

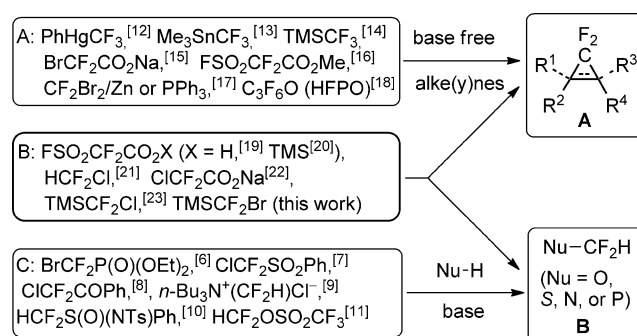


# Synthesis of *gem*-Difluorocyclopropa(e)nes and O-, S-, N-, and P-Difluoromethylated Compounds with TMSCF<sub>2</sub>Br\*\*

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Selective incorporation of fluorine atoms or fluorinated moieties into organic molecules has become a routine and powerful strategy in drug design and new functional-material development.<sup>[1]</sup> Among various fluorinated moieties that are employed to modify the property of a molecule, difluoromethylene (-CF<sub>2</sub>-) and difluoromethyl (-CF<sub>2</sub>H) groups are two of the most prevailing ones.<sup>[1,2]</sup> The past decade has witnessed an increasing demand for structurally diverse *gem*-difluorocyclopropa(e)nes (**A**) and heteroatom difluoromethyl compounds (**B**).<sup>[3]</sup> Although these compounds can be synthesized in various ways,<sup>[4,5]</sup> the difluoromethylation of alkenes/alkynes and difluoromethylation of heteroatom nucleophiles with a difluorocarbene reagent are the most widely used approaches.<sup>[1a]</sup> On one hand, the reactions of difluorocarbene with all but the most electron-rich alkynes/alkenes usually proceed at sufficiently high temperatures to overcome their substantial activation barriers.<sup>[4a]</sup> On the other hand, the reactions of difluorocarbene with heteroatom nucleophiles are relatively insensitive to the reaction temperatures. However, an alkaline base (such as KOH) is usually needed to activate the pronucleophiles (Nu-H) by deprotonation.<sup>[6–11]</sup> These interesting and unique features of difluorocarbene chemistry have led to the extensive studies of various reagents which are suitable to generate difluorocarbene under various conditions (Scheme 1).

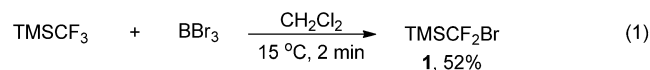
However, a major limitation of most of the difluorocarbene sources is that they focus on only one type of reaction, either [2+1] cycloaddition with alkenes/alkynes under non-basic conditions (Category A)<sup>[12–18]</sup> or  $\alpha$ -addition with Nu-H under basic conditions (Category C).<sup>[6–11]</sup> Although difluorocarbene generated from FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>H<sup>[19]</sup> and FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>TMS (TFDA; Category B)<sup>[20]</sup> under nonbasic conditions is reactive towards both alkenes/alkynes and Nu-H, the synthesis of difluoromethyl compounds with these reagents is subject to low yields<sup>[19]</sup> or narrow substrate scope.<sup>[20b–d]</sup> As the most commonly used reagent for hetero-



**Scheme 1.** Examples of difluorocarbene sources and their application. HFPO = hexafluoropropylene oxide, TMS = trimethylsilyl, Ts = tosyl.

oatom difluoromethylation, HCF<sub>2</sub>Cl (Category B) itself is an ozone-depleting substance (ODS) and its [2+1] cycloaddition only works with electron-rich alkenes.<sup>[21]</sup> Sodium chlorodifluoroacetate (Category B) has found practical applications in both *gem*-difluorocyclopropanation (usually at 180 °C)<sup>[22a,b]</sup> and O and N difluoromethylation (> 80 °C).<sup>[22c,d]</sup> However, the reactions suffer from disadvantages such as high temperatures or large excess of reagent. Although TMSCF<sub>2</sub>Cl is arguably one of the most versatile difluorocarbene reagents,<sup>[23]</sup> its preparation from ozone-depleting BrCF<sub>2</sub>Cl<sup>[24]</sup> makes its wide application less attractive. Therefore, the development of an operationally simple and environmentally benign difluorocarbene precursor which is effective with a broad substrate scope under relatively mild conditions is highly desirable. Herein, we report the use of (bromodifluoromethyl)trimethylsilane (TMSCF<sub>2</sub>Br; **1**)<sup>[25]</sup> as a general difluorocarbene source for the difluoromethylation of alkenes/alkynes initiated by a bromide salt as well as the difluoromethylation of O-, S-, N-, and P-nucleophiles promoted by the alkaline bases.

Our research started with the development of a Freon-free method to prepare TMSCF<sub>2</sub>Br (**1**). We found that **1** could be obtained by an extremely fast halogen-exchange reaction between TMSCF<sub>3</sub> (Ruppert–Prakash reagent) and BBr<sub>3</sub>. Meanwhile, dibromofluoro- and tribromomethylated silanes were also produced in varying yields under different reaction conditions. TMSCF<sub>2</sub>Br (**1**) was isolated in 52 % yield by reacting 1.0 equivalent of TMSCF<sub>3</sub> and 0.4 equivalent of BBr<sub>3</sub> at 15 °C for 2 minutes [Eq. (1)]. Prolonging reaction time could result in a decrease of the yield of **1**. Moreover, heating the mixture of *N*-bromosuccinimide (NBS)<sup>[26]</sup> and TMSCF<sub>2</sub>H



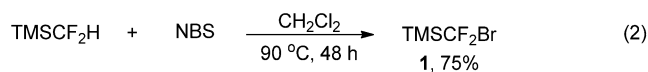
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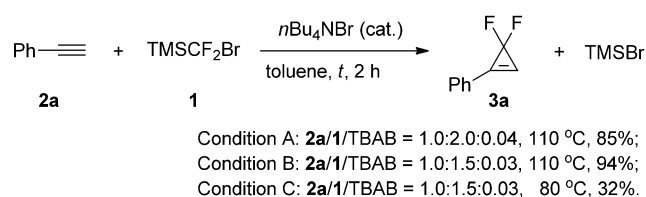
[\*\*] Support of our work by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (20825209 and 21202189), and the Chinese Academy of Sciences is gratefully acknowledged.  
TMS = trimethylsilyl.

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could also afford **1** in 75 % yield [Eq. (2)].<sup>[27]</sup> However, TMSCF<sub>2</sub>Cl could not be prepared using similar methods because of the sluggish reaction between TMSCF<sub>3</sub> and BCl<sub>3</sub>, and the undesired chlorination of the methyl group (CH<sub>3</sub>) in TMSCF<sub>2</sub>H by *N*-chlorosuccinimide (NCS).



We first carried out the difluoromethylenation of C–C multiple bonds with **1**. In a previous report, the unoptimized reaction between the alkyne **2a** and **1** catalyzed by tetrabutylammonium chloride gave the *gem*-difluorocyclopropene **3a** in only 67 % yield (based on <sup>19</sup>F NMR spectroscopy).<sup>[23a]</sup> In this research, we observed that tetrabutylammonium bromide (TBAB) was a better catalyst (Scheme 2; for details, see the

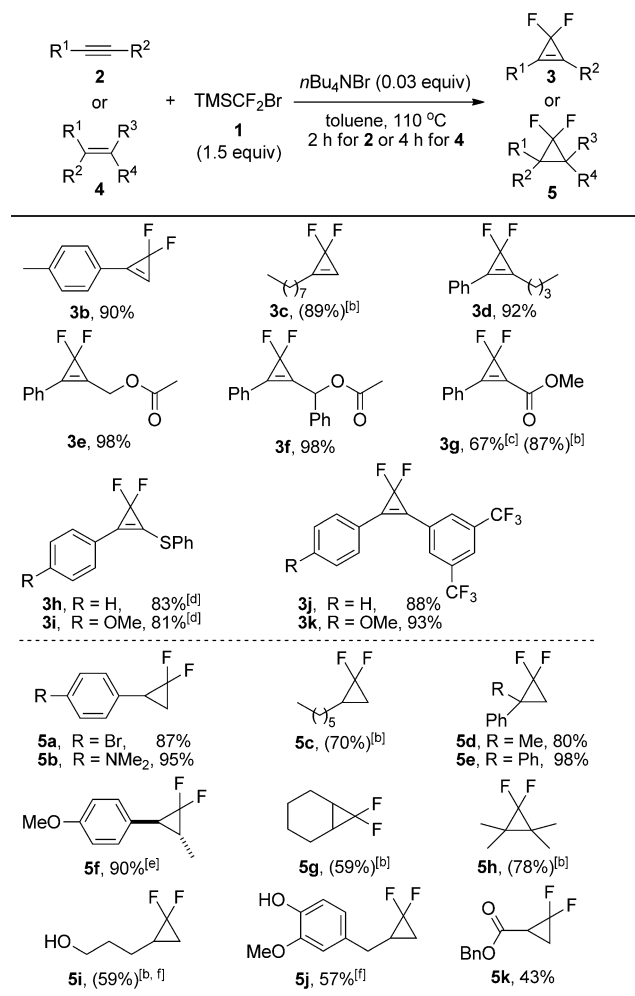


**Scheme 2.** Screen of reaction conditions for the difluoromethylenation of alkyne **2a** using **1**.

Supporting Information). When the reaction employing 2.0 equivalents of **1** was performed in a sealed tube at 110 °C for 2 hours, **3a** was obtained in 85 % yield (Condition A). A decrease of the amount of **1** from 2.0 to 1.5 equivalents gave a higher yield of **3a** (Condition B). The relatively lower yield of **3a** with 2.0 equivalents of **1** probably arose from the formation of the unstable bicyclobutane through an additional [2+1] cycloaddition.<sup>[14b]</sup> A comparison of the reaction temperatures (Conditions B and C) showed that a high temperature is beneficial for this reaction. Finally, we chose Condition B to perform most of the reactions with alkynes.

As shown in Table 1, **1** could react with a variety of structurally diverse alkynes and alkenes. Both mono- and disubstituted alkynes were readily converted into *gem*-difluorinated cyclopropenes (**3b–k**) in high yields. Not only alkynes with electron-donating groups, but also those with electron-withdrawing groups could undergo the reactions. Note that propiolates and alkynyl sulfides are also reactive under these reaction conditions (**3g–i**), and this had never been demonstrated in the previously reported difluoromethylenation of alkynes. Although alkenes are known to be less reactive than alkynes towards difluorocarbene,<sup>[28]</sup> our protocol could be extended to various alkenes by simply prolonging the reaction time to 4 hours. The [2+1] cycloaddition of the aryl- and alkyl-substituted alkenes with difluorocarbene proceeded smoothly, thus affording the *gem*-difluorocyclopropanes **5a–j** in moderate to excellent yields. In the cases of alkenes bearing an OH, only difluoromethylenation of the C=C bond was observed (**5i** and **5j**). This result indicates that the OH is inert towards difluoro-

**Table 1:** Difluoromethylenation of various alkynes **2** and alkenes **4** using **1**.<sup>[a]</sup>

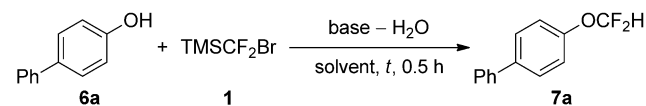


[a] All reactions were performed on 0.5 mmol scale in a pressure tube. Yields given refer to the yields of isolated product. [b] Yields within parentheses were determined by <sup>19</sup>F NMR spectroscopy using an internal standard. [c] Yield of product after recrystallization. [d] Reactions were performed at 80 °C. [e] d.r. > 99:1. [f] Used 2.5 equiv of **1**.

carbene under the neutral conditions, wherein the nucleophilic RO<sup>−</sup> could not be generated. It is remarkable that the electron-deficient alkene such as benzyl acrylate was also successfully difluoromethylenated to give **5k** in 43 % yield.

Subsequently, we investigated the difluoromethylation of heteroatom nucleophiles with **1** by using the phenol **6a** as a model substrate to optimize the reaction conditions (Table 2). Initial results with CH<sub>3</sub>CN as the solvent and KOH aqueous solution as the base showed that **1** was reactive towards **6a** even at 0 °C, and the reaction was complete within 0.5 hours (entries 1–3). Such a low reaction temperature and short reaction period indicate that this protocol would tolerate base-sensitive functional groups. A screening of the solvents revealed that CH<sub>2</sub>Cl<sub>2</sub> was the best choice among various solvents (entries 4–11). As for the base, in addition to KOH, NaOH was also suitable for this reaction (entry 12). However, K<sub>2</sub>CO<sub>3</sub> was not efficient to activate **1** in a short period of time because of its weak basicity (entry 13). Finally,

**Table 2:** Screen of reaction conditions for the difluoromethylation of phenol **6a** using **1**.<sup>[a]</sup>



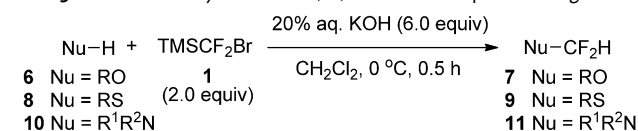
| Entry | <b>6a</b> / <b>1</b> /Base <sup>[b]</sup> | Base <sup>[c]</sup>            | Solvent                         | T [°C] | Yield [%] <sup>[d]</sup> |
|-------|-------------------------------------------|--------------------------------|---------------------------------|--------|--------------------------|
| 1     | 1.0:2.5:8.0                               | KOH                            | CH <sub>3</sub> CN              | 50     | 44 (> 99)                |
| 2     | 1.0:2.5:8.0                               | KOH                            | CH <sub>3</sub> CN              | RT     | 40 (> 99)                |
| 3     | 1.0:2.5:8.0                               | KOH                            | CH <sub>3</sub> CN              | 0      | 63 (> 99)                |
| 4     | 1.0:2.5:8.0                               | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 84 (> 97)                |
| 5     | 1.0:2.5:8.0                               | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | RT     | 78 (> 99)                |
| 6     | 1.0:2.5:8.0                               | KOH                            | PhCH <sub>3</sub>               | 0      | 74 (95)                  |
| 7     | 1.0:2.5:8.0                               | KOH                            | DCE                             | 0      | 77 (93)                  |
| 8     | 1.0:2.5:8.0                               | KOH                            | Et <sub>2</sub> O               | 0      | 65 (> 99)                |
| 9     | 1.0:2.5:8.0                               | KOH                            | THF                             | 0      | 28 (> 99)                |
| 10    | 1.0:2.5:8.0                               | KOH                            | DMF                             | 0      | 0 (> 99)                 |
| 11    | 1.0:2.5:8.0                               | KOH                            | DME                             | 0      | 23 (> 99)                |
| 12    | 1.0:2.5:8.0                               | NaOH                           | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 84 (78)                  |
| 13    | 1.0:2.5:8.0                               | K <sub>2</sub> CO <sub>3</sub> | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 28 (34)                  |
| 14    | 1.0:1.5:8.0                               | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 77 (> 99)                |
| 15    | 1.0:2.0:3.0                               | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 66 (82)                  |
| 16    | 1.0:2.0:6.0                               | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 83 (> 97)                |
| 17    | 1.0:2.0:10.0                              | KOH                            | CH <sub>2</sub> Cl <sub>2</sub> | 0      | 85 (> 99)                |

[a] Reactions were performed on 0.5 mmol scale. [b] Molar ratio. [c] Concentration of the bases used: KOH (20 wt%); NaOH (15 wt%); K<sub>2</sub>CO<sub>3</sub> (38 wt%). [d] Yields were determined by <sup>19</sup>F NMR spectroscopy using PhCF<sub>3</sub> as an internal standard. Conversions of **1** are given within the parentheses. DME = 1,2-dimethoxyethane; DCE = 1,2-dichloroethane.

using a 20 % KOH aqueous solution as the base and CH<sub>2</sub>Cl<sub>2</sub> as the solvent, the optimal molar ratio of **6a**, **1**, and KOH was identified as 1.0:2.0:6.0 (entry 16).

With the optimized reaction conditions in hand (Table 2, entry 16), we studied the substrate scope of this heteroatom difluoromethylation (Table 3). The results for O nucleophiles showed that this reaction is compatible with both phenols and alcohols (**7b–r**). The difluoromethylation of mono- and multisubstituted phenols occurred in moderate to excellent yields and with high functional-group tolerance (**7b–n**). Both electron-rich functional groups such as ether (**7b** and **7e**), amide (**7m**), and alkenyl (**7n**), and electron-deficient ones such as nitro (**7c**), nitrile (**7d**), ester (**7i**), carbonyl (**7j** and **7r**), and aldehyde (**7k** and **7l**) are amenable to this reaction. The chemoselective reaction of difluorocarbene with OH rather than with the C=C bond (see **7n** and **7r**) indicates that the C=C bond is less reactive towards difluorocarbene under basic conditions, which is interesting especially when compared with the chemoselective reactions affording **5i** and **5j** (see Table 1). Furthermore, the difluoromethylation of a primary alcohol using **1** afforded the corresponding difluoromethyl ether in moderate yields (**7p** and **7q**). This protocol is suitable for the late-stage O difluoromethylation of complex molecules. (+)- $\delta$ -Tocopherol underwent the difluoromethylation reaction to give the difluoromethyl ether **7o** in 70 % yield. The secondary alcohol pregnenolone reacted to form **7r** in synthetically useful yields. The S difluoromethylation with **1** could also be achieved under similar reaction conditions (**9a–k**). Various aryl thiols with electron-donating or electron-

**Table 3:** Difluoromethylation of O-, S-, and N nucleophiles using **1**.<sup>[a]</sup>



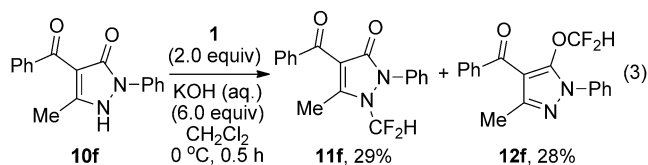
|                                                         |                                              |                                       |
|---------------------------------------------------------|----------------------------------------------|---------------------------------------|
| <p><b>7b</b>, 81%</p>                                   | <p><b>7c</b>, R = NO<sub>2</sub>, 91%</p>    | <p><b>7e</b>, 94%</p>                 |
| <p><b>7d</b>, R = CN, 95%</p>                           | <p><b>7f</b>, 53%</p>                        | <p><b>7g</b>, 57%</p>                 |
| <p><b>7i</b>, R = CO<sub>2</sub>Me, 93%</p>             | <p><b>7j</b>, R = Ac, 85%</p>                | <p><b>7m</b>, 58%</p>                 |
| <p><b>7k</b>, R = CHO, 70%</p>                          | <p><b>7l</b>, 74%</p>                        | <p><b>7n</b>, 87%</p>                 |
| <p><b>7o</b>, 70%</p>                                   | <p><b>7p</b>, (65%)<sup>[b]</sup></p>        | <p><b>7q</b>, 52%</p>                 |
| <p><b>7r</b>, (22%)<sup>[b]</sup> 42%<sup>[c]</sup></p> | <p><b>9a</b>, R = F, (91%)<sup>[b]</sup></p> | <p><b>9b</b>, R = Br, 97%</p>         |
| <p><b>9c</b>, R = NO<sub>2</sub>, 86%</p>               | <p><b>9d</b>, 99%</p>                        | <p><b>9e</b>, 99%</p>                 |
| <p><b>9f</b>, 96%</p>                                   | <p><b>9g</b>, 99%</p>                        | <p><b>9h</b>, 61%<sup>[d]</sup></p>   |
| <p><b>9i</b>, 99%</p>                                   | <p><b>9j</b>, 93%</p>                        | <p><b>9k</b>, (83%)<sup>[b]</sup></p> |
| <p><b>11a</b>, 38%</p>                                  | <p><b>11b</b>, 31%</p>                       | <p><b>11c</b>, 49%</p>                |
| <p><b>11d</b>, 81%</p>                                  | <p><b>11e</b>, 70%</p>                       | <p><b>11e'</b>, 25%</p>               |

[a] All reactions were performed on 0.5 mmol scale. Yields given refer to those of isolated products. [b] Yields within parentheses were determined by <sup>19</sup>F NMR spectroscopy using an internal standard. [c] Yield of isolated product when **1** (4.0 equiv) and KOH (10 equiv) were used. [d] The starting material was PhSO<sub>2</sub>Na.

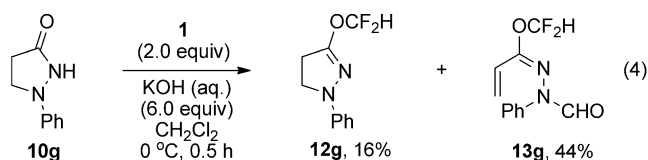
withdrawing substituents and alkyl thiols afforded difluoromethyl thioethers in good to excellent yields (**9a–e** and **9i–k**). The heteroarylthiols benzo[d]thiazole-2-thiol and 1-phenyl-

1*H*-tetrazole-5-thiol were difluoromethylated regioselectively at the S atoms (**9f** and **9g**). It is noteworthy that the sulfonates were also reactive substrates, for example, the reaction of phenylsulfonate gave the difluoromethyl sulfone **9h** in 61 % yield.

In contrast with the difluoromethylation of (thio)phenols and (thio)alcohols, the difluoromethylation of heterocyclic amines with **1** is more complicated. Although several imidazoles could undergo the reaction, the yields of the N-difluoromethyl compounds **11a–c** were only moderate (31–49 %; see Table 3). The low yields presumably arose from a further difluoromethylation of the desired products, thus forming unstable difluoromethyl ammonium salts. The reaction of 1*H*-benzo[*d*]-1,2,3-triazole (**10d**) and 5-phenyl-1*H*-tetrazole (**10e**) provided the N-difluoromethyl products in high yields. However, two separable regiomers, **11e** and **11e'**, were obtained in the latter case (see Table 3). In the case of the pyrazolone **10f**, both N- and O-difluoromethylation products **11f** and **12f**, respectively, were obtained when the reaction was conducted at 0 °C [Eq. (3)].<sup>[29]</sup> In the case of the



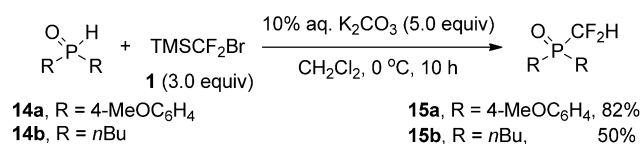
pyrazolidinone **10g**, the reaction at 0 °C not only gave the heterocyclic ether **12g**, but also the ring-opening product **13g** [Eq. (4)]. The formation of **13g** is proposed to proceed by



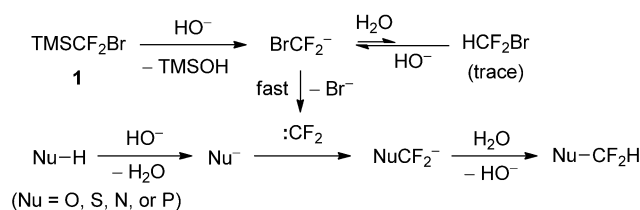
a Hofmann elimination of the 1-difluoromethyldihydropyrazolium salt of **12g** with subsequent hydrolysis of the N'-CF<sub>2</sub>H group (for details, see the Supporting Information).

To further extend the synthetic utility of **1**, we tested the reactivity of P nucleophiles. It was found that the phosphinite anions were less reactive than any other heteroatom nucleophile investigated. When a weak base K<sub>2</sub>CO<sub>3</sub> was used instead of KOH, the hydrolysis of difluorocarbene was minimized, and the reactions of the hydrophosphine oxides **14a** and **14b** proceeded smoothly, thus giving difluoromethyl phosphine oxides **15a** and **15b** in 82 and 50 % yield, respectively (Scheme 3).

Concerning the mechanism of the difluoromethylation of heteroatom nucleophiles with **1**, the reaction is believed to occur by an anionic chain reaction involving the addition of difluorocarbene to the nucleophile anion (Nu<sup>−</sup>) (Scheme 4).<sup>[28]</sup> The generation of difluorocarbene from **1** is postulated to proceed through initial desilylation with a base



**Scheme 3.** Difluoromethylation of the hydrophosphine oxides **14** using **1**.



**Scheme 4.** Proposed mechanism for difluoromethylation of heteroatom nucleophiles using **1**.

(such as HO<sup>−</sup>) and subsequent α elimination of a bromide ion. The protonation of the bromodifluoromethyl anion (BrCF<sub>2</sub><sup>−</sup>) at 0 °C should be much slower than its fragmentation to difluorocarbene, as was determined by the observation of only trace amounts (ca. 1 % based on <sup>19</sup>F NMR spectroscopy) of HCF<sub>2</sub>Br during the difluoromethylation of **6a**. The formed HCF<sub>2</sub>Br, if any, would also participate in the reaction in the presence of base.

In conclusion, we have developed a highly efficient method for the difluoromethylation of C–C multiple bonds and difluoromethylation of heteroatom nucleophiles with TMSCF<sub>2</sub>Br (**1**) as the single difluorocarbene source. This method allows *gem*-difluorocyclopropa(e)nes and O-, S-, N-, and P-difluoromethylated compounds to be prepared using very simple procedures. The bromide catalyzes the fragmentation of **1** at a higher temperature (110 °C) to generate difluorocarbene, which is reactive towards both electron-rich and electron-deficient alkynes and alkenes. Compared with the difluoromethylation protocols using the common reagent TFDA,<sup>[20]</sup> and the newly developed TMSCF<sub>3</sub><sup>[14]</sup> and FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>Me (MDFA),<sup>[16]</sup> this homogeneous reaction is much safer and more convenient for large-scale application because of the avoidance of the gaseous by-products. The hydroxyl-ion-promoted fragmentation of **1** at a lower temperature (0 °C) facilitates the difluoromethylation of (thio)phenols with broad functional-group tolerance. The mild reaction conditions of this reaction are also applicable for the difluoromethylation of (thio)alcohols, sulfonates, heterocyclic amines, and even hydrophosphine oxides. Since **1** is readily available from TMSCF<sub>3</sub> but more robust than the latter,<sup>[30]</sup> this new synthetic method is expected to find many applications in the synthesis of difluoromethylene- and difluoromethyl-containing compounds.

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**Keywords:** carbenes · cycloaddition · heterocycles · fluorine · synthetic methods

- [1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd ed., Wiley-VCH, Weinheim, **2013**; b) J.-P. Bégue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, **2008**; c) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, Chichester, **2009**; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369.
- [2] a) D. O'Hagan, Y. Wang, M. Skibinski, A. M. Z. Slawin, *Pure Appl. Chem.* **2012**, *84*, 1587–1595; b) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478; c) S. K. Ritter, *Chem. Eng. News* **2012**, *90*(9), 10–17; d) S. K. Ritter, *Chem. Eng. News* **2013**, *91*(8), 32–33.
- [3] A SciFinder search for the syntheses of *gem*-difluorocyclopropenes/anes showed that 235 references were published from 2003 to 2012, and it consists of 65 % of all the published references on this topic. For O-CF<sub>2</sub>H, S-CF<sub>2</sub>H, and N-CF<sub>2</sub>H compounds, the statistical results are 1732 (85 %), 72 (50 %), and 159 (66 %), respectively.
- [4] a) W. R. Dolbier, Jr., M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071–1098; b) M. Fedoryński, *Chem. Rev.* **2003**, *103*, 1099–1132.
- [5] a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827–856; b) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140–158.
- [6] Y. Zafrani, G. Sod-Moriah, Y. Segall, *Tetrahedron* **2009**, *65*, 5278–5283.
- [7] a) J. Zheng, Y. Li, L. Zhang, J. Hu, G. J. Meuzelaar, H.-J. Federsel, *Chem. Commun.* **2007**, 5149–5151; b) F. Wang, L. Zhang, J. Zheng, J. Hu, *J. Fluorine Chem.* **2011**, *132*, 521–528.
- [8] L. Zhang, J. Zheng, J. Hu, *J. Org. Chem.* **2006**, *71*, 9845–9848.
- [9] F. Wang, W. Huang, J. Hu, *Chin. J. Chem.* **2011**, *29*, 2717–2721.
- [10] W. Zhang, F. Wang, J. Hu, *Org. Lett.* **2009**, *11*, 2109–2122.
- [11] P. S. Fier, J. F. Hartwig, *Angew. Chem.* **2013**, *125*, 2146–2149; *Angew. Chem. Int. Ed.* **2013**, *52*, 2092–2095.
- [12] For examples, see: a) D. Seyferth, S. P. Hopper, K. V. Darragh, *J. Am. Chem. Soc.* **1969**, *91*, 6536–6537; b) I. Nowak, J. F. Cannon, M. J. Robins, *J. Org. Chem.* **2007**, *72*, 532–537.
- [13] For examples, see: a) D. Seyferth, H. Dertouzos, R. Suzuki, J. Y. P. Mui, *J. Org. Chem.* **1967**, *32*, 2980–2984; b) W. R. Cullen, M. C. Waldman, *Can. J. Chem.* **1969**, *47*, 3093–3098.
- [14] a) F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem.* **2011**, *123*, 7291–7295; *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157; b) P. W. Chia, D. Bello, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2013**, 49, 2189–2191.
- [15] K. Oshiro, Y. Morimoto, H. Amii, *Synthesis* **2010**, 2080–2084.
- [16] a) Q.-Y. Chen, *J. Fluorine Chem.* **1995**, *72*, 241–246; b) S. Eusterwiemann, H. Martinez, W. R. Dolbier, Jr., *J. Org. Chem.* **2012**, *77*, 5461–5466.
- [17] For examples, see: a) W. R. Dolbier, Jr., H. Wojtowicz, C. R. Burkholder, *J. Org. Chem.* **1990**, *55*, 5420–5422; b) D. J. Burton, D. G. Nae, *J. Am. Chem. Soc.* **1973**, *95*, 8467–8468.
- [18] For examples, see: a) P. B. Sargeant, *J. Org. Chem.* **1970**, *35*, 678–682; b) T. Huang, J. M. Messman, K. Hong, J. W. Mays, *J. Polym. Sci. Part A* **2001**, *50*, 338–345.
- [19] For examples on [2+1] cycloaddition and O, S, and N difluoromethylation under base-free conditions, see: a) Q.-Y. Chen, S.-W. Wu, *J. Org. Chem.* **1989**, *54*, 3023–3027; b) Q.-Y. Chen, S.-W. Wu, *J. Fluorine Chem.* **1989**, *44*, 433–440; c) M. Ando, T. Wada, N. Sato, *Org. Lett.* **2006**, *8*, 3805–3808.
- [20] For examples on [2+1] cycloaddition, see: a) W. R. Dolbier, Jr., et al., *J. Fluorine Chem.* **2004**, *125*, 459–469, and references therein; for examples on O difluoromethylation of ketones and amides, see: b) X. Cai, Y. Zhai, I. Ghiviriga, K. A. Abboud, W. R. Dolbier, Jr., *J. Org. Chem.* **2004**, *69*, 4210–4215; c) K. Fuchibe, Y. Koseki, T. Aono, H. Sasagawa, J. Ichikawa, *J. Fluorine Chem.* **2012**, *133*, 52–60; for a two-step synthesis of aryl difluoromethyl ethers from cyclic ketones, see: d) K. Fuchibe, Y. Koseki, H. Sasagawa, J. Ichikawa, *Chem. Lett.* **2011**, *40*, 1189–1191.
- [21] a) “Chlorodifluoromethane”: D. J. Burton, W. Qiu, A. Jończyk, A. Kowalkowska in *e-EROS Encyclopedia of Reagents for Organic Synthesis* (Ed.: R. A. Paquette), Wiley, **2010**, DOI: 10.1002/047084289X.rc090.pub2; b) Ref. [28].
- [22] For examples on [2+1] cycloaddition, see: a) J. M. Birchall, G. W. Cross, R. N. Haszeldine, *Proc. Chem. Soc. London* **1960**, 81–81; b) Y. Fujioka, H. Amii, *Org. Lett.* **2008**, *10*, 769–772; for examples on difluoromethylation, see: c) J. B. Sperry, K. Sutherland, *Org. Process Res. Dev.* **2011**, *15*, 721–725; d) Ref. [19c].
- [23] a) F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, *Chem. Commun.* **2011**, 47, 2411–2413; b) J. Hu, F. Wang, W. Zhang, **2009**, CN 101538193A.
- [24] V. Broicher, D. Geffken, *J. Organomet. Chem.* **1990**, *381*, 315–320.
- [25] For the use of **1** as a nucleophilic bromodifluoromethylation reagent, see: a) V. Broicher, D. Geffken, *Arch. Pharm.* **1990**, *323*, 929–931; during the progress of this work, Dilman and co-workers reported the use of **1** as the source of difluorocarbene or difluorocarbenoid species to prepare TMSCF<sub>2</sub>CN and RCF<sub>2</sub>ZnX: b) M. D. Kosobokov, A. D. Dilman, V. V. Levin, M. I. Struchkova, *J. Org. Chem.* **2012**, *77*, 5850–5855; c) V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2013**, *15*, 917–919.
- [26] T. Fuchikami, I. Ojima, *J. Organomet. Chem.* **1981**, *212*, 145–153.
- [27] For an alternative method using NaBr/H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>O<sub>2</sub>, see: Ref. [25b].
- [28] D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585–1632.
- [29] The structures of **12 f** and **12 g** were incorrectly assigned as N-difluoromethyl compounds in the literature. For details, see Refs. [7, 9, 10].
- [30] We found that, under the optimized reaction conditions used for heteroatom difluoromethylation with **1**, TMSCF<sub>3</sub> was readily hydrolyzed to CF<sub>3</sub>H and no desired product could be obtained.