

# Communications

## Synthesis of *N,N*-Bis(nonaflyl) Squaric Acid Diamide and its Application to Organic Reactions<sup>†</sup>

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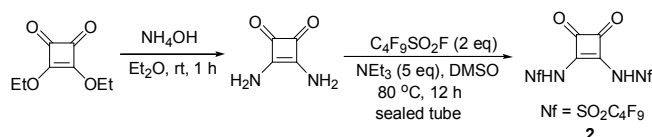
**Key Words:** Brønsted acid catalysis, Squaric acid, Mukaiyama Michael reaction, Carbonyl ene reaction

Brønsted acid catalysis is one of the growing fields in modern organic synthesis.<sup>1</sup> Although 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, other Brønsted acid scaffolds have been much less explored. Recently, Rawal *et al* have developed a Brønsted acid catalyst based on squaric acid moiety and successfully applied it as a catalyst for conjugate addition of 1,3-dicarbonyl compounds to nitroolefins.<sup>5</sup> More recently, we have developed a strong Brønsted acid derived from squaric acid by introducing a strong electron withdrawing trifluoromethanesulfonyl (Tf) group and applied it to Mukaiyama aldol and Michael reaction of a variety of aldehydes, ketones, and  $\alpha,\beta$ -unsaturated ketones.<sup>6,7</sup> As a continuing effort to develop strong Brønsted acids based on the squaric acid scaffold, it was expected that replacement of Tf group with a longer perfluoroalkanesulfonyl group would be able to tune the physical properties, such as solubilities in organic solvents and fluorophilicity, without loss of reactivity (Figure 1). Herein, we report the development of a new Brønsted acid based on the squaric acid scaffold carrying two nonafluorobutanesulfonyl (Nf) groups and the preliminary results of its reactivity to various organic reactions.

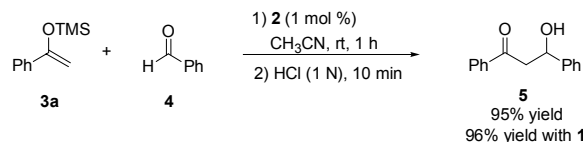
Squaric acid diamide **2** carrying two Nf groups was attempted to be synthesized by the same method for the synthesis of bis-triflyl squaramide **1**.<sup>6</sup> In the conditions for the synthesis of com-

ound **1**, however, only mono-nonafluorinated squaramide was obtained as a product.<sup>8</sup> Thus, we investigated a different synthetic route to compound **2** as shown in Scheme 1. Squaric acid diamide was easily prepared from squaric acid diethyl ester according to the literature procedure.<sup>9</sup> Next, we moved our attention to the nonafluorination of the resulting diamide. Nonafluorination of the diamide was carried out with nonafluor fluoride in the presence of triethylamine in a sealed tube<sup>10</sup> (IMPORTANT: The reaction must be carried out in a sealed tube. Otherwise, the yield of the reaction will be quite low due to the low boiling point of nonafluor fluoride). To our delight, the desired product **2** was obtained in 57% yield after column chromatography on silica.

With this compound in hand, we employed this newly developed Brønsted acid **2** in the Mukaiyama aldol reaction<sup>11</sup> of benzaldehyde **4** with silyl enol ether of acetophenone **3a** to compare its reactivity with that of compound **1** (Scheme 2). With 1 mol % of **1** and **2**, aldol product **5** was obtained in 96 and 95% yield after deprotection of silyl group, respectively. The reactivity of compound **2** was further tested in the Mukaiyama Michael reaction of  $\alpha,\beta$ -unsaturated carbonyl compound **6** with pentamethyldisilyl (PMDS) enol ether of acetophenone **3b** (Scheme 3). With PMDS enol ether **3b**, both Brønsted acids **1** and **2** gave almost the same result. These results implied that the replacement of Tf group with Nf group may have little effect on the reactivities of both acids. However, with TMS enol



Scheme 1. Synthetic route to a new Brønsted acid **2**



Scheme 2. Mukaiyama aldol reaction

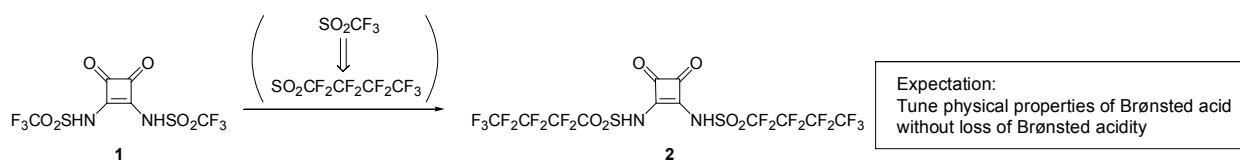
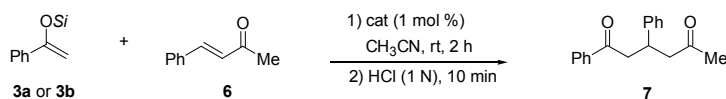


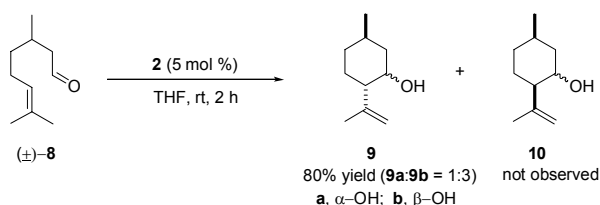
Figure 1

<sup>†</sup>This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



compound	Si	cat	% yield
<b>3a</b>	TMS	<b>1</b>	65
		<b>2</b>	97
<b>3b</b>	PMDS	<b>1</b>	98
		<b>2</b>	97

Scheme 3. Mukaiyama Michael reaction

Scheme 4. Carbonyl ene reaction of *rac*-citronellal

ether, the two catalysts showed dramatic difference in yields. Brønsted acid **2** gave the Michael adduct in 97% yield, whereas Brønsted acid **1** afforded the product only in 65% yield. This might be because the protons in Brønsted acid **2** might be buried inside probably due to steric effect of two longer perfluorobutyl chains. These buried protons might retard the protodesilylation of **3a**, which increased the yield of this reaction.

To further investigate the utility of Brønsted acid **2**, we applied it to intramolecular carbonyl ene reaction of *rac*-citronellal **8** (Scheme 4).<sup>12,13</sup> Unlike Mukaiyama reaction, this ene reaction showed a high dependence on the reaction media. No detectable cyclized product was obtained in CH<sub>3</sub>CN after 24 h, but cyclization took place in etherated solvents within 2 h. Among the solvents tested, THF gave the best result in terms of yield as well as diastereoselectivity. The mixture of two diastereomers **9a** and **9b** was obtained in 1:3 ratio with 80% overall yield.<sup>14</sup> The other two possible diastereomers were not detected in the crude mixture. However, other etherated solvents, such as ether and DME, were inferior to THF in terms of both yield and diastereoselectivity.

In conclusion, we have developed a new strong Brønsted acid bearing two nonaflyl groups based on the squaric acid scaffold. The Brønsted acid **2** showed the almost same reactivity as bistriflyl squaramide **1** in Mukaiyama aldol and Michael reactions of benzaldehyde with silyl enol ether. Moreover, the utility of Brønsted acid **2** could be expanded to carbonyl ene reaction of *rac*-citronellal. Further application of this new Brønsted acid to organic reactions and to flow system reactors is currently underway in our laboratory.

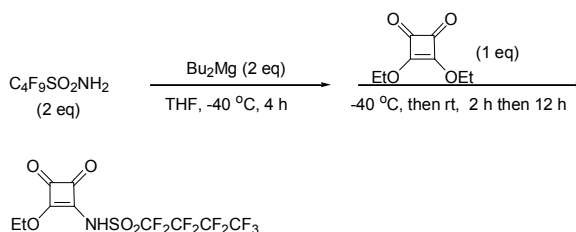
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- In this reaction condition, only monononafluorated product was obtained exclusively as shown below.



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