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Enantioselective Brønsted Acid Catalyzed Transfer Hydrogenation: Organocatalytic Reduction of Imines

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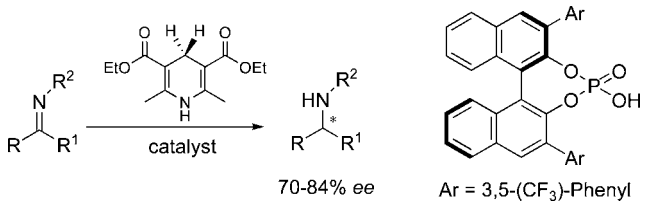
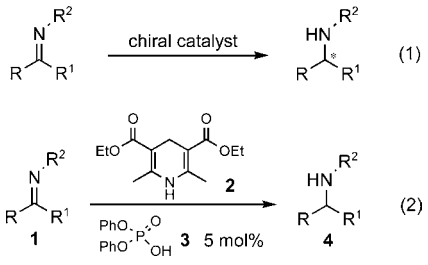
ABSTRACT



The first enantioselective Brønsted acid catalyzed reduction of imines has been developed. This new organocatalytic transfer hydrogenation of ketimines with Hantzsch dihydropyridine as the hydrogen source offers a mild method to various chiral amines with high enantioselectivity. The stereochemistry of the chiral amines can be rationalized by a stereochemical model derived from an X-ray crystal structure of a chiral BINOL phosphate catalyst.

The enantioselective reduction of imines to obtain chiral amines still represents a challenging topic. Although many highly enantioselective hydrogenations of ketones and alkenes are known, only less effective reductions of imines are available. Current methods include transition metal catalyzed high-pressure hydrogenations,[1] hydrosilylations,[2] or transfer hydrogenations,[3] using a variety of chiral Pd, Ti, Rh, Ru, and Ir-complexes (eq 1).



Recently, chiral Brønsted acids[4] have become an important alternative to metal catalysts, and examples of highly enantioselective nonmetallic transformations, based on chiral thiourea,[5] diol,[6] amidinium,[7] and phosphate[8] catalysts have been reported. These reactions, similar to several enzymatic processes, proceed through hydrogen bonding activation.

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(2) Recent reviews, see: (a) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943. (b) Carpentier, J. F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913. Organocatalytic hydrosilylation: Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Koèovský, P. *Org. Lett.* **2004**, *6*, 2253.

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(4) For reviews on chiral Brønsted acid catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062.

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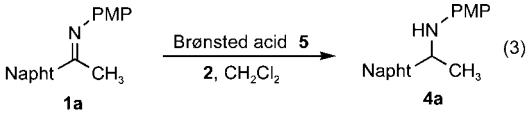
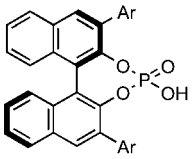
The purpose of this communication is to describe the first enantioselective Brønsted acid-catalyzed hydrogenation of ketimines.[9] We found that several proton acids, such as diphenyl phosphate **3**, catalyze the reduction of imines **1** under hydrogen-transfer conditions with Hantzsch dihydropyridine **2** as the hydrogen source (eq 2).[10]

This observation encouraged us to explore a catalytic enantioselective variant of this process, as it would be the first example of an enantioselective proton-acid-catalyzed hydrogenation of imines. Initial experiments focused the asymmetric reduction by examining various commercial chiral proton acids. However, none of the acids tested afforded satisfactory yields and selectivities. Therefore, we decided to prepare chiral Brønsted acids **5a**−**f** and tested these catalysts in the reduction of ketimine **1a** (Table 1).

Table 1. Survey of Chiral Catalysts for the Hydrogenation





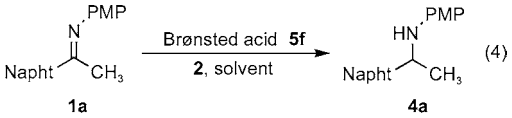
5a: Ar = Mesityl
5b: Ar = 9-Phenanthryl
5c: Ar = 1-Naphthyl
5d: Ar = 2-Naphthyl
5e: Ar = 4-Biphenyl
5f: Ar = 3,5-(CF_3)-Phenyl

entry[a]	catalyst	yield [%][b]	ee [%][c]
1	**5a**	20	*rac*
2	**5b**	42	38
3	**5c**	37	44
4	**5d**	54	40
5	**5e**	59	48
6	**5f**	57	62

[a] Reactions were performed with imine **1a** and **2** (1.4 equiv) at 0.02 M concentration in dichloromethane for 16 h. [b] Yield after chromatography. [c] Enantiomeric excess was determined by HPLC using Chiracel OD-H or AD-H columns.

First asymmetric transfer-hydrogenations were perfomed with imine **1a** and Hantzsch dihydropyridine **2** in dichloromethane catalyzed by the corresponding Brønsted acid **5a**−**f**. From this survey Brønsted acids **5b**−**f** emerged as catalysts with promising levels of enantioselection (Table 1, entry 2−6). Best selectivities were obtained with catalyst **5f** providing amine **4a** with 62% ee (Table 1, entry 6) and showing that not only steric but also electronic effects play a role in this transformation. Further examination of the reduction concentrated on the solvent employed (Table 2).

Table 2. Solvent Survey of the Transfer Hydrogenation



entry[a]	solvent	yield [%][b]	ee [%][c]
1	methanol	-	-
2	acetonitrile	34	14
3	dichloromethane	57	62
4	chloroform	47	50
5	toluene	38	70
6	benzene	59	70

[a] Reactions were performed with imine **1a** and **2** (1.4 equiv) at 0.02 M concentration in dichloromethane for 16 h. [b] Yield after chromatography. [c] Enantiomeric excess was determined by HPLC using Chiracel OD-H or AD-H columns.

From this comparison, nonpolar solvents proved to be essential. No reaction was observed in polar protic media such as methanol (Table 2, entry 1). However, better selectivities were observed in chlorinated solvents (Table 2, entry 3 and 4), and the best yields and selectivities were obtained with catalyst **5f** in benzene at 60 °C (Table 2, entry 6). Lowering the temperature resulted in a lower conversion, and lowering the concentration yielded diminished enantioselection. Both conversion and enantioselectivity decreased when the reaction was performed in more concentrated solution, indicating that the generated Hantzsch pyridine is inhibiting the reaction rate.

Under the optimized conditions we explored the scope of the Brønsted acid catalyzed hydrogenation of various imines (Table 3). In general, high enantioselectivities and good yields of several *N*-aryl-ketimines derived from methyl-aryl

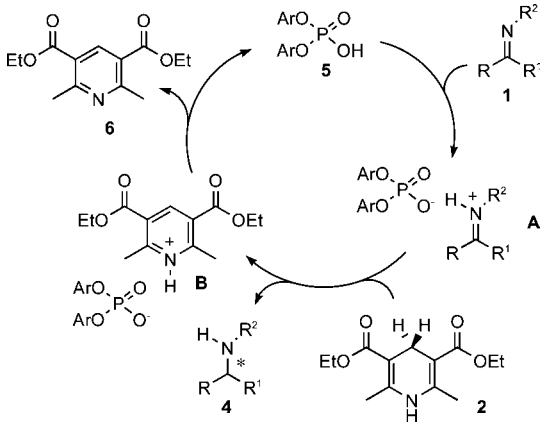


Figure 1. Proposed mechanism for the transfer hydrogenation.

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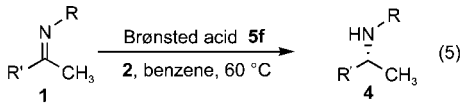
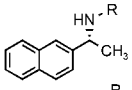
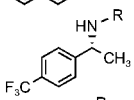
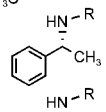
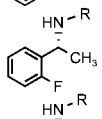
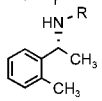
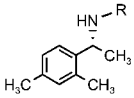
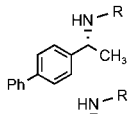
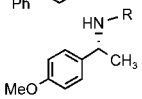
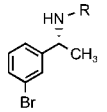
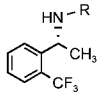
Table 3. Scope of the Catalytic Enantioselective Reduction



Entry[a]		Amine 4	Yield [%][b]	*ee* [%][c]
1	**4a** R = PMP		82	70 94[d]
2	**4b** R = Ph		69	68
3	**4c** R = PMP		71	72
4	**4d** R = Ph		58	70
5	**4e** R = PMP		76	74
6	**4f** R = Ph		71	72
7	**4g** R = PMP		82	84
8	**4h** R = PMP		74	78
9	**4i** R = PMP		91	78
10	**4j** R = PMP		71	74 98[d]
11	**4k** R = PMP		76	72
12	**4l** R = PMP		62	72
13	**4m** R = PMP		46	82

[a] Reactions were performed with imine **1** (0.2 mmol) and dihydropyridine **2** (1.4 equiv) at 60 °C in benzene using 20 mol % catalyst **5f** at 0.05 M concentration. [b] Yield of **4** after chromatography. [c] Enantiomeric excess was determined by HPLC using Chiracel OD-H or AD-H columns. [d] After one recrystallization from methanol.

ketones are observed. Recrystallization of amines **4a** and **4j** from methanol increased the enantioselectivities up to 94% and 98% ee, respectively.

Mechanistically we assume that activation of ketimine **1** by protonation through Brønsted acid **5** will generate the iminium **A**. Subsequent hydrogen transfer from the dihydropyridine **2** yields the chiral amine **4** and pyridinium salt **B**, which undergoes proton transfer to regenerate Brønsted acid **5** (Figure 1).

The absolute configuration of the amines **4** can be explained by stereochemical model derived from the X-ray crystal structure **5c** (Figure 2). In the transition state, the ketimine is activated by the Brønsted acid, thereby favoring approach of the nucleophile from the less hindered *si* face, as the *re* face is effectively shielded by the aryl group of the catalyst.

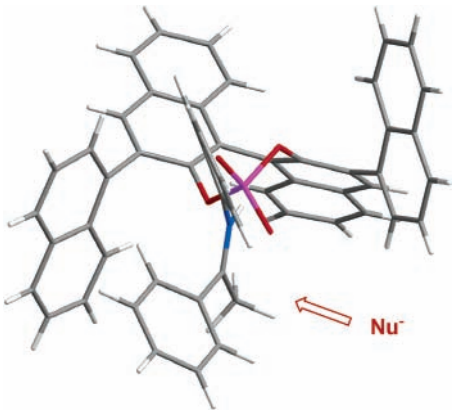


Figure 2. Plausible transition structure **A** derived from an X-ray crystal structure of chiral Brønsted acid **5c**. Stereochemical rationale for the transfer hydrogenation.

In summary, we developed the first enantioselective Brønsted acid catalyzed reduction of ketimines. The mild reaction conditions and generally good chemoselectivity of this metal-free transfer hydrogenation render this transformation an attractive approach to optically active amines.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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