*Organocatalysis*

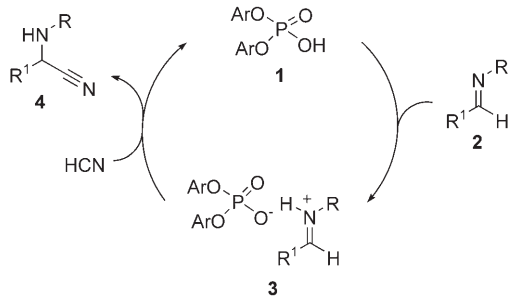
DOI: 10.1002/anie.200504344

# A Highly Enantioselective Brønsted Acid Catalyst for the Strecker Reaction**

*Magnus Rueping,* Erli Sugiono, and Cengiz Azap*

The hydrocyanation of imines, the Strecker reaction, is a practical and direct method to α-amino acids.[1] Consequently, various attempts to develop asymmetric Strecker reactions have been made.[2] In addition to metal-catalyzed cyanations using chiral Al, Ti, Zr, and lanthanide catalysts,[3] promising metal-free, enantioselective variants of this reaction have recently been disclosed. These include processes based on chiral guanidines,[4] ureas and thioureas,[5] bis(*N*-oxides),[6] and ammonium salts.[7] Given the importance of the Strecker reaction and the resulting products, we report herein a new type of Brønsted acid catalyst[8] for this transformation, a chiral binol phosphate (binol = 2,2′-dihydroxy-1,1′-binaphthyl).

The starting point for our development of this new catalyst for the enantioselective Strecker reaction was the successful application of Brønsted acid catalysts of type **1** in asymmetric transformations,[9,10] originally reported by Akiyama and Terada. Recently we reported a Brønsted acid catalyzed transfer hydrogenation of imines and quinolines[10] using binol phosphates **1**. Based on this reaction, we reasoned that activation of imine **2** by catalytic protonation would generate the iminium **3** which would subsequently undergo addition of HCN to give the desired amino nitrile **4** and the regenerated Brønsted acid **1** (Scheme 1). Thus we prepared




***Scheme 1.*** Assumed catalytic cycle for imine activation by binol phosphate **1**.

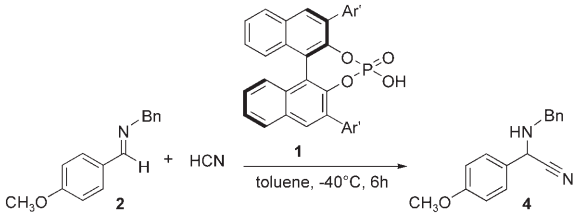
[*] Prof. M. Rueping, E. Sugiono, C. Azap
Degussa Endowed Professorship
Institute for Organic Chemistry und Chemical Biology
Johann Wolfgang Goethe University Frankfurt am Main
Marie-Curie-Strasse 11, 60439 Frankfurt am Main (Germany)
Fax: (+49) 69-798-29248
E-mail: M.rueping@chemie.uni-frankfurt.de

[**] The authors acknowledge Degussa AG for generous funding.
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

several binol phosphates and tested the corresponding catalysts **1a–g** in the enantioselective Strecker reaction. Initial explorations, however, concentrated on varying reaction parameters, such as different protected imines, cyanide sources, catalyst loading, temperature, and concentration.[11] The best results, with respect to yield and selectivity, were obtained with benzyl-protected imines and HCN at −40 °C using 10 mol % of catalyst.

The influence of the substituent Ar′ on the catalytic behavior was studied (Table 1). From this survey sterically more congested Brønsted acids emerged as catalysts with good to excellent levels of enantioselectivity. Best selectivities were obtained with catalyst **1g** providing the benzyl-protected amino nitrile **4** in 93 % *ee* (Table 1, entry 7).

***Table 1:*** Survey of chiral Brønsted acid catalysts **1a–g** for the Strecker reaction.

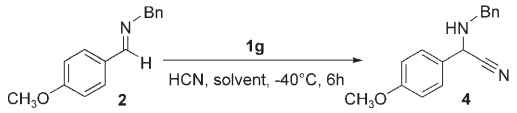



| Entry[a] | Ar′ | *ee* [%][b] |
|---|---|---|
| 1 | phenyl (**1a**) | 26 |
| 2 | 4-biphenyl (**1b**) | 60 |
| 3 | 1-naphthyl (**1c**) | 84 |
| 4 | 2-naphthyl (**1d**) | 32 |
| 5 | 3,5-$(CF_3)_2C_6H_3$ (**1e**) | 38 |
| 6 | 3,5-$(C_6H_5)_2C_6H_3$ (**1f**) | *rac* |
| 7 | 9-phenanthryl (**1g**) | 93 |

[a] Reactions were performed with imine **2** (Bn = benzyl), HCN (1.5 equiv) at 0.15 M concentration in toluene using 10 mol % of catalyst **1**. [b] Determined by HPLC analysis using a Chiralcel OD-H column.

Futher examinations concentrated on the solvent employed (Table 2). While the hydrocyanations could be performed in all the solvents tested, the best selectivities were achieved in nonpolar aromatic solvents (Table 2, entry 1), followed by chlorinated solvents (entries 2 and 3). This trend

***Table 2:*** Influence of solvent on the enantioselectivity of the Strecker reaction.




| Entry[a] | Solvent | *ee* [%][b] |
|---|---|---|
| 1 | toluene | 93 |
| 2 | chloroform | 60 |
| 3 | dichloromethane | 44 |
| 4 | acetonitrile | *rac* |
| 5 | THF | *rac* |

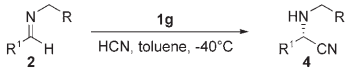
[a] Reactions were performed with imine **2**, HCN (1.5 equiv) at 0.15 M concentration using 10 mol % of catalyst. [b] Determined by HPLC analysis using a Chiralcel OD-H column.

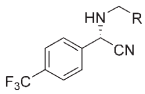
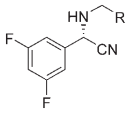
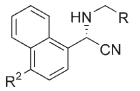
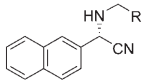
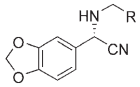
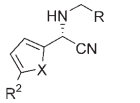
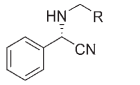
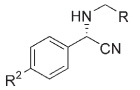
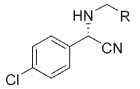
is in accordance with our observations on Brønsted acid catalyzed hydride transfer reactions.[10]

With the optimized conditions we explored the scope of the Brønsted acid catalyzed hydrocyanation of various imines (Table 3). In general, aromatic and heteroaromatic, *N*-benzyl- and *N*-*para*-methoxybenzyl-protected amines, bearing either electron-withdrawing or electron-donating groups were obtained in high enantioselectivities and good yields.[12]

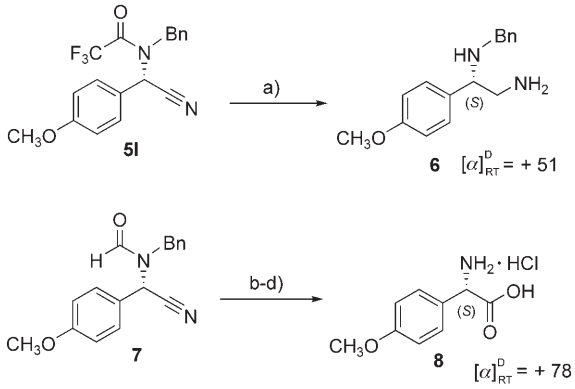
Important products from the Strecker reaction are the amino nitriles which can be converted into amino acids and diamines. Hence, to demonstrate the preparation of these compounds and to determine the absolute configuration of the products, amino nitrile **5l** was reduced and deacetylated to afford the corresponding diamine **6** (Scheme 2).[13] In addition, the formylated amino nitrile **7** was subjected to hydrolysis with subsequent debenzylation to yield amino acid **8**.[5b]

***Table 3:*** Scope of the Strecker reaction.




| Entry[a] | 2 | R | 4 | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **2a** | Ph |  | 75 | 97 |
| 2 | **2b** | *p*-$H_3COC_6H_4$ | | 53 | 96 |
| 3 | **2c** | Ph |  | 59 | 98 |
| 4 | **2d** | Ph, $R^2=H$ |  | 85 | 99 |
| 5 | **2e** | Ph, $R^2=OCH_3$ | | 70 | 94 |
| 6 | **2f** | Ph |  | 71 | 85 |
| 7 | **2g** | Ph |  | 88 | 93 |
| 8 | **2h** | Ph, X=S, $R^2=H$ |  | 77 | 95 |
| 9 | **2i** | Ph, X=O, $R^2=H$ | | 84 | 89 |
| 10 | **2j** | Ph, X=O, $R^2=CH_3$ | | 85 | 92 |
| 11 | **2k** | *p*-$H_3COC_6H_4$ |  | 87 | 89 |
| 12 | **2l** | Ph, $R^2=OCH_3$ |  | 97 | 93 |
| 13 | **2m** | Ph, $R^2=CH_3$ | | 55 | 87 |
| 14 | **2n** | Ph |  | 69 | 85 |
| 15 | **2o** | *p*-$H_3COC_6H_4$ | | 60 | 86 |

[a] Reactions were performed with imine **2**, HCN (1.5 equiv) at −40 °C in toluene at 0.15 M concentration for 2–3 days using 10 mol% of catalyst. [b] Yield of the isolated trifluoroacetamides **5** after acetylation of the corresponding amino nitriles **4** and chromatography. [c] Determined by HPLC analysis using Chiralcel OD-H or ADH-columns.




***Scheme 2.*** Reduction and hydrolysis of amino nitriles **5l** and **7**. a) $LiAlH_4$, $Et_2O$; b) 65% (w/v) $H_2SO_4$, 45 °C, 20 h; c) HCl (conc.), 70 °C, 12 h; d) $H_2$/Pd-C, MeOH.

The observed *S*-configuration of the products can be explained by a stereochemical model derived from the X-ray crystal structure of binol phosphate **1g**. In the transition state, the imine is activated by the Brønsted acid **1g**, thereby forming iminium **3**. This process favors the approach of the cyanide nucleophile from the less hindered *Re*-face rather than the *Si*-face which is efficiently shielded by the large phenanthryl group of the catalyst (Figure 1).

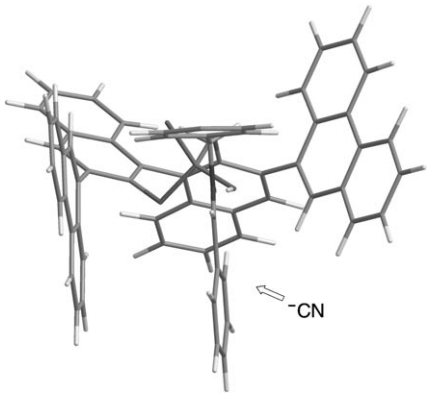



***Figure 1.*** Conceivable transition structure derived from an X-ray crystal structure of chiral Brønsted acid **1g** and optimization calculations.

In summary, we have developed an organocatalytic hydrocyanation of imines, which provides direct access to a diverse range of aromatic amino nitriles and the corresponding amino acids and diamines in high enantioselectivity. The use of binol phosphates as efficient Brønsted acid catalysts in the enantioselective Strecker reaction not only increases the diversity of possible transformations with this catalyst but also shows the great potential of this type of Brønsted acid in asymmetric catalysis. Experiments to establish a more detailed mechanism of activation and the application of this

catalyst to the hydrocyanation of ketimines and to other reactions of imines with related nucleophiles are currently under investigation.

Received: December 6, 2005
Published online: March 17, 2006

**Keywords:** amino acids · binol phosphate · Brønsted acids · organocatalysis · Strecker reaction

[1] A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27.
[2] For reviews, see: a) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795; b) L. Yet, *Angew. Chem.* **2001**, *113*, 900; *Angew. Chem. Int. Ed.* **2001**, *40*, 875; c) C. Spino, *Angew. Chem.* **2004**, *116*, 1796; *Angew. Chem. Int. Ed.* **2004**, *43*, 1764.
[3] Al catalysts: a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315; b) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716; *Angew. Chem. Int. Ed.* **2000**, *39*, 1650; Ti catalysts: c) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284; d) J. J. Byrne, M. Chavarot, P.-Y. Chavant, Y. Valleé, *Tetrahedron Lett.* **2000**, *41*, 873; e) N. S. Josephsohn, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 11594; Zr catalysts: f) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186; g) S. Kobayashi, H. Ishitani, *Chirality* **2000**, *12*, 540; Lathanide catalysts: h) M. Chavarot, J. J. Byrne, P.-Y. Chavant, Y. Valleé *Tetrahedron: Asymmetry* **2001**, *12*, 1147; i) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634.
[4] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157.
[5] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; d) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; e) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, 1919; f) S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995.
[6] For the application of stoichiometric amounts of bis(*N*-oxides), see: a) B. Liu, X. Feng, F. Chen, G. Zhang, X. Cui, Y. Jiang, *Synlett* **2001**, 1551; b) Z. Jiao, X. Feng, B. Liu, F. Chen, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2003**, 3818.
[7] J. Huang, E. J. Corey, *Org. Lett.* **2004**, *6*, 5027.
[8] For reviews on chiral Brønsted acid catalysis, see: 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.
[9] 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) S. Hofmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; f) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 13; g) T. Akiyama, Y. Tamura, J. Itoh, H. Morita, K. Fuchibe, *Synlett* **2006**, 141; h) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.
[10] 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, *Angew. Chem./Angew. Chem. Int. Ed.* **2006**, in press.
[11] *N*-Boc-, *N*-tosyl-, *N*-phenyl-, *N*-benzhydryl-, and *N*-phosphinoyl-protected imines gave inferior results compared to the *N*-benzyl-protected ones. As cyanide sources we tested acetone cyanohydrine, trimethylsilyl cyanide, and HCN. Reduction of catalyst loading, temperature, and concentration resulted in loss of enantioselectivities.
[12] Enantioselectivities decreased in the case of aliphatic imines, for example, 2-(benzylamino)-3-methylbutane nitrile was obtained in 55% *ee*.
[13] N. A. Hassan, E. Bayer, J. C. Jochims, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3747.