JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Chiral Brønsted Acid as a True Catalyst: Asymmetric Mukaiyama Aldol and Hosomi−Sakurai Allylation Reactions

Masahiro Sai* and Hisashi Yamamoto*

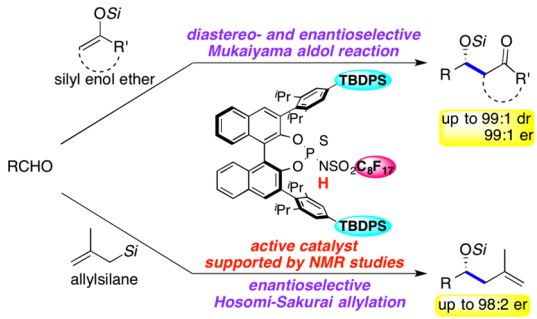
Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan

Supporting Information

ABSTRACT: Highly diastereo- and enantioselective Mukaiyama aldol reaction catalyzed by a new chiral Brønsted acid, *N*-(perfluorooctanesulfonyl)-thiophosphoramide, is described. The perfluorooctyl substituent on the sulfonyl group of the catalyst plays an essential role in the stereoselection. The catalyst also allows the asymmetric Hosomi−Sakurai allylation, which has been considerably challenging due to the low reactivity of allylsilanes. ^{29}Si and ^{31}P NMR monitoring reveals the characteristic feature of the thiophosphoramide catalyst, acting as a strong Brønsted acid even in the presence of excess silyl nucleophiles, which cannot be found in other related phosphoric acid analogues.

The addition of silyl enol ethers to carbonyl compounds, known as the Mukaiyama aldol reaction, has been the subject of extensive investigation due to the usefulness of products containing one new carbon−carbon bond and up to two new stereogenic centers.[1,2] Many successful examples of the asymmetric version of this reaction have been developed employing either Lewis acid[3] or Lewis base[4] catalysts. In contrast, chiral Brønsted acid-catalyzed asymmetric reactions are less explored. Rawal et al. reported a TADDOL-catalyzed asymmetric Mukaiyama aldol reaction of aldehydes and acylphosphonates with *O*-silyl-*N*,*O*-ketene acetals.[5] Jørgensen et al. described a chiral bis(sulfonamide) catalyst in an asymmetric Mukaiyama aldol reaction of electron-deficient aldehydes with ketene silyl acetals.[6] However, these two-proton systems generally require highly activated substrates for both nucleophiles and electrophiles because such catalysts activate the carbonyl group via weak hydrogen bonding. Thus, the development of chiral single Brønsted acid catalysts with enhanced acidity is highly desirable as they are expected to activate carbonyl compounds for the addition of weak nucleophiles. Recently, List et al. designed a new class of chiral binaphthyl-derived disulfonimide catalysts[7] and accomplished the asymmetric Mukaiyama aldol reaction with a broad substrate scope.[7a] In this reaction, the actual catalyst is shown to be the silyl Lewis acid *in situ* generated by the reaction of the chiral disulfonimide with ketene silyl acetals. Independently, we also developed the asymmetric Mukaiyama aldol reaction using *N*-triflylthiophosphoramides as the catalyst, which have expanded the substrate scope by allowing the use of less reactive silyl enol ethers.[8,9] However, the mechanism and the true catalyst of the reaction were not fully investigated. Here, we disclose the unique feature of the thiophosphoramide catalyst, acting as a strong Brønsted acid even in the presence of excess silyl enol ethers. We also describe the synthesis of a new chiral *N*-(perfluorooctanesulfonyl)thiophosphoramide catalyst and the application to the asymmetric Mukaiyama aldol and Hosomi−Sakurai allylation reactions (Scheme 1). The longer perfluorooctyl group of the catalyst plays a decisive role in the stereoselection.

Scheme 1. Asymmetric Reactions of Aldehydes Catalyzed by a New Chiral BINOL-Based Brønsted Acid



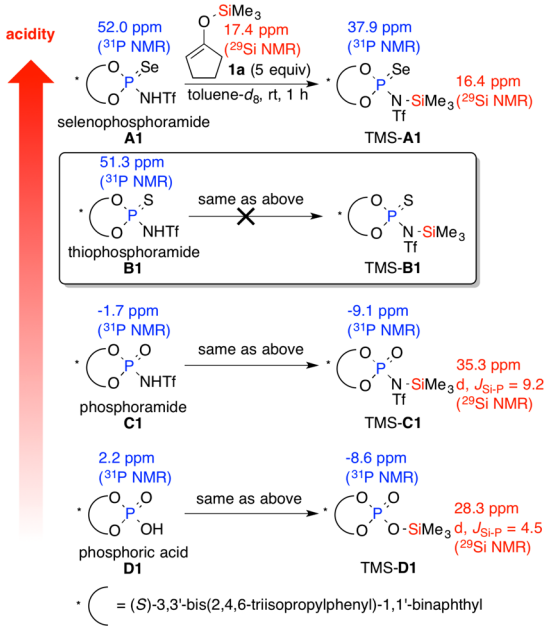
To probe the actual catalyst of reactions involving chiral BINOL-based phosphoric acid analogues[10] and silyl enol ethers, catalysts **A1**−**D1** were treated with silyl enol ether **1a** and monitored by ^{29}Si and ^{31}P NMR spectroscopy (Scheme 2).[11,12] Upon mixing the most acidic selenophosphoramide **A1** with **1a**, the new signals appeared at 16.4 ppm (^{29}Si NMR) and at 37.9 ppm (^{31}P NMR), which would correspond to the silylated **A1**.[13] In the case of thiophosphoramide **B1**, no new signal was detected. The reaction of phosphoramide **C1** with **1a** generated TMS-**C1**, which exhibited ^{29}Si NMR signal at 35.3 ppm (J_{Si-P} = 9.2 Hz) and ^{31}P NMR signal at −9.1 ppm. Phosphoric acid **D1** was also silylated, and new signals at 28.3 ppm (J_{Si-P} = 4.5 Hz, ^{29}Si NMR) and −8.6 ppm (^{31}P NMR) were observed.[14] As a result, only thiophosphoramide **B1** was not silylated by **1a**. Silyl enol ether **1a** is considered to be protonated by the catalysts to generate the oxonium ion **1a**′ (Scheme 3). In the case of catalyst **B1**, the counteranion causes the deprotonation of **1a**′ to regenerate catalyst **B1** and **1a**. On the other hand, in the case of catalysts **A1**, **C1**, and **D1**, the counteranion can attack the TMS group of **1a**′ to generate the silyl Lewis acid and the ketone.[15] These results clearly demonstrate the unique feature of the thiophosphoramide of activating the carbonyl group as a Brønsted acid even in the presence of excess silyl enol ethers in contrast to other phosphoric acid analogues.

Received: April 29, 2015
Published: May 27, 2015

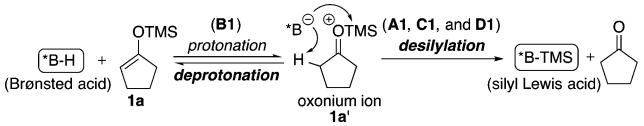
ACS Publications © 2015 American Chemical Society

DOI: 10.1021/jacs.5b04168
J. Am. Chem. Soc. 2015, 137, 7091−7094

Scheme 2. Investigation of the Actual Catalyst

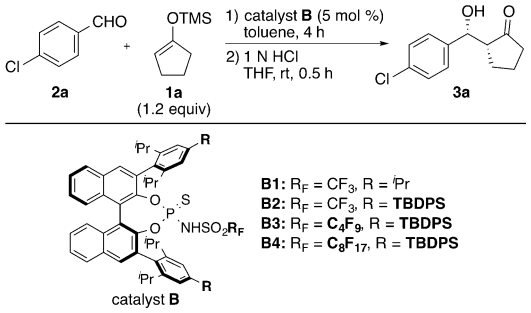


Scheme 3. Reactivity Difference of the Catalysts



Knowing this characteristic feature of thiophosphoramides, we next aimed at exploring their catalytic activity toward a diastereo- and enantioselective Mukaiyama aldol reaction. To realize the reaction, we synthesized chiral BINOL-based thiophosphoramides **B2**–**B4** bearing bulky silyl groups onto the *ortho* aromatic substituents. The carbon–silicon bond is longer than the carbon–carbon bond, and thus such thiophosphoramides are expected to effectively shield one enantiotopic face of the aldehyde and influence the orientation of the approaching silyl enol ether.[16] We investigated the catalytic activities of several chiral BINOL-derived thiophosphoramides **B** in the reaction of silyl enol ether **1a** with aldehyde **2a** (Table 1). With catalyst **B1**, the desired aldol product **3a** was obtained but in poor stereoselectivity (entry 1). As expected, catalyst **B2**, which possesses *tert*-butyldiphenylsilyl (TBDPS) groups onto the *ortho* aromatic substituents, enabled the reaction with a promising diastereo- and enantioselectivity (entry 2). Next, trifluoromethyl substituent on the sulfonyl group of the catalyst was replaced with a more sterically demanding perfluorobutyl group (**B3**). Surprisingly, the use of catalyst **B3** led to a drastic improvement in both diastereo- and enantioselectivity (96:4 dr and 95:5 er, entry 3). To the best of our knowledge, this is the first report of the R_F group of the phosphoramide catalyst affecting the stereoselectivity.[17] Further optimization of the catalyst structure revealed that thiophosphoramide **B4**, bearing a perfluorooctyl substituent on the sulfonyl group, was the best catalyst (entry 4). Catalyst **B4** was highly active even at −100 °C, and the catalyst loading could be reduced to 3 mol % without erosion of yield and stereoselectivity (entry 5). It should be noted that the reaction of **1a** with **2a** under optimized conditions, but with a proton scavenger, 2,6-di-*tert*-butylpyridine,[18] resulted in no formation of **3a** (entry 6). This result is consistent with the experimental

Table 1. Optimization of Reaction Conditions



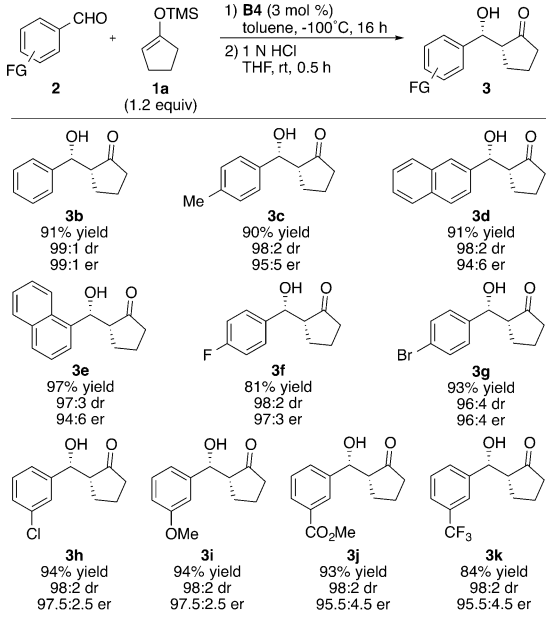
entry	catalyst	temp. (°C)	yield (%)[a]	dr[b] *syn*/*anti*	er[c] *syn*
1	**B1**	−78	93	74:26	79:21
2	**B2**	−78	95	85:15	88:12
3	**B3**	−78	92	96:4	95:5
4	**B4**	−78	93	96:4	96:4
5[d]	**B4**	−100	92	97:3	96.5:3.5
6[d,e]	**B4**	−100	0	–	–

[a]Isolated yield (containing *syn*- and *anti*-diastereomers). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by supercritical fluid chromatography on a chiral stationary phase. [d]With 3 mol % catalyst **B4** for 16 h. [e]With 12 mol % 2,6-di-*tert*-butylpyridine.

observation in Scheme 2 that the actual catalyst of the reaction is the Brønsted acid itself, not the *in situ* generated silyl Lewis acid. The absolute configuration of **3a** was unambiguously established by X-ray crystallography.

Having in hand the optimum conditions, we explored the generality of the reaction in terms of aldehyde scope (Scheme 4). Electron-rich and electron-neutral aldehydes underwent the reaction with high stereoselectivities. Performing the reaction with benzaldehyde gave the highest diastereo- and enantioselectivity (**3b**, 99:1 dr and 99:1 er). An *ortho*-substituted aldehyde could be used (**3e**). The reaction tolerated a variety of functional groups such as fluoro, chloro, bromo, methoxy, ester, and

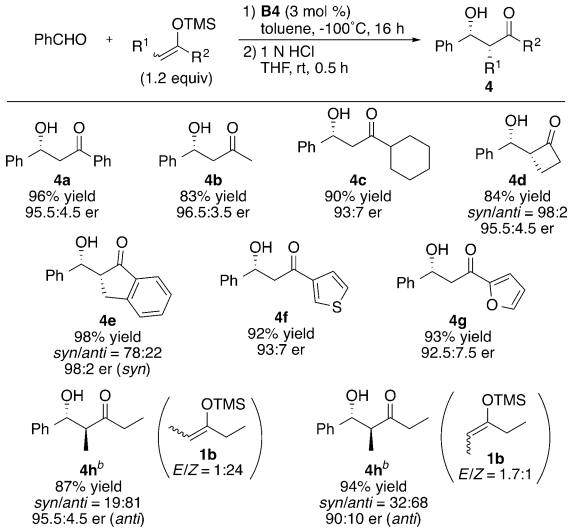
Scheme 4. Scope of Aldehydes[a]



[a]Reaction conditions: **2** (0.25 mmol), **1a** (0.30 mmol), and catalyst **B4** (3 mol %) in toluene (3.0 mL) at −100 °C for 16 h.

DOI: 10.1021/jacs.5b04168
J. Am. Chem. Soc. 2015, 137, 7091−7094

Scheme 5. Scope of Silyl Enol Ethers[a]



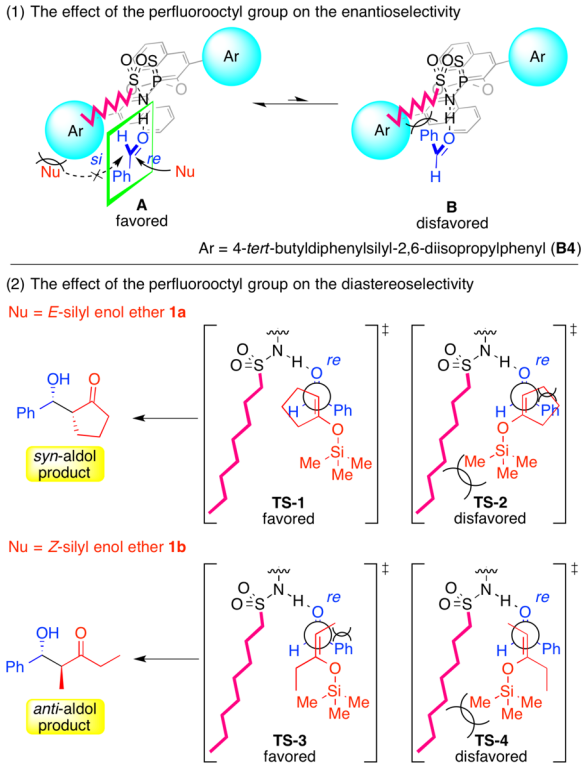
[a]Reaction conditions: benzaldehyde (0.25 mmol), silyl enol ether (0.30 mmol), and catalyst **B4** (3 mol %) in toluene (3.0 mL) at −100 °C for 16 h. [b]With 7.5 mol % catalyst **B4** and 1.5 equiv of silyl enol ether **1b**.

trifluoromethyl, maintaining excellent diastereo- and enantioselectivities. Unfortunately, aliphatic aldehydes did not undergo the reaction probably due to the low reactivity.

The scope of silyl enol ethers was then examined (Scheme 5). A variety of silyl enol ethers were suitable for the reaction to give the corresponding aldol products **4** in high yields and stereoselectivities. Interestingly, the stereochemistry of the major product (**4h**) was altered from *syn* to *anti* when silyl enol ether *Z*-**1b** (*E*/*Z* = 1:24) was used.[19] Additionally, *anti*-**4h** was mainly obtained even when *E*-**1b** (*E*/*Z* = 1.7:1) was used. This selectivity with *E*-**1b** is in contrast to that observed with cyclic *E*-**1a**. Thus, we conducted control experiments and found that the isomerization of *E*-**1b** to *Z*-**1b** occurred under Brønsted acid catalysis.[20,21]

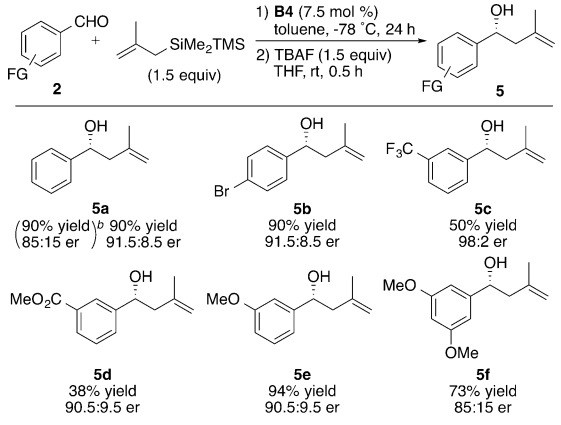
Although the exact role of the perfluorooctyl group of the catalyst in the stereoselection is not yet clear, a plausible stereochemical model is illustrated in Scheme 6. There are two modes of the aldehyde coordination to the chiral Brønsted acid catalyst (**A** and **B**). **A** is more favored than **B** as it avoids a steric interaction between the phenyl group of the aldehyde and the perfluorooctyl group of the catalyst. The *si*-face of the aldehyde in **A** is effectively shielded by the bulky TBDPS-substituted aryl group of the catalyst. Thus, the aldehyde is attacked preferentially on its *re*-face. The role of the longer perfluorooctyl group of the catalyst is likely to increase the steric interaction in **B**. When *E*-**1a** is used as a nucleophile, the *syn*-selective aldol reaction via **TS-1** is operating exclusively. **TS-2** is disfavored due to two simultaneous steric repulsions between the TMS group of **1a** and the bulky perfluorooctyl group as well as the methylene group of **1a** and the aldehyde phenyl group. In the case of *Z*-**1b**, although **TS-3** has an unfavorable steric interaction between the methyl group of **1b** and the aldehyde phenyl group, **TS-4** suffers a more severe steric repulsion between the TMS group of **1b** and the perfluorooctyl group. Thus, the *anti*-aldol product via **TS-3** is mainly obtained with high enantioselectivity. The presence of the longer perfluorooctyl group of the catalyst leads to the increased steric congestion in **TS-2** and **TS-4**, which contributes to the enhanced diastereoselectivity.

Scheme 6. Role of the Perfluorooctyl Group of the Catalyst in the Stereoselection



The success of asymmetric Mukaiyama aldol reaction prompted us to apply the catalytic system to the asymmetric Hosomi−Sakurai allylation of carbonyl compounds,[7d,22] which was considerably more challenging because of the low reactivity of allylsilanes. The asymmetric allylation of benzaldehyde with various allylsilanes was examined using **B4** as the catalyst. The use of methallyltrimethylsilane gave full conversion to the desired homoallylic alchohol **5a** in 90% yield with 85:15 er at −70 °C (Scheme 7).[23] However, the reaction was highly sensitive to the reaction temperature, and **5a** was obtained in only 8% yield at −78 °C. The replacement of the TMS group with the more reactive $SiMe_2TMS$ group[24] allowed the reaction at −78 °C,

Scheme 7. Asymmetric Hosomi−Sakurai Allylation[a,b]



[a]Reaction conditions: **2** (0.25 mmol), allylsilane (0.375 mmol), and catalyst **B4** (7.5 mol %) in toluene (2.5 mL) at −78 °C for 24 h. [b]Methallyltrimethylsilane (1.5 equiv) was used at −70 °C.

DOI: 10.1021/jacs.5b04168
J. Am. Chem. Soc. 2015, 137, 7091−7094

providing **5a** in 90% yield and 91.5:8.5 er. Various functional groups were tolerated, and the methallylated products were obtained with high enantioselectivities.

In conclusion, we have designed and synthesized a new chiral BINOL-based thiophosphoramide catalyst, which possesses TBDPS groups onto the *ortho* aromatic substituents and the perfluorooctyl substituent on the sulfonyl group. ^{29}Si and ^{31}P NMR monitoring reveals the characteristic feature of the thiophosphoramide catalyst, acting as a strong Brønsted acid even in the presence of excess silyl enol ethers, which cannot be found in other related phosphoric acid analogues. The catalyst is highly effective to the asymmetric Mukaiyama aldol reaction, and the reaction proceeds with excellent diastereo- and enantioselectivities. The catalyst can be applied to the asymmetric Hosomi−Sakurai allylation, which has been considerably challenging due to the low reactivity of allylsilanes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04168.

■ AUTHOR INFORMATION

Corresponding Authors

*sai@isc.chubu.ac.jp

*hyamamoto@isc.chubu.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (no. 23225002), Advanced Catalytic Transformation Program for Carbon Utilization, Nippon Pharmaceutical Chemicals Co., Ltd, and Advance Electric Co., Inc.

■ REFERENCES

(1) For a seminal reference of Mukaiyama aldol reaction, see: Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011.

(2) Ishihara, K.; Yamamoto, H. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, Chapter 2.

(3) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2009.

(4) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, Chapter 7.

(5) (a) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130. (b) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 776.

(6) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284.

(7) Asymmetric catalysis of chiral binaphthyl-derived disulfonimides with silyl nucleophiles, see: (a) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363. (b) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754. (c) Guin, J.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 8859. (d) Mahlau, M.; García-García, P.; List, B. *Chem.—Eur. J.* **2012**, *18*, 16283. (e) Gandhi, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2573. (f) Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334. (g) Ratjen, L.; van Gemmeren, M.; Pesciaioli, F.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8765. (h) Wang, Q.; van Gemmeren, M.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13592. (i) Wang, Q.; List, B. *Synlett* **2015**, *26*, 807. (j) Guin, J.; Wang, Q.; van Gemmeren, M.; List, B. *Angew. Chem., Int. Ed.* 2015, *54*, 355. Asymmetric catalysis of chiral binaphthyl-derived disulfonimides as Brønsted acids, see: (k) Chen, L.-Y.; He, H.; Chan, W.-H.; Lee, A. W. M. *J. Org. Chem.* **2011**, *76*, 7141. (l) Prévost, S.; Dupré, N.; Leutzsch, M.; Wang, Q.; Wakchaure, V.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8770. For a review, see: (m) van Gemmeren, M.; Lay, F.; List, B. *Aldrichimica Acta* **2014**, *47*, 3.

(8) Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476.

(9) TMS silyl enol ether of acetophenone is 10^3 times less reactive than TMS silyl ketene acetal of methyl isobutylate, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(10) For reviews on chiral phosphoric acid catalysis, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (d) Terada, M. *Synthesis* **2010**, 1929. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (f) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(11) For ^{29}Si and ^{31}P NMR spectra, see the Supporting Information.

(12) Computational study on the pK_a values of various chiral Brønsted acids, see: (a) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569. (b) Yang, C.; Xue, X.-S.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2014**, *79*, 4340.

(13) TMS-A1 and TMS-**C1** may exist in equilibrium with their isomers (P-*N*-SiMe$_3$, P-Se/*O*-SiMe$_3$, and S-*O*-SiMe$_3$).

(14) *In situ* generation of silyl Lewis acids by the reaction of chiral phosphoric acids with silyl compounds, see: (a) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (b) Zamfir, A.; Tsogoeva, S. B. *Org. Lett.* **2010**, *12*, 188. (c) Serdyuk, O. V.; Zamfir, A.; Hampel, F.; Tsogoeva, S. B. *Adv. Synth. Catal.* **2012**, *354*, 3115.

(15) The reason for such a reactivity difference of the catalysts remains unclear, and computational studies to rationalize this result are underway.

(16) For the beneficial effect of bulky *para* substituents at the 3,3′-aryl groups on enantioselectivity in chiral phosphoric acid catalysis, see: (a) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (b) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (c) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (d) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411.

(17) It is reported that the substituent on the sulfonyl group of the phosphoramide catalyst has a significant influence on the yield but not on the enantioselectivity; see: ref 10f and references therein.

(18) For usage of this base to differentiate the reaction pathway between Lewis acid and Brønsted acid catalysis, see: (a) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219. (b) Hara, K.; Akiyama, R.; Sawamura, M. *Org. Lett.* **2005**, *7*, 5621.

(19) This result implies that our new catalyst has the potential to enable the asymmetric *anti*-selective Mukaiyama aldol reaction.

(20) Treatment of a 1.5:1 mixture of *E*- and *Z*-**1b** with 5 mol % of catalyst **B4** at −100 °C for 1 h resulted in a 1:7.7 mixture of *E*- and *Z*-**1b**, see the Supporting Information.

(21) For examples of Brønsted acid-catalyzed isomerization of silyl enol ethers, see: (a) Deyine, A.; Dujardin, G.; Mammeri, M.; Poirier, J.-M. *Synth. Commun.* **1998**, *28*, 1817. (b) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444. (c) Inanaga, K.; Ogawa, Y.; Nagamoto, Y.; Daigaku, A.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *Beilstein J. Org. Chem.* **2012**, *8*, 658.

(22) For reviews on catalytic asymmetric allylation of carbonyl compounds with allylsilanes, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (d) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

(23) Unsubstituted or γ-substituted allylsilanes did not react even at room temperature.

(24) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795.

DOI: 10.1021/jacs.5b04168
J. Am. Chem. Soc. 2015, 137, 7091−7094