Asymmetric Catalysis

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A Highly Enantioselective Brønsted Acid Catalyzed Reaction Cascade**

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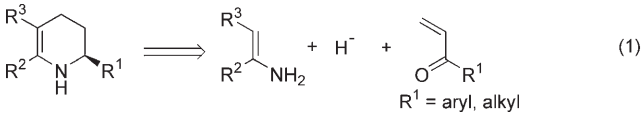
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 75th birthday

Enantioselective domino reactions have emerged as powerful methods for the rapid synthesis and construction of complex target molecules starting from simple and readily available precursors.[1] Asymmetric organocatalytic cascade reactions represent an important and promising area in organic synthesis, providing direct access to enantioenriched compounds under mild and environmentally friendly reaction conditions. Generally these organocascades are based on biomimetic principles, and often aminocatalytic activation is the key for successful execution.[2]

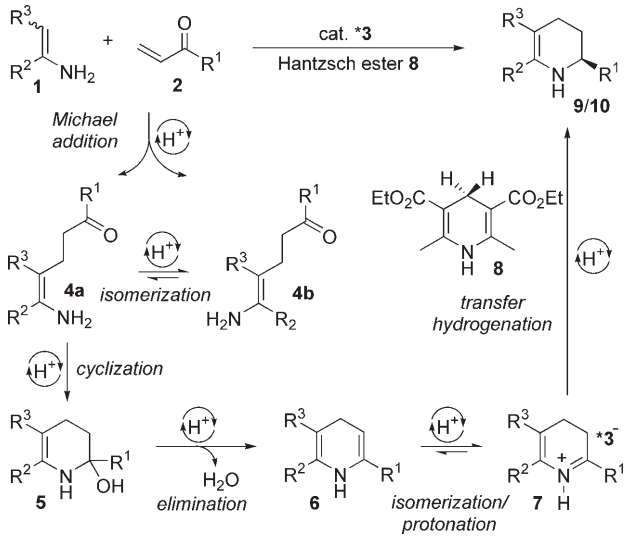
Over the past few years Brønsted acid catalysts, including chiral phosphoric acids,[3] have been applied in asymmetric synthesis, whereby the chiral phosphate counterion formed as a intermediate induces high enantioselectivities. As part of our studies we have recently demonstrated that chiral Brønsted acids can serve as powerful catalysts for the enantioselective activation of imines[4] and carbonyl functionalities.[5] Here we report a new asymmetric organocatalytic cascade reaction in which multiple steps are catalyzed by a chiral Brønsted acid catalyst and which provides valuable tetrahydropyridines[6] and azadecalinones[7] with high enantioselectivities [Eq. (1)].



(1)

Chiral azadecalinones are important starting materials for numerous biologically active molecules, such as the alkaloids pumiliotoxin and gephyrotoxin, as well for over 200 2,5-disubstituted decahydroquinolines. Whereas the tetrahydropyridines are precursors for the synthesis of 2,6-dialkyl-substituted 3-hydroxypiperidines such as cassin, spectaline, corydendramine, leptophylline, morusimine, and juliprosopine.[7–9]

We have previously demonstrated that chiral 1,1′-bi-2-naphthyl (binol) phosphates are excellent catalysts for the enantioselective metal-free reduction of imines, quinolines as well as pyridines. Based on our original biomimetic strategy and our experience in chiral ion-pair catalysis, we envisioned a new organocatalytic multiple-reaction cascade sequence comprising a Michael addition, isomerization, cyclization, elimination, isomerization, and transferhydrogenation in which each single step is catalyzed by a chiral Brønsted acid (Scheme 1).



Scheme 1. Brønsted acid catalyzed multiple-reaction cascade.

In our reaction design we assumed that exposure of a mixture of enamine **1** and α,β-unsaturated ketone **2** to catalytic amounts of the Brønsted acid should lead to formation of the corresponding 1,4-addition products[5b] **4a** and **4b**. Subsequent Brønsted acid catalyzed cyclization of **4a**, which is in an acid-catalyzed equilibrium with **4b**, would give the hemiaminal **5**, which upon rapid elimination of water results in the formation the dihydropyridine **6**, an intermediate also observed in the enantioselective reduction of pyridine.[2l] The following Brønsted acid catalyzed protonation should effect the generation of an iminium ion, the chiral ion pair **7**, which is activated for an enantioselective hydride transfer[10] to give the desired product **9**.[11] Central to the

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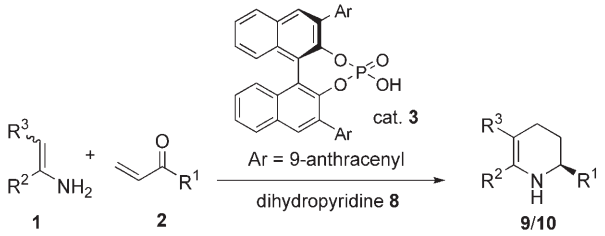
utility of this new multiple reaction cascade in asymmetric synthesis is the requirement that the last Brønsted acid catalyzed activation step in this sequence would proceed with high enantiocontrol.

Preliminary studies revealed that the proposed new Brønsted acid catalyzed cascade could indeed be performed and that the three-component reaction of enamine **1**, vinyl ketone **2**, and dihydropyridine **8** results in the corresponding products **9**/**10** when, for instance, phosphates are employed as catalysts. The subsequent survey of different chiral phosphates revealed that binol phosphates with large aromatic substituents in 3,3-position of the binaphthyl backbone provided good enantioselectivities, and the best results were obtained with catalyst **3** (aryl = 9-anthracenyl; Scheme 2).



Scheme 2. Brønsted acid catalyzed enantioselective multiple-reaction cascade for the synthesis of tetrahydropyridines.

In further optimization we focused on varying the reaction parameters including solvent, concentration, temperature, catalyst loading, and hydride source. In these experiments the best results with regard to reactivity and selectivity were obtained when the reaction cascade was performed at elevated temperatures in aromatic or halogenated solvents.

Using the optimal reaction conditions we investigated the scope of the new Brønsted acid catalyzed reaction cascade (Table 1). In general different enamines **1** as well as vinyl ketones **2** could be applied successfully in this multiple-reaction cascade, providing a diverse set of tetrahydropyridines[7] **9a–g** and azadecalinones[8] **10a–i** with different aromatic and aliphatic substitutents in good yields and with excellent enantioselectivities (89–99% *ee*). The constitution and absolute configuration of the new products was proven by X-ray crystal structure analysis as we were able to obtain suitable single crystals of tetrahydropyridine **9b** (Figure 1).

In summary, we have developed a new highly enantioselective Brønsted acid catalyzed multiple-reaction cascade based on a biochemical blueprint. In this new three-component reaction each step of the six-step sequence is catalyzed by the same chiral Brønsted acid allowing rapid, direct, and efficient access to valuable tetrahydropyridines and azadecalinones from simple readily available starting materials with the highest levels of enantiocontrol (Table 1). The work described here demonstrates that a single chiral Brønsted acid catalyst can facilitate a series of different reaction steps to construct complex molecular structures in a highly stereoselective fashion; this again proves chiral Brønsted acids to be powerful and effective tools for organic synthesis.

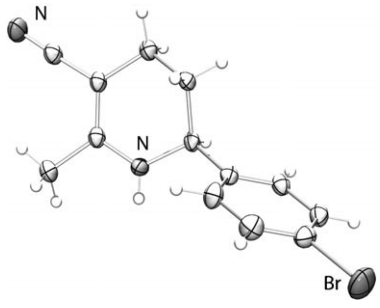
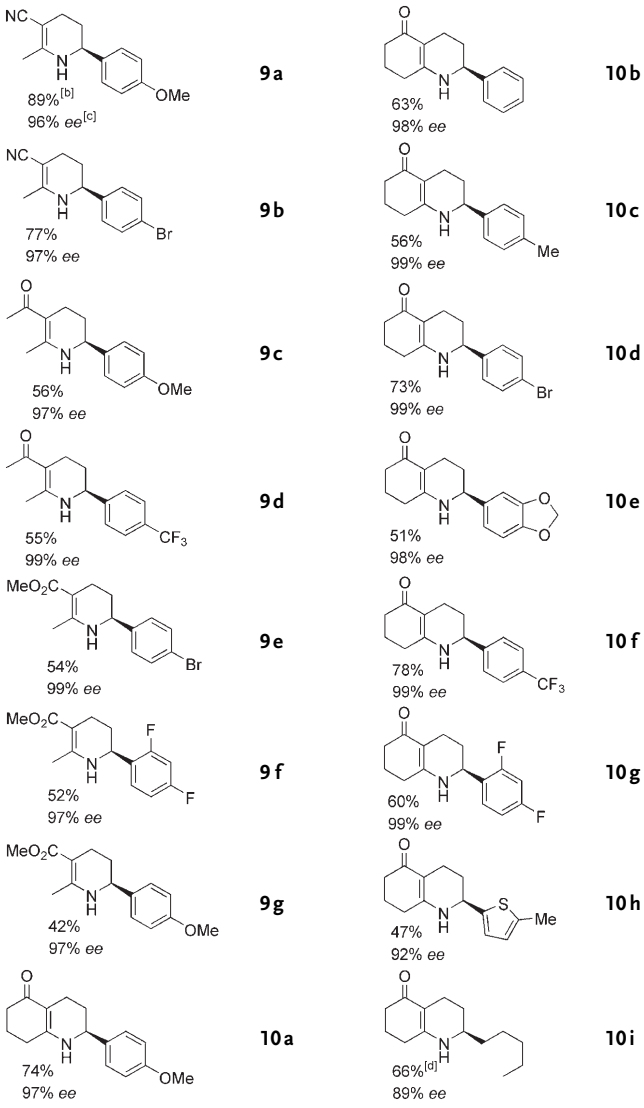


Figure 1. Molecular structure of tetrahydropyridine **9b**.

Table 1: Scope of the enantioselective Brønsted acid catalyzed cascade reaction.[a]



[a] Reactions were performed with enamine **1**, vinyl ketone **2** (1.2 equiv), Hantzsch ester **8** (1.1 equiv), and catalyst **3** (5 mol%) at 50°C in chloroform or benzene [b] Yields were determined after column chromatography. [c] Determined by HPLC on using a stationary phase. [d] Ketone (2 equiv) and Hantzsch ester (2 equiv).

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[11] Intermediates **4**, **6**, and **7** can be detected by GC-MS analysis of the reaction mixture. Additionally, small amounts of 1,2-dihydropyridine have been isolated which are presumably formed from 1,4-dihydropyridine **6**.

