Carbenes

International Edition: DOI: 10.1002/anie.201611823
German Edition: DOI: 10.1002/ange.201611823

Efficient Difluoromethylation of Alcohols Using $TMSCF_2Br$ as a Unique and Practical Difluorocarbene Reagent under Mild Conditions

Qiqiang Xie, Chuanfa Ni, Rongyi Zhang, Lingchun Li, Jian Rong, and Jinbo Hu**

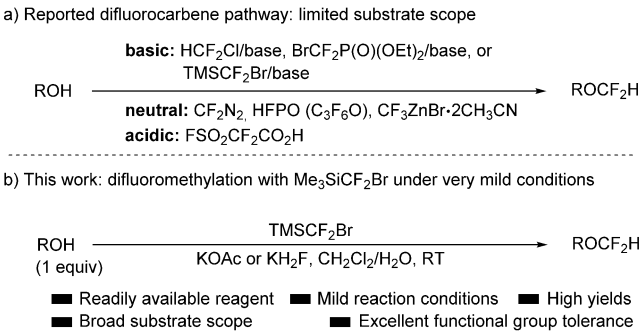
Abstract: *A general method for the efficient difluoromethylation of alcohols using commercially available $TMSCF_2Br$ (TMS = trimethylsilyl) as a unique and practical difluorocarbene source is developed. This method allows primary, secondary, and even tertiary alkyl difluoromethyl ethers to be synthesized under weakly basic or acidic conditions. The reaction mainly proceeds through the direct interaction between a neutral alcohol and difluorocarbene, which is different from the difluoromethylation of phenols. Moreover, alcohols containing other moieties that are also reactive toward difluorocarbene can be transformed divergently by using $TMSCF_2Br$. This research not only solves the synthetic problem of difluorocarbene-mediated difluoromethylation of alcohols, it also provides new insights into the different reaction mechanisms of alcohol difluoromethylation and phenol difluoromethylation with difluorocarbene species.*

α-Fluoroethers, as a valuable class of organofluorine compounds, have found wide application in pharmaceuticals, agrochemicals, and functional materials, owing to the impressive conformational changes and maximal shifts in electron distribution brought by fluorine.[1,2] Moreover, the α-fluorine substitution of alkyl ethers shortens and strengthens the C–O bond[3] and thus improves the in vivo oxidative stability of the ether moiety of a drug.[4] Among various α-fluoroethers, difluoromethyl ethers are of particular interest as the difluoromethyl group is capable of acting as a lipophilic hydrogen-bond donor.[5] In the past decades, difluoromethyl ethers have been applied in developing enzyme inhibitors/activators, anti-HIV agents, antimicrobial agents, and anesthetic drugs.[2b,c,6,7] For instances, Desflurane, a widely used anesthetic drug,[7a] and Roflumilast, a newly approved respiratory system drug for treatment of chronic obstructive pulmonary disease (COPD) exacerbations,[7b] are both difluoromethyl ethers.

[*] Q. Xie, Dr. C. Ni, R. Zhang, Dr. L. Li, J. Rong, Prof. Dr. J. Hu
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry
University of Chinese Academy of Sciences
Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai, 200032 (China)
E-mail: nichuanfa@sioc.ac.cn
jinbohu@sioc.ac.cn
R. Zhang, Prof. Dr. J. Hu
School of Physical Science and Technology
ShanghaiTech University
100 Haike Road, Shanghai 201210 (China)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201611823.

To access difluoromethyl ethers,[8–11] the difluoromethylation of alcohols and phenols with difluorocarbene ($:CF_2$) is a facile approach owing to the ready availability of many reagents.[10,11] However, current syntheses of difluoromethyl ethers with $:CF_2$ reagents mainly focus on the difluoromethylation of phenols under basic conditions;[10] the difluoromethylation of alcohols under similar reaction conditions is usually less productive as a result of the competitive reactions caused by the base. To date, only several reagents, including HCF_2Cl,[12] $BrCF_2P(O)(OEt)_2$,[13] and $TMSCF_2Br$,[14] have been reported for difluoromethylation of alcohols under basic conditions with limited functional group compatibility (Scheme 1 a, basic). Although some methods that can avoid strongly basic conditions by the use of special $:CF_2$ reagents, such as CF_2N_2,[15] HFPO,[16] and $CF_3ZnBr{\cdot}2\,CH_3CN$,[17] have been exploited for alcohol difluoromethylation, these methods usually require excess amounts of alcohols and suffer from narrow substrate scope (Scheme 1 a, neutral). Recently, a modification of Chen's method has led to an effective difluoromethylation of primary and secondary alcohols with $FSO_2CF_2CO_2H$ (Scheme 1 a, acidic);[18] however, the reaction with tertiary alcohols is still unmet. Furthermore, the elution of SO_2, an air pollutant,[19] as a byproduct may prohibit this method from wide application. In general, efficient difluoromethylation of structurally diverse alcohols with $:CF_2$ still remains a challenge, which is strikingly different from the difluoromethylation of phenols.[10] Therefore, it is not only of great demand, but also of immense fundamental interest to seek a mild and general approach for the difluoromethylation of alcohols with readily available $:CF_2$ reagents.



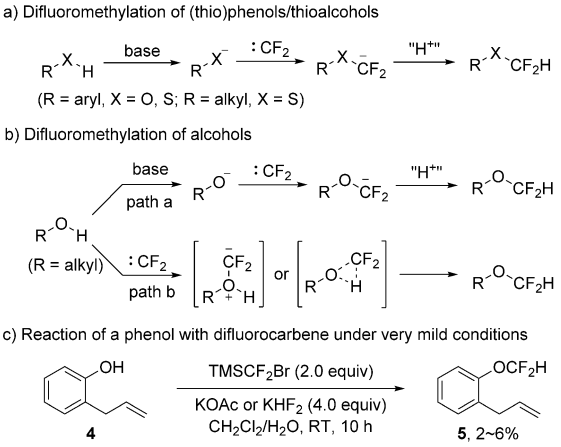
Scheme 1. Difluoromethylation of alcohols with various difluorocarbene reagents. HFPO = hexafluoropropylene oxide, TMS = trimethylsilyl.

Previously, we developed $TMSCF_2Br$ as a versatile $:CF_2$ reagent for difluoromethylation/difluoromethylenation of

phenols, thiols, amines, alkenes, and alkynes, among others.[10,14] During our continuous pursuit of alcohol difluoromethylation with $TMSCF_2Br$, we found that the reaction conditions for generating $:CF_2$ are crucial, and mild conditions are optimal for the conversion of alcohols (Scheme 1b). Thus, the difluoromethylation of alcohols can be achieved as easily as that of phenols, provided that proper conditions for the generation of $:CF_2$ are chosen. Herein, we report the development of KOAc- or KHF_2-promoted highly efficient difluoromethylation of alcohols with $TMSCF_2Br$ as a unique $:CF_2$ source, a reaction proceeding through a mechanism different from the difluoromethylation of phenols.

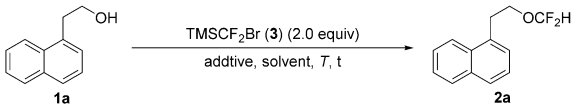
Our research started with optimization of the difluoromethylation of alcohols with $TMSCF_2Br$ under commonly used strongly basic conditions.[10,14] Experiments were conducted by adding an aqueous KOH solution to an organic solution of model substrate **1a** and $TMSCF_2Br$ (Table 1, entries 1–9). Under our reported conditions,[14a] the desired product **2a** was obtained in a low yield (entry 1). Solvent screening showed that $PhCH_3$ and CH_2Cl_2 were superior to acetonitrile, and the reaction could be somewhat improved by using $PhCH_3$ instead of CH_2Cl_2. After exhaustive optimization on the reaction parameters, we found that when using $PhCH_3$ or CH_2Cl_2 as the solvent, the reaction was sensitive to the concentration of the reactants (entries 1, 8, and 9; entries 4–7). Increasing the concentration of the organic phase significantly enhanced the yield of **2a**, indicating an improvement on the transfer of in-situ-generated $:CF_2$ to the alcohol substrate. This concentration effect was not observed in the difluoromethylation of (thio)phenols/thioalcohols under similar conditions. We inferred that alcohols and (thio)phenols/thioalcohols may react with $:CF_2$ in different pathways. In the cases of (thio)phenols/thiols, which are acidic enough to be efficiently deprotonated by a strong base such as KOH, the corresponding anions should be the major nucleophilic species to react with $:CF_2$ (Scheme 2a). However, in the case of alcohols, which are less acidic than (thio)phenols/thiols, the alcoholate anion presents in weak equilibrium even in the presence of KOH, thus both the alcoholate anion (Scheme 2a, path a) and the alcohol (Scheme 2a, path b) would react with $:CF_2$, with the reaction of the alcohol being the major pathway. The remarkable concentration effect of alcohols should arise from the lower nucleophilicity of alcohols than that of phenolate anions. Based on the above rationalizations, we further investigated the difluoromethylation of **1a** by using many other activators, ranging from strongly basic NaOH to weakly acidic KHF_2 (Table 1, entries 10–16). To our delight, all of the reactions proceeded smoothly, giving **2a** in good to excellent yields. For comparison, we performed the reaction between phenol **4** and $TMSCF_2Br$ by using KOAc or KHF_2 as the mild activator (Scheme 2c); however, although $TMSCF_2Br$ was consumed completely, product **5** was formed in very low yield.[20] It is obvious that alcohols can react with $:CF_2$ directly without predeprotonation (Scheme 2b, path b), which is distinct from the reaction of (thio)phenols/thioalcohols with difluorocarbene (Scheme 2a).

We also investigated the role of water in this reaction (Table 1, entries 17–19). When NaOH or KOAc was used in the absence of water, the complete conversion of $TMSCF_2Br$ needed 24 hours and led to low yields of **2a** (entries 17 and 18). The difluorocarbene mainly reacted with the activator to form the hydrolysis product or $AcOCF_2H$. When KHF_2 was used without water, although a high yield of **2a** could be obtained, it required much longer reaction time (entry 19). These results indicate that the two-phase system consisting of an organic solution of the alcohol/$TMSCF_2Br$ and an aqueous solution of the activator not only promoted the formation and



Scheme 2. a, b) Proposed mechanisms of phenol and alcohol difluoromethylation. c) Difluoromethylation of phenol under mild conditions.

Table 1: Screen of reaction conditions for the difluoromethylation of alcohol **1a** with $TMSCF_2Br$.[a]

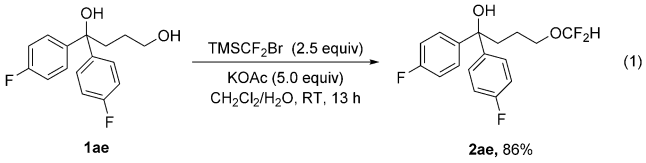


Entry	Additive [equiv]	Solvent [mL]	T [°C]	t [h]	Yield [%]
1	20% aq. KOH (6.0)	CH_2Cl_2 (2.0)	0	0.5	33
2	20% aq. KOH (6.0)	MeCN (2.0)	0	0.5	13
3	20% aq. KOH (6.0)	$PhCH_3$ (2.0)	0	0.5	45
4	20% aq. KOH (6.0)	$PhCH_3$ (2.0)	0	1	36
5	20% aq. KOH (6.0)	$PhCH_3$ (1.0)	0	1	65
6	20% aq. KOH (6.0)	$PhCH_3$ (0.5)	0	2	76
7	20% aq. KOH (6.0)	$PhCH_3$ (0.3)	0	2	78
8	20% aq. KOH (6.0)	CH_2Cl_2 (0.3)	0	2	82
9	20% aq. KOH (5.0)	CH_2Cl_2 (0.3)	0	2	85
10	20% aq. NaOH (5.0)	CH_2Cl_2 (0.3)	0	2	86
11	8% aq. LiOH (5.0)	CH_2Cl_2 (0.3)	0	2	81
12	30% aq. Na_2CO_3 (4.0)	CH_2Cl_2 (0.3)	RT	10	70
13	NH_4OAc (4.0)	CH_2Cl_2 (0.3)[b]	RT	10	86
14	KOAc (4.0)	CH_2Cl_2 (0.3)[b]	RT	10	92
15	KF (4.0)	CH_2Cl_2 (0.3)[b]	RT	10	69
16	KHF_2 (4.0)	CH_2Cl_2 (0.3)[b]	RT	10	88
17	NaOH (4.0)	CH_2Cl_2 (0.3)	RT	24	29
18	KOAc (4.0)	CH_2Cl_2 (0.3)	RT	24	48
19	KHF_2 (4.0)	CH_2Cl_2 (0.3)	RT	48	87

[a] All of the reactions were performed on 0.5 mmol scale. The yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] H_2O (0.3 mL) was used as co-solvent.

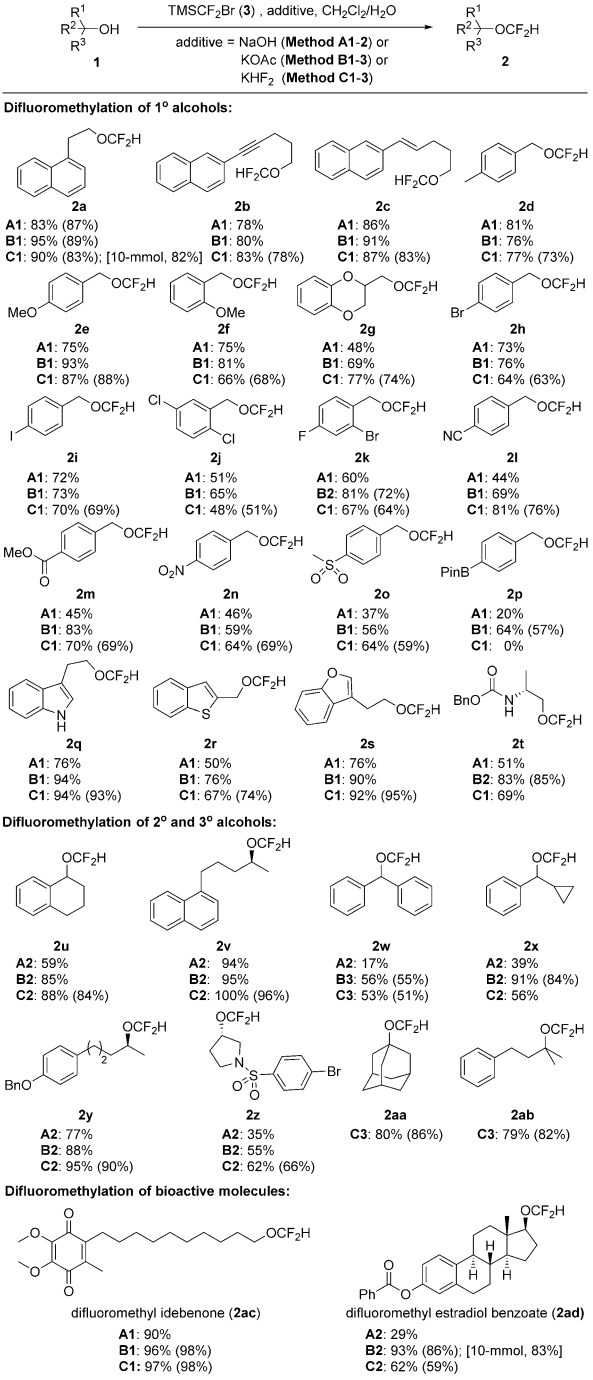
transfer of :CF_2, but also could confine the base to the aqueous phase to minimize the competitive consumption of :CF_2.[11c]

Next, we examined the substrate scope by using two mild activators, weakly basic KOAc and weakly acidic KHF_2. For comparison, we also conducted the reactions using strongly basic NaOH. As shown in Scheme 3, primary, secondary, and tertiary alcohols reacted smoothly to give difluoromethyl ethers in moderate to excellent yields. Mild activators KOAc and KHF_2 were suitable for almost all of the alcohols examined, although the strongly basic NaOH were only suitable for the reaction of electron-rich and less sterically hindered alcohols (**2a**–**f**, **2h**,**i**, **2q**, **2v**, and **2y**). Functional groups such as cyano (**2l**), nitro (**2n**), halogen (**2h**–**k**), ester (**2m**), and protected amino groups (**2t** and **2z**) are well tolerated under the conditions of KOAc and KHF_2. In the case of alcohol **2p** with a boronic ester group, KOAc is superior to KHF_2. Moreover, alkene (**2b**), alkyne (**2c**), alkyl aryl ether (**2e**–**g** and **2y**), and heteroarene (**2r**, **2s**, and **2q**) are compatible with the difluoromethylation of alcohols, and no competing reaction occurs. This procedure is also applicable for the late-stage difluoromethylation of bioactive alcohols. Idebenone, a drug for treatment of Alzheimer's disease,[21] was converted to **2ac** in excellent yields under all three sets of conditions. Estradiol benzoate, the first form of estrogen to be marketed,[22] underwent KOAc-promoted reaction to give **2ad** in 86% yield. Note that the reactions can be easily scaled up to 10-mmol scale (**2a** and **2ad**). Overall, the difluoromethylation of alcohols is affected by both the electronic and the steric effects of the substrates: the electron-rich alcohols (**2e**,**f**) gave somewhat higher yields than the electron-deficient ones (**2n**,**o**), and the secondary and tertiary alcohols were normally less reactive than the primary ones, thus requiring more excess amounts of $TMSCF_2Br$. The influence of the steric effect is further demonstrated by the reaction of 1,4-diol **1ae**, with the primary alcohol being selectively difluoromethylated to give **2ae** in 86% yield [Eq. (1)].

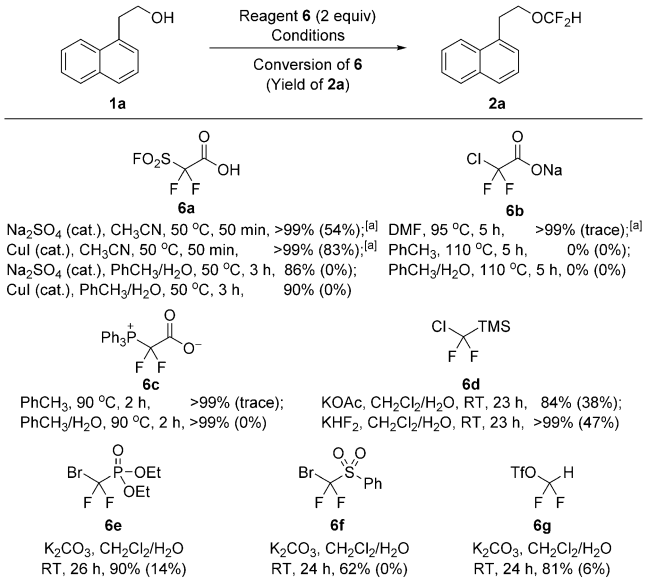


(1)

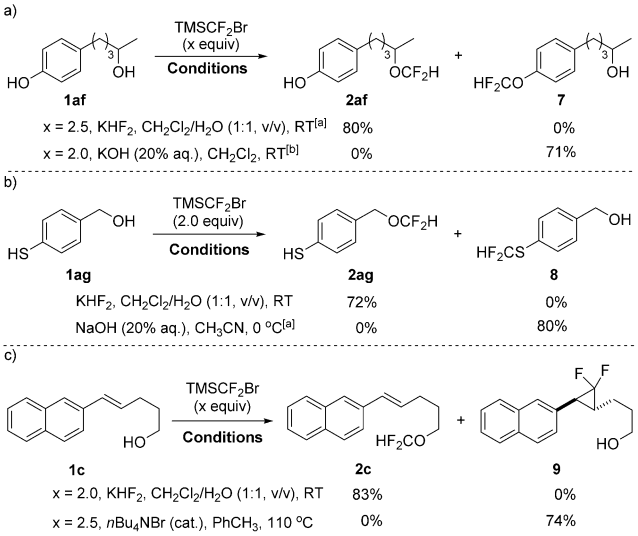
To demonstrate the unique feature of $TMSCF_2Br$, we investigated the difluoromethylation of alcohol **1a** by using other :CF_2 sources that have been employed for difluoromethylation of phenols.[10,11] Due to the potential substrate limitation of the strongly basic conditions (such as NaOH), we only considered reagents that can release :CF_2 under mild conditions (Scheme 4). The acidic reagent $FSO_2CF_2CO_2H$ (**6a**) could efficiently difluoromethylate **1a**;[18] however, its slow addition was required to avoid the competing consumption of :CF_2 by itself (Supporting Information). As for the neutral reagents $ClCF_2CO_2Na$ (**6b**) and $Ph_3P^+CF_2CO_2^-$ (**6c**), the former reacted very rapidly with :CF_2 even when it was slowly added to the reaction system,[23] while the latter readily



Scheme 3. Difluoromethylation of alcohols with $TMSCF_2Br$. Unless otherwise noted, reactions were performed on 0.5 mmol scale. Method A1: **3** (2.0 equiv), 20% aq. NaOH (5.0 equiv), CH_2Cl_2 (0.3 mL), 0°C, 2 h; Method A2: **3** (3.0 equiv), 20% aq. NaOH (8.0 equiv), CH_2Cl_2 (0.3 mL), 0°C, 2 h; Method B1: **3** (2.0 equiv), KOAc (4.0 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 10 h; Method B2: **3** (3.0 equiv), KOAc (6.0 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 10 h; Method B3: **3** (3.8 equiv), KOAc (7.6 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 15 h; Method C1: **3** (2.0 equiv), KHF_2 (4.0 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 10 h; Method C2: **3** (3.0 equiv), KHF_2 (6.0 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 10 h; Method C3: **3** (3.8 equiv), KHF_2 (7.6 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 15 h. The yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. The isolated yields of analytically pure compounds are given in the parentheses.



Scheme 4. Difluoromethylation of alcohol **1a** with other difluorocarbene reagents. For details of the reaction conditions, see the Supporting Information. Conversions of reagent **6** and yields of **2a** (the data in the parentheses) were determined by ^{19}F NMR spectroscopy.
[a] Reagent **6** was added during a period of 20 min.



Scheme 5. Divergent transformation of functionalized alcohols with $TMSCF_2Br$. [a] The bis(difluoromethylation) product was formed in 6% yield. [b] The bis(difluoromethylation) product was formed in 15% yield.

underwent decarboxylative protonation to afford the difluoromethyl phosphonium salt. Comparing $TMSCF_2Cl$ (**6d**) with $TMSCF_2Br$ (**3**), we found that the different halogen-substitutions can affect the reaction of **1a**, with **3** being more effective owing to the better leaving ability of the bromide ion. When reagents **6e–g** were used to generate $:CF_2$ in two-liquid-phase systems, the low yields of **2a** probably arose from the high hydrophilicity of the activated $:CF_2$ precursors, which resulted in more contact between $:CF_2$ and the aqueous base.

Because $:CF_2$ is of diverse reactivity and can be generated from $TMSCF_2Br$ under a variety of mild conditions, we considered that it would react divergently with ambident substrates. Thus, we finally investigated the transformation of several functionalized alcohols with $TMSCF_2Br$ as a $:CF_2$ source (Scheme 5). The reactions of phenol-alcohol **1af** and thiophenol-alcohol **1ag** under weakly acidic conditions afforded predominantly the alcohol difluoromethylation products, whereas their reactions under strongly basic conditions preferred the (thio)phenol difluoromethylation (Scheme 5a,b). These results further supported different mechanisms of difluoromethylation of alcohols and (thio)phenols with $:CF_2$. In the case of unsaturated alcohol **1c** (Scheme 5c), the two-phase system consisting of water and CH_2Cl_2 facilitated the difluoromethylation of alcohol at 0 °C, while the homogenous organic system of $PhCH_3$ at 110 °C promoted the selective difluorocyclopropanation of the alkene.

In summary, we have developed a general method for the efficient difluoromethylation of alcohols by using $TMSCF_2Br$ as a unique and practical difluorocarbene source under very mild conditions. The reaction proceeds through a mechanism that is different from the difluoromethylation of phenols, and allows primary, secondary, and tertiary alkyl difluoromethyl ethers to be synthesized using very simple procedures. Compared with other reagents, $TMSCF_2Br$ is particularly suitable for the generation of difluorocarbene in the organic phase of a two-liquid-phase system, which reduces the contact between difluorocarbene and the aqueous solution of the activator and promotes the difluoromethylation of alcohols. We also showed that $TMSCF_2Br$ is able to transform ambident substrate such as alcohol-phenol divergently by switching its activation methods. This work not only solves the synthetic problem of difluorocarbene-mediated difluoromethylation of alkyl alcohols, it also provides new insights into the different reaction mechanisms of alcohol difluoromethylation and phenol difluoromethylation with difluorocarbene.

Acknowledgements

This work was supported by the National Basic Research Program of China (2015CB931900), the National Natural Science Foundation of China (21632009, 21421002, 21472221, 21372246), Shanghai Academic Research Leader Program (15XD1504400), Shanghai Rising-Star Program (16QA1404600), the Youth Innovation Promotion Association CAS (2014231), and the Chinese Academy of Sciences. J.H. thanks Professor Long Lu (SIOC) for helpful discussions.

Conflict of interest

The authors declare the following competing financial interest: The Shanghai Institute of Organic Chemistry holds a patent on the chemistry described herein.

Keywords: alcohols · difluorocarbene · difluoromethyl ethers · fluorine · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 3206–3210
Angew. Chem. **2017**, *129*, 3254–3258

[1] a) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, **2008**; b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd ed., Wiley-VCH, Weinheim, **2013**.
[2] a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; b) P. Jeschke, E. Baston, F. R. Leroux, *Mini-Rev. Med. Chem.* **2007**, *7*, 1027, and references therein; c) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140, and references therein; d) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315; e) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726; *Angew. Chem.* **2016**, *128*, 11900.
[3] C. Wang, Z. Chen, W. Wu, Y. Mo, *Chem. Eur. J.* **2013**, *19*, 1436.
[4] N. Chauret, D. Guay, C. Li, S. Day, J. Silva, M. blouin, Y. Ducharme, J. A. Yergey, D. A. Nicoli-Griffith, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2149.
[5] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626–1631; b) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797.
[6] a) D. McKerrecher, K. G. Pike, M. J. Waring, PCT Int. Appl. WO 2007007042 A1, **2007**; b) T. J. Hoffman, S. Sulzer-Mosse, PCT Int. Appl. WO 2016/071239 A1, **2016**.
[7] a) S. S. Patel, K. L. Goa, *Drugs* **1995**, *50*, 742; b) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.
[8] For examples on multistep difluoromethylation of phenols and alcohols, see: a) Y. Hagooly, O. Cohen, S. Rozen, *Tetrahedron Lett.* **2009**, *50*, 392; b) W. R. Dolbier, F. Wang, X. Tang, C. S. Thomoson, L. Wang, *J. Fluorine Chem.* **2014**, *160*, 72.
[9] For examples on direct difluoromethylation of alcohols via electrophilic transfer of CF_2H unit, see: a) G. K. S. Prakash, Z. Zhang, F. Wang, C. Ni, G. A. Olah, *J. Fluorine Chem.* **2011**, *132*, 792; b) J. Zhu, Y. Liu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 9050; *Angew. Chem.* **2016**, *128*, 9196.
[10] C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842, and references therein.
[11] a) D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585; b) W. R. Dolbier Jr., M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071; c) M. Fedoryński, *Chem. Rev.* **2003**, *103*, 1099; d) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Coord. Chem. Rev.* **2014**, *261*, 28.
[12] a) J. Hine, K. Tanabe, *J. Am. Chem. Soc.* **1957**, *79*, 2654; b) J. Mizukado, Y. Matsukawa, H.-d. Quan, M. Tamura, A. Sekiya, *J. Fluorine Chem.* **2006**, *127*, 400, and references therein.
[13] R. M. Flynn, D. J. Burton, *J. Fluorine Chem.* **2011**, *132*, 815.
[14] a) L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390; *Angew. Chem.* **2013**, *125*, 12616; b) J. Hu, F. Wang, W. Zhang, China Patent, CN 101538193 A, **2009**; c) F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, *Chem. Commun.* **2011**, *47*, 2411; d) J. Hu, F. Wang, W. Zhang, China Patent, CN 101538186 A, **2009**; e) A. D. Dilman, V. V. Levin, *Mendeleev Commun.* **2015**, *25*, 239, and references therein; f) O. V. Fedorov, M. I. Struchkova, A. D. Dilman, *J. Org. Chem.* **2016**, *81*, 9455; g) A. L. Trifonov, A. A. Zemtsov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2016**, *18*, 3458; h) X. Song, S. Tian, Z. Zhao, D. Zhu, M. Wang, *Org. Lett.* **2016**, *18*, 3414.
[15] R. A. Mitsch, J. E. Robertson, *J. Heterocycl. Chem.* **1965**, *2*, 152.
[16] J. Mizukado, Y. Matsukawa, H.-d. Quan, M. Tamura, A. Sekiya, *J. Fluorine Chem.* **2005**, *126*, 365.
[17] R. Miethchen, M. Hein, D. Naumann, W. Tyrra, *Liebigs Ann. Chem.* **1995**, 1717.
[18] a) Q.-Y. Chen, S.-W. Wu, *J. Fluorine Chem.* **1989**, *44*, 433; b) K. Levchenko, O. P. Datsenko, O. Serhiichuk, A. Tolmachev, V. O. Iaroshenko, P. K. Mykhailiuk, *J. Org. Chem.* **2016**, *81*, 5803.
[19] M. Kampa, E. Castanas, *Environ. Pollut.* **2008**, *151*, 362.
[20] Similarly, the difluoromethylations of thiophenols and thioalcohols with difluorocarbene also proceed through the reaction between an anionic species and difluorocarbene. For details, see the Supporting Information.
[21] a) D. Praticò, N. Delanty, *Am. J. Med.* **2000**, *109*, 577; b) K. A. Lyseng-Williamson, *Drugs* **2016**, *76*, 805.
[22] E. Ravina, *The Evolution of Drug Discovery : From Traditional Medicines to Modern Drugs*, Wiley-VCH, Weinheim, **2011**, p. 175.
[23] a) T. J. Williams, M. F. Greaney, *Org. Lett.* **2014**, *16*, 4024; b) F. E. Herkes, D. J. Burton, *J. Org. Chem.* **1967**, *32*, 1311.

Manuscript received: December 5, 2016
Revised: January 24, 2017
Final Article published: February 9, 2017

