



## A new Brønsted acid derived from squaric acid and its application to Mukaiyama aldol and Michael reactions

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### ABSTRACT

Bis-*N*-trifluoromethanesulfonyl squaramide was prepared as a new bench-stable strong Brønsted acid and applied to the Brønsted acid-catalyzed Mukaiyama aldol and Michael reactions with silyl enol ethers. The resulting Mukaiyama aldol products of aldehydes were obtained in quantitative yields, whereas expansion of the utility of this Brønsted acid to ketones was limited to electron-deficient ketones presumably due to lower reactivity of ketones as well as competing protodesilylation of silyl enol ether. The Brønsted acid was further applied to Mukaiyama Michael reaction of  $\alpha,\beta$ -unsaturated ketones. It is noted that catalyst loading of all Mukaiyama reactions was only 1 mol % or less, which demonstrated the high reactivity of this acid. Mechanistic studies implied that the Mukaiyama aldol reaction might proceed through Brønsted acid catalysis, rather than through Lewis acid catalysis with silylated Brønsted acid.

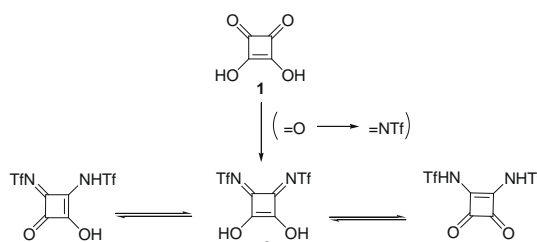
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Brønsted acid catalysis is one of the growing fields in modern organic synthesis.<sup>1</sup> Several Brønsted acids, such as urea/thiourea,<sup>2</sup> TADDOL,<sup>3</sup> and phosphoric acid,<sup>4</sup> have been applied to a variety of organic reactions. However, compared to metal-based Lewis acid catalysts, the utility of Brønsted acid catalysts is still limited to reactive substrates, mainly due to relatively lower reactivities of these Brønsted acids. Moreover, the catalyst scaffolds of Brønsted acids are limited to several catalophores, such as urea/thiourea, diols, carboxylic acid, and phosphoric acid. Furthermore, strong acids such as triflic acid (TfOH) and triflic imide (Tf<sub>2</sub>NH) are not bench stable and special care is needed to handle these strong acids. Thus, the development of new bench-stable Brønsted acids derived from new scaffolds that display broader applicabilities is highly desirable.

Squaric acid **1** has been known as a relatively strong acid.<sup>5</sup> Despite its intriguing acidity, squaric acid itself has not been used in organic reactions mainly due to extremely poor solubility in organic solvents. Very recently, Rawal et al. has developed a new chiral Brønsted acid based on a squaric acid scaffold and has successfully applied this Brønsted acid as a catalyst for conjugate addition of 1,3-dicarbonyl compounds to nitroolefins.<sup>6</sup> We have been interested in the development of novel Brønsted acids with higher reactivities by introducing a strong electron-withdrawing group.<sup>7</sup> For example, we have developed the *N*-triflyl (NTf) oxo-, thio-, and seleno-phosphoramides and demonstrated their higher reactivities for various organic reactions.<sup>8</sup> In the

course of our continuing investigation aimed at developing strong Brønsted acids with wider utility by introducing a strong electron-withdrawing NTf group, we expected that introducing NTf group into squaric acid will increase its acidity, and thus its reactivity. Furthermore, this group is expected to increase the solubility of squaric acid diamide **2** in common organic solvents, which makes this acid more suitable for organic reactions (Scheme 1).

The addition of silyl enol ethers to carbonyl compounds, known as Mukaiyama 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.<sup>9</sup> Although many successful examples employing either Lewis acid or Lewis base catalysts have been developed, few examples of Brønsted acid-catalyzed Mukaiyama reactions have



1. Enhance the acidity
2. Increase the solubilities in organic solvents

Scheme 1.

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been reported with very limited substrate scopes.<sup>10,11</sup> This limited application of Brønsted acids in the Mukaiyama aldol reaction is presumably due to either the lability of silyl enol ethers in the presence of strong Brønsted acids or the inefficient activation of electrophiles with weak Brønsted acids. Herein, we reported the development of a new bench-stable strong Brønsted acid based on squaric acid catalyphore and application of this Brønsted acid catalyst to the Mukaiyama aldol and Michael reactions with silyl enol ethers.

Squaric acid diamide **2**, carrying two NTF groups, was synthesized by modification of a patent procedure.<sup>12</sup> This Brønsted acid has remarkable stability and no special care is needed to handle this reagent.<sup>13</sup> With this acid in hand, we employed this Brønsted acid in the Mukaiyama aldol reaction of benzaldehyde with TMS-silyl enol ether of acetophenone **3a**. The results are summarized in Table 1. Squaric acid **1** itself did not promote the Mukaiyama aldol reaction mainly due to poor solubility in aprotic solvent (entry 1). In protic solvent, **3a** was hydrolyzed to acetophenone via protodesilylation. As we expected, introduction of NTF group in squaric acid increased its solubility in organic solvents, which should increase applicability of this acid to a variety of organic reactions. With 10 mol % of **2**, the aldol product was obtained in quantitative yield in 1 h (entry 2). Next, we investigated the effect of solvent on the reactivity (entries 2–6). Interestingly, even in the non-polar solvents where **2** is not completely soluble, Mukaiyama aldol reaction still proceeded (entries 5 and 6). Among the solvents tested, acetonitrile was found to be the best choice of solvent. Then, we wanted to test the reactivity and robustness of the Brønsted acid by decreasing the catalyst loading (entries 2, 7–10). Remarkably, the catalyst loading could be decreased as low as 0.1 mol %, although longer reaction time was necessary for the reaction to go to completion (entry 10). 1 mol % of catalyst was chosen as an optimal catalyst loading to obtain reasonable reactivity for further investigation (entry 8).

With these optimized conditions, we investigated the aldol reaction to various aldehydes and ketones with silyl enol ethers (Table 2). The aldol products of aldehydes were obtained in quantitative yields within 2 h (entries 1–8). The electronic properties of aldehydes have little influence on the reactivity. The aldol products were obtained in quantitative yields with either electron-donating groups or electron-withdrawing groups (entries 2–7). Even sterically hindered aldehydes carrying *ortho*-substituents to the carbonyl group did not show any diminished reactivities (entries 2 and 4). Aliphatic aldehydes were also

**Table 1**  
Optimization of reaction conditions<sup>14</sup>

Entry	Cat. (mol %)	Solvent	Time (h)	% Yield <sup>a</sup>
1	<b>1</b> (10)	H <sub>2</sub> O/THF (1:10)	6	N.R. <sup>b,c</sup>
2	<b>2</b> (10)	CH <sub>3</sub> CN	1	96
3	<b>2</b> (10)	THF	2	93
4	<b>2</b> (10)	Et <sub>2</sub> O	2	92
5	<b>2</b> (10)	CH <sub>2</sub> Cl <sub>2</sub>	2	94
6	<b>2</b> (10)	Toluene	2	95
7	<b>2</b> (5)	CH <sub>3</sub> CN	2	96
8	<b>2</b> (1)	CH <sub>3</sub> CN	2	96
9	<b>2</b> (0.5)	CH <sub>3</sub> CN	6	95
10	<b>2</b> (0.1)	CH <sub>3</sub> CN	12	96

<sup>a</sup> Isolated yields after chromatographic purification.

<sup>b</sup> N.R. means no reaction.

<sup>c</sup> Compound **3a** was completely hydrolyzed to the ketone.

**Table 2**  
Mukaiyama aldol reaction of aldehydes and ketones with silyl enol ether<sup>14</sup>

Entry	Carbonyl compound ( <b>4</b> )	Time (h)	% Yield <sup>a</sup>
1	<b>4a</b> ; R <sup>1</sup> = H, R <sup>2</sup> = Ph	2	96
2	<b>4b</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 2-MePh	2	95
3	<b>4c</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 4-MePh	2	97
4	<b>4d</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 2-MeOPh	2	92
5	<b>4e</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 4-MeOPh	2	93
6	<b>4f</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 4-NO <sub>2</sub> Ph	2	98
7	<b>4g</b> ; R <sup>1</sup> = H, R <sup>2</sup> = 4-BrPh	2	97
8	<b>4h</b> ; R <sup>1</sup> = H, R <sup>2</sup> = Cy	3	89
9	<b>4i</b> ; R <sup>1</sup> = Me, R <sup>2</sup> = Ph	8	82
10	<b>4j</b> ; R <sup>1</sup> = Me, R <sup>2</sup> = 4-NO <sub>2</sub> Ph	6	80 (4.4) <sup>b</sup>
11	<b>4k</b> ; R <sup>1</sup> = Me, R <sup>2</sup> = 4-BrPh	6	55 (20) <sup>b</sup>
12	<b>4l</b> ; R <sup>1</sup> = Me, R <sup>2</sup> = 4MeOPh	2	—(10) <sup>b</sup>
13 <sup>c</sup>	<b>4a</b> ; R <sup>1</sup> = H, R <sup>2</sup> = Ph	3	87 (4:1) <sup>d</sup>

<sup>a</sup> Isolated yields after chromatographic purification.

<sup>b</sup> The values in parentheses are the yield of **5i** formed by homo-coupling of silyl enol ether **3a**.<sup>15</sup>

<sup>c</sup> TMS-silyl enol ether of cyclohexanone was used.

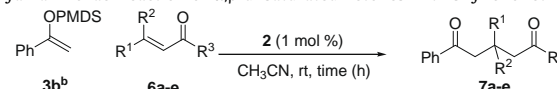
<sup>d</sup> The value in parentheses refers to diastereoselectivity of the product.

exploited in the aldol reaction, although the yield of **5h** was slightly lower than that of aromatic aldehydes (entry 8). With these successful results with aldehydes, we extended the utility of the Brønsted acid catalyst to ketones (entries 9–12). The aldol reaction with ketones was not as efficient as that with aldehydes. The yields of aldol products were much lower than those of aldehydes probably due to the protodesilylation of silyl enol ether.<sup>15</sup> Moreover, the electronic properties of the ketones have a significant effect on the yield of the aldol products. Electron-deficient ketones afforded the aldol products in good to moderate yields (entries 10 and 11), whereas electron-rich ketones gave almost no desired product (entry 12). Instead, **4l** gave unexpected Michael addition products as well as **5i**.<sup>16</sup> Furthermore, silyl enol ether derived from an aliphatic ketone rather than from aromatic ketones was also utilized in aldol reaction. TMS silyl enol ether of cyclohexanone gave the aldol product in 87% yield and 4:1 diastereoselectivity (entry 13).

The unexpected products of aldol reaction with electron-rich ketone (Table 2, entry 12)<sup>16</sup> strongly suggest that **2** can be applied to Mukaiyama Michael reaction of  $\alpha,\beta$ -unsaturated ketones. Thus, we surveyed the utility of **2** to Mukaiyama Michael addition of  $\alpha,\beta$ -unsaturated ketones with silyl enol ether (Table 3). After quick optimization of the reaction conditions, we found that the yield of the reaction was highly sensitive to the silyl group. With the TMS silyl enol ether **3a**, the Michael product was obtained in only moderate yield due to protodesilylation of **3a** (entry 1). Fortunately, it was found that pentamethyldisilyl enol ether **3b** could retard the protodesilylation and could increase the yield of the Michael adduct (entry 2). With this silyl enol ether **3b**, we explored the scope of reaction to various  $\alpha,\beta$ -unsaturated ketones. Cyclic and acyclic enones gave the desired products in quantitative yields (entries 2–6). Furthermore,  $\beta,\beta$ -disubstituted enone afforded the Michael adduct generating a quaternary carbon center, although the yield was moderate (entry 7). However, cyclopentenone gave the desired Michael adduct in moderate yield presumably because of oligomerization of resulting silyl enol ether after Michael reaction with another cyclopentenone (entry 4).

With these successful applications of **2** to Mukaiyama reactions, we investigated the reaction mechanism of Mukaiyama aldol reaction with our catalyst system. Mukaiyama aldol reaction

**Table 3**  
Mukaiyama Michael reaction of  $\alpha,\beta$ -unsaturated ketones with silyl enol ether



Entry	Enone	Time (h)	% Yield <sup>a</sup>
1 <sup>c</sup>		3	65
2		2	98
3		2	95
4		2	45
5		2	98
6		2	91
7		12	42

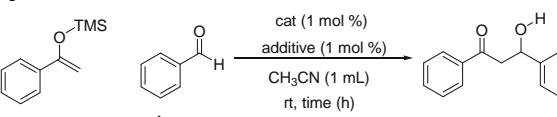
<sup>a</sup> Isolated yields after chromatographic purification.

<sup>b</sup> Compound **3b** is pentamethyldisilyl (PMDS) enol ether.

<sup>c</sup> TMS-silyl enol ether **3a** was used.

may proceed through either a real Brønsted acid catalyst or a Lewis acid catalyst<sup>11</sup> with silylated squaramide in situ generated by proton-silyl group exchange reaction between **2** and **3a**. To distinguish these two possible pathways, we carried out several controlled experiments (Table 4). On addition of the stoichiometric **3a** to **2**, **3a** was immediately hydrolyzed to the corresponding ketone and mono-silylated squaramide **TMS-2** was generated. When another 1 equiv of **3a** was added to the same

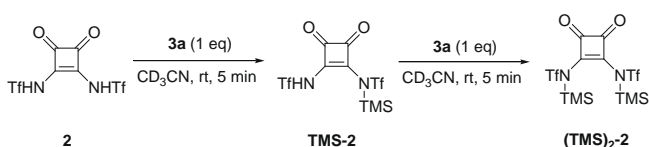
**Table 4**



Entry	Cat	Additive (mol %)	Time (h)	% Conversion <sup>a</sup>
1	<b>2</b>	—	<30 min	100
2	<b>2-TMS</b>	—	2	85
3	<b>2-TMS<sub>2</sub></b>	—	2	70
4	<b>2</b>	DTBP <sup>b</sup> (2 mol %)	2	60
5	<b>2-TMS</b>	DTBP <sup>b</sup> (2 mol %)	2	55
6	<b>2-TMS<sub>2</sub></b>	DTBP <sup>b</sup> (2 mol %)	2	40

<sup>a</sup> Conversion was determined by <sup>1</sup>H NMR.

<sup>b</sup> DTBP is 2,6-di(*t*-butyl)pyridine.



**Scheme 2.**

reaction mixture, protodesilylation of **3a** still took place and finally the di-silylated squaramide (**TMS**)<sub>2</sub>-**2** was generated (Scheme 2). When the in situ generated silylated Brønsted acid, **TMS-2** or (**TMS**)-**2**, was used as a catalyst, aldol reaction still proceeded. However, the yields of the reactions with these silylated Brønsted acids were much lower than those with Brønsted acid **2** itself (entries 1–3). Furthermore, when reactions were carried out with 2,6-di-*t*-butylpyridine (DTBP), a Brønsted acid scavenger,<sup>17</sup> the yields of aldol reactions were dramatically decreased (entries 4–6). Although we cannot exclude the Lewis acid-catalyzed aldol reaction by the silylated Brønsted acid, at this moment it is more reasonable that the aldol reaction may proceed through Brønsted acid catalysis rather than through silylated Lewis acid catalysis.

In conclusion, we have developed a new strong Brønsted acid based on squaric acid scaffold. This new Brønsted acid **2** is bench stable and no special care is required for its handling. Compound **2** was applied to Mukaiyama aldol reactions of aldehydes and ketones with silyl enol ether. The corresponding products of aldehydes were obtained in quantitative yields, whereas the products of ketones were obtained in moderate yields with limited substrate scope. The utility of **2** was further expanded to Mukaiyama Michael reaction of  $\alpha,\beta$ -unsaturated ketones. Remarkably, the catalyst loading was as low as 1 mol % for all Mukaiyama reactions and could be decreased below this level. Mechanistic studies implied that the Mukaiyama aldol reaction might proceed through Brønsted acid catalysis, rather than through Lewis acid catalysis by silylated Brønsted acid. Further applications of this Brønsted acid to other organic reactions are underway in our laboratory, and will be reported in due course.

## Acknowledgments

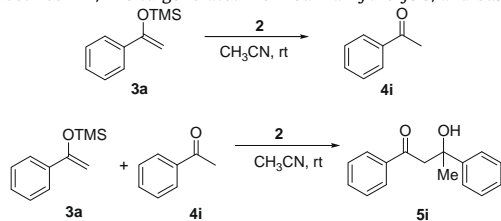
We would like to thank Toyota company for financial support and Dr. V.H. Rawal for his kind discussion for this project.

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- Compound **2** is air- and moisture-stable for more than 3 months. Even in solution **2** still keeps its catalytic reactivity after 2 months.
- Representative procedure:** To a solution of **2** (0.75 mg; 0.0020 mmol; 0.010 equiv) in acetonitrile (1 mL) was added **4a** (21 mg; 0.20 mmol; 1.0 equiv) and the mixture was stirred for 10 min. After that, **3a** (42 mg; 0.22 mmol; 1.1 equiv) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir at room temperature while the reaction was monitored by TLC. When the **4a** was completely consumed, 1 N HCl (1 mL)

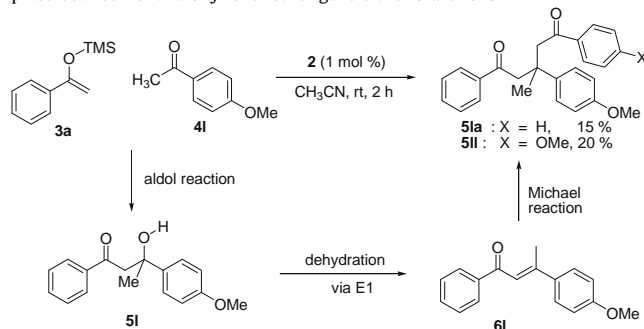
was added to the reaction mixture and stirred until all the silyl ether was converted to free alcohol. The reaction mixture was neutralized with  $\text{NaHCO}_3$ , extracted with ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Column chromatography on silica (15% ethyl acetate in hexanes solution) gave **5a** as a white solid. (43.4 mg; 96% yield).

15. In all cases of ketones, the undesired by-product **5i** was obtained, which was formed between **4i**, in situ generated from **3a** via hydrolysis, and **3a**.



16. After careful analysis, these compounds were found to be **5ia** and **5ii**, respectively. Presumably, aldol product **5i** was initially formed, but was not stable in this reaction condition. Dehydration presumably took place to

produce  $\alpha,\beta$ -unsaturated carbonyl compound **6i**. Finally, Michael reaction took place between **6i** and silyl enol ether gave either **5ia** or **5ii**.



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