herein we disclose a highly efficient and remarkably chemoselective but completely metal-free catalytic transfer hydrogenation of α,β-unsaturated aldehydes.

The hydrogenation of α,β-unsaturated carbonyl compounds is a useful but challenging transformation. As both 1,2- and conjugate reductions readily occur, low selectivity for either of the two pathways is common. Catalytic hydrogenations of α,β-unsaturated aldehydes are possible, but the chemoselectivity is often low, and additional functional groups that are sensitive to hydrogenation conditions such as the benzyloxy, nitro, and nitrile groups are usually not tolerated.[2] Alternative conjugate reductions have been realized with various substrate classes,[3] but a mild, general, highly chemoselective, and catalytic variant that is applicable to α,β-unsaturated aldehydes has not been described. Reported conjugate reductions of aldehydes are either non-catalytic and require stoichiometric amounts of an (organo)-metallic hydride source,[4] require elevated temperatures,[5] or show only modest selectivity.[6] Clearly, a mild, catalytic, and highly chemoselective variant is highly desirable.

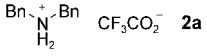
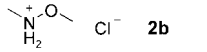
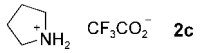
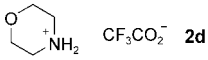
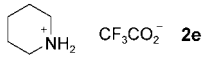
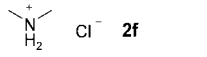
Recently iminium catalysis emerged as a powerful method for the asymmetric catalysis of cycloadditions and conjugate additions to enals and enones.[7] We reasoned that this catalysis strategy might be applicable to the conjugate reduction of α,β-unsaturated carbonyl compounds if a suitable hydride donor could be identified.[8] Such a process would constitute the first metal-free catalytic transfer hydrogenation.

We found that several ammonium salts (5 mol%) readily catalyze the conjugate reduction of *o*-nitrocinnamaldehyde (**3a**) to the corresponding saturated analogue **4a** when the Hantzsch ester **1** (1.1 equiv) is also added at room temperature [Eq. (1), Table 1]. No reduction was observed in the absence of catalyst after 48 h at room temperature. Cyclic as well as acyclic ammonium salts could be used, and the highest rate and yield was obtained with dibenzylammonium trifluoroacetate (**2a**). Interestingly, this catalyst was introduced in the 1970s by Corey et al. as an efficient catalyst for intramolecular aldol reactions of aldehydes.[9] Under our reaction conditions aldolization did not occur to any measurable extent. In addition to catalyst **2a**, the corresponding pyrrolidinium, morpholinium, and piperidinium salts as well as the Weinreb salt **2b** can be used as catalysts.[10] Ammonium salt **2b** has been used previously in the iminium catalysis of the Diels–Alder reaction.[11]



(1)

Table 1: Catalyst screening for the iminium catalytic conjugate reduction of α,β-unsaturated aldehydes.

Entry	Catalyst **2**	Yield [%]	
1	 **2a**	**2a**	94
2	 **2b**	**2b**	65
3	 **2c**	**2c**	81
4	 **2d**	**2d**	92
5	 **2e**	**2e**	90
6	 **2f**	**2f**	35

After identifying an efficient and chemoselective iminium catalyst for the conjugate reduction of enal **3a**, we decided to explore the scope of this new process with a variety of

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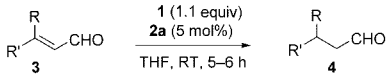
[**] We thank Degussa for donations of chemicals, Dr. Nicola Vignola for technical assistance, and the analytical departments of the Max-Planck-Institut für Kohlenforschung.

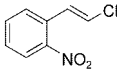
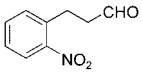
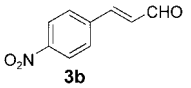
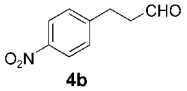
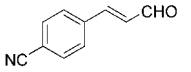
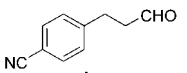
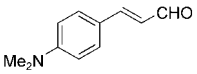
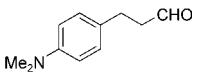
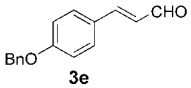
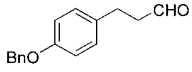
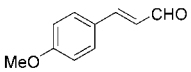
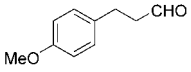
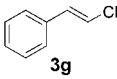
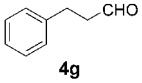
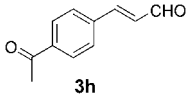
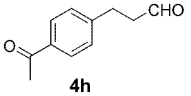
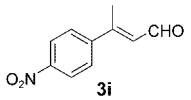
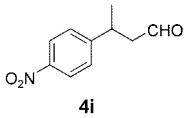
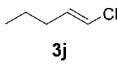
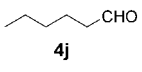
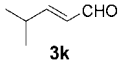
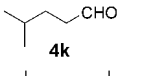
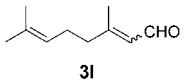
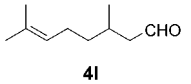
  DOI: 10.1002/anie.200461816

different aldehydes [Eq. (2), Table 2)]. The reduction works extremely well with a diverse set of unsaturated aldehydes, including substituted aromatic and aliphatic ones, and the process. These include the nitro, nitrile, benzyloxy, and alkenyl functional groups, which all survive the reaction conditions, illustrating the remarkable chemoselectivity of this novel organocatalytic reaction.



(2)

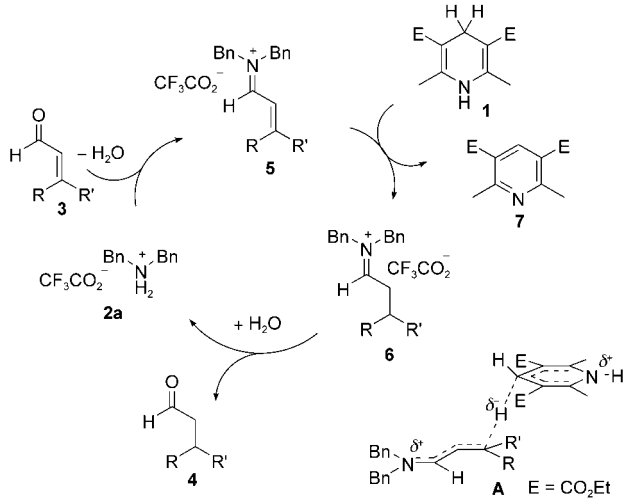
Table 2: Organocatalytic conjugate reduction of α,β-unsaturated aldehydes.

Entry	Substrate	Product	Yield [%][a]
1	 **3a**	 **4a**	94
2	 **3b**	 **4b**	96
3	 **3c**	 **4c**	93
4	 **3d**	 **4d**	81[b]
5	 **3e**	 **4e**	92
6	 **3f**	 **4f**	92
7	 **3g**	 **4g**	92[c]
8	 **3h**	 **4h**	90
9	 **3i**	 **4i**	94
10	 **3j**	 **4j**	90[b,c]
11	 **3k**	 **4k**	86[b,c]
12	 **3l**	 **4l**	92

[a] Yield of isolated product. [b] Reaction time of 15 h. [c] Yield determined by GC.

yields exceed 90% in almost all cases. Both β-mono- and β,β′-disubstituted enals can be reduced, although so far we have been unable to use enals with an additional substituent at the α-position. Besides the carbonyl group of aldehydes and ketones, a variety of functional groups that are sensitive to standard hydrogenation conditions are tolerated in the

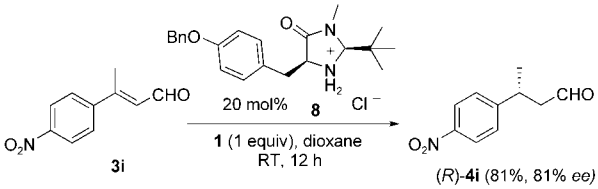
In terms of the mechanism we assume the reaction to proceed by the iminium catalysis cycle illustrated in Scheme 1. Accordingly, after an initial reversible formation



Scheme 1. Proposed mechanism of iminium catalysis.

of iminium ion **5** (which effectively lowers the LUMO energy of the substrate), conjugate hydride and proton transfer from dihydropyridine **1** follows. This step generates pyridine **7** along with iminium ion **6**. Hydrolysis then releases saturated aldehyde product **4** and regenerates catalyst **2a**. We suggest the hydride transfer to proceed via transition state **A**.

We are also developing an asymmetric variant of this reaction. For example, treating aldehyde **3i** with dihydropyridine **1** in the presence of catalyst **8** furnished (*R*)-**4i** in good yield and in 81% *ee* [Eq. (3)].



(3)

In summary, we have developed the first metal-free catalytic transfer hydrogenation. This novel iminium catalytic conjugate reduction of α,β-unsaturated aldehydes is highly efficient and chemoselective. It requires low catalyst loadings and tolerates various functional groups that are sensitive to the conditions of standard hydrogenations and alternative conjugate reductions. Current work in our laboratory focuses on a) expanding the scope of the reaction even further to include other substrate classes such as ketones and α-substituted α,β-unsaturated aldehydes, b) improving the overall atom economy, potentially by regeneration of the cofactor in situ,[12] c) including the reaction in tandem sequences

utilizing the presumed enamine intermediate,[13] and d) developing an efficient catalytic asymmetric variant. First results will be reported shortly.

Experimental Section

General procedure for the transfer hydrogenation reaction: Synthesis of aldehyde **4a**: To a solution of *o*-nitrocinnamaldehyde (**3a**, 88.6 mg, 0.5 mmol) and catalyst **2a** (7.8 mg, 0.025 mmol, 5 mol%) in dry THF (2 mL) was added dihydropyridine **1** (140 mg, 0.55 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 5 h under argon, after which the solvent was removed and the residue was chromatographed on silica gel (30% diethyl ether/*n*-hexane) to give 84 mg (94%) of **4a** as an oil. All aldehydes **3** and **4** are commercially available or have been described previously, and their analytical data match literature values.

Received: August 28, 2004
Published online: November 12, 2004

Keywords: chemoselectivity · Hantzsch dihydropyridine · iminium salts · organocatalysis · transfer hydrogenation

[1] For mechanistic studies on the base-catalyzed and transition-metal-free hydrogenation of ketones, see: a) A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 8693–8698; Also see: b) J. H. Teles, S. Brode, A. Berkessel, *J. Am. Chem. Soc.* **1998**, *120*, 1345–1346; c) E. J. Lyon, S. Shima, G. Buurman, S. Chowdhuri, A. Batschauer, K. Steinbach, R. K. Thauer, *Eur. J. Biochem.* **2004**, *271*, 195–204.

[2] See for example: a) V. V. Grushin, H. Alper, *Organometallics* **1991**, *10*, 831–833; b) J. M. Grosselin, C. Mercier, G. Allmang, F. Grass, *Organometallics* **1991**, *10*, 2126–2133; c) M. Sommovigo, H. Alper, *Tetrahedron Lett.* **1993**, *34*, 59–62, and references therein.

[3] For selected examples: a) U. Leutenegger, A. Madin, A. Pfaltz, *Angew. Chem.* **1989**, *101*, 61–62; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 60–61; b) M. Misun, A. Pfaltz, *Helv. Chim. Acta* **1996**, *79*, 961–972; c) D. S. Hays, M. Scholl, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 6751–6752; d) D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474; e) Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798; f) G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258; g) B. H. Lipshutz, J. M. Servesko, *Angew. Chem.* **2003**, *115*, 4937–4940; *Angew. Chem. Int. Ed.* **2003**, *42*, 4789–4792; h) C. Czekelius, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 4941–4943; *Angew. Chem. Int. Ed.* **2003**, *42*, 4793–4795.

[4] a) E. Keinan, N. Greenspon, *J. Am. Chem. Soc.* **1986**, *108*, 7314–7325; b) D. M. Brestensky, J. M. Stryker, *Tetrahedron Lett.* **1989**, *30*, 5677–5680; c) S. Saito, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 2928–2929; d) H.-Y. Lee, M. An, *Tetrahedron Lett.* **2003**, *44*, 2775–2778.

[5] a) B. E. Norcross, P. E. Klinedinst, Jr., F. H. Westheimer, *J. Am. Chem. Soc.* **1962**, *84*, 797–802; b) K. Nakamura, M. Fujii, A. Ohno, S. Oka, *Tetrahedron Lett.* **1984**, *25*, 3983–3986; c) S. Torchy, G. Cordonnier, D. Barbry, J. J Vanden Eynde, *Molecules* **2002**, *7*, 528–533.

[6] T. Suwa, I. Shibata, A. Baba, *Organometallics* **1999**, *18*, 3965–3967.

[7] See for example: a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; b) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194, and references therein; c) B. List, *Synlett* **2001**, 1675–1686.

[8] For reported conjugate reductions of preformed α,β-unsaturated iminium ions with Hantzsch esters, see: a) T. Makino, N. Baba, J. Oda, Y. Inouye, *Chem. Ind.* **1977**, 277–278; b) N. Baba, T. Makino, J. Oda, Y. Inouye, *Can. J. Chem.* **1980**, *58*, 387–392.

[9] a) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, J.-L. Gras, *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034; see also: b) A. Takahashi, M. Shibasaki, *Tetrahedron Lett.* **1987**, *28*, 1893–1896; c) W. R. Roush, D. A. Barda, *Tetrahedron Lett.* **1997**, *38*, 8785–8788.

[10] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[11] J. L. Cavill, J. L. Peters, N. C. O. Tomkinson, *Chem. Commun.* **2003**, 728–729.

[12] For an example of an enzymatic process in which the NADH cofactor can be regenerated in situ, see: M. R. Kula, C. Wandrey, *Methods Enzymol.* **1987**, *136*, 9–21.

[13] For elegant catalytic C–C coupling reactions that proceed by capture of hydrogenation intermediates, see: H.-Y. Jang, M. J. Krische, *Acc. Chem. Res.* **2004**, *37*, 653–661.

