CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201700515

Link to VoR: http://dx.doi.org/10.1002/chem.201700515

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FULL PAPER

2-(Pyridinium-1-yl)-1,1-bis((perfluoroalkyl)sulfonyl)ethan-1-ide: a practical reagent for synthesis of strongly acidic 1,1-bis((perfluoroalkyl)sulfonyl)alkanes

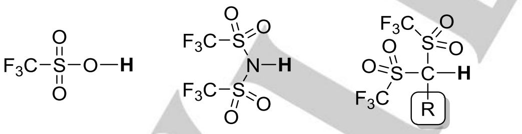
Hikaru Yanai,*[a] Ryuta Takahashi,[a] Yoichi Takahashi,[a] Akira Kotani,[a] Hideki Hakamata,[a] and Takashi Matsumoto*[a]

Dedicated to Professor Takeo Taguchi on the occasion of his 70th birthday.

Abstract: By mixing $(R_fSO_2)_2CH_2$ (R_f = perfluoroalkyl), paraformaldehyde, and substituted pyridines, a three-component reaction proceeded smoothly to give unusual zwitterions bearing both pyridinium and stabilized carbanion moieties in good to excellent yields. Of these, 2-fluoropyridinium derivatives rapidly dissociated in acetonitrile to give equilibrium mixtures of the zwitterions and $(R_fSO_2)_2C{=}CH_2$/2-fluoropyridine, as confirmed by detailed temperature-variable NMR studies. The dynamic behavior of such 2-fluoropyridiniums prompted us to examine their utility as shelf-stable, easy-to-handle $(R_fSO_2)_2C{=}CH_2$ sources. With these reagents, we successfully synthesized strongly acidic carbon acids $(R_fSO_2)_2CHR$, which served as a new type of acid catalysts. Moreover, the C–C bond forming reactions using a ketene silyl acetal proceeded efficiently by the *in-situ* generated $Tf_2C{=}CH_2$.

Introduction

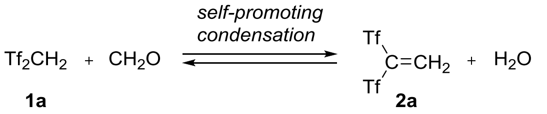
The organic superacidic compounds,[1] such as TfOH (Tf = CF_3SO_2) and Tf_2NH, have been attracting considerable interest from various fields of chemistry. For example, the acids are utilized as catalysts in organic synthesis,[2] and their conjugate bases, as stable organic anions, represent an important structure for ionic liquids[3] and electrolytes for lithium ion secondary batteries.[4] The structurally related carbon acids depicted as Tf_2CHR are also attractive because the acidities are comparable to that of sulfuric acid (Figure 1).[5,6]



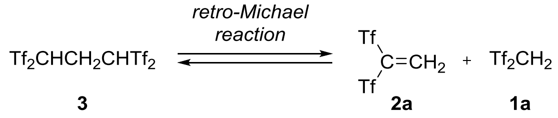
for acidity tuning and additional properties

Figure 1. Structures of Triflylated Acids.

In this carbon acid structure, the third substituent "R" makes the acidity tunable and endows additional, unique properties. This structural feature is an advantage for the development of novel strong acids. For instance, in several synthetic reactions including the Mukaiyama aldol and related reactions, higher catalytic performance of Tf_2CHR over conventional TfOH and Tf_2NH has been reported by us[7,8], Yamamoto and Ishihara,[9] and List.[10] However, flexible molecular design for the carbon acid catalysts were still difficult owning to a lack of general and effective synthetic methods.[11] For example, α-alkylation reactions of commercially available bis(triflyl)methane **1a** (Tf_2CH_2) with alkyl halides gave unsatisfactory results owning to the remarkably low nucleophilicity of the bis(triflyl)methanide ion.[11a] To overcome the situation, we previously reported an addition reaction of neutral nucleophile "H–Nu" with *in-situ* generated $Tf_2C{=}CH_2$ **2a** to give the acid "Tf_2CHCH_2Nu". Since highly electrophilic **2a** was easily hydrolyzed into Tf_2CH_2 **1a** and formaldehyde, two methods for the *in-situ* generation of **2a** were developed as follows: 1) self-promoting condensation of **1a** and formaldehyde[12] and 2) the retro-Michael reaction of easily available $Tf_2CHCH_2CHTf_2$ **3**[13] (Eqns. 1 and 2). The latter method was successfully applied to the reactions with neutral nucleophiles such as electron-rich arenes[13a] and 1,3-dicarbonyls[13b] to give the corresponding carbon acids, which worked as effective acid catalysts.[7,13a]



(1)



(2)

However, applicable nucleophiles were still limited. One of the most serious drawbacks was that strongly basic nucleophiles including organometallic reagents were rapidly rendered inactive by acids **1a** and **3** existing in the reaction mixture. Application of acid-sensitive neutral nucleophiles was also problematic. Furthermore, in spite of a fundamental interest in the acidities of carbon acids bearing longer perfluoroalkyl (R_f) groups,[14] their syntheses failed because of the fluorous properties of $(R_fSO_2)_2CH_2$ and $(R_fSO_2)_2CHCH_2CH(SO_2R_f)_2$.

We recently developed a convenient synthetic method for 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides **4** through the three component reaction of Tf_2CH_2 **1a**, paraformaldehyde, and

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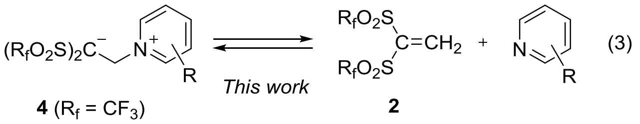
pyridine derivatives.[15] Moreover, their unusual zwitterionic structures were confirmed on the basis of X-ray crystallography and computational analysis.[15a] Herein we report that such pyridinium-type zwitterions provide a practical solution to the problems with the carbon acid synthesis stated above (Eqn. 3): The 2-fluoropyridinium congener of **4** specifically dissociated in the solution phase,[16] realizing the *in-situ* generation of $Tf_2C{=}CH_2$ **2a** without formation of any acidic compounds. Likewise, by using new zwitterions **5** and **6** bearing different R_f groups (R_f = n-C_4F_9 and -$(CF_2)_3$-), the corresponding carbon acids and related compounds were synthesized. This achievement presents a general and practical way to generate highly electrophilic $(R_fSO_2)_2C{=}CH_2$ **2**, which can be used as not only effective species for installing several carbon acid functionalities but also building blocks for fluorinated chemicals, and novel catalysts.

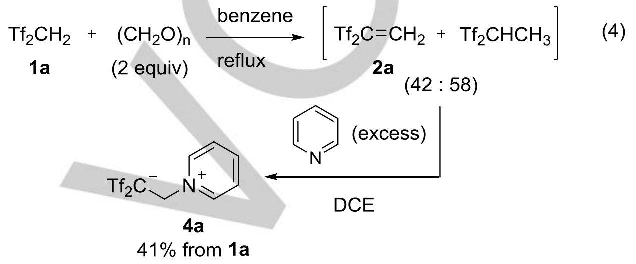


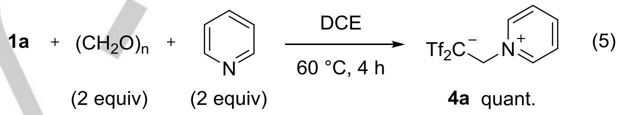
4 (R_f = CF_3)
5 (R_f = n-C_4F_9)
6 (R_f = -$(CF_2)_3$-)

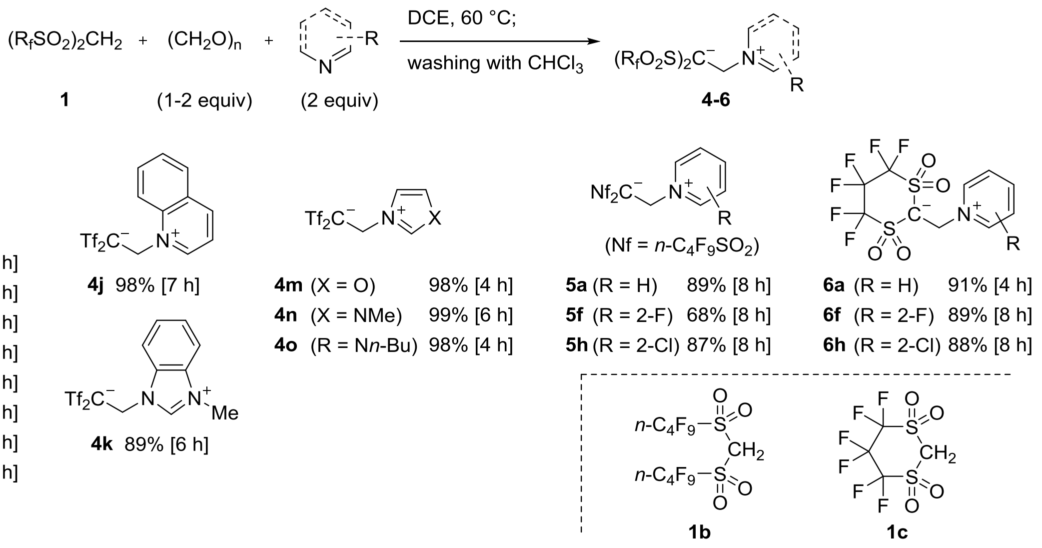
Results and Discussion

Synthesis of Pyridinium-type Zwitterions

Upon starting the development of the desired new reagents for *in-situ* generation of $(R_fSO_2)_2C{=}CH_2$ **2**, we focused our attention on 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanide **4a**, which was originally reported by Koshar and co-workers in 1976 (Eqn. 4).[12b] They synthesized this compound by self-promoting condensation of Tf_2CH_2 **1a** with formaldehyde and the subsequent treatment with a large amount of pyridine. However, owning to competitive formation of Tf_2CHCH_3 (a hydrogenated product of $Tf_2C{=}CH_2$ **2a**) in the condensation step, the overall yield was not satisfactory. In addition, its chemical structure was proposed only on the basis of elemental analysis. At first, we reinvestigated the reaction conditions and the structure of the product. As a result, we found that by mixing **1a**, paraformaldehyde, and pyridine in 1,2-dichloroethane (DCE) at 60 °C, Koshar's salt **4a** was obtained in quantitative yield (Eqn. 5). An X-ray crystallographic analysis of **4a** was in agreement with the originally proposed structure (Figure 2), in which the planar geometry around C7 (∠C6–C7–S1 = 118.9°, ∠S1–C7–S2 = 122.1°, and ∠S2–C7–C6 = 118.6°) and reasonable atom length between C6 and N1 (150.4(3) pm) were key pieces of evidence.[17]







4b (R = 2-Me) 97% [4 h]
4c (R = 2-Et) 97% [8 h]
4d (R = 2-*i*-Bu) 96% [6 h]
4e (R = 2-OMe) 99% [5 h]
4f (R = 2-F) 91% [8 h]
4g (R = 3-F) 87% [8 h]
4h (R = 2-Cl) 98% [5 h]
4i (R = 2-Br) 98% [3 h]
4j 98% [7 h]
4k 89% [6 h]
4m (X = O) 98% [4 h]
4n (X = NMe) 99% [6 h]
4o (R = N*n*-Bu) 98% [4 h]
5a (R = H) 89% [8 h]
5f (R = 2-F) 68% [8 h]
5h (R = 2-Cl) 87% [8 h]
6a (R = H) 91% [4 h]
6f (R = 2-F) 89% [8 h]
6h (R = 2-Cl) 88% [8 h]

Figure 3. Three Component Synthesis of Pyridinium-type Zwitterions.

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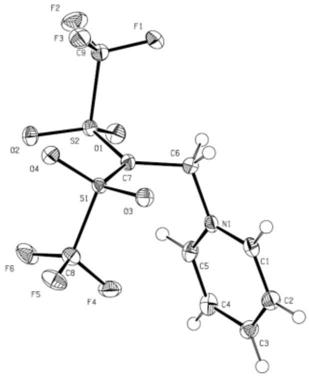

Figure 2. ORTEP Drawing of Koshar's Salt **4a**. The thermal ellipsoids are shown at 50% probability.

Our conditions for the three-component reaction were successfully applied to the synthesis of a variety of zwitterions (Figure 3). For example, pyridiniums **4b**-**4e** bearing electron-donating groups on the pyridinium ring were obtained in excellent yields. 2-Halo- or 3-halopyridines also worked as nice reaction components to produce pyridiniums **4f**-**4i**. Although 2,6-dimethylpyridine, 2,3- and 2,4-difluoropyridines did not yield the corresponding zwitterions, some nitrogen-containing heterocycles such as quinoline, *N*-methylbenzimidazole, oxazole, and *N*-substituted imidazoles did give the zwitterions **4j**-**4o**, respectively, in good to excellent yields. Under similar conditions, bis(nonaflyl)methane **1b** (Nf_2CH_2, Nf = n-$C_4F_9SO_2$) and six-membered cyclic derivative **1c**[18] were converted to the corresponding zwitterions **5** and **6**. Their zwitterion structures were confirmed by X-ray crystallographic analysis of **4b**-**4o**, **5a**, and **6a** (see, Supporting Information).

Synthesis of Strongly Acidic Carbon Acid Derivatives

Among zwitterions derived from Tf_2CH_2 **1a**, 2-fluoropyridinium **4f** showed an interesting aspect in the temperature-variable ^{1}H NMR study (performed using a 0.010 M solution in CD_3CN, 400 MHz). Increasing temperature caused a significant down-field shift of the signals of the methylene hydrogens H1 (Figure 4a).[19] At the same time, all signals of hydrogens H2-H5 on the 2-fluoropyridinium ring were shifted up-field. Similar temperature-dependent shifts were observed for 2-chloropyridinium **4h**, whereas significantly smaller shifts were observed in the cases of non-halogenated pyridinium **4a** and 3-fluoropyridinium **4g** (Figure 4b). The phenomenon strongly suggested very rapid, probably on the order of milliseconds, interconversion between zwitterion **4f** and $Tf_2C{=}CH_2$ **2a**/2-fluoropyridine **7** (Figure 4c) (*vide infra*).

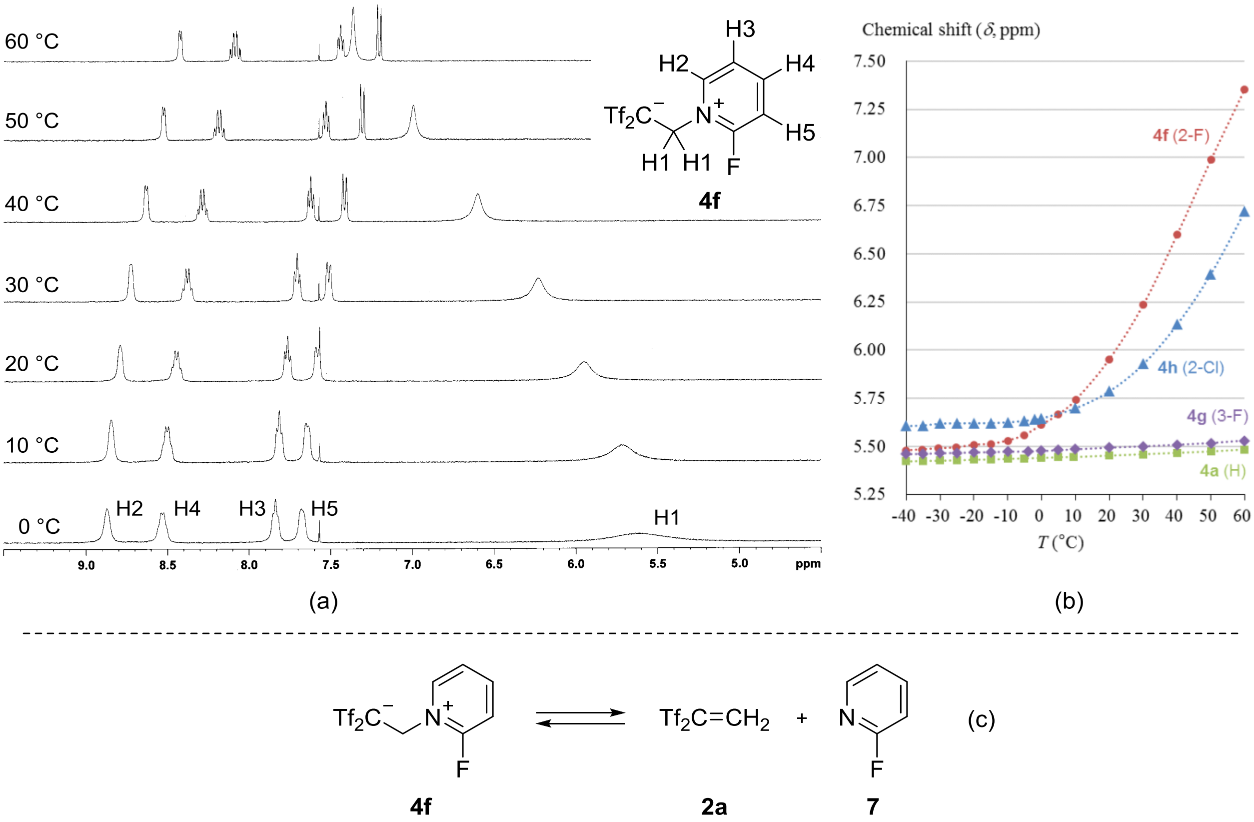

Figure 4. (a) Temperature dependency of ^{1}H chemical shifts in a 0.010 mol L^{-1} solution of 2-fluoropyridinium **4f** in CD_3CN (400 MHz, δ ppm). (b) Plots of chemical shifts of the methylene hydrogens versus NMR measurement temperature (0.010 mol L^{-1} solutions of zwitterions **4f**, **4h**, **4a**, and **4g** in CD_3CN). (c) The reversible dissociation of **4f**.

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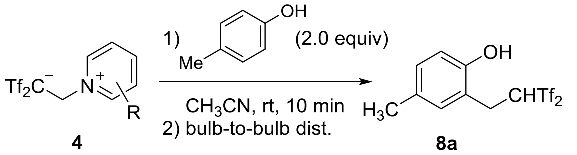
Table 1. Carbon Acid Synthesis with Pyridinium-type Zwitterions.



Entry	4	R	Yield[a] (%)
1	**4f**	2-F	98 (92)
2	**4h**	2-Cl	84 (81)
3	**4g**	3-F	0
4	**4a**	H	0
5	**4b**	2-Me	<5
6[b]	$Tf_2CHCH_2CHTf_2$ **3**		90
7	Tf_2CH_2 **1a** + $(CH_2O)_n$		7

[a] Yield on the basis of ^{19}F NMR of crude mixture. Isolated yield is shown in parenthesis. [b] For 3 h at room temperature. Ref. 13a

To evaluate the performance of 2-fluoropyridinium **4f** as a reagent for the carbon acid synthesis, we examined the reaction with *p*-cresol (Table 1). The reaction of **4f** with 2.0 equiv of *p*-cresol in acetonitrile went to completion within only 10 min at room temperature. ^{1}H NMR analysis of the crude material showed clean formation of the desired carbon acid **8a** and 2-fluoropyridine **7**. This result evidences that **4f** smoothly produces $Tf_2C{=}CH_2$ **2a**. The carbon acid **8a** was isolated in 92% yield by bulb-to-bulb distillation (180-200 °C at 3 mmHg) (entry 1). Although 2-chloropyridinium **4h** brought about an acceptable result under the same conditions (entry 2), no formation of **8a** was observed in the case with 3-fluoropyridinium **4g** in place of 2-fluoro derivative **4f** (entry 3). Likewise, non-halogenated and 2-methylated pyridiniums did not show suitable reactivity (entries 4 and 5). The use of $Tf_2CHCH_2CHTf_2$ **3** as a precursor of $Tf_2C{=}CH_2$ **2a** was possible in this case, although a longer time (3 h) was required (entry 6).[13a] The three-component reaction of Tf_2CH_2 **1a**, paraformaldehyde, and *p*-cresol resulted in a poor conversion because of slow formation of **2a** through the self-promoting condensation (entry 7).

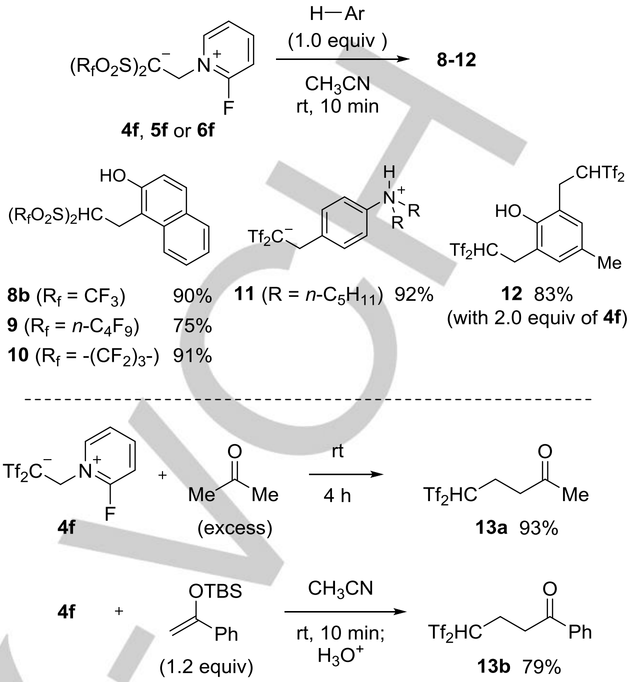
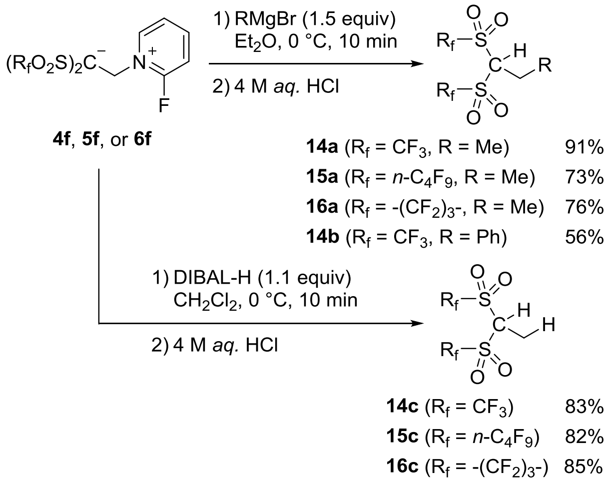


Figure 5. Synthesis of Carbon Acid Derivatives.

With 2-fluoropyridiniums on hand, we successfully synthesized carbon acid derivatives bearing different R_f groups (Figure 5). For example, by using **4f**, **5f**, and **6f**, a series of carbon acids **8b**, **9**, and **10** were obtained in good to excellent yields by the reaction with naphthalen-2-ol. Likewise, anilinium-type zwitterion **11** was formed in 92% yield from *N*,*N*-dipentylaniline. It should be noted that the 1:2 reaction of *p*-cresol with **4f** gave disubstituted product **12** in 83% yield. Enolizable acetone and enol silyl ether, derived from acetophenone, also worked as suitable nucleophiles to give carbon acids **13a** and **13b** in 93% and 79% yields, respectively.

As shown in Scheme 1, the reactions with organometallic reagents were successful. 2-Fluoropyridiniums **4f**, **5f**, and **6f** smoothly reacted with both Grignard reagents and *i*-Bu_2AlH (DIBAL-H) to give substituted carbon acids **14**-**16** in good to excellent yields. To estimate the structure-acidity relationship in this type of carbon acid, we determined the pK_a values of **14c**-**16c** bearing different perfluoroalkyl (or alkylene) groups in acetonitrile by a voltammetric method.[20,21] The acidity of Nf_2CHCH_3 **15c** (pK_a = 11.9) was about 100 times stronger than those of **14c** (14.0) and **16c** (14.1).[22] Similarly, Nf_2CH_2 **1b** (9.0) was a stronger acid than Tf_2CH_2 **1a** (10.4) and cyclic derivative **1c** (11.3). By methylation of Tf_2CH_2 **1a**, the pK_a value decreased by about 3 units. In contrast, phenylation of **1a** elevated the acidity by about 3 pK_a units (Tf_2CHPh, 7.85).[23] These data would serve as clues for the design of stronger carbon acids directed toward superacid catalysts.



Scheme 1. Reaction of **4f**-**6f** with Organometallic Reagents.

As a good example to understand the specific reactivity of the 2-fluoropyridinium **4f**, we found the unique ammonium-exchange reaction (Figure 6). When 1.05 equiv of pyridine itself was added to a solution of 2-fluoropyridinium **4f** in acetonitrile at room temperature, pyridinium **4a** was formed quantitatively. Under similar conditions, **4f** was successfully converted to 3-fluoropyridinium **4g** in 93% yield. Although a 1:1 reaction of **4f** and 2-chloropyridine yielded a mixture of 2-fluoropyridinium **4f** and 2-chloropyridinium **4h** in a ratio of 1:7.0, the use of 2.0 equiv of 2-chloropyridine was enough to realize one-sided formation of **4h** (96% yield). These data demonstrated that the thermodynamic stability of 2-fluoropyridinium was specifically lower than other analogues. With strongly basic 4-(dimethylamino)pyridine and aliphatic amines such as diethylamine, quinuclidine, and 1,4-diazabicyclo[2.2.2]octane, this reaction well proceeded and the corresponding zwitterions **4p**-**4s** were isolated in excellent yields. Note that these amines never gave the zwitterions under the three-component conditions using Tf_2CH_2 **1a** and paraformaldehyde, but caused neutralization of **1a** giving rise to the intermolecular salts.

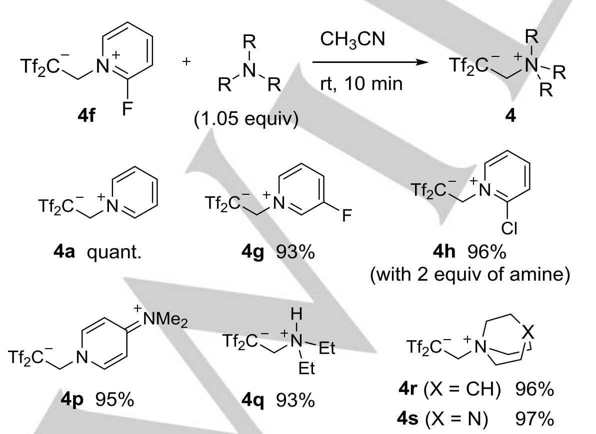


Figure 6. Ammonium-exchange Reaction from 2-Fluoropyridinium **4f** to Other Ammoniums.

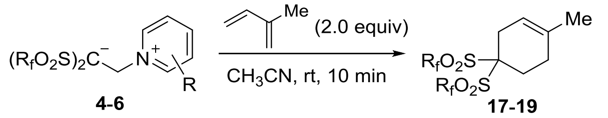
These results indisputably demonstrated that a series of 2-fluoropyridiniums served as the desired new reagents for *in-situ* generation of $(R_fSO_2)_2C{=}CH_2$ **2**. Though 2-fluoropyridine accompanies as a side product, this highly volatile compound can be easily removed by evaporation. The low basicity also works as an advantage to isolate the desired, strongly acidic products.[24] As shown in Figure 7, **4f** and other 2-fluoropyridiniums **5f** and **6f** are non-hygroscopic, crystalline compounds and they are shelf-stable for at least several months.

Figure 7. A Picture of 2-Fluoropyridinium **4f** under Air Atmosphere.

Application of 2-Fluoropyridiniums as Building Block for Fluorinated Chemicals

To show synthetic applications of the 2-fluoropyridiniums as building blocks for fluorinated chemicals, we next tried trapping $(R_fSO_2)_2C{=}CH_2$ **2** with 1,3-dienes via (4+2) cycloaddition. Previously, we reported that three-component reaction of Tf_2CH_2 **1a**, paraformaldehyde, and isoprene proceeded at room temperature to give *gem*-bis(triflyl)cyclohexene **17a**, which was a valuable synthetic intermediate for poly-substituted triflyl arenes.[12a] In that case, a long reaction time (2.5 h) was required (Table 2, entry 8). Although the use of $Tf_2CHCH_2CHTf_2$ **3** was possible, the yield of **17a** decreased with competitive oligomerization of isoprene (entry 9).[12a] Note that reagent **3** itself and Tf_2CH_2 **1a** accompanying the *in-situ* generation of $Tf_2C{=}CH_2$ **2a** are strongly acidic. On the other hand, 2-fluoropyridinium **4f** immediately gave **17a** in 89% yield (within 10 min) without the formation of any oligomers (entry 1). 2-Chloropyridiniums **4h** also gave comparable results (entry 2), whereas the reaction using 3-fluoropyridinium **4g** was unsatisfactory (entry 3). Moreover, the use of non-halogenated pyridiniums **4a** and **4b** did not lead to suitable production of **17a** (entries 4 and 5). Likewise, 2-fluoropyridiniums **5f** and **6f** derived from $(R_fSO_2)_2CH_2$ **1b** and **1c**, respectively, could be subjected to similar reaction to give cyclohexenes **18** and **19**, respectively (entries 6 and 7).

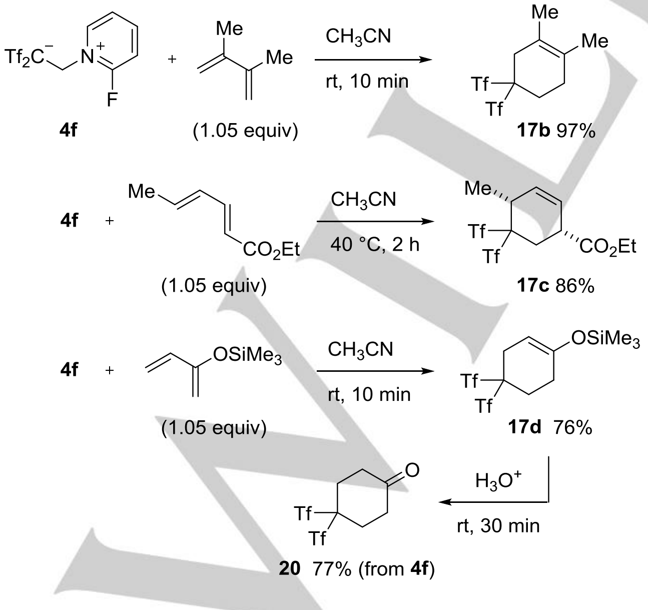
Table 2. Trapping of *In-situ* Generated $(R_fSO_2)_2C{=}CH_2$ **2** by isoprene.



Entry	4-6	R_f	X	17-19	Yield[a] (%)
1	**4f**	CF_3	2-F	**17a**	89
2	**4h**	CF_3	2-Cl	**17a**	78
3	**4g**	CF_3	3-F	**17a**	2
4	**4a**	CF_3	H	**17a**	0
5	**4b**	CF_3	2-Me	**17a**	0
6	**5f**	*n*-C_4F_9	2-F	**18**	91
7	**6f**	-$(CF_2)_3$-	2-F	**19**	90
8[b]	Tf_2CH_2 **1a** + $(CH_2O)_n$			**17a**	76
9[b]	$Tf_2CHCH_2CHTf_2$ **3**			**17a**	61

[a] Isolated yield. [b] For 2.5 h at room temperature. Ref. 12a.

As shown in Scheme 2, some 1,3-dienes including less reactive ethyl sorbate smoothly reacted with **4f** under mild conditions to give the cycloadduct **17**. Here it should be noted that the reaction with 2-(silyloxy)buta-1,3-diene, which is susceptible to hydrolysis even under slightly acidic conditions, was realized by using **4f** and cyclohexene **17d** was isolated in 76% yield. One-pot formation of the corresponding cyclohexanone **20** was also achieved by a subsequent H_3O^+ workup (77% yield from **4f**).



Scheme 2. Synthesis of *gem*-Bis(triflyl)cyclohexenes.

Formal Catalysis by 2-Fluoropyridinium

By using 2-fluoropyridinium **4f**, we achieved the carbon acid synthesis with acid-sensitive nucleophiles and (4+2) cycloaddition chemistry with buta-1,3-dienes including acid-sensitive 2-(silyloxy)buta-1,3-diene. These results inspired us to attempt formal catalysis by 2-fluoropyridinium **4f**. As described above, notably high performance of Tf_2CH-based carbon acids as acid catalysts in C-C bond forming reactions with silicon enolate equivalents has been reported. Recently, List and co-workers also reported an effective asymmetric carbon acid catalyst, in which a disulfonylated, acidic C–H moiety was embedded in a binaphthyl scaffold.[25] In such carbon acid-induced Mukaiyama aldol type reactions, it was proposed that protonation of ketene silyl acetals by the carbon acids initially occurred to give ion pair **A** (or silyl alkanide **A'**),[26] which worked as Lewis acidic "R_3Si^+" equivalents (Figure 8).[27] If silyl carboxonium species **B** (or the corresponding silyl alkanide **B'**) generated by the Michael reaction of the $Tf_2C{=}CH_2$ **2a** with ketene silyl acetals, electrophilic activation of carbonyl substrates would also be possible by silyl transfer reaction from this species. Owning to the absence of any Brønsted acids in such a reaction system, we expected a chemoselective transformation of the carbonyl group over other acid-sensitive functionalities in the reaction substrate.

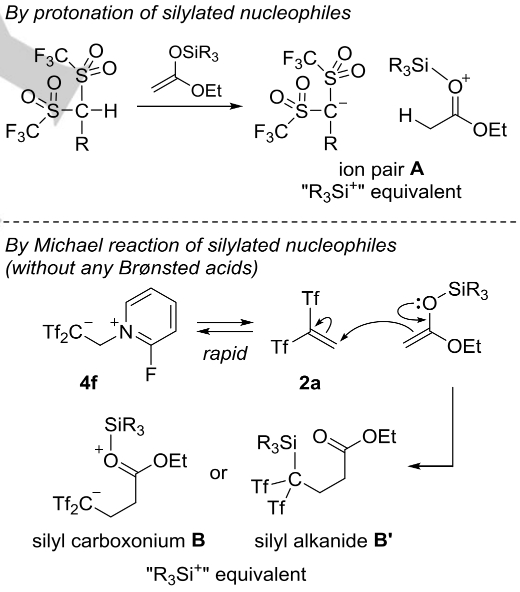
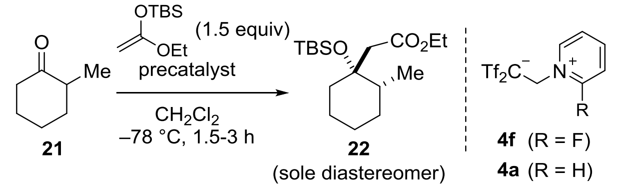


Figure 8. Generation of Catalytically Active "R_3Si^+" Equivalents.

With this idea in mind, we conducted the Mukaiyama aldol reaction of 2-methylcyclohexanone **21** with a ketene silyl acetal derived from ethyl acetate as a test case (Table 3). In our previous work, $Tf_2CHCH_2CHTf_2$ **3** was found to be one of the most effective acids (entry 1).[28] β-Branched acid **23** also worked as a formal catalyst (entry 2).[29] On the other hand, despite the absence of any acidic moieties, 2-fluoropyridinium **4f** efficiently promoted the reaction (entries 3 and 4), whereas non-halogenated pyridinium **4a** proved less fruitful (entry 5). These results explicitly showed

Table 3. Carbon Acid- and 1,1-Bis(triflyl)alkene-induced Mukaiyama Aldol Reaction.

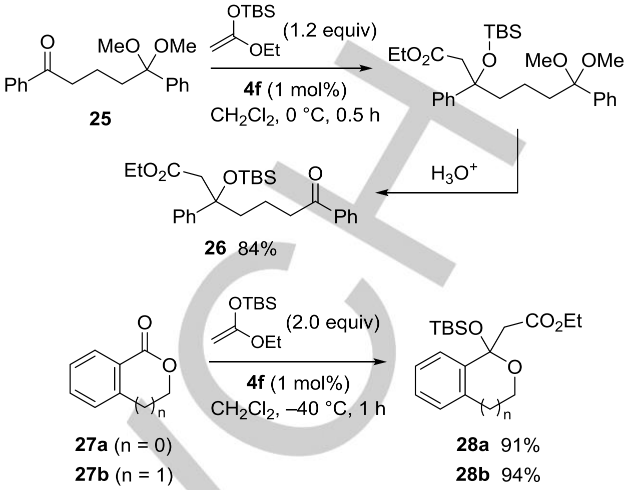


Entry	Precatalyst (mol%)	Yield[a] (%)
1	$Tf_2CHCH_2CHTf_2$ **3** (0.05)	94
2	$Tf_2CHCH(Me)CH{=}CHPh$ **23** (0.25)	85
3	**4f** (0.5)	87
4[b]	**4f** (0.5)	97
5	**4f** (0.5)	13
6	$Tf_2C{=}CHCH{=}CHPh$ **24** (1)	90

[a] Isolated yield. [b] Reaction was carried out at 0 °C.

that the thermodynamic stability of the zwitterions played a crucial role for the formal precatalysis. As mentioned above, initial reaction of $Tf_2C{=}CH_2$ **2a**, generated from zwitterion **4f**, with ketene silyl acetal would be a trigger for the Mukaiyama aldol reaction. To obtain further evidence for this point, we examined the same reaction in the presence of easily isolable 1,1-bis(triflyl)alkadiene **24**[29a] instead of **4f** (entry 6). Although a relatively high loading was required, the desired reaction proceeded to give **22** in 90% yield.

As shown in Scheme 3, 2-fluoropyridinium **4f** did not affect acid-sensitive acetal moieties. For example, the reaction of δ,δ-dimethoxyketone **25** proceeded in a ketone-selective manner to give the adduct **26** in 84% yield after acidic workup. Furthermore, the addition reaction of ketene silyl acetal to less reactive lactones **27a** and **27b** also gave the adducts **28a** and **28b** in 91% and 94% yields, respectively. Here, any side products arising from a ring-opening reaction were not detected.



Scheme 3. Carbonyl-selective Addition Reactions.

Dynamic Structure of Pyridinium Zwitterions in Solution Phase

Finally, to quantify the dynamic behavior of 2-fluoropyridinium **4f** and related zwitterions**,** we obtained dynamic parameters from the temperature-variable ^1H NMR data (Figure 4). As mentioned above, the NMR study demonstrated very rapid, probably on the order of milliseconds, interconversion between zwitterion **4f** and a mixture of $Tf_2C{=}CH_2$ **2a**/2-fluoropyridine **7**. Here the observed chemical shift δ_{obs} of the methylene hydrogens at each temperature is the weighted mean of $Tf_2C{=}CH_2$ **2a** (δ_A = 8.15 ppm) and zwitterion **4f** (δ_B = 5.48 ppm) as illustrated in Eqn 6 (where K = [**2a**]/[**4f**]).[30] The equilibrium constant K_{eq} can be obtained by using the molar ratio K (Eqn. 7, where [**4f**]+[**2a**] = 0.010 mol L^{-1} and [**2a**] = [**7**]). We determined thermodynamic parameters $\Delta_r H$ and $\Delta_r S$ by a van't Hoff plot (where R = 8.314 J K^{-1} mol^{-1}; Eqn 8) and calculated the $\Delta_r G$ value (Eqn 9).

$$\delta_{obs} = \frac{K\,\delta_A + \delta_B}{1+K} \qquad (6)$$

$$K_{eq} = \frac{[\mathbf{2a}][\mathbf{7}]}{[\mathbf{4f}]} = K\left(\frac{0.010\cdot K}{1+K}\right) \qquad (7)$$

$$R\ln K_{eq} = -\frac{\Delta_r H}{T} + \Delta_r S \qquad (8)$$

$$\Delta_r G = \Delta_r H - T\Delta_r S \qquad (9)$$

As shown in Figure 9, a linear relation between $R\ln K_{eq}$ and $1/T$ was obtained in the van't Hoff plot of all four zwitterions. The values of $\Delta_r H$, $\Delta_r S$ and $\Delta_r G_{298}$ for 2-fluoropyridinium **4f** were 89.6 kJ mol^{-1}, 238 J K^{-1} mol^{-1}, and 18.6 kJ mol^{-1}, respectively. Recently, Alcaide and Almendros have reported the $\Delta_r G_{298}$ of this reaction as 18.8 kJ mol^{-1} by DFT computation.[16a] Their calculation agrees well with our experimental data. A similar analysis was applied to **4h**, **4a**, and **4g**. Although the $\Delta_r G_{298}$ value of 2-chloropyridinium **4h** was moderate (22.6 kJ mol^{-1}), those of pyridinium **4a** and 3-fluoropyridinium **4g** were larger (33.4 kJ mol^{-1} and 33.0 kJ mol^{-1}, respectively).

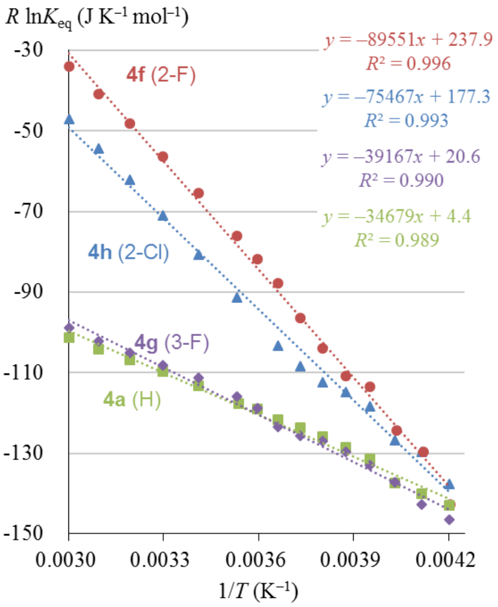


Figure 9. Van't Hoff Plots of Zwitterions **4f**, **4h**, **4a**, and **4g**.

Conclusions

We have developed a concise synthetic method of pyridinium-type zwitterions bearing highly stabilized carbanion moieties. Among the thus obtained zwitterions, 2-halopyridiniums, in particular 2-fluoropyridiniums, showed very interesting dynamic behavior in the solution phase. That is, a very rapid equilibrium between the 2-fluoropyridinium **4f** and $Tf_2C{=}CH_2$ **2a**/2-fluoropyridine **7** was fully confirmed by a temperature-variable NMR study. From a synthetic point of view, such 2-fluoropyridiniums have several advantages as precursors of $(R_fSO_2)_2C{=}CH_2$ **2** compared to the known methods. Firstly, 2-fluoropyridine, which is formed simultaneously with the release of **2**, is a volatile and virtually non-basic compound. In the synthesis of strongly acidic carbon acids and their derivatives, the fact that 2-fluoropyridine **7** can be easily removed by evaporation played an important role. Secondly, no acidic species were present in this equilibrium mixture. This led to effective reactions of $(R_fSO_2)_2C{=}CH_2$ with acid-sensitive reagents such as organometallic reagents and 2-silyloxydiene. Thirdly, 2-fluoropyridiniums were successfully obtained from several $(R_fSO_2)_2CH_2$ **1**, and such pyridiniums could be used as effective reagents for generating $(R_fSO_2)_2C{=}CH_2$. This realized easy access to new types of strongly acidic carbon acid derivatives. Finally, a very fast reaction rate in the dissociation reaction of $(R_fSO_2)_2C{=}CH_2$ (on the order of milliseconds) was one of the most characteristic points. On the basis of this physicochemical feature, we found that non-acidic zwitterion **4f** could be used as a formal catalyst for Mukaiyama aldol-type reactions.

Experimental Section

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide (**4f**): To a solution of Tf_2CH_2 **1a** (281 mg, 1.00 mmol) in 1,2-dichloroethane (6.0 mL), paraformaldehyde (90% purity, 69.8 mg, 2.07 mmol) and 2-fluoropyridine (172 μL, 2.00 mmol) were added at room temperature. After being stirred for 8 h at 60 °C, the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with $CHCl_3$ (1.0 mL x 3) to give zwitterion **4f** in 91% yield (356 mg, 0.915 mmol). The structure was also confirmed by an X-ray crystallographic analysis. Due to its low stability in several organic solvents, we could not detect suitable peaks in mass spectrometry. Colorless crystals (CH_3CN/hexane); Mp. 151-153 °C; IR (ATR) ν 1351, 1183, 1106, 861, 776, 579 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 5.73 (2H, brs), 7.73-7.78 (1H, dd, J_{HH} = 8.4 Hz, J_{HF} = 4.0 Hz), 7.93 (1H, t, J = 6.8 Hz), 8.57-8.65 (1H, m), 8.92-9.01 (1H, m); ^{13}C NMR (100 MHz, CD_3CN) δ 60.2, 64.5, 115.1 (d, J_{CF} = 21.7 Hz), 121.5 (q, J_{CF} = 326 Hz), 125.3 (d, J_{CF} = 3.7 Hz), 142.9 (d, J_{CF} = 6.1 Hz), 147.4 (d, J_{CF} = 11.5 Hz), 159.6 (q, J_{CF} = 279 Hz); ^{19}F NMR (376 Hz, CD_3CN) δ –17.1 (6F, s), –16.0 (1F, brs). Anal. Calcd for $C_9H_6F_7NO_4S_2$: C, 27.77; H, 1.55; N, 3.60. Found: C, 27.49; H, 1.49; N, 3.69.

1,1-Bis((trifluoromethyl)sulfonyl)propane (**14a**): To a solution of 2-fluoropyridinium **4f** (97.1 mg, 0.249 mmol) in Et_2O (1.2 mL), MeMgBr (a 3.0 M solution in Et_2O, 0.12 mL, 0.36 mmol) was added at 0 °C. After being stirred for 10 min at the same temperature, the reaction mixture was quenched with 4 M hydrochloric acid (15 mL). The resulting mixture was extracted with Et_2O (20 mL x 3) and the combined organic layer was evaporated. Then the residue was purified by bulb-to-bulb distillation using a Kugelrohr oven (60 °C, 5 mmHg) to give the corresponding carbon acid **14a** in 91% yield (70.0 mg, 0.227 mmol). Colorless oil; IR (neat) ν 1462, 1393, 1383, 1219, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 7.4 Hz), 2.51-2.60 (2H, m), 4.75 (1H, t, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 19.7, 78.5, 119.2 (q, J_{CF} = 328 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –10.4 (6F, s); MS (ESI-TOF) *m/z* 331 $[M{+}Na]^+$; HRMS calcd for $C_5H_6F_6NaO_4S_2$ $[M{+}Na]^+$, 330.9509; found, 330.9525; Anal. Calcd for $C_5H_6F_6O_4S_2$: C, 19.49; H, 1.96. Found: C, 19.25; H, 1.85.

Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-7-oxo-3,7-diphenylheptanoate (**26**): To a solution of 5,5-dimethoxy-1,5-diphenylpentan-1-one **25** (149 mg, 0.499 mmol) and *tert*-butyl((1-ethoxyvinyl)oxy)dimethylsilane (122 mg, 0.601 mmol) in CH_2Cl_2 (1.0 mL), 2-fluoropyridinium **4f** (1.9 mg, 4.9 μmol) was added at 0 °C. After being stirred for 30 min at the same temperature, the reaction was quenched with Et_3N (0.5 mL). After evaporation of the resulting mixture, the residue was dissolved in acetone-water (1:1 v/v, 2.0 mL). This solution was treated with acetic acid (1.0 mL) for 1 h at room temperature. The reaction was quenched with a saturated $NaHCO_3$ aqueous solution (25 mL), extracted with EtOAc (25 mL x 3), and dried over anhydrous $MgSO_4$. After removal of organic solvents under reduced pressure, the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc = 10 : 1) to give the product **26** in 84% yield (191 mg, 0.420 mmol). Colorless oil; IR (neat) ν 2952, 2852, 1716, 1690, 1444, 1314, 1260, 1078, 820, 778, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, m), 0.09 (3H, s), 0.94 (9H, s), 1.04 (3H, t, J = 7.1 Hz), 1.56-1.65 (1H, m), 1.71-1.82 (1H, m), 2.07 (1H, ddd, J = 13.7, 11.9, 4.5 Hz), 2.25 (1H, ddd, J = 13.7, 12.1, 4.7 Hz), 2.86 (1H, d, J = 14.3 Hz), 2.91 (2H, d, J = 7.3 Hz), 2.97 (1H, d, J = 14.3 Hz), 3.93 (2H, q, J = 7.1 Hz), 7.19-7.32 (1H, m), 7.28-7.32 (2H, m), 7.41-7.45 (4H, m), 7.52-7.56 (1H, m), 7.89-7.91 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ –2.3, –2.2, 13.9, 18.7, 19.0, 26.1, 38.7, 41.2, 47.8, 60.1, 78.3, 125.8, 127.8, 128.0, 128.5, 132.9, 136.9, 145.1, 169.9, 199.9; MS (ESI-TOF) *m/z* 477 $[M{+}Na]^+$; HRMS calcd for $C_{27}H_{38}NaO_4Si$ $[M{+}Na]^+$, 477.2437; found, 477.2440. Anal. Calcd for $C_{27}H_{38}O_4Si$: C, 71.32; H, 8.42. Found: C, 71.22; H, 8.50.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from the MEXT, Mitsubishi Gas Chemical Co. Ltd., the Kurata Memorial Hitachi Science and Technology Foundation, and the Hoansha Foundation. We thank Mr. Haruhiko Fukaya (Tokyo University of Pharmacy and Life Sciences, TUPLS) for the X-ray crystallographic studies, and Mr. Yuki Yamamoto (TUPLS) for his experimental assistance. Prof. Benito Alcaide (Universidad Complutense de Madrid) and Prof. Pedro Almendros (Instituto de Química Orgánica General, CSIC) are also acknowledged for helpful discussions.

Keywords: zwitterions • Brønsted acids • acidity • homogeneous catalyst • Lewis acids

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10.1002/chem.201700515

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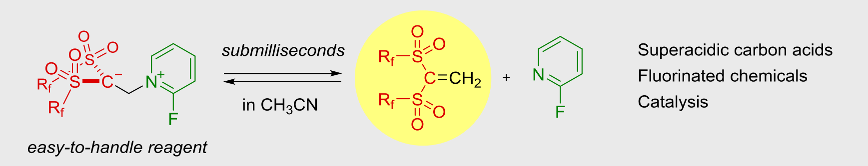

2-Fluoropyridiniums, which were prepared from $(R_fSO_2)_2CH_2$, paraformaldehyde, and 2-fluoropyridine, were found as shelf-stable, easy-to-handle $(R_fSO_2)_2C{=}CH_2$ sources: by using the reaction of several nucleophiles with such reagents, superacidic carbon acids $(R_fSO_2)_2CHR$ were successfully synthesized.

Hikaru Yanai, Ryuta Takahashi, Yoichi Takahashi, Akira Kotani, Hideki Hakamata, and Takashi Matsumoto**

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2-(Pyridinium-1-yl)-1,1-bis((perfluoroalkyl)sulfonyl)ethan-1-ide: a practical reagent for synthesis of strongly acidic 1,1-bis((perfluoroalkyl)sulfonyl)alkanes