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Design of Brønsted Acid-Assisted Chiral Brønsted Acid Catalyst Bearing a Bis(triflyl)methyl Group for a Mannich-Type Reaction

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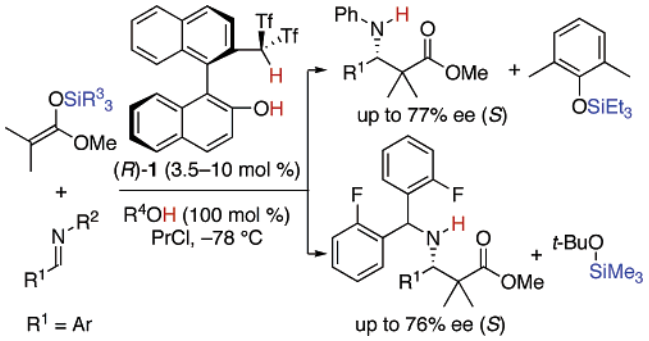
ABSTRACT



A new Brønsted acid-assisted chiral Brønsted (chiral BBA) acid catalyst (1) was developed by substituting a hydroxy group of optically active 1,1′-bi(2-naphthol) with a stronger Brønsted acidic group such as a bis(trifluoromethanesulfonyl)methyl group. The enantioselective Mannich-type reaction of ketene silyl acetals with aldimines catalyzed by (*R*)-1 in the presence of stoichiometric achiral proton sources gave (*S*)-β-amino esters in high yield with moderate to good enantiomeric excesses.

The development of chiral catalysts for the Mannich-type reaction of ketene silyl acetals with aldimines has attracted the attention of synthetic organic chemists.[1] As a pioneering work in this field, we have previously reported Brønsted acid-assisted chiral Lewis acid (chiral BLA), which is prepared from a 1:2 molar mixture of $B(OMe)_3$ and optically active binaphthol as a chiral activator.[2] Recently, Akiyama et al. reported a Mannich-type reaction of silyl enolates with aldimines catalyzed by strong achiral Brønsted acids such as HBF_4 in aqueous media[3] and its enantioselective version for ketene silyl acetals with *N*-2-hydroxyphenylaldimines catalyzed by chiral monophosphoric acids derived from bulky 3,3′-disubstituted 1,1′-bi(2-naphthol)[4a,c,5] or TADDOL[4b] in

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(1) For reviews, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873.

(2) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

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(4) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523. (c) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.

(5) Asymmetric catalysis of chiral monophosphoric acids has been explained through two hydrogen bondings or tight ion pairs on a case-by-case basis (see also ref 4a,c): (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am.*

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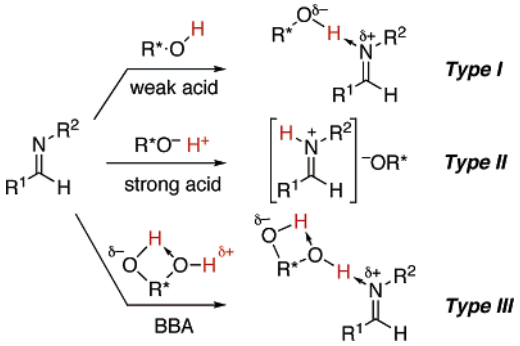
toluene. We report here the enantioselective Mannich-type reaction of *N*-alkylaldimines with ketene silyl acetals catalyzed by chiral Brønsted acid through hydrogen bonding with the nitrogen of imine. Our catalytic cycle was attained by capturing a trialkylsilyl cation from a siloxocarbenium ion intermediate[6] with stoichiometric amounts of achiral proton sources under anhydrous conditions.[7]

Scheme 1 shows the activation of *N*-alkylaldimine with

Scheme 1. Activation of Aldimine with Chiral Brønsted Acid



chiral Brønsted acid. If *N*-alkylaldimine is activated by OH···N hydrogen bonding with chiral Brønsted acid (R*OH), moderate enantioselectivity may be induced because this hydrogen bond can rotate around the R*−O axis (Type I). In contrast, if *N*-alkylaldimine is activated as an iminium cation intermediate with a relatively strong chiral Brønsted acid, the enantioselectivity may be induced through a tight ion pair between the protonated iminium cation and the chiral Brønsted base, but it is relatively difficult to induce higher enantioselectivity than that of Type I (Type II).[5] Therefore, the suitable Brønsted acidity and conformational control of the OH···N hydrogen bond are important for the design of Brønsted acid catalysts. To overcome these problems, we introduced the concept of Brønsted acid-assisted chiral Brønsted (BBA)[8] for the design of a new Brønsted acid catalyst (Type III). The OH···N hydrogen bond may be rotationally fixed with regard to the R*−O axis and its proton may be suitably activated by intramolecular OH···OH hydrogen bonding.

On the basis of the concept of BBA (Type III), we designed chiral 2-bis(triflyl)methyl-2′-hydroxy-1,1′-binaphthyl (**1**)[9] as a new asymmetric Mannich catalyst (Figure 1).

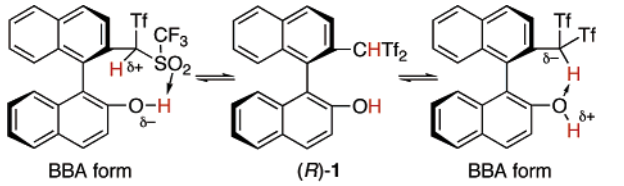


Figure 1. Possible intramolecular hydrogen bondings in (*R*)-**1**.

1 is a chiral dibasic Brønsted acid[10−13] bearing a hydroxy proton and a bis(triflyl)methyl proton. Recently, we developed a practical method for not only aromatic but also aliphatic alkylbis(triflyl)methanes.[14] In general, the acidity of arylbis(triflyl)methane is the same as that or stronger than that of the corresponding sulfonic acid. For example, the p*K* value of $PhCHTf_2$ in MeCN is 7.83,[15] while that of TsOH is 8.6. We expected that **1** might be effective as a chiral BBA catalyst for the enantioselective Mannich-type reaction.

(*R*)-**1** was prepared from (*S*)-2′-(methoxymethoxy)-2-methyl-1,1′-binaphthyl (**3**), which was easily derived from

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(6) (a) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun.* **2002**, 1564. (b) Hiraiwa, Y.; Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 1837.

(7) If we consider our experimental results, the HBF_4-promoted Mannich reaction in aqueous media reported by Akiyama et al.[3] might also catalytically proceed by capturing a trialkylsilyl cation with excess amounts of aqueous solvents. Furthermore, in the case of Akiyama's enantioselective version catalyzed by chiral monophosphoric acid in toluene,[4] *N*-2-hydroxyphenylaldimine might play a role as a stoichiometric achiral proton source as well as our present catalytic system.

(8) The concept of a chiral BBA originates in that of a Lewis acid-assisted chiral Brønsted acid (chiral LBA). For LBA, see: (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *Croat. Chem. Acta* **1996**, *69*, 513. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (d) Ishihara, K.; Ishida, Y.; Nakamura, S.; Yamamoto, H. *Synlett* **1997**, 758. (e) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444. (f) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (g) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (h) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (i) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (j) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (k) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (l) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (m) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (n) Muhammet, U.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (o) Muhammet, U.; Ishihara, K.; Yamamoto, H. *Bioorg. Med. Chem.* **2005**, *13*, 5055.

(9) triflyl = trifluoromethanesulfonyl; triflate = trifluoromethanesulfonate.

(10) For a review of asymmetric catalysis by chiral hydrogen bond donors, see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(11) For chiral α-hydroxycarboxylic acid catalysts, see: Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080.

(12) For chiral diol catalysts, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (c) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. (d) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (e) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. *J. Am. Chem. Soc.* **2005**, *127*, 1336. (f) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657.

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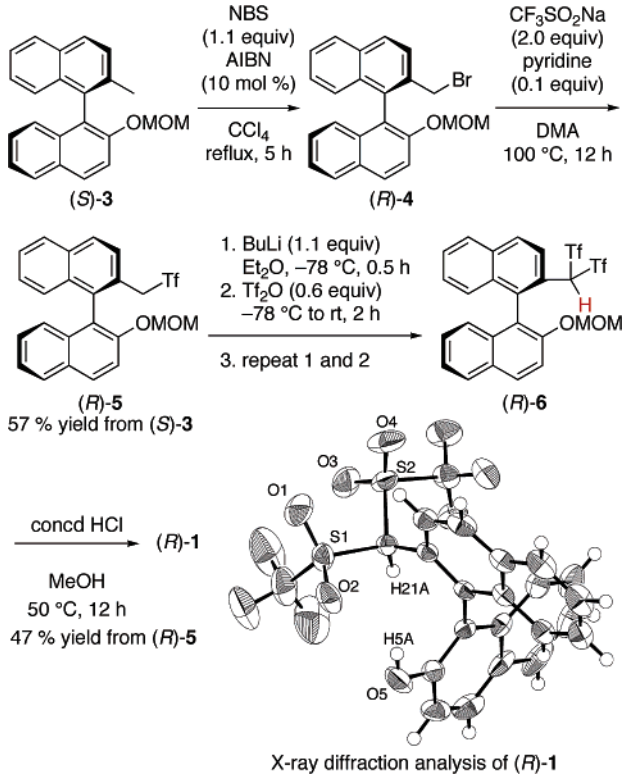
(15) Leito, I.; Kaljurand, I.; Koppel, I. A.; Yagupolskii, L. M.; Vlasov, V. M. *J. Org. Chem.* **1998**, *63*, 7868.

commercially available (*R*)-1,1′-bi(2-naphthol) (**2**) in 4 steps (Scheme 2). First, (*S*)-**3** was transformed to (*R*)-2-(methoxymethoxy)-2′-[(triflyl)methyl]-1,1′-binaphthyl (**5**) by monobromination of (*S*)-**3** with *N*-bromosuccinimide (NBS) in the presence of AIBN to give (*R*)-2-(bromomethyl)-2′-(methoxymethoxy)-1,1′-binaphthyl (**4**), and a subsequent nucleophilic substitution reaction of (*R*)-**4** with sodium trifluoromethanesulfinate gave (*R*)-**5** in 57% overall yield from (*S*)-**3**. (*R*)-**5** was transformed to (*R*)-2-(methoxymethoxy)-2′-[bis(triflyl)methyl]-1,1′-binaphthyl (**6**) by deprotonation with BuLi and the subsequent addition of Tf_2O.[14f] This deprotonation−addition was repeated for (*R*)-**5** twice without workup. Finally, (*R*)-**1** was obtained in 47% overall yield from (*R*)-**5** by the hydrolysis of (*R*)-**6**. The structure of (*R*)-**1** was confirmed by not only ^1H and ^{13}C NMR spectral analyses but also single-crystal X-ray analysis[16] (Scheme 2).

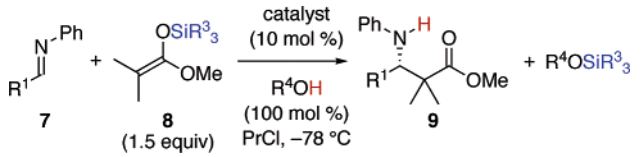
Scheme 2. Synthesis and X-ray Diffraction Analysis of (*R*)-**1**



X-ray diffraction analysis of (*R*)-**1**

First, the Mannich-type reaction of (*E*)-*N*-benzylideneben-zenamine (**7a**) with (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (**8a**) was examined in 1-chloropropane at −78 °C in the presence of 10 mol % of (*R*)-**1** (entry 1, Table 1). The reaction proceeded smoothly and the desired (*S*)-*β*-amino ester **9a** was obtained in 90% yield with 14% ee. In contrast, (*R*)-**2** was inert as a catalyst under the same conditions as in entry 1 (entry 2). Next, triethylsilyl derivative **8b** was examined instead of **8a** under the same conditions as in entry 1 (entry 3). Interestingly, the chemical yield of **9a** was decreased to 53%, while the enantioselectivity was increased to 59% ee. Fortunately, the reactivity was improved by adding a stoichiometric amount of sterically bulky alcohols (entries 4 and 5). 2,6-Xylenol was the most suitable achiral proton source (entry 5). Thus, (*S*)-**9a** was obtained in 91% yield with 69% ee (entry 5). (*R*)-**1** was effective for the Mannich-type reaction of *N*-phenylaldimines **7a**−**g** derived from not only benzaldehyde but also *o*-, *m*-, or *p*-substituted-benzaldehydes in the presence of 2,6-xylenol (entries 5−12). In particular, the Mannich-type reaction of **7f** derived from *p*-(trifluoromethyl)benzaldehyde with a 3.5 mol % catalyst loading of (*R*)-**1** gave **9f** in quantitative yield with 77% ee (entry 11).

Table 1. The Enantioselective Mannich Reaction of **7** with **8**

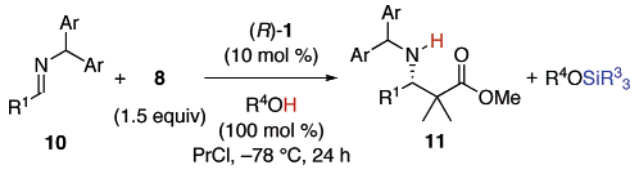


entry	**7** (R^1)	**8** (R^3)	catalyst	R^4OH[b]	time (h)	yield (%), ee (%)
1	**7a** (Ph)	**8a** (Me)	(*R*)-**1**	−	24	**9a** 90, 14 [*S*]
2	**7a**	**8a**	(*R*)-**2**	−	24	**9a** 0, −
3	**7a**	**8b** (Et)	(*R*)-**1**	−	24	**9a** 53, 59 [*S*]
4	**7a**	**8b**	(*R*)-**1**	*t*-BuOH	24	**9a** >99, 42 [*S*]
5	**7a**	**8b**	(*R*)-**1**	2,6-xyl	24	**9a** 91, 69 [*S*]
6	**7b** (*p*-MeC_6H_4)	**8b**	(*R*)-**1**	2,6-xyl	24	**9b** 91, 62
7	**7c** (*o*-FC_6H_4)	**8b**	(*R*)-**1**	2,6-xyl	24	**9c** 86, 69
8	**7d** (*m*-FC_6H_4)	**8b**	(*R*)-**1**	2,6-xyl	24	**9d** >99, 69
9	**7e** (*p*-FC_6H_4)	**8b**	(*R*)-**1**	2,6-xyl	24	**9e** 89, 72
10	**7f** (*p*-$CF_3C_6H_4$)	**8b**	(*R*)-**1**	2,6-xyl	7	**9f** 95, 74
11[a]	**7f**	**8b**	(*R*)-**1**	2,6-xyl	48	**9f** >99, 77
12	**7g** (*p*-$NO_2C_6H_4$)	**8b**	(*R*)-**1**	2,6-xyl	24	**9g** 99, 70

[a] 3.5 mol % of (*R*)-**1** was used. [b] xyl = xylenol.

N-(Diphenylmethyl)aldimines **10** derived from aromatic aldehydes were also suitable substrates for the Mannich-type reaction catalyzed by (*R*)-**1** (Table 2). Since **10** was much less reactive than the corresponding *N*-phenylaldimines **7**,

Table 2. The Enantioselective Mannich Reaction of **10** with **8**



entry	**10** (Ar, R^1)	**8**	R^4OH	**11** yield (%), ee (%)
1	**10a** (Ph, Ph)	**8a**	−	**11a** 21, 55 [*S*]
2	**10a**	**8a**	2,6-xylenol	**11a** <97, 58 [*S*]
3	**10a**	**8a**	*t*-BuOH	**11a** 96, 61 [*S*]
4	**10a**	**8b**	*t*-BuOH	**11a** 96, 23 [*S*]
5	**10b** (*o*-MeC_6H_4, Ph)	**8a**	*t*-BuOH	**11b** 69, 69
6	**10c** (*o*-EtC_6H_4, Ph)	**8a**	*t*-BuOH	**11c** <29, 87
7	**10d** (*o*-FC_6H_4, Ph)	**8a**	*t*-BuOH	**11d** 91, 72
8	**10e** (*o*-FC_6H_4, *p*-FC_6H_4)	**8a**	*t*-BuOH	**11e** 85, 76

the reaction of **10a** with **8a** did not proceed catalytically in the absence of achiral proton sources (entry 1). However, this reaction proceeded quantitatively in the presence of a stoichiometric amount of 2,6-xylenol (entry 2). *tert*-Butyl alcohol was more suitable as an achiral proton source than 2,6-xylenol for the Mannich-type reaction of **10** (entry 3). Unexpectedly, when **8b** was used instead of **8a**, the enantioselectivity of (*S*)-**11a** was decreased from 61% ee to 23% ee (entry 4). The ortho-substituent effect of an *N*-diphenylmethyl group increased the enantioselectivity up to 87% ee (entries 5−7). In particular, the introduction of an *N*-di(*o*-fluorophenyl)methyl group to aldimines increased both the enantioselectivity and reactivity (entries 7 and 8). Thus, we found that two types of *N*-alkylaldimines, **7** and **10**, were effective for the Mannich-type reaction catalyzed by (*R*)-**1**. **10** was synthetically useful because *N*-diarylmethyl groups were easily cleaved from **11** by hydrogenolysis.[2]

A proposed catalytic cycle of **1** is shown in Figure 2. The

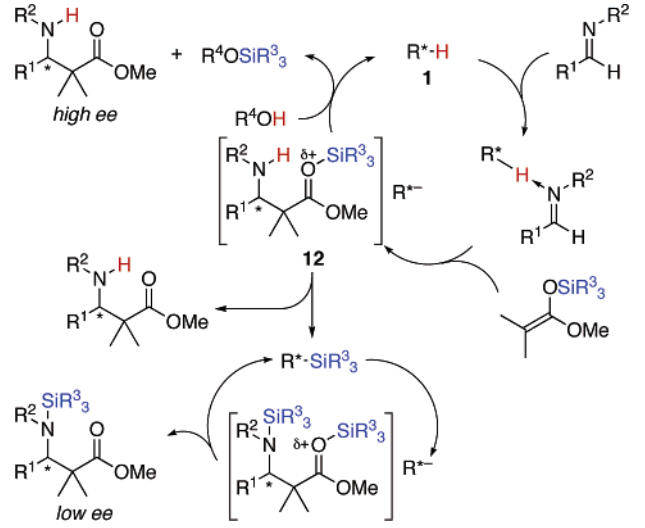


Figure 2. Proposed catalytic cycle of **1**.

protonation of siloxocarbenium ion intermediate **12**[6] with an achiral proton source (R^4OH) regenerated **1** and produced *β*-amino ester with silyl ether ($R^4OSiR^3_3$).[8c,g] Therefore, an achiral proton source was stoichiometrically required as a trapping agent of silicon species. However, the reaction of **7a** with **8a** proceeded quantitatively even in the absence of an achiral proton source (entry 1, Table 1). This result can be understood in terms of the spontaneous generation of chiral silyl Lewis acid from **12**. Thus, the enantioselectivity was quite low (14% ee).[7]

Two possible transition-state assemblies **13** and **14** are shown in Figure 3.[16] **13** is more reasonable than **14** because

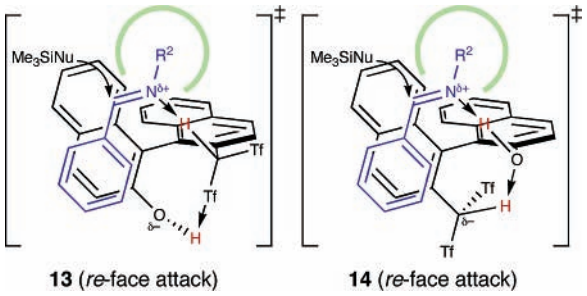


Figure 3. Two postulated transition-state assemblies **13** and **14**.

13 is activated by hydrogen bonding between the bis(triflyl)methyl proton more acidic than the hydroxy proton and the imino nitrogen more basic than the hydroxy oxygen. Nevertheless, the possibility of TS-**14** is not negligible. The conformation of protonated aldimines in **13** or **14** may be fixed by $\pi-\pi$ attractive interaction between the naphthyl group of (*R*)-**1** and the Ar−C═N group of **7** or **10** and/or steric repulsion between the naphthyl group of (*R*)-**1** and the *N*-alkyl group of **7** or **10**. The absolute stereochemical course can be explained by the nucleophilic attack of **8** to the *re*-face of **7** or **10** through **13** or **14**. Although we have no direct evidence for intramolecular hydrogen bonding of (*R*)-**1** in **13** or **14**, (*R*)-**2** and 2′-methoxy and 2′-methyl analogues of (*R*)-**1** and were much less active than (*R*)-**1** for the present Mannich-type reactions (entry 2, Table 1). These experimental results support the possibility of intramolecular hydrogen bonding as BBA in **13** or **14**.

In summary, we have demonstrated a new entry to a chiral Brønsted acid bearing a bis(triflyl)methyl group as a chiral Brønsted acid catalyst. Furthermore, the addition of a stoichiometric achiral proton source is required to accomplish a catalytic cycle of chiral Brønsted acid catalysts for the Mannich-type reaction of aldimines with ketene silyl acetals.[7] This work offers good examples for the design of chiral Brønsted acid catalysts for various enantioselective reactions with silyl nucleophiles.

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Supporting Information Available: Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) According to the X-ray diffractional analysis, any intramolecular hydrogen bondings were existed in the solid state of (*R*)-**1** (H5A···O2 = 2.305 Å; H21A···O5 = 3.267 Å). However, the possibilty of **13** or **14** is not denied by this result.