Synthetic Methods

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A General Protocol for C–H Difluoromethylation of Carbon Acids with $TMSCF_2Br$

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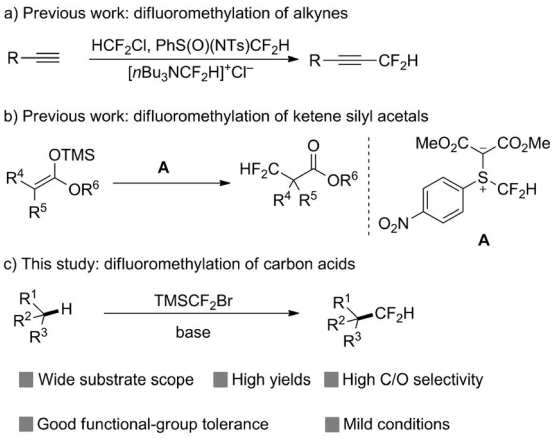
Abstract: *An efficient method for the selective C-difluoromethylation of carbon acids with the reagent $TMSCF_2Br$ has been developed. A variety of structurally diverse sp^3- and sp-hybridized carbon nucleophiles, including esters, amides, fluorenes, terminal alkynes, β-ketoesters, malonates, and other activated C–H nucleophiles, could be efficiently and selectively transformed into 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 readily scaled up. Moreover, ambident substrates with more than one reactive site towards difluorocarbene can be difluoromethylated orthogonally using $TMSCF_2Br$.*

Fluorinated molecules have found wide application 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 the 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 example, 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 is a powerful strategy, and difluoromethylation involving difluorocarbene has attracted consideration attention.[6] Difluorocarbene, a moderately electrophilic species, is an ideal intermediate for difluoromethylation. Various types of difluorocarbene reagents have been developed and their reactivity towards different nucleophiles studied.[6,7] Most of these reactions are focused on the difluoromethylation of heteroatoms, such as O, S, N, P, and Se nucleophiles, and [2+1] cycloaddition with alkenes or alkynes. However, examples of the difluoromethylation of C–H nucleophiles are sparse, with limited success being reported.[7a,8–14]

β-Ketoesters and malonates are the most studied C–H nucleophiles,[7a,8] and their efficient difluoromethylation with high C/O selectivity was reported very recently by the research groups led by Shibata,[9] Shen,[10] and Liu.[11] However, the reactivity of many other C–H nucleophiles, such as common esters, amides, fluorenes, and alkynes, 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 1 a), but these methods suffer from several drawbacks, such as low efficiency, narrow substrate scope, and/or the requirement of ozone-depleting substances (ODSs). In the study by Shen and co-workers, although some oxindoles, benzofuranones, and ketene silyl acetals were shown to react with the difluoromethylated sulfonium ylide **A**, the yields were typically low to moderate (Scheme 1 b).[10] Moreover, no examples of the direct difluoromethylation of common esters or amides were demonstrated with reagent **A**. Therefore, the development of a general method for the efficient difluoromethylation of various C–H nucleophiles with a readily available reagent is highly desirable.[5f,6b]



Scheme 1. Difluoromethylation of C–H nucleophiles. TMS = trimethylsilyl.

TMSCF$_2$Br, a difluorocarbene precursor developed by us,[6d-f,7c] is now 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[7cj] as well as the cyclopropanation or cyclopropenation of alkenes and alkynes,[7c] among other applica-

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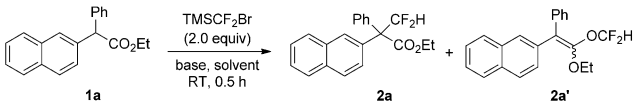
tions.[7g–h,15] In continuation of our effort to develop $TMSCF_2Br$ as a versatile and robust difluorocarbene reagent, we report herein our recent success in the difluoromethylation of carbon acids with $TMSCF_2Br$ (Scheme 1c).

At the onset of our investigation, we chose 2,2-diaryl ethyl acetate **1a** as a model substrate and dichloromethane as the solvent (Table 1). A variety of bases (for both the deprotonation of **1a** and desilylation of $TMSCF_2Br$ to generate difluorocarbene) were screened (Table 1, entries 1–6); only KO*t*Bu gave the desired product **2a** in 17% yield, together with the O-difluoromethylated by-product **2a′** in about 1% yield (entry 3). Next, we examined the solvent effect of this reaction. When THF or DMF was used, **2a** was formed in moderate yield, and significant 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 the solvent, **2a** was formed in 78% yield (Table 1, entry 10), together with **2a′** in 9% yield. The addition of lithium iodide decreased the yield of by-product **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 the reaction conditions for the difluoromethylation of **1a**.[a]

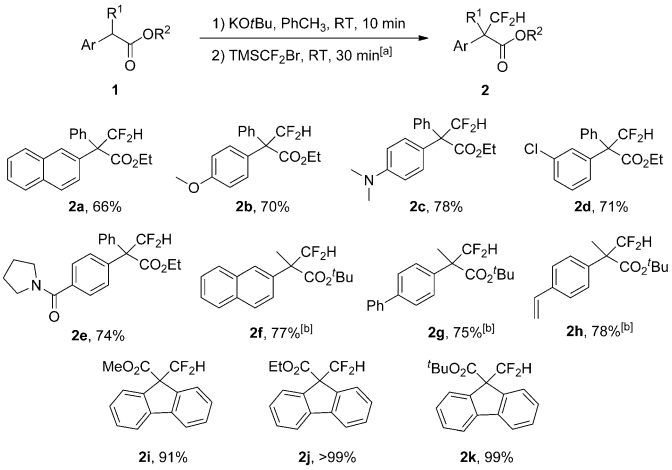


1a **2a** **2a'**

Entry	Base (equiv)	Solvent	Yield [%]	
			2a[b]	**2a′**
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[c]	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 a 0.2 mmol scale (**1a**) in 2 mL of the solvent. Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] The conversion of $TMSCF_2Br$ is given in parentheses. [c] LiI (0.2 equiv) was added. HMDS = hexamethyldisilazide, ND = not detected.

With the optimized conditions in hand (Table 1, entry 12), we examined the scope of the reaction (Scheme 2). A variety of 2,2-diaryl acetates were smoothly difluoromethylated in good yields to give products **2a–e**. A dimethylamino group, which could react with difluorocarbene, was tolerated under the reaction conditions (product **2c**), and no N-difluoromethylated products were detected. An amide group was also compatible with the reaction conditions (product **2e**). 2-Alkyl aryl acetates are also suitable substrates (products **2f–h**); however, owing to their higher pKa value as compared to that of 2,2-diaryl acetates, a mixture of the bases KHMDS and KO*t*Bu was required for 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 (product **2h**). The steric hindrance of the esters does not have an obvious impact on the reaction efficiency; for example, methyl, ethyl, and *tert*-butyl esters gave the corresponding desired products **2i–k** in excellent yield.

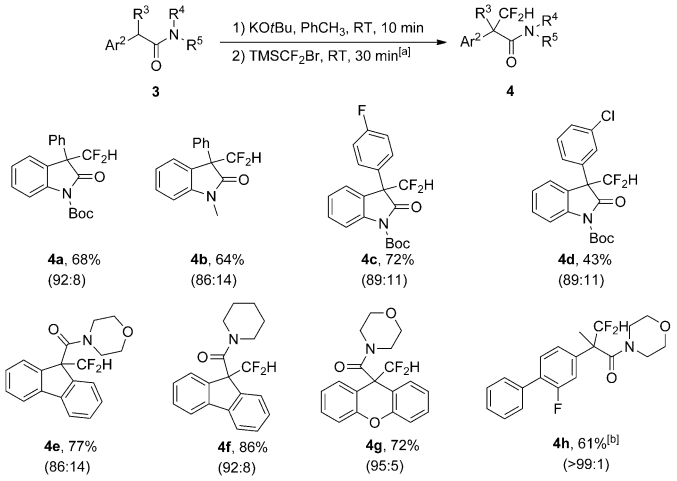


Scheme 2. Difluoromethylation of esters. [a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhCH_3$ (4.0 mL). [b] KO*t*Bu (1.0 equiv) and KHMDS (1.0 equiv) were used instead of KO*t*Bu (2.0 equiv).

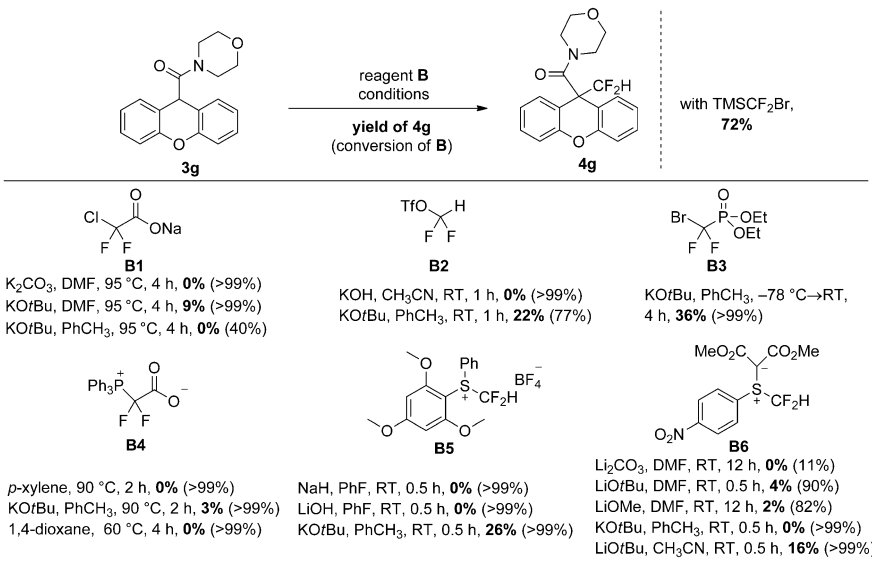
Next, we found that α-aryl amides are also suitable substrates for this difluoromethylation reaction. Although for this type of substrate, O-difluoromethylated by-products were also observed in most cases, the C/O regioselectivity was high (86:14 to >99:1; Scheme 3). Oxindoles with either N-Boc or N-Me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

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**, which underwent difluoromethylation with $TMSCF_2Br$ to give **4g** in 72% yield (Scheme 3), was selected as a model substrate. Under the optimized and modified reaction conditions,[7b,d,10,11,16] difluorocarbene reagents **B1–B6** showed low reactivity towards **3g**, and the desired product **4g** was formed in low yields (0–36%), with most of **3g** being recovered. These results highlight the unique reactivity and advantage of $TMSCF_2Br$ as a privileged difluorocarbene precursor.

Owing to the excellent difluoromethylation ability of the $TMSCF_2Br$ reagent for esters and amides, we further extended the reaction to other C–H carbon nucleophiles.



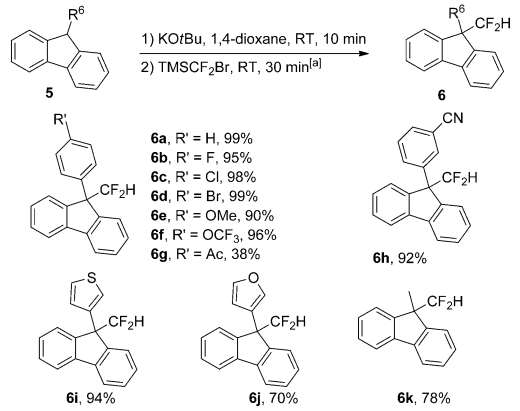
Scheme 3. Difluoromethylation of amides. [a] Reaction conditions: **3** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhCH_3$ (4.0 mL). The ratio of C- and O-difluoromethylated regioisomers, as determined by ^{19}F NMR spectroscopy of the crude mixture, is given in parentheses. Yields are for the isolated products **4**.
[b] KHMDS (3.0 equiv) was used instead of KO*t*Bu (2.0 equiv), and 3.0 equivalents of $TMSCF_2Br$ were used.



Scheme 4. Reactivity of other difluorocarbene reagents towards **3g**. Tf = trifluoromethanesulfonyl.

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 the reaction conditions, 9-aryl/alkyl-substituted fluorenes could be efficiently difluoromethylated (Scheme 5).

This protocol is not only useful for the difluoromethylation of sp^3-hybridized C–H nucleophiles, but also efficient for sp-hybridized C–H nucleophiles. The reaction proceeded smoothly with terminal alkynes, and a variety of difluoromethylated alkynes were obtained (Scheme 6). The use of both electron-rich and electron-neutral aryl alkynes led to the desired products **8a–g** in moderate to good yields. Heterocycles are compatible with the reaction conditions (products

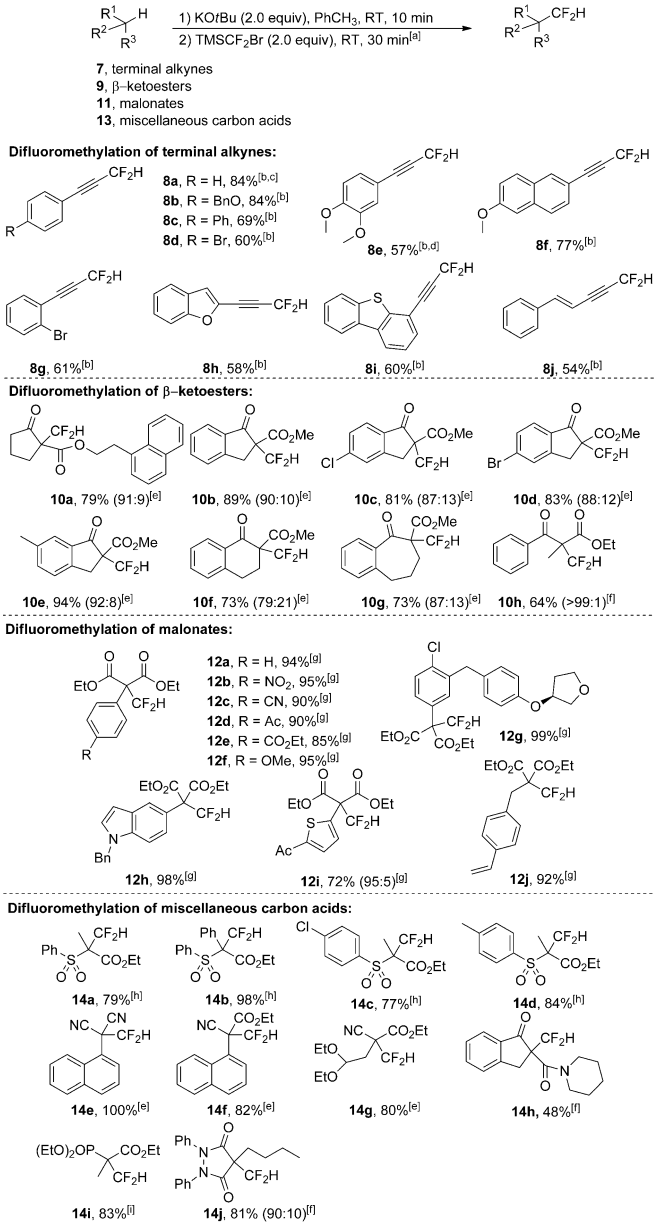


Scheme 5. Difluoromethylation of fluorenes. [a] Reaction conditions: **5** (0.5 mmol, 1.0 equiv), KO*t*Bu (2.0 equiv), $TMSCF_2Br$ (2.0 equiv), 1,4-dioxane (4.0 mL).

8h,i), and this method was also applicable to an enyne substrate, which gave 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 used in the previously reported study (Scheme 6).[9] Under the aqueous basic conditions, cyclic ketoesters were difluoromethylated successfully in good yields (73–94%) to give **10a–g** with high C/O selectivity (79:21 to 92:8). Notably, an acyclic β-ketoester was also a suitable substrate, giving the desired product **10h** in 64% yield with excellent C/O selectivity. However, for 1,3-diketones, such as 1,3-cyclohexanone, only the O-difluoromethylated product was formed, which is in agreement with a 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 to afford the desired products **12a–j** in good to excellent yield. However, when unsubstituted diethyl malonate was used as a substrate, the difluoromethylated product was formed in low yield (24%, determined by ^{19}F NMR spectroscopy), and no diethyl malonate was recovered after the reaction.

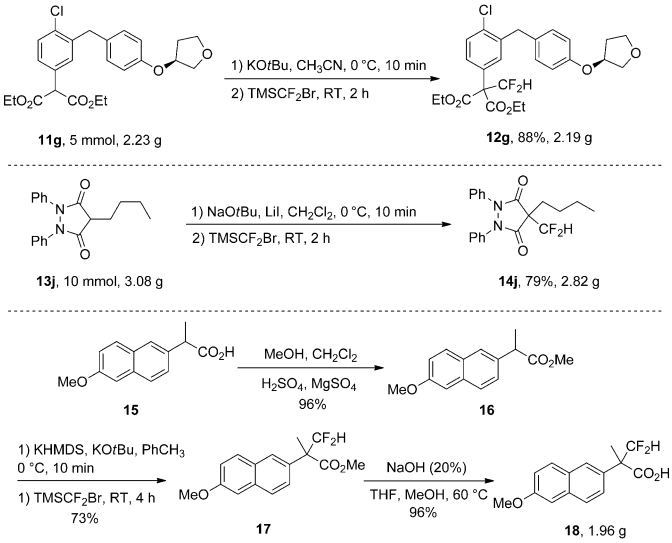
Many other carbon acids containing an activated C–H bond could also be successfully difluoromethylated (Scheme 6). α-Sulfonyl esters (products **14a–d**), a malononitrile (product **14e**), α-cyano esters (products **14f,g**), a β-ketoamide (product **14h**), and an α-phosphono ester (product **14i**) reacted smoothly to give the desired products in moderate to excellent yields (48–100%). Pharmaceutically important molecules are also amenable to difluoromethylation by this method. For example, phenylbutazone,[19] a drug that has anti-inflammatory, antipyretic, and analgesic activ-



Scheme 6. 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] The reaction was carried out at 0 °C instead of room temperature. [c] The 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.

ities, was converted into the corresponding difluoromethylated product **14j** in 81% yield with 90:10 C/O selectivity, which shows the potential of this difluoromethylation protocol for the late-stage modification of bioactive molecules.

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

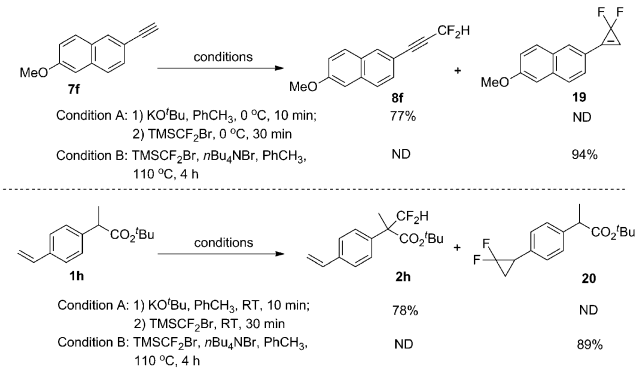


Scheme 7. Late-stage difluoromethylation of bioactive and complex molecules on a gram scale.

When the reaction with complex substrate **11g** was scaled up to 2.23 g, the desired product **12g** was formed in 88% yield (2.19 g). For the drug molecule **13j**, a reaction on a 10 mmol scale (3.08 g) gave the difluoromethylated analogue **14j** in 79% yield. 2-(6-Methoxy-2-naphthyl)propanoic acid (**15**; its *S* isomer is called naproxen), a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain and inflammation,[20] could be readily transformed into ester **16**. Product **16** was efficiently difluoromethylated to provide **17**, which underwent hydrolysis to give **18**. Thus, from racemic naproxen, we readily obtained difluoromethylated naproxen **18** in three steps and 67% overall yield. These examples further showcase the potential of our difluoromethylation protocol in the late-stage difluoromethylation of bioactive compounds for drug discovery.

Owing to the unique properties of $TMSCF_2Br$, which 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). When alkyne **7f** was used under basic conditions, only the difluoromethylated alkyne **8f** was formed in 77% yield, whereas the use of nBu_4NBr as a catalyst at 110 °C led to the exclusive formation of difluorocyclopropene **19** in 94% yield.[21] In the case of the vinyl-containing ester substrate **1h**, the acidic C–H bond was selectively difluoromethylated to give **2h** in 78% yield under basic conditions, and 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 highlights the unique and versatile reactivity of $TMSCF_2Br$ as a difluorocarbene reagent.[22]

In conclusion, a general method for the 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



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

late-stage modification of bioactive compounds. As compared to 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 described for other difluorocarbene reagents. This study not only provides a facile approach to the difluoromethylated analogues of sp^3- and sp-hybridized C-nucleophiles, but also opens a new avenue for studying orthogonal reactivity in difluorocarbene chemistry. Further investigations in this direction are under way in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

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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 °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 (formation of a new C−C bond 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 for the release of difluorocarbene, which can occur under strongly basic (alkoxide, hydroxide), weakly basic (KOAc), neutral ($n$$Bu_4NBr$), and acidic ($KHF_2$) conditions as well as at different temperatures (also see Refs. [7c,j]). However, other known difluorocarbene reagents usually have only one activation mode for the generation of difluorocarbene. For difluorocarbene-involving difluoromethylation with carbanions, basic conditions and a lower temperature are often used (such as conditions A in Scheme 8), whereas for difluorocarbene-involving cyclopropenation or cyclopropanation with alkynes or alkenes, nonbasic conditions and a sufficiently high temperature are usually required (such as conditions B in Scheme 8). Therefore, the orthogonal reactivity of $TMSCF_2Br$ (as a difluorocarbene reagent) towards carbanions and unsaturated carbon–carbon bonds can be tuned well by changing the acidity/basicity of the reaction medium as well as the reaction temperature. For related discussions, see also Refs. [6d, 7c, j].

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