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Chiral Brønsted Acid Catalysis for Enantioselective Hosomi–Sakurai Reaction of Imines with Allyltrimethylsilane

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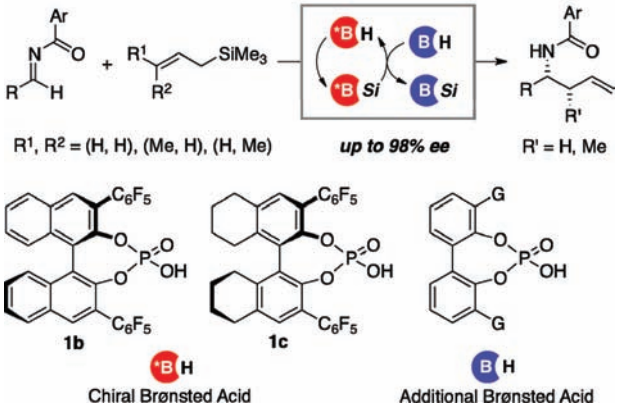
ABSTRACT



The chiral Brønsted acid (1b or 1c) has been shown to initiate the Hosomi–Sakurai reaction of imines with excellent enantioselectivities. The combined Brønsted acid system has been developed to offer a new class of chiral Brønsted acid catalysis. The present system proceeds through regeneration of the chiral Brønsted acid by proton transfer from additional Brønsted acid to silylated chiral Brønsted acid, a newly elucidated mechanism for the role of the additional Brønsted acid.

Chiral Brønsted acid catalysis has been explosively widespread in asymmetric synthesis over the past decade.[1] Our laboratory and others have focused on the development of chiral binaphthol-derived monophosphoric acid as the chiral Brønsted acid catalyst in a variety of organic transformations.[2] During the development of chiral Brønsted acid catalyzed enantioselective reactions, seminal advances have been made in the reaction of highly reactive nucleophiles[3] including dienes, enolsilanes and enols, enamine, enamides and enecarbamates, cyanide, furanes, indoles and pyrroles, diazoacetates, azidos, and allyl, alkenyl, and alkynyl boronates, etc.[1,2,4] However, its ability to deliver both the reactivity and stereoselectivity over a range of less nucleophilic substrates has been an enduring challenge in chiral Brønsted acid catalysis. This report describes our investigation regarding the use of allyltrimethylsilanes[5] as stable but potential reagents in the chiral Brønsted acid catalysis. We developed a new

(1) (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (b) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009.

(2) (a) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (b) Terada, M. *Synthesis* **2010**, 1929–1982.

(3) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.

(4) For references of each reaction, see the Supporting Information.

(5) (a) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200–206. (b) For other representative reviews, see the Supporting Information.

(6) (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854–12855. (b) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihhara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175–3178. Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141–143. (d) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247. (e) Zamfir, A.; Tsogoeva, S. B. *Org. Lett.* **2010**, *12*, 188–191. (f) For other examples, see the Supporting Information.

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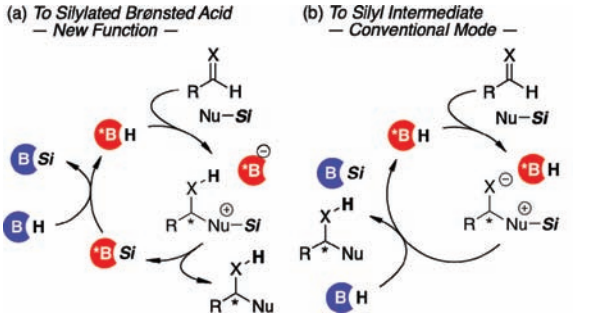
approach, *chiral Brønsted acid catalysis by a combined Brønsted acid system*, in which additional Brønsted acid can facilitate proton transfer to silylated chiral Brønsted acid (Scheme 1a) that is *NOT* the conventional mode previously reported for silicon nucleophiles (Scheme 1b).[6]

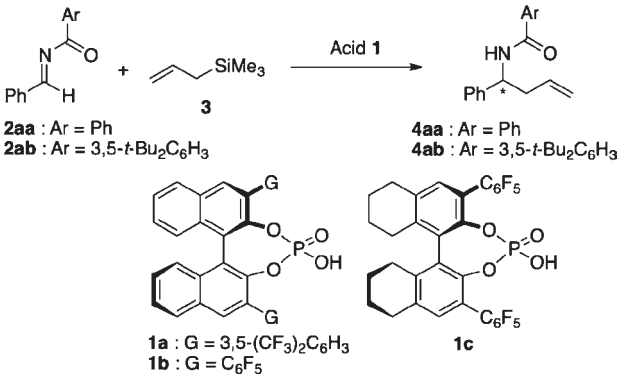
Scheme 1. Role of Additional Brønsted Acid in Combined Brønsted Acid System



Because of the specific character as well as the low nucleophilicity of allyltrimethylsilane, the proper choice of Brønsted acidity, neither too strong nor too weak, has to be of primary importance.[7,8] The chiral phosphoric acids possessing an electron-withdrawing group were chosen as the chiral Brønsted acid catalyst in view of their relatively strong acidity. Initial investigation using 20 mol % catalyst loading revealed that while 20 mol % of **1a**, with a 3,5-bis-trifluoromethylphenyl group, was able to initiate the reaction of *N*-acyl imine **2aa**, enantioselectivity was very low (Table 1, entry 1). In contrast, the reaction with **1b**, possessing a pentafluorophenyl group, afforded the homoallylamine **4aa** with moderate enantioselectivity (entry 2). Next, a survey of appropriate solvents for this reaction was undertaken in the presence of 20 mol % of **1b**. The use of solvents other than toluene or ethyl acetate led to either a significant decline in enantioselectivity or no reaction (entries 2 and 3). To improve the chemical yields, the reactions were examined at higher temperatures and/or extended reaction times. When the reaction was conducted at 40 °C for 2 days, no effects was observed on either chemical yield or enantioselectivity (entry 4). In sharp contrast, continuing the reaction for 7 days resulted in a considerable improved in the chemical yield, accompanied by a significant decrease in enantioselectivity (entry 5).

It is evident that the inferior enantioselectivity obtained with extended reaction time may be due to the distinctive pathways facilitated by different catalyst species during the reaction. The details associated with the catalyst species responsible for enantioselectivity were investigated by employing stoichiometric amounts of chiral phosphoric acid **1b** in toluene and ethyl acetate (entries 6 and 7). In both cases, the reactions afforded higher enantioselectivity that was observed when the reaction was conducted with 20 mol % of **1b** in toluene (entry 2 vs 6) or in ethyl acetate (entry 3 vs 7). This outcome suggested that (i) the sense of the enantioselectivity is dominated by chiral phosphoric acid **1b**, (ii) the present catalysis does not allow chiral phosphoric acid **1b** to regenerate, and (iii) silylated phosphoric acid catalyzes the reaction quite slowly which reduces enantioselectivity, indicating that the present reaction proceeds via chiral Brønsted acid initiated silyl Lewis acid catalysis among previously reported mechanisms.[7]

Table 1. Initial Survey of the Reaction of Allyltrimethylsilane



entry[a]	**1** (mol %)	**2**	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**1a** (20)	**2aa**	toluene	30	20	5 (*R*)
2	**1b** (20)	**2aa**	toluene	30	19	60 (*R*)
3	**1b** (20)	**2aa**	EtOAc	30	34	50 (*R*)
4	**1b** (20)	**2aa**	toluene	40	18	58 (*R*)
5[d]	**1b** (20)	**2aa**	toluene	40	56	45 (*R*)
6	**1b** (100)	**2aa**	toluene	30	80	68 (*R*)
7	**1b** (100)	**2aa**	EtOAc	30	95	55 (*R*)
8	**1b** (100)	**2ab**	toluene	30	77	97 (*R*)
9	**1b** (100)	**2ab**	EtOAc	30	93	95 (*R*)
10	**1c** (100)	**2ab**	EtOAc	30	94	98 (*R*)

[a] The reactions were conducted with **2a** and **3** for 2 days in the presence of **1**. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was conducted for 7 days.

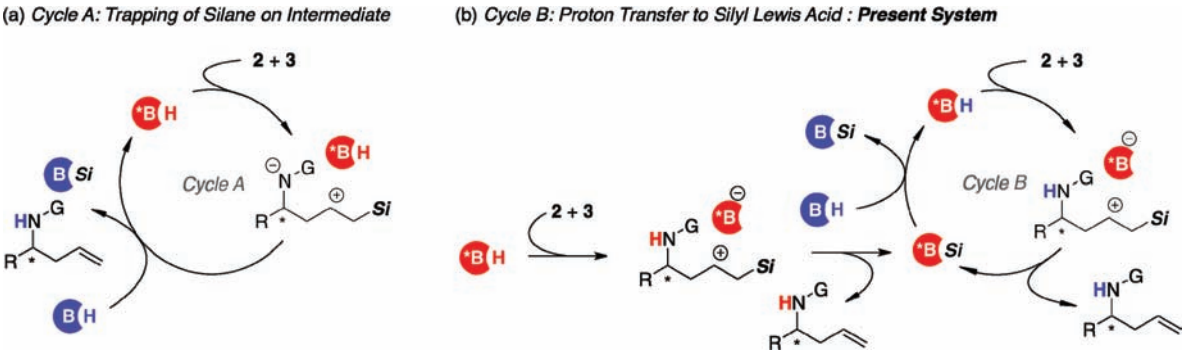
Encouraged by this implementation of a chiral **1b** initiated Hosomi–Sakurai reaction, we conducted a survey of structures with an acyl group using stoichiometric **1b** to improve the enantioselectivity.[9] From this survey, the 3,5-bis-*tert*-butylbenzoyl group (imine **2ab**) surfaced as an attractive substituent that afforded promising levels of enantioselection (entries 8 and 9). In terms of the chemical yield, reaction in ethyl acetate gave better results than that in toluene (entry 9). Furthermore, the replacement of binaphthyl with octahydrobinaphthyl as the catalyst led to an increase in enantioselectivity (98% ee) with no detrimental effect on the yield (entry 10).

(7) (a) Olah, G. A.; Laali, K.; Farooq, O. *J. Org. Chem.* **1984**, *49*, 4591–4594. (b) Davis, A. P.; Jaspars, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1176–1178. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570–4581.

(8) For recent examples, see: (a) Kampen, D.; List, B. *Synlett* **2006**, 2589–2592. (b) Kampen, D.; Ladepeche, A.; Claben, G.; List., B. *Adv. Synth. Catal.* **2008**, *350*, 962–966.

(9) For detailed experimental results, see the Supporting Information.

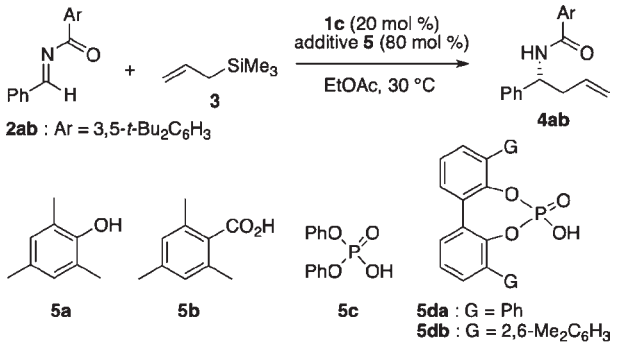
Scheme 2. Combined Brønsted Acid Catalysis for Catalytic Enanioselective Process



With optimal imines and chiral phosphoric acid in hand, we focused on transforming this reaction into a catalytic asymmetric process. There are two plausible approaches that the regeneration of chiral Brønsted acid could be initiated by additional Brønsted acid as shown in Scheme 2: (a) attack on silane in the β-cation intermediate (cycle A) and (b) proton transfer to silylated chiral phosphoric acid (cycle B). The screening of the additional Brønsted acid is summarized in Table 2. The use of phenol **5a** and carboxylic acid **5b** was expected to have an effect in cycle A that would resemble previously reported additional Brønsted acid in the reaction of silyl enolates, trapping silane on a siloxocarbenium ion intermediate.[6] However, phenol **5a** and carboxylic acid **5b** did not prove to be practical solutions for improvement of the product yield (entries 2 and 3). Commercially available phosphoric acid **5c** did not increase the product yield without loss of enantioselectivity (entry 4). In contrast, although biphenol-derived phosphoric acid **5da** decreased the enantioselectivity, the reaction did achieve high conversion with moderate enantioselectivity (entry 5). We envisioned that the substituents at the 3,3′-position in **5d** could be the key to facilitate the regeneration of chiral phosphoric acid **1c** such that loss of enantioselectivity might be prevented. After screening of substituents at the 3,3′-position, biphenol-derived phosphoric acid **5db**, with its 2,6-dimethylphenyl group, was fortuitously found to meet the criteria and afforded the homoallylamine **4ab** in good yield with high enantioselectivity (entry 6).

To gain insight into the mode of additional Brønsted acid **5db** in a combined Brønsted acid system, the following experiments were conducted. Treatment of imine **2ab** with allylsilane **3** in the presence of 20 mol % of **1c** under the same conditions as in Table 2, entry 1, yielded the product **4ab** and concomitantly formed the expected silylated chiral phosphoric acid, and then a further 80 mol % of **5db** was added (Scheme 3). This yielded the product **4ab** in 81% yield with 92% ee, an improvement on the product yield in Table 2, entry 1, and the same as that in Table 2, entry 6. This experiment clearly demonstrated that biphenol-derived phosphoric acid **5db** is able to involve proton transfer to regenerate chiral phosphoric acid **1c** from the silylated phosphoric acid and that the reaction in the combined system might proceed through cycle B in Scheme 2.

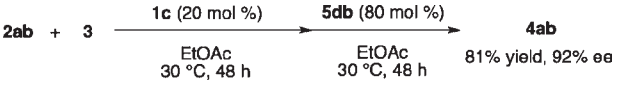
Table 2. Screening of Additional Brønsted Acid



entry[a]	5	yield[b] (%)	ee[c] (%)
1		22	95
2	**5a**	29	94
3	**5b**	45	93
4	**5c**	42	50
5	**5da**	75	50
6	**5db**	83	92

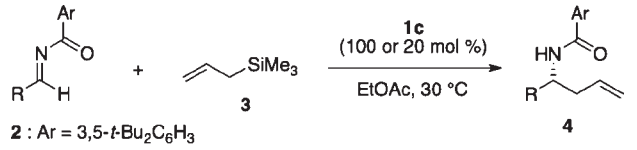
[a] The reactions were conducted with **2ab** and **3** at 30 °C in the presence of **1c** or **5**. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Scheme 3. Control Experiment for Proton Transfer to Silylated Chiral Phosphoric Acid



The scope of the reaction using chiral phosphoric acid **1c** was evaluated by investigating a range of imines **2** with a 3,5-di-*tert*-butyl benzoyl group on the imine nitrogen

Table 3. Scope of Chiral Phosphoric Acid Catalyzed Hosomi–Sakurai Reaction



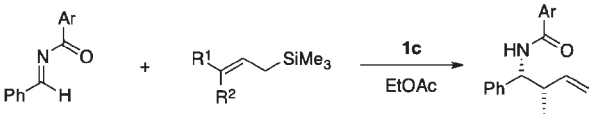
2 : Ar = 3,5-*t*-$Bu_2C_6H_3$

entry[a]	R	condition	yield[b] (%)	ee[c] (%)
1	Ph	A	94	98
2		B	83	92
3	2-MeC_6H_4	A	70	94
4		B	58	82
5	3-MeC_6H_4	A	88	96
6		B	54	93
7	4-MeC_6H_4	A	92	97
8		B	76	87
9	4-ClC_6H_4	A	92	95
10		B	75	86
11	4-$CF_3C_6H_4$	A	84	92
12		B	80	75
13	4-$MeOC_6H_4$	A	70	96
14		B	66	83

[a] The reactions were conducted with **2** and **3** under condition A or B. Condition A: 100 mol % of **1c**. Condition B: 20 mol % of **1c** and 80 mol % of **5db**. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

(Table 3). Good yields and excellent enantiomeric excesses were observed for each of the products formed when using aromatic imines as the electrophile. Unfortunately, aliphatic imines proved not to be synthesized when the substituent on the imine nitrogen was a 3,5-di-*tert*-butyl benzoyl group. It should be noted that although the reaction in the combined system provided desired adducts in slightly lower yields and enantioselectivities, high enantioselectivities were obtained in all cases even with 80 mol % of additional Brønsted acid **5db** in the reaction media. Furthermore, the crotylation reaction of (*E*)-crotyltrimethylsilane (E/Z = 84/16) completed at 30 °C, afforded the syn adduct **7ab** with high enantioselectivity (*syn*/*anti* = 93/7, 98% ee (*syn*)) (Scheme 4). While the reaction of (*Z*)-crotyltrimethylsilane (E/Z = 1/>99) resulted in significantly lower conversion at 30 °C, an increase in conversion was observed when the reaction was run at 40 °C, providing *syn* adduct **7ab** with good diastereo- and high enantioselectivity (*syn*/*anti* = 84/16, 94% ee (*syn*)) (Scheme 4). This correlation of crotyl geometry and product stereochemistry suggests that the reaction proceeds *via* an acyclic transition-state,[10] in which pentafluorophenyl groups on binaphthyl and/or the bulkier *tert*-dibutyl benzoyl group on the imino nitrogen could be playing an organizing role in this reaction.

Scheme 4. Enantio- and Diastereoselective Crotylation Reaction of Acyl Imine **2ab**



2ab : Ar = *t*-$Bu_2C_6H_3$ **6a** : R^1 = Me, R^2 = H (*E*/*Z* = 84/16) **7ab**
6b : R^1 = H, R^2 = Me (*Z*/*E* = >99/<1)

6a Condition A : 80% yield, *syn* / *anti* = 93 / 7, 98% ee (*syn*)
Condition B : 80% yield, *syn* / *anti* = 93 / 7, 95% ee (*syn*)

6b Condition A : 86% yield, *syn* / *anti* = 84 / 16, 94% ee (*syn*)

In summary, we have demonstrated a chiral Brønsted acid catalyzed highly enantio- and *syn* diastereoselective Hosomi–Sakurai reaction of imines with allyl- and crotyltrimethylsilane.[11,12] The pentafluorophenyl introduced chiral phosphoric acid exhibits robust activity to induce stereoselectivities in the case of *N*-acyl imine **2ab**. In particular, a combined Brønsted acid system with chiral phosphoric acid **1c** and additional Brønsted acid **5db** was shown to be an enantioselective catalytic process. The present system proceeds through regeneration of the chiral Brønsted acid *by proton transfer from additional Brønsted acid to chiral silylated phosphoric acid*, which is a newly discovered function of biphenol-derived phosphoric acid and a completely different mode than the previously developed reaction of silicon nucleophiles. The combined Brønsted acid system described herein is an innovative and new entry into chiral Brønsted acid catalysis that should find wide application in enantioselective synthesis using stable silicon reagents.

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

(10) (a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109. (b) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedoron* **1984**, *40*, 2239–2246. (c) Bottoni, A.; Costa, A. L.; Tommaso, D. D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* **1997**, *119*, 12131–12135.

(11) For representative example of enantioselective reaction of imines with allyltrimethylsilane, see: (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614–2615. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell., R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849. (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67–77.

(12) For allylation of other examples using allylsilanes, see the Supporting Information.