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Development of *N*,*N*-bis(perfluoroalkanesulfonyl)squaramides as new strong Brønsted acids and their application to organic reactions

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ABSTRACT

New strong Brønsted acids derived from a squaric acid scaffold bearing different perfluoroalkanesulfonyl groups have been developed and applied to several organic reactions. These squaramides are bench-stable and exhibit much higher reactivities in several organic reactions than squaric acid itself. *N*,*N*-Bis(trifluoromethanesulfonyl)squaramide **2a** was applied to the Mukaiyama aldol reaction and Mukaiyama Michael reaction. Mechanistic studies revealed that the Brønsted acid might be the predominant catalyst through direct protonation of carbonyl compound by the acid itself rather than the silylated Brønsted acid. The utility of this acid **2a** was further extended to Hosomi–Sakurai allylation of aldehydes and a carbonyl-ene reaction. Furthermore, other squaramides **2b** and **c** bearing longer perfluoroalkyl chains have been developed, which are also bench-stable and displayed similar reactivities with squaramide **2a** in several organic reactions.

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1. Introduction

Brønsted acid catalysis has been one of the growing fields in modern organic synthesis.[1] Several Brønsted acids, such as urea/thiourea,[2] TADDOL,[3] and phosphoric acid,[4] have been widely used as catalysts in carbon–carbon bond forming reactions including asymmetric reactions. However, the utility of these Brønsted acid catalysts is somewhat limited to reactive substrates due to relatively lower reactivities of these Brønsted acids. On the other hand, although strong acids, such as triflic acid (TfOH) and triflic imide (Tf_2NH), have been employed in organic reactions, such as the Mukaiyama aldol reaction,[5] these strong acids are not generally bench-stable and special care is needed to handle them.[6] Moreover, the catalyst scaffolds of Brønsted acids are limited to the above catalophores and other Brønsted acid scaffolds have been less explored. Thus, the development of new bench-stable Brønsted acids derived from new scaffolds that display broader applicability is highly desirable.

Although squaric acid **1** has been known as a relatively strong acid,[7] squaric acid itself has attracted little attention from the synthetic community mainly due to its extremely poor solubility in organic solvents. Recently, Rawal and co-workers have developed a new chiral Brønsted acid from the squaric acid scaffold and successfully applied it to conjugate addition of nitroolefins with 1,3-dicarbonyl compounds and phosphites.[8] Although they have successfully introduced a squaric acid scaffold as a new catalophore to the synthetic organic community, the substrate scope with this catalyst was limited due to the lower acidity.

We have been interested in the development of novel Brønsted acids with higher reactivities by introducing a strong electron withdrawing group.[9] For example, we have developed the *N*-triflyl (NTf) oxo-, thio-, and seleno-phosphoramides and demonstrated their higher reactivities in several organic reactions.[10] In the course of our continuing investigation aimed at developing strong Brønsted acids with wider utility by introducing a strong electron withdrawing group, we expected that introduction of a perfluoroalkanesulfonyl group into the squaric acid moiety will increase its acidity, and thus its reactivity.

Moreover, this group is expected to increase the solubility of squaramide **2** in common organic solvents, which makes this acid more suitable for organic reactions. Furthermore, introduction of longer perfluoroalkyl chains, such as perfluorobutyl and perfluorooctyl, will tune the physical properties of these acids, such as fluorophilicity, without any loss of the acidity of these Brønsted acids (Scheme 1). This tuning of physical properties with different perfluoroalkyl chains will provide further application of these acids, such as an immobilized catalyst in flow reactor system by fluorous–fluorous interaction.[11,12]

Based on this idea, we have developed new Brønsted acids derived from the squaric acid scaffold bearing strong electron withdrawing perfluoroalkanesulfonyl groups.[13] Herein, we wish to report the full details of the development of these Brønsted acids and their application to organic reactions.

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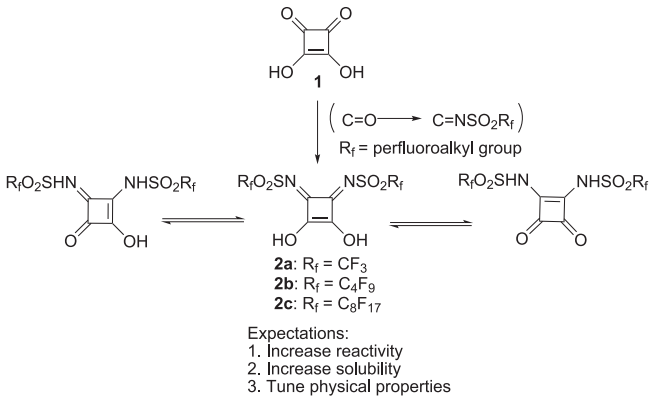
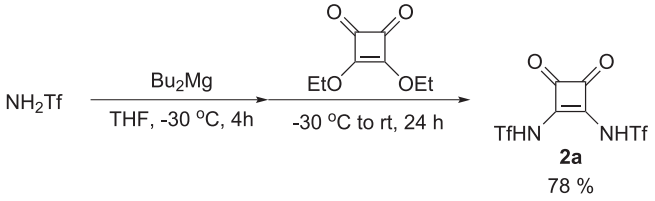


Scheme 1.

2. Results and discussion

2.1. Development of *N,N*-bis(trifluoromethanesulfonyl)squaramide 2a

Squaramide **2a** bearing triflyl (Tf) group was synthesized by following the procedure reported in patent (Scheme 2).[14] The new Brønsted acid **2a** is bench-stable[15] and, as we expected, exhibits much higher solubility toward common organic solvents than the parent squaric acid **1**.



Scheme 2. Synthetic route of squaramide **2a**.

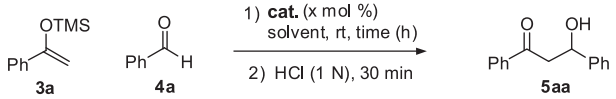
2.2. Mukaiyama aldol reaction

With squaramide **2a** in hand we employed this Brønsted acid in the Mukaiyama aldol reaction[16,17] of benzaldehyde **4a** with the 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 solvents. However, in protic solvents, **3a** was hydrolyzed into acetophenone via protodesilylation (entry 1). As we expected, introduction of NTf group into squaric acid increased its solubility in organic solvents, which would increase applicability of this acid to a variety of organic reactions. With 10 mol % of **2a**, 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). Even in non polar solvents where **2a** is not completely soluble, the Mukaiyama aldol reaction proceeded smoothly (entries 5 and 6). Among the solvents tested, acetonitrile was found to be the best choice of solvent. Then, we decreased the catalyst loading; remarkably, the catalyst loading could be lowered to 0.1 mol % even though a longer reaction time was necessary for the reaction to go to completion (entries 7–10). However, 1 mol % of catalyst was chosen as an optimal catalyst loading (entry 8) for further investigation.

With these optimized conditions, we investigated the generality of squaramide **2a** catalyzed Mukaiyama aldol reaction of aldehydes with the silyl enol ether of acetophenone **3a** (Table 2). A variety of aromatic aldehydes gave the desired aldol adducts in excellent yields (entries 1–11).

Electronic effects of aromatic aldehydes have little effect on the Mukaiyama aldol reaction (entries 1–6). Aldehydes bearing either electron donating or withdrawing substituents at the *para* position of aromatic ring gave the aldol products in excellent yield. In addition, steric effects did not influence the yield of aldol reaction

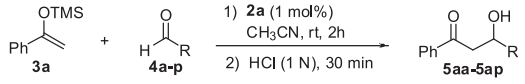
Table 1
Optimization of Mukaiyama aldol reaction



Entry	**cat.** (×mol %)	Solvent	Time (h)	Yield[a] %
1	**1** (10)	H_2O/THF(1:10)	6	N.R.[b,c]
2	**2a** (10)	CH_3CN	1	96
3	**2a** (10)	THF	2	93
4	**2a** (10)	Et_2O	2	92
5	**2a** (10)	CH_2Cl_2	2	94
6	**2a** (10)	Toluene	2	95
7	**2a** (5)	CH_3CN	2	96
8	**2a** (1)	CH_3CN	2	96
9	**2a** (0.5)	CH_3CN	6	95
10	**2a** (0.1)	CH_3CN	12	96

[a] Isolated yields after chromatographic purification.
[b] N.R. means no reaction.
[c] Compound **3a** was completely hydrolyzed into the ketone.

Table 2
Mukaiyama aldol reaction of aldehydes



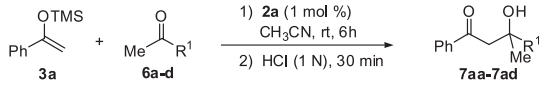
Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1	(5aa)	96	9	(5ai)	95
2	(5ab)	97	10	(5aj)	95
3	(5ac)	93	11	(5ak)	94
4	(5ad)	97	12	(5al)	92
5	(5ae)	97	13	(5am)	91
6	(5af)	98	14	(5an)	89
7	(5ag)	96	15	(5ao)	91
8	(5ah)	96	16	(5ap)	92

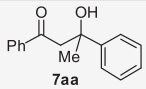
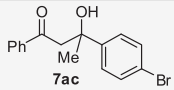
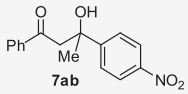
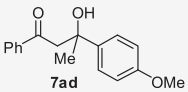
[a] Isolated yields after chromatographic purification.

(entries 7–11). Furthermore, Brønsted acid **2a** was able to be extended to non-aromatic aldehydes (entries 12–16). α,β-Unsaturated aldehyde and heteroaromatic aldehyde were also applicable to this catalyst system (entries 12 and 13). It is noted that aliphatic aldehydes including enolizable aldehydes were also applicable to this squaramide **2a** (entries 14–16).

After this successful application of squaramide **2a** to Mukaiyama aldol reaction of aldehydes, we tried to extend the scope of this Brønsted acid catalyzed Mukaiyama aldol reaction to ketones (Table 3). Unlike the Mukaiyama aldol reaction of aldehydes, the electronic properties of ketones had a dramatic effect on yields of the reaction. Ketones bearing electron withdrawing substituents gave the aldol products in high yields (entries 2 and 3), whereas a ketone with electron donating group provided no aldol product (entry 4).

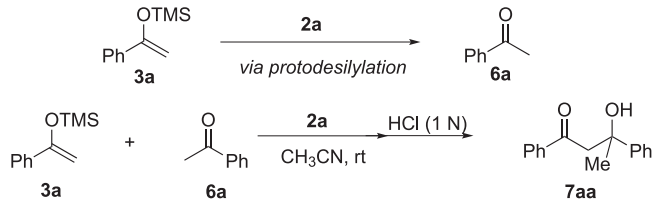
Table 3
Mukaiyama aldol reaction of ketones



Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1	 **7aa**	82	3	 **7ac**	55 (13)[b]
2	 **7ab**	80 (4.4)[b]	4	 **7ad**	0 (10)[b]

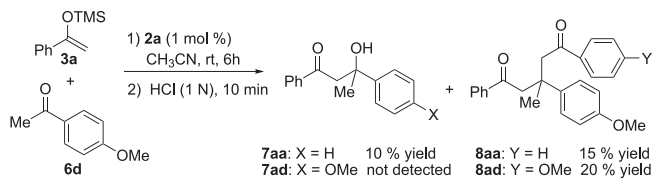
[a] Isolated yields after chromatographic purification.
[b] The values in parentheses are the yield of **7aa** formed by homo-coupling of silyl enol ether **3a** with acetophenone.

In all cases, the homo aldol product **7aa** of acetophenone **6a** was obtained as a minor product (entries 2–4). The product was obtained from Mukaiyama aldol reaction of silyl enol ether **3a** with acetophenone **6a**, which is generated via protodesilylation (Scheme 3).



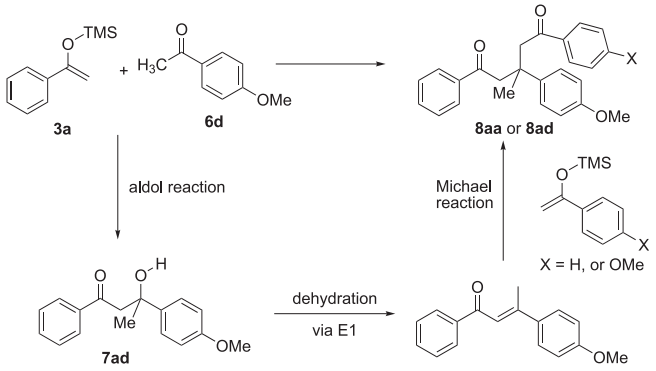
Scheme 3. Formation of homo aldol product **7aa** of acetophenone **6a** as a side product.

However, an electron rich ketone, 4-methoxyacetophenone **6d**, gave no desired aldol product (entry 4). Instead, two unexpected products were obtained along with homo-coupled product **7aa** of acetophenone (Scheme 4).



Scheme 4. Mukaiyama aldol reaction with electron-rich 4-methoxyacetophenone **6d**.

After careful structural analysis, these two products were assigned to be compounds **8aa** and **8ad**. These products might be formed by the following reaction pathway (Scheme 5). Initially, the Mukaiyama aldol adduct **7ad** was formed in the reaction mixture,

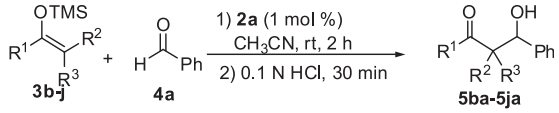


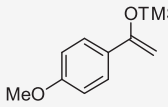
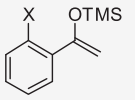
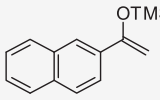
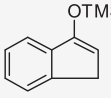
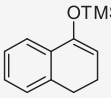
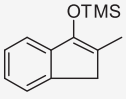
Scheme 5. Rationale of unexpected Michael addition products **8aa** and **8ad** with an electron rich ketone **6d**.

which might not be stable in this reaction system. Then, dehydration took place to afford the α,β-unsaturated ketone. Michael addition with silyl enol ethers gave the two unexpected products.

Then, we investigated the scope of silyl enol ethers with benzaldehyde **4a** (Table 4). Various silyl enol ethers derived from aryl

Table 4
Scope of silyl enol ethers

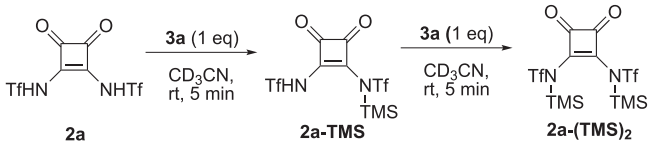


Entry	Nucleophile	Yield[a] (%)	dr (syn/anti)[b]
1	 (**5ba**)	97	—
2	 X=OMe (**5ca**)	98	—
3	X=Me (**5da**)	98	—
4	 (**5ea**)	94	—
5	 (**5fa**)	86	1.7:1
6	 (**5ga**)	93	1.7:1
7	 (**5ha**)	86	1:4
8	 (**5ia**)	87	4:1
9	 (**5ja**)	91	1.1:1

[a] Isolated yields after chromatographic purification.
[b] Diastereoselectivity was determined by ^{1}H NMR analysis.

methyl ketones gave the aldol product in excellent yields (entries 1–4). Furthermore, this catalyst system could be applied to diastereoselective Mukaiyama aldol reaction with silyl enol ethers of cyclic ketones (entries 5–9). The desired aldol adducts were obtained in excellent yields although diastereoselectivities were moderate in some cases. It is worthwhile to mention that β,β-disubstituted silyl enol ether **5j** was also applied to this catalyst system, which generated a quaternary carbon center (entry 9).

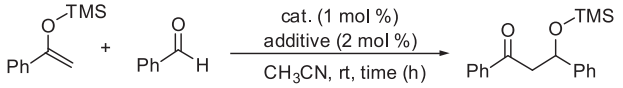
To further understand the active catalytic species, we investigated the reaction mechanism. This reaction proceeds with either direct activation of carbonyl compound by the Brønsted acid itself (Brønsted acid catalysis)[10d,13a] or activation of carbonyl compound with the silylated Brønsted acid (Lewis acid catalysis).[18,19] Actually, the silylated Brønsted acids, **2a-TMS** and **2a-TMS2**, were easily generated by protodesilylation of silyl enol ether of acetophenone **3a** with Brønsted acid **2a** (Scheme 6).



Scheme 6. Generation of Silylated Brønsted Acids **2a-TMS** and **2a-TMS2**.

To discriminate these two possible reaction mechanisms, we carried out some control experiments (Table 5). First, the reactivity of **2a** was compared with those of mono- and di-silylated Brønsted acids **2a-TMS** and **2a-TMS$_2$**. The acid **2a** afforded the aldol adduct in quantitative yield in 30 min, whereas the mono- and di-silylated Brønsted acids provided the aldol adduct in much less yields even after longer reaction times (entries 1–3). This diminished reactivity with the silylated Brønsted acids **2a-TMS** and **2a-(TMS)$_2$** suggested that the Brønsted acid itself may be more reactive than the silylated Brønsted acids. To further prove this hypothesis, the Mukaiyama aldol reaction was carried out in the presence of 2,6-di(*tert*-butyl)pyridine (DTBP), which is known to inhibit any possible Brønsted acid catalysis (entries 4–6).[20] DTBP significantly decreased the yield of aldol reaction with Brønsted acid itself (entry 4), whereas it slightly decreased the yields of aldol reaction with the silylated Brønsted acids (entries 5–6).

Table 5
Reactivity comparison of Brønsted acid **2a** and silylated Brønsted acids **2a-TMS** and **2a-(TMS)$_2$**



Entry	cat.	Additive	Time (h)	Yield[a] (%)
1	**2a**	—	<30 min	100
2[b]	**2a-TMS**	—	2	85
3[b]	**2a-(TMS)$_2$**	—	2	70
4	**2a**	DTBP	2	60
5[b]	**2a-TMS**	DTBP	2	57
6[b]	**2a-(TMS)$_2$**	DTBP	2	52

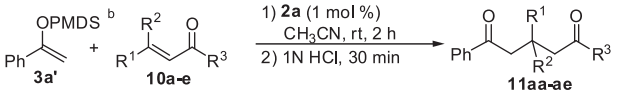
[a] Yields were determined by ^{1}H NMR analysis.
[b] Silylated Brønsted acids were generated by protodesilylation as shown in Scheme 6.

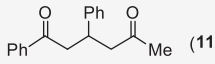
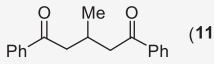
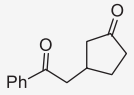
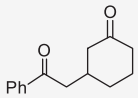
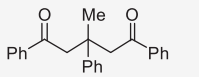
From these results, we believe that although both Brønsted acid and Lewis acid pathways are operative in this Mukaiyama aldol reaction, the Brønsted acid pathway may be faster than the Lewis acid pathway. This result suggested that this new Brønsted acid may have significant potential in further development of chiral Brønsted acids derived from the squaric acid scaffold because the silylated Brønsted acid is generally known to be associated with a non-enantioselective pathway.[21]

2.3. Mukaiyama Michael reaction

The unexpected products **8aa** and **8ad** with the electron rich ketone **6d** (Table 3, entry 4) suggested that the squarmaide **2a** might be able to activate α,β-unsaturated ketones. Thus, we tried to apply this Brønsted acid **2a** to the Mukaiyama Michael reaction[22] of α,β-unsaturated ketones with silyl enol ether of acetophenone (Table 6). With TMS enol ether **3a**, the desired Michael product **11aa** was obtained in 65% yield along with acetophenone **6a** hydrolyzed in this reaction condition (entry 1). However, simply changing the silyl group from TMS to pentamethyldisilyl (PMDS) significantly improved the yield of this reaction presumably due to slow hydrolysis of PMDS silyl enol ether **3a′** (entry 2). With this condition, several other α,β-unsaturated ketones were tested with PMDS enol ether **3a′**. The desired Michael adducts were obtained in quantitative yields for both cyclic and acyclic α,β-unsaturated ketones (entries 2, 3, and 5). Furthermore, β,β-disubstituted α,β-unsaturated ketone could be also applied to this system, which generated a quaternary carbon center, although the yield was only moderate (entry 6). However, cyclopentenone **10c** afforded the desired Michael adduct **11ac** in moderate yield due to the oligomerization of the resulting silylated product with cyclopentenone **10c**.[23]

Table 6
Mukaiyama Michael reaction of α,β-unsaturated ketones



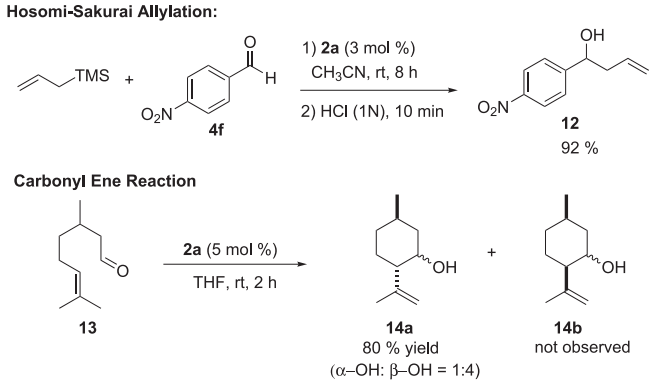
Entry	Product		Yield[a] (%)
1[c]		(**11aa**)	65
2			98
3		(**11ab**)	95
4		(**11ac**)	45
5		(**11ad**)	98
6		(**11ae**)	42

[a] Isolated yield after chromatographic purification.
[b] **3a′** is pentamethyldisilyl (PMDS) enol ether.
[c] TMS-silyl enol ether **3a** was used.

2.4. Application to other reactions

With successful application of Brønsted acid **2a** to Mukaiyama aldol and Michael reactions, we made efforts to further extend the utility of squaramide **2a** to other organic reactions (Scheme 7).

First, **2a** was applied to Hosomi–Sakurai allylation[24] of 4-nitrobenzaldehyde **4f** with allyltrimethylsilane. The desired allylation product **12** was obtained in excellent yield with 3 mol % of catalyst. We could further apply this Brønsted acid **2a** to the carbonyl-ene

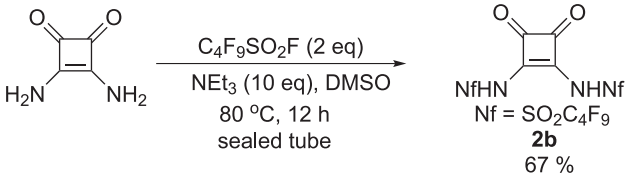


Scheme 7. Other application of squaramide **2a**.

reaction of *rac*-citrolleral **13**.[25,26] The yield and diastereoselectivity were highly dependant on the solvent. Etherated solvents provided the ene product **14** in better yield and diastereoselectivity. THF proved to be the best choice of solvent affording the ene product **14a** in 80% yield and 4:1 dr (α-OH/β-OH) among four possible diastereomers.[27]

2.5. Development of *N,N*-bis(perfluoroalkanesulfonyl)-squaramides 2band c bearing longer perfluoroalkyl chains

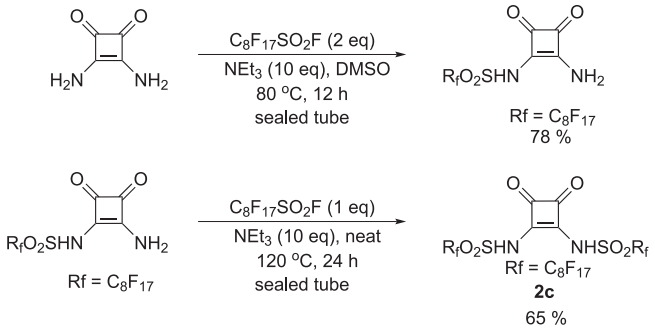
With successful application of squaramide **2a** to several organic reactions, we have focused on the development of other squaramides bearing longer perfluoroalkyl chains. We expected that the introduction of a longer perfluoroalkyl chain into the squaramide would tune the physical properties, such as fluorophilicity, without any change in its reactivity. This increased fluorophilicity may provide further application of these acids, such as an immobilized catalyst in flow reactor system by fluorous–fluorous interaction.[11,12] Based on this idea, first we attempted to synthesize *N,N*-bis(nonafluorobutanesulfonyl) squaramide **2b**.[13b] Initially, the same synthetic strategy for synthesis of squaramide **2a** was applied to synthesis of squaramide **2b**. However, in this condition only monononaflylated product was obtained along with a mixture of unidentifiable compounds. After screening several synthetic routes, the desired bisnonaflyl squaramide **2b** was able to be synthesized through direct nonaflylation with nonaflyl fluoride in a sealed tube (Scheme 8). This newly synthesized squaramide **2b** is also benchstable and shows improved solubility toward organic solvents.



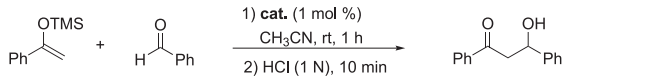
Scheme 8. Synthesis of *N,N*-bis(nonafluorobutane)sulfonyl squaramide **2b**.

Furthermore, we attempted to synthesize squaramide **2c** bearing much longer perfluorooctyl chain. Initially, synthesis of squaramide **2c** was attempted by applying the route used for squaramide **2b**. However, under this condition, only mono- perfluorooctanesulfonylated product was obtained. After screening several reaction conditions, we were fortunately able to synthesize the squaramide **2c** under neat reaction conditions from the monosulfonylated compound (Scheme 9).

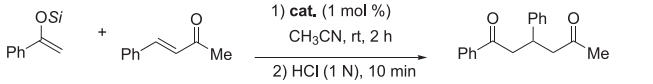
With these squaramides **2b** and **c** in hand, we compared the reactivities of squaramides **2b** and **c** with that of **2a** in Mukaiyama aldol and Michael reactions (Scheme 10). In the Mukaiyama aldol reaction



Scheme 9. Synthesis of *N,N*-bis(perfluorooctanesulfonyl) squaramide **2c**.



entry	cat	% yield
1	**2a**	96
2	**2b**	95
3	**2c**	96



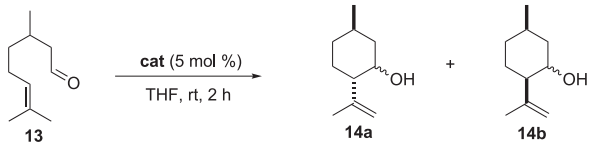
Si	cat	% yield
TMS	**2a**	65
	2b	97
	2c	95
PMDS	**2a**	98
	2b	97
	2c	95

Scheme 10. Reactivity comparison of **2b** and **c** with **2a**.

of benzaldehyde **4a** with TMS enol ether of acetophenone **3a**, all the Brønsted acids **2a**–**c** exhibited similar reactivities. However, in the Mukaiyama Michael reaction, the two Brønsted acids **2b** and **c** bearing longer perfluoroalkyl chains showed dramatic differences in reactivity compared with Brønsted acid **2a**. With PMDS enol ether **3a′**, all the Brønsted acids **2a**–**c** gave the Michael adduct **11aa** in excellent yield. However, with more labile TMS enol ether **3a**, triflyl squaramide **2a** gave the Michael adduct in 65% yield, whereas squaramides **2b** and **c** gave the product in quantitative yield. The improved yield with squaramide **2b** and **c** might be due to the steric bulkiness of the long perfluoroalkyl groups. Protons in squaramides **2b** and **c** are buried inside of the long perfluoroalkyl group, which retards protodesilylation of labile TMS enol ether **3a**.

The reactivities of **2b** and **c** were further tested in carbonyl-ene reaction of *rac*-citronellal **13** (Scheme 11). All three squaramides **2a**–**c** showed very similar reactivity and the cyclized product was obtained in high yield with all the Brønsted acids. However, diasteroselectivity decreased with the length of perfluoroalkyl chain. Squaramides **2a**-**b** gave the ene product as a mixture of two diastereomres (**14a**-α and **14a**-β) among four possible diastereomers, whereas squaramide **2c** afforded the ene product as a mixture of three diastereomers.

Then, we moved our interest to the application of long perfluoroalkyl substituted squaramides **2b** and **c** to an immobilized catalyst in flow reactor system through non-covalent fluorous–fluorous interaction between the perfluoroalkyl chain in the squaramide and fluorinated silica.[12] First, we applied squaramide **2b** to flow reactor system with perfluorinated silica. However, this



cat	% yield	14a α–OH : β–OH	14a α–OH	14a β–OH
2a	80	1 : 4	-	-
2b	82	1 : 3	-	-
2c	77	1 : 2	0.5	-

Scheme 11. Reactivity comparison in carbonyl-ene reaction.

attempt to apply squaramide **2b** to flow reactor system as an immobilized catalyst was not successful. This might be because there is not enough fluorous–fluorous interaction between perfluorinated silica and perfluoroalkyl chains in squaramide **2b**, probably due to the relatively short perfluorobutyl chain in **2b**.

After failure to apply squaramide **2b** to flow reactor system as an immobilized catalyst, we assumed that the longer perfluoroalkyl chain in squaramide **2c** might help immobilize the acid in perfluorinated silica. With this idea in mind, we sought to apply this squaramide **2c** to flow reactor system as an immobilized catalyst with perfluorinated silica. Unfortunately, Brønsted acid **2c** was not able to be adsorbed into perfluorinated silica, and thus was not able to be applied to flow reactor system based on non-covalent interaction.

3. Conclusions

We have developed new Brønsted acids based on a squaric acid scaffold bearing different perfluoroalkanesulfonyl groups. The new Brønsted acids are bench-stable and have better solubility toward common organic solvents. Squaramide **2a** was successfully applied to the Mukaiyama aldol reaction of aldehydes including aliphatic aldehydes. However, in Mukaiyama aldol reaction with ketones, the yields of aldol adducts showed strong dependence on the electronic properties of substituents on the aromatic ring. Various silyl enol ethers were also applicable to this new Brønsted acid catalyst. Mechanistic studies revealed that the Brønsted acid pathway via direct activation of carbonyl compounds may be predominant over a Lewis acid pathway by the silylated Brønsted acid. In addition, the utility of squaramide **2a** could be extended to Mukaiyama Michael reactions. Squaramide **2a** was shown to efficiently activate carbonyl functional groups in other types of reactions, such as Hosomi–Sakurai allylation and carbonyl-ene reactions. Other squaramides **2b** and **c** bearing longer perfluoroalkanesulfonyl groups have been also developed. These squaramides **2b** and **c** exhibited similar reactivities with squaramide **2a** in organic reactions. However, these squaramides **2b** and **c** seemed to be more suitable with more labile silyl enol ethers. **2b** and **c** afford the Michael adducts in excellent yields with even labile TMS enol ether, whereas **2a** gave the product in only moderate yield. However, further application of squaramides **2b** and **c** to an immobilized catalyst in flow reactor system with perfluorinated silica through fluorous–fluorous interaction was not successful. Further application of these Brønsted acids to other organic reactions and development of a chiral strong Brønsted acid derived from squaric acid are underway in our laboratory.

4. Experimental section

4.1. Synthesis of *N,N*-bis(perfluoroalkanesulfonyl)-squaramides

*4.1.1. N,N-Bis(perfluoromethanesulfonyl)squaramide (**2a**).* To a solution of trifluoromethanesulfonamide (2.98 g; 20 mmol; 2.0 equiv) in THF (30 mL) was added a 1 M solution of Bu_2Mg in heptane (20 mL; 20 mmol; 2.0 equiv, Aldrich) dropwise at −30 °C. The reaction mixture was stirred at the same temperature for 4 h. After that, squaric acid diethyl ester (1.70 g; 10 mmol 1.0 equiv) was added to the reaction mixture and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was warmed up to room temperature and stirred for 24 h at the same temperature and monitored by TLC. After 24 h, the reaction mixture was quenched with H_2O, acidified with aqueous HCl (4 N; 100 mL) (Important: without acidification, the yield of this reaction would be quite low because compound **2a** would stay in aqueous layer without acidification), extracted with diethyl ether (4×100 mL), dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/MeOH (20:1)) on silica gave the desired product as a white solid. The product was redissolved in ether (50 mL) and acidified again with aqueous HCl (4 N; 50 mL). The organic layer was combined, dried over Na_2SO_4, and concentrated. 2.86 g of the product was obtained (76% yield). ^{1}H NMR (DMSO, 500 MHz) δ: no peak; ^{13}C NMR (DMSO, 125 MHz) δ: 120.2 (q, J=322.5 Hz), 181.3, 191.5.; ^{19}F NMR ($CDCl_3$, 471 MHz) δ:−77.11. MS (APCI) Exact mass calcd for $C_6H_2F_6N_2O_6S_2$ (M−1) 374.9. Found: 374.8.

*4.1.2. N,N-Bis(perfluorobutanesulfonyl)squaramide (**2b**).* Squaramide (1.12 g; 10.0 mmol; 1.0 equiv) and triethyl amine (10.1 g; 100 mmol; 10 equiv) were added to a flame-dried sealed tube and dissolved in DMSO (30 mL). (Important: the reaction must be carried out in sealed tube. Otherwise, the yield of the reaction will be very low due to the low boiling point of perfluorobutanesulfonyl fluoride). To the above solution was added perfluorobutanesulfonyl fluoride (6.04 g; 20.0 mmol; 2.0 equiv) in one portion. The reaction mixture was allowed to stir at 60 °C and monitored by TLC and ^{13}C NMR. When the squaramide was completely consumed, the reaction mixture was cooled to room temperature. Then, the reaction mixture was acidified with aqueous HCl (4 N; 100 mL), extracted with ether (4×100 mL), dried over Na_2SO_4, and concentrated. After column chromatography (EtOAc/MeOH (20:1)) on silica, the product was obtained. This solid was redissolved in acetone, acidified with aqueous HCl (4 N; 50 mL), re-extracted with ether, dried over Na_2SO_4, and concentrated. The product was obtained as a white solid (4.53 g; 67%). ^{1}H NMR (DMSO, 500 MHz) δ: no peak; ^{13}C NMR (DMSO, 125 MHz) δ: 108.6–1118.8 (m, $CF_2CF_2CF_2CF_3$), 183.4, 193.6.; ^{19}F NMR ($CDCl_3$, 471 MHz) δ:−80.5 (s, 3F), −113.0 (s, 2F×1.5), −114.9 (s, 2F×0.5), −120.9 (s, 2F×1.5), −121.4 (s, 2F×0.5), −125.7 (s, 2F). MS (APCI) Exact mass calcd for $C_{12}H_2F_{18}N_2O_6S_2$ (M−1) 674.8. Found: 674.8.

*4.1.3. N,N-Bis(perfluorooctanesulfonyl)squaramide (**2c**).* To a solution of squaramide (0.56 g; 5.0 mmol; 1.0 equiv) and NEt_3 (5.06 g; 50 mmol; 10 equiv) in DMSO (3.0 mL; keep concentration as low as possible) in a sealed tube was added perfluorooctanesulfonyl fluoride (5.0 g; 10 mmol; 2.0 equiv). The reaction mixture was stirred at 80 °C for 12 h. Then, the reaction mixture was cooled to room temperature, poured into water, acidified with aqueous HCl (4 N; 100 mL), extracted with ether (4×100 mL), dried over Na_2SO_4. The crude mixture was analyzed by ^{13}C NMR. The mono-sulfonylated product was obtained as a major product. ^{13}C NMR (DMSO, 125 MHz) δ: 108.6–118.8 (m, $CF_2CF_2CF_2CF_2CF_2CF_2CF_2CF_3$), 173.1, 175.4, 188.6, 191.2.

The crude mixture was transferred into a sealed tube. To the above solution in a sealed tube were added perfluorooctanesulfonyl fluoride (2.5 g; 5.0 mmol; 1.0 equiv) and NEt_3 (5.1 g; 50 mmol; 10 equiv) without any solvent. The reaction mixture was stirred at 120 °C for 24 h and monitored by ^{13}C NMR. When the mono-sulfonlyted squaramide was completely consumed, the reaction mixture was cooled to room temperature. Then, the reaction mixture was acidified with aqueous HCl (4 N; 100 mL), extracted with ether (4×100 mL), dried over Na_2SO_4, and concentrated. After

column chromatography (EtOAc/MeOH (20:1)) on silica, the product was obtained. This solid was re-dissolved in acetone, acidified with aqueous HCl (4 N, 50 mL), re-extracted with ether, dried over Na_2SO_4, and concentrated. The product was obtained as a pale brown solid. ^1H NMR (DMSO, 500 MHz) δ: no peak; ^{13}C NMR (DMSO, 125 MHz) δ: 108.6–118.8 (m, $CF_2CF_2CF_2CF_2CF_2CF_2CF_3$), 183.2, 193.9.; ^{19}F NMR ($CDCl_3$, 471 MHz) δ: −71.4 (s, 2F), −80.3 (s, 3F), −114.6 (s, 2F), −120.5 (s, 2F), −121.5 (s, 2F), −121.8 (s, 2F), −122.5 (s, 2F), −125.8 (s, 2F). MS (APCI) Exact mass calcd for $C_{20}H_2F_{34}N_2O_6S_2$ (M−1) 1074.8. Found: 1074.7.

4.2. Application of squaramides 2a–c to organic reactions

4.2.1. Representative procedure for Mukaiyama aldol reaction. To a solution of **2a** (0.0020 M; 1.0 mL; 0.0020 mmol; 0.010 equiv) in acetonitrile was added **4a** (21 mg; 0.20 mmol; 1.0 equiv) and the mixture was stirred for 10 min at room temperature. After that, silyl enol ether **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 aldehyde **4**a was completely consumed, aqueous HCl (1 N; 1 mL) was added to the reaction mixture and stirred at the same temperature until all the silyl ether was converted to the free alcohol. The reaction mixture was neutralized with $NaHCO_3$, extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/hexanes (15:85)) on silica gave the desired product **5aa** in white solid. (43 mg; 96% yield).

4.2.2. Representative procedure for Mukaiyama Michael reaction. To a solution of **2a** (0.0020 M; 1.0 mL; 0.0020 mmol; 0.010 equiv) in acetonitrile was added **10a** (29 mg; 0.20 mmol; 1.0 equiv) and the mixture was stirred for 10 min at room temperature. After that, silyl enol ether **3a**′ (55 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 enone **10a** was completely consumed, aqueous HCl (1 N; 1 mL) was added to the reaction mixture and stirred at the same temperature until all the silyl ether was converted to the free alcohol. The reaction mixture was neutralized with $NaHCO_3$, extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/hexanes (15:85)) on silica gave the desired product **11aa** in white solid. (49 mg; 98% yield).

4.2.3. Representative procedure for Hosomi–Sakurai allylation reaction. To a solution of **2a** (2.3 mg; 0.0060 mmol; 0.030 equiv) in acetonitrile was added **4f** (30 mg; 0.20 mmol; 1.0 equiv) and the mixture was stirred for 10 min. After that, allyltrimethylsilane (34 mg; 0.30 mmol; 1.5 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. After 8 h, aqueous HCl (1 N; 1 mL) was added to the reaction mixture and stirred at room temperature until all the silyl ether was converted to the free alcohol. The reaction mixture was neutralized with $NaHCO_3$, extracted with ether, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/hexanes (15:85)) on silica gave the desired product **12** in white solid. (35 mg; 92% yield).

4.2.4. Representative procedure for carbonyl-ene reaction of rac-citronellal. To a solution of **2a** (68 mg; 0.10 mmol; 0.050 equiv) in THF (20 mL) was added *rac*-citronellal **13** (0.31 g; 2.0 mmol; 1.0 equiv) dropwise at room temperature. The reaction was allowed to stir at room temperature while the reaction was monitored by TLC. After all the starting material was consumed, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with ether. The organic layer was combined, dried with Na_2SO_4, and concentrated. Column chromatography on silica (hexanes/ethyl acetate (6:1)) gave the mixture of two diastereomers **14a**-α and **14a**-β in 4:1 ratio with 80% overall yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.03.120.

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