Brønsted Acid Catalysis

DOI: 10.1002/anie.200701158

Organocatalytic Enantioselective Reduction of Pyridines**

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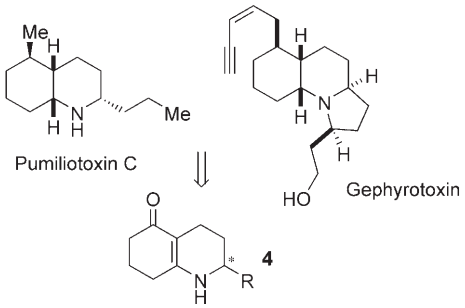
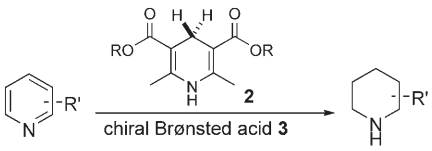
Asymmetric hydrogenation is one of the most important enantioselective reactions. Although the hydrogenation, transfer hydrogenation, and hydrosilylation of various substrates in the presence of metal catalysts have been described, the asymmetric reduction of aromatic and heteroaromatic compounds still represents a great challenge.[1] This situation is particularly true for the enantioselective hydrogenation of substituted pyridine derivatives,[2] which can be readily prepared using various methods. The corresponding chiral piperidines are not only important starting materials for numerous biologically active compounds, but are also important structural building blocks of many alkaloids, including pumiliotoxins, gephyrotoxins, and over 50 other members of the class of 2,5-disubstituted decahydroquinolines (Scheme 1).[3]



Scheme 1.

We considered it most important to investigate a Brønsted acid catalyzed enantioselective reduction of pyridines [Eq. (1)]. This approach would not only be the first example of such an organocatalytic transformation but more significantly it would give us direct access to enantiomerically pure piperidines

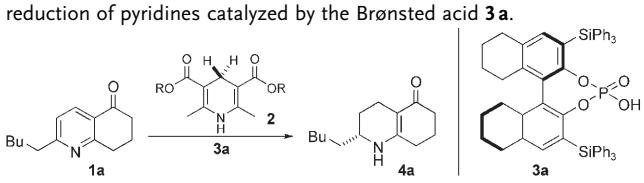


(1)

Building on our previous results from chiral ion-pair catalysis,[4] we decided to examine the reduction of pyridines in the presence of the binol phosphates **3** (binol = 2,2′-dihydroxy-1,1′-binaphthyl).[4,5] We assumed that the activation of pyridines by catalytic protonation using a Brønsted acid would allow a cascade hydrogenation, in which a Hantzsch dihydropyridine (**2**) would function as the hydride source.[6]

Hence, we began our study with the catalytic reduction of the trisubstituted pyridine **1a** in the presence of the binol phosphate **3a**, whereby the reaction parameters (solvent, temperature, catalyst loading, substrate concentration, and hydride source) were varied (Table 1). The initial results demonstrated the success of the new method, and the partially reduced enantiomerically enriched pyridine derivative **4a** was isolated.

Table 1: Evaluation of the reaction parameters for the enantioselective reduction of pyridines catalyzed by the Brønsted acid **3a**.



Entry[a]	Solvent	R	**3a** [mol %]	*ee* [%][b]
1	toluene	Et	5	71
2	DCE[c]	Et	5	52
3	Bu_2O	Et	5	76
4	benzene	Et	5	78
5	benzene	Et	10	79
6	benzene	Et	15	78
7	benzene	*t*Bu	5	75
8	benzene	*i*Pr	5	51
9	benzene	allyl	5	76

[a] Reaction conditions: **1a**, **3a** (5–15 mol %), **2** (4 equiv), 60 °C. [b] Determined by HPLC on a chiral phase (Chiralcel OD-H). [c] DCE = 1,2-dichloroethane.

The best results, with respect to reactivity, yield, and selectivity, were achieved with the Hantzsch diethyl ester (**2**, R = Et) in benzene at 60 °C (Table 1, entries 4–6). Under these conditions, **4a** was isolated in up to 79 % *ee*. Other solvents, such as toluene or dibutyl ether, yielded **4a** with comparable enantioselectivities (Table 1, entries 1 and 3). However, the application of other Hantzsch esters resulted in lower selectivities (Table 1, entries 7–9).

In further experiments, differently substituted binol phosphates **3b–g** were examined in the reduction of pyridine **1a** (Table 2). The best enantioselectivities were achieved

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[**] The authors thank Degussa AG and the DFG (Priority Program Organocatalysis) for financial support.

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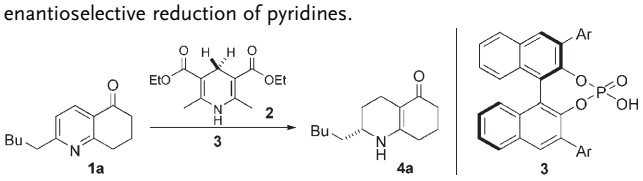
Table 2: Evaluation of the chiral Brønsted acids **3** as catalysts in the enantioselective reduction of pyridines.

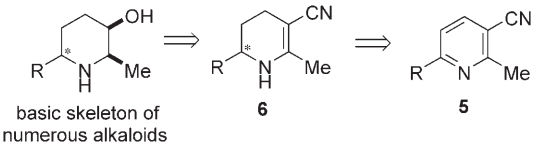


Entry[a]	Ar (**3**)	*ee* [%][b]
1	Ph_3Si, $[H]_8$ (**3a**)	78
2	phenyl (**3b**)	21[c]
3	4-biphenyl (**3c**)	19[c]
4	3,5-$(CF_3)_2C_6H_3$ (**3d**)	8[c]
5	3,5-tBu$_2$-4-MeOC_6H_2 (**3e**)	16[c]
6	anthracenyl (**3f**)	91
7	9-phenanthryl (**3g**)	82

[a] Reaction conditions: **1a**, **3** (5 mol%), **2** (4 equiv), benzene, 60°C. [b] Determined by HPLC on a chiral phase (Chiralcel OD-H). [c] The opposite enantiomer was obtained.

using the Brønsted acid catalyst **3f**, which gave the product **4a** in 91% *ee* (Table 2, entry 6). All the other binol phosphates yielded the product with lower enantioselectivities, in correlation with the steric demand of the substituents on the catalyst.[4]

The method developed for the enantioselective organocatalytic reduction of pyridines **1** allows access to hexahydroquinolinones **4**, which are precursors for the synthesis of various natural products.[7] We decided to apply this new method to the reduction of trisubstituted pyridines **5** (Scheme 2). The resulting products **6** are also of great



Scheme 2.

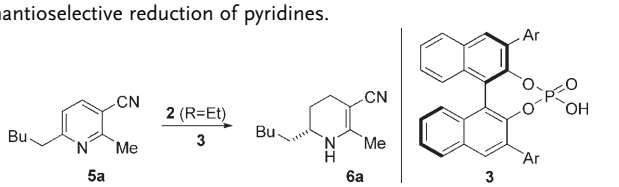
significance, as they can be used as starting compounds for the synthesis of 2,6-dialkyl 3-hydroxypiperidine natural products, such as cassine, spectaline, corydendramine, leptophylline, morusimine, and juliprosopine.[8]

Using our optimized conditions, we evaluated the different chiral binol phosphates **3a–i** as Brønsted acid catalysts in the enantioselective reduction of pyridine **5a** to tetrahydropyridine **6a** (Table 3). Once again, the reaction with the anthracenyl-substituted binol phosphate catalyst **3f** gave the best enantioselectivities. We were able to isolate the product **6a** in 89% *ee* (entry 6).

In further experiments, we explored the scope of the reduction by using differently substituted pyridines **1** and **5** as substrates (Table 4). The corresponding azadecalinones **4a–f** and tetrahydropyridines **6a–d** were isolated in good yields and with excellent enantioselectivities (up to 92% *ee*).

The newly developed enantioselective organocatalytic reduction of pyridines can be used as a key step in the synthesis of decahydroquinolines from the pumiliotoxin

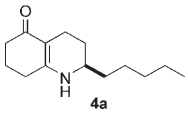
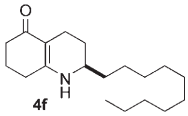
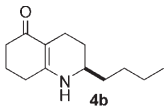
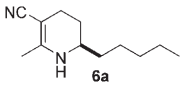
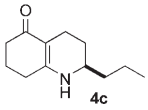
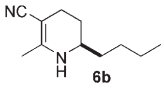
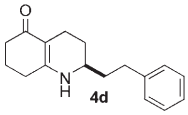
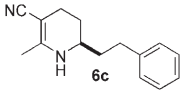
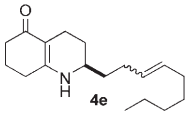
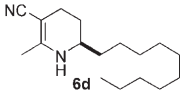
Table 3: Evaluation of the chiral Brønsted acids **3** as catalysts in the enantioselective reduction of pyridines.



Entry[a]	Ar (**3**)	*ee* [%][b]
1	Ph_3Si, $[H]_8$ (**3a**)	67
2	phenyl (**3b**)	46[c]
3	4-biphenyl (**3c**)	44[c]
4	3,5-$(CF_3)_2C_6H_3$ (**3d**)	36[c]
5	3,5-tBu$_2$-4-MeOC_6H_2 (**3e**)	56[c]
6	anthracenyl (**3f**)	89
7	9-phenanthryl (**3g**)	75
8	1-naphthyl (**3h**)	35
9	2-naphthyl (**3i**)	32[c]

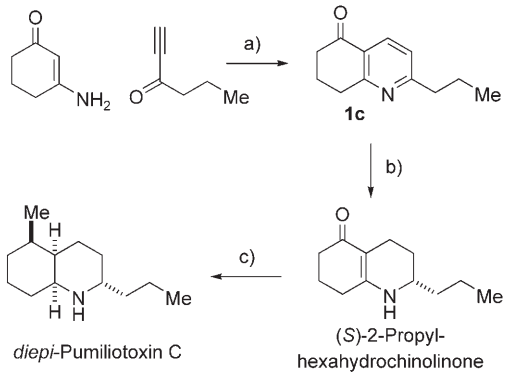
[a] Reaction conditions: **5a**, **3** (5 mol%), **2** (4 equiv), benzene, 60°C. [b] Determined by HPLC on a chiral phase (Chiralcel AS-H). [c] The opposite enantiomer was obtained.

Table 4: Substrate scope of the enantioselective reduction of pyridines catalyzed by the Brønsted acid **3f**.

Product[a]	Yield[b] *ee*[c]	Product[a]	Yield[b] *ee*[c]
 **4a**	84% 91% *ee*	 **4f**	73% 92% *ee*
 **4b**	72% 91% *ee*	 **6a**	73% 90% *ee*
 **4c**	69% 89% *ee*	 **6b**	55% 84% *ee*
 **4d**	66% 92% *ee*	 **6c**	47% 86% *ee*
 **4e**	83% 87% *ee*	 **6d**	68% 89% *ee*

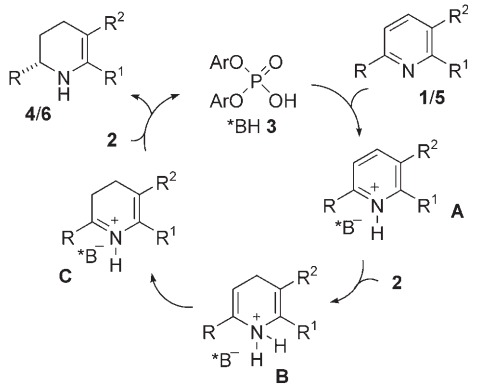
[a] Reaction conditions: **1** or **5**, **3f** (5 mol%), **2** (4 equiv), benzene, 50°C. [b] Yields pf product isolated after purification by column chromatography. [c] Determined by HPLC on a chiral phase (Chiralcel OD-H, AS-H, or ADH).

family (Scheme 3). Hence, the reduction of pyridine **1c**, which can be readily prepared according to the procedure of Bohlmann and Rahtz,[9] gives the corresponding 2-propylhexahydroquinolinone. This compound can subsequently be transformed, according to a sequence reported by Hsung et al.,[7e] into *diepi*-pumiliotoxin C.



Scheme 3. a) EtOH, 50 °C, 12 h, then 140 °C, 2 h;[9] b) (*S*)-**3 f** (5 mol %), **2** (4 equiv), benzene, 50 °C; c) Ref. [7e].

Regarding the mechanism of the reduction, we assume that, in the first step, the pyridine **1** or **5** is activated through catalytic protonation by the Brønsted acid **3**, resulting in the formation of a chiral ion pair **A** (Scheme 4). A subsequent



Scheme 4. Postulated mechanism for the enantioselective organocatalytic reduction of pyridines.

first hydride transfer from the Hantzsch ester **2** gives the adduct **B**, which is transformed into the iminium ion **C** through an acid-catalyzed isomerization. A second hydride transfer results in the desired product **4** or **6**, and the binol phosphate catalyst **3** is regenerated.

In summary, we have developed the first enantioselective reduction of pyridines catalyzed by Brønsted acids. The products, hexahydroquinolinones and tetrahydropyridines, are isolated in good yields and with excellent enantioselectivities (up to 92 % *ee*). These products serve as starting compounds for the synthesis of various natural products. As only metal-catalyzed enantioselective hydrogenations of pyridines, which did not give the valuable products described herein and yielded lower enantioselectivities, were described previously, our newly developed metal-free Brønsted acid catalyzed procedure represents an important advance.

Received: March 16, 2007
Published online: May 11, 2007

Keywords: Brønsted acids · ion-pair catalysis · piperidines · reduction · transfer hydrogenation

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