Synthesis of *gem*-Difluorocyclopropa(e)nes and O-, S-, N-, and P-Difluoromethylated Compounds with TMSCF₂Br**

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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.^[1] Among various fluorinated moieties that are employed to modify the property of a molecule, difluoromethylene (-CF₂-) and difluoromethyl (-CF₂H) groups are two of the most prevailing ones.^[1,2] The past decade has witnessed an increasing demand for structurally diverse gemdifluorocyclopropa(e)nes (A) and heteroatom difluoromethyl compounds (B).^[3] Although these compounds can be synthesized in various ways,^[4,5] the difluoromethylenation of alkenes/alkynes and difluoromethylation of heteroatom nucleophiles with a difluorocarbene reagent are the most widely used approaches.^[1a] 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.^[4a] 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.^[6-11] 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 nonbasic conditions (Category A)^[12-18] or α -addition with Nu-H under basic conditions (Category C).^[6-11] Although difluorocarbene generated from FSO₂CF₂CO₂H^[19] and FSO₂CF₂CO₂TMS (TFDA; Category B)^[20] 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^[19] or narrow substrate scope.^[20b-d] As the most commonly used reagent for heter-

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oatom difluoromethylation, HCF₂Cl (Category B) itself is an ozone-depleting substance (ODS) and its [2+1] cycloaddition only works with electron-rich alkenes.^[21] Sodium chlorodifluoroacetate (Category B) has found practical applications in both gem-difluorocyclopropanation (usually at 180°C)^[22a,b] and O and N difluoromethylation (>80 °C).^[22c,d] However, the reactions suffer from disadvantages such as high temperatures or large excess of reagent. Although TMSCF₂Cl is arguably one of the most versatile difluorocarbene reagents,^[23] its preparation from ozone-depleting BrCF₂Cl^[24] 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 (TMSCF₂Br; 1)^[25] as a general difluorocarbene source for the difluoromethylenation 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 Freonfree method to prepare TMSCF₂Br (1). We found that 1 could be obtained by an extremely fast halogen–exchange reaction between TMSCF₃ (Ruppert–Prakash reagent) and BBr₃. Meanwhile, dibromofluoro- and tribromomethylated silanes were also produced in varying yields under different reaction conditions. TMSCF₂Br (1) was isolated in 52% yield by reacting 1.0 equivalent of TMSCF₃ and 0.4 equivalent of BBr₃ 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)^[26] and TMSCF₂H

$$\mathsf{TMSCF}_3 + \mathsf{BBr}_3 \xrightarrow{\mathsf{CH}_2\mathsf{Cl}_2} \mathsf{TMSCF}_2\mathsf{Br} \tag{1}$$

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could also afford **1** in 75% yield [Eq. (2)].^[27] However, TMSCF₂Cl could not be prepared using similar methods because of the sluggish reaction between TMSCF₃ and BCl₃, and the undesired chlorination of the methyl group (CH₃) in TMSCF₂H by *N*-chlorosuccinimide (NCS).

TMSCF₂H + NBS
$$\xrightarrow{CH_2Cl_2}$$
 TMSCF₂Br (2)
90 °C, 48 h 1, 75%

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 ¹⁹F NMR spectroscopy).^[23a] 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.^[14b] 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 gemdifluorinated 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,^[28] 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 $\mathbf{1}^{[a]}$



[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 ¹⁹F 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^- 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 CH₃CN 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 CH₂Cl₂ 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, K₂CO₃ was not efficient to activate **1** in a short period of time because of its weak basicity (entry 13). Finally,

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Table 2: Screen of reaction conditions for the difluoromethylation of phenol 6a using 1.^[a]

	OH + TMSC	CF ₂ Br —	base – H ₂ O olvent. <i>t</i> . 0.5 h	->	OCF ₂ H
Ph	6a -	1		Ph	~7a
Entry	6a/1/Base ^[b]	Base ^[c]	Solvent	<i>T</i> [°C]	Yield [%] ^[d]
1	1.0:2.5:8.0	кон	CH₃CN	50	44 (>99)
2	1.0:2.5:8.0	КОН	CH₃CN	RT	40 (>99)
3	1.0:2.5:8.0	КОН	CH₃CN	0	63 (>99)
4	1.0:2.5:8.0	КОН	CH_2CI_2	0	84 (>97)
5	1.0:2.5:8.0	КОН	CH_2CI_2	RT	78 (>99)
6	1.0:2.5:8.0	КОН	PhCH₃	0	74 (95)
7	1.0:2.5:8.0	КОН	DCE	0	77 (93)
8	1.0:2.5:8.0	КОН	Et ₂ O	0	65 (>99)
9	1.0:2.5:8.0	КОН	THF	0	28 (>99)
10	1.0:2.5:8.0	КОН	DMF	0	0 (>99)
11	1.0:2.5:8.0	КОН	DME	0	23 (>99)
12	1.0:2.5:8.0	NaOH	CH ₂ Cl ₂	0	84 (78)
13	1.0:2.5:8.0	K ₂ CO ₃	CH_2CI_2	0	28 (34)
14	1.0:1.5:8.0	КОН	CH_2CI_2	0	77 (>99)
15	1.0:2.0:3.0	КОН	CH ₂ Cl ₂	0	66 (82)
16	1.0:2.0:6.0	КОН	CH ₂ Cl ₂	0	83 (>97)
17	1.0:2.0:10.0	кон	CH ₂ Cl ₂	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%); K₂CO₃ (38 wt%). [d] Yields were determined by ¹⁹F NMR spectroscopy using PhCF₃ 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_2Cl_2 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. (+)- δ -Tocopherol underwent the difluoromethylation reaction to give the difluoromethyl ether 70 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-



[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 ¹⁹F 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 PhSO₂Na.

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-

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1*H*-tetrazole-5-thiol were difluoromethylated regioselectively at the S atoms (9 f and 9 g). It is noteworthy that the sulfinates were also reactive substrates, for example, the reaction of phenylsulfinate gave the difluoromethyl sulfone 9 h 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 Ndifluoromethyl compounds **11** a-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, **11 e** and **11 e'**, were obtained in the latter case (see Table 3). In the case of the pyrazolone **10 f**, both N- and O-difluoromethylation products **11 f** and **12 f**, respectively, were obtained when the reaction was conducted at 0°C [Eq. (3)].^[29] 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 **12 g** with subsequent hydrolysis of the N'-CF₂H 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_2CO_3 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^-) (Scheme 4).^[28] 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⁻) and subsequent α elimination of a bromide ion. The protonation of the bromodifluoromethyl anion (BrCF₂⁻) 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 ¹⁹F NMR spectroscopy) of HCF₂Br during the difluoromethylation of **6a**. The formed HCF₂Br, if any, would also participate in the reaction in the presence of base.

In conclusion, we have developed a highly efficient method for the difluoromethylenation of C-C multiple bonds and difluoromethylation of heteroatom nucleophiles with TMSCF₂Br (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 difluoromethylenation protocols using the common reagent TFDA,^[20] and the newly developed TMSCF₃^[14] and FSO₂CF₂CO₂Me (MDFA),^[16] 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 diffuoromethylation of (thio)phenols with broad functional-group tolerance. The mild reaction conditions of this reaction are also applicable for the difluoromethylation of (thio)alcohols, sulfinates, heterocyclic amines, and even hydrophosphine oxides. Since 1 is readily available from TMSCF₃ but more robust than the latter,^[30] this new synthetic method is expected to found many applications in the synthesis of difluoromethylene- and difluoromethyl-containing compounds.

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- [30] We found that, under the optimized reaction conditions used for heteroatom difluoromethylation with 1, TMSCF₃ was readily hydrolyzed to CF₃H and no desired product could be obtained.

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Communications

Synthetic Methods

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Synthesis of gem-

Difluorocyclopropa(e)nes and O-, S-, N-, and P-Difluoromethylated Compounds with $\mathsf{TMSCF}_2\mathsf{Br}$



Two-in-one: Me₃SiCF₂Br is an efficient difluorocarbene source and is compatible with both neutral and aqueous basic conditions. Bromide-ion-initiated [2+1] cycloaddition with alkenes/alkynes and hydroxide-ion-promoted α -addition with (thio)phenols, (thio)alcohols, sulfinates, heterocyclic amines, and H-phosphine oxides give the corresponding *gem*-difluorinated compounds with broad functional-group tolerance.

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