J|A|C|S COMMUNICATIONS

Published on Web 05/11/2009

Chiral Arylaminophosphonium Barfates as a New Class of Charged Brønsted Acid for the Enantioselective Activation of Nonionic Lewis Bases

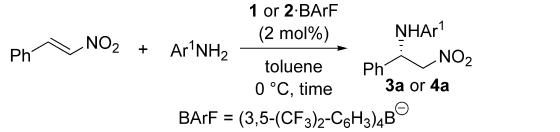
Daisuke Uraguchi, Daisuke Nakashima, and Takashi Ooi*

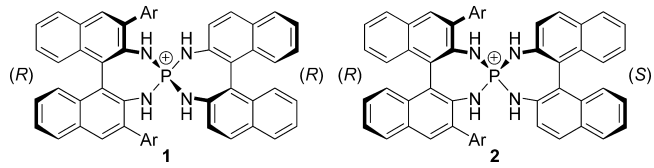
Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan

Received April 23, 2009; E-mail: tooi@apchem.nagoya-u.ac.jp

The proton is the smallest yet most ubiquitous Lewis acid and plays crucial roles in nature in the construction of the secondary and tertiary structures of proteins, substrate recognition, and functional-group activation through hydrogen-bonding. In organic synthesis, such properties of the proton have been exploited, particularly in the development of hydrogen-bonding catalysis (Brønsted acid catalysis) of chiral small molecules, which nowadays represents one of the most rapidly progressing areas in asymmetric synthesis.[1−3] The majority of previously elaborated chiral Brønsted acid catalysts can be classified as electronically neutral compounds.[2] On the other hand, the hydrogen-bonding donor capability of a charged, cationic molecule with a requisite anion has also been documented.[4−9] However, probably because this type of chiral Brønsted acid is prepared or generated as the conjugate acid of a nonionic organic Brønsted base such as an amine,[4] amidine,[5] guanidine,[6] or pyridine,[7] its high performance has mainly been demonstrated as an ion-pair catalyst for controlling the reactivity and selectivity of pairing nucleophilic anions. In fact, limited efforts toward developing a charged Brønsted acid catalyst for the stereoselective activation of nonionic Lewis bases have been made,[4a,5,6g,7] and hence, its characteristic features as a "chiral proton"[7c] remain poorly explored. Here, we present our own approach for addressing this issue: the design of a new class of chiral charged Brønsted acids **2** and its successful application to the development of a hitherto unknown catalytic enantioselective conjugate addition of arylamines to nitroolefins (shown in the scheme in Table 1).[10]

Table 1. Effect of the Structure of the Arylamine and Catalyst[a]





entry	catalyst (Ar)	Ar^1	time (h)	yield (%)[b]	ee (%)[c]	prod.
1	**1a** (H)	4-MeO−C_6H_4	23	37	19	**3a**
2	**1a** (H)	2,4-$(MeO)_2$−C_6H_3	23	42	41	**4a**
3	**1b** (Ph)	2,4-$(MeO)_2$−C_6H_3	23	86	61	**4a**
4	**2b** (Ph)	2,4-$(MeO)_2$−C_6H_3	27	87	83	**4a**
5	**2c** (3,4,5-F_3−C_6H_2)	2,4-$(MeO)_2$−C_6H_3	11	98	94	**4a**
6[d]	**2c** (3,4,5-F_3−C_6H_2)	2,4-$(MeO)_2$−C_6H_3	12	98	95	**4a**

[a] Reactions were performed on a 0.1 mmol scale with 2 equiv of Ar^1NH_2 in toluene (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. See the Supporting Information for determination of the absolute configuration of **4a**. [d] Reaction was conducted at −15 °C.

Our strategy for the molecular design was to employ a chiral *P*-spiro tetraaminophosphonium cation framework, a unique structural motif recently introduced by us,[8a,b] as a primary structure, and the three-dimensionally regulated HN−P^+−NH moiety was expected to function as a Brønsted acid on the basis of its anion-recognition ability through double hydrogen-bonding. Additionally, we envisioned that the introduction of aromatic amines into the phosphorus center would be suitable for imparting sufficient acidity to the N−H protons to enable them to engage in the activation of electronically neutral substrates.[11] For the actual assembly of the requisite molecular structure, a binaphthyl-derived chiral diamine was chosen as a readily accessible and modifiable subunit.[12] A *homochiral* arylaminophosphonium cation **1** with a [7.7]-spirocyclic core was initially prepared as a chloride salt. It is important to note that the chloride anion had to be exchanged with barfate[9b] [(3,5-$(CF_3)_2$−$C_6H_3)_4B^-$ (BArF)] in order to fully realize the potential of **1** as a Brønsted acid catalyst.

For experiments to explore the catalytic and stereocontrolling abilities of **1**, we selected nitroolefins as the appropriate electrophile to be activated and arylamines as nucleophiles, in the hope of developing this effort into a synthetically valuable, enantioselective aza-Michael protocol.[13−15] Thus, initial attempts were made by treating nitrostyrene with anisidine (2 equiv) under the influence of **1a** (2 mol %) in toluene at 0 °C. This revealed that **1a** indeed catalyzed this transformation to give the desired product **3a** in 37% yield with 19% ee after 23 h of stirring (Table 1, entry 1). The use of 2,4-dimethoxyaniline as an arylamine component led to an improvement in enantioselectivity (entry 2).[16] Notably, the introduction of phenyl substituents at the 3 and 3′ positions of one of the binaphthyl subunits (the left one in the structures shown in Table 1) to give **1b** had a beneficial effect on both reactivity and stereoselectivity (entry 3). An even more intriguing observation was that switching the unsubstituted binaphthyl unit (the right one in the Table 1 structures) to the opposite enantiomer (to give **2b**) resulted in a dramatic enhancement of the enantioselectivity (entry 4); moreover, *heterochiral* **2c** bearing a 3,4,5-trifluorophenyl group facilitated a smooth reaction to furnish **4a** almost quantitatively with 94% ee (entry 5). Finally, the highest enantioselectivity was attained without sacrificing the chemical yield by decreasing the reaction temperature (entry 6).

The three-dimensional molecular structures of the homo- and heterochiral arylaminophosphonium cations were unequivocally determined by single-crystal X-ray diffraction analysis of **1b**·Cl and **2b**·Cl, respectively (Figure 1). In contrast to the planar structure of **1b**, the two diaminobinaphthyl units of **2b** are twisted at the phosphorus center and are nearly perpendicular. This structural feature might affect the directions of the N−H protons and thus be associated with the ability of **2b** to offer higher enantiofacial discrimination of nitroolefin.[8a]

The scope of nitroolefin was then evaluated under optimized reaction conditions. As summarized in Table 2, a range of nitrostyrene derivatives can be transformed to the corresponding β-arylamino nitroalkanes uniformly in excellent chemical yields with a high level of enantiomeric excess (entries 1−10). In addition, nitroolefins with an alkyl substituent at the β position appeared to be good candidates,

10.1021/ja903271t CCC: $40.75

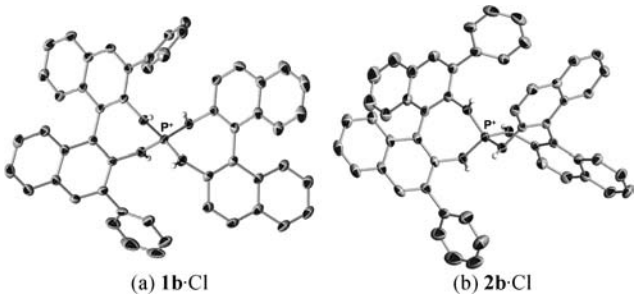
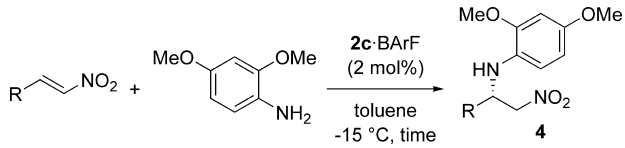


Figure 1. Crystal structures of arylaminophosphonium chlorides: (a) homochiral **1b**·Cl and (b) heterochiral **2b**·Cl. Counteranions, calculated hydrogen atoms, and solvent molecules have been omitted for clarity.

Table 2. Scope of Nitroolefin in the **2c**·BArF-Catalyzed Aza-Michael Reaction[a]



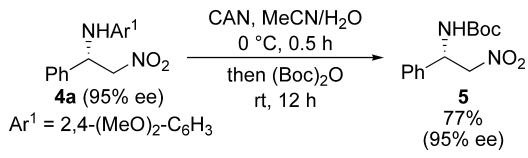
entry	R	time (h)	yield (%)[b]	ee (%)[c]	prod.
1	4-F−C_6H_4	12	98	94	**4b**
2	4-Cl−C_6H_4	4	99	95	**4c**
3	4-Br−C_6H_4	4	99	94	**4d**
4	4-Me−C_6H_4	12	99	97	**4e**
5	3-MeO−C_6H_4	4	99	93	**4f**
6	3-Br−C_6H_4	9	99	93	**4g**
7	2-F−C_6H_4	12	99	92	**4h**
8	1-naphthyl	19	99	91	**4i**
9	2-naphthyl	19	99	95	**4j**
10	3-furyl	24	89	94	**4k**
11[d]	Me_2CHCH_2	7	98	86	**4l**
12[d,e]	$Me(CH_2)_4$	0.5	93	87	**4m**

[a] Unless otherwise noted, reactions were conducted with 0.1 mmol of nitroolefin and 2 equiv of 2,4-$(MeO)_2$−$C_6H_3NH_2$ in toluene (1 mL) at −15 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. Absolute configurations were deduced from that of **4a**. [d] Diisopropyl ether was used as solvent instead of toluene. [e] Reaction was performed at room temperature.

and use of diisopropyl ether as the solvent seemed to be essential (entries 11 and 12).[17]

To increase the synthetic utility of the present system, exchange of the nitrogen-protecting group of the product was pursued (Scheme 1). For instance, exposure of **4a** (95% ee) to CAN in

Scheme 1. Deprotection−Reprotection Process



aqueous acetonitrile at 0 °C for 30 min and subsequent one-pot treatment with $(Boc)_2O$ afforded Boc-protected β-amino nitro compound **5**[7c] in 77% yield with complete preservation of the enantiopurity (95% ee).

In conclusion, we have successfully introduced heterochiral [7.7]-*P*-spirocyclic arylaminophosphonium barfates **2** as novel charged, cationic Brønsted acid catalysts; their reactivity and selectivity have been clearly visualized in the development of the first highly enantioselective conjugate addition of arylamines to nitroolefins. This study reveals new functions of chiral aminophosphonium cations, and the potential utility of asymmetric hydrogen-bonding catalysis is currently under close investigation in our laboratory.

Acknowledgment. We gratefully acknowledge Dr. Satoru Hiroto and Prof. Hiroshi Shinokubo (Nagoya Univ.) for kindly allowing us access to HRMS facilities and Dr. Atsushi Wakamiya and Prof. Shigehiro Yamaguchi (Nagoya Univ.) for their kind support for the X-ray crystallographic analysis. This work was supported by the Global COE Program in Chemistry of Nagoya University, Grants for Scientific Research from JSPS, and the Mitsubishi Foundation.

Supporting Information Available: Representative experimental procedures, spectral data for **1**−**5**, and crystallographic data for **1b**·Cl and **2b**·Cl (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected recent reviews on Brønsted acid catalysis, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516.
(2) Reviews on nonionic Brønsted acid catalysis using thiourea: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. Using phosphoric acid: (c) Terada, M. *Chem. Commun.* **2008**, 4097.
(3) For a review of the use of Brønsted acid catalysts for asymmetric protonation, see: Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653.
(4) For selected recent examples, see: (a) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (d) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 1810. (f) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (g) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (h) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872. (i) Tan, B.; Zhang, X.; Chua, P. J.; Zhong, G. *Chem. Commun.* **2009**, 779. For an example of stoichiometric usage of a chiral charged Brønsted acid for the reaction of a nonionic Lewis base, see: (j) Jang, D. O.; Kim, S. Y. *J. Am. Chem. Soc.* **2008**, *130*, 16152.
(5) (a) Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179. (b) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697. (c) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661. (d) Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618.
(6) For reviews, see: (a) Leow, D.; Tan, C.-H. *Chem.—Asian J.* **2009**, *4*, 488. (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737. For selected recent examples, see: (c) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (d) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692. (e) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (f) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem.—Asian J.* **2007**, *2*, 1150. (g) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228.
(7) Pyridinium salt: (a) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524. (b) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. Quinolinium salt: (c) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (d) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147. (e) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. (f) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (g) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.
(8) (a) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (b) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. Also see: (c) Fetterly, B.; Jana, N. K.; Verkade, J. G. *Tetrahedron* **2006**, *62*, 440.
(9) For examples of achiral charged Brønsted acid catalyses, see: (a) Takenaka, N.; Sarangthem, R. S.; Seerla, S. K. *Org. Lett.* **2007**, *9*, 2819. (b) Annamalai, V. R.; Linton, E. C.; Kozlowski, M. C. *Org. Lett.* **2009**, *11*, 621.
(10) For the nonenantioselective reaction, see: Ziyaei-Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2008**, *49*, 1244, and references therein.
(11) Bickley, J. F.; Copsey, M. C.; Jeffery, J. C.; Leedham, A. P.; Russell, C. A.; Stalke, D.; Steiner, A.; Stey, T.; Zacchini, S. *Dalton Trans.* **2004**, 989.
(12) (a) Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716. (b) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *J. Org. Chem.* **2008**, *73*, 7387.
(13) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
(14) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.
(15) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.
(16) The use of an aliphatic amine such as benzylamine as the nucleophile was less effective (27% yield, racemic, after 22 h of stirring at 0 °C with **2b**·BArF), probably because of an acid−base equilibrium between the catalyst and the amine. See the Supporting Information for a pK_a estimate for **2b**·BArF.
(17) When the reaction in entry 11 of Table 2 was performed in toluene at −15 °C for 12 h, considerable loss of enantioselectivity was observed (96% yield, 72% ee).

JA903271T