Organocatalysis

Metal-Free, Organocatalytic Asymmetric Transfer Hydrogenation of α,β-Unsaturated Aldehydes**

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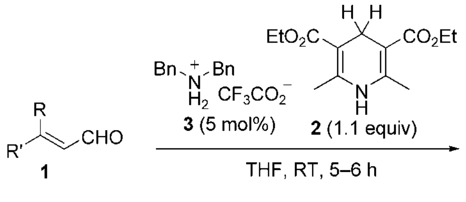
Asymmetric catalytic hydrogenations are used in the large-scale industrial production of pharmaceuticals and fine chemicals and also by all living organisms. While chemical hydrogenations require metal catalysts or the use of stoichiometric amounts of metal hydrides,[1] living organisms typically rely on organic cofactors such as nicotinamide adenine dinucleotide (NADH) in combination with metalloenzymes.[2] Until now, metal-free catalytic asymmetric hydrogenations have been unknown in chemical synthesis and seem to be rare in nature.[3] Here we show that a small organic molecule effectively catalyzes a highly enantioselective biomimetic transfer hydrogenation of α,β-unsaturated aldehydes using a synthetic dihydropyridine cofactor.

Industrially, metal-catalyzed hydrogenations are the most often used catalytic asymmetric processes. The complete removal of metal impurities from the reaction product, though difficult, is generally required in the production of pharmaceutical intermediates because of toxicity concerns.[4] Organocatalysis is a rapidly growing area of research, and one of its advantages is the general lack of metals.[5] We have recently developed an amine-catalyzed nonasymmetric transfer hydrogenation of α,β-unsaturated aldehydes **1** with Hantzsch ester **2** [Eq. (1)].[6]



(1)

This reaction is the first example of a completely metal-free transfer hydrogenation of olefins.[7] We could also show that enantioselective iminium catalysis of the reaction is in principle possible. Iminium catalysis has recently been introduced as a powerful organocatalytic method for carbonyl transformations such as conjugate additions and cycloadditions.[8] We have now completed an extensive screening of several synthetic and commercially available Hantzsch dihydropyridines and chiral ammonium salt catalysts and report here on an efficient enantioselective variant of our transfer hydrogenation.

We found that upon treating aromatic, trisubstituted α,β-unsaturated aldehydes **5** with a slight excess of dihydropyridine **6** and a catalytic amount of MacMillan imidazolidinone salt **7** at 13 °C in dioxane, the corresponding saturated aldehydes **8** were obtained in high yields and excellent enantioselectivities [Eq. (2), Table 1].

Like our nonasymmetric variant, the enantioselective reactions are generally clean and highly chemoselective, and carbonyl reduction or aldolization products were not detected. We also investigated the influence of the stereochemistry at the double bond. Remarkably, when we subjected both the isolated pure *E* or *Z* isomers of 4-nitro-substituted derivative **5c** to our reaction conditions, the same *R* enantiomer of product **8c** was obtained and with the same enantiomeric ratio of 97:3. Similarly, (*E*)/(*Z*)-**5c** mixtures always gave the same result and, independent of their exact ratio, all furnished (*R*)-**8c** in 97:3 e.r. Thus, our process is *enantioconvergent*, a highly desirable yet rare feature of a catalytic asymmetric reaction, where a mixture of stereoisomers furnishes only one product enantiomer. As a practical

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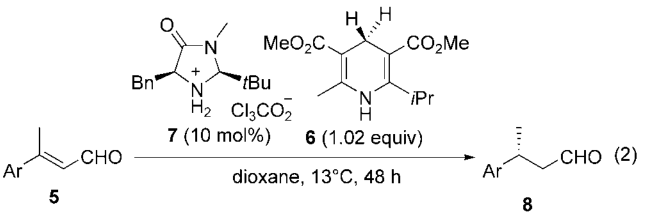
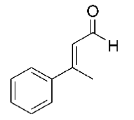
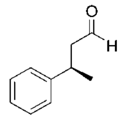
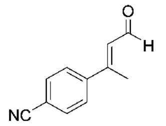
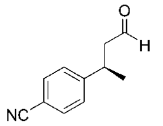
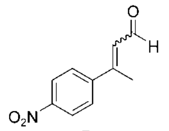
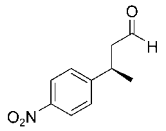
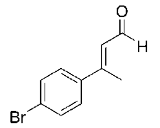
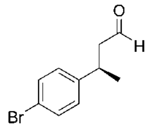
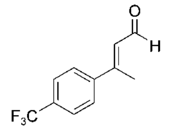
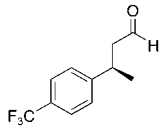
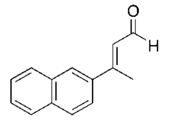
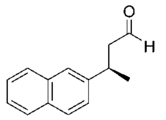


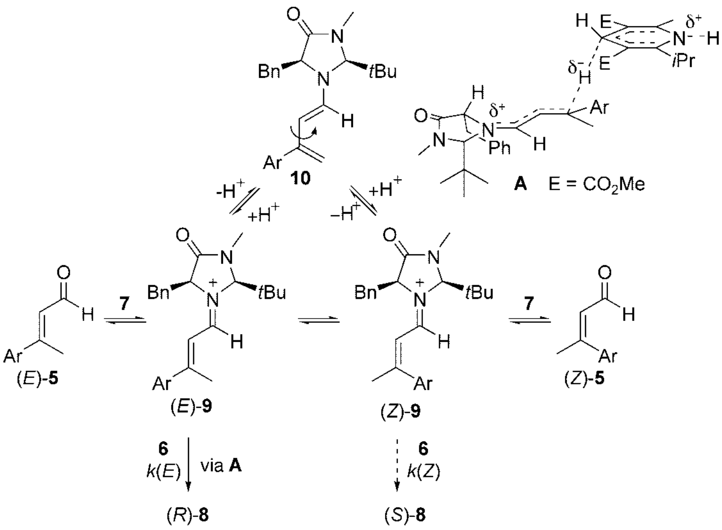
Table 1: Organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.

Entry	Starting material	Product	Yield [%]	e.r.
1	 **5a**	 **8a**	77[a]	95:5
2	 **5b**	 **8b**	89	98:2
3	 **5c**	 **8c**	83 (from (*E*)-**5c**) 80 (from (*Z*)-**5c**) 81 (from (*E*)/(*Z*)-**5c** (1:1))	97:3 97:3 97:3
4	 **5d**	 **8d**	90	97:3
5	 **5e**	 **8e**	85	97:3
6	 **5f**	 **8f**	86	96:4

[a] Yield of the 2,4-dinitrophenylhydrazone derivative.

consequence of this feature, the unsaturated aldehyde starting material of our reaction may be used as a mixture of *E* and *Z* isomers as obtained from common synthetic procedures such as the Wittig reaction.

Mechanistically, we assume the reaction to proceed by formation of iminium ion **9**, which presumably isomerizes quickly via dienamine **10** (Scheme 1). The following rate-determining hydride transfer from dihydropyridine **6** to enal (*E*)-**9** via transition state **A** proceeds faster than to (*Z*)-**9** [$k(E) > k(Z)$] and, as a result, saturated aldehyde (*R*)-**8** is formed predominantly.



Scheme 1. Proposed mechanism of the organocatalytic asymmetric transfer hydrogenation.

In summary we have described the first completely metal-free catalytic asymmetric transfer hydrogenation. In our iminium catalytic reaction α,β-unsaturated aldehydes are highly efficiently reduced by means of transfer hydrogenation from a dihydropyridine. Attractive features of the process are 1) its high yields, chemo-, and enantioselectivities, 2) its enantioconvergence, and 3) its simplicity and practicability. Applications in the synthesis of natural products, pharmaceuticals, and fine chemicals may be envisioned.

Experimental Section

General procedure for the asymmetric transfer hydrogenation reaction: To a stirred solution of α,β-unsaturated aldehyde **5** (0.5 mmol) in dioxane (7 mL) at 13 °C was added catalyst **7** (20.4 mg, 0.05 mmol, 10 mol%) and, after five minutes, crystalline dihydropyridine **6** (129.2 mg, 0.51 mmol). After a reaction time of 48 h the mixture was poured into distilled water (20 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was isolated by flash chromatography (SiO_2, ethyl acetate/hexane) to give the saturated aldehyde product **8**. Aldehydes **5a–f** were synthesized according to previously reported methods and their analytical data as well of those of aldehydes **8** match literature values.[9] The absolute configuration of (*R*)-**8f** was determined by measurement of its optical rotation and comparision to the literature value.[10] Enantiomeric ratios were determined by chiral stationary phase GC-analysis.

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Keywords: asymmetric catalysis · chemoselectivity · enantioselectivity · hydrogenation · organocatalysis

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