China's flourishing synthetic organofluorine chemistry: innovations in the new millennium

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ABSTRACT

The new millennium has witnessed the rapid development of synthetic organofluorine chemistry all over the world, and chemists in China have made significant contributions in this field. This review aims to provide a brief introduction to China’s primary innovations from 2000 to early 2017, covering fluorination, fluoroalkylation, fluoromethylthiolation, fluoroolefination and polyfluoroarylation, as well as synthesis with fluorinated building blocks. Recent advances in the chemistry of difluorocarbene and the chemistry of carbon–fluorine bond activation are also discussed. As a conclusion, the review ends with some personal perspectives on the future development of China’s synthetic organofluorine chemistry.

Keywords: fluorine, organic chemistry, synthetic methods, fluorination, trifluoromethylation, trifluoromethylthiolation, difluoromethylthiolation, difluoroalkylation, fluoromethylation, fluoroolefination

INTRODUCTION

In the field of organic chemistry, fluorine is a supersubstituent due to its high electronegativity (4.0 on the Pauling scale), small atomic radius ($r_v = 1.47 \, \text{Å}$) and the great strength of the carbon–fluorine (C–F) bond (averages about 116 kcal/mol) [1]. The incorporation of fluorine atoms or fluorinated moieties into organic molecules can often lead to profound changes in the latter’s physical, chemical and biological properties, and a variety of fluorine-containing materials, pharmaceuticals and agrochemicals have been developed [2]. However, although fluorine is an abundant halogen element and ranks number 13 among all elements in the Earth’s crust, naturally occurring organofluorine compounds (organic compounds bearing a C–F bond) are rare [3]. Therefore, the development of efficient ways to introduce fluorine into organic compounds has become one of the hottest areas of organic synthesis research in recent years. Many efficient methodologies for the synthesis of organofluorine compounds have been developed by chemists all over the world [3–14].

China is rich in fluorspar deposits and most of the fluorine-containing basic chemicals, such as simple fluorocarbons, are readily available from the Chinese chemical industry. Chinese chemists have engaged in organofluorine chemistry since the 1950s and have made significant contributions. In the past decade, many young Chinese scientists have joined this intriguing research field. Several books and book chapters have already described the development of China’s organofluorine chemistry efforts prior to 2000 [15–17]. This Review focuses on providing a brief summary of China’s primary innovations in the field of synthetic organofluorine chemistry from 2000 to early 2017, covering fluorination, fluoroalkylation, fluoromethylthiolation, fluoromethylation, and polyfluoroarylation, as well as synthesis with fluorinated building blocks. Special topics on the chemistry of difluorocarbene and the chemistry of the C–F bond activation are also discussed.

FLUORINATION

C–F bond formation is one of the core contents in the field of organofluorine chemistry. In recent years, increasing attention has been paid to the development of selective fluorination reagents and exploration of conceptually new methods for the formation of C–F bonds [6,13,18].
Nucleophilic fluorination is a fundamental methodology for the synthesis of organofluorine compounds. Huang and Guo’s pioneering work at the Shanghai Institute of Organic Chemistry (SIOC) in 1981 described the deoxyfluorination of sterols with phenyl sulfur trifluorides [19]; however, the low efficiency of this method limited its adoption for widespread use. Hou et al. at SIOC, in 2004 developed an efficient and highly regioselective method for the fluorination of aziridines using $\text{BF}_3 \cdot \text{Et}_2 \text{O}$ as the fluoride source [20], which is one of the earliest reports of the use of boron trifluoride for nucleophilic ring-opening fluorination reactions [12].

In more recent organofluorine chemistry, more attention has been paid to controlling selectivity and exploiting new reactivity [21]. Hu et al. at SIOC recently developed a novel deoxyfluorination strategy based on cyclopropenium cation activation via the use of 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors) (Scheme 1, Eq 1) [21] to tackle the problem of deoxyfluorination of alcohols not usually being sensitive toward the electronic nature of the substrates. The key to the success of this approach is the fine-tuning of the electronic nature of the CpFluor reagents to improve the nucleophilic fluorination. Moreover, the challenge of taming direct nucleophilic fluorination of arenes with fluoride ions has been achieved by the same group by using a diphenyliodonium salt as the catalyst (Scheme 1, Eq 2) [22]. In addition, transition metals have also been utilized to promote reactions that are otherwise difficult to achieve. Liu et al. at SIOC [23,24], Weng et al. at Fuzhou University (FZU) [25] and Jiang et al. at the South China University of Technology [26] (Scheme 1, Eqs 3–6) have published representative works on copper-catalyzed/mediated or silver-mediated nucleophilic fluorination.

Electrophilic fluorination

Electrophilic fluorination reactions are mainly performed with ‘N-F’ reagents, Selectfluor and N-fluorobenzenesulfonylimide (NFSI) [27–35]. Ma et al. at Zhejiang University (ZJU) demonstrated the fluorohydroxylation of simple allenes with high regioselectivity, using Selectfluor as the electrophilic fluorination reagent in 2008 (Scheme 2) [27]. The regioselectivity was proposed to be determined by the electronic effect, while the reactivity was controlled by the stabilization effect of the aryl group in the allylic cationic intermediates.

Recently, the combination of metal catalysis with electrophilic fluorination has led to the development of new methods for the synthesis of organofluorine compounds (Scheme 2) [28–35]. Liu et al. at SIOC reported a palladium(II)-catalyzed intermolecular fluoroamination of styrenes with NFSI in 2010, which was the first report of the application of NFSI as a source of both nitrogen and fluorine [28]. Shi et al. at ZJU and Xie et al. at SIOC have subsequently reported the first examples of asymmetric fluorination of an unactivated C(sp$^3$)–H bond [34] and highly selective fluorination of the B–H bonds of α-carboranes [35], respectively, by employing palladium catalysis.

Nucleophilic fluorination

Nucleophilic fluorination reactions. Representative nucleophilic fluorination reactions. Representative electrophilic fluorination reactions.
Since 2012, radical fluorination with Selectfluor and NFSI has developed rapidly (Scheme 3) [18]. Li et al. at SIOC reported the first silver-catalyzed decarboxylative radical fluorination of aliphatic carboxylic acids with Selectfluor in aqueous solution [36] in the middle of 2012, when the renaissance in radical fluorination emerged [18]. Since then, a series of novel radical fluorination reactions with Selectfluor or NFSI have been exploited by Chinese chemists [18,37–44].

The asymmetric synthesis of fluorinated molecules via fluorination is also a fascinating aspect of modern organofluorine chemistry [45]. Featured reactions developed by Chinese chemists include diastereoselective electrophilic fluorination-terminated asymmetric tandem reactions and asymmetric electrophilic fluorination-induced rearrangements [46–52]. Ma et al. at Tianjin University (TJU) reported the first stereoselective tandem fluorination reaction in 2007, achieved by performing Nazarov cyclization/electrophilic fluorination using a combination of NFSI and the (R,R)-Ph-BOX-Cu(II) complex to yield fluorine-containing 1-indanone derivatives with the concomitant formation of two new stereocenters with high diastereoselectivity (up to 49/1 trans/cis) and moderate to high enantioselectivity (up to 95.5% ee) (Scheme 4, Eq 1) [46]. Tu et al. at Lanzhou University (LZU) reported a novel asymmetric fluorination/semipinacol rearrangement reaction catalyzed by cinchina-alkaloid derivatives in 2012. Depending on the catalyst, both enantiomers of the corresponding β-fluoroketones were obtained in modest yields with moderate to high ee values (Scheme 4, Eq 2) [48].

**Oxidative fluorination with fluoride ion**

Considering that the fluoride ion is stable and abundant in nature, the direct oxidative fluorination of substrates with a fluoride ion is an ideal alternative method for the current electrophilic fluorination reactions [53]. Among various oxidants, hypervalent iodine compounds are the most usually used mild and selective oxidants.

Liu et al. at SIOC reported a highly regioselective palladium-catalyzed intramolecular aminofluorination of amino-functionalized alkenes using the combination of bis(tert-butylcarboxyloxy)iodobenzene [PhI(OPiv)₂] and AgF (Scheme 5) [54] in 2009. The reaction is believed to proceed through aminopalladation of alkenes followed by oxidative fluorination involving a Pd(IV)−F complex [53]. In recent years, more fluorination reactions have been similarly developed by oxidation of the substrate to form an electrophilic carbon center followed by nucleophilic fluorination either under metal catalysis/mediation or metal-free conditions (Scheme 5) [55–59]. Wang et al. at Tsinghua University have demonstrated the aromatic C−H fluorination of azacalix[1]arene[3]pyridines via Cu(III) using a fluoridesalt and a Cu(II)salt, which provides direct evidence to support the mechanism of copper-mediated fluorination of aryl halides involving a Cu(1)/Cu(III) cycle [6,59].

**DIFLUOROCARBENE**

Difluorocarbene is a versatile and reactive intermediate in organic synthesis. The chemistry of difluorocarbene is an important aspect of organofluorine chemistry [2]. Chen et al. at SIOC have, since the 1980s, reported 18 difluorocarbene precursors by virtue of tetrafluoroethane β-sultone, among which difluoro(fluorosulfonyl)acetic acid (FSO₂CF₂CO₂H) was the first that was reported to generate difluorocarbene under acidic conditions [60]. Chen and Dolbier cooperatively developed trimethylsilyl difluoro(fluorosulfonyl)acetate (FSO₂CF₂CO₂TMS) in 2000, which can release...
difluorocarbene in a controlled, acid-free environment and is one of the most widely used precursors for difluoromethylation of alkenes and alkynes, including electron-poor alkenes such as α,β-unsaturated esters [61,62]. However, in the new millennium, the development of novel difluorocarbene precursors is still highly desirable due to the regulation of the use of ozone-depleting substances (ODS) that are usually employed for the difluoromethylation of heteroatom nucleophiles by the Montreal protocol [63]. Moreover, exploring new reactions of difluorocarbene also requires new precursors that are compatible with various substrates (Scheme 6).

Hu et al. at SIOC have, since 2006, developed several novel difluorocarbene reagents, including the non-ODS-based 2-chloro-2-difluoroacetophenone and chlorodifluoromethyl phenyl sultone for difluoromethylation of O- and N-nucleophiles under aqueous basic conditions, as well as the silicon-based (bromodifluoromethyl) and (chlorodifluoromethyl)trimethylsilane (TMSCF₂Br and TMSCF₂Cl) for versatile difluorocarbene reaction under mild conditions [64,65]. Hu and Prakash cooperatively developed the widely used nucleophilic trifluoromethylation reagent (trifluoromethyl)trimethylsilane (TMSCF₃) as an efficient difluorocarbene source. Xiao et al. at SIOC, in 2013, found that the difluoromethylene ylide precursor difluoromethylene triphenylphosphobetaine (PDFA) could be turned into an efficient difluorocarbene reagent [66–68]. Weng et al. at FZU recently reported one more difluorocarbene reagent, [Cu(phen)₂][O₂CCF₂Cl], the molecular structure of which adopts an ionic form consisting of a [Cu(phen)₂]⁺ cation and a chlorodifluoroacetate anion [69].

By using both newly developed and traditional difluorocarbene reagents, novel synthetic methods including gem-difluoroolefination of diazo compounds [70–72], ¹⁸F-labeled trifluoromethylthiolation [73,74], direct difluoromethylation of aryl boronic acids [75–77] and fluorinative rearrangement of ketones [78–80] have been developed in recent years (Scheme 6).

**TRIFLUOROMETHYLATION AND PERFLUOROALKYLATION**

**Nucleophilic trifluoromethylation and perfluoroalkylation**

The trifluoromethyl group (−CF₃) has a privileged role in agrochemicals and pharmaceuticals because its incorporation into drug candidates could enhance chemical and metabolic stability, improve lipophilicity and bioavailability, and increase protein binding affinity [81]. In addition, trifluoromethylated organic compounds are widely applied in materials science [2].

China’s research on nucleophilic trifluoromethylation dates back to the 1980s. Chen et al. at SIOC devoted a large amount of effort to difluorocarbene chemistry and developed eight types of difluorocarbene reagents, aiming at trifluoromethylating halogenated aromatics and aliphatics via in situ formation of CuCF₃ species [60]. Among them, easily available and stable methyl difluoro(fluorosulfonyl)acetate (FSO₂CF₂CO₂Me) has been widely used with either stoichiometric or catalytic amounts of copper and named ‘Chen’s...
Representative reagents/methods for nucleophilic trifluoromethylation.

\[
\text{Scheme 7.}
\]

Metal-mediated nucleophilic trifluoromethylation.

\[
\text{Scheme 8.}
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A typical application of Chen’s reagent is the first synthesis of 20 \( \pi \)-electron non-aromatic isophlorin \[84, 85\]. Very recently, a new trifluoromethylation reagent copper(II) difluoro(’fluorosulfonyl)acetate \([\text{Cu(O}_2\text{CCF}_2\text{SO}_2\text{F)}_2]\), which easily decomposes to generate active \(\text{CuCF}_3\) species in N,N-dimethylformamide at room temperature, has been conveniently prepared from inexpensive starting materials on a large scale \[86\]. Despite the high efficiency of Chen’s reagents for the trifluoromethylation of aryl, alkenyl and alkyl halohydrocarbons, it is not suitable for the nucleophilic trifluoromethylation of aldehydes, ketones and imines. Hu et al. at SIOC subsequently reported the nucleophilic trifluoromethylation of aldehydes using PhSO_2CF_3 as a practical reagent in 2010, through a magnesium metal-mediated reductive desulfonylation process \(\text{Scheme 7, Eq 3}\) \[87\]. In their continuous research, PhSO_CF_3 was developed as a practical trifluoromethyl source for the preparation of ‘ligandless’ \(\text{CuCF}_3\) species under the activation of potassium tert-butoxide, which can be used as an alternative to the prevailing TMSCF_3 reagent in both copper-mediated nucleophilic and oxidative trifluoromethylation reactions \(\text{Scheme 7, Eq 4}\) \[88\].

Umemoto et al. and others initially developed \(S\)-trifluoromethylsulfonium salts as electrophilic trifluoromethylation reagents \[89\]. Xiao et al. at SIOC first disclosed that the less effective \(S\)-trifluoromethyl-S,S-diphenylsulfonium salt can be reduced by elemental copper to form \(\text{CuCF}_3\) via a single electron transfer (SET) process in 2011 \[90\]. The in-situ formed \(\text{CuCF}_3\) species is of very high reactivity and is capable of effective trifluoromethylation of iodo-substituted heteroaromatic compounds, which is otherwise difficult to achieve \(\text{Scheme 7, Eq 5}\).

By using the trifluoromethyl metal species generated from either the Ruppert-Prakash (TMSCF_3) or Umemoto reagents, several novel nucleophilic trifluoromethylation reactions of aromatic and aliphatic compounds have been disclosed. Hu et al. at SIOC reported a copper-mediated trifluoromethylation of \(\alpha\)-diazo esters as a new method for the preparation of \(\alpha\)-trifluoromethyl esters in 2012. This trifluoromethylation reaction proceeds via the transformation of a trifluoromethylcopper−carbene complex and represents the first example of fluoroalkylation of a non-fluorinated carbene precursor \(\text{Scheme 8, Eq 1}\) \[91\].

Arynes are one of the most useful and structurally unique intermediates in synthetic chemistry. However, the combination of perfluoroalkyl anions with arynes is difficult because of their mismatched reactivities. Hu et al. at SIOC developed an unprecedented one-step protocol for trifluoromethylation of arynes via the use of \(\text{AgCF}_3\) in 2013. This method provides an efficient route to various ortho-trifluoromethylated iodoarenes that are otherwise difficult to synthesize by traditional trifluoromethylation methods \(\text{Scheme 8, Eq 2}\) \[92\].

The Sandmeyer reaction is a classical and fundamental named reaction for the transformation of aryl amines to substituted aromatics via displacement of their diazonium salts with a nucleophile. Wang et al. at Peking University (PKU) and Fu et al. at University of Science and Technology of China (USTC) independently reported the first Sandmeyer-type trifluoromethylation reactions in 2013 by using \(\text{AgCF}_3\) and \(\text{CuCF}_3\), respectively \(\text{Scheme 8, Eq 3}\) \[93, 94\].

The asymmetric nucleophilic trifluoromethylation of carbonyl compounds is challenging due to
the interference of the autocatalytic background reaction [45]. Feng et al. at Sichuan University developed a new combinatorial catalyst system in 2007, composed of the disodium (R)-binaphtholate and a chiral quaternary ammonium salt for enantioselective trifluoromethylation of aromatic aldehydes with TMSCF₃ (Scheme 9, Eq 1) [95,96]. The reaction proceeds in moderate to good enantioselectivity, which represents one of the few examples of highly enantioselective trifluoromethylation of aldehydes. Tang et al. at SIOC reported an asymmetric 1,2-perfluoroalkyl migration reaction of hydrate of 1-perfluoroalkyl-1,2-diketones with chiral alcohols as an alternative method for asymmetric nucleophilic perfluoroalkylation. The reactions are promoted by a Zn(II)/bisoxazoline complex and form enantioenriched α-hydroxy-α-perfluoroalkyl esters (Scheme 9, Eq 2) [97].

**Oxidative trifluoromethylation and perfluoroalkylation**

The study of oxidative perfluoroalkylation has a strong background in China. Huang et al. at SIOC first proposed the direct generation of perfluoroalkyl radicals from perfluoroalkanesulfinate salts through single electron oxidation [98] as early as 1989. In this context, perfluoroalkanesulfinate salts have been developed to be useful perfluoroalkylation reagents for the transformation of alkenes and (hetero)aromatic compounds under the action of various oxidants [5,16]. Langlois, Baran and others have used a similar methodology for trifluoromethylation with CF₃SO₂Na [599–105] since 1991. Liu et al. [102] at LZU’s oxidative decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids is particularly noteworthy. Wang et al. [103] at Sun Yat-sen University’s development of trifluoromethylation oxidative of alkyl boronates is similarly significant.

Qing et al. at SIOC first proposed the concept of ‘oxidative trifluoromethylation’, namely, the reaction of nucleophilic substrates and nucleophilic trifluoromethylation reagents in the presence of oxidants (Scheme 10) [104], in 2010. Mechanically, the reactions proceed through three different pathways: the oxidation of the substrates, the oxidation of the CF₃ anion, and a transition metal-mediated or -catalyzed oxidative coupling reaction. Based on this concept, copper-mediated or -catalyzed or metal-free oxidative C–H trifluoromethylation of terminal alkynes, tertiary amines, arenes, heteroarenes and terminal alkenes was developed. In addition to various C–H bonds, aryl boronic acids are also suitable nucleophilic partners for copper-mediated or -catalyzed cross-coupling reactions with TMSCF₃. They also developed silver-catalyzed hydrotrifluoromethylation of unactivated olefins and silver-mediated O-trifluoromethylation of phenols and alcohols [104–106]. These investigations have explored boronic acids, C–H bonds, P–H bonds and O–H bonds as novel nucleophiles in transition metal-mediated or -catalyzed cross-coupling reactions with TMSCF₃, opening up new avenues for future trifluoromethylation reactions. O-trifluoromethylation constitutes one of the most straightforward methods by which trifluoromethyl ethers can be obtained [9,105,106]. Qing et al. also achieved the oxidative trifluoromethylthiolation of aryl boronic acids and terminal alkynes to synthesize trifluoromethyl sulfoxides by employing TMSCF₃ and S₈ as the CF₃S anion source. All these oxidative trifluoromethylation and trifluoromethylthiolation reactions tolerate a wide range of functional groups, affording structurally diverse CF₃- and CF₃S-containing compounds with high efficiencies, and provide elegant and complementary alternatives to classical trifluoromethylation and trifluoromethylthiolation reactions [104–106]. Similar synthetic strategies have also found application in the trifluoromethylation of primary and secondary
aliphatic and aromatic substrates, and in a variety of carbon−carbon and carbon−heteroatom bond formations.

**Electrophilic trifluoromethylation and perfluoroalkylation**

Electrophilic trifluoromethylation of nucleophilic substrates has been on its way since the development of the Umemoto reagent, which constitutes one of the most popular electrophilic trifluoromethylating agents (Scheme 12) [89]. To date, the trifluoromethylation of many substrates including alkylboronic acids, alkenes, arenes, and organometallic reagents, which had been unattainable by merely relying on the innate reactivity of the Umemoto or Togni reagent, has been achieved by utilizing metal or non-metal catalysis [115–117].

Chemists in China have made elegant contributions to expand the synthetic applications of the Umemoto and Togni reagents. Most of the reports on trifluoromethylative cross-coupling [118, 119], the trifluoromethylative difunctionalization of alkenes (alkynes) [120–123] and trifluoromethylative rearrangements [124–127] can be found in recent comprehensive reviews on trifluoromethylation [8,115].

Liu et al. at USTC and Shen et al. at SIOC independently reported the first copper(I)-catalyzed cross-coupling trifluoromethylations with aryl boronic acids using electrophilic trifluoromethylating reagents under mild conditions in early 2011 (Scheme 13, Eq 1) [128,129]. Xiao et al. at SIOC have developed a reductive system with elemental copper that is also applicable to the trifluoromethylation of aryl boronic acids with S trifluoromethylsulfonium salt in the absence of an additional ligand (Scheme 13, Eq 2) [130].

Buchwald et al. at the Massachusetts Institute of Technology, Wang et al. at PKU and Liu et al. at USTC independently reported, in the middle of 2011, an unprecedented type of reaction for copper(I)-catalyzed direct trifluoromethylation of terminal alkenes to prepare trifluoromethylated allylic compounds using the Togni or Umemoto reagents (Scheme 13, Eq 3) [131–133]. The copper-catalyzed reactions mentioned here constitute early examples of the construction of a C(sp^3)−CF3 bond from alkenes with electrophilic trifluoromethylating agents, and opened the door for the trifluoromethylation transformation of alkenes [8].

Liu et al. at Northeast Normal University first demonstrated, in 2013, that the acyclic hypervalent iodide trifluoromethylating species [PhICF3]^+ can be generated in situ by simple mixing of Ph(OAc)2, TMSCF3, and KF under metal-free conditions [134]. This species is capable of sp^3 C−H trifluoromethylation of indoles with higher reactivity than Togni’s cyclic hypervalent iodine reagent (Scheme 14) [115,134,135].

Furthermore, Chinese chemists have also developed a cooperative catalytic system for trifluoromethylative asymmetric reactions [136,137]. Liu et al. at the South University of Science and Technology of China reported a trifluoromethylation-induced asymmetric C−H functionalization
Scheme 13. Copper-promoted electrophilic trifluoromethylation.

Scheme 14. Phl(OAc)$_2$-mediated oxidative sp$^2$ C–H trifluoromethylation via [PhICF$_3$]$^+$. 

Scheme 15. Dual-catalytic strategy for direct asymmetric electrophilic trifluoromethylation of alkenes via radicals.

reaction for the construction of C–CF$_3$ and C–O bonds by virtue of a copper(I)/Brønsted acid cooperative catalytic system in 2014 (Scheme 15, Eq 1) [136]. This reaction may proceed through radical trifluoromethylation of an unactivated alkene to initiate a subsequent 1,5-hydrogen shift and enantioselective functionalization of $\alpha$–C–H bonds of the amides. Very recently, the same group developed another novel asymmetric radical amidotrifluoromethylation of alkenes [137], providing straightforward access to CF$_3$-containing aza-heterocycles with excellent enantioselectivity (Scheme 15, Eq 2).

In terms of radical trifluoromethylation, in addition to the commonly used reagents, several reagents derived from triflic acid, such as triflones [138–140], triflates [141] and triflyl hydrazides [142], have emerged as novel CF$_3$ radical sources. Perfluoroalkyl halides R$_f$–X (X = I, Br) can form donor–acceptor complexes with heteroatoms such as N, O and S through halogen bonding. Zhu et al. at SIOC reported two different kinds of endless chains of alternating $\alpha$,$\omega$-diodoperfluoroalkane and oxygen in 2001, which represent the earliest examples of stable O...I–R$_f$ complexes [143]. Very recently, this kind of interaction has been applied to initiate radical perfluoroalkylation reactions of R$_f$–X [144].

DIFLUOROMETHYLATION AND DIFLUOROALKYLATION

Difluoromethylation, including difluoromethylation, is a streamlined synthetic methodology for introducing the CF$_2$ and CF$_2$H group into molecules. The CF$_2$ group can function as a bioisostere for an oxygen atom or a carbonyl group, and the CF$_2$H group can be used as a bioisostere of a carbonyl moiety and as a more lipophilic hydrogen bond donor [145]. The selective incorporation of difluoroalkyl groups has gained much attention in recent years [146]. Due to the easy availability of many difluorinated building blocks from the industry, China has unique advantages for the development of difluoromethylation and other difluoroalkylation chemistry. Indeed, Chinese chemists have been leading the development of this field and have made many major contributions [5,145–149].

Nucleophilic difluoromethylation

Di- and monofluoromethylation are featured topics in fluoroalkylation chemistry. Although nucleophilic trifluoromethylation has been known for a long time, less attention has been paid to nucleophilic di- and monofluoromethylation [145,147–149]. Hu et al. at SIOC have studied nucleophilic di- and monofluoromethylation since 2005 [150].

Hu et al. conducted a study of nucleophilic ring-opening fluoroalkylation of epoxides in 2006 that summarized the influence of $\alpha$-fluorine substitution on the chemical reactivities of various carbanions. In this paper, they first proposed a ‘negative fluorine effect’ (NFE) in nucleophilic fluoroalkylation
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Scheme 16. Nucleophilic difluoromethylating reagents and their representative applications.

[151]. Hu et al., guided by the concept of NFE, have subsequently developed several strategies to tune and improve nucleophilic fluoroalkylation reactions. Meanwhile, dozens of original fluoroalkylating reagents and methods have been developed for efficient di- and monofluoromethylation (Scheme 16) [5,64,65,147–149]. Among them, PhSCF2TMS, PhSO2CF2H, PhSO2CF2TMS, (2-Py)SO2CF2H, PhSO(NTBS)CF2H, and (difluoromethyl)trimethylsilane (TMSCF2H) have been successfully used by them and others for a wide range of nucleophilic difluoromethylation reactions.

TMSCF2H, as an analogue of TMSCF3, is a potentially useful CF2H anion source for direct nucleophilic difluoromethylation. However, due to the weaker electron-withdrawing ability of a CF2H group compared to a CF3 group, nucleophilic difluoromethylation with TMSCF2H under mild conditions had been considered to be unattainable. Hu et al. made a systematic study on the difluoromethylation of carbonyl compounds with TMSCF2H in 2011, and were the first to disclose that both the solvent effect and base effect are important for the activation of TMSCF2H, which paved the way for the application of TMSCF2H in direct difluoromethylation reactions [152]. Very recently, during investigation of the difluoromethylation of enolizable ketones, a pentacoordinate silicate intermediate [Me3Si(CF2H)2] anion was observed and characterized for the first time. This species is a very mild nucleophilic difluoromethylating agent and is recognized to be a key intermediate in the difluoromethylation of enolizable ketones [153].

Hu et al. at SIOC developed the first highly stereoselective difluoromethylation of carbonyl compounds in 2012, by employing a ‘choreographed’ chiral S-difluoromethyl sulfoximine reagent [154]. The chemistry of fluorinated sulfoximines, which originate from the research on fluorinated sulfoxides, not only provides useful methods for synthesizing organofluorine compounds, but also expands our knowledge of sulfoximine chemistry and represents a featured topic in organofluorine chemistry [155].

Hu et al. used the (2-Py)SO2CF2H reagent initially designed for gem-difluoroolefination to develop a formal nucleophilic iodo- and bromodifluoromethylation method for carbonyl compounds by ‘hijacking’ of the sulfinate intermediates in the Julia–Kocienski reaction [156]. This work is the first example concerning the application of the Julia–Kocienski olefination intermediate for a non-olefination reaction and has inspired the further investigation of nucleophilic halodifluoromethylation [157,158].

Since the first publication of direct nucleophilic difluoromethylation, TMSCF2H has been used by many groups for various transformations [153, 159–161]. Qing et al. at SIOC reported copper-mediated direct difluoromethylation of electron-deficient aryl iodides (Scheme 17, Eq 1) [159]. Shen et al. at SIOC have developed a cooperative dual palladium/silver catalyst system for direct difluoromethylation of aryl bromides and iodides (Scheme 17, Eq 2) [160,161]. This difluoromethylation method is compatible with a wide range of functional groups, including both electron-rich and electron-poor groups.

Scheme 17. Metal-mediated/catalyzed direct difluoromethylation of aryl halides.

Electrophilic difluoromethylation

Chen et al. at SIOC reported a smooth reaction of HCF2I with alkenes and alkynes in the presence of Na2S2O4, providing difluoromethylated adducts in moderate to good yields [162], as early as 1994. However, HCF2I is not an ideal difluoromethylation
Electrophilic difluoromethylating reagents and their representative applications.

Hu et al. at SIOC, by taking advantage of the excellent softening ability of sulfur on the 'hard' fluorine and the 'chemical chameleon' character of the phenylsulfonyl and related groups, flipped the reactivity of fluorinated sulfones from nucleophilicity to electrophilicity by slightly changing the substituents and thus invented a series of electrophilic difluoromethylating reagents, ranging from sulfones, sulfoximines and sulfinates (Scheme 18) [5,139,163]. Together with the developed difluorocarbene reagents [64], these reagents have been successfully used to exploit novel or practical electrophilic difluoromethylation reactions. Hu et al. reported the first examples of decarboxylative fluoroalkylation of α,β-, and β,γ-unsaturated carboxylic acids by employing the I(III)-CF₂SO₂Ph reagent [164,165]. Very recently, heteroaryl difluoromethyl sulfones have been exploited for practical radical difluoromethylation under photocatalysis. Note that this radical fluoroalkylation strategy is capable of incorporating both difluoromethyl and many other fluoroalkyl groups such as trifluoromethyl, difluoromethyl and monofluoromethyl groups [139]. Qing et al. at SIOC have also reported the use of bromodifluoromethyl- and difluoromethyltriphenylphosphonium bromide as an alternative photocatalyzed radical difluoromethylation reagent [166,167].

Previously, the electrophilic difluoromethylation of heteroatoms mainly relied on difluorocarbene reagents. Mechanistically, the CF₂H group is not introduced as a whole, but is constructed via a stepwise reaction involving the protonation of a difluorinated carbanion intermediate. In this context, Shen et al. at SIOC developed a S-difluoromethylsulfonylpyrrolidone for direct electrophilic difluoromethylation of alcohols [168].

Representative nucleophilic difluoroalkylation reactions.

Nucleophilic difluoroalkylation

Nucleophilic difluoroalkylation involving the introduction of a functionalized difluormethyl anion or its equivalent is a traditional research topic [146]. In recent years, the development of asymmetric synthesis and metal catalysis has extended the research scope of this topic.

Zhou et al. at East China Normal University reported a highly efficient ‘on-water’, catalyst-free nucleophilic addition reaction of silyl difluorenol ethers in 2014, which exhibits dramatic fluorine effects. The C–F/H–O interactions between difluorinated enol ethers and the hydrogen bond network of water at the phase boundary of the reactants may promote the formation of a unique microstructure, thus facilitating the ‘on-water’ catalyst-free addition reaction (Scheme 19, Eq 1) [169]. Zhou et al. subsequently developed a chiral secondary amine phosphoramide catalyst for the highly enantioselective Michael addition of both difluorinated enol silyl ethers to tetrasubstituted olefins [170], which belongs to one of the few examples of efficient syntheses of quaternary chiral carbon atoms with a mono- or difluoroalkyl group (Scheme 19, Eq 2). Hao et al. at Shanghai University first studied the copper(0)-promoted direct reductive gem-difluoromethylation of aryl or alkenyl halides with bromodifluoromethylated heteroaromatics, expanding the scope of...
The field of electrophilic difluoroalkylation has undergone rapid development over the last five years [172–187]. Shen, Lu and coworkers at SIOC reported the first example of copper-mediated difluoroalkylation of aryl boronic acids in the presence of air in 2012 [172]. The reaction is able to proceed smoothly under mild conditions without the addition of ligands, but it is essential to use a stoichiometric amount of copper powder and a relatively expensive fluoroalkyl iodide.

Zhang et al. at SIOC have, since 2014, systematically studied the palladium- or nickel-catalyzed difluoroalkylation of boronic acids with a broad range of functionalized halodifluoroalkylating reagents such as bromodifluoroacetates, bromodifluorophosphonates, bromodifluoromethyl alkenes, bromodifluoromethyl alkynes and even unactivated 1-bromo-1,1-difluoroalkanes (Scheme 20) [173–177]. When the catalyst is used with nickel, which is abundant in nature, the organic boronic acid is capable of reacting with a less reactive chlorodifluoroalkylating agent. Moreover, the first example of a transition metal-catalyzed carbonylation-fluoroalkylation reaction has been achieved by using a palladium catalyst in the presence of CO [178]. Zhang et al. at SIOC and Wang et al. at USTC have, complementarily, reported palladium- and nickel-catalyzed difluoroalkylation of alkenes, respectively [179,180]. These investigations not only broaden the scope of electrophilic difluoroalkylation, but also reveal the principle that metal catalysts such as palladium and nickel exhibit higher activities in difluoroalkylation than perfluoroalkylation.

Recent advances in photocatalysis with visible light have provided new opportunities for electrophilic difluoroalkylation with bromodifluoroalkylated compounds [181–184], and representative work in China has been summarized in a recent review [185].

**MONOFLUOROMETHYLATION AND MONOFLUOROALKYLATION**

**Nucleophilic monofluoromethylation**

Hu et al. at SIOC have recently developed several unprecedented nucleophilic monofluoromethylation methods (Scheme 21) [5]. In 2006, they reported the first stereoselective nucleophilic monofluoromethylation with fluoromethyl phenyl sulfone (PhSO₂CH₂F) and imines [188]. More recently, the first highly stereoselective synthesis of fluorinated cyclopropanes and nucleophilic monofluoromethylation of ketones has been realized by using fluorinated sulfoximine reagents [189].

**Electrophilic monofluoromethylation**

N-Tosyl-S-monofluoromethyl-S-phenylsulfoximine has been used as a new efficient monofluoromethylation reagent for O-, S-, N- and P-nucleophiles.
Scheme 22. Asymmetric deacetylative aldol reaction of substituted 2-Fluoro-1,3-diketones.

Scheme 23. Metal-catalyzed trifluoroalkylation reactions.

The preliminary mechanistic study suggests that the reaction proceeds through a radical mechanism involving a SET process. This is the first example of a trifluoroalkylation using a sulfoximine as a trifluoroalkyl radical precursor [190].

In the case of metal-catalyzed reactions, examples of electrophilic monofluoromethylation of arylboronic esters [191], arylboronic acids [192,193] and isocyanides [139,194] employing the monofluorinated alkyl halides have been reported. Of note is the use of CH$_2$FI and CH$_2$FBr as the direct monofluoromethylating reagents [191,193].

**Nucleophilic monofluoroalkylations**

Asymmetric alkylation of an activated fluorinated methylene carbon is an important method for the construction of a fluorinated chiral carbon center [195,196]. Han et al. at Nanjing University reported the first asymmetric deacetylative aldol reaction of substituted 2-fluoro-1,3-diketones in 2015, providing a new approach for the preparation of biologically relevant products containing C–F quaternary stereogenic centers (Scheme 22) [196].

Xu et al. at Xiamen University recently reported an efficient and highly chemoselective electrochemical intramolecular oxidative cross-coupling reaction of activated monofluoroalkanes with electron-rich arenes employing Cp$_2$Fe as the redox catalyst, which was proved to be a straightforward, modular and efficient approach for the synthesis of functionalized 3-fluorooxindoles [197].

**TRIFLUOROALKYLATION**

$\beta,\beta,\beta$-Trifluoroalkylation is an alternative approach for incorporating a trifluoromethyl group, which is an important topic of organofluorine chemistry due to the unique $\beta$-fluorine effect. Previously, much attention has been paid to the chemistry of activated $\alpha$-trifluoromethyl carbanions (2,2,2-trifluoroalkane anion) and organometallic species, whose spontaneous release of fluoride ions to produce difluoroalkanes was inhibited by the activation groups. However, the use of non-activated (2,2,2-trifluoroalkyl)metal species in trifluoroalkylation had been largely unexplored.

Hu et al. at SIOC developed the first palladium-catalyzed 2,2,2-trifluoroethylation reaction by using the readily available reagent CF$_3$CH$_2$I in 2012, proceeding through the reductive elimination of the Ar–Pd(II)–CH$_2$CF$_3$ intermediate accelerated by a phosphine ligand (Scheme 23, Eq 1) [198]. Fu et al. at California Institute of Technology and Zhang et al. at SIOC have independently reported nickel-catalyzed 2,2,2-trifluoroalkylation reactions by using transition metal catalysis (Scheme 23, Eq 2) [199,200]. Transition metal catalysis has also found applications in the cascade C–H trifluoroethylation-Heck reaction of aryl iodides with CF$_3$CH$_2$I [201], fluorinative coupling with gem-difluoroolefins [202,203], as well as trifluoroethylation of alkynes [204], aryl boronic acids [205] and heteroatom-nucleophiles [206] with 2,2,2-trifluorodiazoethane (CF$_3$CHN$_2$). Xiao et al. at SIOC have further developed the trifluoroethylidenation reaction with trifluoroethylsulfonium triflate by utilizing fluoride salt as the base to inhibit $\beta$-fluorine elimination [207].

**TRI- AND DIFLUOROMETHYLTHIOLATION**

The trifluoromethylthio group ($-$SCF$_3$) is an important structural motif in many pharmaceuticals and agrochemicals because of its high lipophilicity and strong electron-withdrawing properties [14, 208,209]. Chen et al. at SIOC reported, as early as 1993, a direct trifluoromethylthiolation reaction of aryl halides employing elemental sulfur and the trifluoromethylating reagent FSO$_2$CF$_2$CO$_2$Me under the promotion of a stoichiometric amount of copper iodide [210]. However, the concept of trifluoromethylthiolation has only become prevalent in recent years. Qing et al. at SIOC developed copper-catalyzed oxidative trifluoromethylthiolation of aryl boronic acids, TMSCF$_3$ and elemental sulfur in 2012 [211]. Tang et al. at Nankai University and Chen et al. simultaneously demonstrated the first example of oxidative trifluoromethylthiolation of unactivated C(sp$^3$)-H bond in 2014 by using silver trifluoromethylthiolate (AgSCF$_3$) as the reagent [212,213].
Representativemethodsfor
gem-difluoroolefination.

FLUOROOOLEFINATION AND FURTHER TRANSFORMATIONS

gem-difluoroolefination

Fluoroalkenes are structurally unique fluoroorganic compounds in materials, medicinal and synthetic chemistry [222, 223]. Previously, the most important method for gem-difluoroolefination of carbonyl compounds was the Wittig-type reaction using ClCF₂CO₂Na or CF₂Br₂ [223]. Hu et al. at SIOC reported the first Julia–Kocienski-type gem-difluoroolefination reaction with a previously unknown compound in 2010, difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H), providing facile access to 1,1-difluoroalkenes from carbonyl compounds (Scheme 25) [224]. It is worth noting that difluoromethyl 2-pyridyl sulfone exhibits unexpectedly better reactivity in gem-difluoroolefination reactions than other difluoromethyl heteroaryl sulfones. Since then, the synthesis and transformation of 1,1-difluoroalkenes has attracted the attention of many chemists. Xiao et al. at SIOC revisited Fuqua’s Wittig-type olefination in 2013, using ClCF₂CO₂Na and Ph₃P, and isolated the key reaction intermediate PDFA, which has become an important gem-difluoroolefination reagent towards aldehydes under neutral conditions (Scheme 25) [66]. They also modified 2-PySO₂CF₂H and developed a decarboxylative Julia–Kocienski reaction of aldehydes [225]. Hu et al., Wang et al. and Xiao et al. have independently developed gem-difluoroolefination via transformation of diazo compounds, in addition to carbonyl olefination [70–72, 205, 226].
Scheme 26. Representative transformations of gem-difluoroolefins.

Scheme 27. Highly stereoselective synthesis of monofluoroalkenes.

Transformation of gem-difluoroolefins

The C–F bond is commonly regarded as the strongest single bond formed with carbon, and the selective activation of the C–F bond has emerged as an interesting methodology to obtain fluorinated compounds [227]. Chinese chemists began to investigate the selective cleavage of C–F bonds in the 1980s. Huang et al. at SIOC found that the ‘Cr-H’ species could enable defluorinative hydrogenation of the trimer of perfluorinated propylene [15]. Over the last five years, numerous efforts have been made to develop useful reactions via the selective cleavage of C–F bonds in gem-difluoroolefins (Scheme 26) [228–231]. Cao et al. at East China University of Science and Technology recently summarized advances in this research area [223].

On the other hand, fluoride addition-induced β,β,β-trifluoroalkylation with difluoroolefins has been developed as a new method for the transformation of gem-difluoroolefins [232,233], which is highly efficient for the generation of β,β,β-trifluorinated carbanions compared to the traditional deprotonative approach (Scheme 26). Hu et al. at SIOC reported an AgF-mediated fluorinative homocoupling of gem-difluoroolefins in 2014 [234]. On the basis of this finding, a AgF-mediated fluorinative cross-coupling of gem-difluoroolefins and non-fluorinated olefins was developed for the first time (Scheme 26) [202]. Loh et al. at Nanjing Tech University more recently demonstrated a palladium-catalyzed allylic β,β,β-trifluoroalkylation by using similar method (Scheme 26) [203].

Monofluoroolefination

For monofluoroolefination, controlling Z/E-stereoselectivity still remains a challenging task. In the past decade, scholars of China have developed a series of stereoselective monofluoroolefination methods. Hu et al. at SIOC disclosed a novel olefination method for the first highly stereoselective one-step synthesis of Z-monofluoroalkenes by reacting nitrones with the fluorosulfoximine reagents in 2009 (Scheme 27) [235]. Very recently, by slightly changing the S-substituent of sulfoximine from phenyl to 2-pyridyl with a modification of the electronic property of the N-substituent, the highly stereoselective carbonyl olefination for both di- and trisubstituted terminal monofluoroalkenes has become reality (Scheme 27) [236]. Interestingly, although the sulfonyl group is not a good stereocontrol element, it can facilitate isomer separation. Thus, monofluoroolefination with 2-pyridyl sulfone reagents has led to the easy preparation of both isomers of monofluoroalkenes in one pot, which is due to the spontaneous kinetic resolution of the syn-/anti-sulfinate intermediates during their decomposition to Z/E-monofluoroalkenes [237]. In addition to the direct construction of C=C bonds, the functionalization of gem-difluoroolefins [223,228] and gem-difluorocyclopropanes [238] via selective activation of the C–F bonds has also been exploited for the stereoselective synthesis of monofluoroalkenes.

POLYFLUOROARYLATION AND FURTHER TRANSFORMATION

Polyfluoroarylation

Perfluorinated aromatic rings are prominent structural motifs that have numerous applications in materials and life science. Chen et al. at SIOC studied the photoinduced reactions of perfluoroaryl perfluoro- and polyfluoroalkanesulphonates (RSO₂C₆F₅) for the synthesis of
pentafluorophenylated molecules as early as the 1990s [239]. Zhang et al. at SIOC first reported palladium-catalyzed dehydrogenative cross-coupling of polyfluoroarenes with activated alkenes and heteroaromatics under the action of a silver salt in 2010 (Scheme 28) [240–242]. A series of perfluoroarene-containing compounds were synthesized with potential applications in functional materials for electronic devices. Su et al. at the Fujian Institute of Research on the Structure of Matter [243] and Shi et al. at PKU [244] shortly after reported similar reactions for the C–H/C–H cross-coupling of polyfluoroarenes and simple arenes. Of note, these recent reports constitute the few early examples of oxidative coupling reactions with electron-deficient arenes. This concept has been extended to oxidative polyfluoroarylation of aromatic carboxylic acids [245], aromatic sulfinate salts [246] and aryl ethyl ketones [247].

In addition to palladium-catalyzed oxidative polyfluoroarylation, the palladium/copper-cocatalyzed Tsuji–Trost allylation of polyfluoroarenes [248], copper-catalyzed alkylation of polyfluoroarenes [249] and copper-catalyzed decarboxylative coupling of potassium polyfluorobenzoates with aryl halides [250] have also been developed, broadening the scope of polyfluoroarylation reactions.

**Selective C–F bond activation of polyfluoroarenes**

Li et al. at Shandong University reported the selective C–F bond activation of fluorine-containing arenes in the presence of stoichiometric amounts of cobalt or iron complexes in 2006 [251,252]. Although many methods have been developed for the selective cleavage of C–F bonds, either catalytically or stoichiometrically, most of them are based on the electronic effects of the substituents [253,254]. Zhang et al. at SIOC and others have investigated the chelating group-oriented ortho-selective C–F activation of polyfluoroarenes since 2012 (Scheme 29) [255–260].

**SYNTHESIS WITH FLUORINATED SUBSTRATES**

Synthesis with fluorinated building blocks/substrates is a very important method for the introduction of fluorine atoms or fluoroalkyl groups into target molecules. In the building blocks/substrates, where the fluorine or fluoroalkyl substitution is directly connected at a reactive site, the fluorine effect has significant influence on the outcome of their reactions. Indeed, most of this review has concentrated on synthesis with fluorinated building blocks, either C-1 or C-2. Ma et al. at TJU have published a comprehensive review on asymmetric synthesis with prochiral trifluoromethylated substrates [261]. Here, we only list some tri- or difluorinated substrates recently designed or extensively studied by Chinese chemists (Scheme 30) [262–270] to demonstrate that the transformation of fluorinated substrates has attracted extensive attention in China.
CONCLUSIONS

The past 16 years has witnessed rapid development of Chinese synthetic organofluorine chemistry. On the one hand, a number of novel fluoroalkylation reagents have been developed to facilitate the introduction of privileged fluorine-containing groups, which can impart desirable chemical and biological properties on organic molecules such as materials, pharmaceuticals and agrochemicals. On the other hand, many new methods for the construction of C–F bonds and fluoroalkyl bonds with known fluorination and fluoroalkylation reagents have been developed, which permits the preparation of fluorinated molecules with structural diversity.

However, most of the new strategies still lack practicality and cost efficiency with regard to industrial production. Future research will need to focus on the development of green synthetic methods for the more general and practical introduction of fluorine atoms and fluoroalkyl groups, which is in line with the concept of sustainable development advocated by Chinese government. Because the formation of C–F bonds is the basic foundation of organofluorine chemistry, the development of efficient fluorination methods with inorganic fluorides is also highly desirable.

In the future, attention should also be paid to challenging tasks such as synthesis of trifluoromethyl ethers (ROCF₃) \[9,105,106,271–275\], synthesis of pentafluorosulfanyl compounds (RSF₅) \[10\], \[^{18}F\] radiisotope-labeled synthesis of organic molecules for positron emission tomography \[11\], as well as region- and stereoselective fluorination and fluoroalkylation \[45\]. Moreover, exploiting new methods for the conversion of difluorocarbene and fluorinated alkenes, both of which have a close relationship with fluorinated polymers, is also a fascinating field that deserves much attention.

Since nature lacks efficient mechanisms to construct C–F bonds, almost all organofluorine compounds that we use today have to be man-made. Therefore, synthetic organofluorine chemistry in China still has a long way to go, not only to meet the increasing demand for various organic fluorochemicals, but also to gain deeper insights into the unique features of fluorine in organic reactions and related sciences. Last but not least, we would like to emphasize that fluorspar, as the most basic material for developing organofluorine chemistry and industry, is a limited and non-renewable natural resource in China, so we must make rational utilization of fluorspar deposits and develop new methods and technologies for the recovery and reuse of fluorochemicals.

FUNDING

This work was supported by the National Natural Science Foundation of China (21632009, 21472221, 21421002 and 21372246), the National Basic Research Program of China (2015CB931900), the Key Programs of the Chinese Academy of Sciences (KZGD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), the Shanghai Academic Research Leader Program (15XD1504400), the Shanghai Rising-Star Program (16QA1404600), and the Youth Innovation Promotion Association CAS (2014231).

Conflict of interest statement. None declared.

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