J|A|C|S COMMUNICATIONS

Published on Web 08/17/2010

Catalytic Asymmetric Protonation of α-Amino Acid-Derived Ketene Disilyl Acetals Using *P*-Spiro Diaminodioxaphosphonium Barfates as Chiral Proton

Daisuke Uraguchi, Natsuko Kinoshita, and Takashi Ooi*

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

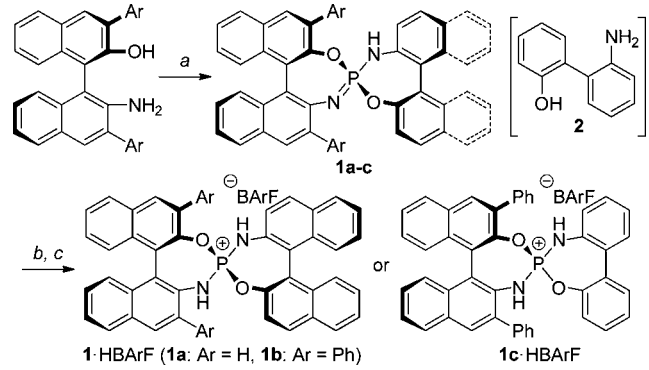
Received July 6, 2010; E-mail: tooi@apchem.nagoya-u.ac.jp

Abstract: Chiral diaminodioxaphosphonium salts have been developed and their unique abilities as a chiral proton have been revealed through the establishment of a highly enantioselective protonation of α-amino acid-derived ketene disilyl acetals.

Ever since deracemization procedures were introduced by Yoshikawa[1] and Duhamel[2] in the late 1970s, enantioselective protonation of prochiral enols or enolates has been extensively studied as one of the simplest and most straightforward methods for the preparation of optically active α-tertiary carbonyl compounds.[3] However, despite the considerable progress that has been made in this field, the development of a highly efficient and enantioselective protonation protocol, especially with a catalytic quantity of a chiral controller, still remains a difficult task. This is true because of the unusual methodological challenges associated with this fundamental yet extremely useful transformation, such as manipulating a very small proton, controlling the enolate geometry, and preventing racemization of the resulting chiral center. The asymmetric proton transfer reaction to silyl-masked enolates represents an attractive approach to address this problem, as a wide range of silyl enolates are frequently isolated with defined *E*/*Z* geometry.[4] Seminal research on this strategy was reported by Yamamoto and Ishihara in 1996; their research was based on the elegant use of a $SnCl_4$-activated BINOL derivative as a catalytic chiral proton source.[5a] Furthermore, several efficient systems have been elaborated for the stereoselective protonation of particular substrates, such as α-tertiary cyclic ketone- and α-aryl carboxylic acid-derived silyl enol ethers.[5−9] These studies have revealed that a suitably acidic catalyst[5,6] or Lewis basic activation of the silyl nucleus[7,8] seemed to be required for effective promotion of this type of protonation reaction. In conjunction with our recent efforts to develop chiral charged Brønsted acid catalysts and their applications,[10] we here communicate the prominent proton transfer ability of a weakly acidic chiral *P*-spiro diaminodioxaphosphonium cation **1**·H, which enables the highly enantioselective protonation of new class of substrate, α-amino acid-derived ketene disilyl acetals of type **3**,[11] without the assistance of any Lewis base.

Our interest in the proton transfer ability of ionic Brønsted acids, specifically, chiral *P*-spiro arylaminophosphonium cations, originated from the inherent structural feature of this series of organic cations whereby they can be regarded as nonionic chiral Lewis base-coordinated protons (i.e., chiral protons),[12] with promising advantages for creating a discrete chiral environment around such a small atom. Because our original arylaminophosphonium cation bearing a $(HN)_4P^+$ core[10] was not sufficiently acidic even for the protonation of electron-rich olefins,[13] it was crucial to appropriately tune its primary structure to enhance the Brønsted acidity. For this purpose, we decided to partially introduce electronically more negative oxygen atoms instead of nitrogen atoms to form a $(HN)_2P^+O_2$ core. We expected that this key modification, if successful, would not only enhance the Brønsted acidity but also provide insights into the properties of this largely unexplored class of phosphonium salts, thereby expanding the possibilities for their molecular design. Preliminary investigations of the synthetic feasibility of the newly devised chiral *P*-spiro diaminodioxaphosphonium barfate of type **1**·HBArF fortunately revealed that its molecular framework can be readily constructed in one step by reaction of aminohydroxybiaryls such as (*R*)-NOBIN derivatives with PCl_5. Subsequent treatment with an aqueous solution of $NaHCO_3$ or triethylamine in the same pot afforded iminophosphorane **1** in a diastereomerically pure form (Scheme 1). The absolute three-dimensional structures of **1a** and **1b** were unequivocally determined by X-ray crystallographic analysis, and a representative ORTEP diagram of **1b** is shown in Figure 1.[14] The central spiro chirality was assigned as *P*, which allows the two N−H protons of its conjugate acid to be disposed on the same side.[15] Finally, the requisite diaminodiox-

Scheme 1. Preparation of Chiral Phosphonium Barfate **1**·HBArF[a]



[a] Reagents and conditions: (a) PCl_5, (*R*)-NOBIN or **2**, toluene, rt to 110 °C, 10 h, then $NaHCO_3$(aq) or Et_3N, rt, 0.1 h, 38−79%; (b) 1 M HCl/MeOH, CH_2Cl_2, rt, 0.1 h; (c) $Na[B(3,5\text{-}(CF_3)_2C_6H_3)_4]$ (NaBArF), CH_2Cl_2, rt, 0.1 h, quant. (two steps).

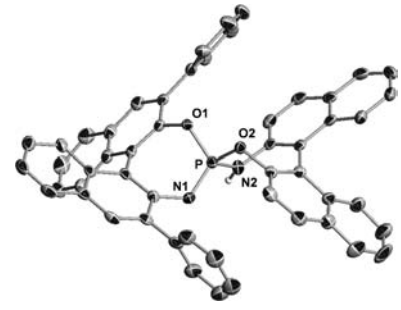


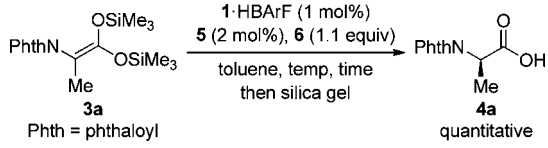
Figure 1. ORTEP drawing of **1b** with thermal ellipsoids set at 50% probability. All of the calculated hydrogens and solvent molecules have been omitted for clarity. Key bond lengths (Å): P−N1, 1.541(3); P−N2, 1.619(3); P−O1, 1.615(2); P−O2, 1.602(2).

10.1021/ja105945z

aphosphonium barfate **1**·HBArF was prepared from **1** in quantitative yield through protonation and anion-exchange processes.[16]

The catalytic performance of **1**·HBArF as a chiral proton was evaluated in the enantioselective protonation of ketene disilyl acetal **3**, which can be conveniently prepared from the corresponding α-amino acid and purified by standard silica gel column chromatography (Table 1). The initial trial was carried out with alanine-derived ketene disilyl acetal **3a** in the presence of **1a**·HBArF (1 mol %) and 2,6-di-*tert*-butylpyridine (**5**, 2 mol %)[17] in toluene, using 2,6-dimethylphenol (**6**) as a stoichiometric proton source (entry 1). As expected, the reaction was completed in 20 min at 0 °C, and *N*-phthaloylalanine (**4a**) was isolated quantitatively. After treatment of **4a** with Ag_2O/MeI at room temperature, the enantiomeric excess of the methyl ester thus obtained was determined to be 66% by HPLC analysis. We then examined the substituent (Ar) effect of the catalyst on the stereoselectivity and found that the use of **1b**·HBArF having a phenyl group led to a significant enhancement in the enantioselectivity (entry 2). Interestingly, critical selectivity improvement was attained by replacing the nonsubstituted binaphthyl subunit with the sterically less demanding biphenyl structure (**1c**·HBArF) (entry 3), and performing the reaction at a lower temperature (−20 °C) allowed for even more rigorous enantiofacial control, affording **4a** with 97% ee (entry 4). Here it is important to note that the protonation of **3a** under the influence of a stoichiometric amount of **1c**·HBArF gave **4a** quantitatively with 96% ee, which suggests that a proton is directly transferred from the chiral diaminodioxaphosphonium cation **1c**·H.[18]

Table 1. Optimization of Reaction Conditions for **1**·HBArF-Catalyzed Asymmetric Protonation of Ketene Disilyl Acetal **3a**[a]



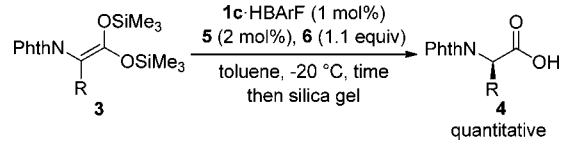
entry	**1**	temp (°C)	time (h)	ee (%)[b]
1	**1a**	0	0.3	66
2	**1b**	0	0.3	85
3	**1c**	0	0.3	93
4	**1c**	−20	1	97

[a] Reactions were performed with 0.1 mmol of **3a**, 0.11 mmol of **6**, 2 mol % **5**, and 1 mol % **1**·HBArF in 1.0 mL of toluene. [b] The enantiomeric excess of **4a** was determined by chiral stationary phase HPLC after derivatization to the corresponding methyl ester.

After the optimized conditions had been established, the substrate generality was investigated, and selected examples are summarized in Table 2. Ketene disilyl acetals **3** with various alkyl side chains, including branched and functionalized ones, were well-accommodated, and although the reactivity was strongly affected by the steric hindrance of **3**, excellent enantioselectivities were uniformly observed (entries 1−4).[19] The present system was also applicable to substrates with benzylic substituents having different electronic properties, which were transformed to the parent N-protected α-amino acids with high levels of enantiocontrol (entries 5−7). These results demonstrate that this new protocol represents a unique approach for overcoming the challenges inherent in the asymmetric synthesis of α-amino acids by catalytic enantioselective protonation.

The phthaloyl moiety of the methyl ester of **4** was easily removed upon exposure to hydrazine monohydrate in methanol without any loss of enantiomeric purity; this was confirmed by HPLC analysis after consecutive nitrogen reprotection, as exemplified in Scheme 2.

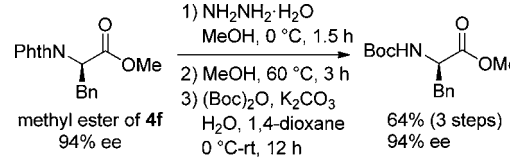
Table 2. Substrate Generality[a]



entry	R	**3**	time (h)	ee (%)[b]	**4**
1	$MeCH_2$	**3b**	2	95	**4b**
2	$Me(CH_2)_3$	**3c**	4	95	**4c**
3[c]	Me_2CHCH_2	**3d**	10	90	**4d**
4	$MeO(CH_2)_2$	**3e**	5	94	**4e**
5	$PhCH_2$	**3f**	20	94	**4f**
6[c]	*p*-$ClC_6H_4CH_2$	**3g**	6	90	**4g**
7	*p*-$MeOC_6H_4CH_2$	**3h**	18	93	**4h**

[a] Unless otherwise noted, reactions were conducted on a 0.1 mmol scale with 1 mol % **1c**·HBArF in 1.0 mL of toluene at −20 °C. [b] The enantiomeric excess of the methyl ester of **4** was analyzed by use of chiral HPLC. [c] The reaction was performed at 0 °C.

Scheme 2. Deprotection−Reprotection Sequence



In conclusion, we have developed chiral *P*-spiro diaminodioxaphosphonium barfates, and their unique reactivity and selectivity as chiral protons have been revealed through the establishment of highly enantioselective protonation of α-amino acid-derived ketene disilyl acetals. This study not only adds to the body of research on catalytic asymmetric protonation of enolates but also offers unprecedented opportunities for the molecular design of this class of chiral organic cations as well as for the development of related applications.

Acknowledgment. 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 and analytical data for all new compounds, and crystallographic data for **1a** and **1b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Matsushita, H.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3715. (b) Matsushita, H.; Noguchi, M.; Yoshikawa, S. *Chem. Lett.* **1975**, 1313. (c) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3629. (d) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Saburi, M.; Yoshikawa, D. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 862.

(2) (a) Duhamel, L. *C. R. Acad. Sci.* **1976**, *282C*, 125. (b) Duhamel, L.; Plaquevent, J.-C. *Tetrahedron Lett.* **1977**, *18*, 2285. (c) Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. (d) Duhamel, L.; Plaquevant, J.-C. *Tetrahedron Lett.* **1980**, *21*, 2521.

(3) For reviews, see: (a) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411. (b) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. (c) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (d) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359.

(4) For examples of the utilization of a stoichiometric amount of a chiral proton source, see: (a) Cavelier, F.; Gomez, S.; Jacquier, R.; Verducci, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2501. (b) Cavelier, F.; Gomez, S.; Jacquier, R.; Verducci, J. *Tetrahedron Lett.* **1994**, *35*, 2891. (c) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

(5) (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (c) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24.

(6) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246.
(7) (a) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090. (b) Poisson, T.; Oudeyer, S.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, 2447.
(8) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1546.
(9) (a) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366. (b) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858.
(10) Uraguchi, D.; Nakashima, D.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7242.
(11) Although there has been no report on the preparation of **3**, other types of α-amino acid-derived ketene disilyl acetals have been applied to organic synthesis. For examples, see: (a) Ruhlmann, K.; Kuhrt, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 809. (b) Okano, K.; Morimoto, T.; Sekiya, M. *Chem. Pharm. Bull.* **1985**, *33*, 2228. (c) Hvidt, T.; Martin, O. R.; Szarek, W. A. *Tetrahedron Lett.* **1986**, *27*, 3807. (d) Simchen, G.; Püerkner, E. *Synthesis* **1990**, 525.
(12) (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (b) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.
(13) The pK_a range of 2,2′-diamino-1,1′-binaphtharene-derived phosphonium barfate is 16−18 in CD_3CN (see the Supporting Information for ref 9).
(14) An ORTEP diagram of **1a** is shown in the Supporting Information.
(15) Although the spiro chirality of **1c** has not yet been determined, it is assumed to be *P* by analogy to **1a** and **1b**.
(16) The pK_a of **1b**·HBArF in CD_3CN is ∼12.6, which is comparable to that of a common weak Brønsted acid catalyst such as a pyridinium salt (pK_a = 12.53).[20]
(17) The addition of **5** is preferable in order to reproduce the high enantioselectivity, presumably because it avoids the influence of the non-enantioselective background reaction by the liberated HBArF.
(18) Under catalytic conditions, use of sterically rather demanding 2,6-dimethylphenol as a stoichiometric proton source seems to be important in order to realize the full potential of **1** as a chiral proton, judging from the fact that replacement of 2,6-dimethylphenol with phenol in the **1c**·HBArF-catalyzed protonation of **3a** under conditions otherwise identical to the optimized conditions afforded **4a** quantitatively with 94% ee. The observed decrease in enantioselectivity might suggest the intervention of either a different mechanism or non-stereoselective protonation by phenol.
(19) Valine-derived ketene disilyl acetal (**3i**, R = ^{i}Pr) was significantly less reactive, probably because of its steric hindrance, and it was necessary to perform the protonation at room temperature (2 h, quant., 35% ee). Although ketene disilyl acetals **3** of α-amino acids having an aromatic side chain, such as phenylglycine, are attractive candidates to be examined, the preparation of this type of substrate has been unsuccessful to date.
(20) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

JA105945Z