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A General *C-H* Difluoromethylation Protocol for Carbon Acids Using $TMSCF_2Br$

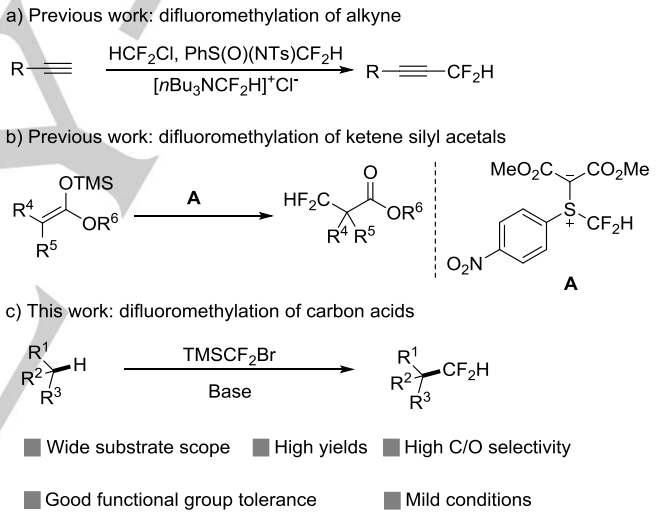
Qiqiang Xie, Ziyue Zhu, Lingchun Li, Chuanfa Ni, and Jinbo Hu*

Abstract: An efficient method for selective *C*-difluoromethylation of carbon acids with $TMSCF_2Br$ reagent has been developed. A variety of structurally diverse sp^3- and sp-hybridized carbon nucleophiles, including esters, amides, fluorenes, terminal alkynes, β-ketoesters, malonates, and other activated *C-H* nucleophiles, could be efficiently and selectively transformed to the corresponding *C*-difluoromethylated products under mild conditions. This protocol is also effective for the late-stage difluoromethylation of pharmaceutically relevant molecules, and can be easily scaled up. Moreover, ambident substrates which have more than one reactive site towards difluorocarbene can be difluoromethylated orthogonally using $TMSCF_2Br$.

Fluorinated molecules have found wide applications in pharmaceuticals, agrochemicals, and advanced materials.[1] Among them, the difluoromethyl (CF_2H) group is of special interest because it is known to be isosteric to OH/SH unit and can act as a lipophilic hydrogen bond donor.[2] As a consequence, many marketed drugs contain the CF_2H group. For examples, Roflumilast is an orally administered drug for the treatment of inflammatory conditions of the lungs such as chronic obstructive pulmonary disease (COPD),[3] and Pantoprazole is a drug used for the treatment of erosive esophagitis in patients with gastroesophageal reflux.[4] Therefore, it is of great importance to develop efficient methods to introduce the CF_2H motif into organic molecules.

Over the past decades, numerous methods have been developed to access CF_2H-containing molecules.[5] Among them, electrophilic difluoromethylation represents a powerful strategy, of which difluorocarbene-involved difluoromethylation has attracted consideration attention.[6] Difluorocarbene, a moderately electrophilic species, is an ideal intermediate for difluoromethylation. Various types of difluorocarbene reagents have been developed in recent years and their reactivity towards different nucleophiles have been studied.[6,7] Most of these reactions are focused on 1) the difluoromethylation of heteroatoms, such as *O*-, *S*-, *N*-, *P*- and *Se*-nucleophiles, and 2) the [2+1] cycloaddition with alkenes or alkynes. However, the difluoromethylation of *C-H* nucleophiles is sparse, with limited success being reported.[7a,8-14]

β-Ketoestes and malonates are the most studied *C-H* nucleophiles[7a,8], and their efficient difluoromethylation with high C/O selectivity were achieved very recently by the groups led by Shibata[9], Shen[10] and Liu[11]. However, for many other *C-H* nucleophiles, such as common esters, amides, fluorenes and alkynes, their reactivity towards difluorocarbene is largely underexplored or unknown. Chlorodifluoromethane[12], *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine[13] and difluoromethyltri(*n*-butyl)ammonium chloride[14] were used for the difluoromethylation of alkynes (Scheme 1a), but these methods suffer from several drawbacks such as low efficiency, narrow substrate scope and/or the requirement of ozone-depleting substance (ODS). In Shen's work, although some examples of oxindoles, benzofuranones and ketene silyl acetals were showed to react with difluoromethylated sulfonium ylide (**A**), the yields were typically low to moderate (Scheme 1b)[10]. Moreover, no examples of direct difluoromethylation of common esters or amides were demonstrated with reagent **A**. Therefore, the development of a general method for efficient difluoromethylation of various *C-H* nucleophiles with readily available reagent is highly desirable.[5f,6b]



Scheme 1. The difluoromethylation of *C-H* nucleophiles.

$TMSCF_2Br$, a difluorocarbene precursor developed by us[6d,7c], now is commercially available and is one of the most versatile difluorocarbene reagents.[6] It has been applied in the difluoromethylation of (thio)phenols, alcohols, thiols and amines[7c,7j], cyclopropa(e)nation of alkenes and alkynes[7c], among others.[7g-h,15] As our continuing effort in developing $TMSCF_2Br$ as a versatile and robust difluorocarbene reagent, herein, we report our recent success in the difluoromethylation of carbon acids using $TMSCF_2Br$ (Scheme 1c).

At the onset of our investigation, we chose 2,2-diaryl ethyl acetate **1a** as a model substrate and dichloromethane as solvent (Table 1). A variety of bases (for both deprotonation of **1a** and desilylation of $TMSCF_2Br$ to generate difluorocarbene) were screened (Table 1, entries 1-6), and only KO*t*Bu could give the desired product **2a** in 17% yield, together with about 1% of the *O*-difluoromethylated byproduct **2a'** (entry 3). Next, we examined the solvent effect of this reaction. When THF or DMF was used, **2a** was formed in moderate yields, and significant

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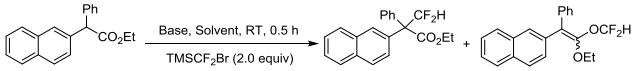
amounts of **2a'** were also formed (Table 1, entries 7 and 8). When the reaction was carried out in CH_3CN, although $TMSCF_2Br$ was fully consumed, **2a** was formed in very low yield (Table 1, entry 9). When 1,4-dioxane was used as solvent, **2a** was formed in 78% yield (Table 1, entry 10), together with **2a'** being formed in 9% yield. Adding lithium iodide could decrease the yield of byproduct **2a'** to 2% (Table 1, entry 11). To our delight, when the reaction was carried out in toluene, **2a** was formed in 84% yield, and no **2a'** was detected (Table 1, entry 12).

Table 1. Optimization of reaction conditions for the difluoromethylation of **1a**.[a]

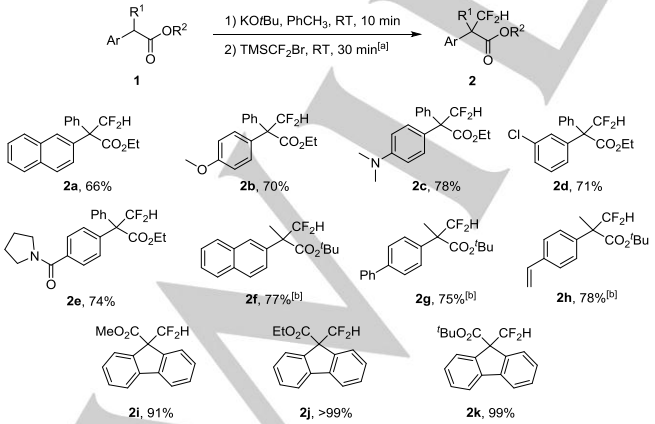


1a 2a 2a'

Entry	Base [equiv]	Solvent	**2a**, yield [%][c]	**2a'**, yield [%]
1	LiO*t*Bu (2.0)	CH_2Cl_2	ND (15%)	ND
2	NaO*t*Bu (2.0)	CH_2Cl_2	ND (60%)	ND
3	KO*t*Bu (2.0)	CH_2Cl_2	17 (39%)	1
4	LiHMDS (2.0)	CH_2Cl_2	ND (18%)	ND
5	NaHMDS (2.0)	CH_2Cl_2	ND (41%)	ND
6	KHMDS (2.0)	CH_2Cl_2	ND (7%)	ND
7	KO*t*Bu (2.0)	THF	64 (88%)	13
8	KO*t*Bu (2.0)	DMF	67 (>99%)	18
9	KO*t*Bu (2.0)	CH_3CN	13 (>99%)	7
10	KO*t*Bu (2.0)	1,4-dioxane	78 (>99%)	9
11[b]	KO*t*Bu (2.0)	1,4-dioxane	76 (>99%)	2
12	KO*t*Bu (2.0)	$PhCH_3$	84 (>99%)	ND

[a] Reactions were performed on 0.2 mmol scale (**1a**); solvent (2 mL) was used. Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] 0.2 equiv. of LiI was added. ND = not detected. [c] Conversion of $TMSCF_2Br$ was given in parentheses.

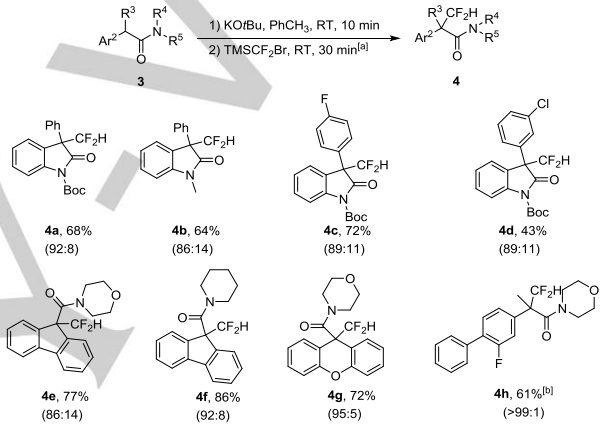
With the optimized conditions in hand (Table 1, entry 12), we examined the scope of esters (Scheme 2). A variety of 2,2-diaryl acetates were smoothly difluoromethylated in good yields (**2a**-**e**). Dimethylamino group, which could react with difluorocarbene, was tolerated under the reaction conditions, and *N*-difluomethylated product was not detected (**2c**). Amide group was compatible with the reaction conditions (**2e**). 2-Alkyl arylacetates are also suitable substrates (**2f**-**h**); however, owing to their relatively higher pKa value comparing to 2,2-diaryl acetates, a mixed base of KHMDS and KO*t*Bu were required to achieve a full conversion of the substrates **1f**-**h**. Notably, the vinyl group, which could undergo [2+1] cycloaddition with difluorocarbene species, was found to be tolerated under the present difluoromethylation reaction conditions (**2h**). The steric



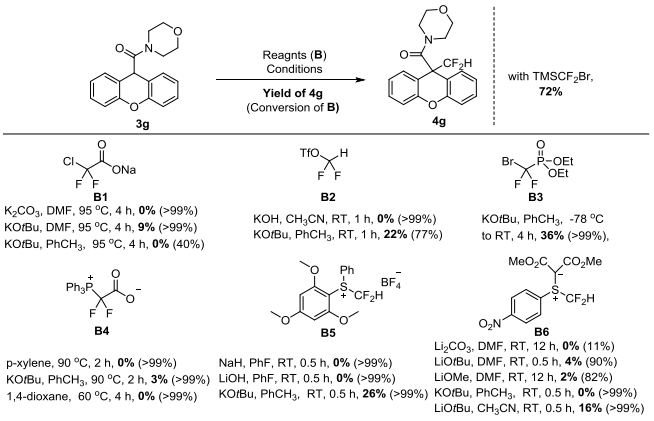
Scheme 2. Difluoromethylation of esters. [a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhCH_3$ (4.0 mL). [b] KO*t*Bu (1.0 equiv) and KHMDS (1.0 equiv) were used instead of KO*t*Bu (2.0 equiv).

hindrance of the esters does not have obvious impact on the reaction efficiency; for instance, all of the methyl, ethyl and *tert*-butyl esters gave the corresponding desired products in excellent yields (**2i**-**k**).

Next, we found that α-aryl amides are also suitable substrate for this difluoromethylation reaction. However, for this type of substrate, *O*-difluoromethylated byproducts were also observed in most cases, but the C/O regioselectivity were high (86:14 to >99:1) (Scheme 3). Oxindoles, either with *N*-Boc or *N*-Me protection, could give the desired products in moderate yields (**4a**-**b**). Functional groups such as halogens (**4c**-**d**) are tolerated. For morpholine- and piperidine-derived amides, the desired products were formed in good yields (**4e**-**g**). Of special note is that for flurbiprofen, a member of the phenylalkanoic acid family of nonsteroidal anti-inflammatory drugs (NSAIDs), its amide analog was successfully difluoromethylated to give **4h** in 61% yield with >99:1 C/O regioselectivity.



Scheme 3. The difluoromethylation of amides. [a] Reaction conditions: **3** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhCH_3$ (4.0 mL). The data in parentheses refer to the ratio of *C*- and *O*-difluomethylated regioisomers and was determined by ^{19}F NMR spectroscopy of the crude mixture. Isolated yield of **4** were given. [b] KHMDS (3.0 equiv) was used instead of KO*t*Bu (2.0 equiv), and 3.0 equiv of $TMSCF_2Br$ was used.



Scheme 4. The reactivity of other difluorocarbene reagents towards **3g**.

Inspired by these exciting results, we turned our attention to the unique reactivity of $TMSCF_2Br$ and carried out some comparison experiments using other difluorocarbene sources **B1**-**B6** (Scheme 4). Amide **3g** was selected as a model substrate. As described in Scheme 3, $TMSCF_2Br$ can difluoromethylate **3g** to give product **4g** in 72% yield. However, under the optimized and modified reaction conditions[7b,7d,10-11,16],

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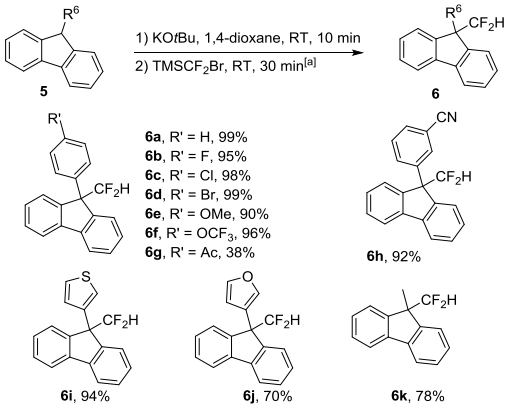
difluorocarbene reagents **B1**-**B6** showed low reactivity towards **3g**, and desired product **4g** was formed in low yields (0-36%), with most of **3g** being recovered. These data highlights the unique feature and advantage of $TMSCF_2Br$ as a privileged difluorocarbene precursor.

Owing to the distinguished difluoromethylation power of $TMSCF_2Br$ reagent for esters and amides, we further extend the substrate scope to other *C-H* carbon nucleophiles. Fluorene is an important structure scaffold with wide application in advanced materials because of its unique electronic and photonic properties.[17] After brief optimization of reaction conditions, 9-aryl/alkyl substituted fluorenes could be efficiently difluoromethylated (Scheme 5).

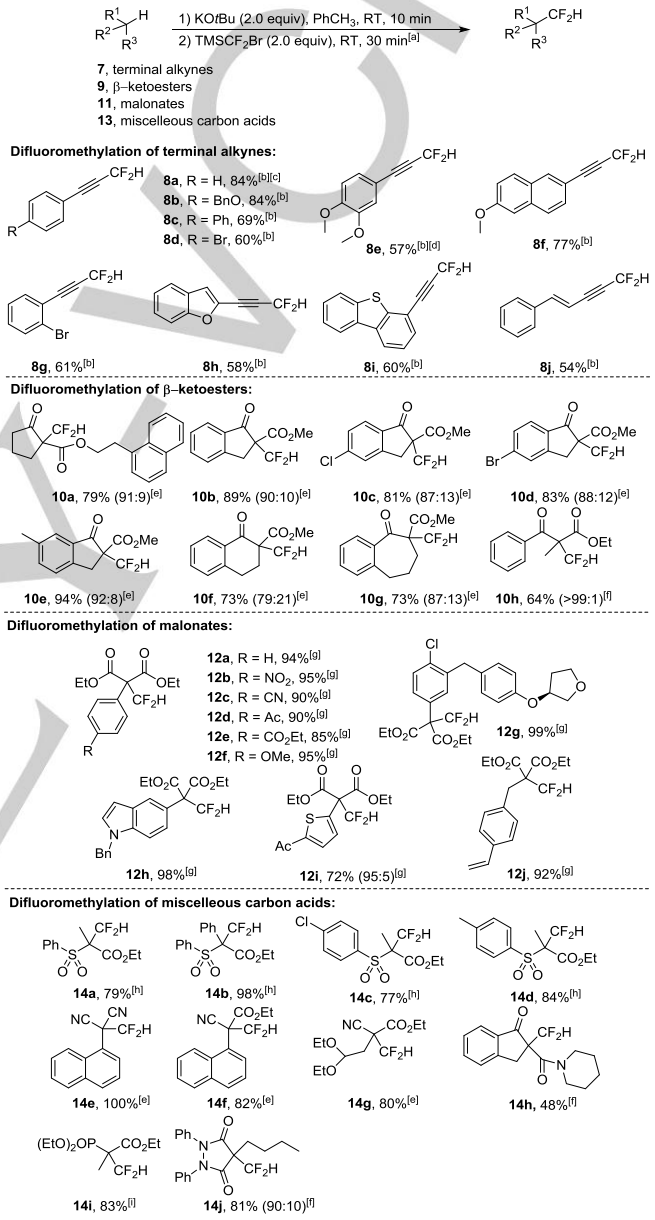


Scheme 5. The difluoromethylation of fluorenes. [a] Reaction conditions: **5** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), 1,4-dioxane (4.0 mL).

This protocol is not only useful for the difluoromethylation of sp^3-hybridized *C-H* nucleophiles, but also efficient for sp-hybridized ones. The reaction proceeded smoothly with terminal alkynes, and a variety of difluoromethylated alkynes were obtained (Scheme 6). Both electron-rich and electron-neutral aryl alkynes resulted in moderate to good yields (**8a**-**g**). Heterocycles are compatible with the reaction conditions (**8h**-**i**), and this method is also applicable to the enyne substrate, giving the difluoromethylated product **8j** in 54% yield.

Our $TMSCF_2Br$-mediated difluoromethylation protocol is also applicable to β-ketoesters with lower loadings of $TMSCF_2Br$ than the previous report (Scheme 6).[9] Under the aqueous basic conditions, cyclic ketoesters (**10a**-**g**) were difluoromethylated successfully in good yields (73%-94%) with high C/O selectivity (79:21 to 92:8). It is worth noting that acyclic β-ketoesters are also suitable substrates, giving the desired product in 64% yield and excellent C/O selectivity (**10h**). However, for 1,3-diketones, such as 1,3-cyclohexanone, only *O*-difluoromethylated product was formed, which is in consistence with previous report.[18] Malonates also exhibited good reactivity in this difluoromethylation reaction (Scheme 6). A variety of 2-aryl, 2-heteroaryl, and 2–alkyl substituted malonates reacted smoothly, affording the desired products in good to excellent yield (**12a**-**j**). However, when un-substituted malonate (diethyl malonate) was used as a substrate, the difluroromethylated product was formed in low yield (24%, determined by ^{19}F NMR) and no diethyl malonate was recovered after the reaction.

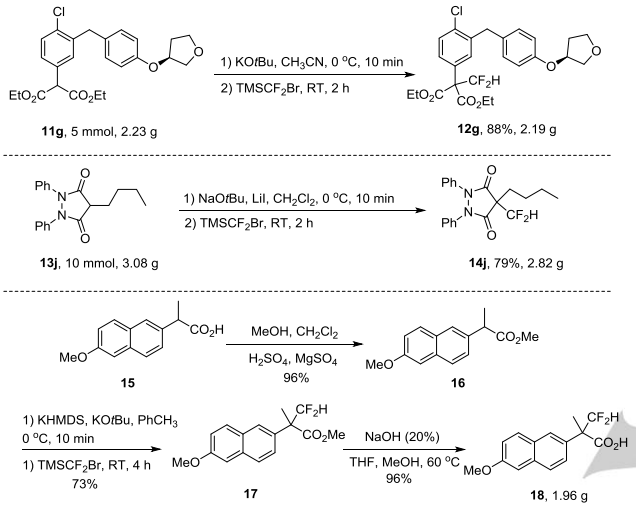
Apart from the above mentioned carbon acids, many other carbon acids which contain an activated *C-H* bond could also successfully difluoromethylated (Scheme 6). α-Sulfonyl esters (**14a**-**d**), malononitrile (**14e**), α-cyano esters (**14f**-**g**), β-ketoamide (**14h**) and α-phosphono ester (**14i**) reacted smoothly, giving the desired products in moderate to excellent yields (48%-100%). It is noteworthy that pharmaceutically important molecules such as phenylbutazone[19], a drug that has anti-inflammatory, antipyretic, and analgesic activities, is also amenable in our protocol, and the corresponding difluoromethylated product **14j** was formed in 81% yield and with 90:10 C/O selectivity. This example shows the potential of this difluoromethylation protocol for the late-stage modification of other bioactive molecules.



Scheme 6. The difluoromethylation of alkynes, β-ketoesters, malonates and miscellaneous carbon acids. [a] Reaction conditions: **7**, **9**, **11** or **13** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhCH_3$ (2.0 mL); The C/O selectivity is given in parentheses. [b] 0 °C instead of RT. [c] Yield was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [d] $TMSCF_2Cl$ (2.0 equiv) was used instead of $TMSCF_2Br$. [e] NaOH (20% aq., 6.0 equiv) was used instead of KO*t*Bu; CH_2Cl_2 was used instead of $PhCH_3$. [f] NaO*t*Bu was used instead of KO*t*Bu; LiI (0.2 equiv) was added; CH_2Cl_2 was used instead of $PhCH_3$. [g] CH_3CN was used instead of $PhCH_3$. [h] LiO*t*Bu was used instead of KO*t*Bu; THF was used instead of $PhCH_3$. [i] LiO*t*Bu was used instead of KO*t*Bu.

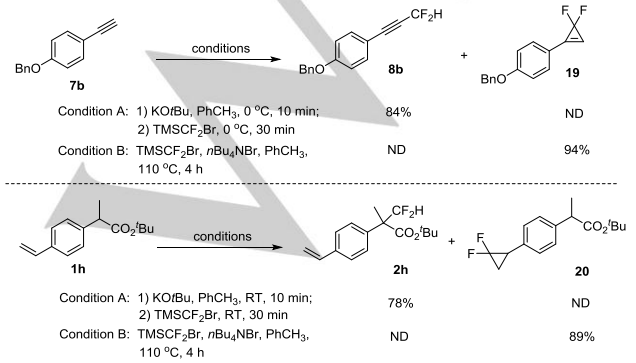
To further demonstrate the practicability of our method, the gram-scale syntheses were performed (Scheme 7). When the

reaction with complex substrate **11g** was scaled up to 2.23 grams, the desired product **12g** was formed in 88% yield (2.19 g). For the drug molecule **13j**, 10 mmol-scale (3.08 g) reaction could give the difluoromethylated analog **14j** in 79% yield. 2-(Methoxy-2-naphthyl)-propanoic acid **15** (its *S*-isomer is called naproxen), a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain or inflammation[20], could be easily transformed to ester **16**. **16** could be efficiently difluoromethylated to **17**, which underwent hydrolysis to give **18**. Thus, from the racemic naproxen, we could easily obtain the difluoromethylated naproxen **18** in three steps with 67% overall yield. These examples further showcase the potency of our difluoromethylation protocol in the late-stage difluoromethylation of bioactive compounds for drug discovery.



Scheme 7. Late-stage difluoromethylation of bioactive and complex molecules in gram scale.

Due to the unique feature of $TMSCF_2Br$ that can generate difluorocarbene under different conditions, we envisioned that its orthogonal reactivity towards different functional groups in ambident substrates under different conditions could be possible (Scheme 8). For alkyne **7b**, under basic conditions, only the difluoromethylated alkyne **8b** was formed in 84% yield; while with *n*Bu_4NBr being used as a catalyst at 110 °C, the difluorocyclopropene **19** was formed exclusively in 94% yield.[21] For the vinyl-containing ester **1h**, the acidic *C-H* bond was selectively difluoromethylated to give **2h** in 78% yield under basic conditions, and the difluorocyclopropane **20** was exclusively generated in 89% yield at high temperature under neutral conditions. To the best of our knowledge, this type of orthogonal reactivity has never been exhibited by other difluorocarbene sources, which features $TMSCF_2Br$ as a unique and versatile difluorocarbene reagent.[22]



Scheme 8. Orthogonal transformations of ambident substrates. ND = not detected.

In conclusion, a general method for efficient difluoromethylation of a wide range of carbon acids has been developed, using $TMSCF_2Br$ as a powerful difluorocarbene reagent. This protocol is easy to scale up and amenable to the late-stage modification of bioactive compounds. Compared with other difluorocarbene reagents, $TMSCF_2Br$ showed unique reactivity towards *C*-nucleophiles in terms of the reaction efficiency and substrate scope. We also demonstrated the orthogonal reactivity of $TMSCF_2Br$ towards ambident substrates, which has never been exemplified by other difluorocarbene reagents. This work not only provides a facile approach to access the difluoromethylated analog of sp^3- and sp-hybridized *C*-nucleophiles, it also opens a new avenue for the orthogonal reactivity study in difluorocarbene chemistry. Further investigations in this direction are underway in our laboratory.

Acknowledgements

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Keywords: difluorocarbene • difluoromethylation • carbon acids • bromodifluoromethyltrimethylsilane • synthetic method

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[21] We carried out the reaction between (phenylethynyl)potassium (prepared in situ from phenylacetylene and KH) and $TMSCF_2Br$ at 0 ^{o}C for 30 min, and found that $TMSCF_2Br$ was recovered in 93% yield (determined by ^{19}F NMR spectroscopy), with no other fluorinated signal being observed. This result rules out the possibility that the current C-difluoromethylation with $TMSCF_2Br$ proceeds through a stepwise sequence (new C-C bond formation along with C-Br bond cleavage, followed by C-Si bond cleavage).

[22] The unique reactivity of $TMSCF_2Br$ can be attributed to its multiple (and tunable) activation modes to release difluorocarbene, such as under strongly basic (alkoxide, hydroxide), weakly basic (NaOAc), neutral ($n$$Bu_4NBr$), acidic ($KHF_2$) conditions as well as at different temperatures (also see Ref. 7c and 7j). However, other known difluorocarbene reagents usually have only one activation mode to generate difluorocarbene. For difluorocarbene-involved difluoromethylation with carbanions, basic conditions and relatively lower temperature are often used (such as Condition A in Scheme 8); while for difluorocarbene-involved cycloprope(a)nations with alkynes or alkenes, non-basic conditions and sufficiently high temperature are usually required (such as Condition B in Scheme 8). Therefore, the orthogonal reactivity of $TMSCF_2Br$ (as difluorocarbene reagent) towards carbanions and unsaturated carbon-carbon bonds can be well tuned by changing the acidity/basicity of the reaction medium as well as the reaction temperature. For related discussions, also see Ref 6d, 7c and 7j.

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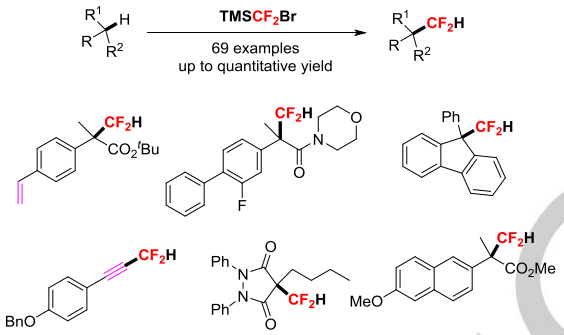
Carbene for carbon: Difluorocarbene (generated from $TMSCF_2Br$) is able to efficiently react with various carbon nucleophiles. This powerful *C-H* difluoromethylation protocol provides an easy access to *C*-difluoromethylated products from corresponding carbon acids under mild conditions.



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