Organocatalysis

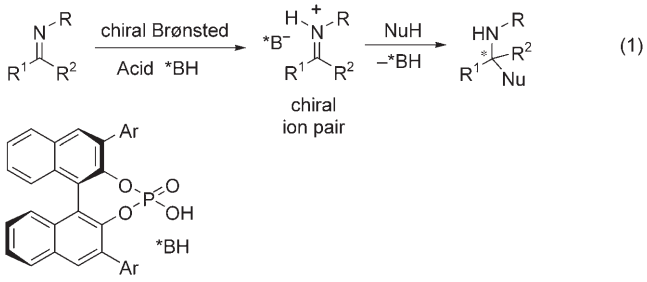
DOI: 10.1002/anie.200604809

# Chiral Brønsted Acids in the Catalytic Asymmetric Nazarov Cyclization—The First Enantioselective Organocatalytic Electrocyclic Reaction**

*Magnus Rueping,* Winai Ieawsuwan, Andrey P. Antonchick, and Boris J. Nachtsheim*

*Dedicated to Professor Gerhard Quinkert on the occasion of his 80th birthday*

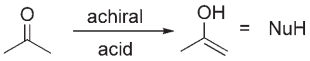
The application of chiral Brønsted acids in metal-free enantioselective catalysis is increasing rapidly.[1] Within the last two years the first highly enantioselective transformations have been developed in which chiral Brønsted acids function as biomimetic catalysts. The central role performed by the Brønsted acids in such reactions is the activation of the electrophile by catalytic protonation, thereby enabling them to react with a nucleophile. In this manner it has been possible to realise enantioselective transformations with aldimines and ketoimines using chiral Brønsted acids such as binol phosphates [Eq. (1)].[2–5] In these transformations a proton is




(1)

initially transferred from the Brønsted acid to an aldimine or ketoimine to form an intermediary chiral ion pair which subsequently reacts with a nucleophile to form the corresponding amine and the regenerated Brønsted acid.

Within this field of chiral ion pair catalysis, only aldimines and ketoimines have been activated to date. More recently, however, we have been successful in the activation of both the electrophile and the nucleophile in a new double Brønsted acid catalyzed reaction.[5] In these reactions the simultaneous and co-operative activation of the aldimine by the chiral binol phosphate *BH [Eq. (1)], and the carbonyl nucleophile by an achiral Brønsted acid [Eq. (2)], result in the desired products.[5]




(2)

The enantioselective Brønsted acid catalyzed activation of a "pure" carbonyl compound using a chiral binol phosphate has not previously been described. Here we report for the first time the development of such a reaction: a Brønsted acid catalyzed enantioselective Nazarov cyclization. The Nazarov reaction belongs to the group of electrocyclic reactions and is one of the most versatile methods for the synthesis of five-membered rings, which are the key structural elements of numerous natural products.[6] In general, the Nazarov cyclization can be catalyzed by Brønsted or Lewis acids. However, only a few asymmetric variations have been described, of which most require the use of large amounts of chiral metal complexes.[7]

Building on our previous results,[3–5] we decided to examine a metal-free Nazarov reaction catalyzed by a binol phosphate. This would not only be the first example of a Brønsted acid catalyzed, enantioselective, electrocyclic reaction but would additionally provide a simple and direct route to optically pure cyclopentenones.

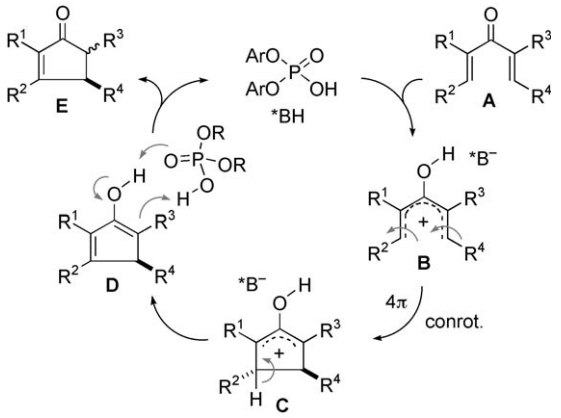
We assumed that the catalytic protonation of a divinylketone **A** by the binol phosphate (*BH) would result in the formation of an adduct **B**, which consisted of a cyclopentadienyl cation and a phosphate anion (Scheme 1). Subsequent conrotatory $4\pi$ electrocyclization would lead to oxyallyl cation **C** which, through the elimination of a proton, would form enolate **D**. Successive protonation of this enolate should then result in the formation of cyclopentenone **E** and the regenerated Brønsted acid catalyst *BH.

At the outset of our experimental work we searched for a suitable Brønsted acid catalyst for the enantioselective electrocyclization of dienone **2** (Table 1).[8] The initial reactions conducted with various binol phosphates **1a**–**1e** in toluene at 60 °C provided cyclopentenones **2a** and **2b** with enantioselectivities of up to 82 % *ee* (Table 1, entries 2 and 3). However, improved reactivity could be achieved by using the corresponding *N*-triflyl phosphoramides[9] **1f** and **1g**, which even at 0 °C gave complete conversion after ten minutes.

[*] Prof. Dr. M. Rueping, W. Ieawsuwan, Dr. A. P. Antonchick, B. J. Nachtsheim
Degussa Endowed Professorship
Institute of Organic Chemistry and Chemical Biology
Johann Wolfgang Goethe-University Frankfurt am Main
Max-von-Laue Strasse 7, 60438 Frankfurt am Main (Germany)
Fax: (+49) 69-798-29248
E-mail: m.rueping@chemie.uni-frankfurt.de

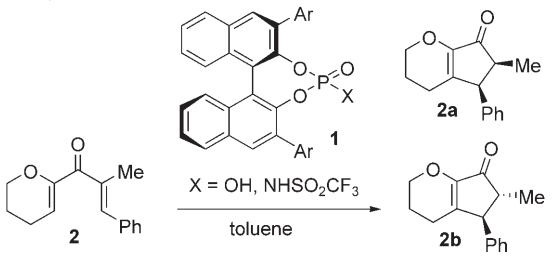
[**] We acknowledge Degussa AG for generous support and the Fonds der Chemischen Industrie for a stipend to B.J.N.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.




***Scheme 1.*** Brønsted acid catalyzed Nazarov cyclization.

***Table 1:*** Evaluation of Brønsted acids **1a**–**1g** in the enantioselective Nazarov cyclization.[a]



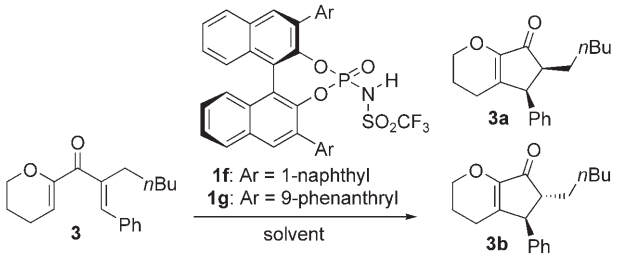

| Entry | Ar | X | **2a**/**2b**[b] | *ee* (**2a**), *ee* (**2b**)[c] |
|---|---|---|---|---|
| 1 | phenyl (**1a**) | OH | 1.5:1 | 64, 8 |
| 2 | 1-naphthyl (**1b**) | OH | 2.3:1 | 81, 55 |
| 3 | 9-anthracenyl (**1c**) | OH | 3.4:1 | 82, 60 |
| 4 | 4-biphenyl (**1d**) | OH | 1:1.5 | 73, 22 |
| 5 | 2-naphthyl (**1e**) | OH | 1:1 | 54, 9 |
| 6 | 1-naphthyl (**1f**) | $NHSO_2CF_3$[d] | 5.2:1 | 83, 96 |
| 7 | 9-phenanthryl (**1g**) | $NHSO_2CF_3$[d] | 7:1 | 86, 94 |

[a] Reaction conditions: **2**, 10 mol% **1**, in toluene at 60°C. [b] Determined by $^1$H NMR spectroscopy and HPLC analysis. [c] Enantiomeric excess (in %) determined by HPLC analysis (Chiralcel OD-H column). [d] Reactions at 0°C, 10 min.

Additionally, it was shown that the use of these catalysts significantly improved both the diastereoselectivity (*cis*/*trans* ratio up to 7:1) and the enantioselectivity (up to 96% *ee*; Table 1, entries 6 and 7).

Apart from various dienones, the solvent, temperature, as well as catalyst loading and concentration were varied in further experiments. These experiments showed that the reactivities and enantioselectivities of the Brønsted acid catalyzed Nazarov cyclization are strongly dependent on the solvent (Table 2). While no reactions are observed in polar solvents such as THF or acetonitrile, the products were formed in good yields and with very good selectivities in aromatic (Table 2, entries 1–4) and halogenated solvents (Table 2, entries 7–12). The best enantioselectivities were obtained in chloroform. Thus, the electrocyclization of **3** using 2 mol% of catalyst **1g**[10] at 0°C for one hour afforded the

***Table 2:*** Influence of solvents on the enantioselectivity of the organocatalytic Nazarov reaction.




| Entry[a] | Solvent | Catalyst | Yield [%][b] | **3a**/**3b**[c] | *ee* (**3a**), *ee* (**3b**)[d] |
|---|---|---|---|---|---|
| 1 | toluene[e] | **1f** | 90 | 1.8:1 | 69, 80 |
| 2 | toluene | **1f** | 90 | 3.8:1 | 75, 81 |
| 3 | benzene | **1f** | 67 | 4.4:1 | 72, 75 |
| 4 | $PhCF_3$ | **1f** | 65 | 2:1 | 67, 71 |
| 5 | $CH_3CN$ | **1f** | – | – | – |
| 6 | THF | **1f** | – | – | – |
| 7 | DCE | **1f** | 53 | 1.9:1 | 51, 68 |
| 8 | $CH_2Cl_2$ | **1f** | 77 | 2.1:1 | 68, 81 |
| 9 | $CHCl_3$ | **1f** | 86 | 2:1 | 89, 95 |
| 10 | $CHCl_3$ | **1g** | 95 | 3.5:1 | 90, 93 |
| 11 | $CHCl_3$ | **1g**[f] | 85 | 2.9:1 | 89, 89 |
| 12 | $CHCl_3$ | **1g**[f,g] | 78 | 3.2:1 | 91, 91 |

[a] Reaction conditions: **3**, 10 mol% **1** in 2 mL solvent at 0°C. [b] Yields of isolated product after chromatography. [c] Determined by $^1$H NMR spectroscopy. [d] Determined by HPLC analysis (*ee* value in %). [e] Reactions at room temperature. [f] 2 mol% catalyst. [g] In 1 mL $CHCl_3$. DCE = 1,2-dichloroethane.

diastereomers **3a** and **3b** with excellent enantiomeric excesses of 91% *ee*.

We applied various dienones to the Brønsted acid catalyzed enantioselective Nazarov reaction procedure under these optimized conditions (Table 3).[11] In general it was possible to successfully transfer differently substituted dienones **2**–**12** to the corresponding cyclopentenones in good yields and with excellent enantioselectivities (86–99% *ee*). The reaction is not only applicable to the alkyl- and aryl-substituted dienones **2**–**10** (Table 3, entries 1–9), but also to the dialkyl-substituted dienones **11** and **12** (Table 3, entries 10 and 11). Interestingly, the conversion of dienones **11** and **12** resulted exclusively in the *cis* isomer—in the latter case with a diastereomeric excess of 98% *de*.

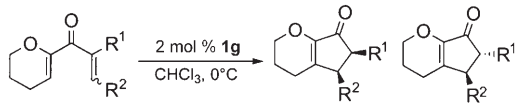
The absolute configuration of the products was obtained from a X-ray crystal-structure analysis. The *cis* product of compound **9a** has the *S* configuration at both stereogenic centers (Figure 1).

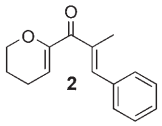
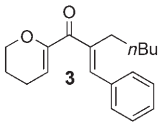
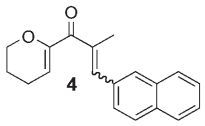
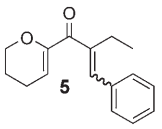
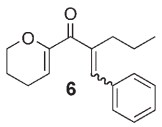
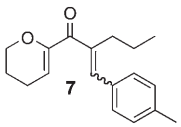
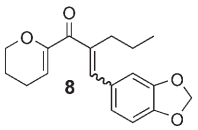
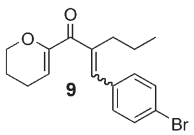
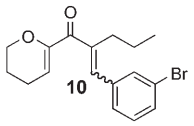
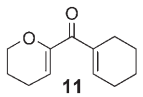
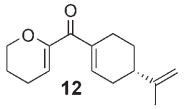
While our newly developed Brønsted acid catalyzed Nazarov reaction primarily generates the *cis*-cyclopentenones, the so far described asymmetric metal-catalyzed variations often provide the *trans* product.[7] To demonstrate that a route to these isomers is also possible we isomerized the *cis*-cyclopentenone **5a** to the corresponding *trans*-cyclopentenone **5b** without loss of enantiomeric purity [Eq. (3)].[10a]

Thus, we have developed an efficient Brønsted acid catalyzed process by which we are able to obtain all four possible stereoisomers with excellent enantioselectivities.

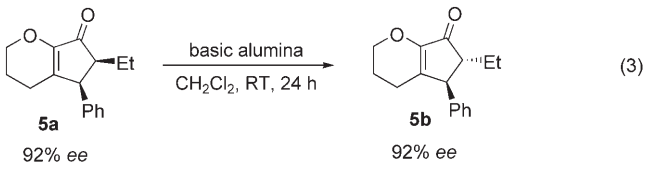
  

***Table 3:*** Scope of the enantioselective Brønsted acid catalyzed Nazarov cyclization.

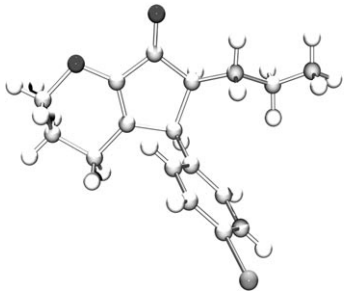



| Entry[a] | Substrate | *t* [h] | Yield [%][b] | *cis*/*trans*[c] | *ee* (*cis*), *ee* (*trans*)[d] |
|---|---|---|---|---|---|
| 1 |  | 2 | 88 | 6:1 | 87, 95 |
| 2 |  | 1 | 78 | 3.2:1 | 91, 91 |
| 3 |  | 2 | 92 | 9.3:1 | 88, 98 |
| 4 |  | 2 | 61 | 4.3:1 | 92, 96 |
| 5 |  | 1 | 85 | 3.2:1 | 93, 91 |
| 6 |  | 1 | 77 | 2.6:1 | 91, 90 |
| 7 |  | 1 | 83 | 1.5:1 | 87, 92 |
| 8 |  | 1.5 | 87 | 4.6:1 | 92, 92 |
| 9 |  | 2 | 72 | 3.7:1 | 90, 91 |
| 10 |  | 4.5 | 68 | *cis* | 86, – |
| 11 |  | 6 | 45 | *cis* | [e] |

[a] Reaction conditions: substrate, 2 mol% **1g** in 1 mL $CHCl_3$ at 0°C. [b] Yields of isolated product after chromatography. [c] Determined by $^1$H NMR spectroscopy. [d] Determined by HPLC analysis. [e] Diastereomeric excess: 98%; 61% *de* with diphenyl phosphate.




(3)



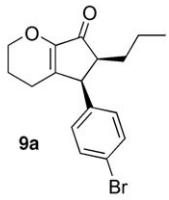



***Figure 1.*** Molecular structure of **9a**.

In conclusion we have developed the first enantioselective Brønsted acid catalyzed Nazarov reaction. This efficient method is not only the first example of an organocatalytic electrocyclic reaction but it also provides the corresponding cyclopentenones in good yields and with excellent enantioselectivities (86–98% *ee*). The Nazarov reaction introduced here represents the first enantioselective activation of a carbonyl group catalyzed by a binol phosphate. Compared to the metal-catalyzed reaction, special features of our new Brønsted acid catalyzed electrocyclization are the lower catalyst loadings (2 mol%), higher enantioselectivities, access to all possible stereoisomers, as well as the mild conditions and fast reaction times.

Received: November 27, 2006
Published online: February 5, 2007

**Keywords:** binol phosphate · Brønsted acids · electrocyclization · ion-pair catalysis · Nazarov cyclization

[1] Reviews: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; c) C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758; d) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; f) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999.

[2] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804; d) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583; e) T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523; f) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696; g) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 13; h) S. Hofmann, A. M. Seayad, B. List,

*Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; i) T. Akiyama, Y. Tamura, J. Itoh, H. Morita, K. Fuchibe, *Synlett* **2006**, 141; j) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; k) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1087; l) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; m) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; n) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; o) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175; p) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; q) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368; r) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; s) application of triflyl phosphoramides: D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626.

[3] a) M. Rueping, C. Azap, E. Sugiono, T. Theissmann, *Synlett* **2005**, 2367; b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; c) M. Rueping, A. P. Antonchick, T. Theissmann, *Synlett* **2006**, 1071; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751.

[4] a) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; b) M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, in press.

[5] M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832.

[6] Reviews on the Nazarov cyclization: a) K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. React.* **1994**, *45*, 1–158; b) S. E. Denmark in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Flemming), Pergamon, Oxford, **1991**, p. 51; c) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577; d) H. Pellissier, *Tetrahedron* **2005**, *61*, 6479; e) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193.

[7] Metal-catalyzed enantioselective Nazarov reactions: a) G. Liang, S. N. Gradl, D. Trauner, *Org. Lett.* **2003**, *5*, 5931; b) V. K. Aggarwal, A. J. Belfield, *Org. Lett.* **2003**, *5*, 5075; asymmetric Nazarov reactions through enantioselective protonations: c) G. Liang, D. Trauner, *J. Am. Chem. Soc.* **2004**, *126*, 9544.

[8] Dienones **2**–**12** have been chosen on the basis of the favored s-*trans*/s-*trans* orientation and the stabilization of the oxyallyl cation formed as an intermediate.

[9] The *N*-triflyl phophoramides **1f** and **1g** were prepared by a slightly modified procedure of Nakashima and Yamamoto (Ref. [2s]).

[10] Examples of Nazarov reactions with low catalyst loadings: a) T. K. Jones, S. E. Denmark, *Helv. Chim. Acta* **1983**, *66*, 2377; b) S. Giese, F. G. West, *Tetrahedron* **2000**, *56*, 10221; c) W. He, X. F. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2003**, *125*, 14278; d) C. Bee, E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 4927; e) M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2004**, *126*, 6846.

[11] A comparison of catalysts **1f** and **1g** is given in the Supporting Information.