Bis(difluoromethyl)trimethylsilicate Anion: A Key Intermediate in Nucleophilic Difluoromethylation of Enolizable Ketones with Me₃SiCF₂H

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

Abstract: A pentacoordinate bis(difluoromethyl)silicate anion, [Me₃Si(CF₂H)₂]⁻, is observed for the first time by the activation of Me₃SiCF₂H with a nucleophilic alkali-metal salt and 18-crown-6. Further study on its reactivity by tuning the countercation effect led to the discovery and development of an efficient, catalytic nucleophilic difluoromethylation of enolizable ketones with Me₃SiCF₂H by using a combination of CsF and 18-crown-6 as the initiation system. Mechanistic investigations demonstrate that [(18-crown-6)Cs]⁺[Me₃Si(CF₂H)₂]⁻ is a key intermediate in this catalytic reaction.

Hypercoordinate silicates are key intermediates in nucleophilic substitution on silicon and activation of organosilicon compounds. 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. However, pentaorganosilicate species containing five Si–C bonds are rare, and little is known about their carbon–ligand transfer reactivity. In 1999, the groups of Naumann and Ritschenthaler independently reported the preparation and characterization of the pentacoorganosilicate anion [Me₃Si(CF₂H)₂]⁻, which is derived from the interaction of a pentacoordinate [Me₃Si(CF₃)]⁻ with the Ruppert–Prakash reagent (Me₃SiCF₃). The formation of such an acyclic pentaorganosilicate is attributed to the pronounced group electron negativity of the trifluoromethyl unit, which renders Me₃SiCF₃ of sufficient Lewis acidity to accept an incoming trifluoromethanide anion (CF₃⁻). In 2014, Prakash and co-workers elegantly demonstrated that the pentacoordinate [Me₃Si(CF₂H)₂]⁻ prepared from a bulky tert-butoxy anion with a [K(18-crown-6)]⁻ countercation and Me₃SiCF₃ can dissociate to give a CF₂⁻ anion. They observed the CF₂⁻ species by NMR spectroscopy and ascertained its reactivity in nucleophilic trifluoromethylations.[5]

Me₃SiCF₂H, as an analogue of Me₃SiCF₃, has recently emerged as a potentially useful difluoromethanide anion (HCF₂⁻) source for the nucleophilic introduction of a difluoromethyl group.[6–9] However, because of the weaker electron-withdrawing ability of the CF₂H group (compared with CF₃ group),[10] the reactivity of Me₃SiCF₂H is distinct from the well-developed Me₃SiCF₃ in nucleophilic fluoroalkylation reactions. The trifluoromethylation with Me₃SiCF₃ readily takes place under the activation of a wide range of Lewis bases,[11] whereas the similar difluoromethylation normally requires harsher reaction conditions, thus limiting the substrate scope.[7–9] To address these challenges in difluoromethylation with Me₃SiCF₂H, it is essential to investigate the hypervalent silicon intermediate in the nucleophilic activation of Me₃SiCF₂H and to probe its difluoromethyl-transfer reactivity. Herein, we describe the discovery and characterization of a unique pentacoordinate bis(difluoromethyl)silicate anion [Me₃Si(CF₂H)₂]⁻ derived from Me₃SiCF₂H and the tuning of its reactivity with the countercation [(18-crown-6)Cs]⁺ as well as its application in the efficient difluoromethylation of enolizable ketones, a reaction which was previously difficult to achieve.[7–9]

We began our study with an investigation on the interaction between Me₃SiCF₂H and various nucleophilic activators in THF without adding the carbonyl substrate (Scheme 1a). Based on our previous report on the difluoromethylation of various aldehydes, diaryl ketones, and imines with Me₃SiCF₃ in THF[10] and Me₃SiCF₂H, as the analogue of Me₃SiCF₃, it is essential to investigate the hypervalent silicon intermediate in the nucleophilic activation of Me₃SiCF₂H and to probe its difluoromethyl-transfer reactivity. Herein, we describe the discovery and characterization of a unique pentacoordinate bis(difluoromethyl)silicate anion [Me₃Si(CF₂H)₂]⁻ derived from Me₃SiCF₂H and the tuning of its reactivity with the countercation [(18-crown-6)Cs]⁺ as well as its application in the efficient difluoromethylation of enolizable ketones, a reaction which was previously difficult to achieve.[7–9]

Scheme 1. Activation of Me₃SiCF₂H with various nucleophiles and observation of the pentacoordinate difluoromethylsilicate. THF = tetrahydrofuran.

a) Activation with fluoride or tert-butoxide

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\text{Me₃SiCF₂H} + \text{CsF or \text{tBuOM}} \xrightarrow{(1.0 \text{ equiv})} \text{CF₂H} \xrightarrow{(1.0 \text{ equiv})} \text{Nu} \xrightarrow{(1.0 \text{ equiv})} \text{CF₂H} \xrightarrow{(1.0 \text{ equiv})} \text{M'}
\]

b) Activation with fluoride or tert-butoxide and 18-crown-6

\[
\text{Me₃SiCF₂H} + \text{18-crown-6} \xrightarrow{\text{THF, RT}} \text{Me₃SiCF₂H} \xrightarrow{(1.0 \text{ equiv})} \text{M'}
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with Me₃SiCF₂H [12b] stoichiometric amounts of CsF and tBuOK were initially tested as the activators. However, only the signals of CF₂H and unreacted Me₃SiCF₂H were detected by ¹⁹F NMR spectroscopy at a wide range of temperatures (−70°C to room temperature). The failure to observe any pentacoordinate difluoromethyl silicate species probably arises from the strong affinity of the HCF₂⁺ to the alkali-metal cations, and thus leads to a spontaneous decomposition of the difluoromethyl silicates into HCF₂⁺, with subsequent protonation by either adventitious water or the solvent THF.

Considering that the counterion effect can significantly influence the stability of hypercoordinate silicate anions [13,15], we turned our attention to the employment of a crown ether [15] as an additive to stabilize the silicate intermediate by minimizing the interaction between HCF₂⁺ and the alkali metal cations (Scheme 1b). To our delight, a weak signal at around δ = −130.0 ppm was observed by ¹⁹F 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°C to room temperature when the combinations of more soluble tBuOK/18-crown-6, tBuOCS/18-crown-6, and even tBuONa/18-crown-6 were used. Compared with the ¹⁹F NMR chemical shift of Me₃SiCF₂H (δ = −140.7 ppm), the downfield shift of the observed signal is likely to correspond to an anionic species [13]. To determine the structure of the observed species, we further carried out ²⁵Si[¹H] NMR, ¹³C[¹H] NMR, ¹H NMR, and heteronuclear multiple quantum coherence (HMQC) experiments of the reaction between Me₃SiCF₂H and tBuOCS/18-crown-6 in [D₈]THF (Figure 1; see Figures S2–S6 and Table S1). [14] In the ²⁵Si[¹H] NMR spectrum, the signal is shifted upfield [δ = −118.4 ppm (quint, JHF = 10.3 Hz)] compared with that of Me₃SiCF₂H [δ = −0.04 ppm (t, JHF = 28.8 Hz)], and it is in good agreement with the corresponding coupling observed in ¹³C NMR [δ = −130.0 ppm (d, JCC = 47.3 Hz)]. According to the ratio (2:9) of integrated area of the ¹H NMR signals of CF₂H and Me, we inferred that the above silicon species is a pentacoordinate bis(difluoromethyl)silicate with five Si–C bonds, that is, [(18-crown-6)M][Me₃Si(CF₂H)₃](·M = Na, K, Cs) [16]. The observed quintet peak in ²⁵Si[¹H] NMR spectrum supports a trigonal-bipyramidal structure with two axial CF₂H groups and three equatorial methyl groups, and it is similar to the structure of [Me₃Si(CF₃)₃]⁻ [16a]. Moreover, the ¹³C NMR signals of CF₂H [δ = 140.3 ppm (t, JCH = 285 Hz)] and Me [δ = −3.2 ppm], which were assigned by ¹³C–¹H HMQC analysis, appear downfield from those of Me₃SiCF₂H [δ(CF₂H) = 123.7 ppm (t, JCF = 253 Hz); δ(Me) = −6.5 ppm]. An increase in JCH coupling as well as a decrease in JCF coupling, which have been observed in the transformation of Me₃SiCF₃ into [Me₃Si(CF₃)₃]⁻ [16b] are probably characters of bipyramidal [R₃Si(RF)₃]⁻ species with two R₃ groups at the axial positions.

It is noteworthy that these pentacoordinate silicates were relatively stable below −30°C and decomposed gradually to CF₂H₂ when slowly raising the temperature from −30°C to 20°C [for variable-temperature (VT) NMR study, see Figures S7 and S17]. Moreover, [Me₃Si(CF₂H)₃]⁻ was the only detectable difluoromethylated hypercoordinate silicon species regardless of the ratio of Me₃SiCF₂H/tBuOM (either 1:1 or not). We also attempted to observe CF₂H⁺ at a wide range of temperatures (from −78°C to 20°C), but no evidence supported the persistence of this species in our system, which is significantly different from the CF₂⁺ anion derived from Me₃SiCF₃ [16c]. The generation of CF₂HD and CF₂H₂ as side products when using [D₈]THF as the solvent indicates that CF₂H⁺ 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 [Me₃Si(CF₂H)₃]⁻, 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 [Me₃Si(CF₂H)₃]⁻ pre-generated from stoichiometric amounts of tBuOM (M = Na, K, Cs), 18-crown-6, and Me₃SiCF₂H in a molar ratio of 1:1:2. To our surprise, enolizable ketones, which are challenging substrates under previously reported difluoromethylation conditions [12b,14a], can be readily difluoromethylated. Thus, the reaction between 1- (2-methoxyphenyl)ethanone (1i) and [Me₃Si(CF₂H)₃]⁻, generated from tBuOCS/18-crown-6/Me₃SiCF₂H, gave the corresponding difluoromethylated alcohol in good yield (Scheme 2a; for details see Figure S8). However, when tBuONa was used instead of tBuOCS, the pre-generated [Me₃Si(CF₂H)₃]⁻ failed to undergo addition to 1i, only affording CF₂H₂ as the detectable side product. Based on these results, we concluded that the counterion effect not only influences the stabilization of [Me₃Si(CF₂H)₃]⁻, but it also dramat-
ically alters the reactivity of $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Cs}$ towards enolizable ketones.

Inspired by the observed excellent reactivity of $[(18\text{-crown-6})\text{Cs}]^+\text{Me}_3\text{Si(CF}_2\text{H)}_2$ 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 countercation effect.\[17\] Thus, substoichiometric amounts of $\text{tBuOM} (M = \text{Na, K, Cs})/18\text{-crown-6}$ 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 countercation.

To determine the role of $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Cs}$ in the catalytic cycle, we investigated the progress of the $(\text{tBuOCs}/18\text{-crown-6})$-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 $\text{tBuOCs}$ (20 mol%) and 18-crown-6 (20 mol%) at $70^\circ\text{C}$. As the reaction temperature gradually rose, the intermediate $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Cs}$ 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 $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Cs}$ during the reaction. In contrast, when $\text{tBuONa}$ was used instead of $\text{tBuOCs}$, although the formation of $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Na}$ 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 $(\text{tBuOCs}/18\text{-crown-6})$-initiated difluoromethylation of enolvable ketones.

Since $[\text{Me}_3\text{Si(CF}_2\text{H)}_2]\text{Na}$ 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 $\text{tBuOCs}$ (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 enolvable ketones.

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

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

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

**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.

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with electron-withdrawing groups (such as Br, Cl, COOMe, and NO2; 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 Me3SiCF2H to afford the products 2t and 2v in 65 and 53% yields, respectively. When conjugated methyl ketone (E)-4-phenyl-but-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 phosphate group. In addition to enolizable ketones, other carbonyl compounds including diaryl ketones, aromatic aldehyde, enolizable aliphatic aldehyde, phthalimide, and phthalide could also be difluoromethylated by Me3SiCF2H 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][Me3Si(CF2H)2] (A) as a key intermediate was proposed. As is shown in Scheme 4, the process commences with the initial generation of [Me3Si(CF2H)2]− from a catalytic amount CsF (or iBuOCS)/18-crown-6 and Me3SiCF2H. The complication of 18-crown-6 with Cs+ inhibits the formation of the strongly basic, free difluoromethanide, thus stabilizing [Me3Si(CF2H)2]− 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 Me3SiCF2H to produce a new pentacoordinate silicate C. This step is followed by the transfer of a difluoromethanide anion to Me3SiCF2H 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 Me3SiCF3,[11] is less likely to occur as a major pathway under our conditions.

In summary, [Me3Si(CF2H)2]−, a pentacoordinate difluoromethanesilicate anion with five Si–C bonds, was observed for the first time through the activation of Me3SiCF2H with a nucleophilic alkali-metal salt and 18-crown-6. It is found that the countercation effect plays important roles in both stabilizing the [Me3Si(CF2H)2]− 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, [Me3Si(CF2H)2]− 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]+ as countercation alleviates the strong basicity of a difluoromethanide, which is of great significance for the catalyzed difluoromethylation of enolizable ketones.

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Keywords: fluorine · ketones · reactive intermediates · reaction mechanisms · silicates


For the NMR data of [Me$_3$Si(CF$_2$)$_2$H]$_2$ generated from Me$_3$SiCF$_2$H and BuONa/18-crown-6, see the Supporting Information.

For example, the $^{29}$Si NMR signal of lithium 2,2-difluoro-1-(trimethylsilyl)propane appears at δ = −116.9 ppm. See Ref. [3c].


During our preparation of this manuscript, a direct nucleophilic difluoromethylation of enolizable ketones with Me$_3$SiCF$_2$H/CsF/HMPA was developed by Radchenko and co-workers. However, the yields are only moderate (see Ref. [7f]). In addition, both our group and that of Radchenko (see Ref. [7f]) were not able to reproduce Tyutyanov’s results of efficient difluoromethylation of enolizable ketones with Me$_3$SiCF$_2$H (see Ref. [7c]).


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Hail to the crown: A pentacoordinate bis(difluoromethyl)silicate anion [Me$_3$Si(CF$_2$H)$_2$]$^-$ is observed for the first time through the activation of Me$_3$SiCF$_2$H with CsF (or tBuOCs) and 18-crown-6. Study on its reactivity leads to the discovery and development of an efficient, catalytic nucleophilic difluoromethylation of enolizable ketones by tuning the counter-ion effect.