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N-Triflylthiophosphoramide Catalyzed Enantioselective Mukaiyama Aldol Reaction of Aldehydes with Silyl Enol Ethers of Ketones

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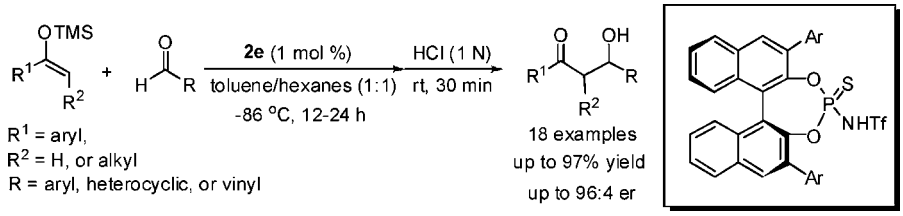
ABSTRACT



The first Brønsted acid catalyzed asymmetric Mukaiyama aldol reaction of aldehydes using silyl enol ethers of ketones as nucleophiles has been reported. A variety of aldehydes and silyl enol ethers of ketones afforded the aldol products in excellent yields and good to excellent enantioselectivities. Mechanistic studies revealed that the actual catalyst may be changed from the silylated Brønsted acid to the Brønsted acid itself depending on the reaction temperature.

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] Although many successful examples employing either Lewis acid[3] or Lewis base[4] catalysts have been developed for enantioselective Mukaiyama aldol reactions, only a few examples of chiral Brønsted acid catalyzed enantioselective Mukaiyama aldol reactions have been reported. Rawal reported a TADDOL catalyzed Mukaiyama aldol reaction of aldehydes and acylphosphonates with silyl enol ethers of amides.[5] Jørgensen described a chiral bis-sulfonamide Brønsted acid catalyst in a Mukaiyama aldol reaction with silyl ketene acetal.[6] However, these Brønsted acid catalyzed asymmetric Mukaiyama aldol reactions generally required highly activated substrates for both nucleophiles and electrophiles presumably because of their lower acidities.

Most recently List and co-workers have developed a disulfonimide derived from BINOL as a new chiral Brønsted acid catalyst and applied it to an asymmetric Mukaiyama aldol reaction.[7] Although this new catalyst showed potential to solve the previous problems of the asymmetric Mukaiyama aldol reaction with weak Brønsted acids, such as limited substrate scope, this catalyst system still needs to use reactive silyl ketene acetals as nucleophiles. In addition, the active

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

(2) For reviews, see: Ishihara, K.; Yamamoto, H. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH, Weinheim, Germany, 2004; Vol. 2, Chapter 2, p 25.

(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, p 229.

(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) Gracía-Gracía, P.; Lay, F.; Gracía-Gracía, P.; Babalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363.

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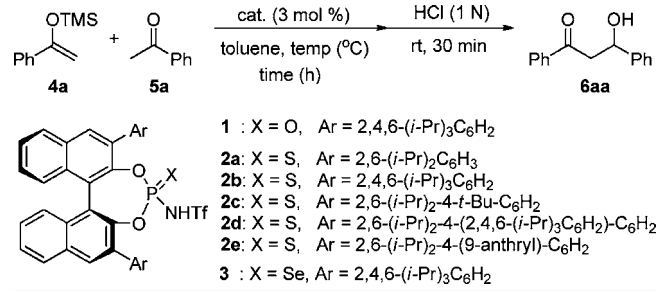
catalyst in this system was shown to be the silylated Brønsted acid acting as Lewis acid rather than Brønsed acid itself. To the best of our knowledge, there have been no reports of Brønsted acid catalyzed enantioselective Mukaiyama aldol reaction using less reactive silyl enol ethers of ketones as nucleophiles.[8] Herein, we report the first Brønsted acid catalyzed asymmetric Mukaiyama aldol reaction of silyl enol ethers of ketones with simple aldehydes. Moreover, mechanistic studies revealed that the actual catalyst in this system is the Brønsted acid itself rather than the silylated Brønsted acid.

Since Akiyama and Terada's seminal reports in 2004,[9,10] chiral phosphoric acid catalysis to activate π-electrophiles toward nucleophilic attacks has been one of the growing fields in asymmetric catalysis.[11] Many enantioselective addition reactions to imines have been achieved with these chiral Brønsted acids;[12] however, successful application of these acids to reactions through carbonyl group activation has remained challenging because of their lower reactivities.[13] In order to increase the reactivities of chiral phosphoric acid catalysts and thus broaden their applicabilities, we have recently developed chiral *N*-triflyl oxo-, thio, and selenophosphoramides **1**−**3** as strong Brønsted acids and successfully applied them to organic reactions.[14,15] To further extend the utilities of these acids, we have employed these acids in the Mukaiyama aldol reaction of a variety of aldehydes with silyl enol ethers of ketones.

First, we began our investigation with a comparison of reactivities of these Brønsted acids **1**−**3** for a Mukaiyama aldol reaction of benzaldehyde **5a** with silyl enol ether of acetophenone **4a** (Table 1). Although these Brønsted acids showed similar reactivities in the asymmetric protonation reaction,[15] Brønsted acids **1**−**3** exhibited a dramatic difference in reactivities toward Mukaiyama aldol reaction (entries 1−3). Brønsted acids **2b** and **3** provided the aldol product **6aa** in excellent yields in 1 h, whereas Brønsted acid **1** did not afford any product even after 2 days. Since thiophosphoramide **2b** gave enantioselectivity slightly better than that of selenophosphoramide **3**, we chose the thiophosphoramide as a catalyst for further investigation. Next, we optimized the catalyst structure by examining the effect of the aryl substituent at 3,3′-position of the binaphthyl scaffold on enantioselectivity (entries 2, 4−7). Introduction of bulky aromatic substituents at the *para*-position of aryl substituents at the 3,3′-position of the binaphthyl scaffold had a beneficial effect on enantioselectivity.[16] Brønsted acid **2e** bearing bulky 9-anthryl at the *para*-position of the aryl group[17] provided the aldol product in 67:33 enantiomeric ratio (*er*) (entry 7). With catalyst **2e**, we further examined the effect of size of the silyl group. Among the silyl groups tested, the TMS group gave the best enantioselectivity.[18] Then, we further optimized the reaction conditions, such as temperature and solvents (entries 8−11).[19] Interestingly, the enantioselectivity showed strong dependence on reaction temperature (entries 7−9). The enantioselectivity significantly increased when the reaction was carried out at −86 °C (entry 9). The enantioselectivity could be improved further by using a mixture of toluene and hexanes as a solvent (entry 10). To our delight, the catalyst loading could be decreased to 1 mol % without any loss of enantioselectivity (entry 11).

Table 1. Optimization of Reaction Conditions

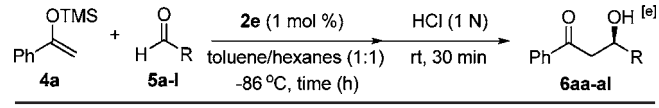


entry	catalyst	temp (°C)	time (h)	yield (%)[a]	er[b]
1	**1**	rt	48	NR	ND
2	**2b**	rt	1	96	57:43
3	**3**	rt	1	93	55:45
4	**2a**	rt	1	95	54:46
5	**2c**	rt	1	96	57:43
6	**2d**	rt	1	94	65:35
7	**2e**	rt	1	96	67:33
8	**2e**	−78	6	95	87:13
9	**2e**	−86	8	94	89:11
10[c]	**2e**	−86	12	96	92:8
11[c,d]	**2e**	−86	16	95	92:8

[a] Yield of isolated product. [b] er was determined by HPLC on OD-H column. [c] Toluene/hexanes (1:1) mixture was used as a solvent. [d] 1 mol % catalyst was used.

With the optimized conditions in hand, we examined the generality of aldehyde scope (Table 2). A variety of aldehydes **5a**−**l** afforded the aldol products **6aa**−**al** in excellent yields and good to excellent enantioselectivities.

Table 2. Aldehyde Scope



entry	R	time (h)	yield (%)[a]	er[b]
1	Ph	12	95	92:8
2[c,d]	4-NO_2-Ph	24	94	96:4
3	3-NO_2-Ph	18	96	94:6
4[c,d]	2-NO_2-Ph	24	91	95:5
5	4-Br-Ph	18	92	91:9
6[c]	4-Cl-Ph	18	93	90:10
7	4-MeO-Ph	12	96	92:8
8	2-naphthyl	18	94	90:10
9	1-naphthyl	18	95	81:19
10	2-Me-Ph	12	97	84:16
11	(*E*)-CH=CH-Ph	12	87	86:14
12[c]	2-thienyl	18	92	85:15

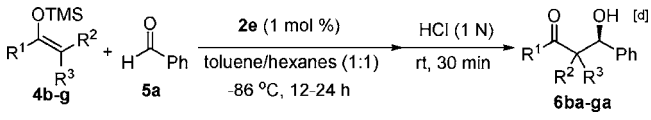
[a] Yield of isolated product. [b] Determined by HPLC on chiral column. [c] Reaction was carried out in toluene. [d] 3 mol % catalyst was used. [e] Absolute configuration was assigned by comparison of optical rotation (see Supporting Information). Remaining products assigned by analogy.

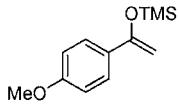
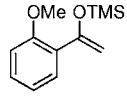
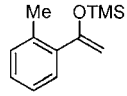
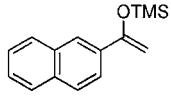
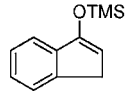
Although the nitro group had a beneficial effect on enantioselectivity (entries 2−4), the electronic properties of aldehydes showed little influence on enantioselectivities (entries 5−7). Aldehydes bearing either electron-donating or electron-withdrawing groups at the 4-position of the phenyl group gave the aldol products with almost the same level of enantioselectivity. However, the electronic properties of aldehydes significantly affected the reaction rate. The electron-withdrawing group at 2- and 4- position of the aryl group decreased reactivities toward aldol reaction due to diminished basicity of aldehydes (entries 2, 4−6). Steric properties of aryl substituents also played a role in enantioselectivity. Bulky substituents at the 2-position of aldehydes had a deleterious effect on the enantioselectivity (entries 9 and 10). It is noteworthy that the application of this catalyst is not limited to benzaldehyde derivatives. α,β-Unsaturated aldehyde as well as heterocyclic aldehyde gave the aldol products in excellent yields and good to high enantioselectivity (entries 11 and 12).

We further investigated the scope of silyl enol ethers of various ketones **4b−g** with benzaldehyde **5a** (Table 3). Silyl enol ethers derived from aryl methyl ketones gave the aldol adducts in excellent yields and high enantioselectivities (entries 1−4). It is noteworthy that electronic and steric properties of aryl group had little to no effect on enantioselectivities. (Table 2 entry 1, Table 3 entries 1−4). We further investigated the applicability of this catalyst system to the diastereoselective Mukaiyama aldol reaction (entries 5 and 6). Silyl enol ether derived from cyclopentanone gave the product in high yield and excellent enantioselectivity with 5:1 dr (entry 5). This method was further extended to the other cyclic silyl enol ethers bearing an aromatic rings, although enantioselectivities were moderate (entry 6).

To gain more information about the reaction mechanism and strong temperature dependence of the enantioselectivity of the aldol product,[20] we hypothesized that a different reaction pathway might be operating depending on the reaction temperature. There are two plausible reaction pathways: Brønsted acid itself directly protonates the carbonyl compound (Brønsted acid pathway), or Brønsted acid may first be silylated with silyl enol ether and the silylated Brønsted acid then activates the carbonyl compound (Lewis acid pathway).[21,22]

Table 3. Scope of Silyl Enol Ethers



entry	silyl enol ether	yield (%)[a]	*dr* (syn:anti)[b]	er[c]
1		97	-	92:8
2		98	-	90:10
3		98	-	92:8
4		94	-	92:8
5		86	16:1	syn: 95:5 anti: 97:3
6		93	1.7:1	syn: 76:24 anti: 73:27

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC on chiral column. [d] Absolute configuration was assigned by comparison of optical rotation (see Supporting Information). Remaining products assigned by analogy.

(8) According to Mayr's π-nucleophilicity scale, TMS silyl enol ether of acetophenone **4a** is 10^3 times less reactive than TMS silyl ketene acetal of methyl isobutylate; see: Mayr, H.; Kempe, B.; Ofial, A. R. *Acc. Chem. Rec.* **2003**, *36*, 66.

(9) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

(10) Uraguchi, D.; Tereda, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(11) For reviews of chiral phosphoric acid catalysis, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Tereda, M. *Chem. Commun.* **2008**, 4097.

(12) Recent examples of activation of imines by chiral phosphoric acids, see: (a) Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075. (b) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (c) Li, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *131*, 6967. (d) Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036. (e) Jiang, J.; Qing, J.; Gong, L.-Z. *Chem.—Eur. J.* **2009**, *15*, 7031. (f) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180. (g) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717. (h) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546. (i) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (j) Li, N.; Chen, X.-H.; Song, J.; Luo, S.-W.; Fan, W.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 15301.

(13) For examples of activation of functionalized carbonyl groups by chiral phosphoric acids, see: (a) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (b) Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882.

(14) (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411.

(15) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246.

(16) For the beneficial effect of bulky *para*-substituent at the aryl substituent 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) Reference 14b. (d) Reference 15.

(17) For the synthesis of BINOL derivative bearing bulky 9-anthryl substituent at the *para*-position at the aryl substituent, see ref.16a

(18) TBS, pentamethyldisilyl (PMDS), and TIPS enol ethers provided the aldol products in 56:14, 64:36, and 59:41 er, respectively.

(19) For more detailed information, see Supporting Information.

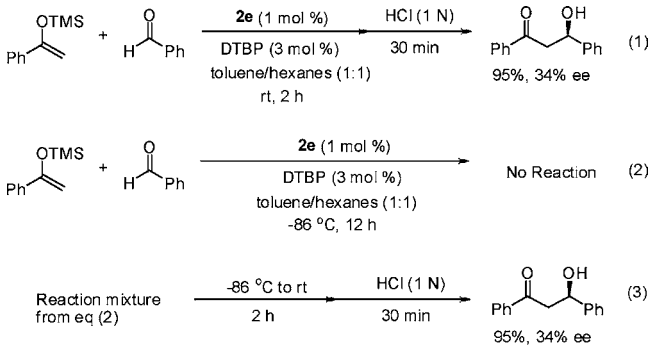
(20) For examples of strong temperature dependence of enantioselectivity in Brønsted acid catalysis, see: (a) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657. (b) Reference 6.

(21) For an example of Lewis acid catalysis via in situ generation of the silylated Lewis acids from strong Brønsted acids, see: Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219.

(22) For recent examples of asymmetric Lewis acid catalysis via in situ generation of the silylated Brønsted acids from Brønsted acids, see: (a) Zamfir, A.; Tsogoeva, S. B. *Org. Lett.* **2010**, *12*, 188. (b) Reference 7. (c) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084.

To differentiate between these two pathways, we carried out Mukaiyama aldol reactions in the presence of 2,6-di(*tert*-butyl)pyridine (DTBP), which is known to inhibit any potential Brønsted acid catalysis (Scheme 1).[23] At room

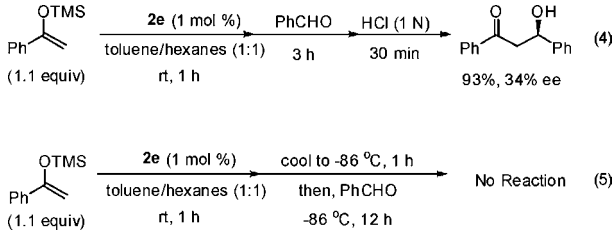
Scheme 1. Mukaiyama Aldol Reaction with DTBP



temperature, DTBP has no effect on the Mukaiyama aldol reaction in terms of either reactivty or enantioselectivity (eq 1 and Table 1 entry 7). However, at low temperature DTBP completely inhibited the Mukaiyama aldol reaction (eq 2 and Table 1 entry 11). Moreover, when the reaction mixture from eq 2 was warmed up to room temperature, the aldol reaction proceeded again with the same yield and enantioselectivity as that of the reaction at room temperature with DTBP (eq 1 and 3). These results suggested that the actual catalyst for the Mukaiyama aldol reaction at room temperature is the silylated Lewis acid (Lewis acid pathway), whereas the acutal catalyst at low temperature is Brønsted acid itself (Brønsed acid pathway).

To further corroborate our hypothesis, the silylated Brønsted acid was pregenerated[24] and subjected to the Mukaiyama aldol reaction (Scheme 2). The silylated Brønsted acid

Scheme 2. Mukaiyama Aldol Reaction with Silylated Lewis Acid



afforded the aldol adduct with the same yield and enantioselectivity at room temperature (eq 4 and Table 1 entry 7). However, no reaction was observed at low temperature with the silylated Brønsted acid (eq 5). This result also supported that two different reaction pathways are operative depending on reaction temperature. At room temperature the Lewis acid catalyzed pathway would be operative, whereas at low temperature Brønsted acid be the actual catalyst.

This direct activation of unfunctionalized carbonyl compounds through protonation is expected to have a significant effect on a Brønsted acid catalyzed asymmetric Mukaiyama aldol reaction. Despite the fact that strong achiral Brønsted acids, such as TfOH and Tf_2NH, have been widely used in Mukaiyama aldol reactions with broad substrate scope,[25] strong acids have rarely been used as catalysts in enantioselective Mukaiyama aldol reactions. This may be because the rapidly generated silylated Brønsted acids, considered as the true catalysts, are associated with a non-enantioselective pathway.[26] Thus, the direct activation of carbonyl groups via protonation with strong Brønsted acids is expected to make a number of Mukaiyama aldol reactions accessible in an enantioselective fashion. This will provide a complementary approach to asymmetric Mukaiyama aldol reactions through carbonyl group activation by chiral silyl cations, which are in situ generated from strong Brønsted acid.[7]

In conclusion, we have demonstrated the first Brønsted acid catalyzed asymmetric Mukaiyama aldol reaction of aldehydes using silyl enol ethers of ketones as nucleophiles. A variety of aldehydes were applicable to this catalyst system and afforded the aldol products in excellent yields and good to excellent enantioselectivities with only 1 mol % catalyst loading. Various silyl enol ethers could be applied to this catalyst system, including a diastereoselective Mukaiyama aldol reaction of silyl enol ethers of cyclic ketones. Furthermore, mechanistic studies have revealed that the silylated Brønsted acid may be an actual catalyst at room temperature (Lewis acid pathway), whereas Brønsted acid itself may be an actual catalyst at low temperature (Brønsted acid pathway). Further mechanistic studies and other applications of this Brønsted acid are currently underway in our laboratory.

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

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(23) For usage of this base to differentiate the reaction pathway between Lewis acid and Brønsted acid catalysis, see: (a) Cheon, C. H.; Yamamoto, H. *Tetrahedron Lett.* **2009**, *50*, 3555. (b) Hara, K.; Akiyama, R.; Sawamura, M. *Org. Lett.* **2005**, *7*, 5621. (c) References 21 and 22.

(24) ^{1}H NMR analysis showed that the silyl enol ether **4a** rapidly silylated Brønsted acid **2e**. Furthermore, a new signal from the silylated Brønsted acid was observed in the ^{31}P NMR. For more detailed information, see Supporting Information.

(25) For a review of strong Brønsted acids catalyzed Mukaiyama aldol reaction, see: Boxer, M. B.; Albert, B. J.; Yamamoto, H. *Aldrichimica Acta* **2009**, *42*, 3.

(26) Ishihara, K.; Yamamato, H. *Chem. Commun.* **2002**, 1564.