Difluoromethylation of alcohols with TMSCF₂Br in water: A new insight into the generation and reactions of difluorocarbene in a two-phase system

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ABSTRACT

Although many difluorocarbene-involved reactions can be performed in the presence of water, the reaction of difluorocarbene using water as the only reaction medium is rare. By using TMSCF₂Br as a unique difluorocarbene reagent and KHF₂ as a mild activator, the difluoromethylation of liquid alcohols in water is described. This research not only develops an environmentally benign process for the synthesis of difluoromethyl ethers, but also provides a new insight into the generation and reactions of difluorocarbene in an oil-water two-phase system.

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1. Introduction

Difluorocarbene is an important intermediate that has been widely used in the synthesis of difluoromethyl (thio)ethers, *gem*-difluorocyclopropa(e)nes, and *gem*-difluoroalkenes (including tetrafluoroethene) [1,2]. More recently, it has also found applications in difluoromethylation of carbon acids [3], ^{18}F-labeled trifluoromethylation [4], metal-mediated fluoroalkylation [5] and fluorocarbon homologation [6], and difluoromethylenative coupling reactions [7], among others [8]. Due to the combined inductive effect of fluorine (destabilization effect) and π-donation from the fluorine to the carbon (stabilization effect), difluorocarbene in its singlet ground state is a moderately electrophilic species and reacts much more easily with the electron-rich substrates than the electron-poor ones [1c]. In this context, structurally diverse difluo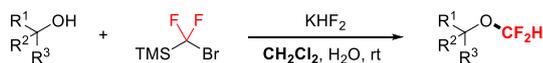rocarbene precursors that allow its efficient generation and further reaction under varying conditions have been developed [1a,2]. It is interesting to note that in heteroatom-difluoromethylation with various difluorocarbene precursors, an alkaline base is usually needed to activate both the pronucleophiles and the difluorocarbene precursor. Correspondingly, either a miscible or biphasic aqueous-organic solvent system is preferred to dissolve the reactants [1a,1e,2a-g]. However, although many difluorocarbene-involved reactions, including some [2 + 1] cyclo-additions with alkenes, have been achieved in the presence of water [1,2,9,10], there has been no report on the reaction of difluorocarbene with organic compounds in water as the sole solvent [11].

In 2017, by using TMSCF₂Br, a general and versatile difluorocarbene source first introduced by us [2h,12], we achieved the difluoromethylation of alcohols under the activation of mild activators such as KHF₂ in a mixed solvent system of dichloromethane/water at room temperature (Scheme 1a) [1a], which not only addressed the synthetic problem of difluoromethylation of alcohols with difluorocarbene under strongly basic conditions, but also showed that the reaction of alcohols with difluorocarbene can proceed readily in a manner different from phenols. Since our last publication of this method, it has found applications in the preparation of alkyl difluoromethyl ethers of potential biological
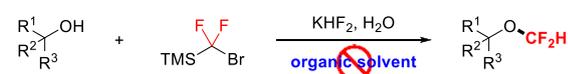
a) **Previous work**: difluorocarbene reaction in aqueous-organic solvent system

b) **This work**: difluorocarbene reaction in water only

Scheme 1. Difluoromethylation of alcohols with TMSCF$_2$Br.

interest [13]. In view of the high reactivity of neutral alcohols towards difluorocarbene and the mildness of the conditions for the generation of difluorocarbene from TMSCF$_2$Br, we were curious about the reaction of alcohols with TMSCF$_2$Br in water as the sole solvent. In organic synthesis, water is not only a green reaction medium, but also can impressively accelerate many reactions [14]. Herein, we present our results on difluoromethylation of alcohols with difluorocarbene generated from TMSCF$_2$Br under more environmentally benign conditions (Scheme 1b). This research also provides a new insight into the generation and reaction of difluorocarbene in a two-phase system. We showed that in a two-phase system, the transfer of an activated difluorocarbene precursor from the interfacial region to the organic phase region, which has been a challenging process even under phase-transfer catalysis [1d,9,15], can be a feasible process when TMSCF$_2$Br is used as a unique reagent in the absence of any catalyst, since TMSCF$_2$Br can form a lipophilic pentacoordinate intermediate in the interfacial region.

2. Results and discussion

2.1. Optimization of reaction conditions

At the onset of our investigation, we chose alcohol **1a** as a model substrate to survey the influence of organic solvent on the reaction

Table 1
Screen of reaction conditions for the difluoromethylation of alcohol **1a** with TMSCF$_2$Br (**2**).

Entry	CH$_2$Cl$_2$ (mL)	H$_2$O (mL)	Time (min)	3a, Yield (%)[a]	2, Conv. (%)[a]
1	0.5	0.3	60	28	32
2	0.3	0.3	60	44	40
3	0.1	0.3	60	60	51
4	0	0.3	10	45	32
5	0	0.3	30	97	85
6	0	0.6	60	82	98
7	0	1.2	60	67	>99
8	0	2.4	60	42	98
9[b]	0	2.4	60 + 60	67	95
10	0	0.15	60	82	61
11[c]	0	0.3	70	–	92
12[c]	0.3	0.3	60	–	36

[a] The yield of **3a** and total conversion of **2** were determined by ^{19}F NMR analysis of the reaction mixture using PhOCF$_3$ as an internal standard.
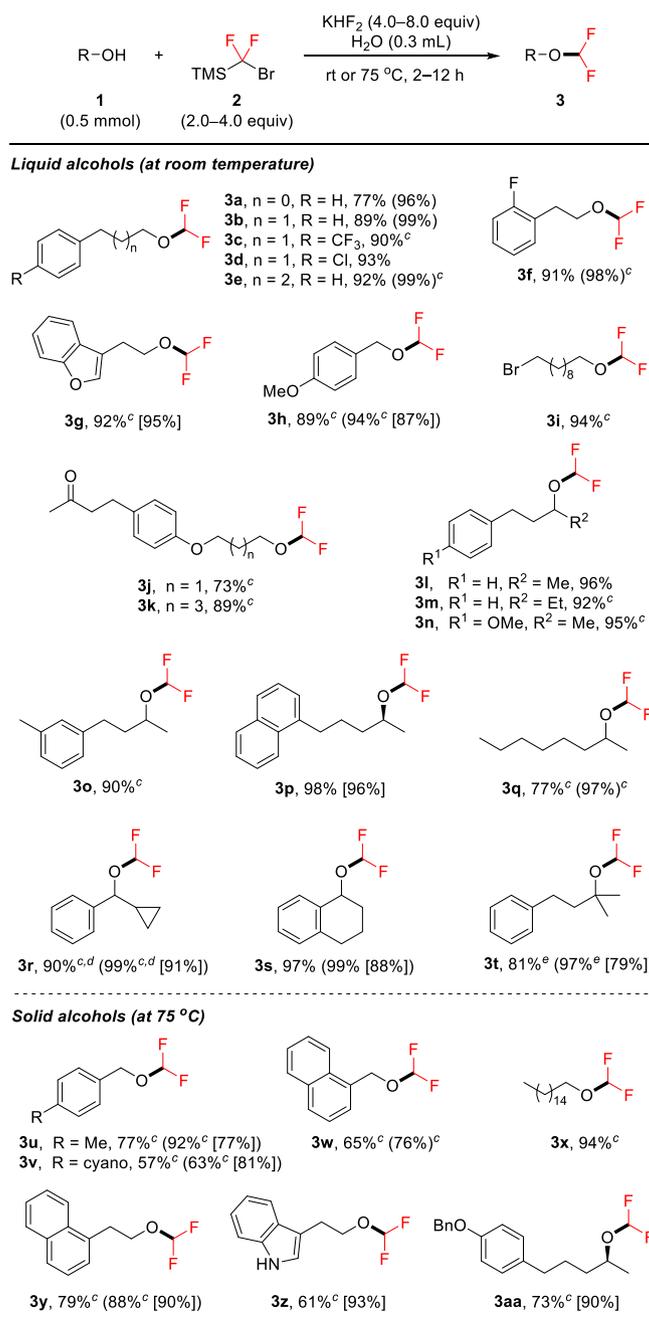[b] A second portion of TMSCF$_2$Br (1.0 mmol) and KHF$_2$ (2.0 mmol) were added after 60 min.
[c] The reaction was conducted in the absence of alcohol **1a**.

(Table 1; and Table S−2 in Supplementary data). In our previous report, the reaction between alcohols and TMSCF$_2$Br (**2**) was performed in a mixed solvent system of CH$_2$Cl$_2$/water (1:1, v/v) under the activation of KHF$_2$. By using the reported optimal reactant ratio, we first investigated the difluoromethylation of **1a** in water (0.6 L per mol of alcohol) in the presence of varying volume of CH$_2$Cl$_2$. To reflect the kinetic profile, the reaction was usually quenched before the full consumption of the starting materials and detected by ^{19}F NMR analysis. As shown in Table 1, the reaction was sensitive to the volume of CH$_2$Cl$_2$. Decreasing the volume of CH$_2$Cl$_2$ significantly accelerated the reaction, which probably arose from the increase of the concentration of both reactants **1a** and TMSCF$_2$Br (Table 1, entries 1−3). Considering that both alcohol **1a** and TMSCF$_2$Br are liquid and of low solubility in water at ambient temperature, we performed the reaction in water. Surprisingly, the reaction proceeded much faster than in the mixed solvent system (Table 1, entries 4 and 5). The difluoromethyl ether **3a** was produced in 97% ^{19}F NMR yield in half an hour (Table 1, entry 5). Encouraged by this finding, we further investigated the influence of the amount of water. When more water was used, a nearly complete consumption of TMSCF$_2$Br gave much lower yields of **3a** (Table 1, entries 6−8), and the addition of a second portion of reagents further improved the yield (Table 1, entry 9). When less water (0.3 L per mol of alcohol) was used, a 61% consumption of TMSCF$_2$Br led to the formation of **3a** in 82% yield, showing an enhanced conversion of TMSCF$_2$Br to **3a** (Table 1, entry 10); however, the reaction was retarded to some extent due to the insufficient dissolution of KHF$_2$ in water (39.2 g/100 mL, 20 °C). This phenomenon is different from the extensively studied "on-water" reaction, where the reaction occurs in the oil-water interface and is not influenced by the amount of water [14]. In our current reaction, if the difluoromethylation of **1a** mainly occurs in the interfacial region, although much more water could dilute the activator KHF$_2$, and thus result in a lower concentration of pentacoordinate silicate intermediate generated at the oil-water interface, the conversion of TMSCF$_2$Br to **3a** should not decrease, because the concentrations of **1a** and TMSCF$_2$Br do not change. The observed decrease of the utilization of TMSCF$_2$Br as the increase of the amount of water indicates that the difluoromethylation mainly occurs in the organic phase, as the transfer rate of the pentacoordinate silicate intermediate can be influenced by its concentration in the interfacial region. Moreover, control experiments showed that TMSCF$_2$Br was consumed at the similar rate no matter in the presence or absence of **1a** (Table 1, entries 10 and 12), suggesting that a controlled release of difluorocarbene from TMSCF$_2$Br and an efficient capture of difluorocarbene by enhancing the concentration of alcohol would be helpful for improving the difluoromethylation.

2.2. Scope and limitation

We examined the substrate scope of the reaction between alcohols and TMSCF$_2$Br in water. As shown in Table 2, primary, secondary, and tertiary cohols that are liquid at ambient temperature readily underwent the reaction to give difluoromethyl ethers in moderate to excellent yields. For primary alcohols (**1a**-**1k**), the reaction was conducted by using 2.0 equiv of TMSCF$_2$Br and 4.0 equiv of KHF$_2$ in water (0.6 mL per mmol of alcohol). The reaction typically completed in 2 h. For secondary alcohols (**1l**-**1s**), 3.0 equiv of TMSCF$_2$Br and 6.0 equiv of KHF$_2$ were needed due to the steric hindrance of alcohols towards difluorocarbene, and prolonged reaction time (6 h) was required to achieve high yields. When a tertiary alcohol (**1t**) was subject to the reaction, the use of more amount of TMSCF$_2$Br (4.0 equiv) and KHF$_2$ (8.0 equiv) was necessary to ensure the efficient conversion of alcohol **1t** into difluoromethyl ether **3t**, and the reaction completed in 12 h. Compared to

Table 2
Scope of alcohols [a,b].

Liquid alcohols (at room temperature)

3a, n = 0, R = H, 77% (96%)
3b, n = 1, R = H, 89% (99%)
3c, n = 1, R = CF$_3$, 90%[c]
3d, n = 1, R = Cl, 93%
3e, n = 2, R = H, 92% (99%)[c]

3f, 91% (98%)[c]

3g, 92%[c] [95%]

3h, 89%[c] (94%[c] [87%])

3i, 94%[c]

3j, n = 1, 73%[c]
3k, n = 3, 89%[c]

3l, R^1 = H, R^2 = Me, 96%
3m, R^1 = H, R^2 = Et, 92%[c]
3n, R^1 = OMe, R^2 = Me, 95%[c]

3o, 90%[c]

3p, 98% [96%]

3q, 77%[c] (97%)[c]

3r, 90%[c,d] (99%[c,d] [91%])

3s, 97% (99% [88%])

3t, 81%[e] (97%[e] [79%])

Solid alcohols (at 75 °C)

3u, R = Me, 77%[c] (92%[c] [77%])
3v, R = cyano, 57%[c] (63%[c] [81%])

3w, 65%[c] (76%)[c]

3x, 94%[c]

3y, 79%[c] (88%[c] [90%])

3z, 61%[c] [93%]

3aa, 73%[c] [90%]

[a] For primary alcohols, 2.0 equiv of **2** and 4.0 equiv of KHF$_2$ were used, and the reaction was typically complete within 2 h; for secondary alcohols, 3.0 equiv of **2** and 6.0 equiv of KHF$_2$ were used, and the reaction was typically complete within 6 h.
[b] Yields determined by ^{19}F NMR analysis using PhOCF$_3$ as an internal standard were given in the parentheses. Reported yields [2a] for the reaction conducted in CH$_2$Cl$_2$/water (0.3 mL/0.3 mL) were given in the square brackets.
[c] The final yields were determined at 12 h.
[d] KOAc was used instead of KHF$_2$.
[e] Conditions: **2** (4.0 equiv), KHF$_2$ (8.0 equiv), 12 h.

our previous report [2a], the reaction in water could afford the difluoromethyl ethers in similar or much higher yields (Table 2, **3g**, **3h**, **3p**, and **3r-t**).

In the cases of solid alcohols, the difluoromethylation at ambient temperature was found to be of very low efficiency. For example, reaction of hexadecan-1-ol (**1x**) gave the difluoromethyl ether **3x** in only 24% yield, despite complete consumption of TMSCF$_2$Br. It was

found that heating, which allows melting the alcohols to liquid, is a viable way to improve the reaction. For alcohols with moderate melting points (**1u-1aa**) (for details, see SI), performing the reaction at a temperature slightly higher than the melting points of these alcohols afforded the corresponding difluoromethyl ethers in good yields (**3u-3aa**).

As a complementary and an alternative approach, the reaction of

solid alcohols can also proceed in water at ambient temperature with the addition of a minimum volume of CH_2Cl_2 to dissolve the alcohols (Table 3). Thus, adding CH_2Cl_2 (0.2 L per mol of alcohol) into the reaction mixture of alcohols with varying melting points, $TMSCF_2Br$ and KHF_2 in water (0.6 mL per mmol of alcohol) resulted in the production of difluoromethyl ether **3** in yields comparable to those obtained by previous method (0.6 L of CH_2Cl_2 per mol of alcohol).

The reaction of triol **1ac** or sugar derivative **1ad** with $TMSCF_2Br$/KHF_2 in water afforded trace amount of difluoromethylation product (Fig. 1), indicating the limitation of the current protocol when applying it to some water-soluble alcohols. However, ethanol, which is also miscible with water, smoothly underwent the difluoromethylation, with $C_2H_5OCF_2H$ being detected in about 30% yield, despite its volatility. $TMSCF_2Br$-water extraction tests of alcohols **1a**, **1ac**, **1ad** and ethanol in the absence of KHF_2 showed that almost no alcohol **1ac** or **1ad** was extracted by $TMSCF_2Br$, while 95% of alcohol **1a** and about 1% of ethanol entered the organic phase (for details, see section 3 in ESI). Obviously, the extraction of the alcohol by $TMSCF_2Br$ is necessary for the difluoromethylation, providing an evidence to support that difluoromethylation of alcohols mainly occurs in the organic phase.

To demonstrate the practicability of current protocol, we conducted the difluoromethylation of alcohol **1a** in water on 10-mmol scale. After the completion of the reaction, a direct ^{1}H NMR analysis of the organic phase showed that difluoromethyl ether **3a** was formed with a purity of almost 90%. After workup, the isolated yield of crude **3a** was 85% (Scheme 2).

2.3. Proposed mechanism

Based on our results and discussion, and taking into account the previous mechanistic studies on reaction of carbenes with hydroxyl groups [1d,2c,16], a plausible mechanism for the difluoromethylation of alcohols with difluorocarbene in water is proposed (Scheme 3). In the two-phase system consisting of $TMSCF_2Br$ with an alcohol and an aqueous solution of KHF_2, $TMSCF_2Br$ was activated by KHF_2 to form a pentacoordinate silicate intermediate at the oil-water interface, which then enters the organic phase under the driving force of its lipophilicity (Scheme 3, Eq. 1). In the organic phase, $BrCF_2K$ is released from the pentacoordinate silicate intermediate (Scheme 3, Eq. 2), and then splits into KBr and the singlet difluorocarbene (Scheme 3, Eq. 3). The latter species interacts with two alcohol molecules to form a five-membered complex with oxonium character [16c], which eventually undergoes double proton transfer to deliver the difluoromethyl ether and regenerate one
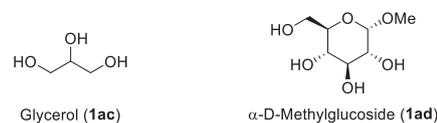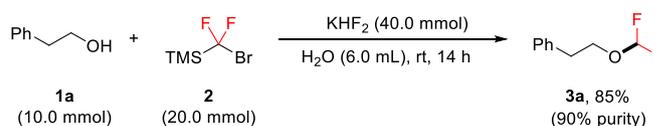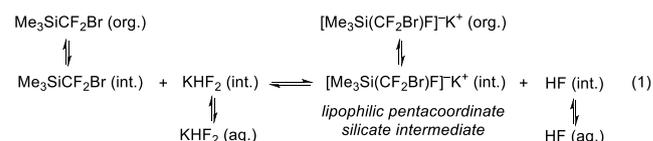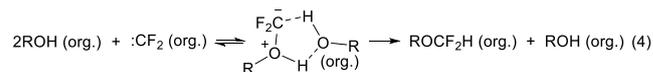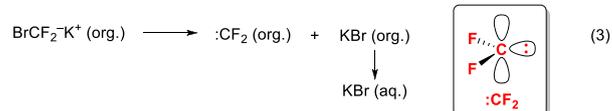

Fig. 1. Unsuccessful examples.

Scheme 2. Large scale synthesis without purification.

Scheme 3. Proposed mechanism for difluoromethylation of alcohols with difluorocarbene in water.

Table 3
Difluoromethylation of solid alcohols with $TMSCF_2Br$ in the presence of minimum amount of dichloromethane ^{a}.
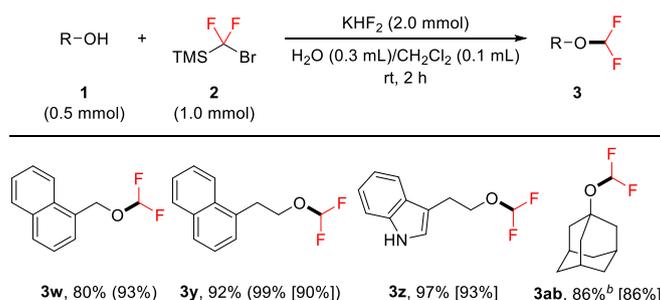

3w, 80% (93%)   **3y**, 92% (99% [90%])   **3z**, 97% [93%]   **3ab**, 86%^{b} [86%]

^{a} Yields determined by^{19}F NMR analysis using $PhOCF_3$ as an internal standard were given in the parentheses. Reported yields [2a] for the reaction conducted in CH_2Cl_2/water (0.3 mL/0.3 mL) were given in the square brackets.
^{b} Conditions: **2** (4.0 equiv), KHF_2 (8.0 equiv), 12 h.

alcohol molecule (Scheme 3, Eq. 4). The complex is probably formed through the interaction of the central carbon's vacant p-orbital with the oxygen's lone pair of the first alcohol molecule and the hydrogen bonding between the central carbon and the second alcohol molecule [16a]. At the oil-water interface, $BrCF_2K$ released from the pentacoordinate silicate intermediate readily undergoes protonation (Scheme 3, Eqs. 5 and 6), which constitutes the major side reaction of $TMSCF_2Br$ when KHF_2 is used as the activator.

The feasibility of generating difluorocarbene from $TMSCF_2Br$ in the organic phase of a biphasic system is further supported by the *gem*-difluorocyclopropanation of an electron-rich alkene, 1,1-diphenylethene (for detail, see section 4 in Supplementary data).

2.4. A comparison with the difluoromethylation of phenols

We compared the difluoromethylation of phenol **4** using water as the only solvent to that in CH_2Cl_2/water (Scheme 4). As previously reported [2g], the basic activator KOH is necessary, which promotes the generation of difluorocarbene and subsequent reaction with phenol (via phenolate anion). Using the reported optimal reactant ratio, the reaction in water (without organic solvent) afforded product **5** in moderate yield, although $TMSCF_2Br$ was consumed completely. In contrast, the reaction in CH_2Cl_2/water was much more efficient, where a 60% conversion of $TMSCF_2Br$ led to the formation of **5** in 86% yield (similar to previous report). The relative low efficiency of the reaction in water may be attributed to the fast consumption of difluorocarbene by KOH at the oil-water interface (for the proposed mechanism, see section 5 in Supplementary data). A dilution of $TMSCF_2Br$ with CH_2Cl_2 would slow down the formation of difluorocarbene; however, the utilization of difluorocarbene would be enhanced due to the relative enrichment of the phenolate anion and pentacoordinate silicate into the organic phase, which would reduce the contact between difluorocarbene and KOH correspondingly.

3. Conclusion

In summary, we have shown that the difluoromethylation of primary, secondary, and tertiary alcohols by using $TMSCF_2Br$ as the difluorocarbene reagent and KHF_2 as a mild activator can proceed in water. Although no organic solvent is used, the liquid alcohol and $TMSCF_2Br$ constitute the organic phase. On the one hand, for primary and secondary alcohols, compared with the reaction in a combined solvent system of CH_2Cl_2/water, the reaction in water proceeded faster due to the enhanced concentration of the reactants in the organic phase. On the other hand, less water can improve the conversion of $TMSCF_2Br$ to difluoromethyl ethers, although the reaction can be retarded when the dissolution of KHF_2 is not sufficient. In the case of solid alcohols, dissolving the alcohols with a minimum amount of organic solvent such as CH_2Cl_2 is necessary. Importantly, by probing the influence of the amount of water on the difluoromethylation of alcohols with $TMSCF_2Br$, we have identified a new mechanism for the generation and reaction of difluorocarbene in a biphasic oil-water system, which is revealing for the design of new difluorocarbene reagents and the

development of new difluorocarbene reactions.

4. Experimental section

The typical procedures for the difluoromethylation of primary alcohols (liquid) are as follows: Into a 10-mL plastic tube containing 2-phenylethanol (**1a**) (61 mg, 0.5 mmol) and KHF_2 (156 mg, 2.0 mmol) was added water (0.3 mL). After stirring for a while to dissolve KHF_2, $TMSCF_2Br$ (**2**) (156 μL, 1.0 mmol) was added. The reaction mixture was vigorously stirred at room temperature for 2 h, and then diluted with CH_2Cl_2 (2.0 mL) for the determination of the ^{19}F NMR yield. For characterization of the product, the above reaction mixture was further treated with water (2.0 mL) and extracted with CH_2Cl_2 (3 × 2.0 mL). The organic layers were combined and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane/CH_2Cl_2, 5:1, v/v) to afford the desired product **3a** in 77% yield (66 mg).

The procedures for the difluoromethylation of other alcohols, the characterization data of isolated compounds, and the ^1H, ^{19}F, and ^{13}C NMR spectra are presented in Supplementary data.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131676.

References

[1] For reviews, see: (a) C. Ni, J. Hu, Recent advances in the synthetic application of difluorocarbene, Synthesis 46 (2014) 842−863;
(b) X. Wang, X. Wang, J. Wang, Application of carbene chemistry in the synthesis of organofluorine compounds, Tetrahedron 75 (2019) 949−964;
(c) W.R. Dolbier Jr., M.A. Battiste, Structure, synthesis, and chemical reactions of fluorinated cyclopropanes and cyclopropenes, Chem. Rev. 103 (2003) 1071−1098;
(d) M. Fedoryński, Syntheses of *gem*-dihalocyclopropanes and their use in organic synthesis, Chem. Rev. 103 (2003) 1099−1132;
(e) D.L.S. Brahms, W.P. Dailey, Fluorinated carbenes, Chem. Rev. 96 (1996) 1585−1632.
[2] For recent examples, see: (a) Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong, J. Hu, Efficient difluoromethylation of alcohols using $TMSCF_2Br$ as a unique and practical difluorocarbene reagent under mild conditions, Angew.Chem. Int. Ed. 56 (2017) 3206−3210;
(b) G.-K. Liu, W.-B. Qin, X. Li, L.-T. Lin, H.N.C. Wong, Difluoromethylation of phenols and thiophenols with the *S*-(difluoromethyl)sulfonium salt: reaction, scope, and mechanistic study, J. Org. Chem. 84 (2019) 15948−15957;
(c) G.-K. Liu, X. Li, W.-B. Qin, X.-S. Peng, H.N.C. Wong, L. Zhang, X. Zhang, Facile difluoromethylation of aliphatic alcohols with an *S*-(difluoromethyl)sulfonium salt: reaction, scope and mechanistic study, Chem. Commun. 55 (2019) 7446−7449;
(d) T. Ding, L. Jiang, W. Yi, One-pot synthesis of difluoromethyl thioethers from thiourea and diethyl bromodifluoromethylphosphonate, Org. Lett. 20 (2018) 170−173;
(e) C. Liu, X.-Y. Deng, X.-L. Zeng, G. Zhao, J.-H. Lin, H. Wang, J.-C. Xiao, Base-free
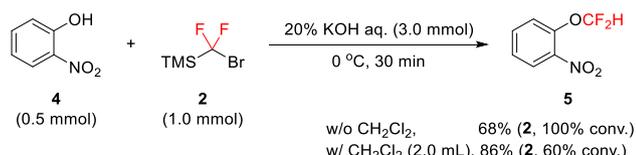
Scheme 4. Effect of organic solvent on the difluoromethylation of phenols.

O-difluoromethylation of 1,3-diones with difluorocarbene, J. Fluorine Chem. 192 (2016) 27−30;
(f) V. Krishnamurti, C. Barrett, X. Ispizua-Rodriguez, M. Coe, G.K.S. Prakash, Aqueous base promoted O-difluoromethylation of carboxylic acids with TMSCF$_2$Br: bench-top access to difluoromethyl esters, Org. Lett. 21 (2019) 9377−9380;
(g) L. Li, F. Wang, C. Ni, J. Hu, Synthesis of gem-difluorocyclopropa(e)nes and O-, S-, N-, and P-difluoromethylated compounds with TMSCF$_2$Br, Angew. Chem. Int. Ed. 52 (2013) 12390−12394;
(h) L. Li, C. Ni, Q. Xie, M. Hu, F. Wang, J. Hu, TMSCF$_3$ as a convenient source of CF$_2$=CF$_2$ for pentafluoroethylation, (aryloxy)tetrafluoroethylation, and tetra-fluoroethylation, Angew. Chem. Int. Ed. 56 (2017) 9971−9975;
(i) B. Xing, L. Li, C. Ni, J. Hu, Pentafluoroethylation of arenediazonium tetra-fluoroborates using on-site generated Tetrafluoroethylene, Chin. J. Chem. 37 (2019) 1131−1136;
(j) W.C. Fu, T.F. Jamison, Deuteriodifluoromethylation and gem-difluoroalkenylation of aldehydes using ClCF$_2$H in continuous flow, Angew. Chem. Int. Ed. 59 (2020) 13885−13890.

[3] For examples, see: (a) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, A general protocol for C-H difluoromethylation of carbon acids with TMSCF$_2$Br, Angew. Chem. Int. Ed. 58 (2019) 6405−6410;
(b) J. Wang, E. Tokunaga, N. Shibata, Highly C-selective difluoromethylation of β-ketoesters by using TMSCF$_2$Br/lithium hydroxide/N, N,N-trimethylhex-adecan-1-ammonium bromide, Chem. Commun. 54 (2018) 8881−8884;
(c) J. Zhu, H. Zheng, X.-S. Xue, Y. Xiao, Y. Liu, Q. Shen, Carbon-selective difluoromethylation of soft carbon nucleophiles with difluoromethylated sulfonium ylide, Chin. J. Chem. 36 (2018) 1069−1074;
(d) S.-L. Lu, X. Li, W.-B. Qin, J.-J. Liu, Y.-Y. Huang, H.N.C. Wong, G.-K. Liu, Air- and light-stable S-(difluoromethyl)sulfonium salts: C-selective electrophilic difluoromethylation of β-ketoesters and malonates, Org. Lett. 20 (2018) 6925−6929.

[4] For examples, see: (a) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T.L. Collier, V. Gouverneur, J. Passchier, A broadly applicable [F-18] trifluoromethylation of aryl and heteroaryl iodides for PET imaging, Nat. Chem. 5 (2013) 941−944;
(b) J. Zheng, L. Wang, J.-H. Lin, J.-C. Xiao, S.H. Liang, Difluorocarbene-derived trifluoromethylthiolation and [18F]trifluoromethylthiolation of aliphatic electrophiles, Angew. Chem. Int. Ed. 54 (2015) 13236−13240.

[5] (a) X.-Y. Zhang, X.-P. Fu, S. Zhang, X. Zhang, Palladium difluorocarbene involved catalytic coupling with terminal alkynes, CCS Chem. 2 (2020) 293−304;
(b) X.-P. Fu, X.-S. Xue, X.-Y. Zhang, Y.-L. Xiao, S. Zhang, Y.-L. Guo, X. Leng, K.N. Houk, X. Zhang, Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes, Nat. Chem. 11 (2019) 948−956;
(c) Z. Feng, Q.-Q. Min, X.-P. Fu, L. An, X. Zhang, Cholorodifluomethane-trig-gered formation of difluoromethylated arenes catalysed by palladium, Nat. Chem. 9 (2017) 918−923;
(d) Z. Feng, Q.-Q. Min, X. Zhang, Access to difluoromethylated arenes by Pd-catalyzed reaction of arylboronic acids with bromodifluoroacetate, Org. Lett. 18 (2016) 44−47;
(e) X.-Y. Deng, J.-H. Lin, J.-C. Xiao, Pd-catalyzed transfer of difluorocarbene, Org. Chem. Front. 18 (2016) 4384−4387;
(f) J. Sheng, H.-Q. Ni, K.-J. Bian, Y. Li, Y.-N. Wang, X.-S. Wang, Org. Chem. Front. 5 (2018) 606−610;
(g) C. Li, Y.-X. Cao, R. Wang, Y.-N. Wang, Q. Lan, X.-S. Wang, Cobalt-catalyzed difluoroalkylation of tertiary aryl ketones for facile synthesis of quaternary alkyl difluorides, Nat. Commun. 9 (2018) 4951;
(h) K.-F. Zhang, K.-J. Bian, C. Li, J. Sheng, Y. Li, X.-S. Wang, Nickel-catalyzed carbofluoroalkylation of 1,3-enynes to access structurally diverse fluoroalky-lated allenes, Angew. Chem. Int. Ed. 58 (2019) 5069−5074.

[6] (a) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, Controllable double CF$_2$-insertion into sp^2 C−Cu bond using TMSCF$_3$: a facile access to tetrafluoroethylene-bridged structures, Chem. Sci. 11 (2020) 276−280;
(b) Q. Xie, L. Li, Z. Zhu, R. Zhang, C. Ni, J. Hu, From C1 to C2: TMSCF$_3$ as a precursor for pentafluoroethylation, Angew. Chem. Int. Ed. 57 (2018) 13211−13215.

[7] For recent examples, see: (a) (a review) A.D. Dilman, V.V. Levin, Difluor-ocarbene as a building block for consecutive bond-forming reactions, Acc.

Chem. Res. 51 (2018) 1272−1280;
(b) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, Nucleophilic (phenylsulfonyl/arylthio)difluor-omethylation of aldehydes with TMSCF$_2$Br: a three-component strategy, Org. Lett. 21 (2019) 9138−9141;
(c) H. Liang, R. Liu, M. Zhou, Y. Fu, C. Ni, J. Hu, Difluorocarbene-triggered cyclization: synthesis of (hetero)arene-fused 2,2-difluoro-2,3-dihydrothiophenes, Org. Lett. 22 (2020) 7047−7051.

[8] For examples, see: (a) J. Yu, J.-H. Lin, J.-C. Xiao, Reaction of thiocarbonyl fluoride generated from difluorocarbene with amines, Angew. Chem. Int. Ed. 56 (2017) 16669−16673;
(b) M. Zhang, J.-H. Lin, J.-C. Xiao, Photocatalyzed cyanodifluoromethylation of alkenes, Angew. Chem. Int. Ed. 58 (2019) 6079−6083;
(c) J. Yu, J.-H. Lin, D. Yu, R. Du, J.-C. Xiao, Oxidation of difluorocarbene and subsequent trifluoromethoxylation, Nat. Commun. 10 (2019), 5362;
(d) X. Ma, S. Mai, Y. Zhou, G.-J. Cheng, Q. Song, Dual role of ethyl bromodi-fluoroacetate in the formation of fluorine-containing heteroaromatic com-pounds, Chem. Commun. 54 (2018) 8960−8963;
(e) X. Ma, J. Su, X. Zhang, Q. Song, Chlorodifluoromethane as a C1 synthon in the assembly of N-containing compounds, iScience 19 (2019) 1−13.

[9] (a) K. Grudzień, T. Basak, M. Barbasiewicz, T.M. Wojciechowski, M. Fedoryński, Synthesis, properties and application of electronically-tuned tetraar-ylarsonium salts as phase transfer catalysts (PTC) for the synthesis of gem-difluorocyclopropanes, J. Fluorine Chem 197 (2017) 106−110;
(b) P. Balcerzak, M. Fedoryński, A. Jończyk, Synthesis of gem-difluorocyclopropanes in a phase-transfer catalysed system, J. Chem. Soc., Chem. Commun. (1991) 826−827.

[10] E. Nawrot, A. Jończyk, Difluoromethyltrialkylammonium salts−their expedi-tious synthesis from chlorodifluoromethane and tertiary amines in the pres-ence of concentrated aqueous sodium hydroxide−the catalytic process, J. Org. Chem. 72 (2007) 10258−10260.

[11] (a) S. Voltrová, I. Putovný, V. Matoušek, B. Klepetářová, P. Beier, Reintroducing azidodifluoromethane: synthesis, stability and [3+2] cycloadditions, Eur. J. Org. Chem. 2018 (2018) 5087−5090, and references therein;
(b) H.-X. Song, Q.-Y. Han, C.-L. Zhao, C.-P. Zhang, Fluoroalkylation reactions in aqueous media: a review,, Green Chem. 20 (2018) 1662−1731.

[12] F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of gem-difluorinated cyclopropenes and cyclopropanes, Chem. Commun. 47 (2011) 2411−2413.

[13] (a) H. Tang, J. Cheng, Y. Liang, Y. Wang, Discovery of a chiral fluorinated azetidin-2-one as a tubulin polymerisation inhibitor with potent antitumour efficacy, Eur. J. Med. Chem. 197 (2020), 112323;
(b) A reaxys search, showed that this method has been used by more than 10 filed patents, for details, see Supplementary.

[14] (a) T. Kitanosono, S. Kobayashi, Reactions in water through "on-water" mechanism, Chem. Eur. J. 26 (2020) 9408−9429;
(b) T. Kitanosono, K. Masuda, P. Xu, S. Kobayashi, Catalytic organic reactions in water toward sustainable society, Chem. Rev. 118 (2018) 679−746;
(c) R.N. Butler, A.G. Coyne, Organic synthesis reactions on-water at the organic−liquid water interface, Org. Biomol. Chem. 14 (2016) 9940−9945;
(d) R.N. Butler, A.G. Coyne, Water: Nature's reaction enforcers−comparative effects for organic synthesis "in-water" and "on-water", Chem. Rev. 110 (2010) 6302−6337;
(e) Organic reactions in water: principles, strategies and applications, in: U.M. Lindström (Ed.), 2007. Blackwell, Oxford;
(f) S. Narayan, J. Muldoon, M.G. Finn, V.V. Fokin, H.C. Kolb, K.B. Sharpless, "On water": unique reactivity of organic compounds in aqueous suspension, Angew. Chem. Int. Ed. 44 (2005) 3275−3279.

[15] P. Weyerstahl, G. Blume, C. Müller, Zur darstellung von 1-fluor-1-brom- und 1-fluor-1-chlor-cyclopropanen, Tetrahedron Lett. 12 (1971) 3869−3872 (in German).

[16] (a) J.R. Pliego Jr., W.B. De Almeida, A new mechanism for the reaction of carbenes with OH groups, J. Phys. Chem. A 103 (1999) 3904−3909;
(b) J.F. Orrego, H. Cano, A. Restrepo, Quantum mechanical study of the gas-phase reactions between a series of substituted singlet carbenes and water, J. Phys. Chem. A 113 (2009) 6517−6523;
(c) S. Gómez, D. Guerra, J.G. López, A. Toro-Labbé, A. Restrepo, A detailed look at the reaction mechanisms of substituted carbenes with water, J. Phys. Chem. A 117 (2013) 1991−1999.