

An Enantioselective Chiral Brønsted Acid Catalyzed Imino–Azaenamine Reaction

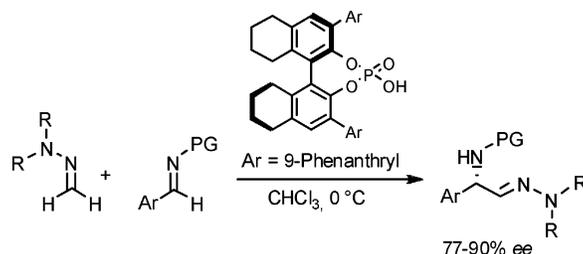
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ABSTRACT



The enantioselective Brønsted acid catalyzed addition of methyleneaminopyrrolidine to *N*-Boc imines has been achieved in the presence of chiral phosphoric acids derived from 3,3'-di(phenanthryl)-H8-BINOL. The corresponding aminohydrazone have been isolated in good yields with enantiomeric excesses up to 90%.

The application of Brønsted acids in organic syntheses continues to rise, and a number of catalytic asymmetric transformations have been developed in recent years.¹ The major function of Brønsted acids in these reactions is the protonation of the electrophile, which is thereby activated to react with a corresponding nucleophile. Often catalytic amounts of Brønsted acids are sufficient to achieve complete product formation.

Recently, we and others reported on the application of chiral BINOL-phosphates in the development of highly enantioselective transformations.^{2–6} In the first step of these

reactions, a proton is transferred from the Brønsted acid to the substrate resulting in the formation of a chiral ion pair which subsequently undergoes reaction with a nucleophile

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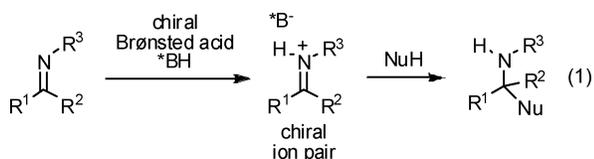
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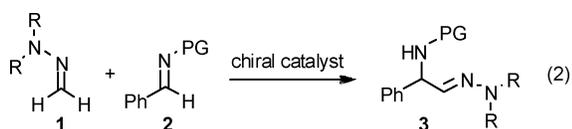
(1) For reviews, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (d) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

to form the corresponding amine and the regenerated Brønsted acid (eq 1).



On the basis of this concept of chiral ion pair catalysis, we were recently successful in developing highly enantioselective reactions, such as the first Brønsted acid catalyzed transfer hydrogenations,³ cascade reductions,⁴ hydrocyanations,⁵ or domino Mannich–Michael reactions.⁶

Herein, we report the development of yet another highly enantioselective Brønsted acid catalyzed transformation, an asymmetric imino ene type reaction (eq 2). The reaction



consists of a new BINOL-phosphate catalyzed addition of methylene-hydrazines **1** to *N*-Boc-protected imines **2** to afford chiral aminohydrazones **3** (eq 2).⁷

Chiral hydrazones have proven to be important synthetic intermediates that can be readily derivatized to many useful chiral blocks, including amino-aldehydes, amino-nitriles, or diamines, without any racemization (Figure 1).⁸

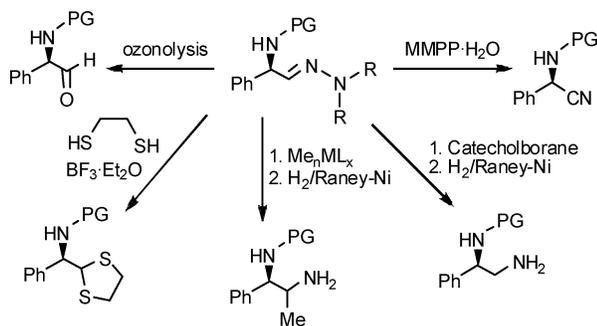


Figure 1. Derivatization of chiral aminohydrazones.

Given the value of these products, we decided to develop an enantioselective Brønsted acid catalyzed synthesis of aminohydrazones.

(4) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Synlett* **2006**, 1071. (b) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683.

(5) (a) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (b) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, in print.

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Initially, we started our investigations with the evaluation of different methylene-hydrazines **1a–d** which can simply be prepared on a large scale.^{8a,9} The BINOL-phosphate catalyzed reactions were performed with *N*-Boc aldimine **2a** in the presence of 5 mol % of Brønsted acid catalyst **4a** (Figure 2) in chloroform at 0 °C (Table 1).

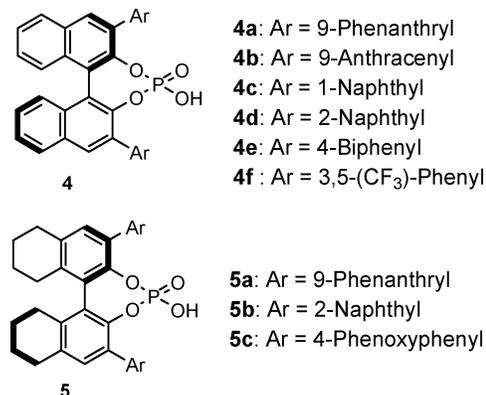


Figure 2. Chiral Brønsted acid catalysts.

From this survey, the best reactivities and selectivities were obtained when piperidine- and pyrrolidine-derived methyl-

Table 1. Survey of Different Methylene-hydrazines

entry ^a	RRN	ee [%] ^b
1	1a	14
2	1b	61
3 ^c	1c	–
4 ^c	1d	–

^a Reactions were performed with aldimine **2a** (1.2 equiv) and methylene-hydrazines **1a–d** at 0.15 M concentration in chloroform at 0 °C for 16 h.

^b Enantiomeric excess was determined by HPLC using Chiralcel OD-H or Chiralpak AD-H columns. ^c No product formation was observed.

ene-hydrazines **1a** and **1b** were employed, and the corresponding products were obtained with 14% ee and 61% ee,

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respectively (Table 1, entries 1 and 2). Interestingly, no reaction to the desired products occurred with methylene-hydrazines **1c** and **1d** (Table 1, entries 3 and 4).

Encouraged by the successful additions, we decided to evaluate various aldimines with different protecting groups¹⁰ in combination with methylene-hydrazines **1a** and **1b** in the Brønsted acid catalyzed imino ene type reaction. The results of this examination are summarized in Table 2. The highest

Table 2. Survey of Different Imines in Combination with **1a,b**

entry ^a	R ¹	hydrazone	ee [%] ^b
1	CO ₂ ^t Bu	1a	14
2	CO ₂ ^t Bu	1b	61
3	CO ₂ CH ₂ Ph	1a	rac
4	CO ₂ CH ₂ Ph	1b	50
5	C(O)Ph	1a	rac
6	C(O)Ph	1b	15
7 ^c	PhCH ₂	1b	-
8 ^c	4-F-PhCH ₂	1b	-
9 ^c	4-BrPh	1b	-

^a Reactions were performed with methylene-hydrazines **1a,b** and aldimines **2** (1.2 equiv) at 0.15 M concentration in chloroform at 0 °C for 16 h. ^b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H or Chiralpak AD-H columns. ^c Cross over product was isolated.¹¹

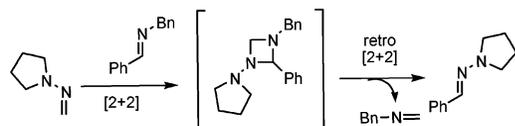
enantioselectivities were obtained with *N*-Boc-protected aldimine **2a** and the pyrrolidine-derived hydrazone **1b** (61% ee, Table 2, entry 2). Application of *N*-benzyloxycarbonyl- or *N*-benzoyl-protected aldimines resulted in the corresponding products with 50% ee and 15% ee (Table 2, entries 4 and 6). In contrast, a dramatic decrease in enantioselectivity was observed when the reaction was performed with the piperidine-derived hydrazone **1a**. For instance, reaction of **1a** with the aldimine **2a** gave the hydrazone **3** with 14% ee (Table 2, entry 1). No enantioselection was observed with *N*-benzyloxy-carbonyl- or *N*-benzoyl-protected aldimines under the otherwise same reaction conditions (Table 2, entries 3 and 5). In the case of *N*-benzyl- and *N*-aryl-protected aldimines (Table 2, entries 7–9), only cross over products were isolated.¹¹

Our further examination of this valuable transformation concentrated on the solvents employed, as earlier experiments

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(11) The formation of the cross over products has been reported before: Fernandez, R.; Martin-Zamora, E.; Lassaletta, J. M. *Synlett* **2001**, 1158.



suggested that solvent effects can play a crucial role in obtaining good yields and high enantioselectivities.^{3–6} Indeed, the survey of the reaction media revealed that the Brønsted acid catalyzed addition is strongly dependent on the solvent, and better enantioselectivities were observed in halogenated solvents (Table 3, entries 1, 2, and 4), as compared to

Table 3. Evaluation of Solvents

entry ^a	solvent	yield [%] ^b	ee [%] ^c
1	CHCl ₃	98	77
2	CH ₂ Cl ₂	88	50
3	CH ₃ -Ph	99	12
4	CF ₃ -Ph	99	50

^a Reactions were performed with **1b** and aldimine **2d** (1.2 equiv) at 0.15 M concentration at 0 °C for 16 h. ^b Isolated yields after column chromatography. ^c Enantiomeric excess was determined by HPLC using Chiralcel OD-H columns.

nonpolar aromatic ones (Table 3, entry 2). The best results with respect to yields and enantioselectivities were obtained when the reaction was conducted in chloroform at 0 °C providing the product **3d** in 77% ee (Table 3, entry 1).¹²

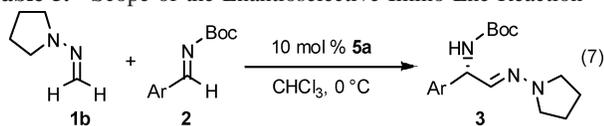
Subsequently, our reaction optimization focused on the catalyst architecture (Table 4). A comparison of various

Table 4. Survey of Chiral Catalysts

entry ^a	catalyst	yield [%] ^b	ee [%] ^c
1	4a	92	61
2	4b	52	61
3	4c	32	54
4	4d	72	25
5	4e	65	22
6	4f	68	rac
7	5a	73	74
8	5b	62	57
9	5c	78	rac

^a Reactions were performed with **1b** and aldimine **2a** (1.2 equiv) at 0.15 M concentration in chloroform at 0 °C for 16 h. ^b Isolated yields after column chromatography. ^c Enantiomeric excess was determined by HPLC using Chiralcel OD-H columns.

tested phosphoric acid catalysts **4a–f** and **5a–c** (Figure 2) reveals that the highest enantioselectivities are obtained with the sterically more demanding 3,3'-substituents (Table 4,

Table 5. Scope of the Enantioselective Imino Ene Reaction

entry ^a	product	Ar	yield [%] ^b	ee [%] ^c
1	3a		73	74 ^d
2	3b		81	90
3	3c		78	82
4	3d		82	85 91 ^e
5	3e		81	82
6	3f		48	83
7	3g		76	86
8	3h		71	77

^a Reactions were performed with **1b** and aldimines **2** (1.2 equiv) at 0.15 M concentration in CHCl_3 at 0 °C for 16 h. ^b Isolated yields after column chromatography. ^c Enantiomeric excess was determined by HPLC using Chiralcel OD-H or Chiralpak AD-H columns. ^d Performed with 5 mol % of catalyst. ^e After one recrystallization from hexane-dichloromethane.

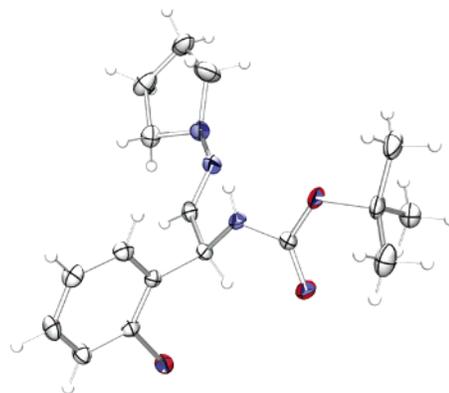
entries 1, 2, and 7), which is in agreement with our earlier findings.^{3–6} The best selectivities were obtained with Brønsted acid **5a** which gave the product **3a** in 73% yield with 74% ee (Table 4, entry 7).

With the optimized reaction conditions in hand, a variety of *N*-Boc-protected imines **2** were prepared and tested in the Brønsted acid catalyzed imino ene reaction. The results are summarized in Table 5. In general, a series of *N*-Boc-

(12) Selectivities did not improve when the reaction temperature was lowered to –20 or –40 °C.

protected aldimines bearing electron-withdrawing or electron-donating groups could be applied in the enantioselective reaction with methyleneamino-pyrrolidine resulting in the corresponding hydrazones **3a–h** in good isolated yields and with high enantioselectivities (77–90% ee).

The absolute configuration of the products was obtained from an X-ray crystal structure analysis of hydrazone **3d**. On the basis of this structure, the aminohydrazones **3** exhibit the *S*-configuration, which is in agreement with our previously described observations for BINOL-phosphate catalyzed reactions (Figure 3).^{3–6}

**Figure 3.** X-ray crystal structure of **3d**.

In summary, we have developed a new highly enantioselective Brønsted acid catalyzed imino–azaenamine reaction of various *N*-Boc-protected aldimines and methylene-aminopyrrolidine. The corresponding valuable aminohydrazones have been isolated in good yields and with high enantioselectivities. The mild reaction conditions of this metal-free process together with the operational simplicity and practicality not only render this approach a useful procedure for the synthesis of optically active aminohydrazones but also further expand the repertoire of enantioselective BINOL-phosphate catalyzed transformations.

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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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