Recent Advances in the Synthetic Application of Difluorocarbene

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Abstract: Difluorocarbene is a versatile, reactive intermediate for use in organic synthesis. Over the past decade, significant progress has been made in difluorocarbene chemistry owing to the increasing demand for various fluorinated molecules. Not only the substrate scope for some classical difluorocarbene reagents has been largely expanded, but also new and environmentally friendly difluorocarbene reagents for difluoromethylation and *gem*-difluorocyclization have been developed. This review summarizes the difluoromethylation, *gem*-difluorocyclopropanation, *gem*-difluorocyclopropenation, *gem*-difluoroolefination, and trifluoromethylation achieved in the last decade using both the classical and the new difluorocarbene sources.

Key words: difluorocarbene, difluoromethylation, cycloaddition, *gem*-difluoroolefination, trifluoromethylation

1 Introduction

'Lightly fluorinated' molecules have become a focus in organic synthesis due to their wide application in drug design and in the development of new functional materials.[1] Among various fluorine-containing moieties that can modify the properties of a molecule, difluoromethyl ($-CF_2H$) and difluoromethylene ($-CF_2-$) groups have attracted great interest.[1,2] The difluoromethyl group is known to be isosteric to a carbinol unit, which can act as a lipophilic hydrogen donor through weak hydrogen bonding interactions.[2b,3] Many difluoromethyl ethers such as Desflurane (an anesthetic)[4a] and Pantoprazole (a proton pump inhibitor),[4b] and *N*-difluoromethyl amines, such as *N*-(difluoromethyl)pyridin-2(1*H*)-one-substituted acetic acids (enzyme inhibitors),[4c] are of great medicinal importance. *gem*-Difluorination of constrained structures can alter their conformation and reactivity, and thus leads to highly important new scaffolds, such as *gem*-difluorocyclopropanes and difluorocyclopropenes, that can be used to build biologically active compounds, unique polymers, and liquid crystal compounds.[1c,5] Moreover, the difluoromethylene group is considered as a bioisostere for an ethereal oxygen atom,[1b,6] and the *gem*-difluorovinyl functionality ($C=CF_2$) has been utilized as a bioisostere for a carbonyl group[7] to design biologically active molecules such as mechanism-based enzyme inhibitors.[8]

Difluoromethylenation with difluorocarbene is the most straightforward approach for the synthesis of structurally diverse *gem*-difluorinated compounds,[1a] although numerous alternative methods are also available.[9,10] Difluorocarbene in its singlet ground state is destabilized by the negative inductive effect of fluorine and stabilized by π-donation from the fluorine to the carbon.[1a] This combination of destabilizing and stabilizing effects renders difluorocarbene a moderately electrophilic species, which reacts much more easily with electron-rich than electron-poor substrates.[1a] Investigations have shown that the reactions of difluorocarbene with negatively charged heteroatom nucleophiles, such as phenolates and thiolates, can be carried out at (or below) ambient temperature,[11] while its reactions with both alkenes and alkynes (except the most electron-rich ones) have to be performed with heating to surpass the substantial activation barrier.[9a] Not only can difluorocarbene react with heteroatom nucleophiles to form difluoromethylated compounds and with C–C multiple bonds to form *gem*-difluorocyclopropanes and difluorocyclopropenes, it can also be used for the synthesis of trifluoromethylated compounds (via copper-mediated reaction) and *gem*-difluoroalkenes (via Wittig olefination).

Several early general reviews[9,11] covering the synthetic application of difluorocarbene have been published; however, these reviews mainly concentrated on *gem*-difluorocyclopropanation and difluorocyclopropenation. In recent years, progress has been made in difluorocarbene chemistry. On one hand, more effective and practical reagents for

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difluoromethylation and *gem*-difluorocyclization have been developed, and some possess a much broader substrate scope than those previously used. On the other hand, the substrate scope of some classical reagents has been largely expanded, and some novel reactions using both previously and newly developed difluorocarbene sources have appeared. This review mainly focuses on these recent developments. In some cases, however, to demonstrate the reactivity of difluorocarbene, reactions using toxic or ozone-depleting-substance (ODS)-based difluorocarbene sources are still included when there is a lack of examples using more environmentally friendly reagents.

2 Difluorocarbene Sources

Sodium chlorodifluoroacetate ($ClCF_2CO_2Na$) was probably the first difluorocarbene reagent used in organic synthesis; it was developed by Haszeldine and co-workers in 1960.[12] Since then, a large number of difluorocarbene sources have been used for chemical reactions.[9,11] However, many of these earlier reagents are hazardous either to the environment (such as ozone-depleting substances HCF_2Cl and HCF_2Br) or to human beings (such as Me_3SnCF_3 and CF_3HgI)[11] and this inhibited their wide application in modern organic synthesis. Although more environmentally friendly classical reagents such as sodium chlorodifluoroacetate ($ClCF_2CO_2Na$),[12] methyl chlorodifluoroacetate ($ClCF_2CO_2Me$),[13] and the tetrafluoroethane β-sultone derivatives[10d] difluoro(fluorosulfonyl)acetic acid ($FSO_2CF_2CO_2H$),[14] methyl difluoro(fluorosulfonyl)acetate ($FSO_2CF_2CO_2Me$),[15] and trimethylsilyl difluoro(fluorosulfonyl)acetate (TFDA, $FSO_2CF_2CO_2TMS$)[16] are readily available, their practical applications still have some limitations. During the past decade, many new and highly efficient difluorocarbene sources[17–28] have been developed (Figure 1), most of which are described as non-ozone-depleting reagents.

Usually, the generation of difluorocarbene is initiated by attack on the reagents with a nucleophile (such as iodide, fluoride, or hydroxy ion)[13,15,16,18–22,27] or by deprotonation with a base.[14,23–26] Sometimes, the reagents undergo thermal pyrolysis to release difluorocarbene in the absence of any additive.[12,17,28]

In the case of the difluoromethylation of heteroatoms, difluorocarbene is usually formed by initiation with a base that is also used to activate the pronucleophile, and the reaction of difluorocarbene with the nucleophile is faster than the competitive reaction of difluorocarbene with the base. However, in the case of the difluoromethylenation of alkenes and alkynes, the fast release of difluorocarbene and its ready reaction with a nucleophilic species (such as a base) can significantly inhibit the desired [2 + 1] cycloaddition reaction between difluorocarbene and the alkene (or alkyne). Therefore, the generation of difluorocarbene under nonbasic conditions is preferred for these [2 + 1] cycloaddition reactions.

Biographical Sketches

Chuanfa Ni was born in Shandong, China in 1982 and obtained his B.S. degree in chemistry from Shandong Normal University in 2003. After graduate work (2003–2009) at the Shanghai Institute of Organic Chemistry under the supervision of Professor Jinbo Hu and postdoctoral work (2009–2012) at the University of Southern California under the supervision of Professor G. K. Surya Prakash, he joined the Hu group as an associate research professor in 2012. His research interests lie in the development of new methodologies for the selective synthesis of fluorinated molecules.

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 during 1997 to 2002 at the University of Southern California with Professors G. K. S. Prakash and G. A. Olah. After his postdoctoral work at USC, he accepted the Research Professorship at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early 2005, where he is currently the Assistant Director of SIOC and Head of the CAS Key Laboratory of Organofluorine Chemistry. He is the recipient of the RSC Fluorine Prize 2009 and Tan Kah-Kee Young Scientists' Award 2012. His current research interests include selective fluorination, defluorination, and fluoroalkylation methodologies, and fluorinated materials.

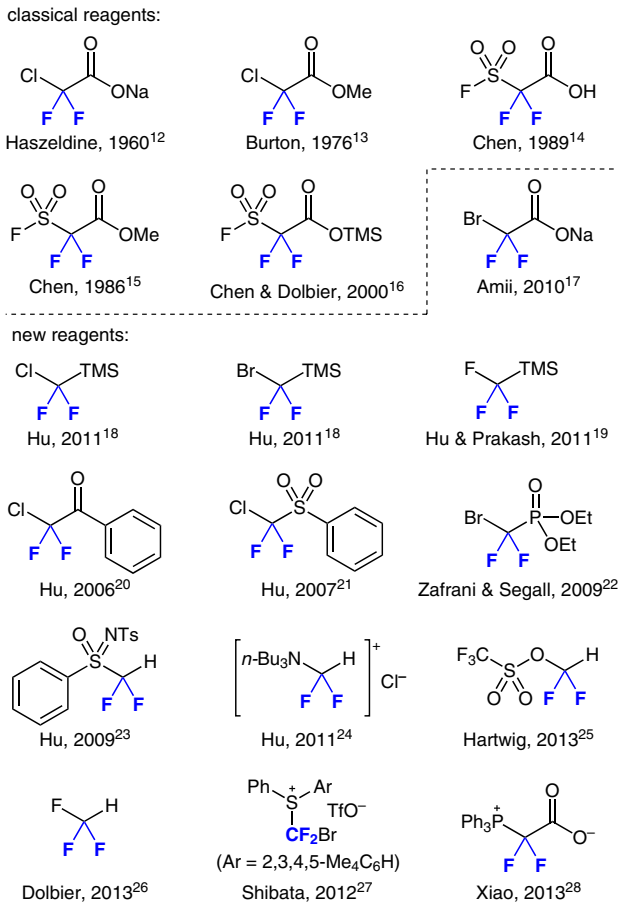


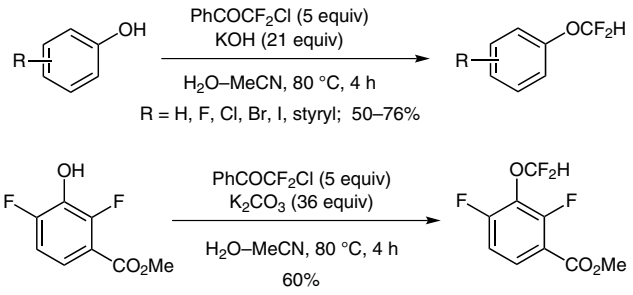
Figure 1 Structures of classical and new difluorocarbene sources used in recent organic synthesis;[12–28] (ozone-depleting reagents such as HCF_2Cl are not listed)

3 Difluoromethylation

Commonly, the difluoromethylation of O-, S-, N-, C-, P-, Se-, and Te-nucleophiles is achieved with chlorodifluoromethane.[10a–c,29] The regulation of ozone-depleting substances by the Montreal Protocol has promoted the development and use of non-ozone-depleting reagents.

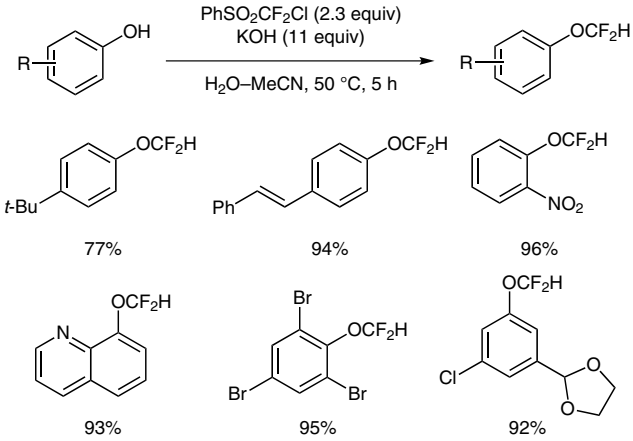
3.1 O-Difluoromethylation

Phenols: In 2006, the Hu group reported that 2-chloro-2,2-difluoroacetophenone reacts with hydroxide (OH^-) to give a chlorodifluoromethyl anion species that readily undergoes α-elimination of a chloride ion.[20] The difluorocarbene intermediate generated in this way reacts with various substituted phenols giving aryl difluoromethyl ethers in good yields (Scheme 1). When the weaker base potassium carbonate is used instead of potassium hydroxide to promote the reaction, a base-sensitive ester group is tolerated on the phenol substrate.[20]

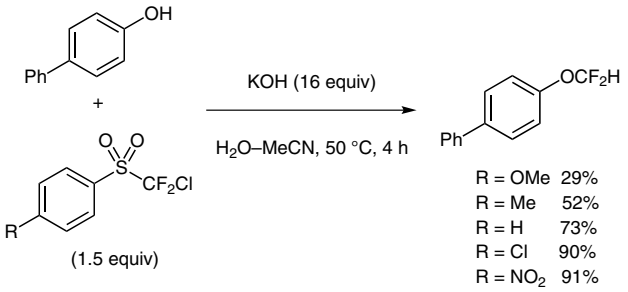


Scheme 1 Difluoromethylation of phenols with 2-chloro-2,2-difluoroacetophenone[20]

In 2007, the Hu group disclosed that chlorodifluoromethyl phenyl sulfone can also be used as a non-ODS-based difluorocarbene reagent under aqueous basic conditions (Scheme 2).[21] The sulfone reagent is prepared in two ways: chlorination of $PhSO_2CF_2H$ or oxidation of $PhSCF_2Cl$.[21] Because the base-promoted SO_2–CF_2Cl bond cleavage is slower than that of the CO–CF_2Cl bond, the formation of difluorocarbene from chlorodifluoromethyl phenyl sulfone is more controllable, and the amount of chlorodifluoromethyl phenyl sulfone needed is largely decreased.[21] The protocol is effective for both electron-rich and electron-deficient phenols. However, the relatively high temperatures required mean that this procedure is not compatible with the aldehyde functional group.[21] Further investigations into the influence of the substituents on the phenyl group of the sulfone reagent showed that an electron-donating group reduces the yield significantly, while an electron-withdrawing group increases the yield (Scheme 3).[30]

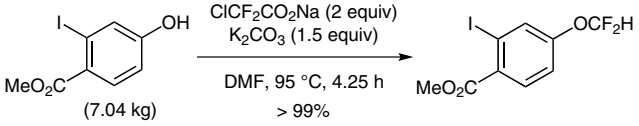


Scheme 2 Difluoromethylation of phenols with chlorodifluoromethyl phenyl sulfone[21]



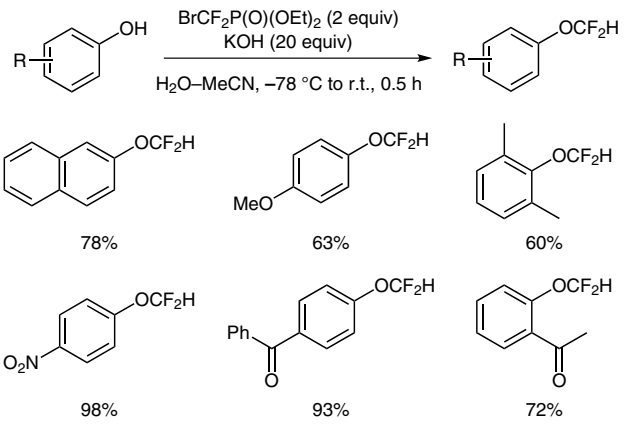
Scheme 3 Influence of substituents on the reactivity of aryl chlorodifluoromethyl sulfones[30]

Chlorodifluoroacetates ($ClCF_2CO_2Na$ or $ClCF_2CO_2Me$) are also useful reagents for the synthesis of difluoromethyl ethers from phenols; however, very few publications on their application are available.[31,32] In 2011, process research on the O-difluoromethylation of methyl 4-hydroxy-3-iodobenzoate on a multikilogram scale showed that high temperatures are needed to promote the generation of difluorocarbene from commercially available $ClCF_2CO_2Na$ (Scheme 4).[32] It was also found that the ability to control the release of CO_2 from the reaction mixture is a critical safety parameter for a large-scale process. Similar to the difluoromethylation of ester-substituted phenols with 2-chloro-2,2-difluoroacetophenone, in this case, potassium carbonate is also the base of choice.



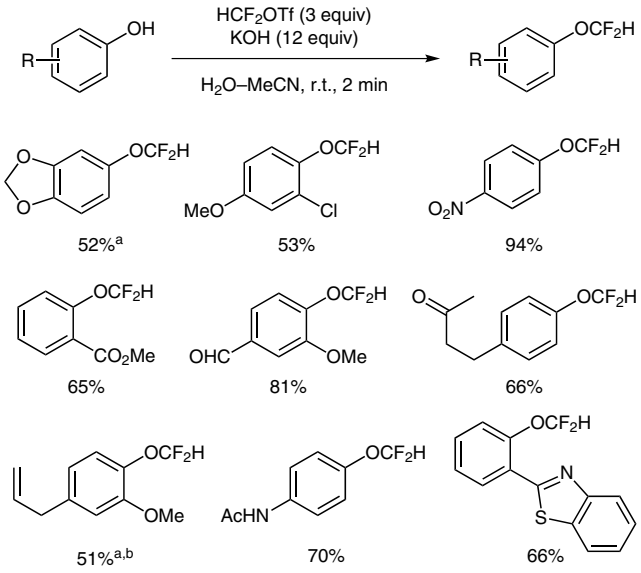
Scheme 4 Difluoromethylation of phenols with $ClCF_2CO_2Na$[32]

Difluoromethylation at low temperatures not only is beneficial for the safe scale-up of industrial applications, it also shows a broader functional group tolerance due to the mildness of the reaction conditions. In 2009, Zafrani et al. reported that diethyl bromodifluoromethylphosphonate can work as a highly efficient and environmentally benign difluorocarbene precursor (Scheme 5).[22] This commercially available phosphonate undergoes an extremely facile P–C bond cleavage on basic hydrolysis (–78 °C to r.t., 0.5 h) leading to the bromodifluoromethyl anion, which subsequently converts into the difluorocarbene intermediate. In this reaction, even phenols bearing an enolizable carbonyl functional group can also be selectively difluoromethylated.



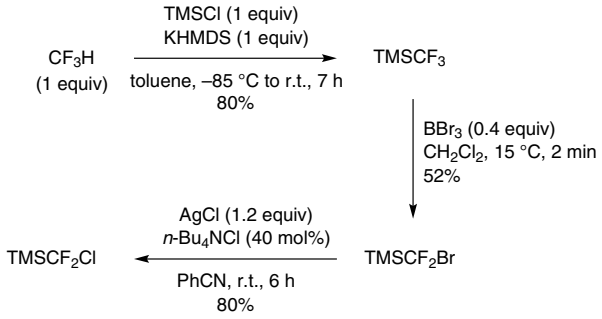
Scheme 5 Difluoromethylation of phenols with diethyl bromodifluoromethylphosphonate[22]

Difluoromethyl triflate,[33] which can be conveniently prepared from $TMSCF_3$ and triflic acid,[33d] is a non-ODS-based liquid. As early as 1985, Chen and co-worker disclosed its difluorocarbene reactivity;[33c] however, it was only in early 2013 that a practical method for difluoromethylation of phenols and thiophenols was developed by the Hartwig group (Scheme 6).[25] Using potassium hydroxide as a base, many difluoromethyl ethers and thioethers were prepared within minutes at room temperature. The broad functional group tolerance and mildness of the reaction conditions enable the introduction of a difluoromethyl group into a wide range of complex phenols. However, the formation of aryl triflate side products is prevalent in the reactions of phenol substrates bearing electron-donating groups. The use of a more highly fluorinated reagent difluoromethyl perfluorobutanesulfonate containing a bulkier group can inhibit the formation of these side products.[25]

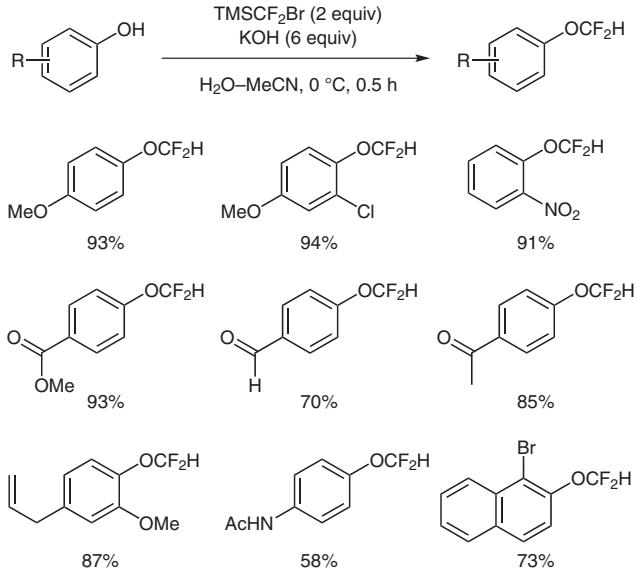


Scheme 6 Difluoromethylation of phenols with difluoromethyl triflate.[25] [a] Significant amounts of aryl triflate were formed as side product. [b] Determined by ^{19}F NMR spectroscopy.

(Bromodifluoromethyl)trimethylsilane ($TMSCF_2Br$) was initially disclosed as a difluorocarbene source for the *gem*-difluorocyclopropenation of alkynes.[18] In 2013, Hu and co-workers developed a new method for the preparation of $TMSCF_2Br$ from $TMSCF_3$ by a halogen-exchange reaction (Scheme 7).[34] As one of the most effective difluoromethylation methods,[22,25,34] the difluoromethylation of heteroatom nucleophiles with $TMSCF_2Br$ can be conducted using much less KOH (only 6 equiv) than similar reactions with diethyl bromodifluoromethylphosphonate and difluoromethyl triflate (Scheme 8).[34] Moreover, not only electron-deficient aromatic phenols, but also electron-rich phenols undergo O-difluoromethylation smoothly with high efficiency. The mild reaction conditions and broad functional group tolerance make this reagent very competitive with diethyl bromodifluoromethylphosphonate[22] and difluoromethyl triflate[25] for late-stage O-difluoromethylation of complex molecules containing phenol motifs. (Chlorodifluoromethyl)trimethylsilane ($TMSCF_2Cl$), which can be prepared by a bromo–chloro exchange reaction (Scheme 7), has similar reactivity to $TMSCF_2Br$.[35]

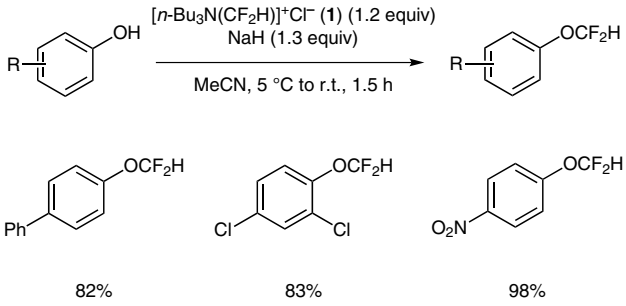


Scheme 7 Non-ODS-based preparations of (difluorohalomethyl)trimethylsilanes[34–36]

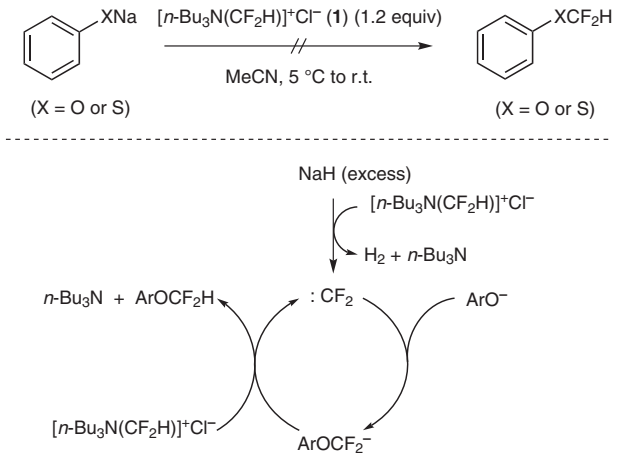


Scheme 8 Difluoromethylation of phenols with (bromodifluoromethyl)trimethylsilane[34]

Tributyl(difluoromethyl)ammonium chloride (**1**), a product from the reaction between tributylamine and difluorocarbene,[37] is also an effective difluorocarbene reagent. Difluoromethylation with this reagent proceeds smoothly in the presence of only a slight excess of base in an organic solvent (Scheme 9).[24] It is worth noting that moderate to excellent yields of the difluoromethylated products are achieved by employing only 1.2 equivalents of this ammonium salt. The possibility of a direct electrophilic difluoromethylation via an S_N2 mechanism is ruled out by the fact that the reaction of sodium phenolate or sodium thiophenolate with **1** did not give the difluoromethylated products in the absence of sodium hydride. In this context, a mechanism involving base-initiated formation of difluorocarbene was proposed by the authors (Scheme 10).[24]



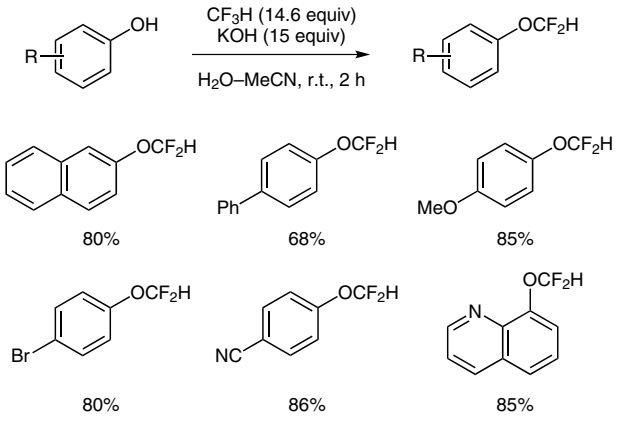
Scheme 9 Difluoromethylation of phenols with tributyl(difluoromethyl)ammonium chloride (**1**)[24]



Scheme 10 Control experiment and proposed mechanism for difluoromethylation with **1**[24]

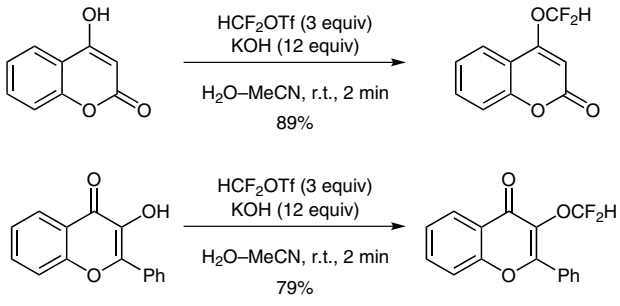
Fluoroform is a byproduct in the manufacture of chlorodifluoromethane used in the production of Teflon, and has been used for the preparation of $TMSCF_3$ by silylation under the action of a base (Scheme 7).[36] Very recently, Dolbier and co-workers found that fluoroform can be employed as a source of difluorocarbene under atmospheric pressure to synthesize aryl difluoromethyl ethers (Scheme 11) and thioethers.[26] However, due to the requirements for a long reaction time and a strong base, the reaction is less compatible with base-sensitive functional

groups. Moreover, a large excess of fluoroform is needed because of the ready consumption of fluoroform by potassium hydroxide. Nevertheless, this protocol is expected to find applications in the industrial production of some simple aryl difluoromethyl ethers and thioethers.



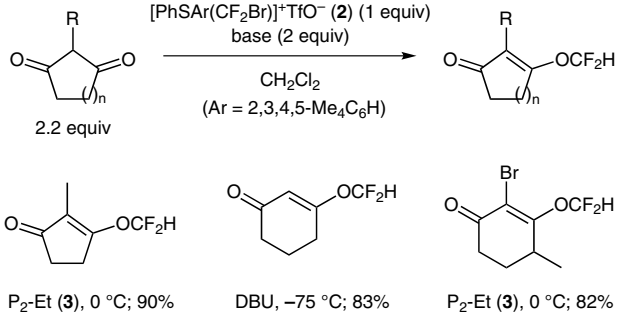
Scheme 11 Difluoromethylation of phenols with fluoroform[26]

Enols and Ketones: Although several difluorocarbene reagents can be used for the difluoromethylation of the phenolic hydroxy group under aqueous basic conditions,[20–22,25,26,29,31,34] the reagents that are suitable for O-difluoromethylation of enolizable carbonyl compounds under similar conditions are scarce. In the case of enolizable carbonyl compounds with relatively weak C–H acidity, the competitive reaction of difluorocarbene with the hydroxy ion predominates. However, some stable enols readily undergo O-difluoromethylation. For example, reactions of chromane-2,4- and 3,4-diones with difluoromethyl triflate afforded alkenyl difluoromethyl ethers in high yields (Scheme 12).[25]



Scheme 12 Difluoromethylation of stable enols with difluoromethyl triflate[25]

Recently, the regioselective O-difluoromethylation of cyclic 1,3-diones has been achieved with in situ generated difluorocarbene from a (bromodifluoromethyl)sulfonium salt **2** (Scheme 13, Figure 2).[38] Shibata et al. found that the 1,3-dione is not only the substrate, but that it is also an activator for sulfonium salt **2** to generate difluorocarbene (Scheme 14).[38a]



Scheme 13 Difluoromethylation of 1,3-diones with (bromodifluoromethyl)sulfonium salt **2**[38a]

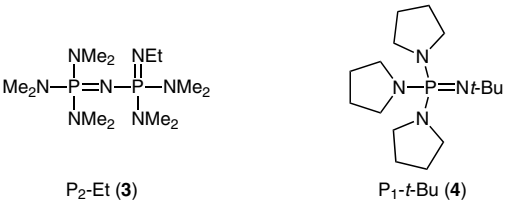
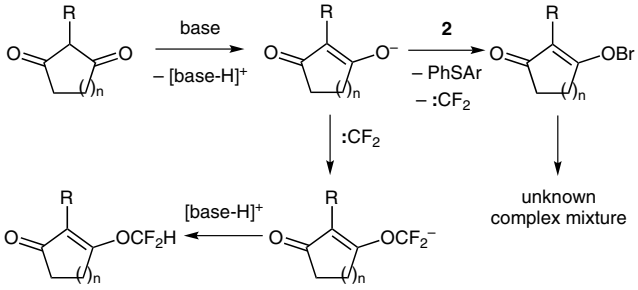


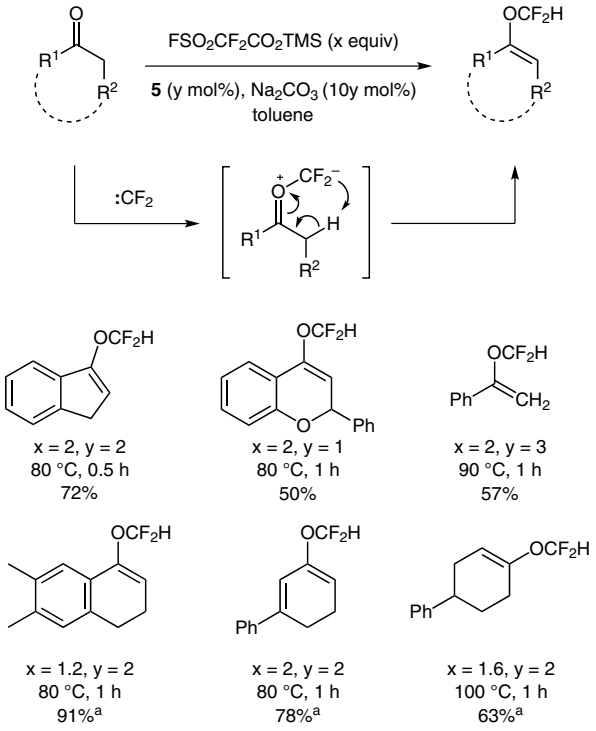
Figure 2 Structures of phosphinimine bases **3** and **4**



Scheme 14 Proposed mechanism for difluoromethylation of 1,3-diones with sulfonium salt **2**[38a]

The O-difluoromethylation of simple ketones containing α-hydrogen can be achieved using TFDA as the difluorocarbene source (Scheme 15).[39] As for the mechanism,[39,40] a neutral oxycarbenium intermediate is believed to be involved as the key intermediate, which undergoes facile 1,4-hydrogen migration to afford the difluoromethyl ethers. In 2011, Ichikawa and co-workers found that the generation and the reactivity of the difluorocarbene are influenced by the catalyst used.[39] When a combination of *N*,*N*′-dimesitylimidazolium chloride (**5**) (Figure 3) and sodium carbonate were used to generate the N-heterocyclic carbene (NHC) catalyst, the ketones are difluoromethylated to afford enol difluoromethyl ethers without difluorocyclopropanation (Scheme 15).[39] Not only cyclic ketones such as cyclohexenones and tetralones, but also acyclic ketones, such as acetophenone, are suitable substrates for O-difluoromethylation under such organocatalyzed conditions. However, when sodium fluoride is used as the catalyst instead of an NHC, the enol difluoromethyl ethers readily undergo a further [2+1] cycloaddition with difluorocarbene to give difluoromethyl 2,2-difluorocyclopropyl ethers (Scheme 16).[40] In the case of indan-1-ones, the

difluoromethyl 2,2-difluorocyclopropyl ethers further rearrange to difluoromethyl 2-fluoro-1-naphthyl ethers.[41]



Scheme 15 Selective synthesis of cyclic and acyclic enol difluoromethyl ethers using TFDA.[39] [a] Isolated as the corresponding aryl ether after oxidative aromatization with DDQ.

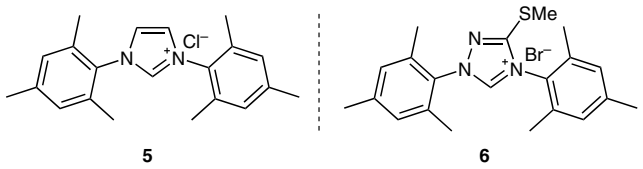
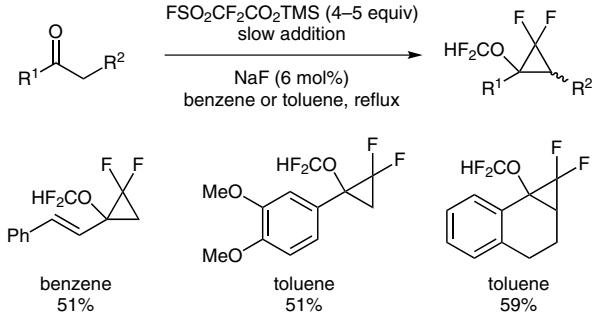


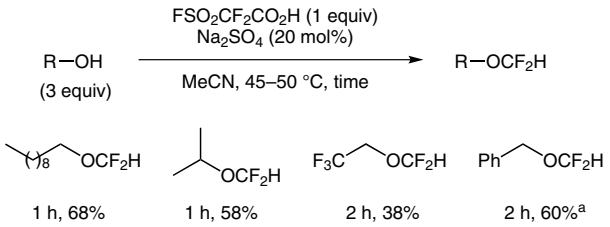
Figure 3 Structures of N-heterocyclic carbene precursors **5** and **6**



Scheme 16 Synthesis of difluoromethyl 2,2-difluorocyclopropyl ethers using TFDA[40]

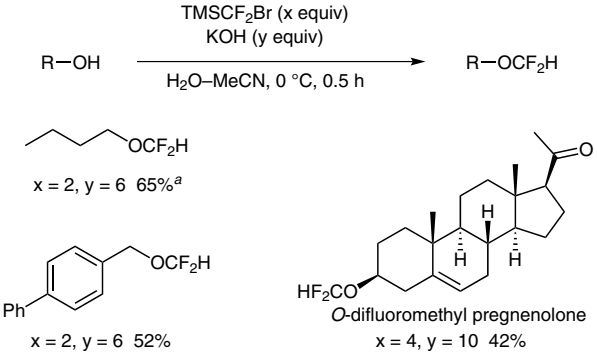
Alcohols: The difluoromethylation of a series of small alcohol molecules, such as MeOH and $CF_3CF_2CH_2OH$, with chlorodifluoromethane under basic conditions has shown that the acidity of the alcohols significantly influences the yields of the difluoromethyl ethers, and sometimes fluoroformals and orthoformates are formed as side products due to the further reaction of difluoromethyl ethers with the alcoholates.[42]

In 1989, Chen and co-workers reported that in the presence of a catalytic amount of sodium sulfate a variety of alkyl difluoromethyl ethers can be synthesized in moderate yields by the reaction of an excess of alcohol with difluoro(fluorosulfonyl)acetic acid (Scheme 17).[43] The difluoro(fluorosulfonyl)acetate anion is believed to readily eliminate SO_2, CO_2, and F^-, thus liberating difluorocarbene, and subsequent insertion of difluorocarbene into the O–H bond results in the formation of ethers. However, this protocol is less effective with phenols.



Scheme 17 Difluoromethylation of alcohols with difluoro(fluorosulfonyl)acetic acid.[43] [a] Isolated yield when 2.5 equivalents of alcohol were used.

In 2013, Hu and co-workers reported that $TMSCF_2Br$ can be used as an effective difluorocarbene source for the O-difluoromethylation of both primary and secondary alcohols under mild and basic conditions (Scheme 18).[34] The reactions proceed smoothly with alcohols as the limiting reactant, giving the corresponding difluoromethyl ethers in moderate yields. This protocol was demonstrated to be suitable for the late-stage selective O-difluoromethylation of pregnenolone.

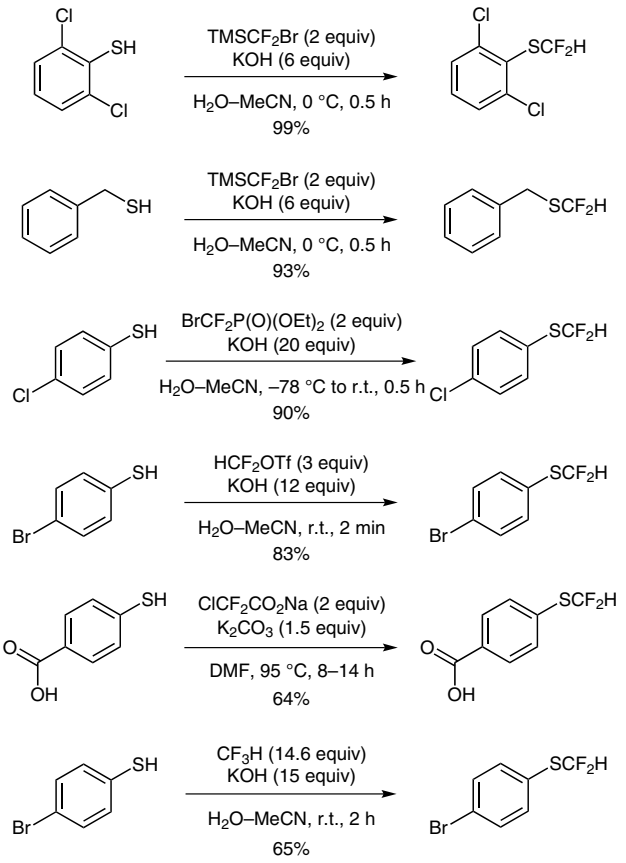


Scheme 18 Difluoromethylation of alcohols with $TMSCF_2Br$.[34] [a] The yield was determined by ^{19}F NMR spectroscopy.

3.2 S-Difluoromethylation

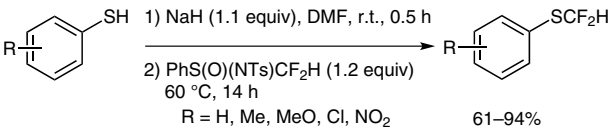
Because sulfur-nucleophiles are generally better difluorocarbene acceptors than oxygen nucleophiles, the difluorocarbene reagents used for difluoromethylation of phenols are also suitable for difluoromethylation of aromatic and heteroaromatic thiols (Scheme 19).[22,25,26,34,44] The reactions are usually performed under basic conditions and

showed similar functional group tolerance to that in the reactions of phenols. It has been demonstrated that not only is $TMSCF_2Br$ reactive towards various thiols to give difluoromethyl thioethers, but it can also transform sulfinates to difluoromethyl sulfones.[34]

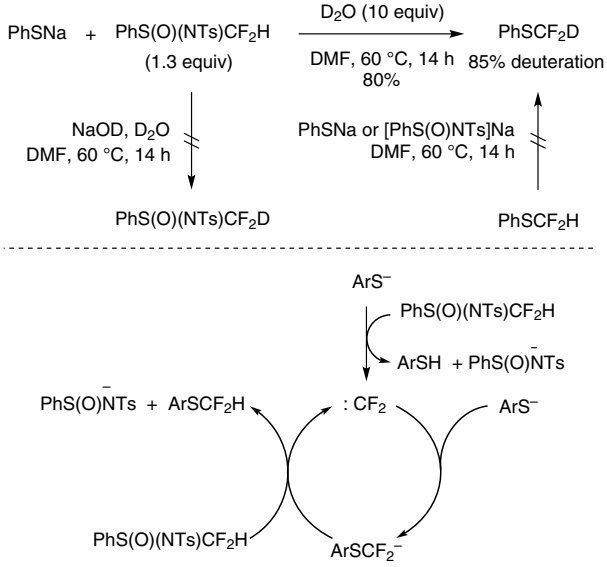


Scheme 19 Difluoromethylation of aromatic thiols using various newly developed difluorocarbene sources[22,25,26,34,44]

In 2009, the Hu group reported that *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine can also be used for the difluoromethylation of thiols (Scheme 20).[23] Deuterium-labeling experiments ruled out the possibility of the involvement of an S_N2 or free radical mechanism as the major pathway in the difluoromethylation with this sulfoximine reagent (Scheme 21), and suggested that a difluorocarbene intermediate is involved.[23] In combination with the fact that a thiolate can react directly with the sulfoximine reagent in the absence of additional base, a reaction cycle starting from difluorocarbene that is generated by deprotonation of *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine was proposed (Scheme 20).[23] However, the reaction of *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine and a phenol under similar conditions was of low yield.



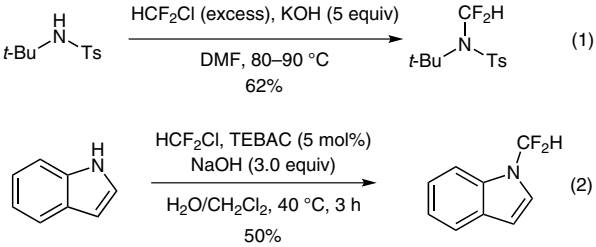
Scheme 20 Difluoromethylation of thiols using *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine[23]



Scheme 21 Deuterium-labeling experiments and proposed reaction mechanism[23]

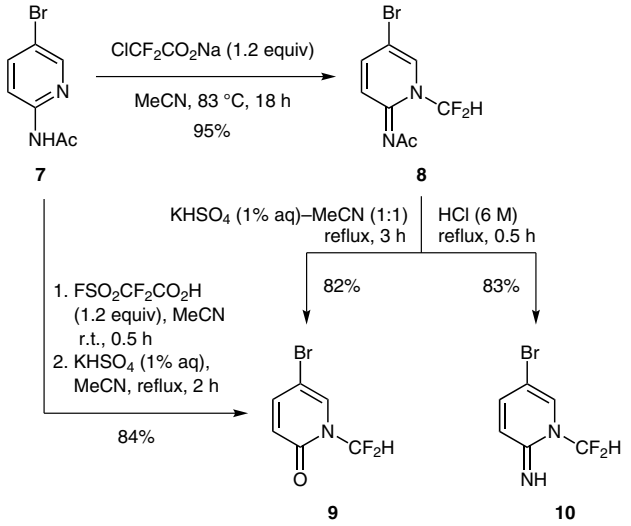
3.3 N-Difluoromethylation

Acyclic *N*-(difluoromethyl)amines readily undergo hydrolysis, so that they are rarely obtained by direct difluoromethylation.[10b] However, when the nitrogen atom of an amine is endocyclic or connected with a strong electron-withdrawing group, the N–CF_2H moiety is stabilized, and thus, can be synthesized by direct difluoromethylation of the nitrogen atom.[45,46] Yagupol'skii et al. reported that reactions of secondary sulfonamides with chlorodifluoromethane and solid potassium hydroxide give the corresponding *N*-difluoromethyl compounds in moderate to good yields [Scheme 22 (1)].[45] Jończyk and co-workers prepared *N*-(difluoromethyl)indole by direct reaction of indole with chlorodifluoromethane in a moderate yield under phase-transfer-catalyzed basic conditions [Scheme 22 (2)].[46]



Scheme 22 Difluoromethylation of sulfonamides and indoles with chlorodifluoromethane[45,46]

In 2006, Ando et al. reported that the reaction of 2-(acetylamino)pyridine **7** with $ClCF_2CO_2Na$ or difluoro(fluorosulfonyl)acetic acid gives acetyl-protected *N*-(difluoromethyl)pyridin-2-imine **8** in high yield (Scheme 23).[47] Acidic hydrolysis of **8** affords *N*-(difluoromethyl)pyridin-2(1*H*)-one **9** and *N*-(difluoromethyl)pyridin-2-imine **10**, respectively. The method is also suitable for other 2-(acetylamino)pyridines, however, the reaction is sensitive to the position of the substituent on the pyridine ring.[47] The 4- and 5-substituted substrates are more reactive than 3-substituted substrates, and the 6-substituted substrates can not participate in the reaction with the exception of the benzo-fused substrate 2-(acetylamino)quinoline.

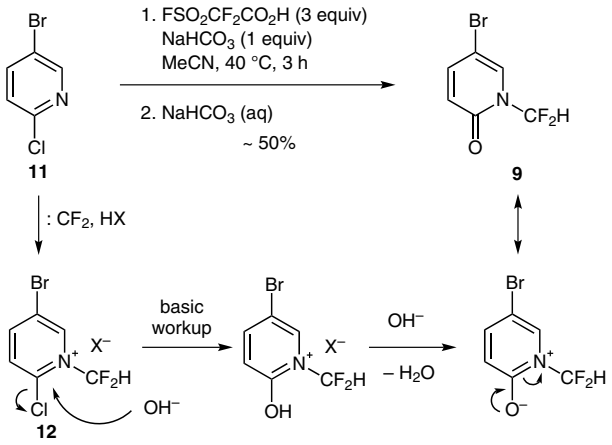


Scheme 23 Difluoromethylation of *N*-(5-bromopyridin-2-yl)acetamide under nonbasic conditions[47]

Ando et al. also reported that the reaction of *ortho*-halogenated pyridine **11** with difluorocarbene generated from difluoro(fluorosulfonyl)acetic acid affords *N*-(difluoromethyl)pyridin-2(1*H*)-one **9** in moderate yield (Scheme 24).[47,48] The pyridine product is probably produced through the hydrolysis of an *N*-(difluoromethyl)halopyridinium intermediate **12**.

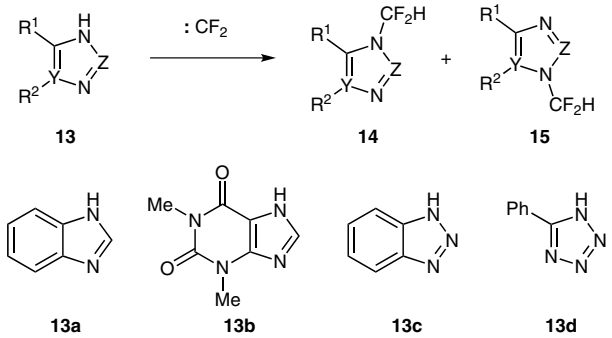
Many difluorocarbene sources have been successfully used for the N-difluoromethylation of five-membered N-heterocycles such as imidazoles, triazoles, and tetrazoles. The N-difluoromethylation can be conducted either under basic conditions or neutral conditions depending on the difluorocarbene source employed.

Under basic conditions, chlorodifluoromethyl phenyl sulfone, tributyl(difluoromethyl)ammonium chloride (**1**), and $ClCF_2CO_2Na$ react with imidazoles and benzimidazoles in good yields (Table 1, entries 1–3).[21,24,44] Although $TMSCF_2Br$ reacts with these substrates in low yields (entry 4), it is an efficient reagent for the transformation of benzotriazole and substituted tetrazoles (entries 5 and 6).[34] *S*-(Difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine can also be applied to the difluoromethylation of imidazoles, triazoles, tetrazoles, and their derivatives, although it gives only moderate yields (entry 7).[23]



Scheme 24 Difluoromethylation of *ortho*-halogenated pyridine[47]

It is noteworthy that $TMSCF_3$, which is incompatible with aqueous basic conditions commonly used for the difluoromethylation of heteroatoms,[34] can react with some N-heterocycles under neutral conditions.[49] Very recently, Prakash et al. demonstrated the selective N-difluoromethylation of imidazoles and their derivatives using lithium iodide as the initiator (entries 8–10).[49] However, such a neutral reaction has to be conducted at high temperatures ranging from 140 °C to 170 °C.



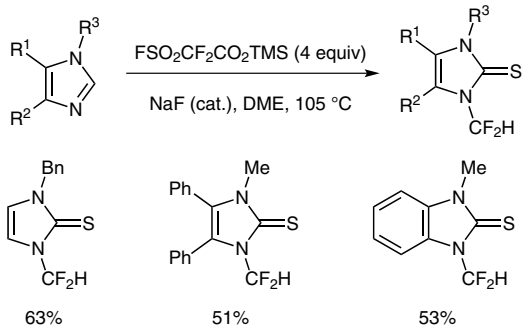
Scheme 25 Difluoromethylation of N-heterocycles

A mechanistically interesting and synthetically useful reaction is the difluoromethylation of N-alkylated imidazoles with TFDA reported by Dolbier, Wnuk, and coworkers in 2006 (Scheme 26).[50] They found that TFDA serves not only as the source of difluorocarbene, but also as the sulfuration reagent. Since SO_2 was the only sulfur-containing byproduct during the releases of difluorocarbene from TFDA, a possible mechanism involving the reaction between the nucleophilic NHC intermediate **16** and SO_2 and subsequent reduction of the sulfinate **17** with difluorocarbene was suggested by the authors (Scheme 27).[50]

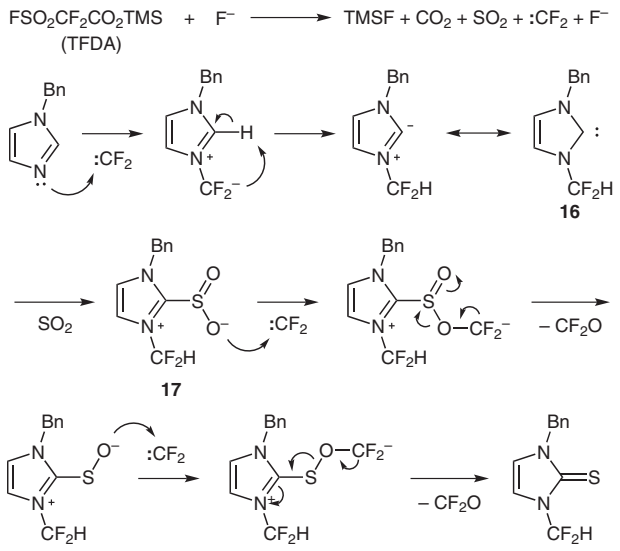
Table 1 Difluoromethylation of N-Heterocycles with Various Difluorocarbene Sources (Scheme 25)

Entry	Substrate	Reagent (equiv)	Conditions	Ratio **14**/**15**	Yield (%)	Ref.
1	**13a**	$PhSO_2CF_2Cl$ (2.3)	KOH (11 equiv), H_2O–MeCN, 50 °C, 5 h	–	86	21
2	**13a**	$[Bu_3N(CF_2H)]^+Cl^-$ **1** (1.2)	NaH (1.3 equiv), MeCN, 5 °C to r.t., 1.5 h	–	83	24
3	**13b**	$ClCF_2CO_2Na$ (2.0)	K_2CO_3 (1.5 equiv), DMF, 95 °C, 8 h	1:2	85	44
4	**13a**	$TMSCF_2Br$ (2.0)	KOH (6.0 equiv), H_2O–CH_2Cl_2, 0 °C, 0.5 h	–	38	34
5	**13c**	$TMSCF_2Br$ (2.0)	KOH (6.0 equiv), H_2O–CH_2Cl_2, 0 °C, 0.5 h	–	81	34
6	**13d**	$TMSCF_2Br$ (2.0)	KOH (6.0 equiv), H_2O–CH_2Cl_2, 0 °C, 0.5 h	2.8:1	95	34
7	**13a**	$PhS(O)(NTs)CF_2H$ (1.2)	NaH (1.1 equiv), DMF, 60 °C, 14 h	–	53	23
8	**13a**	$TMSCF_3$ (2.35)	LiI (0.9 equiv), triglyme, microwave, 170 °C, 1.5 h	–	80 (90)[a]	49
9	**13b**	$TMSCF_3$ (2.35)	LiI (0.9 equiv), triglyme, 170 °C, 3 h	1.3:1	(86)[a]	49
10	**13c**	$TMSCF_3$ (2.35)	LiI (0.9 equiv), triglyme, 170 °C, 3 h	–	(46)[a]	49

[a] Yields in parentheses were determined by ^{19}F NMR spectroscopy.



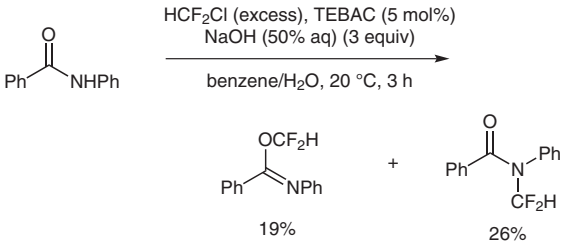
Scheme 26 Reactions of TFDA with imidazoles and benzimidazoles[50]



Scheme 27 Proposed mechanism for the formation of *N*-difluoromethylthioureas[50]

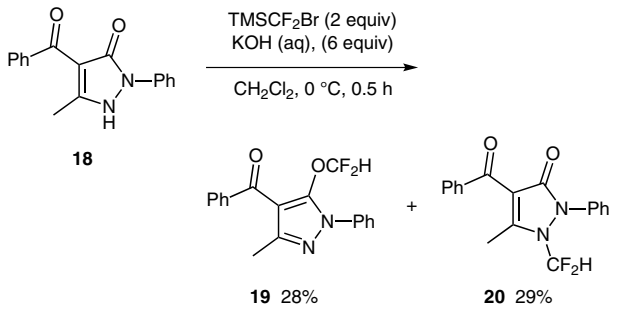
3.4 Difluoromethylation of Ambident N,O- and N,S-Nucleophiles

The difluoromethylation of acyclic secondary amides under basic conditions usually gives a mixture of O- and N-difluoromethyl products (Scheme 28).[51] Although both the N–CF_2H and O–CF_2H products are stable under neutral or basic conditions, hydrochloric acid can cause the decomposition of both isomers with the regeneration of the starting secondary amides; N–CF_2H products react at a much higher rate.[51]



Scheme 28 Difluoromethylation of acyclic secondary amides under basic conditions[51]

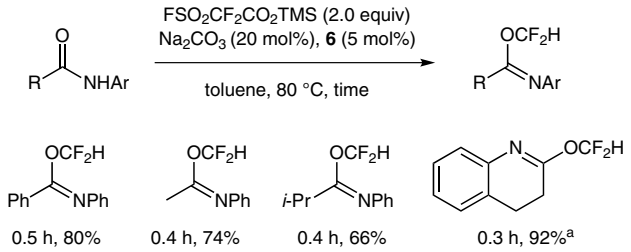
Poor chemoselectivity is also observed in the difluoromethylation of N-heterocyclic amides under basic conditions.[34,52] The reaction of pyrazolone **18** with $TMSCF_2Br$ at 0 °C gives both O- and N-difluoromethylation products **19** and **20**, respectively (Scheme 29).[34] On the other hand, the reaction of **18** with chlorodifluoromethyl phenyl sulfone at 50 °C only affords **19**,[21] probably due to the low thermal stability of the N–CF_2H compound at an elevated temperature.



Scheme 29 Difluoromethylation of N-heterocyclic amides under basic conditions[34]

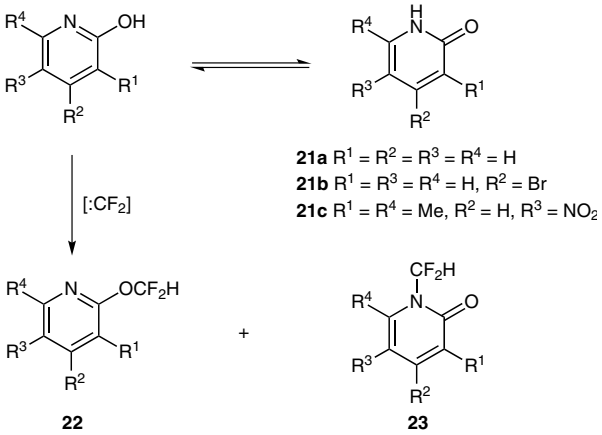
The poor N/O-selectivity can be ascribed to the formation of the ambident anion by deprotonation of the amide with a base.[39] Several reports have shown that difluoromethylation of amides under neutral (or weakly basic) conditions can afford the O–CF_2H products predominantly.[39,47,53]

The NHC-catalyzed generation of difluorocarbene from TFDA developed by Ichikawa et al. is also effective for the selective O-difluoromethylation of secondary *N*-arylamides (Scheme 30).[39] Both benzoic acid derived amides and aliphatic acid derived amides afford the corresponding imidates in high yields.



Scheme 30 Selective O-difluoromethylation of N-arylated amides with TFDA.[39] [a] Isolated as 2-(difluoromethoxy)quinoline after oxidative aromatization with DDQ.

However, when pyridin-2(1*H*)-one (**21a**) is subjected to the TFDA/NHC system, the desired 2-(difluoromethoxy)pyridine **22a** is obtained in 60% yield accompanied by a 9% yield of N-difluoromethylated product **23a** (Table 2, entry 1);[39] a similar result is obtained when $ClCF_2CO_2Na$ is used (entry 2).[47] In the case of pyridinones containing a strong electron-withdrawing group such as **21c**, their tautomerization to 2-hydroxypyridines is preferred and the nucleophilicity of the nitrogen is decreased; therefore, their reaction gives solely the O-difluoromethylated product **22c** (entries 3 and 4).[53]



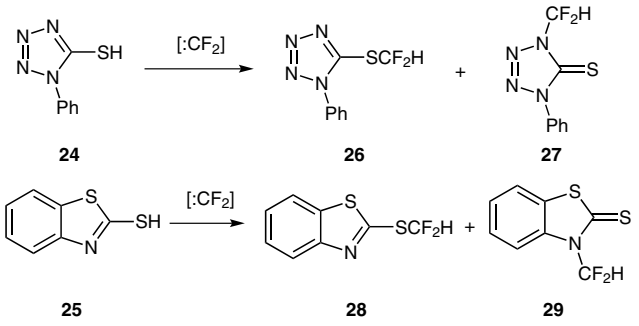
Scheme 31 Tautomerization of pyridin-2(1*H*)-ones and their difluoromethylation

Similarly, there is also N/S-selectivity in the difluoromethylation of N-heteroaromatic thiols. Tetrazole-5-thiol (**24**) and benzothiazole-2-thiol (**25**) are two commonly used substrates to test the reactivity of a difluorocarbene source (Scheme 32 and Table 3).[23,34,44,54–56] It is interesting that the chemoselectivity for the difluoromethylation of **24** is switchable, either the S–CF_2H product **26** or the N–CF_2H product **27** can be obtained depending on the reaction conditions used.[23,34,44] However, in the case of **25**, it is difficult to gain high N-selectivity.[23,44,56] From the product distribution of these reactions, it is clear that both the reaction temperature and the solvent can influence the chemoselectivity, though the reason for such selectivity is still unknown.

Table 2 O- and N-Difluoromethylation of Pyridin-2(1*H*)-ones (Scheme 31, Figure 3)

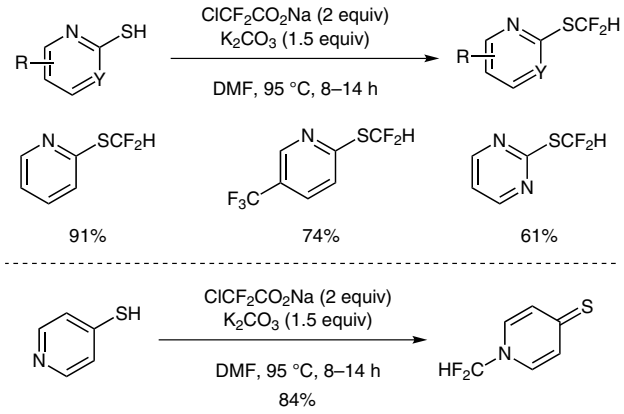
Entry	Substrate	Reagent (equiv)	Conditions	Yield (%)		Ref.
				22	**23**	
1	**21a**	TFDA (2.0)	Na_2CO_3 (20 mol%), **6** (5 mol%), toluene, 80 °C, 0.3 h	60[a]	9[a]	39
2	**21b**	$ClCF_2CO_2Na$ (2.0)	MeCN, 83 °C, 20 h	72	8	47
3	**21c**	TFDA (1.3)	NaH (1.0 equiv), CsF (0.1 equiv), MeCN, r.t., ~1 h	92	0	53
4	**21c**	$FSO_2CF_2CO_2H$ (1.7)	NaH (2.7 equiv), MeCN, r.t., 15 min	96	0	53

[a] Yields were determined by ^{19}F NMR spectroscopy.



Scheme 32 Difluoromethylation of tetrazole-5-thiol (**24**) and benzothiazole-2-thiol (**25**)

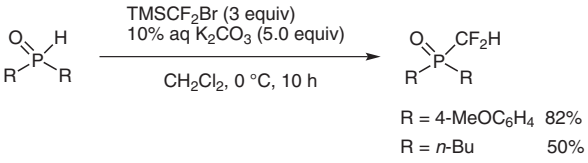
The recent report by Greaney and Mehta on the difluoromethylation of S-, N-, and Se-nucleophiles with $ClCF_2CO_2Na$[44] also indicates that the position of the thiol substituent on the heterocycle can affect the selectivity. Reactions of pyridine-2-thiols and pyrimidine-2-thiols only generate the S–CF_2H products, while the reaction of pyridine-4-thiol gives the N–CF_2H product (Scheme 33).[44]



Scheme 33 Difluoromethylation of pyridinethiols and pyrimidinethiols[44]

3.5 Se- and P-Difluoromethylation

Compared with O-, S-, and N-difluoromethylation, less attention has been paid to Se- and P-difluoromethylation.[10b,29] Very recently, Greaney and Mehta demonstrated that $ClCF_2CO_2Na$ can be used for the synthesis of difluoromethyl phenyl selanide from phenylselenol in 65% yield under similar conditions to those used for the difluoromethylation of S- and N-nucleophiles with $ClCF_2CO_2Na$.[44] In the Wittig olefination of carbonyls with $FSO_2CF_2CO_2Me$, (difluoromethyl)triphenylphosphonium iodide arising from the protonation of (difluoromethylene)triphenylphosphonium ylide was detected as the side product in substantial yields.[57] Hu and co-workers reported that $TMSCF_2Br$ can be used for the transformation of hydrophosphine oxides into (difluoromethyl)phosphine oxides (Scheme 34).[34] However, due to the lower reactivity of phosphinite anions than O-, S-, and N-nucleophiles, the use of a weak base to minimize the hydrolysis of difluorocarbene is necessary.



Scheme 34 Difluoromethylation of the hydrophosphine oxides using $TMSCF_2Br$[34]

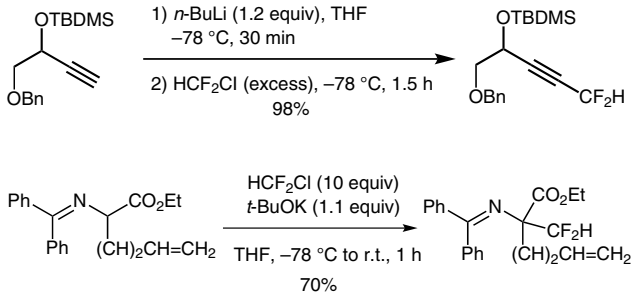
3.6 C-Difluoromethylation

Difluoromethylation of carbon nucleophiles with difluorocarbene is generally more difficult than the difluoromethylation of heteroatom nucleophiles, and the C–H acidity of the carbon nucleophile plays an important role.[2b,10c] Among various difluorocarbene sources, chlorodifluoromethane is the most frequently used reagent for the incorporation of a difluoromethyl group into various nucleophiles (Scheme 35).[2b,10c,58,59]

Table 3 S- and N-Selectivity in Difluoromethylation of Heteroaromatic Thiols under Different Conditions (Scheme 32)

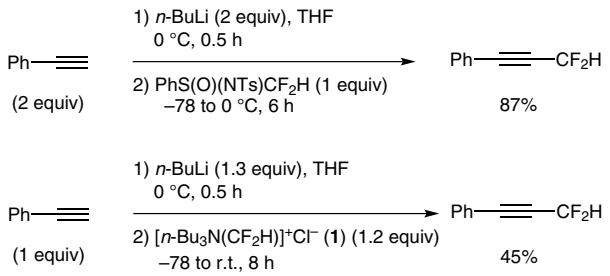
Entry	Reagent	Base	Solvent	T (°C)	Tetrazolethiol **24**		Benzothiazolethiol **25**		Ref.
					26/**27**	Total yield (%)	**28**/**29**	Total yield (%)	
1	$TMSCF_2Br$	KOH	H_2O–CH_2Cl_2	0	100:0	99	100:0	96	34
2	HCF_2Cl	KOH	H_2O	r.t.	100:0	81	100:0[a]	68[a]	54,55
3	HCF_2Cl	KOH	DMF	100–120	~10:90	~90	75:25	66	54,56
4	$ClCF_2CO_2Na$	K_2CO_3	DMF	95	0:100	84	67:33	91	44
5	$ClCF_2CO_2Na$	K_2CO_3	DMF	120	–[b]	–[b]	50:50	–[b]	44
6	$PhS(O)(NTs)CF_2H$	NaH	DMF	60	0:100	57	62:38	71	23

[a] H_2O–DME was used as the solvent.
[b] Not reported.



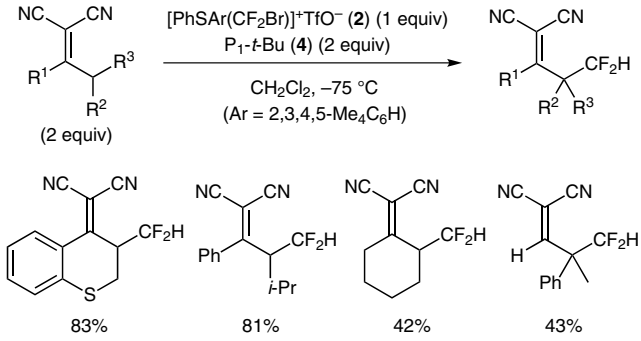
Scheme 35 Difluoromethylation of carbon nucleophiles using chlorodifluoromethane[58,59]

The newly developed *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine and tributyl(difluoromethyl)ammonium chloride (**1**), as alternatives to chlorodifluoromethane, can react with terminal alkynes giving difluoromethylated alkynes in moderate yields (Scheme 36).[23,24]

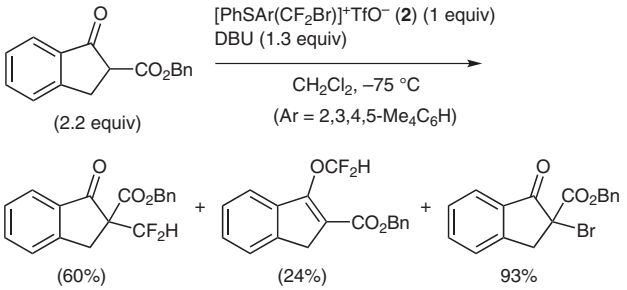


Scheme 36 Difluoromethylation of terminal alkynes using *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine and ammonium salt **1**;[23,24] yields were determined by ^{19}F NMR spectroscopy

In 2012, the Shibata group disclosed that (bromodifluoromethyl)sulfonium salt **2** can be used as difluorocarbene reagent for the direct difluoromethylation of sp^3-carbon acids.[27] The reaction between dicyanoalkylidenes and **2** gives allylic difluoromethyl compounds in good yields without the detection of any C–H bromination product (Scheme 37);[27] while the reaction of β-keto esters gives a mixture of C- and O-difluoromethylation products with the formation of α-bromo-β-keto esters as the major by-products (Scheme 38).[27]



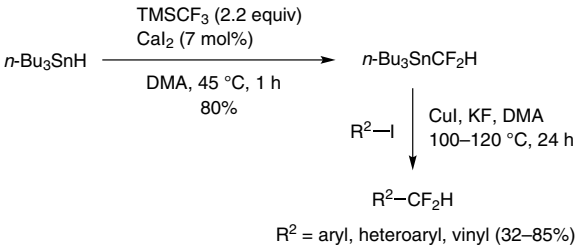
Scheme 37 Difluoromethylation of dicyanoalkylidenes using (bromodifluoromethyl)sulfonium salt **2** (for the structure of **4** see Figure 2)[27]



Scheme 38 Difluoromethylation of β-keto esters using (bromodifluoromethyl)sulfonium salt **2**;[27] the yields in parentheses were determined by ^{19}F NMR

3.7 Sn-Difluoromethylation

The singlet difluorocarbene can insert into a metal–hydrogen bond. The Prakash group found that calcium iodide is an ideal initiator for the reaction between $TMSCF_3$ and compounds of type R_3SnH for the preparation of R_3SnCF_2H.[60] For example, the insertion of difluorocarbene generated from $TMSCF_3$ into the Sn–H bond of Bu_3SnH at 45 °C gives Bu_3SnCF_2H as the major product in 80% yield (Scheme 39). Tributyl(difluoromethyl)stannane has been used as an efficient difluoromethylation reagent in the copper-mediated transformations of iodide compounds.[60]



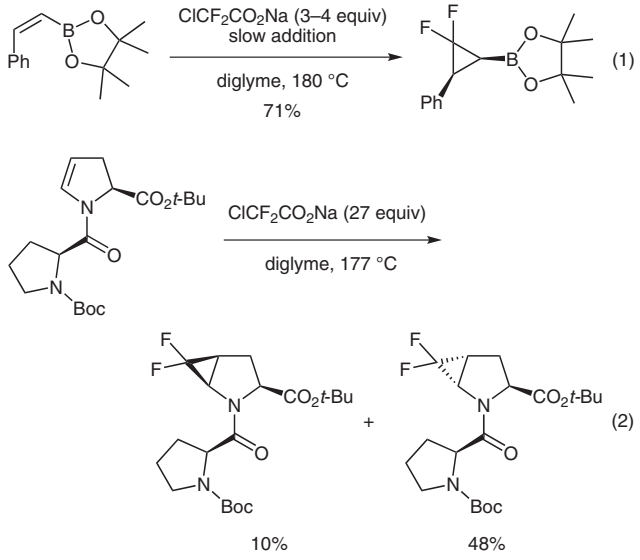
Scheme 39 Preparation and synthetic application of tributyl(difluoromethyl)stannane[60]

4 *gem*-Difluorocyclization

In Dolbier's review[9a] on fluorinated cyclopropanes and cyclopropenes and Fedoryński's review[9b] on *gem*-dihalocyclopropanes, many methods, including the difluoromethylenation of alkenes and alkynes using various difluorocarbene sources, are summarized. Among the difluorocarbene sources that are covered in these two reviews, $ClCF_2CO_2Na$[12] and TFDA[16] are two of the most promising reagents and their use has been extended to a broader substrate scope. In addition, alternative difluorocarbene sources $FSO_2CF_2CO_2Me$,[15] $TMSCF_2X$ (X = F, Cl, Br),[18,19] and $BrCF_2CO_2Na$[17] for [2 + 1] cycloaddition have been developed in recent years. In this section, we consider the reaction of the aforementioned difluorocarbene sources with alkenes and alkynes.

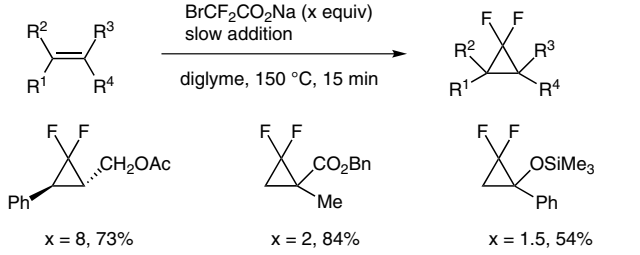
4.1 *gem*-Difluorocyclopropanation

Sodium chlorodifluoroacetate ($ClCF_2CO_2Na$) was first used for the difluoromethylenation of alkenes in 1960.[12] Usually, the reaction with $ClCF_2CO_2Na$ is conducted at a very high temperature (~180 °C) and a large excess of reagent is consumed. Nevertheless, this method remains one of the most favored and reliable ways for the *gem*-difluorocyclopropanation of various alkenes including [60]- and [70]fullerenes[61] owing to the easy availability of $ClCF_2CO_2Na$ and the good functional group tolerance of this reaction (Scheme 40).[62,63]



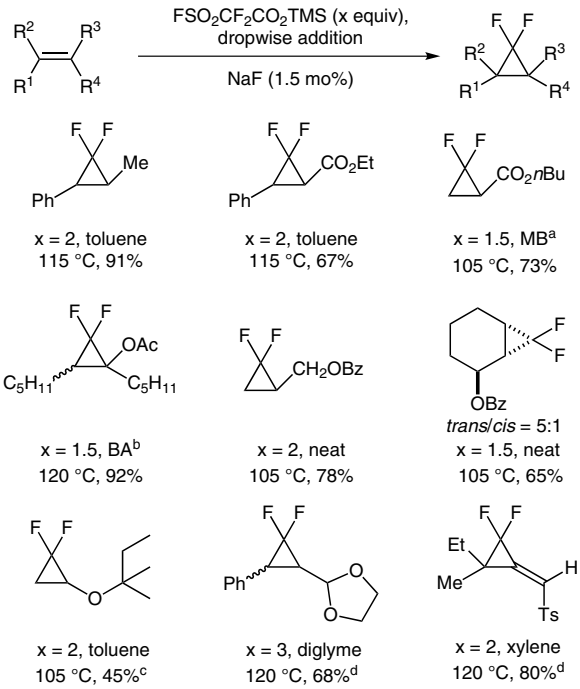
Scheme 40 Typical application of $ClCF_2CO_2Na$ in the synthesis of *gem*-difluorocyclopropanes[62]

In 2010, Amii and co-workers reported the use of sodium bromodifluoroacetate ($BrCF_2CO_2Na$) as a new difluorocarbene source for the effective synthesis of *gem*-difluorocyclopropanes (Scheme 41) and *gem*-difluorocyclopropenes.[17] Because a C–Br bond is weaker than a C–Cl bond, reactions with $BrCF_2CO_2Na$ can be performed with a smaller amount of reagent at a lower temperature than reactions with $ClCF_2CO_2Na$. This method has been used for the synthesis of thermally unstable 1,1-difluoro-2-siloxycyclopropanes that readily undergo further transformations when using $ClCF_2CO_2Na$.[17]



Scheme 41 Synthesis of *gem*-difluorocyclopropanes using $BrCF_2CO_2Na$[17]

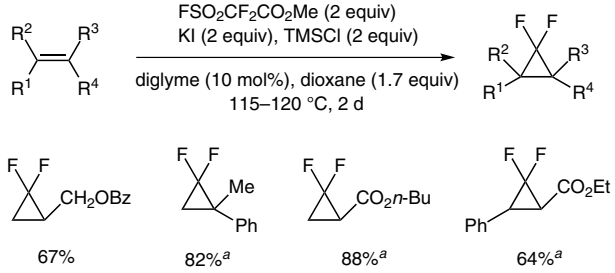
TFDA, as a derivative of difluoro(fluorosulfonyl)acetic acid, is a more convenient and efficient difluorocarbene reagent than the latter.[64] TFDA releases difluorocarbene in a fluoride-catalyzed chain process in which both CO_2 and SO_2 are also generated. The use of TFDA for the synthesis of *gem*-difluorocyclopropanes was developed by the Dolbier and Chen groups in 2000.[16] Since then, many investigations have been performed to extend its synthetic applications.[64–66] The advantages for difluoromethylenation with TFDA include the use of near neutral reaction conditions, relatively low temperatures, broad substrate scope, and high efficiency (Scheme 42).[64,65] However, in cases of acid-sensitive substrates such as enol ethers,[64] the purification of the reagent to remove residual difluoro(fluorosulfonyl)acetic acid is key for the success and reproducibility of the reaction. For example, the reaction of TFDA (containing less than 3% acid) under the usual conditions with the very acid sensitive *tert*-pentyl vinyl ether led to no observable difluorocyclopropane product, but using purified TFDA the reaction with *tert*-pentyl vinyl ether afforded the desired product in moderate yield.[64]



Scheme 42 Difluorocyclopropanation with TFDA.[16,64,65] [a] MB = methyl benzoate. [b] BA = butyl acetate. [c] TFDA was used after removing residual acid with Et_3N. [d] NaF (10 mol%) was used.

Chen and co-workers first reported $FSO_2CF_2CO_2Me$ in 1986 as a difluorocarbene reagent for copper-mediated trifluoromethylation.[15] In 2013, the Dolbier group extended the application of $FSO_2CF_2CO_2Me$ to the synthesis of *gem*-difluorocyclopropanes (Scheme 43).[67] They found that under specific high concentration, high temperature conditions, $FSO_2CF_2CO_2Me$ exhibits carbene reactivity characteristics comparable to those exhibited by TFDA. Although the time required for the difluorocarbene reactions of $FSO_2CF_2CO_2Me$ (2–3 d) is considerably longer

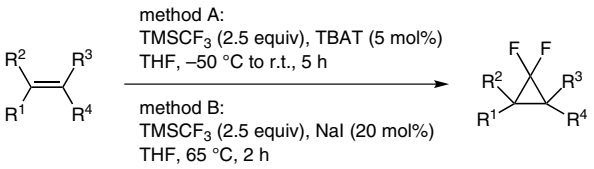
than the five hours generally required for the analogous difluorocarbene reactions of TFDA; it is believed that the overall advantages of the $FSO_2CF_2CO_2Me$ reaction in terms of cost, safety, and ease of reaction should in most cases outweigh the time factor advantage of TFDA.[67]



Scheme 43 Synthesis of *gem*-difluorocyclopropanes using $FSO_2CF_2CO_2Me$.[67] [a] The yield was determined by ^{19}F NMR.

In early 2011, the Hu group reported that tetramethylammonium chloride can be used to catalyze the generation of difluorocarbene from $TMSCF_2Cl$, which is arguably the first report on the use of a halide ion other than F^- to activate the C–Si bond of fluoroalkylated silanes.[18]

Subsequently, the Hu and Prakash groups disclosed that the commonly used nucleophilic trifluoromethylation reagent $TMSCF_3$ (also known as the Ruppert–Prakash reagent) can be used for *gem*-difluorocyclization.[19] Depending on the initiators used, difluorocarbene can be generated from $TMSCF_3$ either at a low temperature or a high temperature (Scheme 44 and Table 4). Like other low temperature methods,[11] the reaction with $TMSCF_3$ initiated by tetrabutylammonium difluorotriphenylsilicate (TBAT) at –50 °C to room temperature only works for electron-rich alkenes. When sodium iodide is used as the initiator, difluorocarbene is generated at high temperatures ranging from 65 °C to 110 °C, and it is reactive towards both electron-rich and relatively electron-poor alkenes.



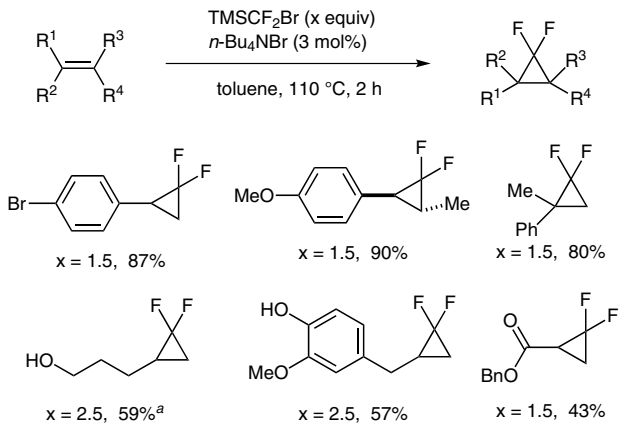
Scheme 44 Synthesis of *gem*-difluorocyclopropanes using $TMSCF_3$[19]

$TMSCF_2Br$, which is more accessible than $TMSCF_2Cl$, was recently developed as a replacement of the latter by the Hu group (Scheme 7).[18,34] Complementary to *gem*-difluorocyclization with $TMSCF_3$, the reaction with $TMSCF_2Br$ requires a low catalyst loading of tetrabutylammonium bromide and produces TMSBr, which has a higher boiling point than TMSF, as the byproduct (Scheme 45); both are beneficial for the practical application of this method. Moreover, $TMSCF_2Br$ can also react with highly electron-deficient alkenes such as benzyl acrylate.[34] In the cases of alkenes bearing a hydroxy group, the hydroxy group is inert towards difluorocarbene and only difluorocyclopropanation occurs.[34]

Table 4 Synthesis of *gem*-Difluorocyclopropanes Using $TMSCF_3$ (Scheme 44)[19]

Entry	R^1	R^2	R^3	R^4	Yield (%) Method A	Method B
1	4-$MeOC_6H_4$	H	H	H	80	82
2	4-FC_6H_4	Me	H	H	82	85
3	(*E*)-CH_2=CHPh	Me	H	H	–[a]	90[b]
4	Me	Me	Me	Me	80	82
5	Ph	$(CH_2)_4$		H	83	82
6	Ph	Br	H	H	0	79
7	Ph	H	H	H	20	81
8	4-FC_6H_4	H	H	H	23	78
9	4-BrC_6H_4	H	H	H	26[c]	83[c]
10	H	$(CH_2)_4$		H	10[c]	83

[a] Not reported.
[b] Reaction was carried out in MeCN at 110 °C for 2 h.
[c] The yield was determined by ^{19}F NMR spectroscopy.

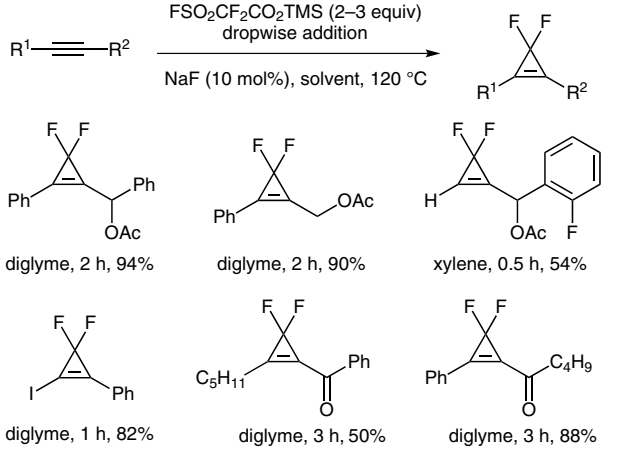


Scheme 45 Synthesis of *gem*-difluorocyclopropanes using $TMSCF_2Br$.[34] [a] The yield was determined by ^{19}F NMR spectroscopy.

4.2 *gem*-Difluorocyclopropenation

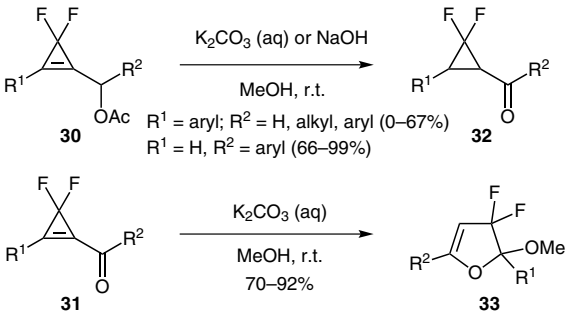
Most of difluorocarbene sources used for *gem*-difluorocyclopropanation are also applicable for the synthesis of *gem*-difluorocyclopropenes. Although *gem*-difluorocyclopropenes readily undergo defluorination[66b] or ring-opening reactions,[66c] they are stable under non-nucleophilic conditions.[68]

Since the development of TFDA as a difluorocarbene reagent, the Chen and Xiao groups have prepared a series of *gem*-difluorocyclopropenes (Scheme 46).[66] They have also studied their further transformations. For examples, difluorocyclopropenylated esters **30** and difluorocyclopropenylated ketones **31** can be converted into difluorocyclopropylated ketones **32** and difluorinated dihydrofurans **33**, respectively, under alkaline conditions (Scheme 47).[66b–d]

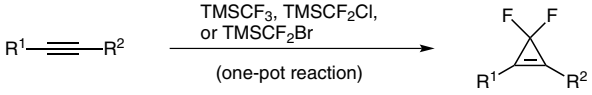


Scheme 46 Synthesis of *gem*-difluorocyclopropenes using TFDA[66]

A comparison of difluorocyclopropenation with three fluoroalkylated silanes ($TMSCF_2X$, X = F, Cl, Br) is illustrated in Scheme 48 and Table 5.[18,19,34] It seems that these three reagents exhibit similar reactivity towards both terminal and disubstituted alkynes. Among the three methods, the difluorocyclopropenation with $TMSCF_2Br$ has been examined using both electron-rich and electron-deficient alkynes.[34]

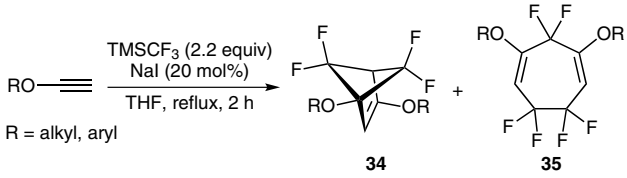


Scheme 47 Transformation of difluorocyclopropenylated esters **30** and difluorocyclopropenylated ketones **31**[66b–d]



Scheme 48 *gem*-Difluorocyclopropenation of alkynes using $TMSCF_2X$ (X = F, Cl, Br)[18,19,34]

However, when alkoxy-substituted alkynes are subject to the difluorocarbene reaction, the difluorocyclopropenation product can undergo further reaction with the difluorocarbene. Very recently, the O'Hagan group reported that reaction of acetylene ethers with difluorocarbene generated from $TMSCF_3$ unexpectedly gives rise to a mixture of fluorinated bicyclo[2.1.1]hex-2-enes **34** and cyclohepta-1,4-diene ring products **35** (Scheme 49).[68]



Scheme 49 Reaction of acetylene ethers with difluorocarbene generated from $TMSCF_3$[68]

5 *gem*-Difluoroolefination and Related Reactions

The Wittig-type deoxygenative olefination of carbonyl compounds is an important method for the synthesis of *gem*-difluoroolefins.[69–71] In the reaction, the undetected difluoromethylenephosphonium ylide ($R_3P{=}CF_2$) is believed to be the key intermediate, which is generated in situ either by the transformation of a difluorinated phosphonium salt such as bromodifluoromethylphosphonium bromide or by the reaction of difluorocarbene with R_3P.[35,71] Calculations have shown that the barrier for the dissociation of the ylide to its carbene and phosphine components is quite low;[57,72] therefore, difluorinated

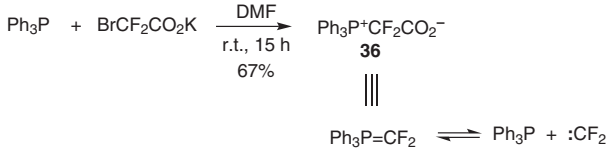
Table 5 *gem*-Difluorocyclopropenation of Alkynes Using Fluoromethylated Silanes (Scheme 48)[18,19,34]

Entry	R^1	R^2	Yields (%)		
			$TMSCF_3$[a]	$TMSCF_2Cl$[b]	$TMSCF_2Br$[c]
1	4-MeC_6H_4	H	95	92	90
2	$(CH_2)_7Me$	H	96[d]	84[d]	89[d]
3	$(CH_2)_7Me$	Bu	99[e]	99[e]	–[f]
4	Ph	Ph	80	93	–[f]
5	Ph	CH_2OAc	88	89	98
6	Ph	CH(Ph)OAc	68	91	98
7	Ph	SPh	–[f]	–[f]	83[e]
8	Ph	CO_2Me	–[f]	–[f]	67 (87)[d]

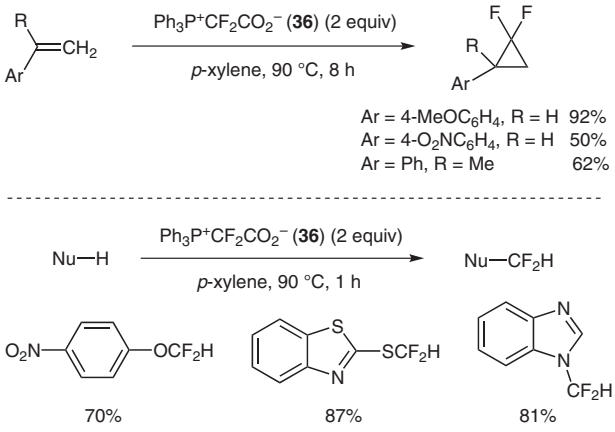
[a] Conditions: $TMSCF_3$ (2 equiv), NaI (2.2 equiv), THF, 110 °C, 2 h.
[b] Conditions: $TMSCF_2Cl$ (2 equiv), 2 mol% Bu_4NCl, toluene, 110 °C, 4 h.
[c] Conditions: $TMSCF_2Br$ (1.5 equiv), 3 mol% Bu_4NBr, toluene, 110 °C, 2 h.
[d] The yield in parentheses was determined by ^{19}F NMR spectroscopy.
[e] Reaction temperature was 80 °C.
[f] Not reported.

phosphonium salts can be used as difluorocarbene sources via the decomposition of the intermediate $R_3P{=}CF_2$.[28,72a]

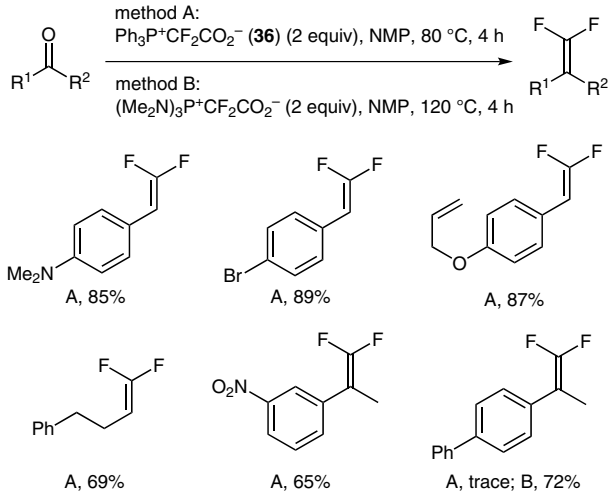
Very recently, the Xiao group reported an interesting reactivity switch of difluoromethylenephosphobetaine **36**[73] (Scheme 50) between difluorocarbene and the difluoromethylene ylide by changing the polarity of the solvent.[28,73] The reaction with alkenes and heteroatom nucleophiles conducted in a nonpolar solvent affords *gem*-difluorocyclopropanes and difluoromethylated compounds, respectively, in good yields (Scheme 51).[28] As an additive-free and neutral difluorocarbene source, difluoromethylenephosphobetaine **36** is expected to find application in the difluoromethylation of heteroatoms. In contrast, when the reaction between **36** and carbonyl compounds is carried out in a polar solvent, the Wittig difluoroolefination readily takes place with good functional group tolerance,[73] which is an improvement on the previously known olefination process with $ClCF_2CO_2Na$ and a phosphine.[69] Moreover, nonactivated ketones can also be *gem*-difluoroolefinated by changing Ph_3P to $(Me_2N)_3P$ (Scheme 52).[73]



Scheme 50 Preparation of phosphobetaine **36**[73]

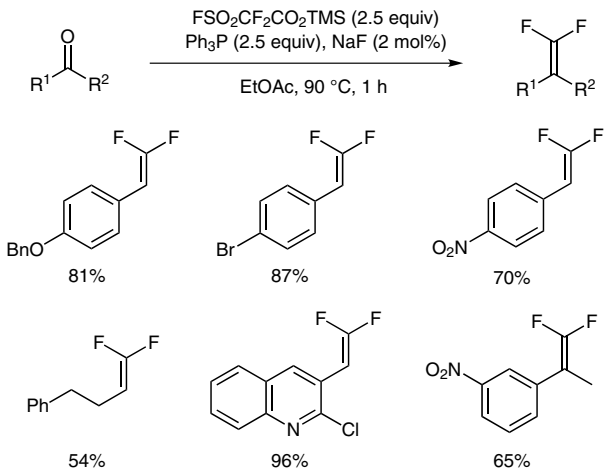


Scheme 51 Difluorocarbene reactivity of phosphobetaine **36**[28]

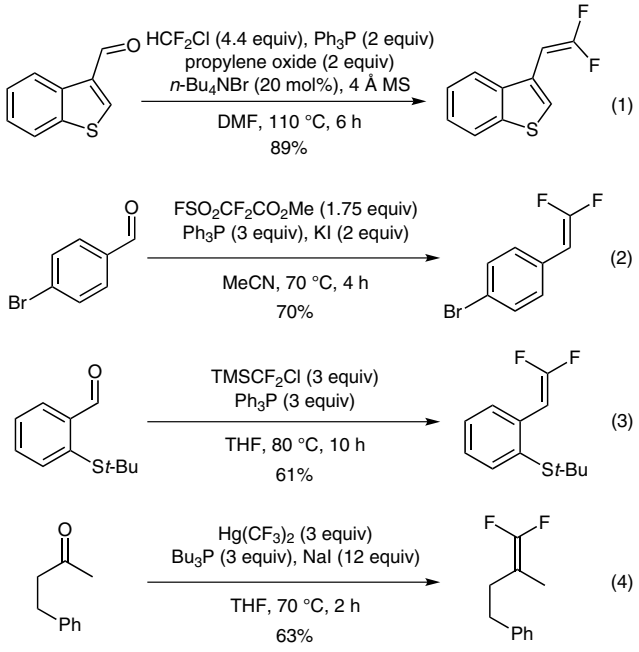


Scheme 52 Difluoromethylene ylide reactivity of phosphobetaine **36**[73]

Xiao and co-workers also disclosed that the classical difluorocarbene reagents TFDA and chlorodifluoromethane can be used to generate a highly reactive difluoromethylene ylide for Wittig *gem*-difluoroolefination.[28] The reaction using TFDA is applicable to aromatic, heteroaromatic, and aliphatic aldehydes and activated ketones (Scheme 53).[28] It is worthy of note that the difluoromethylene ylide obtained in such a way works very well with electron-deficient aldehydes such as 4-nitrobenzaldehyde, which is reported to give a low yield of difluoroolefination product using other methods. Except in the case of electron-deficient aldehydes, the reaction using chlorodifluoromethane in the presence of a base generated in situ from propylene oxide and a catalytic amount of chloride salt gives similar results [Scheme 54 (1)].[28]



Scheme 53 *gem*-Difluoroolefination with TFDA[28]



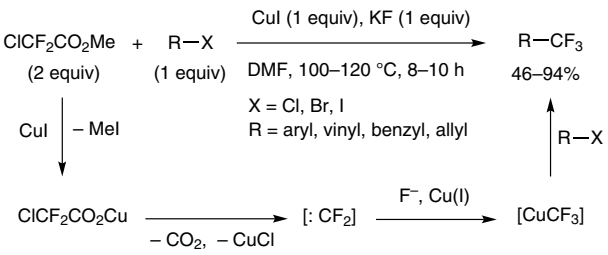
Scheme 54 *gem*-Difluoroolefination with various difluorocarbene sources[28,35,57,74]

Other reported *gem*-difluoroolefinations involving a difluorocarbene intermediate includes reactions with $FSO_2CF_2CO_2Me$,[57] $TMSCF_2Cl$,[35] and $Hg(CF_3)_2$.[74] Triphenylphosphine-promoted reactions with $FSO_2CF_2CO_2Me$ and $TMSCF_2Cl$ have a similar substrate scope to that with chlorodifluoromethane [Scheme 54 (2) and (3)],[35,57] while the reaction with $Hg(CF_3)_2$ in the presence of tributylphosphine works well with nonactivated ketones [Scheme 54 (4)].[74]

6 Trifluoromethylation

Since the first characterization of $CuCF_3$ by Burton and co-workers,[75] numerous methods have been developed for the generation of (trifluoromethyl)copper species,[76] among which, the combination of difluorocarbene and a fluoride constitutes one of the most practical methods. Several reviews on trifluoromethylation have covered this topic.[76–78] In this section, only some new, recent applications of this protocol are considered.

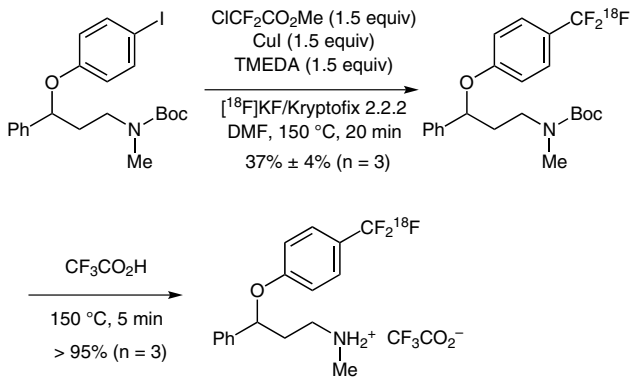
In 1991, the Chen and Burton groups independently disclosed that the combination of a previously known difluorocarbene source $ClCF_2CO_2Me$ together with CuI, and KF serves as a convenient trifluoromethylation reagent.[79] In Chen's work, not only aryl halides, but also benzyl and allyl halides were transformed into the trifluoromethylated compounds in high yields (Scheme 55).[79a]



Scheme 55 Copper-mediated trifluoromethylation with $ClCF_2CO_2Me$[79a]

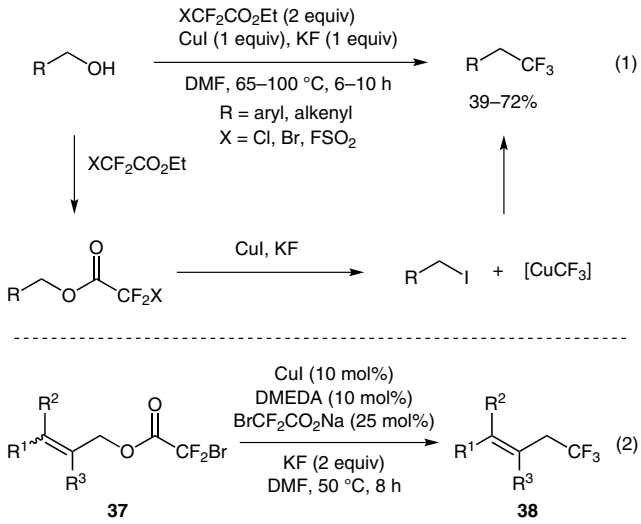
Taking advantage of the reactivity of $ClCF_2CO_2Me$ in the presence of fluoride, Gouverneur, Passchier, and coworkers recently developed a copper-mediated process for the late-stage [^{18}F]trifluoromethylation of (hetero)aryl iodides (Scheme 56).[80] This [^{18}F]$CuCF_3$-based reaction furnishes the [^{18}F]trifluoromethylated compound in acceptable radiochemical yield in 20 minutes. This protocol is expected to find application in positron emission tomography (PET) imaging for clinical diagnosis.

Inspired by Chen's early research on CuI-mediated decarboxylative trifluoromethylation of allylic and benzylic alcohols with a series of difluorinated acetates [Scheme 57 (1)],[81] recently, a copper-catalyzed decarboxylative trifluoromethylation of allylic bromodifluoroacetates has been developed by the Altman group [Scheme 57 (2)].[82] Allyl acetates containing various functional groups undergo the catalytic reaction to afford α-substituted trifluoro-



Scheme 56 Copper-mediated trifluoromethylation for the synthesis of [^{18}F]-labeled Fluoxetine;[80] radiochemical yields based on three experiments

methylated products in moderate to good yield with *E* stereoselectivity (Table 6). Based on the fact that the catalytic reaction proceeds smoothly in the absence of iodide ion, a mechanism different from Chen's was proposed, in which $CuCF_3$ probably reacts directly with the allyl acetates via a π-allylcopper intermediate to afford the trifluoromethylated products.[82]

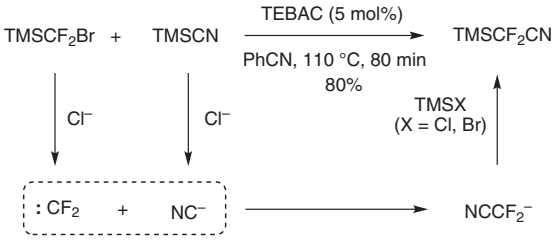


Scheme 57 Copper-mediated and -catalyzed trifluoromethylation of alcohols[81,82]

7 Miscellaneous

The reaction between a nucleophile (Nu^-) and difluorocarbene is usually accomplished by protonation of the $NuCF_2^-$ species to give difluoromethyl compounds. For some nucleophiles, the capture of the $NuCF_2^-$ intermediate by an electrophile other than a proton is possible.[83,84]

In 2012, the Dilman group showed that heating of $TMSCF_2Br$ with trimethylsilyl cyanide catalyzed by chloride ion leads to a clean reaction affording $TMSCF_2CN$ in 80% yield (Scheme 58).[83] The formal insertion of difluorocarbene into the C–Si bond of trimethylsilyl cyanide is likely to proceed through the reaction between difluorocarbene and the cyanide ion, which is formed by the metathesis reaction between a halide ion and trimethylsilyl cyanide, and the subsequent silylation of $NCCF_2^-$ by halotrimethylsilane.



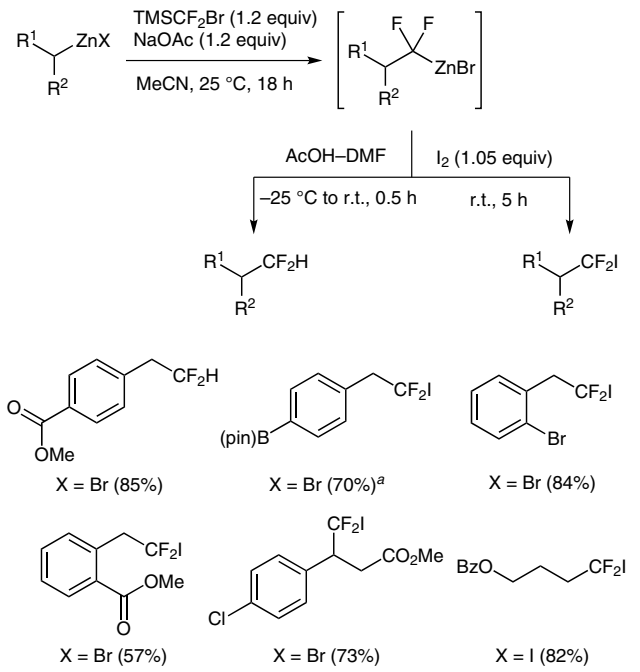
Scheme 58 Synthesis of difluoro(trimethylsilyl)acetonitrile using $TMSCF_2Br$[83]

In early 2013, the Dilman group reported that the reaction between $TMSCF_2Br$/NaOAc and benzyl or alkylzinc halides can afford α-difluorinated organozinc species RCF_2ZnX.[84] The so-obtained fluorinated organozinc reagents are reasonably stable in solution and can be quenched with electrophiles such as proton, iodine, and bromine, affording difluoromethylated and difluorohalomethylated compounds in moderate to excellent yields (Scheme 59).[84] Very recently, a coupling reaction of RCF_2ZnX and allyl halides under CuI catalysis has been developed.[85] As for the possible mechanism for RCF_2ZnX formation, the authors proposed an insertion reaction of difluorocarbene into a C–Zn bond (Scheme 60, path a);[84] however, another pathway involving the migration of R

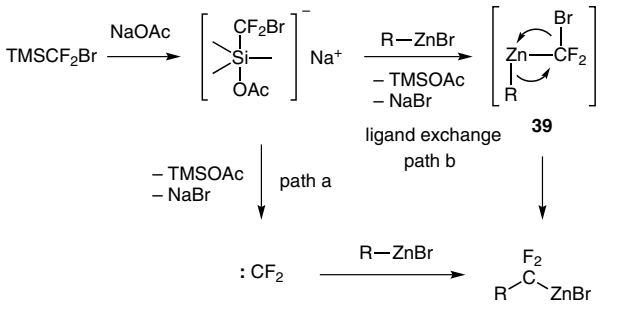
Table 6 Copper-Catalyzed Trifluoromethylation of Alcohols [Scheme 57 (2)][82]

Entry	Ratio *E*/*Z* of **37**	R^1	R^2	R^3	Ratio *E*/*Z* of **38**	Yield (%)
1	*E* only	3-BrC_6H_4	H	H	*E* only	81
2	*E* only	4-$O_2NC_6H_4$	H	H	*E* only	83
3	*E* only	2-$TfOC_6H_4$	H	H	*E* only	75
4	>98:2	Ph	Me	H	>98:2	55
5	>98:2	Ph	H	Me	>98:2	74
6	<2:98	CH_2OBn	H	H	98:2	81

from zinc to the difluorinated carbon via a difluorocarbenoid intermediate **39** could not be ruled out (Scheme 60, path b).[86]

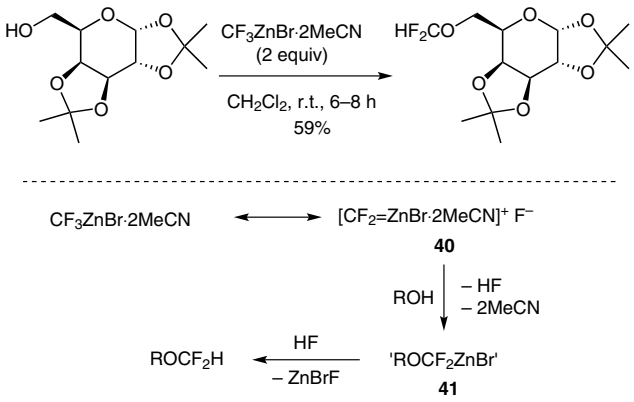


Scheme 59 Difluoromethylation and difluoroiodomethylation of organozinc reagents using $TMSCF_2Br$.[84] [a] pin = $OCMe_2CMe_2O$.



Scheme 60 Proposed mechanism for the formation of difluorinated organozinc reagents

Sometimes, a metal–difluorocarbene rather than a free difluorocarbene intermediate has been proposed in transformations involving zinc or a transition metal, such as difluoromethylation with CF_3ZnBr,[87] the homologation of perfluorinated copper reagents with $CuCF_3$,[88] and the nickel-catalyzed preparation of CF_2I_2 from hexafluoropropylene oxide.[89] Furthermore, the difluoromethylation of alcohols with CF_3ZnBr represents one of the very few methods for direct O-difluoromethylation of alcohols.[34,43,90] (Trifluoromethyl)zinc bromide, prepared by the reaction between bromotrifluoromethane and zinc in acetonitrile, can react with primary (Scheme 61), secondary, and tertiary alcohols.[90] The mechanism was suggested to be a substitution of one fluorine for the alkoxy group via a zinc–difluorocarbene intermediate **40** followed by the protonation of the alkoxydifluoromethylzinc species **41**.



Scheme 61 Difluromethylation of alcohols with CF_3ZnBr[90]

8 Conclusions

In the past decade, many difluorocarbene reagents have been developed and employed for the synthesis of a series of fluorinated compounds, however, most of the reactions with these reagents are based on the classical reactivity of difluorocarbene such as difluoromethylation of nucleophiles, and [2+1] cyclopropanation and cyclopropenation. The metal–difluorocarbene species is expected to have more potential for the further advance of difluorocarbene chemistry. Although several transition-metal–difluorocarbene complexes have been prepared and characterized, their synthetic application is still underdeveloped.[91] In the future, metal-mediated or -catalyzed synthesis involving difluorocarbene should be developed. On the other hand, the number of reported reactions with newly developed difluorocarbene reagents is still relatively small. Further research should aim at the expansion of the substrate scope and the synthesis of more complex molecules using these newly developed difluorocarbene reagents. Meanwhile, the evaluation of the practicality of these new protocols in large-scale applications is also necessary.

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