Selective difluoromethylation and monofluoromethylation reactions

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The selective introduction of fluorine atom(s) and fluorinated moieties into organic molecules has become an important and fast-growing research field, since fluorine atoms play crucial roles in life science and materials science-related applications. Similar to the trifluoromethyl group, both difluoromethyl and monofluoromethyl groups can often bring about many beneficial effects to the target molecules, and a variety of CF_2H- and CH_2F-containing pharmaceuticals and agrochemicals have been developed. Among the synthetic methods for CF_2H- and CH_2F-containing compounds, selective di- and monofluoromethylation (*i.e.*, introduction of CF_2H and CH_2F groups into organic molecules) represent one of the most straightforward synthetic methods and thus can be conveniently used in the synthetic design. This feature article summarizes the presently known selective difluoromethylation and monofluoromethylation methods, including nucleophilic, electrophilic, and free radical di- and monofluoromethylation reagents and reactions.

1. Introduction

Although fluorine is the most abundant halogen element and ranks number 13 among all the elements in the earth's crust, the naturally occurring organofluorine compounds (compounds containing one or more C–F bonds) are rare. Among nearly 3200 known naturally occurring organohalogen compounds, only very few (around 13) belong to organofluorine compounds (all of them are monofluorinated).[1–3] However, despite their rarity in nature, many man-made organofluorine compounds exhibit unique physical, chemical and biological properties in life science- and materials science-related applications. In general, perfluorinated and highly fluorinated compounds (or materials) are widely used in materials science, whereas the selectively fluorinated (from a single F to a C_2F_5 group, sometimes also called "lightly fluorinated") compounds find more applications in pharmaceutical and agrochemical products and in medicinal research.[4] Currently, the efficient and selective incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules to modulate their biological properties has become a routine and powerful strategy in drug design. Many studies showed that the fluorine atom(s) and fluoroalkyl group(s) can often bring about many beneficial effects in a biologically active molecule, such as the enhancement of metabolic stability, bioavailability, lipophilicity and membrane permeability, as well as an increase of binding affinity.[2,5,6] Nowadays, around

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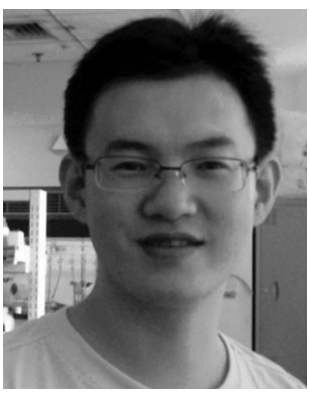

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20% of all pharmaceuticals and 30–40% of all agrochemicals on the market contain fluorine.[7]

Fluorination and fluoroalkylation are the two major synthetic methods to prepare selectively fluorinated organic compounds.[8–11] In the field of fluoroalkylation chemistry, selective trifluoromethylation (selective introduction of a CF_3 group into organic molecules) has been extensively studied over the past 40 years, including nucleophilic, electrophilic, and free radical trifluoromethylations.[12–17] The trifluoromethylation reagents include Me_3SiCF_3 (Ruppert-Prakash reagent),[13a–d] $FSO_2CF_2COOCH_3$ (Chen's reagent),[16] trifluoromethane,[13e] trifluoromethylchalcogen salts (such as Umemoto's reagent),[14] hypervalent iodine(III)–CF_3 reagent (Togni's reagent),[17] CF_3-Johnson reagent,[18] and trifluoromethyl iodide (CF_3I),[13h,15] among others.[12] It should be noted that there are still many challenges and issues to be solved in the enantioselective trifluoromethylations, and further efforts in catalyst and reagent development is currently in progress.[12e,15a,19]

Compared to trifluoromethylation chemistry, the analogous difluoromethylation and monofluoromethylation (selective introduction of a CF_2H or CH_2F group into organic molecules) are less studied. The systematic exploration of di- and monofluoromethylation has just emerged more recently.[20,21] It has been realized that a difluoromethyl group (CF_2H) can act as a more lipophilic hydrogen bond donor (than typical donors such as OH and NH), which makes it an interesting group with respect to the design of bioactive molecules.[22] Compounds with a monofluoromethyl group (CH_2F) are of great importance with regard to isostere-based drug design.[23–25] As a result, a variety of structurally diverse CF_2H- or CH_2F-containing drugs have been developed.[4] For instance, Eflornithine (or called DFMO) is a rationally designed ornithine decarboxylase inhibitor, which can cure sleeping sickness (trypanosomiasis) caused by the *Trypanosoma brucei gambiense* parasite (Fig. 1).[26] Pantoprazole is a proton pump inhibitor drug used for short-term treatment of erosion and ulceration of the esophagus caused by gastroesophageal reflux disease.[4] Afloqualone (with a CH_2F group) is a nicotinic antagonist marketed as a myorelaxant.[4] Fluticasone propionate is widely used against a broad spectrum of inflammatory diseases and to alleviate pains associated with certain cancers (Fig. 1).[27]

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Fei Wang was born in Zhejiang, China (1983). After he obtained his BS degree from the Ocean University of China in 2006, he entered the Shanghai Institute of Organic Chemistry (SIOC), CAS as a graduate student. Currently, he is studying for his PhD degree under the guidance of Professor J. Hu. His thesis work focuses on the synthesis of organofluorine compounds with fluorinated carbenes.

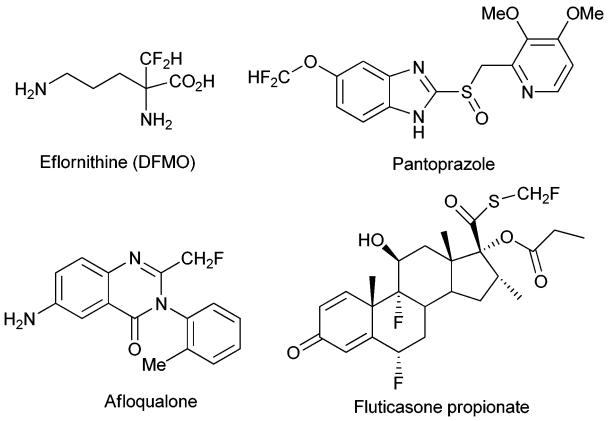


Fig. 1 Representative CF_2H- and CH_2F-containing drugs.

Although the synthesis of difluoromethyl- and monofluoromethyl-containing compounds can be achieved by several methods such as the fluorination of carbonyl compounds or alcohols with SF_4, Et_2NSF_3 (DAST), or other related reagents,[8–11] selective di- and monofluoromethylation (*i.e.*, introduction of CF_2H and CH_2F moities into organic molecules) represent two of the most straightforward synthetic methods and thus can be conveniently used in the synthetic design. Selective di- and monofluoromethylation are generally accomplished by two strategies—one is the direct transfer of a "CF_2H" or "CH_2F" moiety into organic molecules; the other is the transfer of a functionalized moiety (such as "CF_2R" or "CFR_2"), followed by removal of the functional or auxiliary group(s) to give a CF_2H or CH_2F group. In this feature article, we focus on the discussion of the current status of selective difluoromethylations and monofluoromethylations, including the different strategies based on nucleophilic, electrophilic, as well as free radical reactions. In the last part of this article, we discuss the current challenges of this field and suggest future directions.

2. Selective difluoromethylation

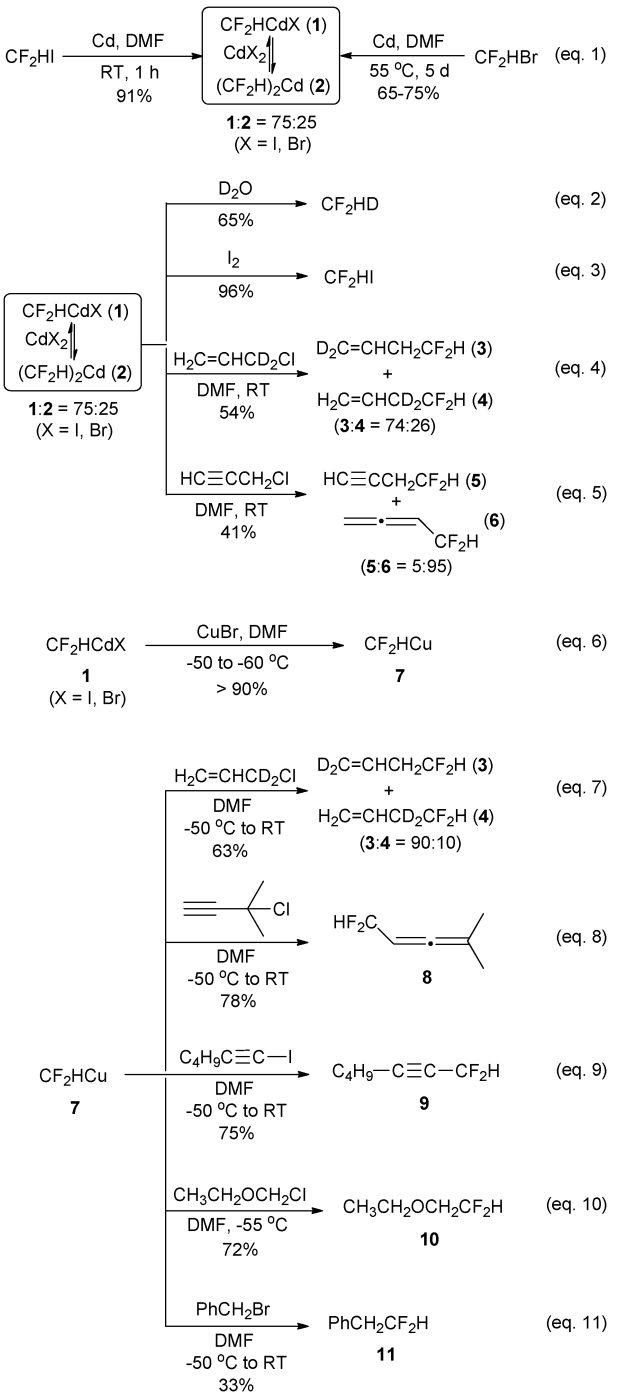
2.1 Nucleophilic difluoromethylation

2.1.1 Using difluoromethyl cadmium, zinc and copper reagents. Nucleophilic difluoromethylation involves the transfer of a difluoromethyl anion ("CF_2H^-") equivalent to an electrophile. Since difluoromethyllithium (CF_2HLi) and difluoromethyl Grignard reagent (CF_2HMgX) are highly unstable due to the α-elimination of a fluoride ion, these fluorinated organometallic species can not be applied as efficient nucleophilic difluoromethylation reagents. However, difluoromethylcadmium, difluoromethylzinc, and difluoromethylcopper reagents have been successfully prepared by Burton *et al.*[28] Difluoromethylcadmium can be prepared in high yield from iododifluoromethane or bromodifluoromethane and acid-washed cadmium metal in DMF, and the mono- and bis(difluoromethyl)cadmium species **1** and **2** are generally formed with a ratio 75 : 25 (Scheme 1, eqn (1)). Upon the addition of CdX_2 salt (X = I, Br), the mono/bis ratio was shifted in favor of the the mono(difluoromethyl)cadmium reagent (**1**).[28c] The difluoromethylcadmium reagent mixture

(**1** and **2**) exhibits good stability at room temperature, with a loss of only 31% activity of the original reagent after 2 months. Even on heating (in DMF), little decomposition of the difluoromethylcadmium species occurs until 65–75 °C.[28c] The mono(difluoromethyl)cadmium **1** (the bis reagent **2** can convert to **1**) can be protonated by water and iodinated by elemental iodine (eqn (2) and (3)). Reagent **1** can also react with deuterated allyl chloride at room temperature in around 4 h to give both γ-substituted product **3** and α-substituted product **4**, with a ratio 74 : 26 (eqn (4)).[28c] Furthermore, the difluoromethylcadmium reagent **1** was found to be able to difluoromethylate the propargyl chloride (3 days at room temperature), giving a mixture of 4,4-difluoro-1-butyne **5** and 4,4-difluoro-1,2-butadiene **6** (with a ratio 5 : 95) (eqn (5)). It should be mentioned that difluoromethylzinc reagent (CF_2HZnBr) can also be prepared in a similar way. However, although this organozinc reagent is thermally stable and is able to react with allylic halides, its reactivity is significantly lower than the corresponding cadmium reagent.[28c]

Difluoromethylcopper reagent (CF_2HCu, **7**) was also successfully prepared in high yield (>90%) from a metathesis reaction between cadmium reagent **1** and CuBr in DMF at −50 to −60 °C (eqn (6)).[28b,c] Unlike perfluoroalkylcopper reagents (R_FCu), the difluoromethylcopper reagent **7** was found to be relatively unstable. At temeperatures above −30 °C, reagent **7** began to decompose rapidly to give HCF_2CF_2H and *cis*-CFH=CFH.[28c] It is particularly interesting that, although the difluoromethylcopper reagent **7** is thermally less stable than cadmium reagent **1**, reagent **7** is more nucleophilic than **1**. The difluoromethylcopper reagent **7** readily reacts with allylic halides at −50 °C, and the regiospecificity of reagent **7** is superior to **1** (eqn (7) and (8)). When reagent **7** reacts with a propargylic halide, the predominant product is the corresponding allene (eqn (8)). Reagent **7** also readily couples with 1-iodoalkynes to give good yields of the corresponding difluoromethylalkynes (eqn (9)). Furthermore, it has been realized that reagent **7** undergoes alkylation only with reactive alkylating agents such as chloromethyl ethyl ether and benzyl bromide (eqn (10) and (11)).[28c]

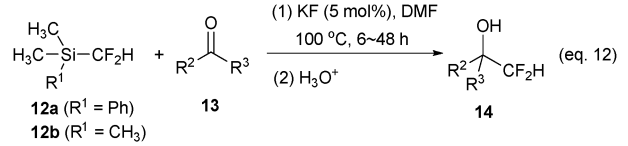
It should be pointed out that, owing to the less free ionic character of the carbon–metal bonds in difluoromethylated cadmium, zinc and copper reagents, these organometallic difluoromethylation reagents are not applicable to many other substrates such as aldehydes, ketones and imines. Furthermore, difluoromethylated silver(I) and silver(III) compounds have also been prepared and characterized, but their use in organic synthesis has not been well explored.[29]



Scheme 1 Preparation and synthetic applications of difluoromethylcadmium (**1**) and copper (**7**) reagents.

2.1.2 Using difluoromethyl- and trifluoromethylsilane reagents. In 1995, Fuchikami *et al*. reported a fluoride-initiated nucleophilic difluoromethylation of aldehydes and ketones with (difluoromethyl)dimethylphenylsilane (**12a**) and (difluoromethyl)-trimethylsilane (**12b**) (Scheme 2).[30] Although the chemistry appeared to be similar to the previously known trifluoromethylation with Me_3SiCF_3 reagent,[31] some drawbacks of this method were found.[30] First of all, reagent **12a** (or **12b**) was found to be inert under the same reaction conditions (at room temperature) as reported for trifluoromethylation, and the elevated temperature (100 °C) was necessary to facilitate the reaction. Secondly, the method is only efficient with non-enolizable adehydes; the product yields are generally low for ketones and enolizable aldehydes (Scheme 2).[30]

The Me_3SiCF_3 reagent was also used to introduce a CF_2H group into substrates. In 1994, Portella *et al*. reported that a fluoride-initiated reaction between an acyl silane **15** and Me_3SiCF_3 reagent provided 2,2-difluoroenol silyl ether **16** in 75% yield (Scheme 3, eqn (13)).[32] The reaction involves a domino sequence: nucleophilic trifluoromethylation–Brook rearrangement–fluoride elimination. Compound **16** can be



For reactions with **12a**:

R^2 = Ph, R^3 = H (**14a**), *Yield* = 82%;

R^2 = *n*-hexyl, R^3 = H (**14b**), *Yield* = 56%;

R^2 = cyclohexyl, R^3 = H (**14c**), *Yield* = 43%;

R^2 = Et, R^3 = Et (**14d**), *Yield* = 25%;

R^2 = Ph, R^3 = CH_3 (**14e**), *Yield* = 20%;

R^2 = Ph, R^3 = CF_3 (**14f**), *Yield* = 35%.

For reactions with **12b**:

R^2 = Ph, R^3 = H (**14a**), *Yield* = 89%;

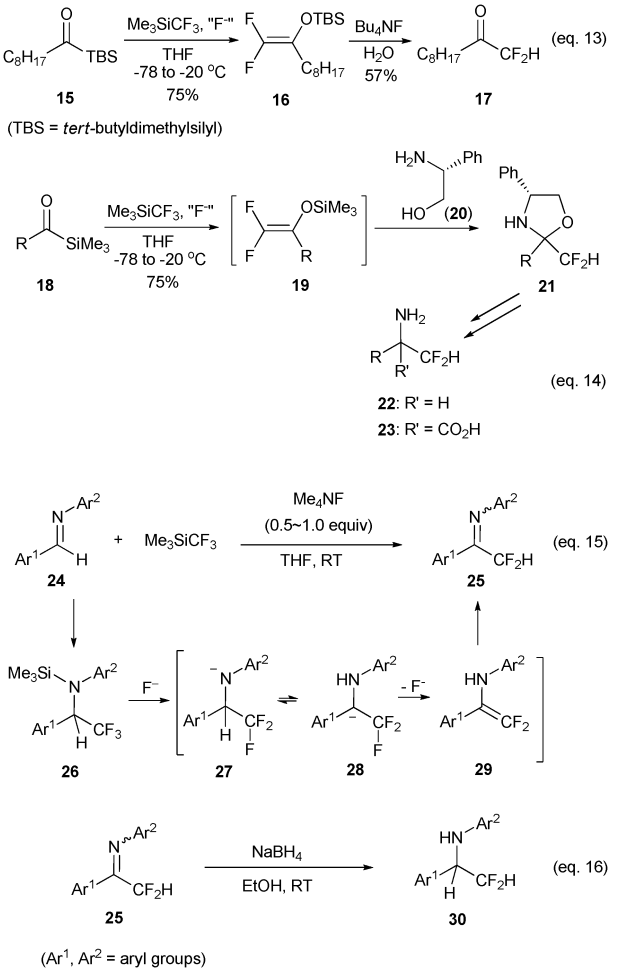
R^2 = Ph, R^3 = CH_3 (**14e**), *Yield* = 20%.

Scheme 2 Nucleophilic difluoromethylation of carbonyl compounds with difluoromethyl silanes **12a** and **12b**.

readily converted to difluoromethyl ketone **17** by a fluoride-mediated desilylative hydrolysis (eqn (13)).[32] The same group also found that the *in situ*-produced difluoroenol silyl ethers **19** could react as electrophiles with amines to give difluoromethyl amines, *via* the corresponding hemiaminal adduct (as evidenced by ^{19}F NMR studies).[33] This discovery was utilized by the authors in the reaction of **19** with (*R*)-phenylglycinol **20** to give 2-difluoromethyloxazolidines **21**. After separation of the diastereomers of **21**, a reduction with LAH and a Strecker-type synthesis gave enantiopure α-difluoromethyl amines **22** and α-difluoromethyl-α-amino acids **23**, respectively (eqn (14)).[33]

The Ruppert-Prakash reagent (Me_3SiCF_3) was also able to react with unactivated aldimines **24** in the presence of 0.5–1.0 equiv. of tetramethylammonium fluoride (TMAF) to give difluoromethyl ketimines **25** in moderate to good yields (eqn (15)).[34,35] The reaction mechanism was also studied, and the reaction was believed to proceed *via* 1,2-H shift from **27** to **28**, the subsequent β-elimination of a fluoride from **28**, and the 1,3-H shift from **29** to **25** (eqn (15)).[35] In some cases, difluoromethyl ketimines **25** were difficult to isolate, but they could undergo *in situ* reduction with $NaBH_4$ to give difluoromethyl amines **30** (eqn (16)).[34]

2.1.3 Using difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) and bromodifluoromethyl phenyl sulfone ($PhSO_2CF_2Br$). Difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) was first prepared by Hine and Porter in 1960,[36] but its use as a powerful nucleophilic difluoromethylation reagent was largely overlooked until recently.[20a,37] In 1989, Stahly reported the preparation of difluoromethylated alcohol **33** from an aldehyde **31** by using a two-step process: nucleophilic (phenylsulfonyl)-difluoromethylation with $PhSO_2CF_2H$, followed by reductive desulfonylation (eqn (17)).[38] However, Stahly's difluoromethylation procedure did not catch much attention in the following 14 years, mainly owing to the fact that this phase-transfer-catalysis method only works with non-enolizable aldehydes, and the Na/EtOH-mediated desulfonylation procedure gives a low yield of products.[39] In 2003, Prakash and co-workers reported that $PhSO_2CF_2H$ could be used as a nucleophilic difluoromethylation reagent in the presence of a reducing metal (such as magnesium). By using this protocol, chlorotrialkylsilanes **34** was successfully



Scheme 3 Synthesis of difluoromethylated compounds by using Me_3SiCF_3 reagent.

difluoromethylated to give difluoromethylsilanes **35** in practically useful yields (eqn (18)).[40] Thereafter, $PhSO_2CF_2H$ reagent was extensively used as a robust "CF_2H^-" synthetic equivalent using a two-step strategy—nucleophilic (phenylsulfonyl)-difluoromethylation and reductive desulfonylation.[37] This two-step nucleophilic difluoromethylation method has been efficiently applied in a wide range of substrates, such as primary alkyl halides,[41] aldehydes, ketones and esters,[42–45,103] imines,[46] cyclic sulfates and sulfamidates[21] (eqn (19)–(23)). The major advantages of using $PhSO_2CF_2H$ as a nucleophilic difluoromethylation reagent lie in three aspects: (a) $PhSO_2CF_2H$ can be conveniently prepared *via* several different methods;[36,47–49] (b) the $PhSO_2CF_2^-$ anion possesses enhanced thermal stability as well as good nucleophilicity towards many electrophiles;[20a,37] (c) the phenylsulfonyl group can be readily removed (commonly by reductive desulfonylation) after desired transformations.[20a,37] It is remarkable that the *in situ* generated $PhSO_2CF_2^-$ anion (from $PhSO_2CF_2H$ and a strong base) can efficiently react with enolizable carbonyl compounds and aza-enolizable imines to give corresponding products in high yields (eqn (20) and (21)).[42,46a] Highly diastereoselective difluoromethylation has also been achieved in the reaction of *N*-*tert*-butylsulfinyl imines with $PhSO_2CF_2H$, which enables a

facile entry into the biologically important chiral difluoromethyl amines.[46] We also attempted the chiral quaternary ammonium salt-catalyzed enantioselective nucleophilic difluoromethylation of aromatic aldehydes with $PhSO_2CF_2H$ reagent, but only moderate enantioselectivity was achieved (eqn (24)).[50]

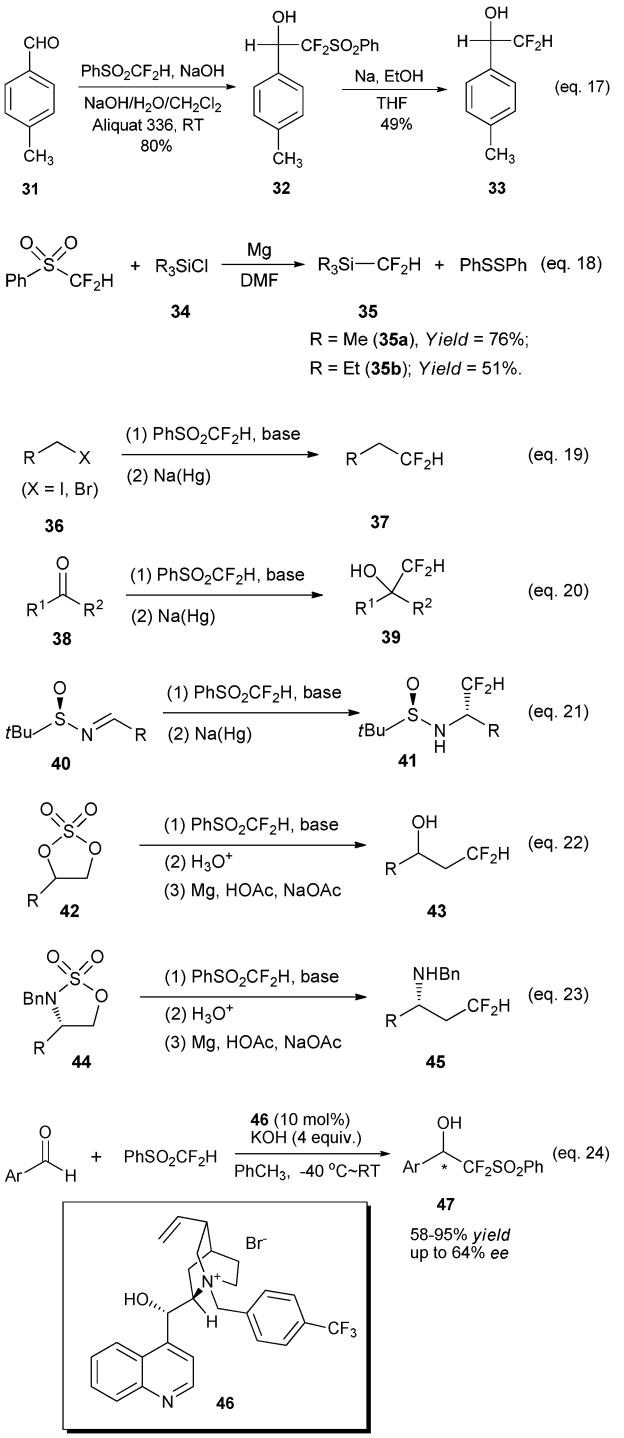
Under the promotion of tetrakis(dimethylamino)ethylene (TDAE), bromodifluoromethyl phenyl sulfone ($PhSO_2CF_2Br$) also acts as a nucleophilic difluoromethylation reagent (eqn (25)).[51] However, the difluoromethylation power of $PhSO_2CF_2Br$/TDAE reagent is relatively weaker than $PhSO_2CF_2H$/base reagent, as evidenced by the fact that the former reagent was unable to efficiently react with ketones.[51]

2.1.4 Using diethyl difluoromethylphosphonate. Similar to difluoromethyl phenyl sulfone ($PhSO_2CF_2H$), diethyl difluoromethylphosphonate [$HCF_2PO(OEt)_2$] is also a useful nucleophilic difluoromethylation reagent. In 1996, Piettre *et al.* reported a three-step synthesis of difluoromethyl ketones **50** from simple aldehydes, *via* (diethoxyphosphoryl)difluoromethylation–oxidation–dephosphonylation strategy (eqn (26)).[52] More recently, the nucleophilic difluoromethylation with $HCF_2PO(OEt)_2$ reagent was successfully extended to prepare difluoromethyl carbinols (eqn (27)).[53]

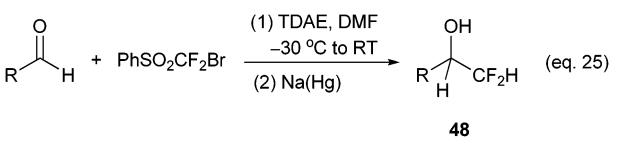
2.1.5 Using functionalized difluoromethylsilanes. Since difluoromethylsilanes (such as Me_3SiCF_2H) are not effective in difluoromethylation with ketones and enolizable aldehydes (see section 2.1.2), several functionalized difluoromethylsilanes have been developed to solve this problem.[20b] In 1997, Prakash *et al.* reported the nucleophilic difluoromethylation of aldehydes with bis(trimethyl)difluoromethane ($Me_3SiCF_2SiMe_3$, **51**).[54] Compared with Me_3SiCF_3, reagent **51** displays rather sluggish reactivity toward carbonyl compounds in THF, and the addition of polar solvents such as NMP and DME accelerates the reaction (Scheme 7). However, although reagent **51** can difluoromethylate aldehydes (both non-enolizable and enolizable) in the presence of a catalytic amount of TBAF (tetrabutylammonium fluoride), it can not effectively difluoromethylate most ketones.[54]

In 2005, [difluoro(phenylthio)methyl]trimethylsilane (Me_3SiCF_2SPh, **52**) was reported as an efficient difluoromethylation reagent (Scheme 8).[55] The advantages of using reagent **52** in nucleophilic difluoromethylation involve: (a) similar to Me_3SiCF_3, reagent **52** exhibits high reactivity at low temperature, and it is amenable to enolizable aldehydes and ketones; (b) the F_2C–SPh bond can be homolytically cleaved under free radical reaction conditions; (c) reagent **52** can be readily prepared from $PhSCF_2Br$, Mg and Me_3SiCl in DMF *via* a Barbier-coupling process.[40] Reagent **52** was successfully applied in the stereoselective synthesis of chiral α-difluoromethyl amine **56** (eqn (30)).[56] It has been used in the Lewis acid-catalyzed nucleophilic difluoromethylation of aldehydes.[59] Moreover, reagent **52** was applied in the difluoromethylation of other substrates such as disulfides,[55] esters,[55] imines,[56] primary alkyl halides,[57] α- and γ-ketoesters,[58] and cyclic imides,[60] among others.

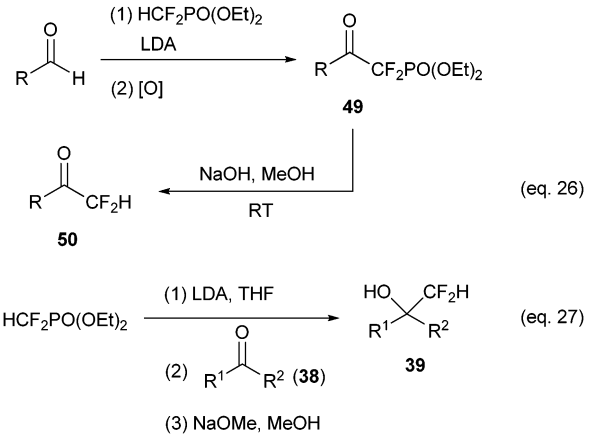
Inspired by excellent difluoromethylating power of $PhSO_2CF_2H$ reagent, we developed $PhSO_2CF_2SiMe_3$ (**57**) as an alternative nucleophilic difluoromethylation reagent Scheme 9).[61] The reactivity of **57** is similar to that of



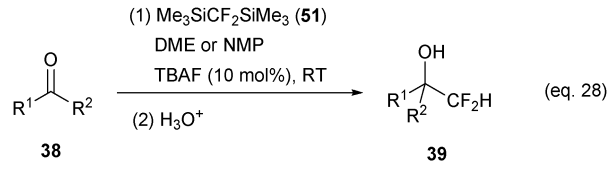
Scheme 4 Nucleophilic difluoromethylation with $PhSO_2CF_2H$ reagent.



Scheme 5 Nucleophilic difluoromethylation with $PhSO_2CF_2Br$ reagent.

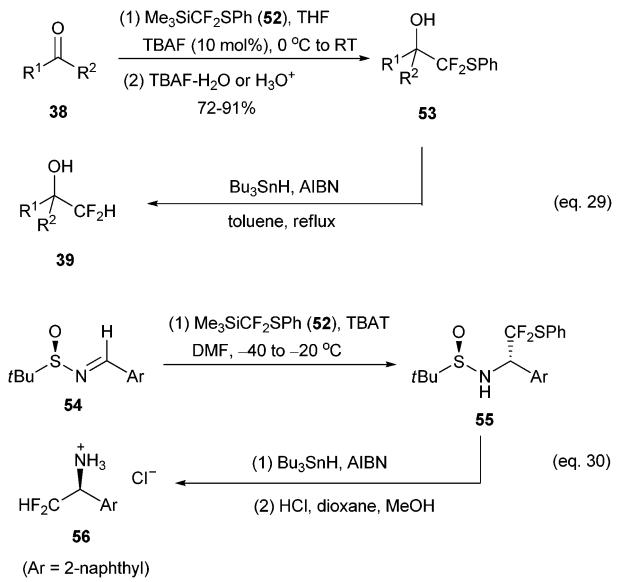


Scheme 6 Nucleophilic difluoromethylation with $HCF_2PO(OEt)_2$ reagent.



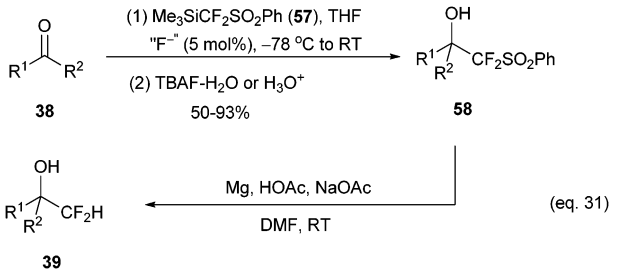
R^1	R^2	39 Yield (%)
Ph	H	75
$PhCH_2CH_2$	H	66
n-C_6H_{13}	H	55
Ph	Ph	40

Scheme 7 Nucleophilic difluoromethylation with $Me_3SiCF_2SiMe_3$ reagent.



Scheme 8 Nucleophilic difluoromethylation with Me_3SiCF_2SPh reagent.

$PhSO_2CF_2H$, except that reagent **57** reacts more effectively with base-sensitive substrates such as enolizable aldehydes.[44,61] It should be noted that the phenylsulfonyl group can be readily removed by using Mg–HOAc–NaOAc reagent, which is a good replacement of conventional Na(Hg) reagent (eqn (31)).[61]



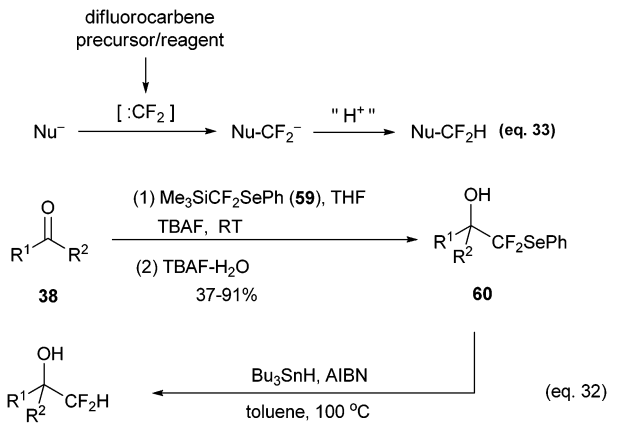
Scheme 9 Nucleophilic difluoromethylation with $Me_3SiCF_2SO_2Ph$ reagent.

Similarly, [difluoro(phenylseleno)methyl]trimethylsilane (**59**) has also been developed as a nucleophilic difluoromethylation reagent (Scheme 10).[62,63] Although reagent **59** reacts with aldehydes (both non-enolizable and enolizable) with good yields, its reactions with ketones are generally less effective.[59,62,63] This indicates that the reactivity of Me_3SiCF_2SePh (**59**) towards carbonyl compounds is lower than those of Me_3SiCF_2SPh (**52**) and $Me_3SiCF_2SO_2Ph$ (**57**). However, the homolytic F_2C–Se cleavage of compounds **60** (eqn (32)) is easier than corresponding F_2C–S cleavage of compounds **53** (eqn (29)).

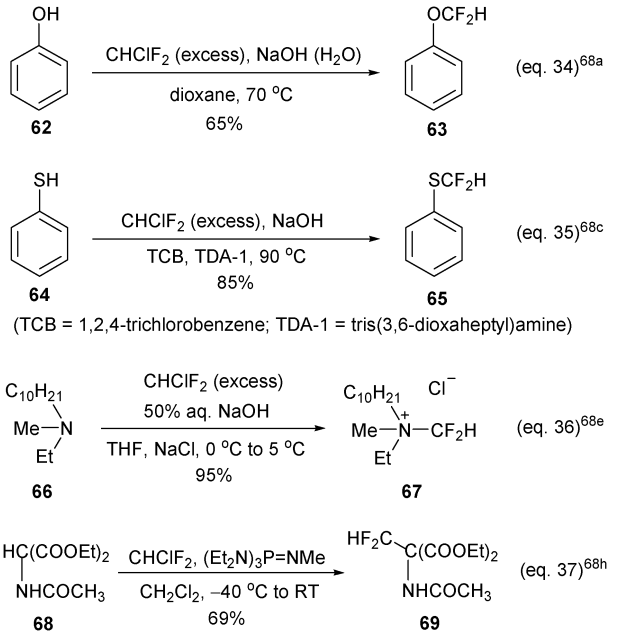
The silylated analog of diethyl difluoromethylphosphonate, diethyl difluoro(trimethylsilyl)methylphosphonate (**61**) is also well-recognized in nucleophilic (diethoxyphosphoryl)difluoromethylation reactions, but its use in the preparation of CF_2H-containing compounds is less known.[53c,64]

2.2 Electrophilic difluoromethylation

2.2.1 Using difluorocarbene reagents. The most widely used method for the incorporation of a CF_2H group into nucleophiles (such as oxygen-, nitrogen-, sulfur-, phosphorus-, and carbon-nucleophiles) is the reaction of the corresponding nucleophile with a proper difluorocarbene reagent (eqn (33))).[8–11,65,66] Chlorodifluoromethane ($CHClF_2$, also



Scheme 10 Nucleophilic difluoromethylation with Me_3SiCF_2SePh reagent.



Scheme 11 Difluoromethylation with $CHClF_2$.

called Freon R-22) is probably the most frequently used difluorocarbene reagent for this purpose (Scheme 11).[47,67–70] It should be noted that although difluoromethylation of phenols with $CHClF_2$ can be readily achieved (eqn (34)),[68a] the corresponding difluoromethylation of normal aliphatic alcohols is often difficult. However, aliphatic alcohols with high O–H acidity can be difluoromethylated to give corresponding difluoromethyl ethers.[8] Furthermore, difluoromethylation of *C*-nucleophiles are generally more difficult than *O*-, *N*- and *S*-nucleophiles, and it has been found that the C–H acidity of the *C*-nucleophile plays an important role in the *C*-difluoromethylations (eqn (37)).[68e,g,70]

Chlorodifluoroacetic acid derivatives, such as $ClCF_2COONa$ and $ClCF_2COOMe$, are also useful difluorocarbene reagents for *O*- and *N*-difluoromethylations.[70] For instance, sodium chlorodifluoroacetate can efficiently difluoromethylate *N*-(5-bromopyridin-2-yl)acetamide (**70**) to give *N*-difluoromethyl-5-bromo-2-pyridone (**72**) in 85% yield (eqn (38)).[70c] Other difluorocarbene reagents such as FSO_2CF_2COOH,[71] CBr_2F_2/Zn,[72] and $BrCF_2COOEt/K_2CO_3$[70a] can also be used for the transformation from **70** to **72**, but with relatively lower yield.[70c] $CF_2Br_2/Zn/HMPT$ [HMPT = $(Me_2N)_3P$] has been used to convert carbonyl compounds (such as **73**) to 1,1-difluoroolefines (such as **74**), and the latter can be further hydrogenated to give the difluoromethyl compound (such as **75**, eqn (39)).[73]

Diastereoselective difluoromethylation of lithium enolates derived from *N*-acyloxazolidinones (such as **76**) with $CHBrF_2$ has been successfully achieved (eqn (40)), and a difluorocarbene-involved reaction mechanism was proposed.[74]

Difluorocarbene species can be generated by pyrolysis of hexafluoropropene oxide (HFPO), by which some fluorinated alcohols were difluoromethylated to give the ether products in low yield (*e.g.*, $CF_3CF_2CH_2OCF_2H$, 45%; $CF_3CH_2OCF_2H$, 41%; $(CF_3)_2CHOCF_2H$, trace).[75] Other difluorocarbene or carbenoid reagents, such as $Zn(CF_3)Br$, $Cd(CF_3)_2$, $Bi(CF_3)_3/AlCl_3$, $(CH_3)_3SnCF_3/BX_3$, have also been used in *N*-difluoromethylations.[76,77] Another excellent difluorocarbene reagent, trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), has been frequently used to react with alkenes (or alkynes) to form *gem*-difluorocyclopropanes (or *gem*-difluorocyclopropenes).[78a,b] However, TFDA reagent was rarely used to facilitate difluoromethylations, that is, the CF_2H-transferring reactions (eqn (41) and (42)).[78c,d] The formation of *N*-difluoromethylthiourea **81** from *N*-benzylimidazole **80** and TFDA is interesting, and this unusual conversion was believed to proceed *via* a one-pot multi-step tandem reaction process.[78d] Difluorodiazirine is also a difluorocarbene reagent for difluoromethylations, but it is less commonly used.[79]

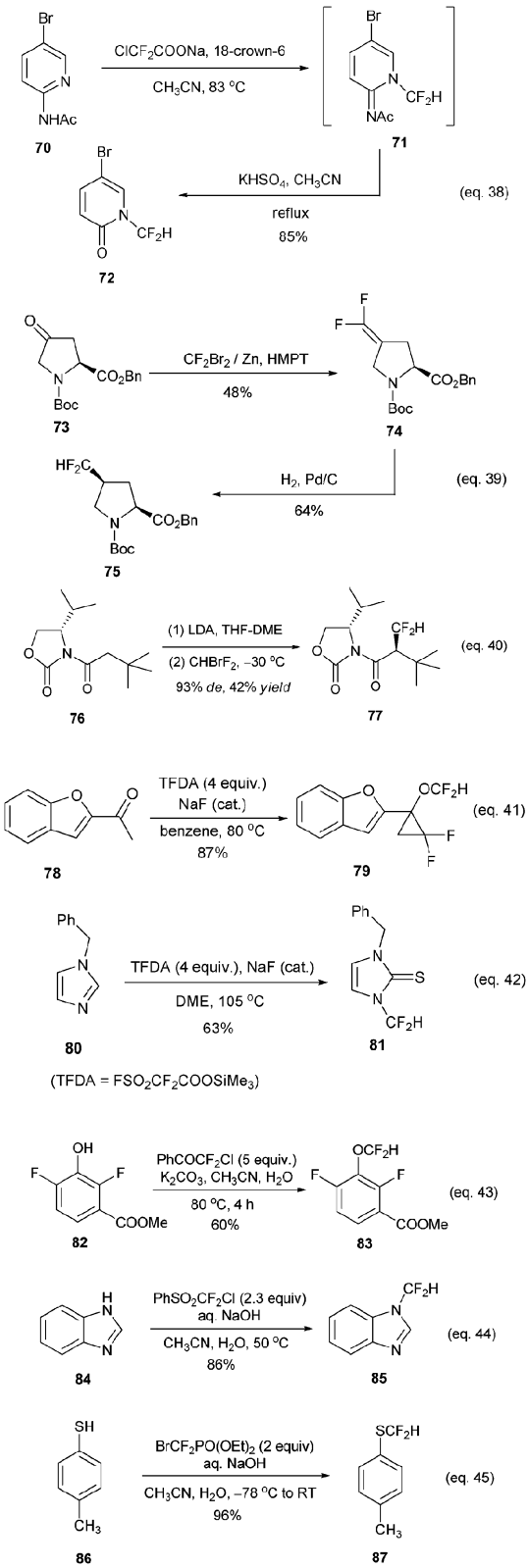
Recently, we reported the non-ODS-based (ODS = ozone depleting substance) preparation of 2-chloro-2,2-difluoroacetophenone ($PhCOCF_2Cl$)[80] and chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$),[81] and their use as efficient difluorocarbene reagents in *O*- and *N*-difluoromethylations (eqn (43) and (44)). Thereafter, Zafrani *et al*. reported the use of diethyl bromodifluoromethylphosphonate [$BrCF_2PO(OEt)_2$] as an efficient difluorocarbene precursor for *O*- and *S*-difluoromethylations (eqn (45)).[49] More recently, we found that *N*-tolsyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**88**) can act as a novel electrophilic difluoromethylation reagent for *S*-, *N*-, and *C*-nucleophiles (Scheme 13).[82] Although the chemistry appears to be S_N2-type difluoromethylation, a mechanistic study showed that the reaction proceeded *via* a difluorocarbene intermediate.[82]

2.2.2 Using *S*-difluoromethylsulfonium salt reagents. In 2007, Prakash *et al*. reported the use of *S*-(difluoromethyl)-diarylsulfonium tetrafluoroborate (**91**) as the first electrophilic reagent for the direct introduction of a "CF_2H^+" building block.[83] Reagent **91** was found to be efficient in difluoromethylation of sodium or potassium sulfonates, tertiary amines, imidazole derivatives, and phosphines (Scheme 14). The reactions are usually performed in dry acetonitrile at room temperature. However, reagent **91** failed to transfer the difluoromethyl group to phenols, carbon nucleophiles, and primary and secondary amines.[83] Similarly, the solid-phase bound electrophilic difluoromethylation reagent derived from **91** have also been developed, which enables the target and/or diversity oriented manual or automated library synthesis.[84]

2.2.3 Using iodine(III)–CF_2SO_2Ph reagents. Inspired by Togni's electrophilic trifluoromethylation reagent,[17,85] we developed a hypervalent iodine(III)–CF_2SO_2Ph compound **97** as an electrophilic difluoromethylation reagent.[86] Reagent **97** can effectively transfer the (phenylsulfonyl)difluoromethyl group to a variety of *S*-nucleophiles under very mild reaction conditions (eqn (53)). Upon reductive desulfonylation, the (phenylsulfonyl)difluoromethylated products can be converted to CF_2H-containing compounds (eqn (54)).[86]

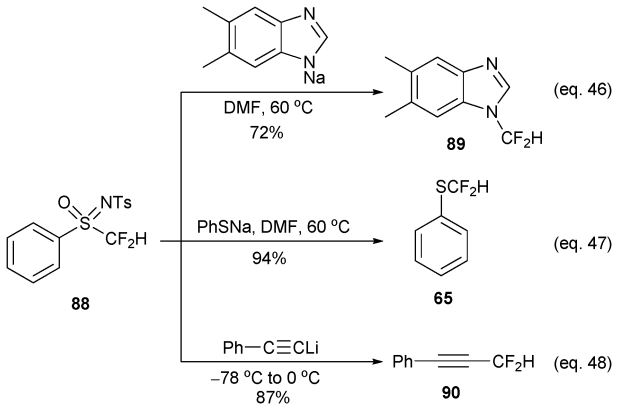
2.3 Free radical difluoromethylation

2.3.1 Using CHF_2I reagent. In 1994, Chen *et al*. reported an efficient preparation of iododifluoromethane (CHF_2I), and the use of CHF_2I as a free radical difluoromethylation reagent

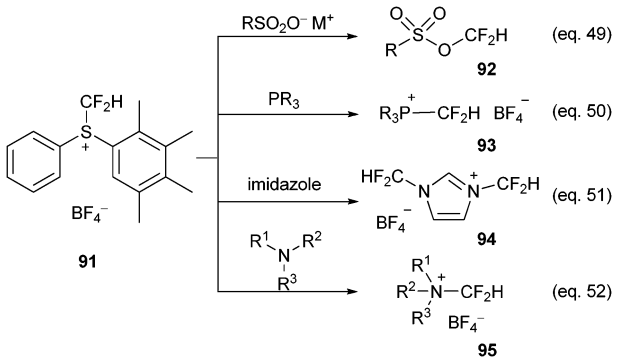


Scheme 12 Difluoromethylations with different difluorocarbene reagents.

for alkenes and alkynes (Scheme 16).[87] It was found that when sodium dithionate ($Na_2S_2O_4$) was used as a free radical initiator, a variety of difluoromethylated products **96** and **97**



Scheme 13 Difluoromethylations with reagent **88**.

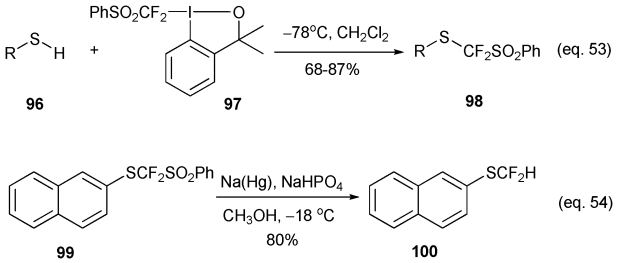


Scheme 14 Electrophilic difluoromethylations with reagent **91**.

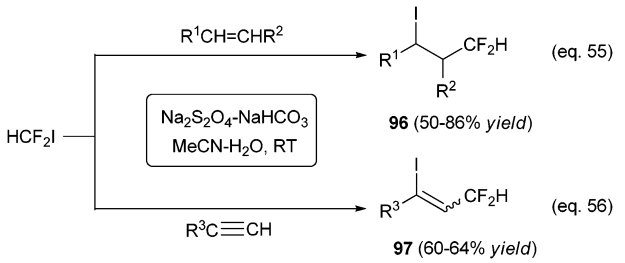
were formed in high yields from alkenes and alkynes under very mild conditions (eqn (55) and (56)).[87]

2.3.2 Using CF_2Br_2 or CF_2BrCl reagent. Free radical difluoromethylation of alkenes can also be achieved *via* a two-step method, that is, CuCl-initiated radical addition with dibromodifluoromethane (CF_2Br_2) followed by reduction with sodium borohydride (eqn (57)).[88] Under the initiation of $Na_2S_2O_4$, free radical difluoromethylation of glucal **101** with CF_2Br_2 gives the product **104** through a three-step procedure (eqn (58)).[89] Similarly, difluoromethylated sugar compound **104** can be prepared by free radical difluoromethylation with bromochlorodifluoromethane (CF_2BrCl) through a radical chlorodifluoromethylation–hydrodechlorination method (eqn (59)).[90,91]

2.3.3 Using $PhSO_2CF_2I$ reagent. Since the (phenylsulfonyl)-difluoromethyl group can be readily converted to a

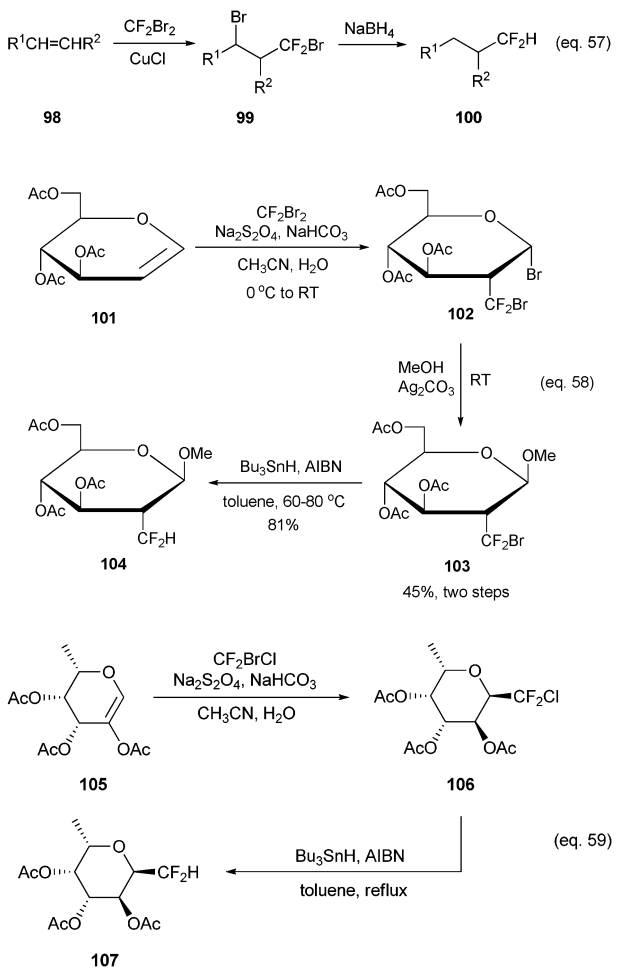


Scheme 15 Electrophilic difluoromethylations with reagent **97**.

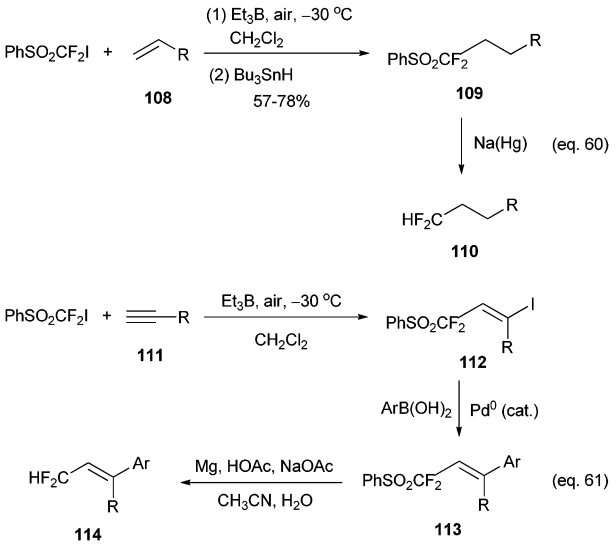


Scheme 16 Free radical difluoromethylations with CHF_2I.

difluoromethyl group by reductive desulfonylation (see section 2.1.3), free radical (phenylsulfonyl)difluoromethylation of alkenes with iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$) has been developed (eqn (60)).[92] Compound $PhSO_2CF_2I$ can be readily prepared from $PhSO_2CF_2H$ and I_2 in the presence of *t*BuOK in 92–95% isolated yields.[41] The unique feature of free radical (phenylsulfonyl)difluoromethylation with $PhSO_2CF_2I$ is that normal radical initiators such as Cu^0, $Pd(PPh_3)_4$, and $Na_2S_2O_4$ are not suitable for the reaction, and Et_3B/air is an efficient initiating system at -30 °C.[92] As shown in Scheme 18, the free radical (phenylsulfonyl)difluoromethylation of terminal alkenes **108** gives the $PhSO_2CF_2$-containing alkanes **109** in 57–78% yields, and the latter



Scheme 17 Free radical difluoromethylations with CF_2Br_2 and CF_2BrCl.



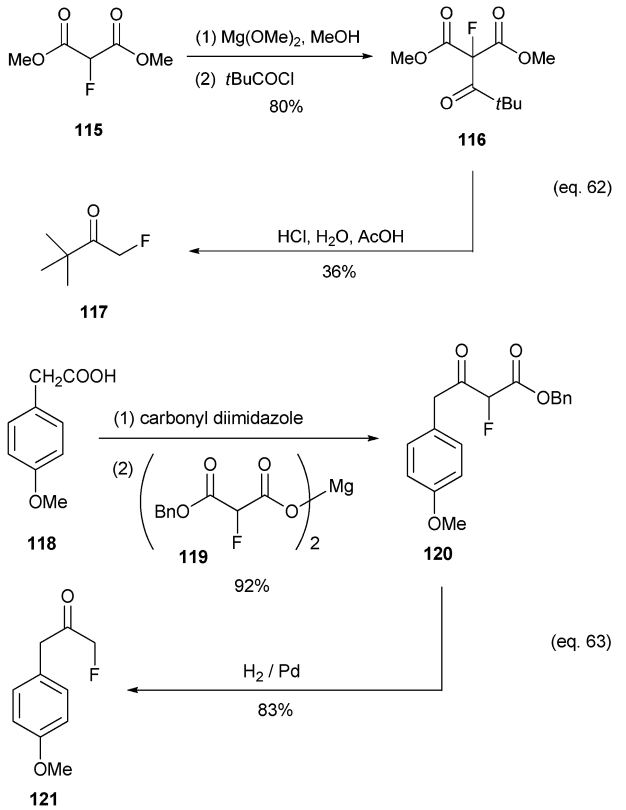
Scheme 18 Free radical difluoromethylations with $PhSO_2CF_2I$.

compounds can be further transformed to CF_2H-containing products **110**.[41] Furthermore, free radical (phenylsulfonyl)-difluoromethylation of terminal alkynes with $PhSO_2CF_2I$ gives $PhSO_2CF_2$-containing iodoalkenes **112**, and compounds **112** can undergo Suzuki-coupling and reductive desulfonylation to give difluoromethylated alkenes **114** (eqn (61)).[93] Similarly, free radical difluoroalkylations with $PhSCF_2Br$,[94a] $PhSCF_2I$,[94b] and $PhSeCF_2P(O)(OEt)_2$[94c] are also potentially useful methods for the preparation of difluoromethylated compounds.

3. Selective monofluoromethylation

3.1 Nucleophilic monofluoromethylation

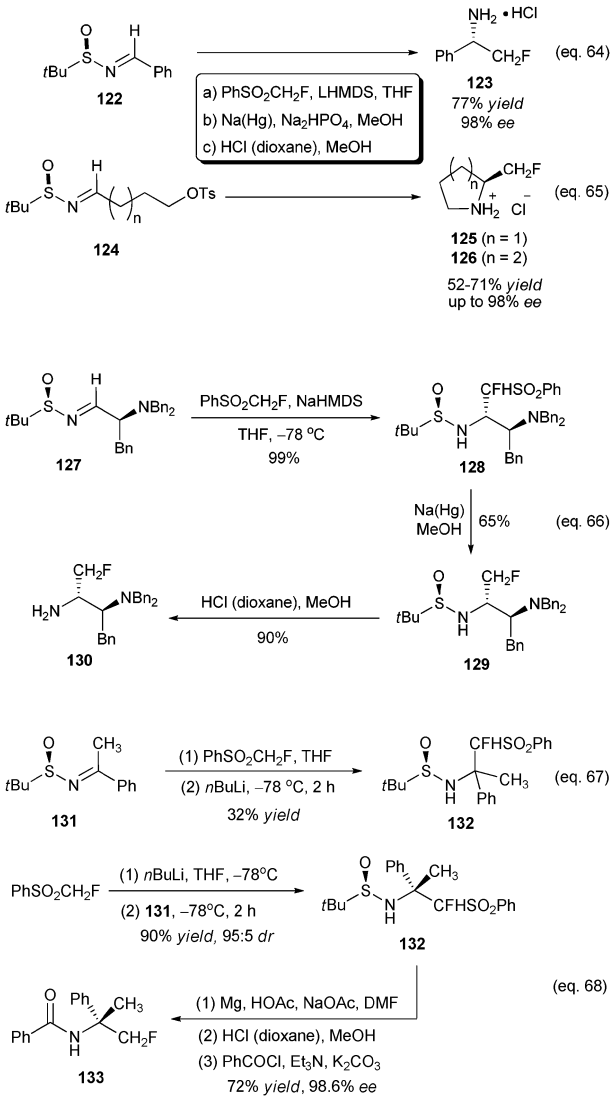
3.1.1 Using fluoromalonates. It has been known that fluoromethyllithium (FCH_2Li) and fluoromethyl Grignard reagent (FCH_2MgX) are highly unstable species, nucleophilic monofluoromethylation with these organometallic reagents has become a challenge.[95] Therefore, other functionalized fluoromethyl anions have been used as nucleophilic monofluoromethylation reagents. The nucleophilic addition of the carbanion of diethyl (or methyl) 2-fluoromalonate to various electrophiles have been known since the 1960s.[96] However, these reactions were rarely used to prepare CH_2F-containing products, since the removal of two carboxylate groups *via* decarboxylation was found to be difficult (eqn (62)).[97] Palmer has disclosed that magnesium benzyl fluoromalonate (**119**) was able to react with a variety of carboxylic acids (including amino acids and peptides) to give corresponding β-keto-α-fluoroesters (such as **120**), which were then converted to α-fluoromethyl ketones (such as **121**) in good yields *via* decarboxylation using hydrogenation (eqn (63)).[98] Although Palmer's method seems like an attractive procedure for nucleophilic monofluoromethylation, it has a major drawback—the large-scale preparation of reagent **119** is rather difficult.[95,98] More recently, catalytic enantioselective nucleophilic addition of fluoromalonates to various substrates has



Scheme 19 Nucleophilic monofluoromethylations with fluoromalonates.

been intensively studied, but none of them was used to prepare enantiomerically enriched CH_2F-containing compounds.[99]

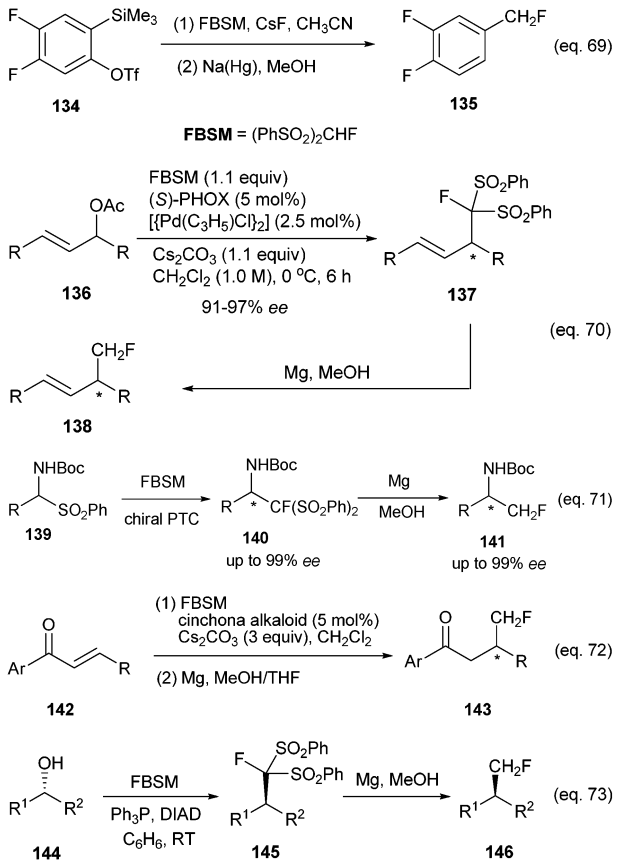
3.1.2 Using fluoromethyl phenyl sulfone. In 2006, we reported the first stereoselective nucleophilic monofluoromethylation with fluoromethyl phenyl sulfone ($PhSO_2CH_2F$).[23] It turned out that the reaction between homochiral *N-tert*-butylsulfinyl aldimines and $PhSO_2CH_2F$ in the presence of a base (LiHMDS) readily gave (phenylsulfonyl)fluoromethylated products, which could be converted to monofluoromethylated chiral amines (*via* removal of both phenylsulfonyl and *tert*-butylsulfinyl groups) in good yields and with excellent optical purity (eqn (64) and (65)).[23] The cyclic chiral fluoromethyl amine **125** has been recently applied in the study of the fluorine-iminium *gauche* effect.[100] We also found that the $PhSO_2CHF^-$ anion derived from $PhSO_2CH_2F$ was able to undergo nucleophilic reaction with simple epoxides, while the analogous difluoromethylated anion $PhSO_2CF_2^-$ failed to react with epoxides.[101] The $PhSO_2CH_2F$ reagent was also successfully used by us in the stereoselective synthesis of monofluoromethylated vicinal ethylenediamine **130** (eqn (66)),[46b] as well as in the nucleophilic monofluoromethylation of α,β-unsaturated ketones.[45] Recently, we achieved the highly stereoselective monofluoromethylation of *N-tert*-butylsulfinyl ketimines by using the pregenerated $PhSO_2CHF^-$ anion (eqn (68)).[102] When the $PhSO_2CHF^-$ anion was generated *in situ* in the presence of ketimine **131**, the chemical yield was much lower (eqn (67)).[102] Another interesting feature of this chemistry is that the stereocontrol mode of the



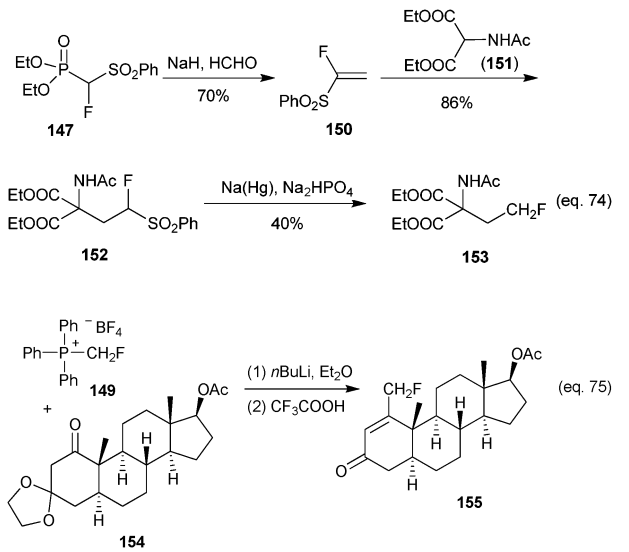
Scheme 20 Nucleophilic monofluoromethylations with $PhSO_2CH_2F$.

diastereoselective monofluoromethylation of ketimines is opposite to the other known fluoroalkylation of *N-tert*-butylsulfinyl aldimines, which suggests that a cyclic six-membered transition state is involved in the reaction.[102]

3.1.3 Using fluorobis(phenylsulfonyl)methane. In 2006, fluorobis(phenylsulfonyl)methane (FBSM) was independently reported by Shibata *et al.*[24a] and us[101] as a new nucleophilic monofluoromethylation reagent. FBSM is commonly prepared by electrophilic fluorination of bis(phenylsulfonyl)-methane, and recently, we developed a new preparation of FBSM by nucleophilic (phenylsulfonyl)fluoromethylation of methyl phenylsulfinate with $PhSO_2CH_2F$ reagent, followed by oxidiation.[103] Owing to the two electron-withdrawing phenylsulfonyl groups, the bis(phenylsulfonyl)fluoromethyl anion [$(PhSO_2)_2CF^-$] derived from FBSM possesses good thermal stability as well as good nucleophilicity towards many electrophiles. The unique X-ray single crystal structure of the $(PhSO_2)_2CF^-$ anion was recently obtained and depicted by computational study.[104] We found that FBSM was able to undergo addition reactions with simple epoxides and

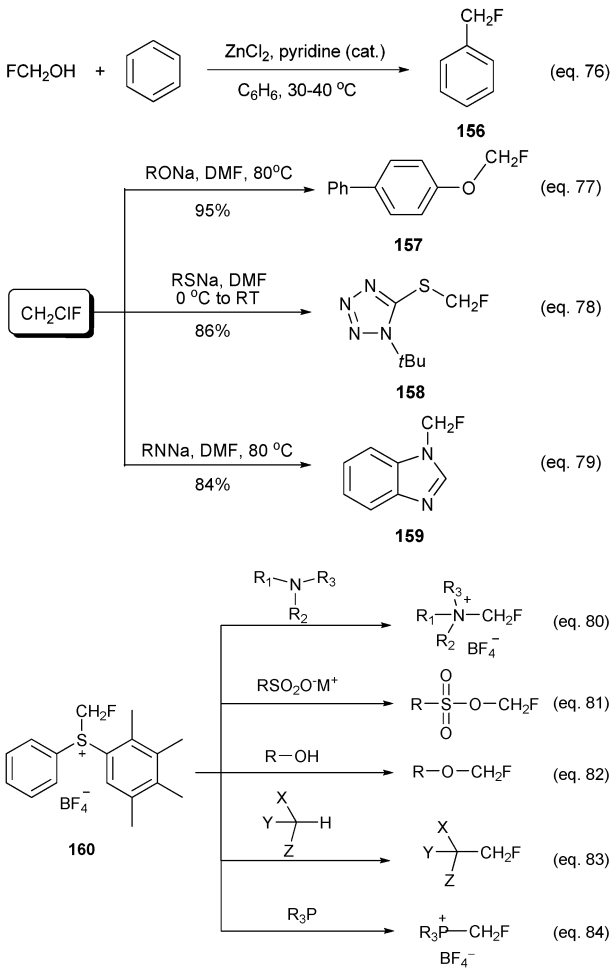


Scheme 21 Nucleophilic monofluoromethylations with $(PhSO_2)_2CHF$ (FBSM).

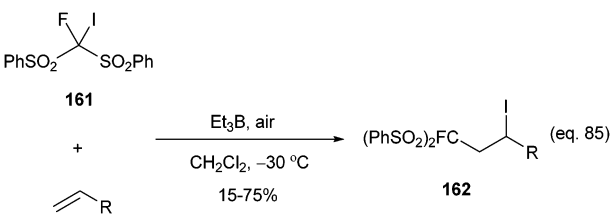


Scheme 22 Nucleophilic monofluoromethylation *via* fluorinated olefins.

aziridines,[101] 1,4-conjugate additions to α,β-enones and alkynyl ketones,[45] and additions to benzynes[45] (eqn (69)). More importantly, FBSM has been frequently applied in the catalytic enantioselective nucleophilic monofluoromethylation reactions. Shibata *et al*. applied FBSM in the palladium-catalyzed enantioselective allylic monofluoromethylation with



Scheme 23 Electrophilic monofluoromethylations.



Scheme 24 Free radical fluorobis(phenylsulfonyl)methylation.

91–97% *ee* values (eqn (70)).[24a] They also achieved highly enantioselective monofluoromethylation of *in situ* generated imines (eqn (71))[105] and α,β-unsaturated ketones (eqn (72)).[24b] Prakash *et al*. reported a stereospecific monofluoromethylation of alcohols with FBSM by using the Mitsunobu reaction condition (eqn (73)),[106] and they also developed 1,4-addition of FBSM to α,β-unsaturated compounds.[107] More recently, nucleophilic monofluoromethylation of alkyl halides with FBSM has been reported.[108] Furthermore, Kim *et al*. reported an enantioselective conjugate addition of FBSM to α,β-unsaturated ketones catalyzed by chiral bifunctional organocatalysts.[109] Wang *et al*. disclosed the catalytic enantioselective conjugate addition of FBSM to enals using iminium catalysis.[110]

3.1.4 Using fluoroolefins. Although it is less known, nucleophilic monofluoro-methylation can be achieved through fluoromethylenation of a carbonyl compound, followed by further transformations. The construction of fluoroolefins from carbonyl compounds usually applies reagents such as 1-fluoro-1-phenylsulfonylmethanephosphonate (**147**),[111] α-fluoromethyl-*N*-methyl-phenylsulfoximine (**148**),[112] or fluoromethyl phosphonium salt (**149**).[113] For instance, reagent **147** reacts with formaldehyde to give fluorinated alkene **150**, which acts as a Michael acceptor to react with **151** giving product **152** in 86% yield (eqn (74)). After reductive desulfonylation, compound **152** can be converted to fluoromethylated product **153** (eqn (74)).[111] Fluoromethyl phosphonium salt **149** can act as a precursor of fluorinated ylide to react with a carbonyl compound **152**, and the intermediate fluoroolefin compound readily isomerizes (under acidic condition) to give fluoromethylated product **155** (eqn (75)).[113]

3.2 Electrophilic monofluoromethylation

The number of known electrophilic monofluoromethylation methods is relatively small. In 1953, Olah and Pavlath reported the first example of electrophilic monofluoromethylation—the acid-catalyzed monofluoromethylation of benzene and other arenes with fluoromethanol (eqn (76)).[114] During the following 32 years, electrophilic monofluoromethylation was almost neglected, with the only example during this period being the synthesis of fluoromethylated androstane analogues using fluoroiodomethane (CH_2FI).[115] Since 1985, electrophilic monofluoromethylation of oxygen-, sulfur-, nitrogen-, and carbon-nucleophiles have been reported, by use of CH_2FI, CH_2FBr, and CH_2FOSO_2R (R = CF_3, CH_3, tolyl) as monofluoromethylation reagents.[116] These methods are mostly used for [^{18}F]-labeled applications. In 2007, we systematically studied the monofluoromethylation of oxygen-, sulfur-, and nitrogen-nucleophiles by using chlorofluoromethane (eqn (77)–(79)).[116] It should be noted that, since the reaction is not sensitive to radical scavengers such as nitrobenzene, the reaction is likely to proceed through an S_N2 mechanism. Although chlorofluoromethane is a powerful monofluoromethylation reagent for many *O*-, *S*-, and *N*-nucleophiles, its reaction with most carbon-nucleophiles was found to be unsuccessful.[116] In 2008, Prakash *et al.* reported the synthesis of *S*-(monofluoromethyl)diarylsulfonium tetrafluoroborate **160** and its use as a new electrophilic monofluoromethylation reagent.[25] Reagent **160** was shown to be effective for the introduction of an electrophilic monofluoromethyl group into *C*-, *S*-, *O*-, *N*-, and *P*-nucleophiles (eqn (80)–(84)), and it was also used in the synthesis of various biologically important compounds.[25]

3.3 Free radical monofluoromethylation

Unlike free radical trifluoromethylation and difluoromethylation, synthetic free radical monofluoromethylation is almost unknown. Although Raymond and Andrews successfully characterized the fluoromethyl radical ($FCH_2^{\bullet}$) by matrix reaction of bromofluoromethane with alkali metals,[117] its application in synthetic chemistry has not been reported. In 2008, Prakash presented a Et_3B/air-initiated free radical fluorobis(phenylsulfonyl)methylation of terminal alkenes with fluoroiodobis(phenylsulfonyl)methane **161** (eqn (85)).[118] However, the obtained product **162** was not further converted to monofluoromethyl compounds. Instead, the authors treated **162** with a base (such as DBU) and obtained fluorobis-(phenylsulfonyl)methylated alkenes.[118]

Conclusions and future directions

The practical importance of introduction of difluoromethyl and monofluoromethyl groups into organic molecules has stimulated the systematic development of various di- and monofluoromethylation methods, and a variety of nucleophilic, electrophilic, and free radical di- and monofluoromethylation reagents and reactions have been developed. Compared to nucleophilic di- and monofluoromethylations, both electrophilic and free radical di- and monofluoromethylations are less explored. In particular, free radical monofluoromethylation has been almost unknown. Although enantioselective nucleophilic monofluoromethylation has been recently accomplished, the enantioselective difluoromethylation needs further improvement. Transition metal-catalyzed (or mediated) di- and monofluoromethylation have rarely been known. More efforts should be focused on the development of more atom-efficient methods, that is, the direct transfer of CF_2H and CH_2F moieties into organic molecules rather than using the auxiliary-group approaches. Another important direction in this field is the use of more environmentally friendly chemicals, such as non-ODS-based reagents or starting materials. All these issues are expected to be answered in future studies.

Acknowledgements

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Notes and references

1 G. W. Gribble, *Chem. Soc. Rev.*, 1999, **28**, 335.
2 K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305.
3 D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton and C. D. Murphy, *Nature*, 2002, **416**, 279.
4 J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008.
5 (*a*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*b*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*c*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637.
6 G. K. S. Prakash and S. Chacko, *Curr. Opin. Drug Discovery Dev.*, 2008, **11**, 793.
7 A. M. Thayer, *Chem. Eng. News*, 2006, **84**(23), 15.
8 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2004.
9 *Organofluorine Compounds: Chemistry and Applications*, ed. T. Hiyama, Springer, New York, 2000.
10 K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006.
11 R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, 2004.
12 General reviews on trifluoromethylation: (*a*) J.-A. Ma and D. Cahard, *J. Fluorine Chem.*, 2007, **128**, 975; (*b*) J.-A. Ma and

D. Cahard, *Chem. Rev*., 2004, **104**, 6119; (*c*) G. K. S. Prakash and J. Hu, in *Science of Synthesis*, ed. A. B. Charette, Thieme, Stuttgart, 2005, vol. 22; (*d*) T. Umemoto, in *Fluorine-Containing Synthons*, ed. V. A. Soloshonok, ACS, Washington, DC, 2005; (*e*) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633.
13 Reviews on nucleophilic trifluoromethylation: (*a*) G. K. S. Prakash and A. K. Yudin, *Chem. Rev*., 1997, **97**, 757; (*b*) G. K. S. Prakash and M. Mandal, *J. Fluorine Chem*., 2001, **112**, 123; (*c*) G. K. S. Prakash and J. Hu, in *Fluorine-Containing Synthons*, ed. V. A. Soloshonok, ACS, Washington, DC, 2005; (*d*) R. P. Singh and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613; (*e*) B. R. Langlois and T. Billard, *Synthesis*, 2003, 185; (*f*) M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555; (*g*) D. J. Burton and Z. Y. Yang, *Tetrahedron*, 1992, **48**, 189; (*h*) M. Médebielle and W. R. Dolbier, Jr, *J. Fluorine Chem*., 2008, **129**, 930.
14 Reviews on electrophilic trifluoromethylation: (*a*) T. Umemoto, *Chem. Rev*., 1996, **96**, 1757; (*b*) Ref. 12.
15 See recent examples of free radical trifluoromethylation: (*a*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc*., 2009, **131**, 10875; (*b*) N. B. Shustova, A. A. Popov, A. Alexey, M. A. Mackey, C. E. Coumbe, J. P. Phillips, S. Stevenson, S. H. Strauss and O. V. Boltalina, *J. Am. Chem. Soc*., 2007, **129**, 11676; (*c*) V. Petrik and D. Cahard, *Tetrahedron Lett*., 2007, **48**, 3327; (*d*) Y. Itoh, K. N. Houk and K. Mikami, *J. Org. Chem*., 2006, **71**, 8918; (*e*) Ref. 12.
16 Q.-Y. Chen, *J. Fluorine Chem*., 1995, **72**, 241.
17 R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann and A. Togni, *Angew. Chem., Int. Ed*., 2009, **48**, 4332; and the references therein.
18 S. Noritake, N. Shibata, S. Nakamura, T. Toru and M. Shiro, *Eur. J. Org. Chem*., 2008, 3465.
19 Kawai, A. Kusuda, S. Nakamura, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed*., 2009, **48**, 6324.
20 (*a*) G. K. S. Prakash and J. Hu, *Acc. Chem. Res*., 2007, **40**, 921; (*b*) K. Uneyama, *J. Fluorine Chem*., 2008, **129**, 550; (*c*) Ref. 6.
21 C. Ni, J. Liu, L. Zhang and J. Hu, *Angew. Chem., Int. Ed*., 2007, **46**, 786; and references therein.
22 J. A. Erickson and J. I. McLoughlin, *J. Org. Chem*., 1995, **60**, 1626.
23 Y. Li, C. Ni, J. Liu, L. Zhang, J. Zheng, L. Zhu and J. Hu, *Org. Lett*., 2006, **8**, 1693; and references therein.
24 (*a*) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura and T. Toru, *Angew. Chem., Int. Ed*., 2006, **45**, 4973; (*b*) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed*., 2008, **47**, 8051; and references therein.
25 G. K. S. Prakash, I. Ledneczki, S. Chacko and G. A. Olah, *Org. Lett*., 2008, **10**, 557; and references therein.
26 C. Dibari, G. Pastore, G. Roscigno, P. J. Schechter and A. Sjoerdsma, *Ann. Inter. Med*., 1986, **105**, 83.
27 M. R. Karagas, G. L. Cushing, Jr, E. R. Greeberg, L. A. Mott, S. K. Spencer and D. W. Nierenberg, *Br. J. Cancer*, 2001, **85**, 683.
28 (*a*) G. A. Hartgraves and D. J. Burton, *J. Fluorine Chem*., 1988, **39**, 425; (*b*) D. J. Burton, G. A. Hartgraves and J. Hsu, *Tetrahedron Lett*., 1990, **31**, 3699; (*c*) D. J. Burton and G. A. Hartgraves, *J. Fluorine Chem*., 2007, **128**, 1198.
29 R. Eujen, B. Hoge and D. J. Brauer, *Inorg. Chem*., 1997, **36**, 3160.
30 T. Hagiwara and T. Fuchikami, *Synlett*, 1995, 717.
31 G. K. S. Prakash, R. Krishnamuti and G. A. Olah, *J. Am. Chem. Soc*., 1989, **111**, 393.
32 T. Brigaud, P. Doussot and C. Portella, *J. Chem. Soc., Chem. Commun*., 1994, 2117.
33 F. Huguenot, A. Billac, T. Brigaud and C. Portella, *J. Org. Chem*., 2008, **73**, 2564.
34 G. K. S. Prakash, R. Mogi and G. A. Olah, *Org. Lett*., 2006, **8**, 3589.
35 N. V. Kirij, L. A. Babadzhanova, V. N. Movchun, Y. L. Yagulpolskii, W. Tyrra, D. Naumann, H. T. M. Fischer and Harald Scherer, *J. Fluorine Chem*., 2008, **129**, 14.
36 J. Hine and J. J. Porter, *J. Am. Chem. Soc*., 1960, **82**, 6178.
37 J. Hu, *J. Fluorine Chem*., 2009, DOI: 10.1016/j.jfluchem.2009.05.016.
38 G. P. Stahly, *J. Fluorine Chem*., 1989, **43**, 53.
39 See one example of samarium iodide-mediated desulfonylation: P. J. Serafinowski and C. L. Barnes, *Synthesis*, 1997, 225.
40 G. K. S. Prakash, J. Hu and G. A. Olah, *J. Org. Chem*., 2003, **68**, 4457.
41 G. K. S. Prakash, J. Hu, Y. Wang and G. A. Olah, *Org. Lett*., 2004, **6**, 4315.
42 G. K. S. Prakash, J. Hu, Y. Wang and G. A. Olah, *Eur. J. Org. Chem*., 2005, 2218.
43 J.-D. Ye, X. Liao and J. A. Piccirilli, *J. Org. Chem*., 2005, **70**, 7902.
44 J. Liu, C. Ni, F. Wang and J. Hu, *Tetrahedron Lett*., 2008, **49**, 1605.
45 C. Ni, L. Zhang and J. Hu, *J. Org. Chem*., 2008, **73**, 5699.
46 (*a*) Y. Li and J. Hu, *Angew. Chem., Int. Ed*., 2005, **44**, 5882; (*b*) J. Liu, Y. Li and J. Hu, *J. Org. Chem*., 2007, **72**, 3119.
47 B. R. Langlois, *J. Fluorine Chem*., 1988, **41**, 247.
48 M. Zupan, *J. Fluorine Chem*., 1976, **8**, 305.
49 Y. Zafrani, G. Sod-Moriah and Y. Segall, *Tetrahedron*, 2009, **65**, 5278.
50 C. Ni, F. Wang and J. Hu, *Beilstein J. Org. Chem*., 2008, **4**, DOI: 10.3762/bjoc.4.21.
51 G. K. S. Prakash, Y. Wang, J. Hu and G. A. Olah, *J. Fluorine Chem*., 2005, **126**, 1361.
52 (*a*) S. R. Piettre, C. Girol and C. G. Schelcher, *Tetrahedron Lett*., 1996, **37**, 4711; (*b*) S. R. Piettre and L. Cabanas, *Tetrahedron Lett*., 1996, **37**, 5881.
53 (*a*) M. Zibinsky, P. Beier and G. K. S. Prakash, *Khimiya Interesakh Ustoichivogo Razvitiya*, 2008, **16**, 71; (*b*) P. Beier, A. V. Alexandrova, M. Zibinsky and G. K. S. Prakash, *Tetrahedron*, 2008, **64**, 10977; (*c*) P. Beier, R. Pohl and A. V. Alexandrova, *Synthesis*, 2009, 957.
54 A. K. Yudin, G. K. S. Prakash, D. Deffieux, M. Bradley, R. Bau and G. A. Olah, *J. Am. Chem. Soc*., 1997, **119**, 1572.
55 G. K. S. Prakash, J. Hu, Y. Wang and G. A. Olah, *J. Fluorine Chem*., 2005, **126**, 529.
56 Y. Li and J. Hu, *Angew. Chem., Int. Ed*., 2007, **46**, 2489.
57 Y. Li and J. Hu, *J. Fluorine Chem*., 2008, **129**, 382.
58 M. Pohmakotr, D. Panichakul, P. Tuchinda and V. Reutrakul, *Tetrahedron*, 2007, **63**, 9429.
59 M. Satoshi, S. Norio, O. Shinichi, F. Hiroyuki, N. Shuichi and T. Takeshi, *Chem. Commun*., 2006, 2575.
60 T. Bootwicha, D. Panichakul, C. Kuhakarn, S. Prabpai, P. Kongsaeree, P. Tuchinda, V. Reutrakul and M. Pohmakotr, *J. Org. Chem*., 2009, **74**, 3798.
61 C. Ni and J. Hu, *Tetrahedron Lett*., 2005, **46**, 8273.
62 Y.-Y. Qin, X.-L. Qiu, Y.-Y. Yang, W.-D. Meng and F.-L. Qing, *J. Org. Chem*., 2005, **70**, 9040.
63 Y.-Y. Qin, Y.-Y. Yang, X.-L. Qiu and F.-L. Qing, *Synthesis*, 2006, 1475.
64 M. Obayashi and K. Kondo, *Tetrahedron Lett*., 1982, **23**, 2327.
65 D. L. S. Brahms and W. P. Dailey, *Chem. Rev*., 1996, **96**, 1585; and the references therein.
66 D. J. Burton and J. L. Hahnfeld, *Fluorine Chem. Rev*., 1977, **8**, 119.
67 J. Hine and J. J. Porter, *J. Am. Chem. Soc*., 1957, **79**, 5493.
68 See selected examples of difluoromethylation with $CHClF_2$: (*a*) T. G. Miller and J. W. Thanassi, *J. Org. Chem*., 1960, **25**, 2009; (*b*) T. Y. Shen, S. Lucas and L. H. Sarett, *Tetrahedron Lett*., 1961, **2**, 43; (*c*) K. Morimoto, K. Makino and G. Sakata, *J. Fluorine Chem*., 1992, **59**, 417; (*d*) E. Nawrot and A. Jonczyk, *J. Org. Chem*., 2007, **72**, 10258; (*e*) E. Nawrot and A. Jonczyk, *J. Fluorine Chem*., 2009, **130**, 466; (*f*) J. W. Lyga and R. M. Patera, *J. Fluorine Chem*., 1998, **92**, 141; (*g*) I. I. Gerus, A. A. Kolomeitsev, M. I. Kolycheva and V. P. Kukhar, *J. Fluorine Chem*., 2000, **105**, 31; (*h*) K. I. Petko and L. M. Yagupolskii, *J. Fluorine Chem*., 2001, **108**, 211; (*i*) K. I. Petko and L. M. Yagupolskii, *Zh. Org. Khim*, 2004, **40**, 627; (*j*) K. I. Petko, T. M. Sokolenko and L. M. Yagupolskii, *Zh. Org. Khim*, 2005, **41**, 437; (*k*) A. Jonczyk, E. Nawrot and M. Kisielewski, *J. Fluorine Chem*., 2005, **126**, 1587; (*l*) E. Nawrot and A. Jonczyk, *J. Fluorine Chem*., 2006, **127**, 943.
69 (*a*) P. Bey, J.-P. Vevert, V. V. Dorsselaer and M. Kolb, *J. Org. Chem*., 1979, **44**, 2732; (*b*) B. W. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara and J. P. Vevert, *J. Am. Chem. Soc*., 1978, **100**, 2551.
70 (*a*) S. B. Christensen, H. E. Dabbs and J. M. Karpinski, PCT Int. Appl., WO 96/23754, 1996; (*b*) P. D. O'Shea, C.-Y. Chen,

W. Chen, P. Dagneau, L. F. Frey, E. J. J. Grabowski, K. M. Marcantonio, R. A. Reamer, L. Tan, R. D. Tillyer, A. Roy, X. Wang and D. Zhao, *J. Org. Chem.*, 2005, **70**, 3021; (*c*) J. M. Ando, T. Wada and N. Sato, *Org. Lett.*, 2006, **8**, 3805.
71 Q.-Y. Chen and S.-W. Wu, *J. Fluorine Chem.*, 1989, **44**, 433.
72 I. Rico and C. Wakselman, *Tetrahedron Lett.*, 1981, **22**, 323.
73 (*a*) X.-L. Qiu and F.-L. Qing, *J. Org. Chem.*, 2002, **67**, 7162; (*b*) W. B. Motherwell, M. J. Tozer and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1989, 1437; (*c*) S. Marcotte, B. Gerard, X. Pannecouke, C. Feasson and J.-C. Quirion, *Synthesis*, 2001, 929.
74 K. Iseki, D. Asada, M. Takahashi, T. Nagai and Y. Kobayashi, *Tetrahedron: Asymmetry*, 1996, **7**, 1205.
75 J. Mizukado, Y. Matsukawa, H.-D. Quan, M. Tamura and A. Sekiya, *J. Fluorine Chem.*, 2005, **126**, 365.
76 S. V. Pasenok, N. V. Kirij, Y. L. Yagupolskii, D. Naumann, W. Tyrra and A. Fitzner, *Z. Anorg. Allg. Chem.*, 1999, **625**, 834.
77 H. Bürger, M. Grunwald and G. Pawelke, *J. Fluorine Chem.*, 1985, **28**, 183.
78 (*a*) F. Tian, V. Kruger, O. Bautista, J.-X. Duan, A.-R. Li, W. R. Dolbier and Q.-Y. Chen, *Org. Lett.*, 2000, **2**, 563; (*b*) W. R. Dolbier, Jr, F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. M. Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste and Q.-Y. Chen, *J. Fluorine Chem.*, 2004, **125**, 459; (*c*) X. Cai, Y. Zhai, I. Ghiviriga, K. A. Abboud and W. R. Dolbier, *J. Org. Chem.*, 2004, **69**, 4210; (*d*) W. Xu, K. A. Abboud, I. Ghiviriga, W. R. Dolbier, M. Rapp and S. F. Wnuk, *Org. Lett.*, 2006, **8**, 5549.
79 R. A. Mitsch and J. E. Robertson, *J. Heterocycl. Chem.*, 1965, **2**, 152.
80 L. Zhang, J. Zheng and J. Hu, *J. Org. Chem.*, 2006, **71**, 9845.
81 J. Zheng, Y. Li, J. Hu, G. J. Meuzelaar and H.-J. Federsel, *Chem. Commun.*, 2007, 5149.
82 W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2009, **11**, 2109.
83 G. K. S. Prakash, C. Weber, S. Chacko and G. A. Olah, *Org. Lett.*, 2007, **9**, 1863.
84 G. K. S. Prakash, C. Weber, S. Chacko and G. A. Olah, *J. Comb. Chem.*, 2007, **9**, 920.
85 (*a*) P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579; (*b*) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754.
86 W. Zhang, J. Zhu and J. Hu, *Tetrahedron Lett.*, 2008, **49**, 5006.
87 P. Cao, J.-X. Duan and Q.-Y. Chen, *J. Chem. Soc., Chem. Commun.*, 1994, 737.
88 J. Gonzalez, C. J. Foti and S. Elsheimer, *J. Org. Chem.*, 1991, **56**, 4322.
89 R. Miethchen, M. Hein and H. Reinke, *Eur. J. Org. Chem.*, 1998, 919.
90 A. Wegert, R. Miethchen, M. Hein and H. Reinke, *Synthesis*, 2005, 1850.
91 A. Wegert, M. Hein, H. Reinke, N. Hoffmann and R. Miethchen, *Carbohydr. Res.*, 2006, **341**, 2641.
92 Y. Li, J. Liu, L. Zhang, L. Zhu and J. Hu, *J. Org. Chem.*, 2007, **72**, 5824.
93 Y. Li, H. Li and J. Hu, *Tetrahedron*, 2009, **65**, 478.
94 (*a*) V. Reutrakul, T. Thongpaisanwong, P. Tuchinda, C. Kuhakarn and M. Pohmakotr, *J. Org. Chem.*, 2004, **69**, 6913; (*b*) X. Fang, X. Yang, X. Yang, S. Mao, Z. Wang, G. Chen and F. Wu, *Tetrahedron*, 2007, **63**, 10684; (*c*) S. Pignard, C. Lopin, G. Gouhier and S. R. Piettre, *J. Org. Chem.*, 2006, **71**, 31.
95 M. R. Reeder and R. M. Anderson, *Chem. Rev.*, 2006, **106**, 2828.
96 (*a*) R. L. Buchanan and F. L. M. Pattison, *Can. J. Chem.*, 1965, **43**, 3466; (*b*) N. Ishikawa, A. Takaoka and M. K. Ibrahim, *J. Fluorine Chem.*, 1984, **25**, 203; (*c*) N. A. Beare and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 541.
97 A. V. Bogolyubskii, A. Y. Il'chenko and L. M. Yagupolskii, *Zh. Org. Khim.*, 1987, **23**, 2300.
98 J. T. Palmer, Eur. Patent Appl. 0442754A2, 1991.
99 See recent examples: (*a*) H. Li, L. Zu, H. Xie and W. Wang, *Synthesis*, 2009, 1525; (*b*) B. K. Kwon, S. M. Kim and D. Y. Kim, *J. Fluorine Chem.*, 2009, **130**, 759; (*c*) M. J. Cho, M. G. Cho, S. C. Huh, S. M. Kim, K. Lee, K. O. Koh, J. Y. Mang and D. Y. Kim, *Bull. Korean Chem. Soc.*, 2006, **27**, 857; (*d*) B. Jiang, Z.-G. Huang and K.-J. Cheng, *Tetrahedron: Asymmetry*, 2006, **17**, 942.
100 C. Sparr, W. B. Schweizer, H. M. Senn and R. Gilmour, *Angew. Chem., Int. Ed.*, 2009, **48**, 3065.
101 C. Ni, Y. Li and J. Hu, *J. Org. Chem.*, 2006, **71**, 6829.
102 J. Liu, L. Zhang and J. Hu, *Org. Lett.*, 2008, **10**, 5377.
103 C. Ni, L. Zhang and J. Hu, *J. Org. Chem.*, 2009, **74**, 3767.
104 G. K. S. Prakash, F. Wang, N. Shao, T. Mathew, G. Rasul, R. Haiges, T. Stewart and G. A. Olah, *Angew. Chem., Int. Ed.*, 2009, **48**, 5358.
105 S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394.
106 G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew and G. A. Olah, *Angew. Chem., Int. Ed.*, 2007, **46**, 4933.
107 G. K. S. Prakash, X. Zhao, S. Chacko, F. Wang, H. Vaghoo and G. A. Olah, *Beilstein J. Org. Chem.*, 2008, **4**, 17.
108 G. K. S. Prakash, S. Chacjo, H. Vaghoo, N. Shao, L. Gurung, T. Mathew and G. A. Olah, *Org. Lett.*, 2009, **11**, 1127.
109 H. W. Moon, M. J. Cho and D. Y. Kim, *Tetrahedron Lett.*, 2009, **50**, 4896.
110 S. Zhang, Y. Zhang, Y. Ji, H. Li and W. Wang, *Chem. Commun.*, 2009, 4886.
111 T. Koizumi, T. Hagi, Y. Horie and Y. Takeuchi, *Chem. Pharm. Bull.*, 1987, **35**, 3959.
112 M. L. Boys, E. W. Collington, H. Finch, S. Swanson and J. F. Whitehead, *Tetrahedron Lett.*, 1988, **29**, 3365.
113 R. Bohlmann, D. Bittler, M. Gottwald, P. Muhn, Y. Nishino, B. Schoenecker and G. Hobe, Ger. Offen., DE 93-4330237, 1995.
114 (*a*) G. A. Olah and A. Pavlath, *Acta Chim. Acad. Sci. Hung.*, 1953, **3**, 425; (*b*) G. A. Olah and A. Pavlath, *Acta Chim. Acad. Sci. Hung.*, 1953, **3**, 203.
115 J. C. Orr, J. Edwards and A. Bowers, *US Patent*, US 3080395, 1963.
116 W. Zhang, L. Zhu and J. Hu, *Tetrahedron*, 2007, **63**, 10569; and the references therein.
117 J. I. Raymond and L. Andews, *J. Phys. Chem.*, 1971, **75**, 3235.
118 G. K. S. Prakash, I. Ledneczki, S. Chacko, S. Ravi and G. A. Olah, *J. Fluorine Chem.*, 2008, **129**, 1036.

