

## Reactive Intermediates

International Edition: DOI: 10.1002/anie.201605280  
German Edition: DOI: 10.1002/ange.201605280**Bis(difluoromethyl)trimethylsilicate Anion: A Key Intermediate in Nucleophilic Difluoromethylation of Enolizable Ketones with Me<sub>3</sub>SiCF<sub>2</sub>H**

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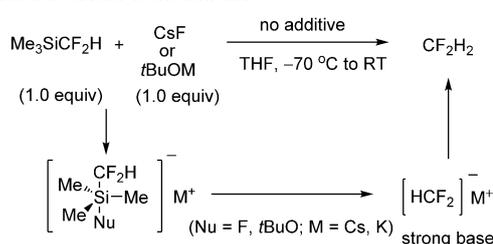
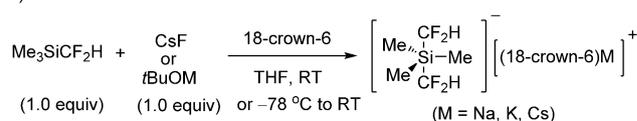
Dedicated to Professor K. Barry Sharpless on the occasion of his 75th birthday

**Abstract:** A pentacoordinate bis(difluoromethyl)silicate anion, [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup>, is observed for the first time by the activation of Me<sub>3</sub>SiCF<sub>2</sub>H with a nucleophilic alkali-metal salt and 18-crown-6. Further study on its reactivity by tuning the counteraction effect led to the discovery and development of an efficient, catalytic nucleophilic difluoromethylation of enolizable ketones with Me<sub>3</sub>SiCF<sub>2</sub>H by using a combination of CsF and 18-crown-6 as the initiation system. Mechanistic investigations demonstrate that [(18-crown-6)Cs]<sup>+</sup>[Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> is a key intermediate in this catalytic reaction.

**H**ypercoordinate silicates are key intermediates in nucleophilic substitution on silicon and activation of organosilicon compounds.<sup>[1]</sup> Many pentacoordinate silicates containing at least one electronegative heteroatom ligand such as F, Cl, O, and N have been prepared to study their structures and reactivities.<sup>[2]</sup> However, pentaorganosilicate species containing five Si–C bonds are rare, and little is known about their carbon–ligand transfer reactivity.<sup>[3–5]</sup> In 1999, the groups of Naumann<sup>[5a]</sup> and Röschenhale<sup>[5b]</sup> independently reported the preparation and characterization of the pentaorganosilicate anion [Me<sub>3</sub>Si(CF<sub>3</sub>)<sub>2</sub>]<sup>−</sup>, which is derived from the interaction of a pentacoordinate [Me<sub>3</sub>SiF(CF<sub>3</sub>)]<sup>−</sup> with the Ruppert–Prakash reagent (Me<sub>3</sub>SiCF<sub>3</sub>). The formation of such an acyclic pentaorganosilicate is attributed to the pronounced group electronegativity of the trifluoromethyl unit, which renders Me<sub>3</sub>SiCF<sub>3</sub> of sufficient Lewis acidity to accept an incoming trifluoromethanide anion (CF<sub>3</sub><sup>−</sup>).<sup>[6]</sup> In 2014, Prakash and co-workers<sup>[5c]</sup> elegantly demonstrated that the pentacoordinate [Me<sub>3</sub>Si(CF<sub>3</sub>)<sub>2</sub>]<sup>−</sup> prepared from a bulky *tert*-butoxy anion with a [K(18-crown-6)]<sup>+</sup> counteraction and Me<sub>3</sub>SiCF<sub>3</sub> can dissociate to give a CF<sub>3</sub><sup>−</sup>. They observed the CF<sub>3</sub><sup>−</sup> species by NMR spectroscopy and ascertained its reactivity in nucleophilic trifluoromethylations.<sup>[5c]</sup>

Me<sub>3</sub>SiCF<sub>2</sub>H, as an analogue of Me<sub>3</sub>SiCF<sub>3</sub>, has recently emerged as a potentially useful difluoromethanide anion (HCF<sub>2</sub><sup>−</sup>) source for the nucleophilic introduction of a difluoromethyl group.<sup>[7–9]</sup> However, because of the weaker electron-withdrawing ability of the CF<sub>2</sub>H group (compared with CF<sub>3</sub> group),<sup>[10]</sup> the reactivity of Me<sub>3</sub>SiCF<sub>2</sub>H is distinct from the well-developed Me<sub>3</sub>SiCF<sub>3</sub> in nucleophilic fluoroalkylation reactions. The trifluoromethylation with Me<sub>3</sub>SiCF<sub>3</sub> readily takes place under the activation of a wide range of Lewis bases,<sup>[11]</sup> whereas the similar difluoromethylation normally requires harsher reaction conditions, thus limiting the substrate scope.<sup>[7–9]</sup> To address these challenges in difluoromethylation with Me<sub>3</sub>SiCF<sub>2</sub>H, it is essential to investigate the hypervalent silicon intermediate in the nucleophilic activation of Me<sub>3</sub>SiCF<sub>2</sub>H and to probe its difluoromethyl-transfer reactivity. Herein, we describe the discovery and characterization of a unique pentacoordinate bis(difluoromethyl)silicate anion [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> derived from Me<sub>3</sub>SiCF<sub>2</sub>H and the tuning of its reactivity with the counteraction [(18-crown-6)Cs]<sup>+</sup>, as well as its application in the efficient difluoromethylation of enolizable ketones, a reaction which was previously difficult to achieve.<sup>[7–9]</sup>

We began our study with an investigation on the interaction between Me<sub>3</sub>SiCF<sub>2</sub>H and various nucleophilic activators in THF without adding the carbonyl substrate (Scheme 1 a). Based on our previous report on the difluoromethylation of various aldehydes, diaryl ketones, and imines

a) Activation with fluoride or *tert*-butoxideb) Activation with fluoride or *tert*-butoxide and 18-crown-6

**Scheme 1.** Activation of Me<sub>3</sub>SiCF<sub>2</sub>H with various nucleophiles and observation of the pentacoordinate difluoromethylsilicate. THF = tetrahydrofuran.

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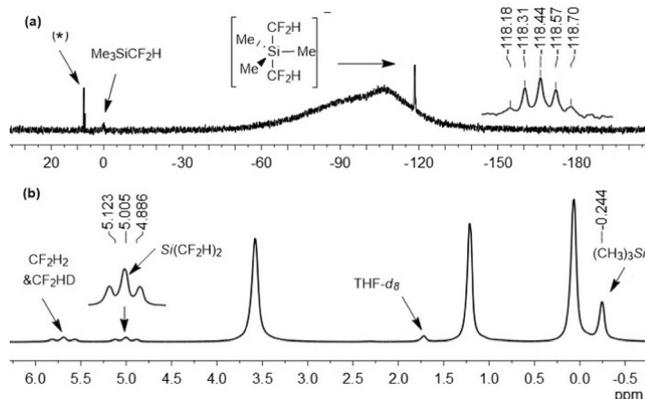
with  $\text{Me}_3\text{SiCF}_2\text{H}$ ,<sup>[7b]</sup> stoichiometric amounts of CsF and *t*BuOK were initially tested as the activators. However, only the signals of  $\text{CF}_2\text{H}_2$  and unreacted  $\text{Me}_3\text{SiCF}_2\text{H}$  were detected by  $^{19}\text{F}$  NMR spectroscopy at a wide range of temperatures ( $-70^\circ\text{C}$  to room temperature). The failure to observe any pentacoordinate difluoromethyl silicate species probably arises from the strong affinity of the  $\text{HCF}_2^-$  to the alkali-metal cations, and thus leads to a spontaneous decomposition of the difluoromethyl silicates into  $\text{HCF}_2^-$ , with subsequent protonation by either adventitious water or the solvent THF.

Considering that the countercation effect can significantly influence the stability of hypercoordinate silicate anions,<sup>[3f,5b]</sup> we turned our attention to the employment of a crown ether<sup>[12]</sup> as an additive to stabilize the silicate intermediate by minimizing the interaction between  $\text{HCF}_2^-$  and the alkali metal cations (Scheme 1b). To our delight, a weak signal at around  $\delta = -130.0$  ppm was observed by  $^{19}\text{F}$  NMR spectroscopy at room temperature using the combination of CsF/18-crown-6 as the activator (see Figure S1 in the Supporting Information). Much stronger signals with the similar chemical shifts were observed at temperatures ranging from  $-78^\circ\text{C}$  to room temperature when the combinations of more soluble *t*BuOK/18-crown-6, *t*BuOCs/18-crown-6, and even *t*BuONa/18-crown-6 were used. Compared with the  $^{19}\text{F}$  NMR chemical shift of  $\text{Me}_3\text{SiCF}_2\text{H}$  ( $\delta = -140.7$  ppm), the downfield shift of the observed signal is likely to correspond to an anionic species.<sup>[13]</sup> To determine the structure of the observed species, we further carried out  $^{29}\text{Si}\{^1\text{H}\}$  NMR,  $^{13}\text{C}\{^1\text{H}\}$  NMR,  $^1\text{H}$  NMR, and heteronuclear multiple quantum coherence (HMQC) experiments of the reaction between  $\text{Me}_3\text{SiCF}_2\text{H}$  and *t*BuOCs/18-crown-6 in  $[\text{D}_8]\text{THF}$  (Figure 1; see Figur-

$-112.1$  ppm) versus  $\text{Me}_3\text{SiCF}_3$  ( $\delta = 5.4$  ppm).<sup>[5a]</sup> In the  $^1\text{H}$  NMR spectrum, both the signals of the  $\text{CF}_2\text{H}$  ( $\delta = 5.00$  ppm) and Me ( $\delta = -0.24$  ppm) groups are also detected to be upfield compared with those of  $\text{Me}_3\text{SiCF}_2\text{H}$  [ $\delta(\text{CF}_2\text{H}) = 5.85$  ppm;  $\delta(\text{Me}) = 0.14$  ppm]. The  $^1J_{\text{H-F}}$  coupling constant is in good agreement with the corresponding coupling observed in  $^{19}\text{F}$  NMR [ $\delta = -130.0$  ppm (d,  $^1J_{\text{H-F}} = 47.3$  Hz)]. According to the ratio (2:9) of integrated area of the  $^1\text{H}$  NMR signals of  $\text{CF}_2\text{H}$  and Me, we inferred that the above silicon species is a pentacoordinated bis(difluoromethyl)silicate with five Si–C bonds, that is,  $[(18\text{-crown-6})\text{M}]^+[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  (M = Na, K, Cs).<sup>[16]</sup> The observed quintet peak in  $^{29}\text{Si}\{^1\text{H}\}$  NMR spectrum supports a trigonal-bipyramidal structure with two axial  $\text{CF}_2\text{H}$  groups and three equatorial methyl groups, and it is similar to the structure of  $[\text{Me}_3\text{Si}(\text{CF}_3)_2]^-$ .<sup>[5a]</sup> Moreover, the  $^{13}\text{C}$  NMR signals of  $\text{CF}_2\text{H}$  [ $\delta = 140.3$  ppm (t,  $^1J_{\text{C-F}} = 285$  Hz)] and Me ( $\delta = -3.2$  ppm), which were assigned by  $^1\text{H}$ - $^{13}\text{C}$  HMQC analysis, appear downfield from those of  $\text{Me}_3\text{SiCF}_2\text{H}$  [ $\delta(\text{CF}_2\text{H}) = 123.7$  ppm (t,  $^1J_{\text{C-F}} = 253$  Hz);  $\delta(\text{Me}) = -6.5$  ppm]. An increase in  $^1J_{\text{C-F}}$  coupling as well as a decrease in  $^2J_{\text{Si-F}}$  coupling, which have been observed in the transformation of  $\text{Me}_3\text{SiCF}_3$  into  $[\text{Me}_3\text{Si}(\text{CF}_3)_2]^-$ ,<sup>[5a]</sup> are probably characters of bipyramidal  $[\text{R}_3\text{Si}(\text{R}'_2)]^-$  species with two  $\text{R}'$  groups at the axial positions.

It is noteworthy that these pentacoordinate silicates were relatively stable below  $-30^\circ\text{C}$  and decomposed gradually to  $\text{CF}_2\text{H}_2$  when slowly raising the temperature from  $-30^\circ\text{C}$  to  $20^\circ\text{C}$  [for variable-temperature (VT) NMR study, see Figures S7 and S17]. Moreover,  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  was the only detectable difluoromethylated hypercoordinate silicon species regardless the ratio of  $\text{Me}_3\text{SiCF}_2\text{H}/t\text{BuOM}$  (either  $>1:1$  or not). We also attempted to observe  $\text{CF}_2\text{H}^-$  at a wide range of temperatures (from  $-78^\circ\text{C}$  to  $20^\circ\text{C}$ ), but no evidence supported the persistence of this species in our system, which is significantly different from the  $\text{CF}_3^-$  anion derived from  $\text{Me}_3\text{SiCF}_3$ .<sup>[5c]</sup> The generation of  $\text{CF}_2\text{HD}$  and  $\text{CF}_2\text{H}_2$  as side products when using  $[\text{D}_8]\text{THF}$  as the solvent indicates that  $\text{CF}_2\text{H}^-$  is kinetically unstable and has a high tendency to abstract a proton from both THF and 18-crown-6 (see Figures S3 and S13).

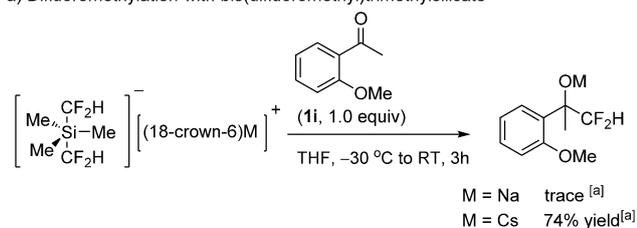
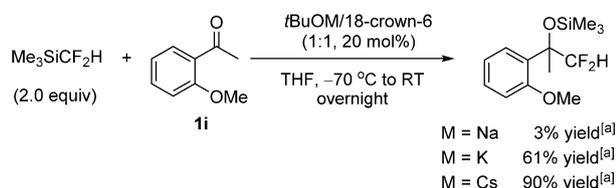
Having identified the relatively stable intermediate  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$ , we next sought to probe its reactivity in nucleophilic difluoromethylation reactions. The experiment was conducted by adding the electrophilic substrate to a THF solution of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  pre-generated from stoichiometric amounts of *t*BuOM (M = Na, K, Cs), 18-crown-6, and  $\text{Me}_3\text{SiCF}_2\text{H}$  in a molar ratio of 1:1:2. To our surprise, enolizable ketones, which are challenging substrates under previously reported difluoromethylation conditions,<sup>[7a,b,d]</sup> can be readily difluoromethylated. Thus, the reaction between 1-(2-methoxyphenyl) ethanone (**1i**) and  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$ , generated from *t*BuOCs/18-crown-6/ $\text{Me}_3\text{SiCF}_2\text{H}$ , gave the corresponding difluoromethylated alcohol in good yield (Scheme 2a; for details see Figure S8). However, when *t*BuONa was used instead of *t*BuOCs, the pre-generated  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  failed to undergo addition to **1i**, only affording  $\text{CF}_2\text{H}_2$  as the detectable side product. Based on these results, we concluded that the countercation effect not only influences the stabilization of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$ , but it also dram-



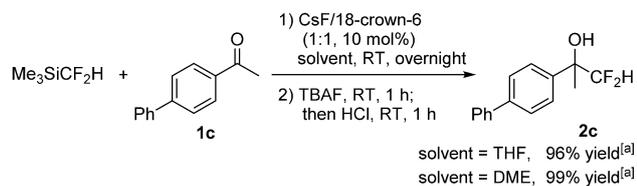
**Figure 1.**  $^{29}\text{Si}\{^1\text{H}\}$  NMR (a) and  $^1\text{H}$  NMR (b) spectra of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$ , generated from *t*BuOCs/18-crown-6 and  $\text{Me}_3\text{SiCF}_2\text{H}$  in  $[\text{D}_8]\text{THF}$  at  $-30^\circ\text{C}$ . In (a), the signals (\*) at  $\delta = 7.5$ – $7.0$  ppm are assigned to  $\text{Me}_3\text{SiOtBu}$  as well as side-products arising from the silylation of  $[\text{D}_8]\text{THF}$  and 18-crown-6.

es S2–S6 and Table S1).<sup>[14]</sup> In the  $^{29}\text{Si}\{^1\text{H}\}$  NMR spectrum, the signal is shifted upfield [ $\delta = -118.4$  ppm (quint,  $^2J_{\text{Si-F}} = 10.3$  Hz)] compared with that of  $\text{Me}_3\text{SiCF}_2\text{H}$  [ $\delta = -0.04$  ppm (t,  $^2J_{\text{Si-F}} = 28.8$  Hz)], and is in accordance with the formation of a pentacoordinated silicate species.<sup>[15]</sup> This chemical shift change is similar to that of the reported  $[\text{Me}_3\text{Si}(\text{CF}_3)_2]^-$  ( $\delta =$

## a) Difluoromethylation with bis(difluoromethyl)trimethylsilicate

b) *tert*-Butoxide-catalyzed difluoromethylation: the counteraction effect

## c) CsF-catalyzed difluoromethylation: optimization of reaction conditions

**Scheme 2.** Nucleophilic difluoromethylation of enolizable ketones.

[a] Yield was determined by  $^{19}\text{F}$  NMR spectroscopy. TBAF = *tert*-*n*-butylammonium fluoride.

ically alters the reactivity of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  towards enolizable ketones.

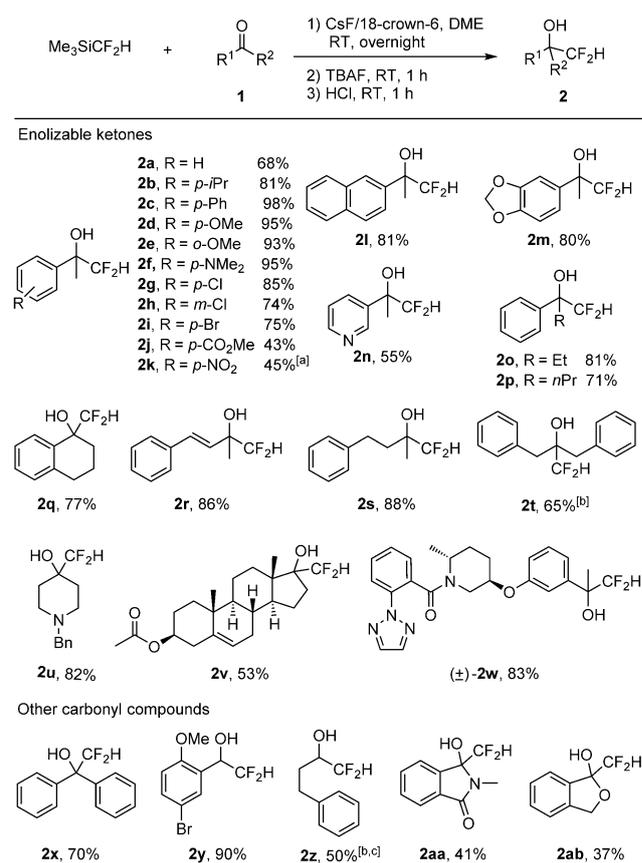
Inspired by the observed excellent reactivity of  $[(18\text{-crown-6})\text{Cs}]^+[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  towards the ketone **1i**, we decided to develop a catalytic difluoromethylation method for synthesizing tertiary carbinols from  $\text{Me}_3\text{SiCF}_2\text{H}$  and the challenging enolizable ketones by employing the impressive counteraction effect.<sup>[17]</sup> Thus, substoichiometric amounts of *t*BuOM ( $M = \text{Na}, \text{K}, \text{Cs}$ )/18-crown-6 were used as an initiator to investigate the reaction between **1i** and  $\text{Me}_3\text{SiCF}_2\text{H}$ . As shown in Scheme 2b, a remarkable metal-ion effect was also found in this catalytic reaction and  $[(18\text{-crown-6})\text{Cs}]^+$  again proved to be the most effective counteraction.

To determine the role of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  in the catalytic cycle, we investigated the progress of the (*t*BuOCs/18-crown-6)-initiated reaction by VT  $^{19}\text{F}$  NMR experiments. The experiment was carried out by adding a mixture of **1i** (1 equiv) and  $\text{Me}_3\text{SiCF}_2\text{H}$  (2 equiv) to a THF solution of *t*BuOCs (20 mol %) and 18-crown-6 (20 mol %) at  $-70^\circ\text{C}$ . As the reaction temperature gradually rose, the intermediate  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  was observed first ( $-70^\circ\text{C}$  to  $-20^\circ\text{C}$ ), followed by the observation of the difluoromethylation product ( $> -20^\circ\text{C}$ ). Interestingly, the silicate intermediate maintained a certain concentration even when the reaction temperature was elevated to  $5^\circ\text{C}$  (see Figures S10 and S11), thus indicating a continuous consumption and regeneration of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  during the reaction. In contrast, when *t*BuONa was used instead of *t*BuOCs, although the formation of  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  was observed first, it could not difluoromethylate **1i** to initiate the reaction. According to these

results, we conclude that the cesium ion played an important role in (*t*BuO<sup>-</sup>/18-crown-6)-initiated difluoromethylation of enolizable ketones.

Since  $[\text{Me}_3\text{Si}(\text{CF}_2\text{H})_2]^-$  can also be generated from the combination of CsF/18-crown-6, albeit in a low yield, we explored the difluoromethylation by employing the more readily available CsF instead of *t*BuOCs (Scheme 2c; for details see Table S1). We were pleased to find that reaction employing 10 mol % of CsF/18-crown-6 also provided a high yield of the difluoromethyl addition product. A screening of the solvent showed that the ether solvent dimethoxyethane (DME) is slightly superior to THF in improving the yield. Therefore, the combination of CsF/18-crown-6 was chosen as the optimal initiation system and DME was chosen as the optimal solvent for the reaction between  $\text{Me}_3\text{SiCF}_2\text{H}$  and enolizable ketones.

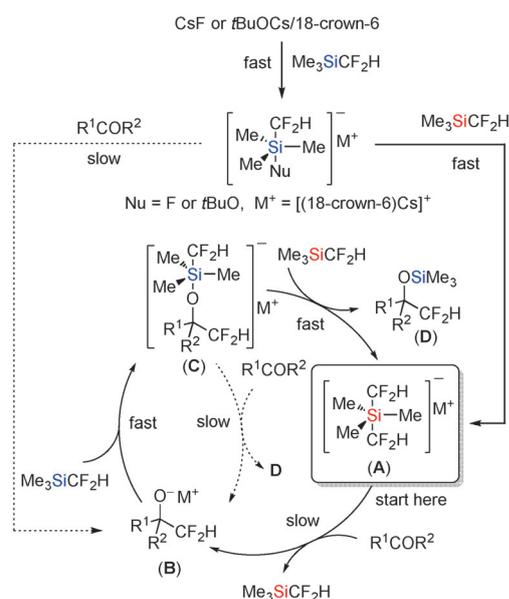
With the optimized reaction conditions in hand, we subsequently investigated the substrate scope. As shown in Scheme 3, most of the enolizable ketones examined provided good to excellent yields. In general, substituted aromatic ketones bearing electron-donating groups (such as Ph, *i*Pr, OMe, and  $\text{NMe}_2$ ) showed higher reactivity (**2b–f**) than those



**Scheme 3.** Direct nucleophilic difluoromethylation of various carbonyl compounds with  $\text{Me}_3\text{SiCF}_2\text{H}$ . Reaction conditions (unless otherwise noted):  $\text{Me}_3\text{SiCF}_2\text{H}$  (1.2 mmol), **1** (0.6 mmol), CsF (10 mol %), 18-crown-6 (10 mol %), DME (3 mL). Yields of isolated products are reported. [a] CsF (100 mol %), 18-crown-6 (100 mol %). [b] CsF (20 mol %), 18-crown-6 (20 mol %). [c] Yield was determined by  $^{19}\text{F}$  NMR spectroscopy.

with electron-withdrawing groups (such as Br, Cl, COOMe, and NO<sub>2</sub>; **2g–k**). 1-Phenylalkyl-1-ones containing alkyl groups of different chain lengths gave difluoromethylated products in good yields (**2o,p**). The CsF/18-crown-6/DME system was also suitable for difluoromethylation of aliphatic ketones (**2s–v**). Particularly, the readily enolizable 1,3-diphenylpropan-2-one and steroid could also react with Me<sub>3</sub>SiCF<sub>2</sub>H to afford the products **2t** and **2v** in 65 and 53% yields, respectively. When conjugated methyl ketone (*E*)-4-phenylbut-3-en-2-one was subjected to the reaction, the alcohol **2r** resulting from the carbonyl addition was obtained as the sole product. To demonstrate both the potential pharmaceutical relevance and the functional-group tolerance of the present direct difluoromethylation protocol, we applied it in the synthesis of the compound (±)-**2w**, a potential antagonist of the orexin receptor. It was previously prepared using a two-step method: nucleophilic (phosphoryl) difluoromethylation of the corresponding ketone followed by removal of the phosphonate group.<sup>[18]</sup> In addition to enolizable ketones, other carbonyl compounds including diaryl ketones, aromatic aldehyde, enolizable aliphatic aldehyde, phthalimide, and phthalide could also be difluoromethylated by Me<sub>3</sub>SiCF<sub>2</sub>H under the similar reaction conditions, thus affording the products **2x–ab** in 37–90% yields.

Finally, based on our investigation, a mechanism involving [(18-crown-6)Cs]<sup>+</sup>[Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> (**A**) as a key intermediate was proposed. As is shown in Scheme 4, the process



**Scheme 4.** Possible mechanism of the difluoromethylation between Me<sub>3</sub>SiCF<sub>2</sub>H and enolizable ketones.

commences with the initial generation of [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> from a catalytic amount CsF (or *t*BuOCs)/18-crown-6 and Me<sub>3</sub>SiCF<sub>2</sub>H. The complexation of 18-crown-6 with Cs<sup>+</sup> inhibits the formation of the strongly basic, free difluoromethanide, thus stabilizing [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> and favoring the carbonyl addition rather than the enolization. The subsequent reaction between **A** and carbonyl substrate leads to the

formation of the alcoholate **B**, which continues to attack the silicon atom of Me<sub>3</sub>SiCF<sub>2</sub>H to produce a new pentacoordinate silicate **C**. This step is followed by the transfer of a difluoromethanide anion to Me<sub>3</sub>SiCF<sub>2</sub>H to release the target product and to regenerate **A**. **A** will be constantly generated until all of the carbonyl substrate is consumed. In view of the fact that **A** is formed much faster than the carbonyl addition product, another pathway involving the difluoromethanide anion addition to the carbonyl group at the initiation stage (Scheme 4, dashed arrow), which is similar to the commonly assumed trifluoromethylation of carbonyl compounds with Me<sub>3</sub>SiCF<sub>3</sub>,<sup>[11]</sup> is less likely to occur as a major pathway under our conditions.

In summary, [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup>, a pentacoordinate difluoromethylsilicate anion with five Si–C bonds, was observed for the first time through the activation of Me<sub>3</sub>SiCF<sub>2</sub>H with a nucleophilic alkali-metal salt and 18-crown-6. It is found that the counteraction effect plays important roles in both stabilizing the [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> intermediate and improving its nucleophilic difluoromethylation potency. By employing the combination of a cesium salt and 18-crown-6 as the initiator, catalytic difluoromethylation of enolizable ketones was achieved in high yields because of the avoidance of the competitive enolization, which is usually encountered when using other initiators. During the whole reaction, [Me<sub>3</sub>Si(CF<sub>2</sub>H)<sub>2</sub>]<sup>−</sup> is not only the difluoromethanide anion source, but also acts as a difluoromethanide reservoir. The formation of the bis(difluoromethyl)trimethylsilicate intermediate with [(18-crown-6)Cs]<sup>+</sup> as counteraction alleviates the strong basicity of a difluoromethanide, which is of great significance for the catalyzed difluoromethylation of enolizable ketones.

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