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Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of *gem*-difluorinated cyclopropenes and cyclopropanes†

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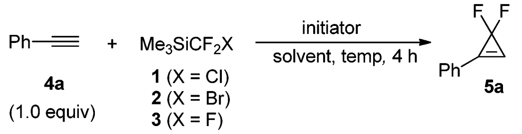
A chloride ion-catalyzed generation of difluorocarbene from a relatively non-toxic and inexpensive precursor, Me_3SiCF_2Cl (1), under mild and neutral conditions leads to an efficient preparation of *gem*-difluorocyclopropenes and difluorocyclopropanes through [2 + 1] cycloaddition reactions with alkynes and alkenes, respectively.

A selective introduction of fluorine atom(s) or fluorinated moieties into organic molecules often leads to a profound change in their physical, chemical and biological activities.[1,2] Over the past three decades, considerable efforts have been devoted to the development of efficient and practically useful fluorination and fluoroalkylation methods,[2] among which the difluoromethylenation reactions with difluorocarbene or difluorocarbenoid species have drawn much attention.[1a,3,4] Difluorocarbene (:CF_2, with a singlet ground state) is the most stable dihalocarbene owing to the interaction of the lone pairs of its fluorine substituents with the carbene center.[3] Typical synthetic applications of difluorocarbene include: (a) homocoupling at very high temperature to produce tetrafluoroethylene (TFE), an important industrial process;[5] (b) reaction with oxygen-, nitrogen-, sulfur-, phosphorous- and carbon-nucleophiles to give difluoromethylated products; and (c) undergoing [2 + 1] cycloaddition with alkynes or alkenes.[3] While the first two types of reactions can be achieved by using $CHClF_2$, $ClCF_2COONa$, or other difluorocarbene reagents,[5,6] the third class of reaction is generally more difficult in terms of substrate scope and efficiency.[3] Sodium halodifluoroacetate,[7] $PhHgCF_3$ (Seyferth reagent),[4f,k,8] $FSO_2CF_2CO_2SiMe_3$,[4l,m] Ph_3P/CF_2Br_2[9] and Zn/CF_2Br_2[10] are among the most commonly used reagents for this [2 + 1] cycloaddition reaction. However, these reagents suffer from disadvantages of high toxicity, harsh reaction conditions and slow addition techniques, and/or low product yields. Herein, we report a remarkable chloride ion-catalyzed generation of difluorocarbene from Me_3SiCF_2Cl and its efficient cycloaddition to alkynes and alkenes.

We have shown that $PhCOCF_2Cl$,[4i] $PhSO_2CF_2Cl$,[4h] and $PhSO(NTs)CF_2H$[4a] can act as difluorocarbene reagents under basic conditions for difluoromethylation of *O*-, *N*-, *S*-, or *C*-nucleophiles. However, these reagents were found to be incapable of undergoing [2 + 1] cycloaddition reactions with alkynes or alkenes. By realizing that the key to a successful difluorocarbene reagent for a [2 + 1] reaction requires the generation of :CF_2 species under *non-basic* conditions and at sufficiently high temperature,[3b,11] we became interested in developing Me_3SiCF_2Cl (**1**) as a new, relatively nontoxic and convenient difluorocarbene reagent. **1** was previously used as a nucleophilic chlorodifluoromethylating agent for carbonyl compounds,[12] but its application as a difluorocarbene reagent has never been reported.

At the onset of our studies, we examined the reactions between **1** and alkynes, by using phenylacetylene (**4a**) as a

Table 1 Survey of reaction conditions



Entry[a]	Me_3SiCF_2X (equiv.)[b]	Solvent	Initiator (mol%)[c]	Temp/ °C	Yield (%)[d]
1	**1** (1.5)	THF or toluene	None	110	0[e]
2	**1** (1.5)	THF	*n*-Bu_4NF (110)	110	0[f]
3	**1** (1.5)	THF	*n*-Bu_4NF (2)	110	39
4	**1** (1.5)	THF	*n*-Bu_4NCl (2)	110	39
5	**1** (1.5)	THF	NaCl	110	0[e]
6	**1** (1.5)	CH_3CN	*n*-Bu_4NCl (2)	110	71
7	**1** (1.5)	Toluene	*n*-Bu_4NCl (2)	110	79
8	**1** (1.5)	Toluene	*n*-Bu_4NCl (2)	110	63
9	**2** (1.5)	Toluene	*n*-Bu_4NCl (2)	110	67
10	**3** (1.5)	Toluene	*n*-Bu_4NCl (2)	110	0[e]
11	**1 (2.0)**	**Toluene**	***n*-Bu_4NCl (2)**	**110**	**91**
12	**1** (2.0)	Toluene	*n*-Bu_4NF (2)	110	82
13	**1** (2.0)	Toluene	*n*-Bu_4NF (110)	110	0[f]
14	**1** (2.0)	Toluene	*n*-Bu_4NCl (2)	25	0[e]
15	**1** (2.0)	Toluene	*n*-Bu_4NCl (2)	80	53[g]

[a] 110 °C for 4 h. [b] Relative to **4a**. [c] Relative to Me_3SiCF_2X. [d] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [e] The Me_3SiCF_2X reagent was recovered. [f] CF_3H and Me_3SiF were detected as the major products. [g] **1** was partly recovered.

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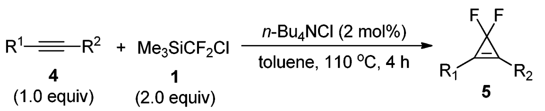
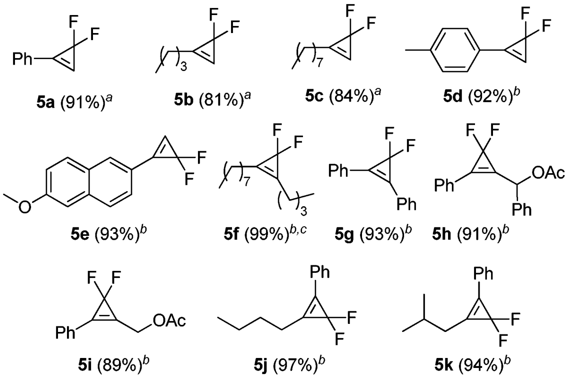
model substrate (Table 1). It was found that the reaction between **1** and **4a** could not proceed in the absence of a Lewis base initiator (entry 1). When an excess amount of *n*-Bu$_4$NF was added to the THF solution of **1** and **4a**, a facile reaction took place resulting in the formation of CF$_3$H and Me$_3$SiF as the major products,[13] but no **5a** was formed (entry 2). When the amount of *n*-Bu$_4$NF was reduced to 2 mol%, the formation of **5a** in 39% yield was observed (entry 3). It was most surprising that, even a catalytic amount (2 mol%) of *n*-Bu$_4$NCl can initiate this reaction (entry 4). Sodium chloride (NaCl) was incapable of initiating the reaction probably owing to its insolubility in THF (entry 5), while *n*-Bu$_4$NBr (2 mol%) was also able to initiate the reaction (entry 8). Toluene was found to be a better solvent than THF and acetonitrile (entries 4, 6 and 7). Interestingly, it was found that Me$_3$SiCF$_2$Br (**2**) could also serve as a difluoromethylenation reagent with slightly lower yield, while Me$_3$SiCF$_3$ was found to be inert under the same reaction conditions (entries 9 and 10). Furthermore, when toluene was used as a solvent, a catalytic amount of *n*-Bu$_4$NF (2 mol%) could efficiently initiate the reaction (entry 12), while an overdose of *n*-Bu$_4$NF (110 mol%) led to a complete failure (entry 13). To examine the temperature effect, we found that *n*-Bu$_4$NCl could not initiate the reaction at 25 °C (entry 14), and only a moderate yield of **5a** (53%) was observed when the reaction was performed at 80 °C (entry 15). The optimal yield of **5a** (91%) was obtained when the reaction was performed at 110 °C in toluene with a reactant ratio **4a** : **1** : *n*-Bu$_4$NCl = 1.0 : 2.0 : 0.04 (entry 11).

As shown in Table 2, with the use of a catalytic quantity of *n*-Bu$_4$NCl (2 mol%), **1** was found to react with a variety of structurally diverse alkynes. This method was amenable to both alkyl- and aryl-substituted alkynes, and in most cases, excellent yields were obtained. It should be mentioned that in the case of tetradec-5-yne (**4f**), the reaction at 110 °C resulted in a complete decomposition of product **5f**; however, when we performed the reaction at 80 °C for 4 h, product **5f** was obtained in almost quantitative yield (Table 2).

Encouraged by the above results, we further extended our method to alkenes. After a quick optimization of reaction conditions, we chose THF as a solvent and used 3 equiv. of **1** for most alkenes **6** (Table 3). It was found that the reaction not only worked for electron-rich alkenes (see **7a–d**), but also worked well with many mono-substituted alkenes (see **7e–j**). Among the mono-substituted alkenes, aryl-substituted alkenes generally gave higher yields (**7e** and **7f**) than alkyl-substituted ones (**7g–j**). It is remarkable that for the alkene bearing a nucleophilic phenoxyl group, difluorocyclopropane **7h** was also obtained in useful yield (56%).

Table 2 [2 + 1] Cycloaddition between **1** and alkynes **4**

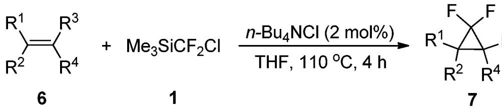


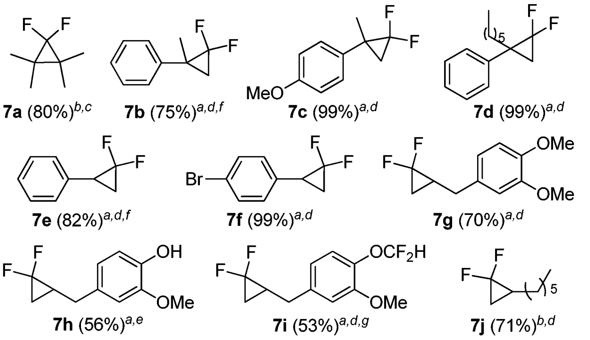


5a (91%)[a]
5b (81%)[a]
5c (84%)[a]
5d (92%)[b]
5e (93%)[b]
5f (99%)[b,c]
5g (93%)[b]
5h (91%)[b]
5i (89%)[b]
5j (97%)[b]
5k (94%)[b]

[a] Determined by ^{19}F NMR using PhCF$_3$ as an internal standard. [b] Isolated yield. [c] The reaction temperature was 80 °C (rather than 110 °C).

Table 3 [2 + 1] Cycloaddition between **1** and alkynes **6**





7a (80%)[b,c]
7b (75%)[a,d,f]
7c (99%)[a,d]
7d (99%)[a,d]
7e (82%)[a,d,f]
7f (99%)[a,d]
7g (70%)[a,d]
7h (56%)[a,e]
7i (53%)[a,d,g]
7j (71%)[b,d]

[a] Isolated yield. [b] Determined by ^{19}F NMR. [c] 2.0 equiv. of **1** was used (relative to **6**). [d] 3.0 equiv. of **1** was used. [e] 4.0 equiv. of **1** was used. [f] Low yield due to volatility of the product. [g] Toluene was used as the solvent.

Density functional theory (DFT) calculations were conducted to evaluate plausible pathways and to examine the role of Cl$^-$ and the fate of **1** (Fig. 1).[14] The process of single electron transfer from Cl$^-$ to **1** to yield Cl$^\bullet$ and **1**$^{\bullet-}$ radical anion was ruled out due to a large calculated Δ*G* of 130.5 kcal mol^{-1}. When the solvent effect is considered using the PCM method, unlike in the gas phase, a stationary point for a pentacovalent silicate anion (Cl–Me$_3$Si–CF$_2$Cl$^-$) could not be located, but an S$_N$2-like transition state (**10**) was identified instead with an activation free energy of 26.2 kcal mol^{-1}. Transition state **10** subsequently led to the formation of Me$_3$SiCl and the chlorodifluoromethyl anion **11**.[15] Anion **11** might react with **6a** in two pathways: (A) elimination of a Cl$^-$ anion to form the difluorocarbene

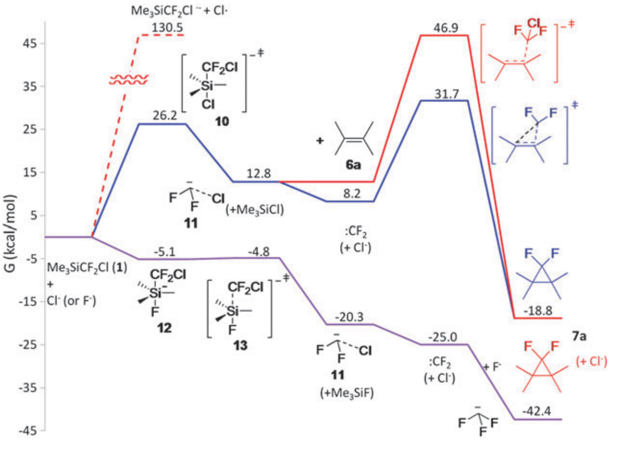


Fig. 1 Energy profile of possible reaction pathways.

intermediate for a [2 + 1] cycloaddition reaction with **6a** as shown in blue, and (B) direct addition to **6a** followed by the production of **7a** and Cl^- without the participation of the difluorocarbene intermediate as shown in red. In pathway A, the formation of $:CF_2$ from anion **11** was found to proceed without an energy barrier. This is consistent with the observation of an elongated C–Cl bond of 2.560 Å in **11**, indicative of a weak interaction and the tendency to lose a Cl^-. Difluorocarbene could then add to **6a** with an overall activation free energy of 31.7 kcal mol^{-1} to generate product **7a**, a process recently well documented by Nagase *et al.*[16a] While this activation free energy may seem excessive, it is indeed in good agreement with those reported in literature[16] and consistent with the required reaction temperatures in our experiments. In comparison, the direct addition pathway B resulted in a much higher overall energy barrier of 46.9 kcal mol^{-1}, and is thus unfavorable. Upon addition of F^- to **1**, in contrast to Cl^-, a pentacovalent fluorosilicate anion (**12**) can be formed with a ΔG of -5.1 kcal mol^{-1}, presumably because the Si–F bond (129 kcal mol^{-1}) is much stronger than the Si–Cl bond (109 kcal mol^{-1}).[17] Intermediate **12** can then undergo the elimination of anion **11** *via* transition state **13** with a small energy barrier of 0.3 kcal mol^{-1}. In the presence of excess F^-,: CF_2 generated by the elimination of Cl^- from **11** will be quenched by F^- to afford CF_3^-, which will eventually be protonated to give CF_3H (shown in purple, Fig. 1).

Based on the above results, we propose that a chloride ion-catalyzed generation of difluorocarbene from **1** plays an important role for the success of the cycloaddition reaction (Scheme 1). A catalytic amount of soluble chloride ion source Cl^- could react with **1** to release Me_3SiCl and chlorodifluoromethyl anion **11**,[15] which should readily undergo α-elimination of a chloride ion to give a singlet difluorocarbene species, reacting with alkynes or alkenes *via* a [2 + 1] cyclization process to give the corresponding products. The resulting chloride ion can enter into the catalytic cycle to activate another Me_3SiCF_2Cl molecule.

In conclusion, we have demonstrated a novel methodology for the chloride ion-catalyzed generation of difluorocarbene from a relatively nontoxic precursor, Me_3SiCF_2Cl, under mild and neutral conditions to prepare *gem*-difluorocyclopropenes and difluorocyclopropanes through [2 + 1] cycloaddition reactions with alkynes and alkenes, respectively. The crucial role of Cl^- is identified to only allow the formation of difluorocarbene at a moderately elevated temperature at which the [2 + 1] cycloaddition reactions can proceed. The extension of the scope of potential applications using this novel approach is currently underway in our laboratories and will be reported in due course.

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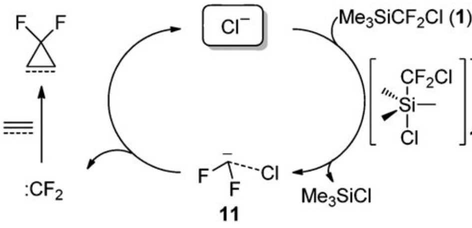

Scheme 1 Proposed reaction mechanism.

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