#### **Brønsted Acid Catalysis**

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### A Highly Enantioselective Brønsted Acid Catalyzed Cascade Reaction: Organocatalytic Transfer Hydrogenation of Quinolines and their Application in the Synthesis of Alkaloids\*\*

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Dedicated to Professor David A. Evans on the occasion of his 65th birthday

The enantioselective hydrogenation of olefins, ketones, and imines still represents an important topic in organic synthesis and catalysis. Although many highly enantioselective processes based on chiral Rh, Ru, and Ir complexes have been reported,<sup>[1]</sup> most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of aromatic and heteroaromatic compounds. Examples of efficient catalysts for these conversions are rare.<sup>[2]</sup> This is also true for the partial reduction of readily available quinoline derivatives,<sup>[3]</sup> the most convenient route to 1,2,3,4-tetrahydroquinolines, which are of great synthetic importance in the preparation of pharmaceuticals and agrochemicals, as well as in material sciences.<sup>[4]</sup> Furthermore, many natural products, particularly alkaloids, consist of this structural key element. We wondered whether it would be possible to extend our recently developed biomimetic, enantioselective Brønsted acid catalyzed transfer hydrogenation of imines<sup>[5]</sup> [Eq. (1)] to the enantioselective

$$R^{+} R^{1} \xrightarrow{\text{chiral Brønsted acid}} R^{+} R^{+} \xrightarrow{\text{chiral Brønsted acid}} R^{+} R^{+} R^{+}$$
(1)

hydrogenation of quinolines. This would not only represent the first example of a metal-free reduction of heteroaromatic compounds but would additionally give straightforward access to optically pure tetrahydroquinoline derivatives.

We reasoned that activation of the quinoline by catalytic protonation would allow a cascade hydrogenation, which involves a 1,4-hydride addition, isomerization, and 1,2-

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hydride addition to generate the desired tetrahydroquinolines [Eq. (2)].<sup>[6]</sup>



We initially focused on the exploration of appropriate Brønsted acid catalysts<sup>[7]</sup> and the examination of reaction parameters, such as catalyst loading, hydride source, temperature, and concentration. The best results, with respect to reactivity, yield, and selectivity, were obtained with catalytic amounts of Brønsted acid catalysts of type **1**,<sup>[5,8,9]</sup> 2-substituted quinoline derivatives **2**, and dihydropyridine **4** as the hydride source.<sup>[5,6,10]</sup>

Further examination of this new Brønsted acid catalyzed transfer hydrogenation concentrated on the catalyst structure (Table 1). From this survey sterically congested Brønsted

Table 1: Survey of chiral Brønsted acid catalysts for the cascade transfer hydrogenation.



Entry <sup>[a]</sup>	Cat.	Ar	ee [%] <sup>[b]</sup>
1	la	phenyl	5
2	1 b	4-biphenyl	35
3	1c	1-naphthyl	84
4	1 d	2-naphthyl	26
5	le	3,5-(CF <sub>3</sub> )-C <sub>6</sub> H <sub>3</sub>	72
6	1 f	9-phenanthryl	97

[a] Reaction conditions: **2**, **4** (2.4 equiv), 5 mol% **1** in benzene at 60°C. [b] Determined by HPLC analysis on a chiral phase (chiralcel OD-H).

acids emerged as the best catalysts for hydride transfer, and gave good to excellent levels of enantioselection. This finding is in agreement with our recently developed binol phosphate catalyzed Strecker reaction.<sup>[9]</sup> The highest selectivities were obtained with catalyst **1 f**, which provided 2-phenyltetrahydroquinoline (**3**) in 97% *ee* (Table 1, entry 6).

Further investigations on the solvent employed (Table 2) showed that nonpolar solvents were essential for a high asymmetric induction. Excellent enantioselectivities of 2-phenyltetrahydroquinolines (95–97 % *ee*) were observed in both chlorinated (CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, CCl<sub>4</sub>) and aromatic solvents (benzene, toluene). The hydrogenation of 2-butylquino-line with a reduced amount of catalyst (2 mol %) could best



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**Table 2:** Influence of the solvent on the Brønsted acid catalyzed transfer hydrogenation of quinolines.



[a] Reaction	conditions: 2 4	(2.4 equiv) and	catalyst 1f at 60°C
5	toluene	97	86
4	benzene	97	87
3	$CH_2Cl_2^{[e]}$	96	81
2	CHCl <sub>3</sub> <sup>[e]</sup>	95	82
	4		

[a] Reaction conditions: 2, 4 (2.4 equiv), and catalyst 1 f at 60 °C.
[b] Determined by HPLC analysis on a chiral phase (Chiralcel OD-H).
[c] With 5 mol% 1 f. [d] With 2 mol% 1 f. [e] Reactions were performed at RT.

be performed in aromatic solvents (Table 2, entries 4 and 5), which is in accordance with our previously developed Brønsted acid catalyzed reactions.<sup>[5,9]</sup>

We explored the scope of the Brønsted acid catalyzed cascade transfer hydrogenation of 2-substituted quinolines under optimized conditions (Table 3). In general, high enantioselectivities and good yields of several tetrahydroquinolines with aromatic and heteroaromatic residues, as well as aliphatic substituents was observed. Interestingly, this metal-

Table 3: Scope of the cascade hydrogenation reaction.



[a] Reaction conditions **2**, **4** (2.4 equiv), 2 mol% catalyst **1** fin benzene at 60 °C. [b] Yields after column chromatography. [c] Determined by HPLC analysis on a chiral phase (Chiralcel OD-H). [d] 45% recovered starting material. [e] 5 mol% **1** f. [f] 1 mol% **1** f.

free hydrogenation procedure is even compatible with halogenated aromatic and aliphatic residues, such as 3bromophenyl or chloromethyl substituents (Table 3, entry 11).

Having established a general and highly enantioselective cascade transfer hydrogenation of 2-substituted quinolines, we applied this new methodology to the synthesis of biologically active tetrahydroquinoline alkaloids: galipinine,<sup>[11]</sup> cuspareine,<sup>[11b,12]</sup> and angustureine.<sup>[11b,13]</sup> Brønsted



acid catalyzed enantioselective hydrogenation of the corresponding 2-substituted quinolines,<sup>[14]</sup> which were prepared by simple alkylation of 2-methylquinoline, generated the tetrahydroquinoline derivatives with excellent enantioselectivity and subsequent N-methylation gave the desired natural products in good overall yields (Table 4).





[a] The absolute configuration was determined by comparison with literature data. [b] Yields over two steps after column chromatography. [c] Determined by HPLC analysis on a chiral phase (Chiralcel OD-H).

The absolute configuration<sup>[15]</sup> of the products can be explained by a stereochemical model derived from the X-ray crystal structure of the catalyst **1 f**. In the transition state the quinoline is activated by protonation of the chiral Brønsted acid **1 f**, thereby favoring approach of the hydride nucleophile from the less hindered *Si* face since the *Re* face is shielded by the large phenanthryl group of the catalyst (Figure 1).

Mechanistically we assume that the first step in the enantioselective cascade hydrogenation is the protonation of the quinoline 2 through the Brønsted acid catalyst 1 to generate the iminium ion A (Scheme 1). Subsequent transfer

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*Figure 1.* Proposed transition structure derived from an X-ray crystal structure of chiral Brønsted acid **1 f** and 2-methylquinoline.



**Scheme 1.** Proposed mechanism for the Brønsted acid catalyzed cascade transfer hydrogenation.

of the first hydride from the dihydropyridine 4 generates the enamine 5 and pyridinium salt **B**, which undergoes proton transfer to regenerate the Brønsted acid 1 and Hantzsch pyridine 6. The enamine 5 reacts in a second cycle with Brønsted acid 1 to produce iminium **C**, which will again be subjected to hydride transfer to give the desired tetrahydroquinoline **3**. Subsequent proton transfer will then recycle the Brønsted acid 1 and generate a second equivalent of the Hantzsch pyridine.

In summary, we have developed a Brønsted acid catalyzed cascade transfer hydrogenation, which provides direct access to a variety of 2-aryl- and 2-alkyl-substituted tetrahydroquinolines with excellent enantioselectivities and good yields. The mild reaction conditions of this metal-free reduction of heteroaromatic compounds, the operational simplicity and practicability, as well as the low catalyst loading render this transformation an attractive approach to optically active tetrahydroquinolines and their derivatives. Further work will be directed toward the application of this enantioselective Brønsted acid catalyzed transfer hydrogenation to multisubstituted quinolines and other heteroaromatic systems.

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