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A Journey of the Development of Privileged Difluorocarbene Reagents $TMSCF_2X$ (X = Br, F, Cl) for Organic Synthesis

Qiqiang Xie and Jinbo Hu*

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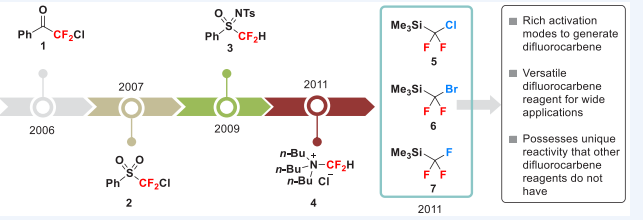
CONSPECTUS: As fluorine has played an increasingly important role in modulating the physical, chemical, and biological properties of organic molecules, the selective introduction of fluorine atom(s) or fluorinated moieties into target molecules has become a powerful tool in the development of new pharmaceuticals, agrochemicals, and functional materials. In this context, the difluoromethylene (CF_2) and difluoromethyl (CF_2H) groups are of special interest because of their ability to serve as bioisosteres of ethereal oxygen atoms and hydroxyl (OH) and thiol (SH) groups, respectively. Difluorocarbene is one of the most versatile reactive intermediates to incorporate CF_2 and CF_2H groups; however, before 2006, most of the previously known difluorocarbene reagents suffered from several drawbacks such as using ozone-depleting substances (ODSs), difficult-to-handle reagents, or harsh reaction conditions or having narrow substrate scope and/or low yields. Moreover, the reactivity of difluorocarbene generated from different precursors (reagents) was often unpredictable, since the difluorocarbene generation conditions (activation modes) of various difluorocarbene precursors are different, and these conditions may mismatch those required for subsequent difluorocarbene-involved transformations. Therefore, the development of new environmentally friendly and versatile difluorocarbene reagents, as well as the investigation of the mechanistic insights into difluorocarbene-involved reactions, has been highly desirable.



In this Account, we summarize our contributions to the development of new difluorocarbene reagents and their applications in organic synthesis since 2006. We have developed seven new difluorocarbene reagents, including 2-chloro-2,2-difluoroacetophenone (**1**), chlorodifluoromethyl phenyl sulfone (**2**), *S*-difluoromethyl-*S*-phenyl-*N*-tosylsulfoximine (**3**), difluoromethyltri(*n*-butyl)-ammonium chloride (**4**), (chlorodifluoromethyl)trimethylsilane ($TMSCF_2Cl$, **5**), (bromodifluoromethyl)trimethylsilane ($TMSCF_2Br$, **6**), and (trifluoromethyl)trimethylsilane ($TMSCF_3$, **7**). In this journey, we realized the key factor for an ideal difluorocarbene reagent that can be used for a broad range of reactions, that is, the reagent should allow various activation modes for the generation of difluorocarbene species, such as under basic/acidic/neutral conditions, at wide range of temperatures, and in different solvents, which are compatible with a wide range of difluorocarbene-involved transformations. Among all known difluorocarbene reagents, silanes $TMSCF_2X$ (X = Br, F, Cl) have stood out as privileged ones, which paves a new avenue for further developing difluorocarbene chemistry. In particular, $TMSCF_2Br$ was recognized as an "all-rounder": $TMSCF_2Br$ can be applied in almost all common difluorocarbene-involved reactions, and more importantly, $TMSCF_2Br$ also enables many other novel transformations that other difluorocarbene reagents cannot achieve, thanks to its unique structure and rich activation modes of releasing difluorocarbene under different reaction conditions. It can be expected that with the commercial availability of $TMSCF_2X$ reagents (X = Br, F, Cl) now, the development of difluorocarbene chemistry will be accelerated in the years to come.

KEY REFERENCES

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- Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Olah, G. A. Synthesis of *gem*-Difluorinated Cyclopropanes and Cyclopropenes: Trifluoromethyltrimethylsilane as a Difluorocarbene Source. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153−7157.[2] In this work, $TMSCF_3$ was developed as an

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efficient difluorocarbene reagent under activation by TBAT or NaI.

- Xie, Q.; Ni, C.; Zhang, R.; Li, L.; Rong, J.; Hu, J. Efficient Difluoromethylation of Alcohols Using $TMSCF_2Br$ as A Unique and Practical Difluorocarbene Reagent under Mild Conditions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3206−3210.[3] In this work, we achieved efficient difluoromethylation of alcohols with $TMSCF_2Br$ and recognized that the difluorocarbene-enabled difluoromethylations of alcohols and phenols proceeded through different mechanisms. The "orthogonal" reactivity of $TMSCF_2Br$ was demonstrated for the first time.
- Wang, X.; Pan, S.; Luo, Q.; Wang, Q.; Ni, C.; Hu, J. Controllable Single and Double Difluoromethylene Insertions into C−Cu Bonds: Copper-Mediated Tetrafluoroethylation and Hexafluoropropylation of Aryl Iodides with $TMSCF_2H$ and $TMSCF_2Br$. *J. Am. Chem. Soc.* **2022**, *144*, 12202−12211.[4] In this work, $TMSCF_2Br$ was used as the difluorocarbene reagent to realize the single and double CF_2 insertion into C−Cu bonds (via a copper difluorocarbene intermediate) in a controllable manner.

1. INTRODUCTION

During the past decades, the importance of the fluorine atom or fluorine-containing moieties has been well recognized in modulating the physical, chemical, and biological properties of organic molecules.[5,6] As such, it has become a powerful strategy to introduce fluorine-containing moieties in drug design and functional materials development.[7−11] Among various fluorine-containing moieties, the difluoromethyl (CF_2H) and difluoromethylene (CF_2) groups have attracted significant attention in recent years,[12−15] because the CF_2H group is known to be isosteric to OH or SH groups and can serve as a lipophilic hydrogen bond donor[16−18] and the CF_2 group can act as a bioisostere of an ethereal oxygen.[13,19,20]

Difluorocarbene is an ideal reactive intermediate for CF_2 incorporation, despite the fact that many other methods are also available.[12,15,21−24] Difluorocarbene, with a singlet ground state, is destabilized by the inductive effect and stabilized by the resonance effect of the fluorine substituent. On one hand, the strong inductive electron-withdrawing effect of the fluorine atom destabilizes difluorocarbene; on the other hand, the stereoelectronic interaction enables π-back-donation of the 2p electron lone pair of fluorine to the empty 2p orbital of carbon, thus stabilizing the difluorocarbene. These combined destabilizing and stabilizing effects render difluorocarbene moderately electrophilic and the most stable among dihalocarbenes.[25−27] As an innately electrophilic species, difluorocarbene has been widely applied in organic syntheses, such as (1) homocoupling to produce tetrafluoroethylene (TFE), (2) reacting with *O*-, *S*-, *N*-, *P*-, and *C*-nucleophiles (among others) to give the difluoromethylated products, (3) undergoing [2 + 1] cycloaddition with alkenes or alkynes, (4) reacting with phosphines or amines to form ylides, and (5) acting as a bridge to connect nucleophiles and electrophiles to form diverse fluorinated and non-fluorinated molecules, among others.[25−33] However, despite the high importance of difluorocarbene in organic synthesis, efficient and environmentally benign reagents that can generate difluorocarbene under mild conditions had been limited until 2006.[25,26] Figure 1 shows the representative classical difluorocarbene reagents developed before 2006.[34−43]

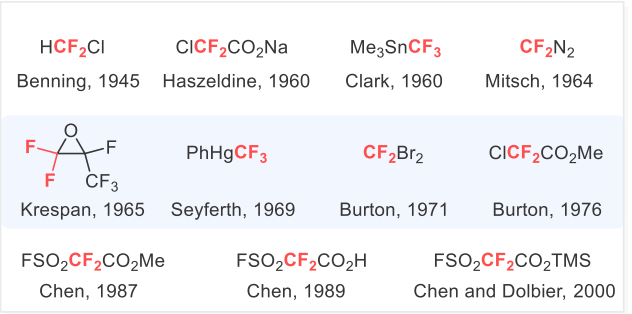

Figure 1. Representative classical difluorocarbene reagents developed before 2006.

Most of these conventional difluorocarbene reagents suffer from drawbacks such as deriving from ozone-depleting substances (ODSs), being highly toxic, difficult to handle, and commercially unavailable, requiring harsh reaction conditions, and having narrow substrate scope, and/or low yields in reactions.[25−28] Moreover, these reagents are only reactive toward limited types of substrates, although the reason remained unclear at that time; therefore, different difluorocarbene reagents usually had to be used for different types of substrates. To meet the demands of modern organic synthesis and drug discovery, the development of environmentally friendly, efficient, and versatile difluorocarbene reagents to circumvent these limitations and gain new insights into difluorocarbene-involved reactions has been highly desirable.

Over the past 17 years, we have devoted our efforts to developing new powerful difluorocarbene reagents and reactions for organic synthesis (Scheme 1). During our study on nucleophilic fluoroalkylation with α-fluoro carbanions, we realized that an α-fluoro carbanion (such as CF_2X^-) tends to undergo α-elimination of a leaving group (X^- or F^-) to give a fluorinated carbene (such as, CF_2) owing to the "negative fluorine effect".[44,45] In 2006, we reported that 2-chloro-2,2-difluoroacetophenone ($PhCOCF_2Cl$, **1**) could serve as a new non-ODS-based difluorocarbene reagent for the difluoromethylation of phenols.[46] One year later, we reported that chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$, **2**) was a more efficient difluorocarbene reagent than $PhCOCF_2Cl$.[47,48] In 2009, we reported that difluoromethyl phenyl sulfoximine [$PhSO(NTs)CF_2H$, **3**] could also serve as a difluorocarbene reagent for *S*-, *N*-, and *C*-nucleophiles.[49] In 2011, we reported that difluoromethyltri(*n*-butyl)ammonium chloride [n-$Bu_3(CF_2H)N^+Cl^-$, **4**] was an efficient difluorocarbene reagent for *O*-, *S*-, *N*-, and *C*-nucleophiles.[50] However, reagents **1**−**4** require basic conditions to generate difluorocarbene, so they are not applicable in base-sensitive reactions (such as [2 + 1] cyclopropanation with alkenes). Therefore, we realized that an ideal difluorocarbene reagent (that can be used for a broad range of reactions) should allow various activation modes for the generation of difluorocarbene species, such as under basic/acidic/neutral conditions, at a wide range of temperatures, and in different solvents. With these considerations in mind, we have developed $TMSCF_2X$ (X = Cl,[1] **5**; X = Br,[1,51] **6**; X = F,[2] **7**) as a new class of versatile difluorocarbene reagents, among which $TMSCF_2Br$ has been most widely used. To date, the $TMSCF_2Br$ reagent has been applied in the difluoromethylation of a range of *O*-, *S*-, *N*-, *P*-, and *C*-nucleophiles, *gem*-difluorocyclopropa(e)nation of alkenes and alkynes, selective fluoro-functionalization of ambident substrates, cross-coupling with diazo compounds,

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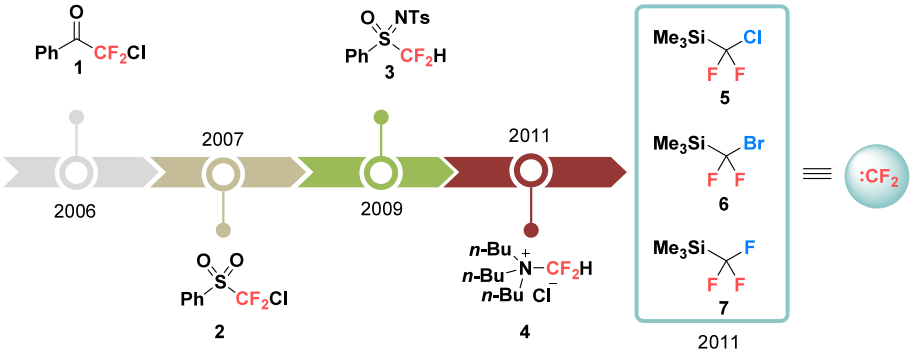
Scheme 1. Seven New Difluorocarbene Reagents Developed by Our Group Since 2006



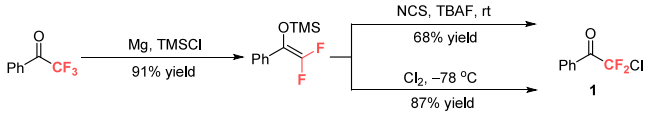
and fluorocarbon chain homologation or elongation reactions, among others.[29,32,33] In this Account, we wish to illustrate the evolution of difluorocarbene reagents in our group and our understanding of the key factors for the success of various difluorocarbene-involved reactions. Moreover, the applications of our reagents in the synthesis of pharmaceutical intermediates as well as the late-stage functionalization of complex molecules are showcased, which demonstrate the practicability of our reagents and related synthetic methods in chemical synthesis.

2. 2-CHLORO-2,2-DIFLUOROACETOPHENONE

Our initial research interest in difluorocarbene chemistry was aroused by an industrial issue. A pharmaceutical company invited us to develop a new method to synthesize aryl difluoromethyl ethers from phenol derivatives without the use of Freon-based reagents. Aryl difluoromethyl ethers have found wide applications in bioactive molecules such as enzyme inhibitors,[52] anti-HIV agents,[53] and even pharmaceuticals on the market such as pantoprazole and roflumilast.[24] The most commonly used method to access this structure is the reaction of phenols with HCF_2Cl (Freon-22) or $ClCF_2CO_2Na$;[54−56] while Freon-22 is an ODS, and $ClCF_2CO_2Na$ is commonly prepared directly or indirectly from an ODS,[57] which have been regulated by the Montreal protocol. Therefore, there was almost no environmentally benign and efficient method to synthesize aryl difluoromethyl ethers at that time. In this context, to overcome this limitation and inspired by the haloform reaction[58] that CX_3^- can be generated from $RCOCX_3$ (X = Cl, Br, I) via deacylation under basic conditions, we developed 2-chloro-2,2-difluoroacetophenone ($PhCOCF_2Cl$, **1**) as an alternative non-ODS-based reagent in 2006.[46]

A non-ODS-based method to prepare $PhCOCF_2Cl$ (**1**) was first developed by us using commercially available trifluoroacetophenone in two steps (Scheme 2).[46] $PhCOCF_2Cl$ turned

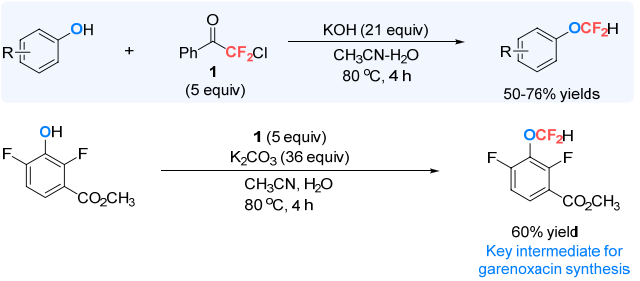
Scheme 2. Non-ODS-Based Preparation of $PhCOCF_2Cl$ (1)



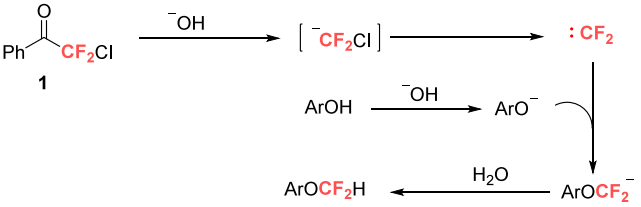
out to be a good difluorocarbene reagent, and a variety of structurally diverse phenol derivatives were difluoromethylated in moderate to good yields (Scheme 3).

A plausible mechanism was proposed, as shown in Scheme 4. $PhCOCF_2Cl$ (**1**) is attacked by hydroxide to generate a chlorodifluoromethyl anion, which subsequently decomposes

Scheme 3. Difluoromethylation of Phenols with 1



Scheme 4. Proposed Mechanism for the Difluoromethylation of Phenols with 1



to difluorocarbene and Cl^-. The in situ generated difluorocarbene is trapped by aryloxide anions followed by protonation to give difluoromethyl aryl ether products.[46]

3. CHLORODIFLUOROMETHYL PHENYL SULFONE

Based on the successful development of $PhCOCF_2Cl$ as a difluorocarbene reagent and inspired by the fact that desulfonylation of $PhSO_2CF_3$ with an *O*-nucleophile could generate CF_3^-,[59] in 2007, we reported chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$, **2**), a previously unknown compound, as a more robust difluorocarbene reagent than $PhCOCF_2Cl$ in terms of reaction efficiency, reagent loading (2.3 equiv vs ≥5.0 equiv), and reaction temperature (50 °C vs 80 °C).[47,48] This reagent can be prepared by a non-ODS-based method using thioanisole as the starting material: chlorination with Cl_2, selective fluorination with Olah's reagent (HF-pyridine), and oxidation with $NaIO_4$ (Scheme 5). A variety of functionalized phenols and *N*-heterocyclic compounds were difluoromethylated with **2** to give the corresponding products in high yields (Scheme 6).

4. *N*-TOSYL-*S*-DIFLUOROMETHYL-*S*-PHENYLSULFOXIMINE

In 2009, during the process of seeking a direct electrophilic difluoromethyl-transfer reagent, we designed and prepared the

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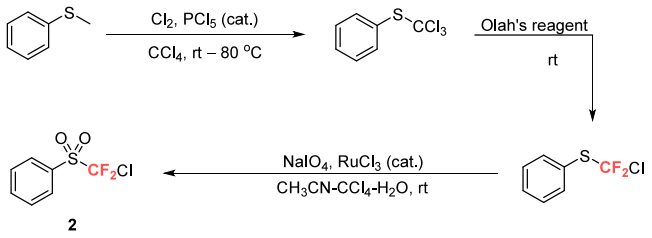
Scheme 5. Preparation of Chlorodifluoromethyl Phenyl Sulfone (2) via a Non-ODS-Based Method



first *S*-difluoromethyl sulfoximine compound **3** by using the copper(II)-catalyzed nitrene transfer reaction (Scheme 7).[49] A number of *S*-, *N*-, and *C*-nucleophiles were readily difluoromethylated with **3** (Scheme 8). Notably, some terminal alkynes were also successfully difluoromethylated with **3**, indicating that the current method is a good alternative to the previously known Freon-based approaches.[60]

Although this reagent was designed as a direct electrophilic difluoromethylation reagent ("CF_2H^+" equivalent), the deuterium-labeling experiments ruled out the possibility of both S_N2 and free-radical-involved pathways and supported a difluorocarbene-involved mechanism.[49]

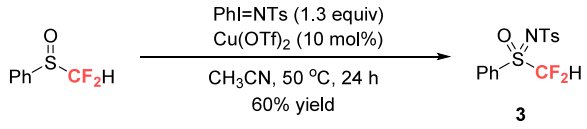
5. DIFLUOROMETHYLTRI(*N*-BUTYL)AMMONIUM CHLORIDE

In 2011, we reported the use of difluoromethyltri(*n*-butyl)-ammonium chloride ($[(n\text{-}Bu)_3NCF_2H]^+Cl^-$, **4**) as a difluorocarbene reagent.[50] The most remarkable feature of this reagent is that it could efficiently difluoromethylate a wide range of *O*-, *S*-, *N*-, and *C*-nucleophiles with relatively low loadings (1.2 equiv) of reagent **4** (Scheme 9).

6. (CHLORODIFLUOROMETHYL)TRIMETHYLSILANE

As mentioned in the section 1, the [2 + 1] cycloaddition between difluorocarbene and an alkene (or alkyne) is an important type of reaction in difluorocarbene chemistry, and the corresponding difluorocyclopropa(e)ne products have found

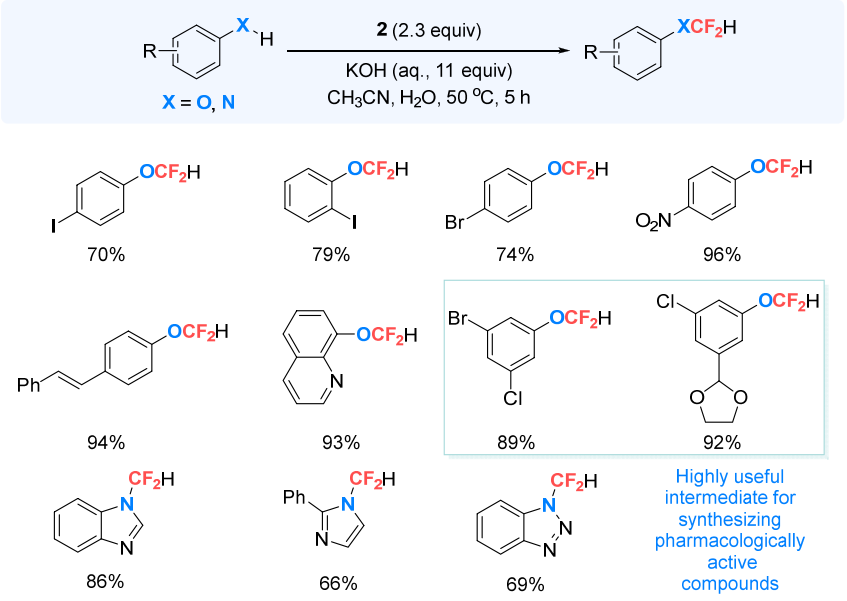
Scheme 7. Preparation of *N*-Tosyl-*S*-Difluoromethyl-*S*-Phenylsulfoximine (3)



many applications in organic synthesis.[26] Although HCF_2Cl,[61] sodium halodifluoroacetate,[62,63] $PhHgCF_3$,[64] Me_3SnCF_3,[65] $FSO_2CF_2CO_2TMS$,[43] and CF_2Br_2[66,67] could be used for this [2 + 1] cycloaddition reaction, these reagents suffer from several drawbacks such as narrow substrate scope, high toxicity, not being easy to handle, and/or low yields. Although our developed difluorocarbene reagents **1**–**4** were useful in difluoromethylation of *O*-, *S*-, *N*-, or *C*-nucleophiles, they were unable to undergo efficient [2 + 1] cycloaddition with alkenes or alkynes. These reagents can only generate difluorocarbene in the presence of alkaline bases such as KOH, and KOH can also deprotonate the pronucleophiles RXH to give RX^-, which is the reactive species toward difluorocarbene to give the difluoromethylated products. However, during our research, we realized that for the [2 + 1] cycloaddition reaction, if a base (such as KOH) is present, the reaction between the base (as a nucleophile) and difluorocarbene is a significantly competitive side reaction, which would hamper the desired [2 + 1] cycloaddition between difluorocarbene and an alkene (or alkyne). The key to the success of this [2 + 1] cycloaddition requires the generation of difluorocarbene under nonbasic conditions and at sufficiently high temperature to conquer the activation energy barrier for the difluorocarbene addition to all except the most reactive alkenes or alkynes.[26]

Inspired by the *gem*-difluorocyclopropanation of alkenes with HCF_2Cl in the presence of an epoxide and catalytic amount of chloride anion (in situ generation of a catalytic amount of alkoxide to deprotonate HCF_2Cl to produce difluorocarbene; see Scheme 10),[61] we envisioned that the same strategy could be used to initiate $TMSCF_2Cl$ (**5**) to undergo Si–C bond cleavage and generate difluorocarbene species. It should be noted that,

Scheme 6. Difluoromethylation of Phenols and *N*-Heterocyclic Compounds with 2



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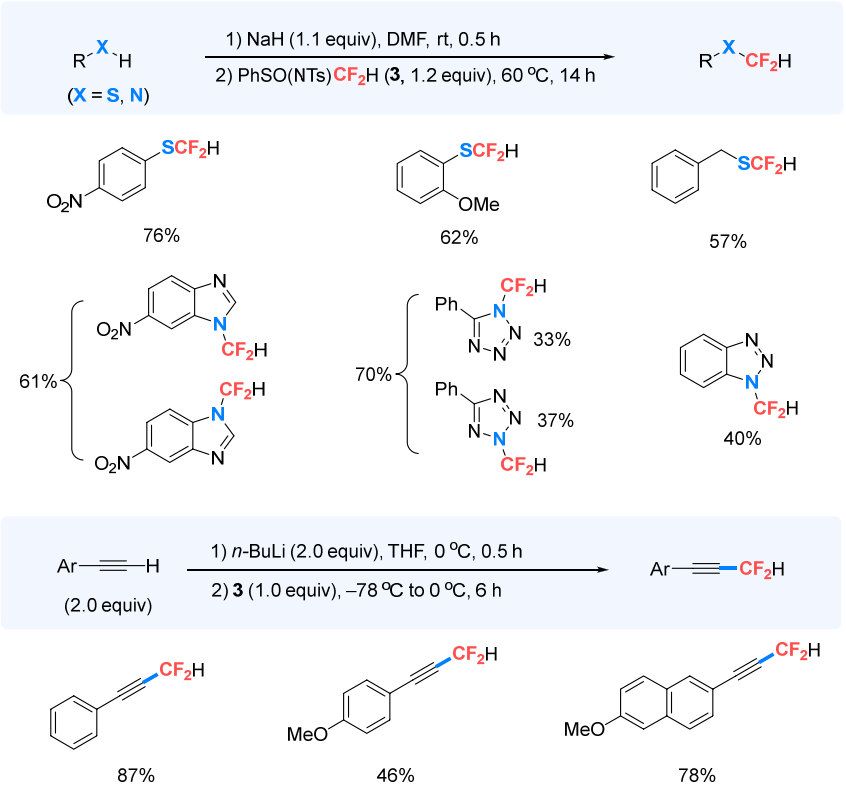
Scheme 8. Difluoromethylation of *S*-, *N*-, and *C*-Nucleophiles with 3



before 2011, $TMSCF_2Cl$ had been used as a nucleophilic chlorodifluoromethylation reagent,[68] but its use as an efficient difluorocarbene precursor had never been reported.

With this hypothesis in mind, in 2011, we indeed successfully developed $TMSCF_2Cl$ (**5**) as a difluorocarbene reagent.[1] To our surprise, unlike the case of HCF_2Cl (Scheme 10), we found that the use of an epoxide is not necessary in the case of $TMSCF_2Cl$. Only a catalytic amount of chloride anion is sufficient to activate $TMSCF_2Cl$ to generate difluorocarbene. Moreover, a comparison of different (halodifluoromethyl)trimethylsilanes showed that $TMSCF_2Br$ (**6**) is also a good difluorocarbene source, while $TMSCF_3$ (**7**) could not generate difluorocarbene under chloride ion catalyzed conditions (Scheme 11).

Under the chloride ion catalysis, a vast array of alkynes and alkenes could easily undergo [2 + 1] cycloaddition with $TMSCF_2Cl$ in high efficiency (Scheme 12). It is noteworthy that when a substrate bearing both an alkene and a phenol moiety was subjected to the chloride ion catalyzed reaction conditions with $TMSCF_2Cl$ (**5**), the phenol group could not react with difluorocarbene under the neutral conditions, and only the corresponding difluorocyclopropane was obtained (see Scheme 12). This may be attributed to the significantly lower nucleophilicity of the neutral phenol than that of the anionic phenoxide group.

The proposed mechanism of this reaction is shown in Scheme 13. A catalytic amount of chloride ion reacts with $TMSCF_2Cl$ (**5**) to liberate the chlorodifluoromethyl anion, which readily undergoes α-chloride elimination to generate difluorocarbene, which is captured by alkenes or alkynes to forge the desired products. The resulting chloride can enter the catalytic cycle to activate another molecule of $TMSCF_2Cl$ (**5**).

$TMSCF_2Cl$ (**5**) was also used for *gem*-difluoroolefination of aldehydes and activated ketones and difluoromethylation of *O*-, *S*-, and *N*-nucleophiles.[69]

7. (TRIFLUOROMETHYL)TRIMETHYLSILANE

$TMSCF_3$ (**7**), known as Ruppert–Prakash reagent, perhaps is the most widely used nucleophilic trifluoromethylation reagent for various substrates.[70,71] In 2011, our group (in collaboration with the Prakash group) disclosed that $TMSCF_3$ is also a good difluorocarbene reagent, which can be applied in the *gem*-difluorocyclopropa(e)nation with alkenes or alkynes.[2] By using tetrabutylammonium triphenyldifluorosilicate (TBAT) as a non-metallic activator, $TMSCF_3$ can generate difluorocarbene at low temperature (−50 to 25 °C), where electron-rich alkenes could react smoothly to give *gem*-difluorocyclopropanes in good yields. For less reactive alkenes, since elevated temperature is required to conquer the activation barrier of the cycloaddition process, NaI was used as a mild initiator to generate difluorocarbene at higher temperature, giving the desired products in good yields (Scheme 14). Alkynes were also efficiently difluoromethylenated using NaI as the activator (Scheme 15). The mechanism of difluorocarbene generation from $TMSCF_3$ and TBAT or NaI was believed to be through the CF_3 anion, followed by α-elimination of a fluoride (based on Lloyd-Jones's studies).[72]

In 2015, we reported the first cross-coupling reactions between diazo compounds and difluorocarbene under transition-metal-free conditions.[73] Using $TMSCF_3$ as a difluorocarbene precursor, a myriad of α-diazoacetates and diaryldiazomethanes were successfully transformed to *gem*-difluoroolefins in moderate to good yields with satisfactory functional group tolerance (Scheme 16). This *gem*-difluoroolefination reaction proceeds through the direct nucleophilic addition of

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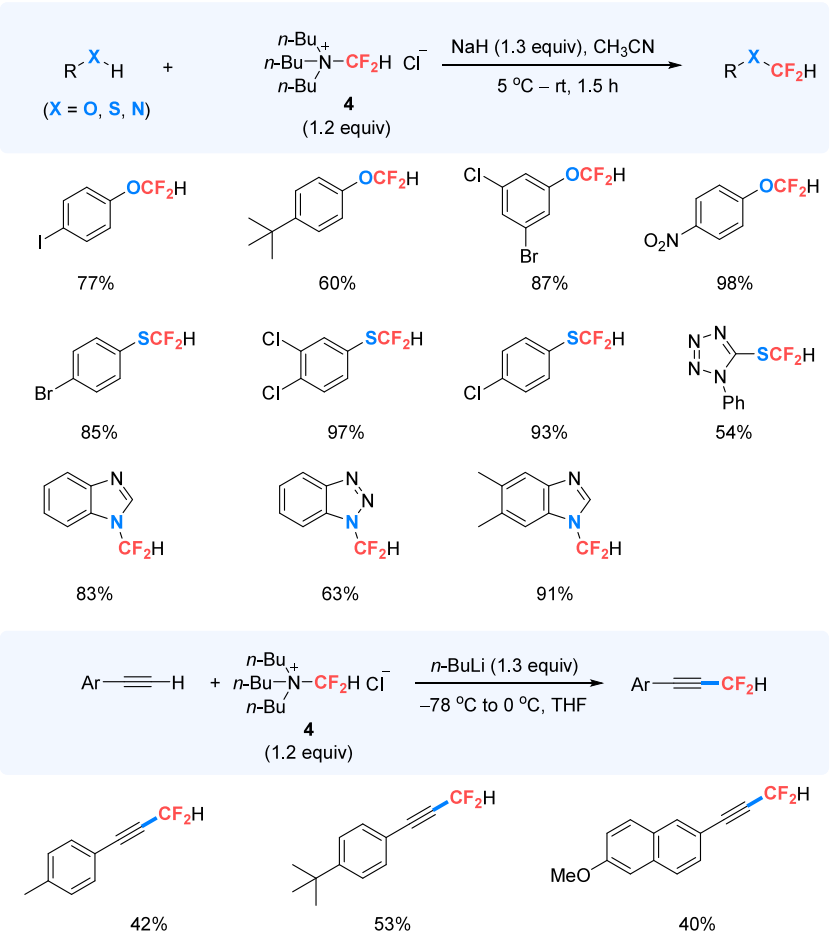
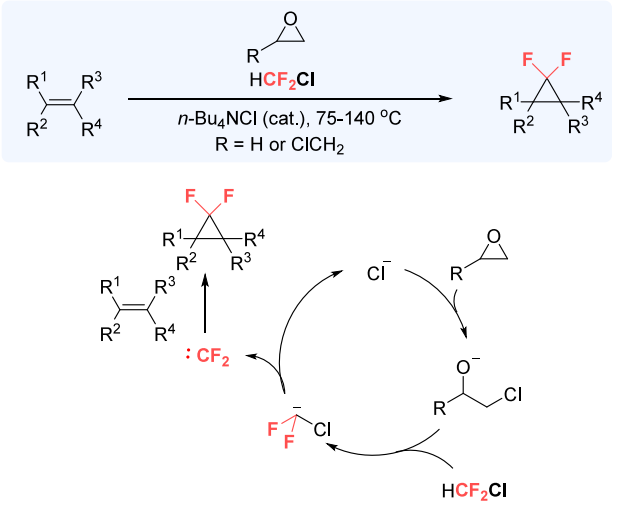
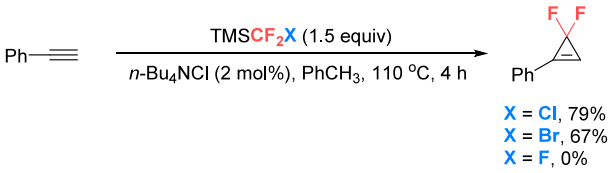
Scheme 9. Difluoromethylation of *O*-, *S*-, *N*-, and *C*-Nucleophiles with 4



Scheme 10. *gem*-Difluorocyclopropanation of Alkenes with HCF_2Cl



Scheme 11. Comparison of $TMSCF_2X$ (X = F, Cl, Br) as Difluorocarbene Reagents



diazo compounds to difluorocarbene followed by the elimination of N_2 (Scheme 16).

During our study of reactions using $TMSCF_3$ as a difluorocarbene source, tetrafluoroethylene (TFE) was often observed as a byproduct. In 2014, the Baker group also found that a mixture of NaI and $TMSCF_3$ could generate TFE.[74] Although TFE is a bulk feedstock in industry, the transportation of TFE is prohibited, owing to its explosive nature. As a consequence, TFE is unattainable by most chemists in academic laboratories, and related research has been retarded.[75] In this context, we developed a new method to prepare TFE in lab from commercially available $TMSCF_3$.[76] With only a catalytic amount of NaI, $TMSCF_3$ could efficiently deliver TFE at 70 °C (a significantly lower temperature compared with the industrial process, >650 °C[12]), and the yield of TFE was calculated by converting it into $BrCF_2CF_2Br$ (Scheme 17).

This $TMSCF_3$-derived TFE could easily undergo fluorocupration, which had never been reported before, to give a $CuCF_2CF_3$ species. $CuCF_2CF_3$ is useful for the pentafluoroethylation of various iodoarenes (Scheme 18). Electron-rich and electron-deficient iodoarenes as well as heterocyclic iodoarenes were all able to smoothly undergo $TMSCF_3$-based pentafluoroethylation, giving the desired products in high yields. Common functional groups, such as nitro, acetyl, bromide, and ester were compatible with the current reaction conditions.[76] Later, the $TMSCF_3$-derived TFE was further used by us in the

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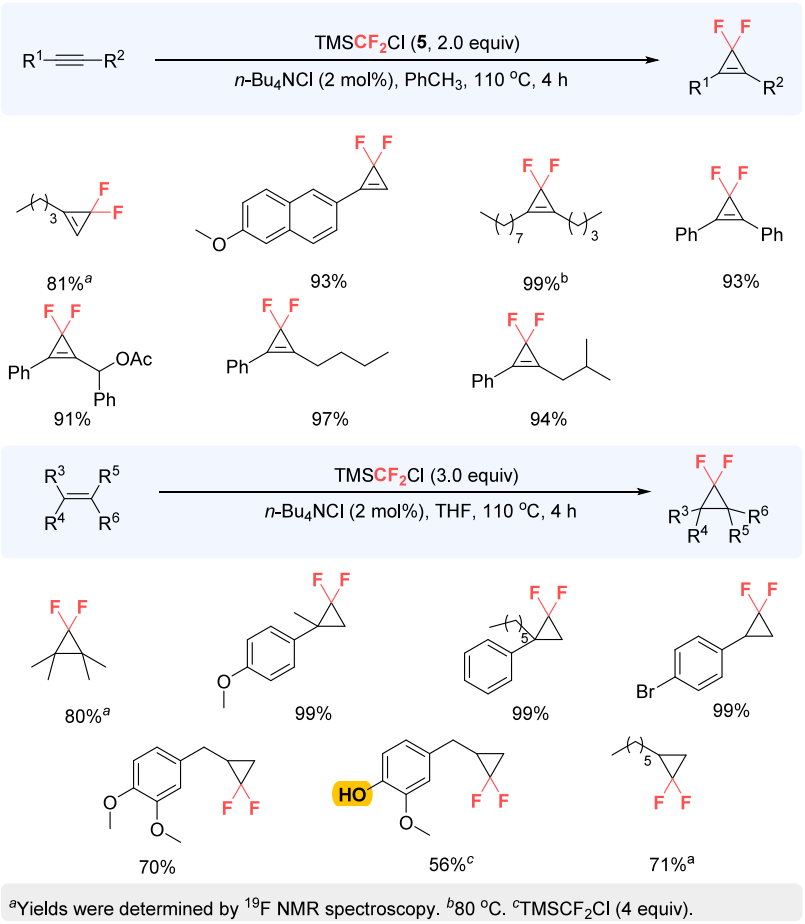
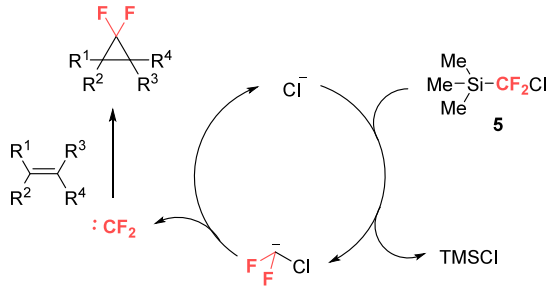
Scheme 12. [2 + 1] Cycloaddition of Alkynes and Alkenes with $TMSCF_2Cl$



Scheme 13. Proposed Mechanism of Chloride Ion Catalyzed Generation of Difluorocarbene from $TMSCF_2Cl$



copper-mediated pentafluoroethylation of arenediazonium tetrafluoroborates, giving pentafluoroethylated arenes in satisfactory yields.[98]

Oxycupration of TFE with PhONa was also realized, and the desired coupling product was formed in excellent yield (Scheme 19).[76]

In addition, the synthetic potential of TFE could also be extended to the tetrafluoroethylation of *O*-, *S*-, and *N*-nucleophiles (Scheme 20).[76] The mildness of this TFE-generation method from commercially available $TMSCF_3$ promises to stimulate further development of TFE-related chemistry in regular chemistry laboratories.

We further developed an efficient aromatic pentafluoroethylation method using $TMSCF_3$ as the sole fluorine source (that is, all the fluorine atoms in the pentafluoroethyl group come from $TMSCF_3$) via a non-TFE pathway.[77] The key to this success was the selective preparation of $CuCF_2CF_3$ from $TMSCF_3$, a process that involves fluorocarbon chain homologation (elongation from C_1 to C_2). Upon simply mixing a mixture of CuCl, KF, and $TMSCF_3$ in DMF/pyridine (1:1, v/v) at 80 °C, $CuCF_2CF_3$ was formed in 80% yield with only 3% of CuC_3F_5 being formed (Scheme 21). The use of an excess of CuCl is pivotal to destabilize the initially formed $CuCF_3$ intermediate and promote its transformation to CuC_2F_5. Furthermore, the use of pyridine is crucial for minimizing the over-homologated byproducts.

A number of (hetero)aryl iodides (0.33−0.39 mmol scale) were successfully pentafluoroethylated with good functional group tolerance. The drug intermediates and complex molecules can also be pentafluoroethylated using this method. This reaction is easy to scale-up and promises to find many applications in the synthesis of pentafluoroethylated bioactive compounds (Scheme 22).[77] This C_1-to-C_2 fluorocarbon chain elongation strategy was later used by us in the copper-mediated pentafluoroethylation of organoboronates and terminal alkynes by using $TMSCF_3$ as the sole fluorocarbon source.[99]

Notably, selective trifluoromethylation could also be achieved by realizing a key factor, namely, stabilizing the $CuCF_3$ by using proper ligands and/or solvents (such as DMPU) (Scheme 23).[77]

Preliminary mechanistic studies revealed that, by mixing CuCl, KF, and $TMSCF_3$, $CuCF_3$ was initially formed. The involvement of TFE or free difluorocarbene can be ruled out in the transformation of $CuCF_3$ to CuC_2F_5, and a copper

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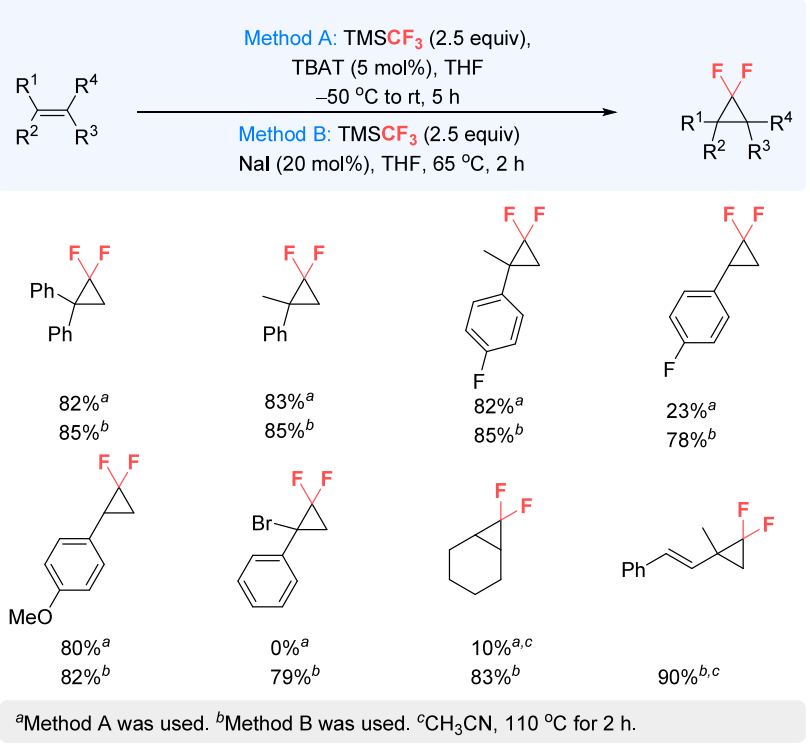
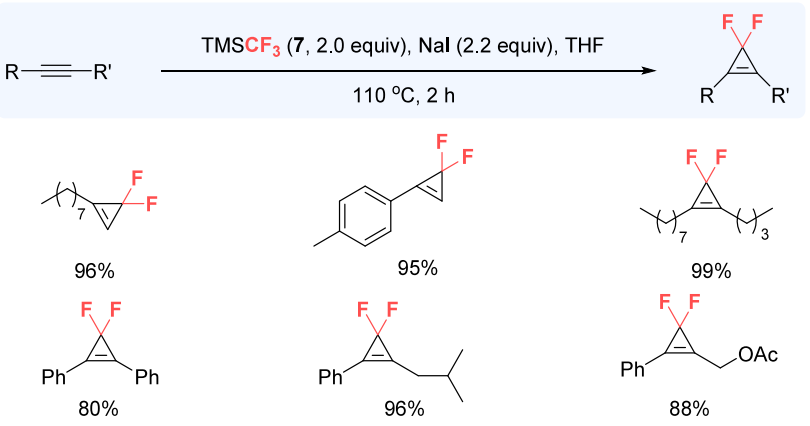
Scheme 14. [2 + 1] Cycloaddition of Alkenes with $TMSCF_3$



Scheme 15. [2 + 1] Cycloaddition of Alkynes with $TMSCF_3$



difluorocarbene species (L–Cu=CF_2) was proposed as the key intermediate (Scheme 24).[77]

Shortly afterward, we extended this controllable fluorocarbon elongation strategy from selective one-carbon homologation (single CF_2 insertion into $CuCF_3$ to generate $CuCF_2CF_3$) to two-carbon homologation, realizing controllable double CF_2-insertions into the pentafluorophenylcopper species.[78] The newly formed $C_6F_5CF_2CF_2Cu$ species showed high reactivity toward a plethora of (hetero)aryl iodides and vinyl iodides, providing a convenient method for facile access to tetrafluoroethylene-bridged structures (Scheme 25).

8. BROMODIFLUOROMETHYLTRIMETHYLSILANE

As shown in section 6, $TMSCF_2Cl$ (**5**) is arguably one of the most versatile difluorocarbene reagents. However, its preparation requires the use of ozone-depleting $BrCF_2Cl$,[1] which precludes its wide application. Following our initial report in 2011 that $TMSCF_2Br$ (**6**) can be used as a difluorocarbene precursor,[1] in 2013 we further reported that $TMSCF_2Br$ (**6**), a compound that can be prepared by a non-ODS-based method,[79,80] is able to serve as a general difluorocarbene reagent.[81] Various alkynes and alkenes reacted smoothly with $TMSCF_2Br$ in the presence of a catalytic amount of *n*-Bu_4NBr, demonstrating good tolerance of both electron-donating and electron-withdrawing groups (Scheme 26). It is worth mentioning that for the alkenes bearing a hydroxyl group, selective reaction at the C=C bond was observed. A variety of heteroatom nucleophiles were also efficiently difluoromethylated with $TMSCF_2Br$ at 0 °C within 30 min under basic conditions (Scheme 27). These mild reaction conditions were compatible with some base-sensitive functional groups (such as aldehyde and ester functionalities).[81]

$TMSCF_2Br$ (**6**) can also be used to undergo *gem*-difluoroolefination of diazo compounds under transition-metal-free conditions (Scheme 28).[73] Because arylalkyldiazo-

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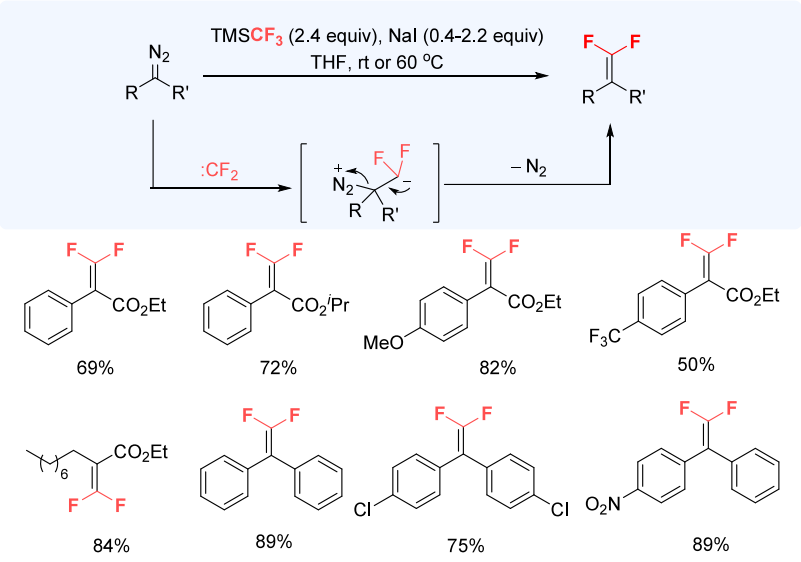
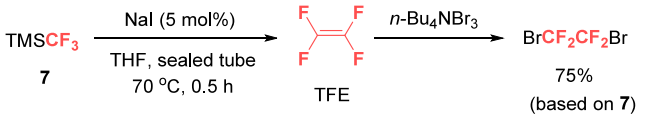
Scheme 16. *gem*-Difluoroolefination of α-Diazoacetates and Diaryldiazomethanes with $TMSCF_3$



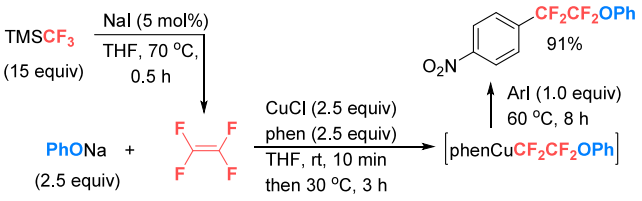
Scheme 17. Generation of TFE from $TMSCF_3$



methanes are unstable and challenging to prepare, their surrogate diazirines, which can isomerize to the diazo compounds upon heating, were used instead. By simply changing the molar ratio of diazirine and $TMSCF_2Br$, *gem*-difluoroolefination and tetrafluorocyclopropanation can be realized (Scheme 29). It is noteworthy that $TMSCF_2Br$ can also be applied in the [2 + 1] cyclopropanation with aryl trifluorovinyl ethers, affording aryl perfluorocyclopropyl ethers in high yields.[100]

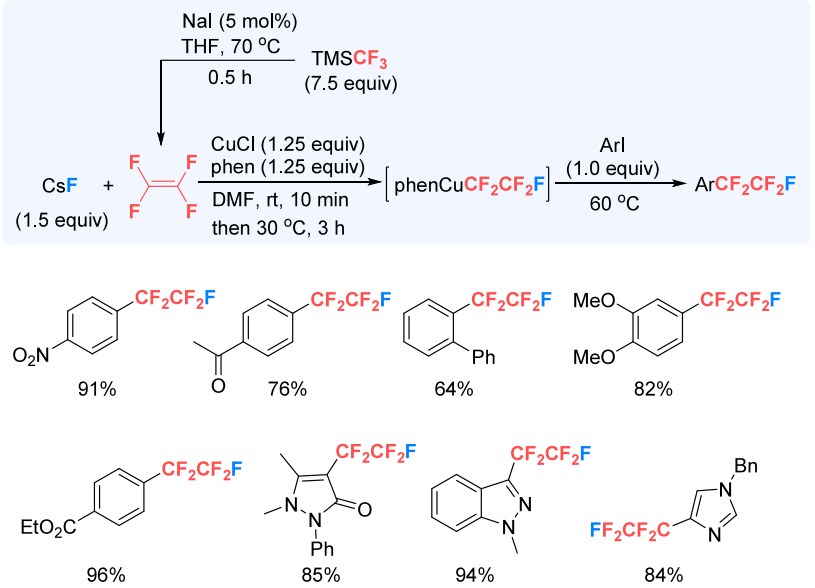
Difluoromethylation of alcohols had been considered much more challenging than that of phenols, and efficient methods to

Scheme 19. Phenoxytetrafluoroethylation of Iodoarene



achieve this goal were sparse.[82−84] In 2017, we reported a general method for the efficient difluoromethylation of alcohols with $TMSCF_2Br$ under weakly acidic (with KHF_2 as the activator) or weakly basic (with KOAc as the activator) conditions.[3] We realized that the difluoromethylation of alcohols and phenols may occur through different mechanisms (Scheme 30). Alcohols themselves are sufficiently nucleophilic to capture difluorocarbene if no strong competitor (such as

Scheme 18. Pentafluoroethylation of Iodoarenes with $TMSCF_3$ via TFE



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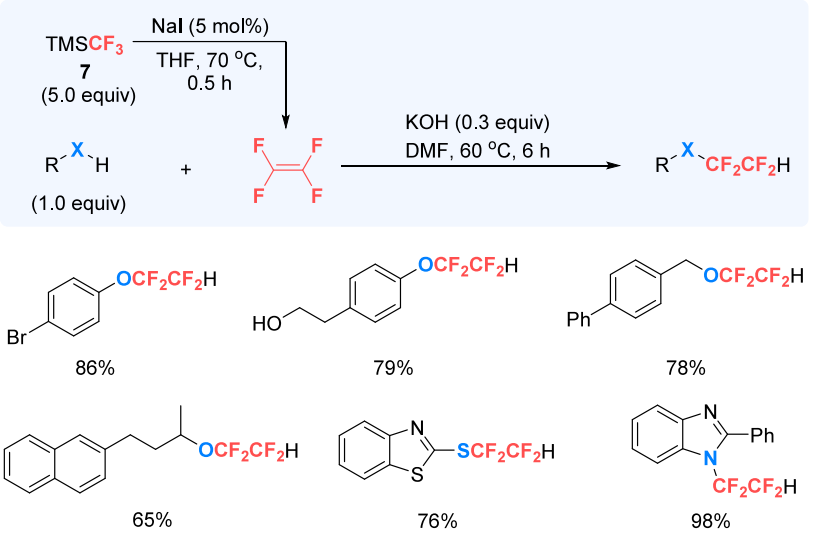
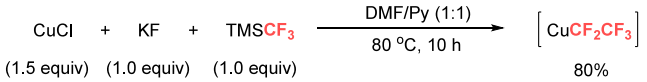
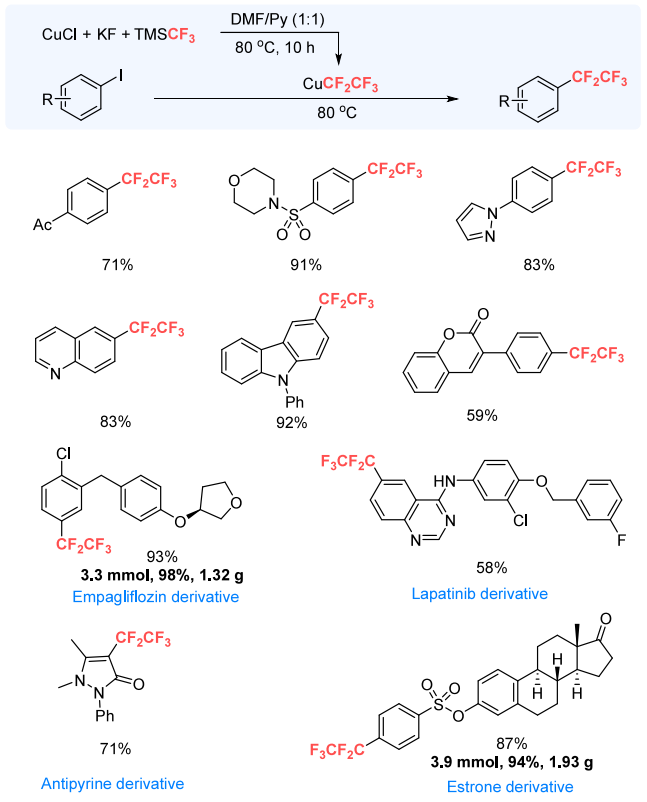
Scheme 20. Tetrafluoroethylation of *O*-, *S*-, and *N*-Nucleophiles with $TMSCF_3$



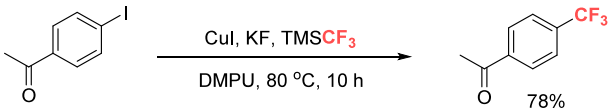
Scheme 21. Preparation of CuC_2F_5 from $TMSCF_3$



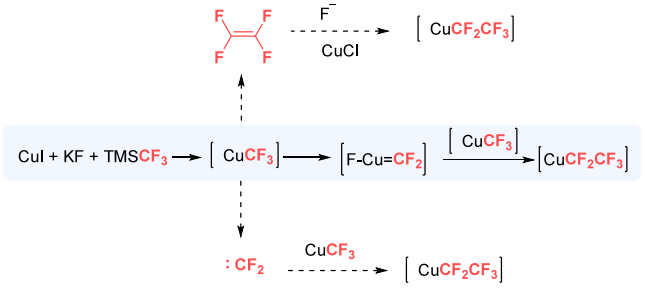
Scheme 22. Pentafluoroethylation of Aryl Iodides with $TMSCF_3$



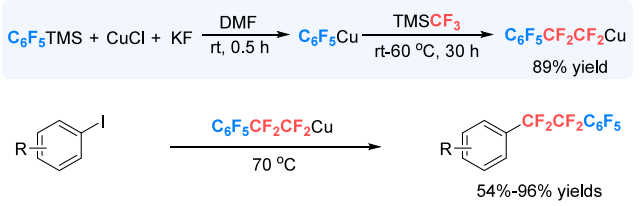
Scheme 23. Selective Trifluoromethylation of Aryl Iodide with $TMSCF_3$



Scheme 24. Proposed Mechanism for the Formation of CuC_2F_5 from $TMSCF_3$



Scheme 25. Controllable Double CF_2 Insertions into C_6F_5Cu with $TMSCF_3$



hydroxide anion) is present. However, neutral phenols are not sufficiently nucleophilic toward difluorocarbene unless they are deprotonated to phenoxide, which is a strong nucleophile. This remarkable difference in the reaction mechanisms can be used to explain why many other difluorocarbene reagents work well for the difluoromethylation of phenols under basic conditions but show low efficiency in difluoromethylation of alcohols.

Under weakly basic or acidic conditions, a broad range of structurally diverse primary, secondary, and tertiary alcohols (both electron-rich and -poor ones) could smoothly undergo difluoromethylation with $TMSCF_2Br$ (**6**), providing difluoromethyl ethers in moderate to good yields (Scheme 31). It should be noted that strongly basic conditions (NaOH as activator) are only suitable for electron-rich and less sterically hindered alcohols. Late-stage difluoromethylation of drug

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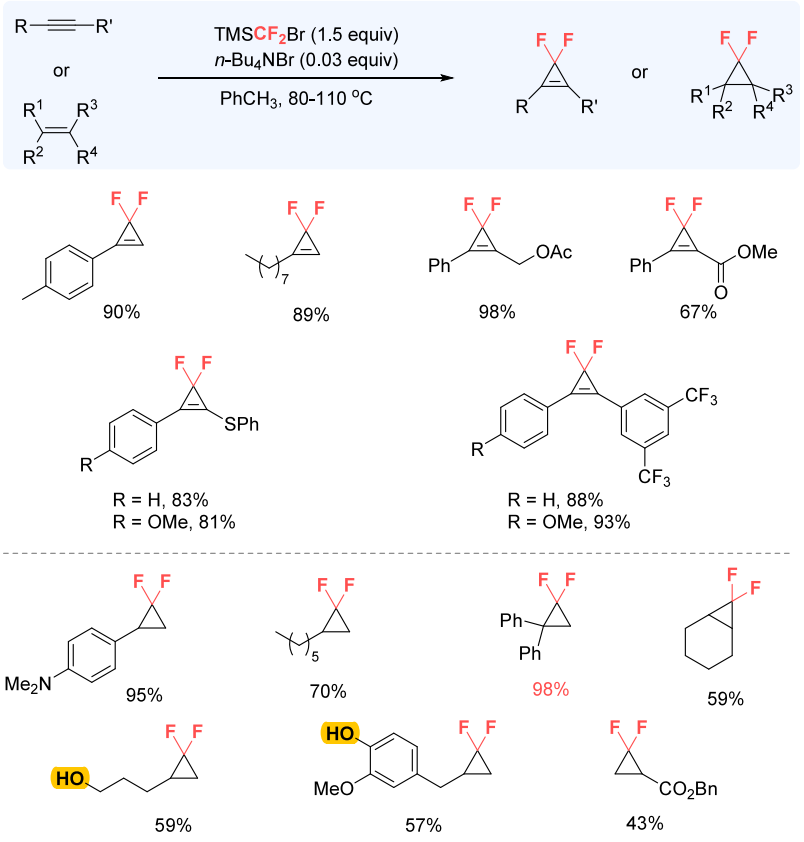
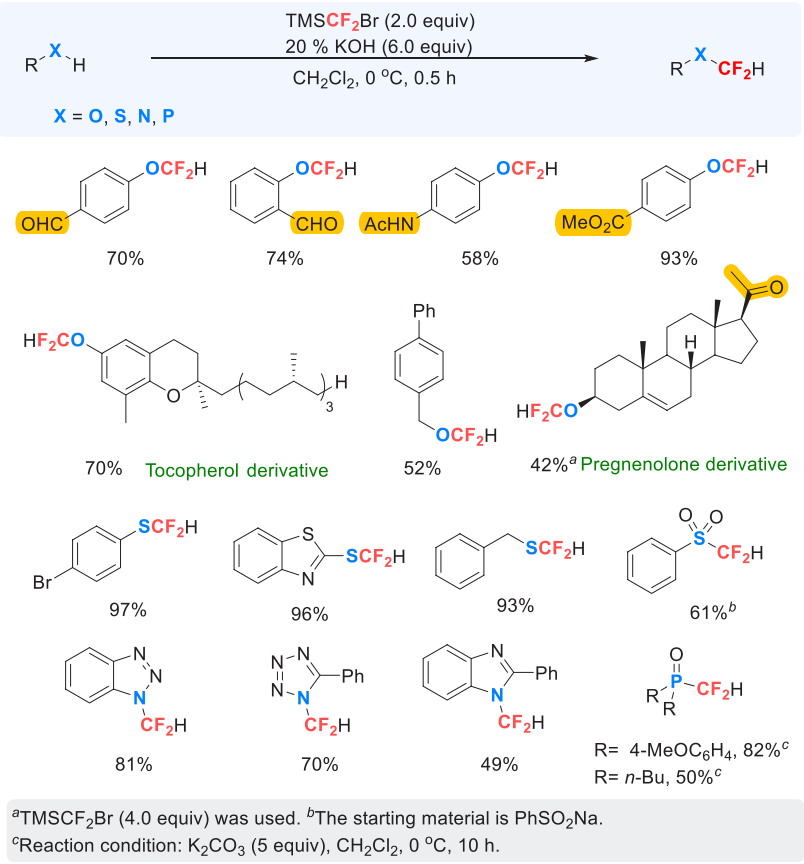
Scheme 26. *gem*-Difluorocyclopropa(e)nation of Alkynes and Alkenes with $TMSCF_2Br$



Scheme 27. Difluoromethylation of *O*-, *S*-, *N*-, and *P*-Nucleophiles with $TMSCF_2Br$



[a]$TMSCF_2Br$ (4.0 equiv) was used. [b]The starting material is $PhSO_2Na$.
[c]Reaction condition: K_2CO_3 (5 equiv), CH_2Cl_2, 0 °C, 10 h.

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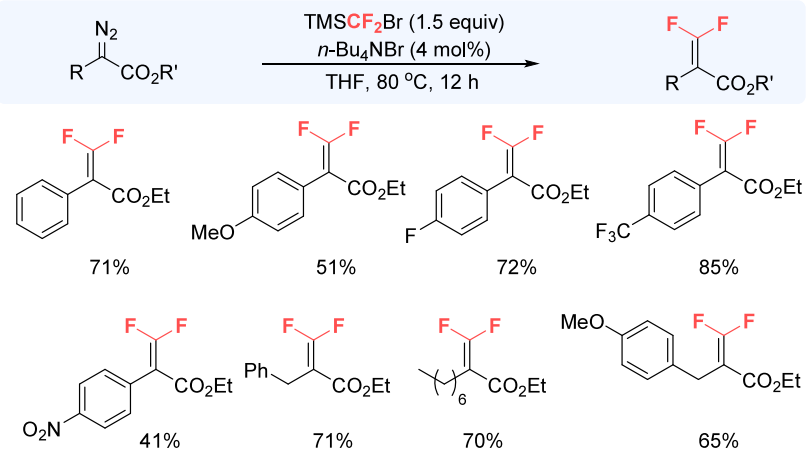
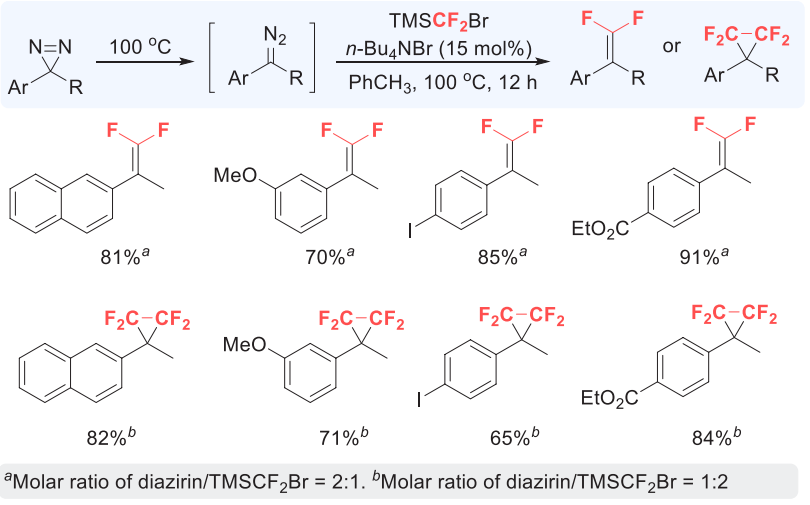
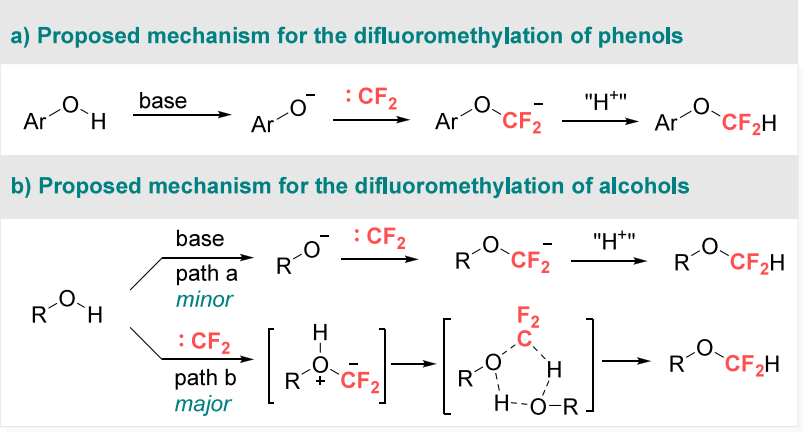
Scheme 28. *gem*-Difluoroolefination of α-Diazoacetates with $TMSCF_2Br$



Scheme 29. *gem*-Difluoroolefination and Tetrafluorocyclopropanation of Diazirines with $TMSCF_2Br$



Scheme 30. Different Mechanisms Proposed for the Difluoromethylation of Phenols and Alcohols



molecules (such as idebenone and estradiol benzoate) was found to be highly efficient and easy to scale up, which demonstrates the great potential of the $TMSCF_2Br$ reagent in drug discovery and development.[3]

We also developed an organic solvent-free difluoromethylation protocol with the $TMSCF_2Br$ reagent, which provided a greener method for the difluoromethylation of alcohols.[85]

With the insights gained from alcohol difluoromethylation that the alkyl-substituted oxygen atom can capture the difluorocarbene directly, we surmised that dialkyl ether might also react with difluorocarbene. Indeed, we found that ring-opening difluoromethylation−halogenation of cyclic (thio)-ethers with $TMSCF_2X$ (X= Br, Cl) can be accomplished (Scheme 32).[86] Notably, in this reaction, both the CF_2

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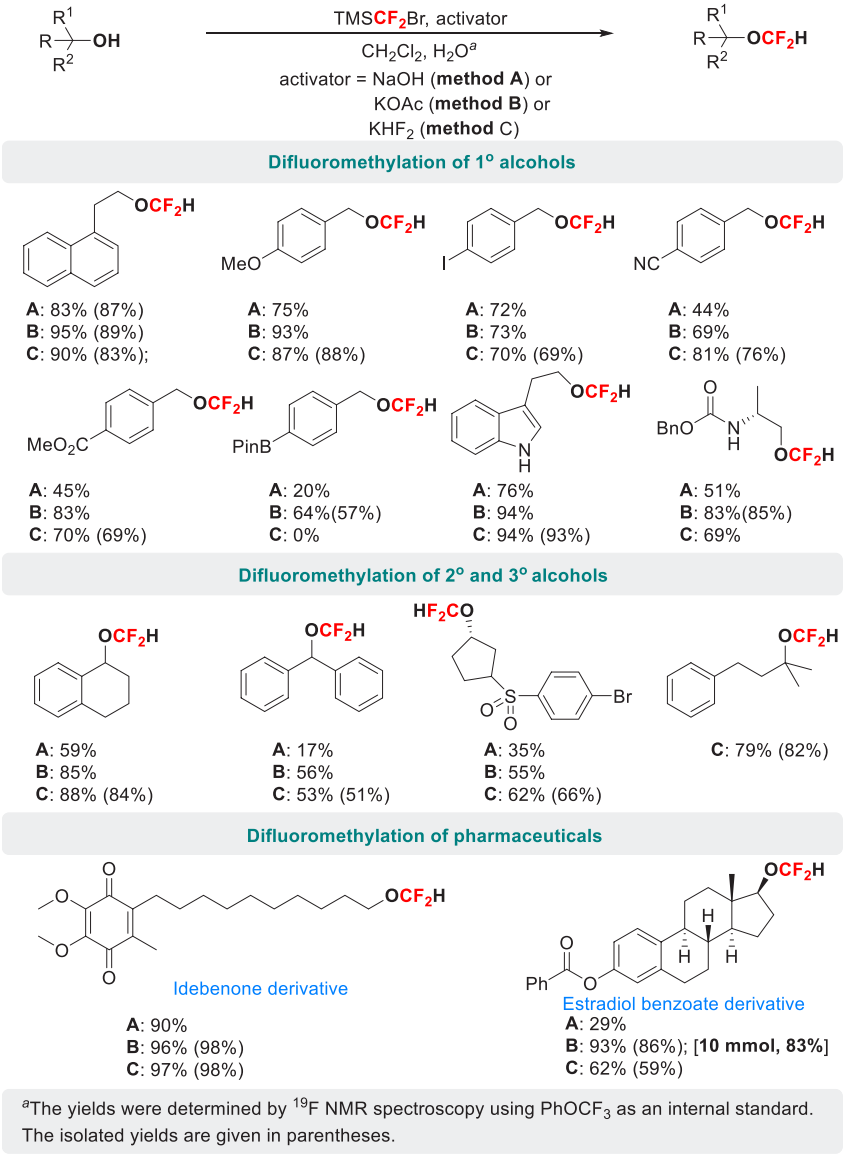
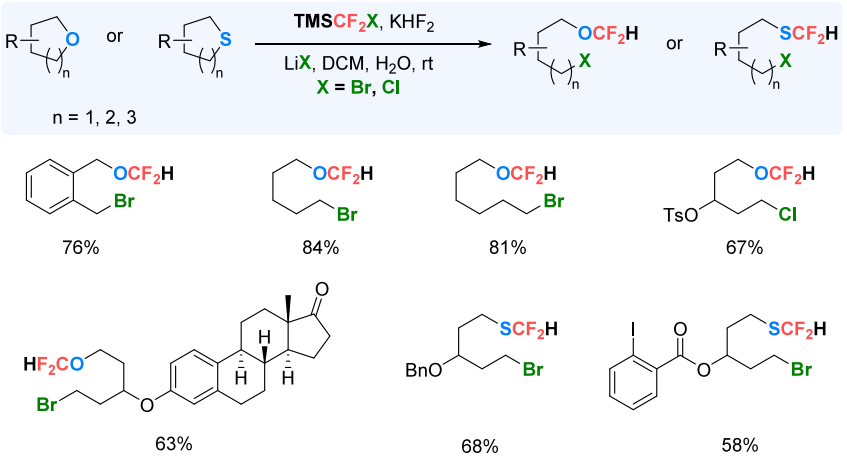
Scheme 31. Difluoromethylation of Alcohols with $TMSCF_2Br$



Scheme 32. Ring-Opening Difluoromethylation−Halogenation of Cyclic (Thio)Ethers with $TMSCF_2Br$



functionality and the halogen atom (X) from $TMSCF_2X$ were incorporated into the products.

We further extended the synthetic application of $TMSCF_2Br$ (**6**) to the selective *C*-difluoromethylation of carbon acids,

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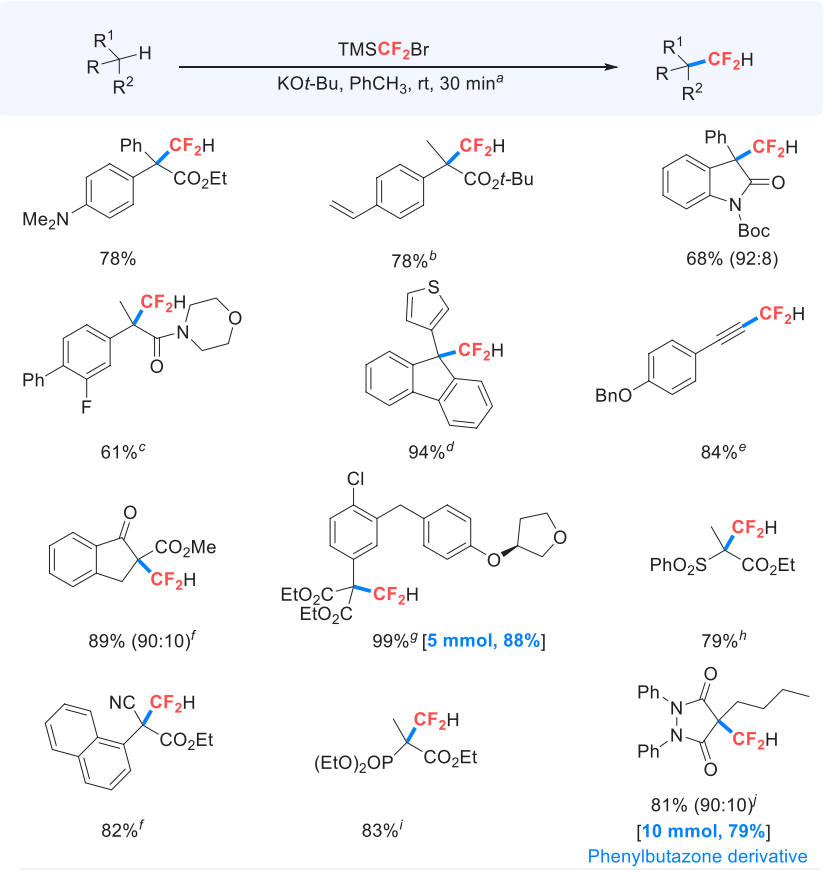
Scheme 33. Selective *C*-Difluoromethylation of Carbon Acids with $TMSCF_2Br$

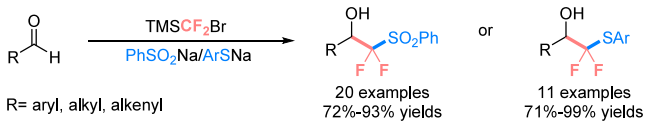


[a]The C/O ratio is given in parentheses. [b]KHMDS and KO*t*-Bu as the base. [c]KHMDS was used as the base. [d]1,4-Dioxane as the solvent. [e]0 °C. [f]NaOH (20% aq.) as the base, and CH_2Cl_2 as the solvent. [g]CH_3CN as the solvent. [h]LiO*t*-Bu as the base, and THF as the solvent. [i]LiO*t*-Bu as the base. [j]NaO*t*-Bu as the base, CH_2Cl_2 as the solvent, and LiI was added.

which had been considered more difficult than that of heteroatoms, and few methods are available to achieve this goal.[87−91] A diverse range of carbon nucleophiles, including esters, amides, fluorenes, terminal alkynes, β-ketoesters, malonates, and many other activated C−H bonds, were successfully difluoromethylated in high yields (Scheme 33).[92] The drug molecule phenylbutazone also worked well, affording the difluoromethylated product in good yield (even in gram scale).

By using $TMSCF_2Br$ (**6**) as the difluorocarbene reagent and $PhSO_2Na$ (or ArSNa) as the nucleophile, a three-component protocol of nucleophilic (phenylsulfonyl)difluoromethylation [or (arylthio)difluoromethylation] of aldehydes was realized in high efficiency (Scheme 34), avoiding the tedious preparation of $PhSO_2CF_2X$ or $PhSCF_2X$ (X = H, Br, TMS) in advance. This work demonstrates the advantage of $TMSCF_2Br$ (**6**) as a difluorocarbene reagent in the construction of $-CF_2-$ bridging structures.[93]

Scheme 34. (Phenylsulfonyl)difluoromethylation/ (Arylthio)difluoromethylation of Aldehydes with $TMSCF_2Br$



Recently, the uniqueness of $TMSCF_2Br$ (**6**) as a difluorocarbene reagent was further demonstrated in the fluorination−aminocarbonylation of aldehydes.[94] A vast array of aromatic and aliphatic aldehydes and tertiary amines can be employed, which provides modular access to α-fluoroamides (Scheme 35). $TMSCF_2Br$ (**6**) plays triple roles in this reaction: (1) the difluorocarbene source, (2) the bromide source for dealkylation, and (3) the "TMS^+" source for stabilizing 1,4-zwitterion intermediate **A** (see Scheme 36). The multiple roles that $TMSCF_2Br$ plays in this reaction highlight the uniqueness of $TMSCF_2Br$ as a difluorocarbene reagent. A plausible mechanism is shown in Scheme 36. In the presence of an initiator (such as a tertiary amine), $TMSCF_2Br$ generates difluorocarbene, which is trapped by the tertiary amine to form a nitrogen ylide. The latter species undergoes nucleophilic addition to the aldehyde to give 1,4-zwitterionic intermediate **A**. Next, **A** reacts with $TMSCF_2Br$ (**6**) via unstable pentacoordinated silicate intermediate **B** to produce difluorocarbene and **C**. Dealkylation of **C** by the bromide ion gives intermediate **D**, which can undergo defluorination to give fluorinated iminium intermediate **E**. Desilylation by fluoride (followed by cyclization) affords epoxide **F**, which undergoes 1,2-fluorine migration via either ion pair intermediate **G** (path a) or a concerted pathway with transition state **H** (path b) to deliver the final product **I**.[94]

Interestingly, in the above-mentioned transformation, the reaction pathway can be changed if water is present (Scheme

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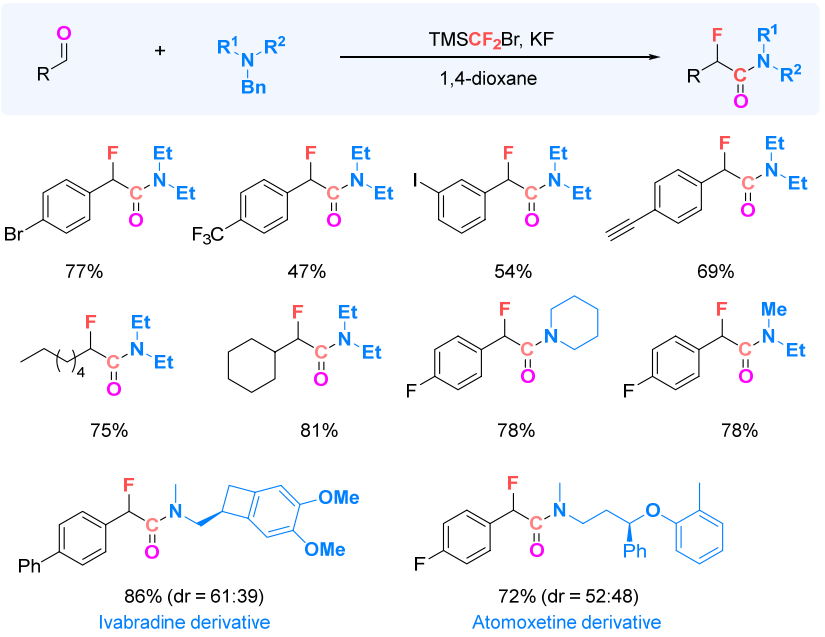
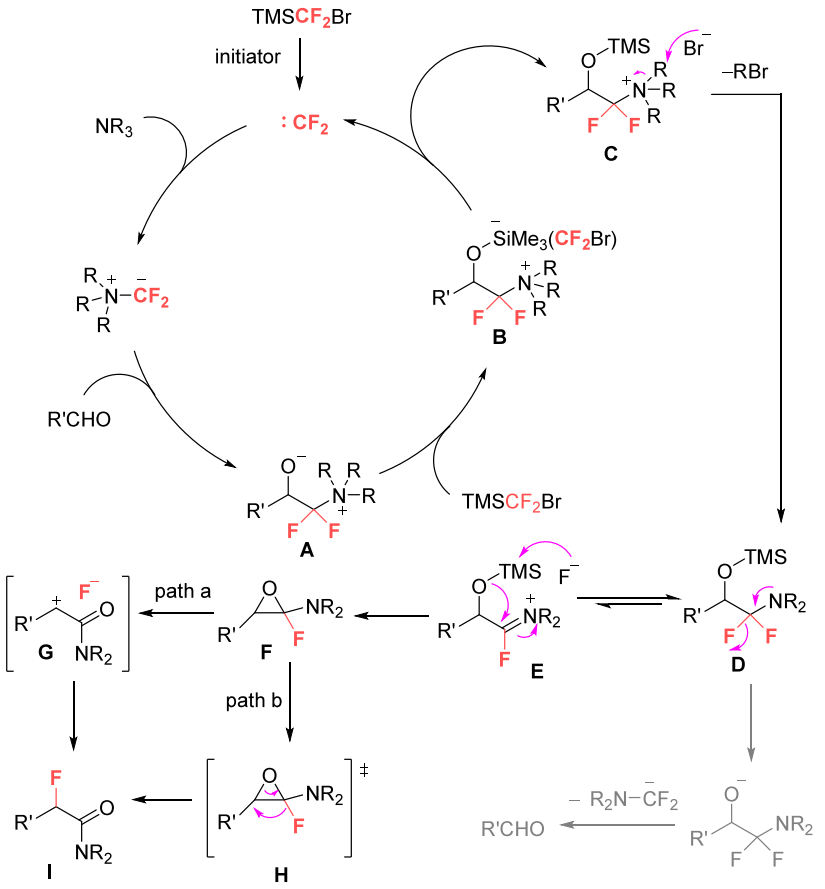
Scheme 35. Fluorination−Aminocarbonylation of Aldehydes with $TMSCF_2Br$



Scheme 36. Proposed Mechanism for Fluorination−Aminocarbonylation of Aldehydes with $TMSCF_2Br$



37).[95] The fluorinated iminium intermediate can be trapped by water to give α-hydroxyamides as major products (instead of undergoing intramolecular cyclization).

Inspired by the unique reaction mechanism of fluorination−aminocarbonylation of aldehydes with $TMSCF_2Br$ (see Scheme 36), we subsequently realized formal controllable single and double CF_2 insertions into the C−H bonds of aldehydes under transition-metal-free conditions.[96] We proposed that the key intermediate **C** (as shown in Scheme 36) may be able to undergo Hofmann elimination in the presence of a strong base to give

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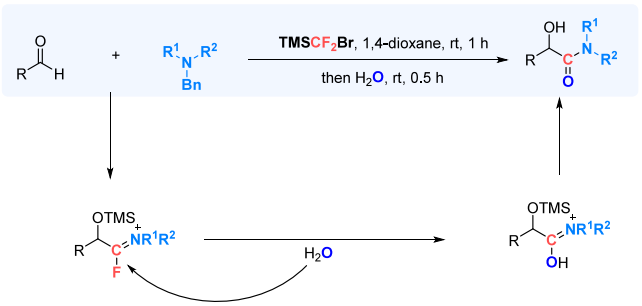
Scheme 37. Aminocarbonylation of Aldehydes with $TMSCF_2Br$

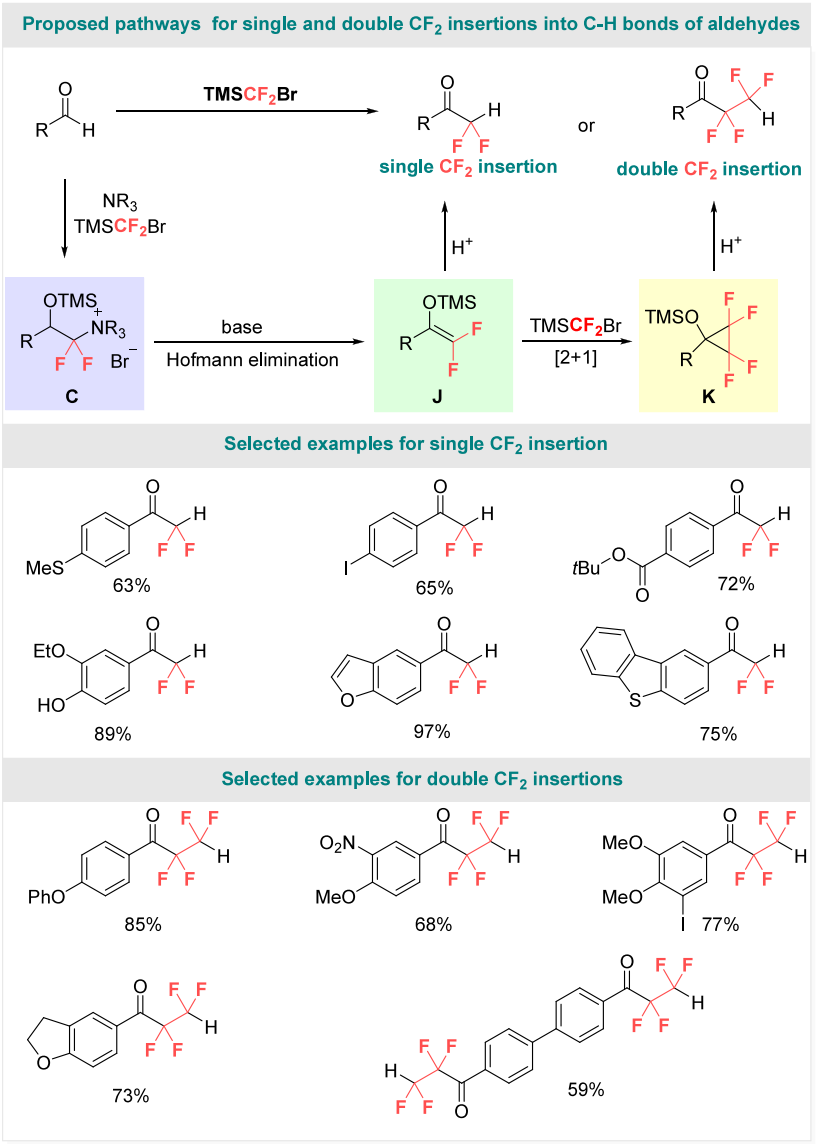


2,2-difluoroenosilyl ethers **J**, which can further react with difluorocarbene to form 2,2,3,3-tetrafluorocyclopropanoxysilyl ethers **K**. Protonation of intermediates **J** and **K** could give single and double CF_2 insertion products, respectively (Scheme 38). This reaction shows broad substrates scope, and aromatic aldehydes bearing various functional groups can be tolerated.

The synthetic power of $TMSCF_2Br$ (**6**) as a difluorocarbene reagent was further demonstrated in the controllable fluorocarbon chain elongation.[4] Selective single and double CF_2 insertions into $CuCF_2H$ species with $TMSCF_2Br$ were accomplished, affording previously unknown fluoroalkylcopper species "$Cu(CF_2)_nCF_2H$" (n = 1, 2). This work represented the first example of selective single and double CF_2 insertions into the same C−Cu bond (Scheme 39).[4] The key to the controllable fluorocarbon chain elongation from C_1 to C_2 and C_1 to C_3 is presumably the different reactivity of "$Cu(CF_2)_nCF_2H$" species (n = 0, 1, 2) and the loading of $TMSCF_2Br$. The synthetic value of the new fluoroalkylcopper species was demonstrated by the tetrafluoroethylation and hexafluoropropylation of aryl iodides (Scheme 40).[4] More recently, we also achieved the $TMSCF_2Br$-enabled trifluorovinylation and pentafluorocyclopropylation of aldehydes.[97]

Although the versatility and robustness of $TMSCF_2Br$ (**6**) has been clearly shown in the fluoroalkylation/fluoroolefination of various substrates under a wide array of mild conditions (as discussed above), perhaps the most unique feature of

Scheme 38. Controllable Single and Double CF_2 Insertions into C−H Bonds of Aldehyes with $TMSCF_2Br$



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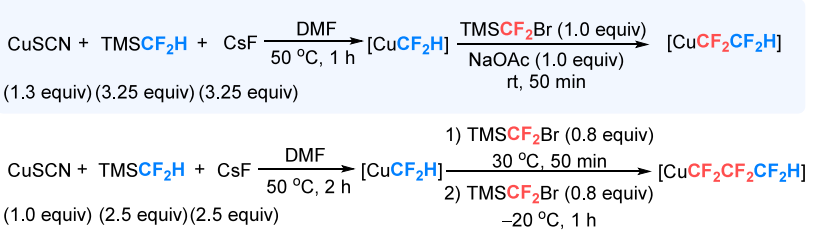
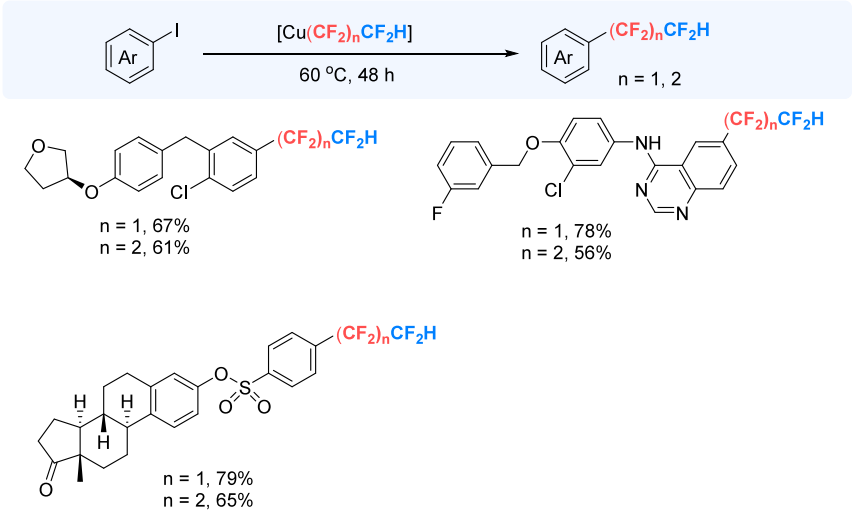
Scheme 39. Controllable Single and Double CF_2 Insertion into "$CuCF_2H$" with $TMSCF_2Br$



Scheme 40. Tetrafluoroethylation and Hexafluoropropylation of Aryl Iodides with $TMSCF_2Br$-Derived "$Cu(CF_2)_nCF_2H$"



$TMSCF_2Br$ (**6**) is its orthogonal reactivity in site-selective functionalization of substrates bearing multiple reactive sites (Scheme 41).[3,86,92] Notably, to the best of our knowledge, this type of orthogonal selectivity has never been demonstrated with other difluorocarbene reagents. For the phenol−alcohol substrate (Scheme 41a), under acidic conditions, i.e., using KHF_2 as an additive, the alcoholic OH group is more nucleophilic than the phenolic OH group; therefore, the alcoholic OH group is selectively difluoromethylated. However, under strongly basic conditions, i.e., using KOH as an additive, the phenol was transformed to phenoxide, which is a stronger nucleophile than the neutral alcohol OH group; therefore, the phenolic OH group is selectively difluoromethylated. Analogously, in the case of the alkene−alcohol substrate (Scheme 41b), alkene−carbon acid substrate (Scheme 41c), and terminal alkyne−cyclic ether substrate (Scheme 41d), all can be selectively functionalized with $TMSCF_2Br$ (**6**) under specific conditions. The success of this selective fluoro-functionalization process is based on (a) the ability of $TMSCF_2Br$ (**6**) to generate difluorocarbene under various conditions (ranging from strongly basic to slightly acidic, low temperature to high temperature, aqueous solution to anhydrous conditions, among others) and (b) the significant reactivity difference of various functional groups toward difluorocarbene under different conditions.

The unique and high reactivity of $TMSCF_2Br$ (**6**) as a difluorocarbene source is remarkable, which makes it stand out as a privileged reagent in difluorocarbene chemistry. It is worthwhile to mention that to achieve the high efficiency of a specific difluorocarbene-involved reaction, the reaction conditions used for difluorocarbene generation from a difluorocarbene reagent (precursor) should match those for a specific difluorocarbene-involved reaction. It is extremely important to realize that $TMSCF_2Br$ is able to release difluorocarbene under different reaction conditions (or say, $TMSCF_2Br$ possesses various activation modes), therefore, $TMSCF_2Br$ is suitable for most difluorocarbene-involved reactions. However, many other known difluorocarbene reagents may have only one or two specific modes to generate difluorocarbene, which narrows their application in limited types of difluorocarbene-involved reactions.

9. CONCLUSIONS

In this Account, we summarized our contributions to the design, synthesis, and synthetic application of difluorocarbene reagents for synthetic chemistry over the past 17 years. Seven new difluorocarbene reagents have been developed, including $PhCOCF_2Cl$ (**1**), $PhSO_2CF_2Cl$ (**2**), $PhSO(NTs)CF_2H$ (**3**), $[(n\text{-}Bu)_3NCF_2H]^+Cl^-$ (**4**), $TMSCF_2Cl$ (**5**), $TMSCF_2Br$ (**6**), and $TMSCF_3$ (**7**), which have preference over the traditional ones with respect to reaction efficiency, substrate scope, and environmental benignity. The ability of these reagents to be used for the late-stage functionalization of bioactive compounds renders them highly attractive in new drug development. During our research, we realized the key factor for an ideal difluorocarbene reagent that can be used for a broad range of reactions; that is, the reagent should allow various activation modes for the generation of difluorocarbene species, such as under basic/acidic/neutral conditions, at a wide range of temperatures, and in different solvents, which are compatible with a wide range of difluorocarbene-involved transformations. Of all known difluorocarbene reagents, $TMSCF_2Br$ (**6**) is perhaps the most unique, versatile, and robust one because it can be used for most of known difluorocarbene-involved reactions

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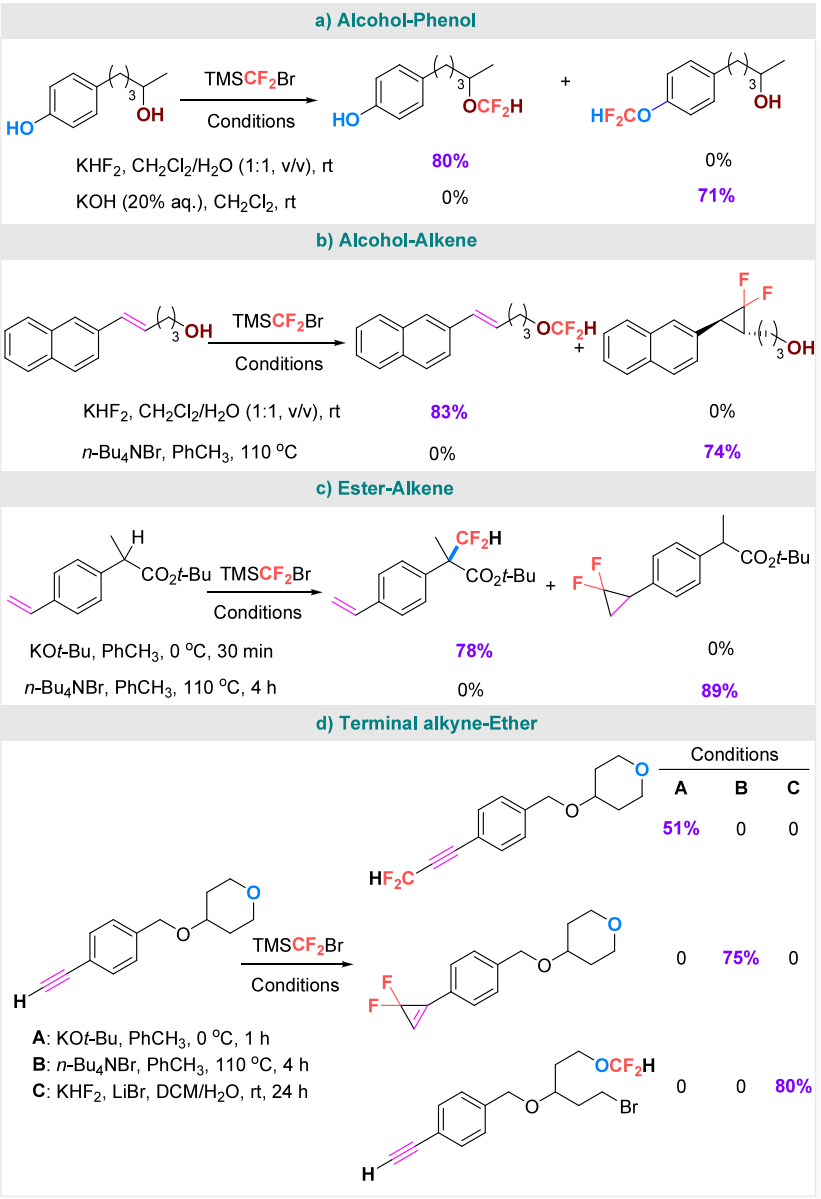
Scheme 41. Site-Selective Functionalization of Substrates Bearing Multiple Reactive Sites with $TMSCF_2Br$ (6)



and even many new reactions, which are difficult to achieve by using other traditional difluorocarbene reagents. In contrast, many other difluorocarbene reagents can only be applied in a narrow scope of reactions due to their limited activation modes. The robustness of $TMSCF_2Br$ (**6**) as a difluorocarbene reagent is largely due to its rich activation modes to generate difluorocarbene under a variety of different conditions. It can be expected that, with the commercial availability of $TMSCF_2X$ reagents (X = Br, F, Cl) now, the development of difluorocarbene chemistry will be accelerated in the years to come, such as novel difluorocarbene-involved multicomponent reactions, controllable fluorocarbon chain elongation reactions, and transition-metal-catalyzed difluorocarbene transfer reactions, among others. In addition, the $TMSCF_2X$ reagents promise to find wide applications in the synthesis of fluorinated pharmaceuticals, agrochemicals, and advanced materials.

AUTHOR INFORMATION

Corresponding Author

Jinbo Hu − *Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China;* orcid.org/0000-0003-3537-0207; Email: jinbohu@sioc.ac.cn

Author

Qiqiang Xie − *Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.3c00719

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Author Contributions

J.H. desiged the theme and structure of the manuscript. Q.X. wrote the draft, and J.H. revised and finished the final version. CRediT: **Qiqiang Xie** writing-original draft; **Jinbo Hu** conceptualization, funding acquisition, project administration, resources, supervision, writing-revision & improvement.

Notes

The authors declare no competing financial interest.

Biographies

Qiqiang Xie was born in Jiangxi, China, in 1993. He received his B.S. degree in 2014 from Shanghai University. He obtained his Ph.D. degree in 2019 under the supervision of Professor Jinbo Hu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS). His current research interests are focused on the synthetic application of fluoroalkylsilane reagents.

Jinbo Hu was born in Zhejiang, China, in 1973. After he completed his B.S. (Hangzhou University) and M.S. (Chinese Academy of Sciences) degrees, he did his Ph.D. work from 1997 to 2002 at the University of Southern California with Professors G. K. S. Prakash and G. A. Olah. After his postdotoral work at USC, he joined the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early 2005, where he is currently a full professor. He was the recipient of the RSC Fluorine Prize (2009), the Tan Kah-Kee Young Scientists' Award (2012), and the ACS Award for Creative Work in Fluorine Chemistry (2022). His current research interests mainly focus on organofluorine chemistry and fluorinated materials, including the development of new reagents and reactions through probing the unique fluorine effects in organic reactions.

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■ DEDICATION

This Account is in memory of Professor Qing-Yun Chen (passed away on March 2, 2023), who made numerous important contributions to organofluorine chemistry including difluorocarbene chemistry.

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