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Abstract:
Fluoroform (CF_3H), a large-volume industrial by-product and potent greenhouse gas, has emerged as an attractive CF_3 source for the development of trifluoromethylation reagents and reactions. This article highlights the recent reports since 2017 on the use of fluoroform in organic synthesis. Topics include direct trifluoromethylation facilitated by organic and inorganic bases, preparation of trifluoromethylation reagents based on transition metals and borazine, and radiolabelled fluoroform.

1. Introduction

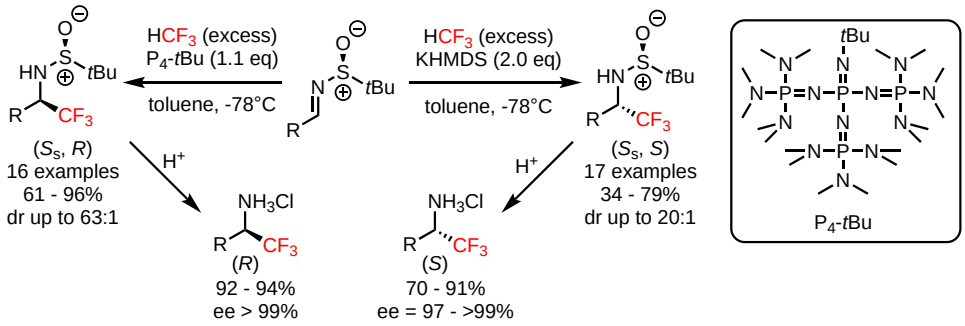
Reaction of chloroform ($CHCl_3$) and hydrogen fluoride (HF) in the presence of antimony pentachloride ($SbCl_5$) as a catalyst produces chlorodifluoromethane ($CHClF_2$ or HCFC-22) that is a gas employed in refrigeration and air conditioners, in foam manufacturing as a blowing agent (dispersive uses), and in synthetic polymer manufacture, in particular Teflon, (non-dispersive use). An unavoidable by-product generated by over-fluorination of chloroform is fluoroform (trifluoromethane, CHF_3 or HFC-23), which is produced in various amounts depending on plant-specific conditions and, until recently, mostly vented to the atmosphere. Fluoroform is a non-flammable and non-toxic gas, it is not an ozone depleting substance but is a very potent greenhouse gas with the highest global warming potential (GWP) of hydrofluorocarbons (HFCs) (12690, 100-year GWP) and an approximatively 228 years atmospheric lifetime [1]. An estimate of global HFC-23 emission in 2018 was 15.9 ± 0.9 Gg yr^{-1} (Gg yr^{-1} = 1000 tonnes/year) [1] and it corresponds to an average of 4% by-product in the manufacturing of HCFC-22 [2]. In rare cases, fluoroform is captured, purified and commercialized but so far remains a small market speciality chemical; it is clearly considered as a waste. Efforts are directed toward reduction of HFC-23 emissions that include incineration or recycling through a fluorine-chlorine exchange reaction to afford HCFC-22; however, these processes are costly because highly energy demanding [3]. Besides, there is a large upsurge in demand to transform this waste into high-value chemicals [4]. Achieving this goal will reduce the negative environmental impacts and create great opportunities in organofluorine chemistry. In this highlight, we present the most recent works from 2017 to present dedicated to the valorisation of fluoroform. The direct trifluoromethylation is presented in section 2 followed by fluoroform-derived MCF_3 (section 3) and other trifluoromethylation reagent (section 4). Finally, radiolabelled fluoroform is discussed (section 5).

2. Direct trifluoromethylation using fluoroform

Fluoroform is the simplest CF_3-containing synthon with only a H atom attached, the most straightforward way to utilize it is to deprotonate it and generate CF_3^- anion. However, fluoroform is only weakly acidic with a pKa of 25–28 and rather inert. In addition, due to the instability of CF_3^- anion, it can easily go through α-fluoride elimination with alkali metal cation and generate CF_2 carbene [5], which is not the desired pathway for trifluoromethylation. Therefore, the exploration of suitable reaction conditions is crucial for

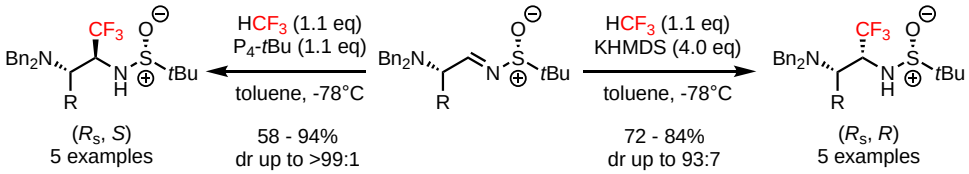
the direct trifluoromethylation using fluoroform, including base, solvent, temperature, additive, etc. In fact, several studies on base-promoted deprotonation of fluoroform have been reported since 1990s, including the use of potassium *tert*-butoxide (*t*-BuOK) or potassium dimsylate [5-9], silicon-containing bases [10, 11], phosphazene bases, [12-14] and electrogenerated bases from 2-pyrrolidinone [15] and iodobenzene [16].

In 2013, Shibata and co-workers [12] discovered that 1-*tert*-butyl-4,4,4- tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene) (P_4-*t*Bu) could be a suitable organo-superbase for the deprotonation of fluoroform at low temperature to generate "naked" CF_3^- anion due to the demanding steric hindrance of the cation. This reagent was applied to the trifluoromethylation of aldehydes, ketones and sulfonyl fluorides, even with catalytic amounts of the superbase [14]. Later, the same group extended the reaction scope to the trifluoromethylation of *N*-sulfinimines [9, 17]. By using (S_s)-*tert*-butanesulfinyl group as a chiral auxiliary, stereodivergent trifluoromethylation of aldimines with fluoroform was achieved with either P_4-*t*Bu or potassium bis(trimethylsilyl)amide (KHMDS) as base, from which both enantioenriched (*R*)- or (*S*)-α-CF_3 amines (ee up to >99%) could be obtained in good yields upon acidic hydrolysis (Scheme 1).

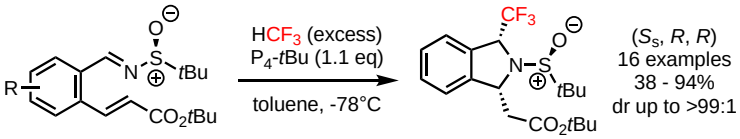


Scheme 1. Stereodivergent trifluoromethylation of *N*-sulfinylimines.

The stereodivergent outcome was explained by the distinction of open or chelated transition states under organic or metallic base system, which could generate a "naked" or chelated CF_3^- anion. More recently, they extended the number of stereogenic centers from one to two in similar reactions by applying enantiopure amino sulfinimines as substrates to obtain chiral CF_3-containing diamines (Scheme 2) [18]. Also, 1-CF_3 isoindolines could be synthesized in high dr values through a tandem nucleophilic addition/intramolecular aza-Michael sequence (Scheme 3) [18].

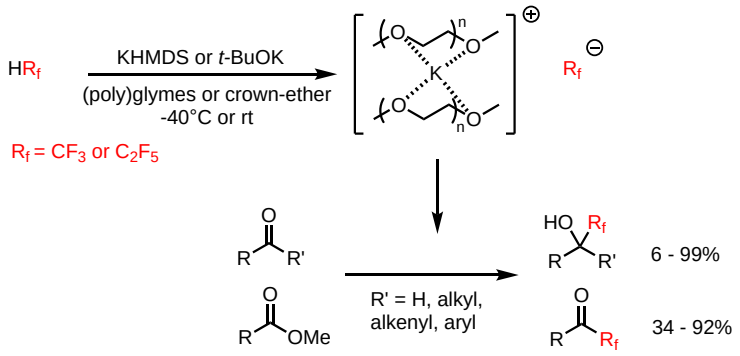


Scheme 2. Stereodivergent diastereoselective synthesis of enantioenriched trifluoromethylated ethylenediamines.

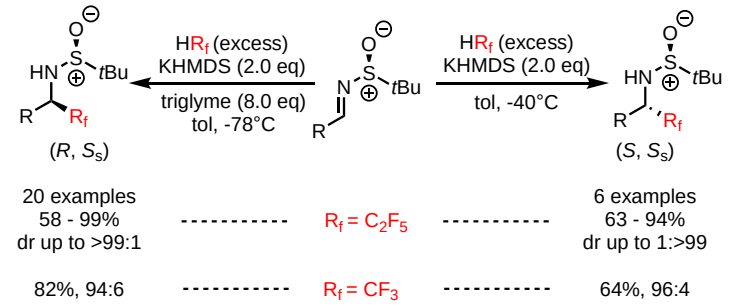


Scheme 3. Diastereoselective synthesis of enantioenriched isoindolines.

In addition to the use of phosphazene and potassium hexamethyldisilazide as bases, the use of *t*-BuOK was further investigated by Shibata's group. Prakash and co-workers had previously reported that using 18-crown-6 with *t*-BuOK could help to stabilize the coordination of K^+ and CF_3^- thus preventing the decomposition of the latter via α-F elimination [5]. (Poly)glymes were found to be as useful in base-promoted trifluoromethylation with fluoroform following similar principle (Scheme 4) [19, 20]. Under this protocol, nucleophilic trifluoromethylation of aldehydes, ketones and esters could be achieved even at room temperature, and the C_2F_5 version was also applicable using pentafluoroethane (HC_2F_5, HFC-125) as the R_f source (Scheme 4) [21, 22]. Analogous stereodivergent trifluoromethylation and pentafluoroethylation of *N*-sulfinylimines were realized using the additive triglyme, in which the key differentiation was whether the R_f^- anion was generated in a "naked" or chelated manner (Scheme 5) [22].



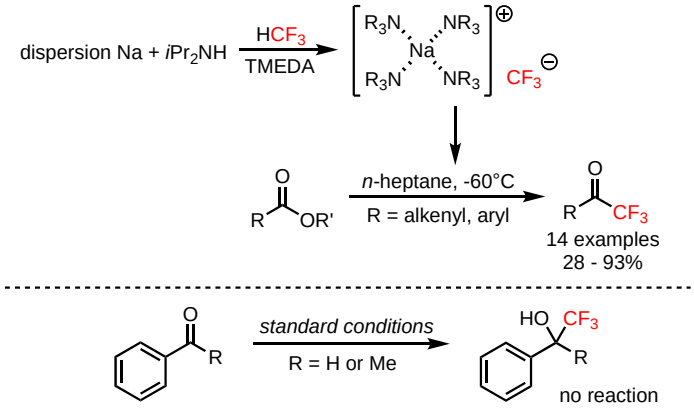
Scheme 4. Glymes and crown ethers to generate naked CF_3^- anion.



Scheme 5. KHMDS/triglyme cryptate as an alternative to P_4-*t*Bu.

Combining KHMDS with triglyme was found to be effective for synthesizing trifluoromethylketones from esters using fluoroform under continuous flow by Shibata and co-workers [23]. The sodium cation was also compatible, as demonstrated in the use of sodium diisopropylamide (NaDA) with trialkylamine and tetramethylethylenediamine (TMEDA) to achieve base-promoted trifluoromethylation of aromatic esters with fluoroform by Han, Lian and co-workers (Scheme 6) [24]. This cationic chelating system was *in situ*

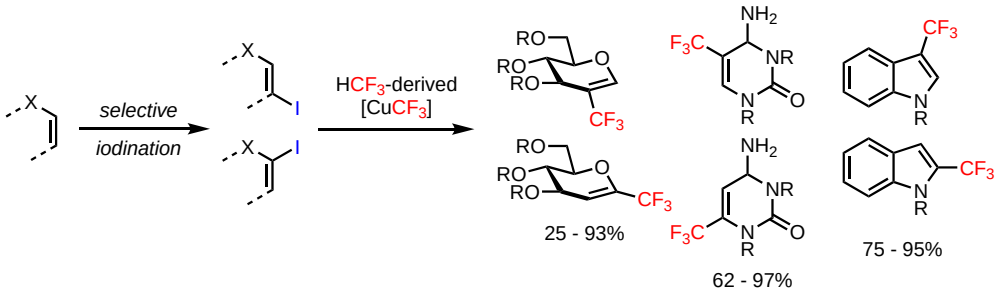
generated by sodium metal and stabilized with bulky amine ligands at low temperature. Such stabilization effect suggested the existence of the reactive $NaCF_3$ species besides previously mentioned KCF_3, despite the strong Na-F interaction which could lead to decomposition of CF_3^- anion. However, the protocol was not applicable to aldehydes or enolizable ketones due to chemoselectivity issue (Scheme 6).



Scheme 6. $NaCF_3$ species in trifluoromethylation of aromatic esters.

3. Transition metal-based trifluoromethylation reagents derived from fluoroform

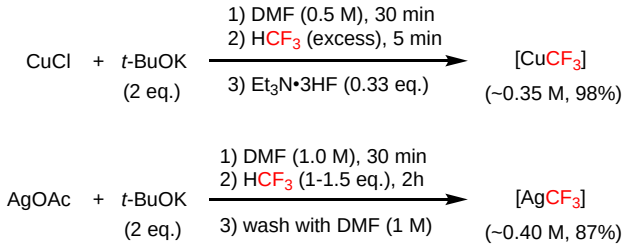
In 2011, Grushin and co-workers developed the first direct cupration of fluoroform to generate a "ligandless" [$CuCF_3$] reagent [25]. The utility and versatility of this reagent have been subsequently showcased in a multitude of trifluoromethylation reactions [26-32]. Tsui and co-workers [33] have explored new reactivities of Grushin's fluoroform-derived [$CuCF_3$], particularly in oxidative processes, to broaden its applications towards the preparation of valuable CF_3-containing building blocks and heterocycles under aerobic conditions. Quite recently, the trifluoromethylation of alkenyl iodide with fluoroform-derived [$CuCF_3$] was developed by Boutureira and co-workers [34]. This process allowed several types of glycals, nucleoside, nitrogenous bases and benzo-fused heterocycles to be trifluoromethylated at specific positions enabled by well-established selective iodination of the alkene (Scheme 7). This method showed an alternative strategy for selective trifluoromethylation of substituted alkenes in biomolecules that can be useful for late-stage functionalization.



Scheme 7. Trifluoromethylation of alkenyl iodides from biomolecules.

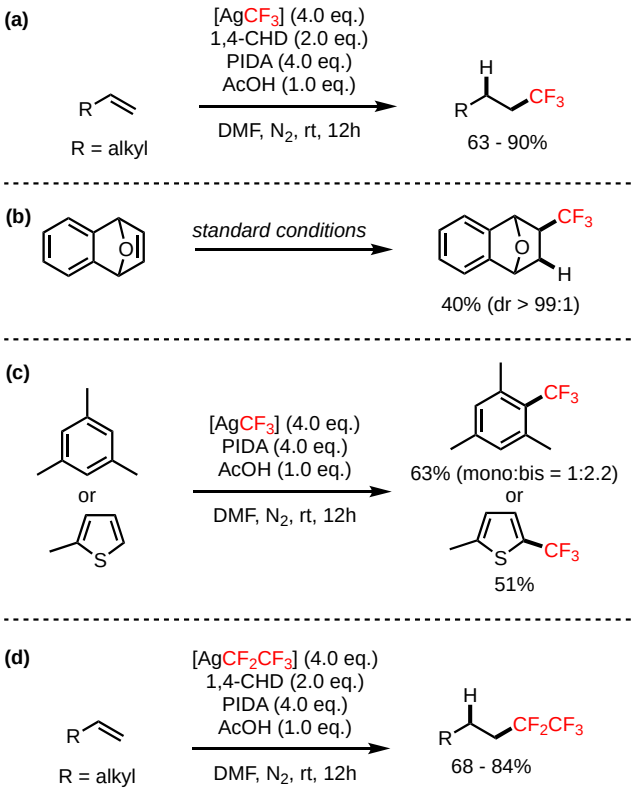
Besides [$CuCF_3$], Qing and co-workers described the direct argentination of fluoroform in 2019 to prepare a [$AgCF_3$] solution [35]. The fluoroform-derived [$AgCF_3$] was obtained through a similar protocol in a slightly higher concentration (Scheme 8). Instead of bubbling

the gaseous HCF_3 into the reaction, a stoichiometric or slightly excess amount of HCF_3 could already give $[AgCF_3]$ in good yield. Notably, the $[AgCF_3]$ solution was quite stable without the stabilizer TREAT-HF, although it was still sensitive to light due to the property of silver. Nevertheless, unlike previously reported $[AgCF_3]$ solution prepared from AgF and $TMSCF_3$, this $[AgCF_3]$ generated from fluoroform showed greater stability towards air and heat due to the effect of *t*-BuOK.



Scheme 8. Preparation of $[CuCF_3]$ and $[AgCF_3]$ reagents from fluoroform.

Despite being a more precious metal than copper, the $[AgCF_3]$ reagent showed unique reactivities such as hydrotrifluoromethylation of non-activated alkenes, which had not been achieved by $[CuCF_3]$. Since $[AgCF_3]$ was too stable to go through spontaneous homolysis under air, an extra oxidant $PhI(OAc)_2$ (PIDA) was needed to promote the generation of CF_3 radical. By using 1,4-cyclohexadiene (1,4-CHD) as H source and AcOH as additive, the anti-Markovnikov hydrotrifluoromethylation products were obtained in 63–90% yields from non-activated terminal alkenes (Scheme 9a). An internal alkene was also demonstrated albeit with a lower yield (Scheme 9b). Besides hydrotrifluoromethylation, C-H trifluoromethylation of electron-rich (hetero)arenes could also be achieved with moderate yields, although overreaction was a potential problem (Scheme 9c). This protocol could be extended to pentafluoroethylation by using gaseous HCF_2CF_3 to generate $[AgCF_2CF_3]$, and the hydropentafluoroethylation products were obtained at 68–84% yields under similar conditions (Scheme 9d).

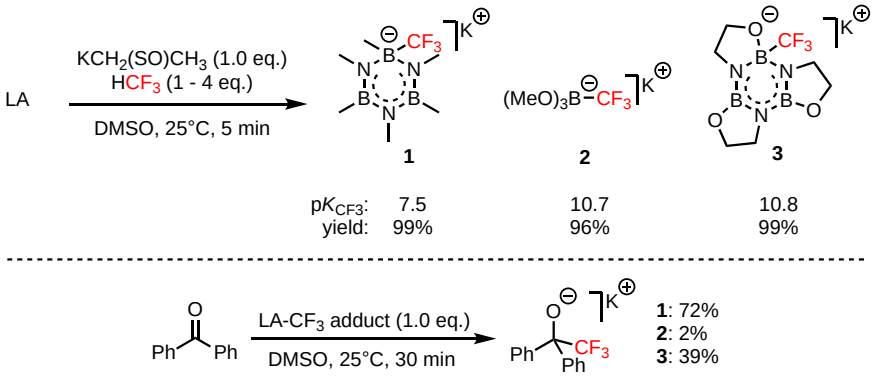


Scheme 9. Applications of [$AgCF_3$] and [$AgCF_2CF_3$] reagents.

4. Other trifluoromethylation reagents derived from fluoroform

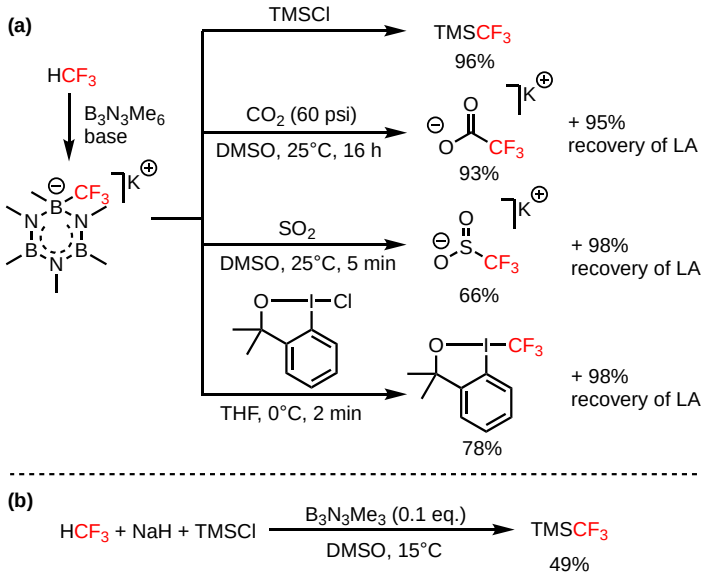
Direct use of fluoroform or using fluoroform-derived MCF_3 reagents for trifluoromethylation can be limited by functional group tolerability and reagent stability/reactivity, thus new routes for preparing stable yet reactive trifluoromethylation reagents from fluoroform is worth exploring. It was not until 2012 that Prakash and co-workers developed the method of using fluoroform to synthesize several commonly used trifluoromethylation reagents including $TMSCF_3$ and CF_3BF_3K, which can serve as nucleophilic, electrophilic and radical CF_3 sources [36].

In 2017, Szymczak and co-workers investigated the CF_3^- affinity of boron-based Lewis acids (LAs) by DFT calculations, followed by experimental studies of various boron-based LAs reacting with fluoroform using *in situ* generated dimsyl potassium as a base [37]. They discovered that a suitable LA should be weak enough to avoid irreversible coordination to the base but strong enough to stabilize the CF_3^- generated from fluoroform before decomposition, which meant its CF_3 adduct's (**1**-**3**) pK_{CF3} value should be between 6 and 11. Hexamethylborazine ($B_3N_3Me_6$) was found to give the highest yield of CF_3 adduct **1**, as well as the best reactivity towards CF_3^- transfer (Scheme 10). Compared with other methods of trapping CF_3^- from fluoroform by LA [36], this protocol was performed at ambient temperature with much shorter reaction time. More importantly, the free borazine LA was regenerated after the reaction and could be separated almost quantitively, which meant $B_3N_3Me_6$ could be recycled for the reagent preparation.



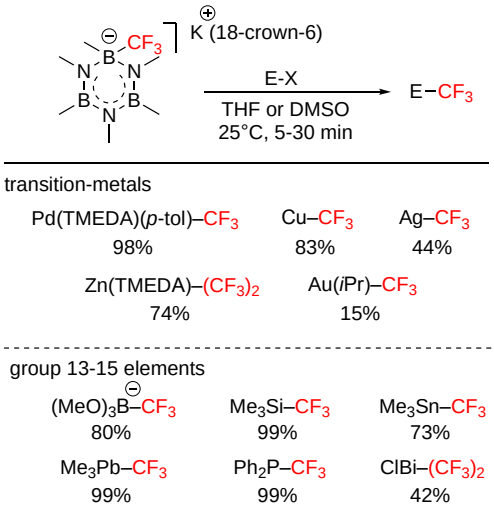
Scheme 10. Trifluoromethylation reagents from boron-based Lewis acids and fluoroform.

Besides nucleophilic trifluoromethylation, the CF_3 group of adduct **1** could be efficiently transferred to precursors of various popular trifluoromethylation reagents, such as Ruppert-Prakash reagent ($TMSCF_3$), K^+ version of Langlois reagent (CF_3SO_2K) and Togni reagent (Scheme 11a). A catalytic version of borazine-promoted synthesis of $TMSCF_3$ was also investigated albeit with low yields and turnovers (Scheme 11b) [37].



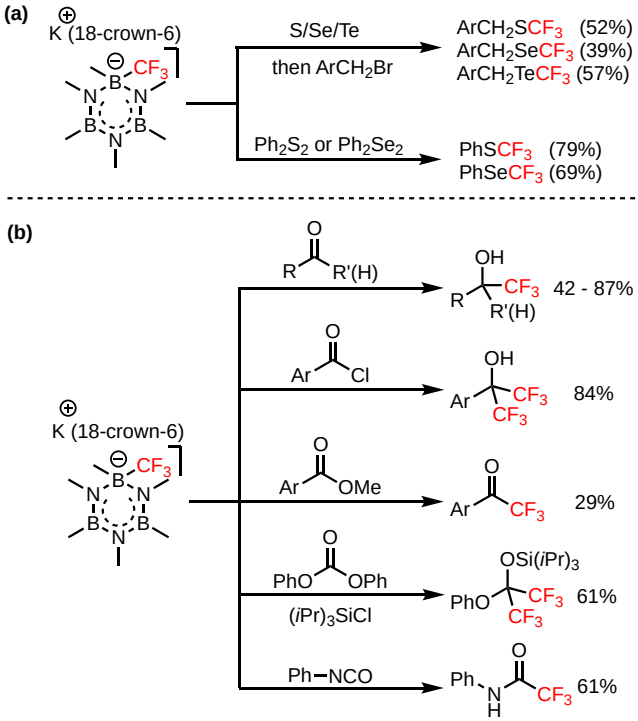
Scheme 11. Synthesis of Me_3SiCF_3, KSO_2CF_3, and Togni reagent from HCF_3.

Later on, the same group further expanded the reaction scope of the borazine-CF_3 reagents [38]. By employing halides of transition metals (groups 10-12) and main-group elements (groups 13-15) as electrophiles, a series of inorganic E-CF_3 compounds were obtained in moderate to excellent yields except for Au(I) (Scheme 12).



Scheme 12. Reactions of borazine-CF_3 reagent with inorganic electrophiles.

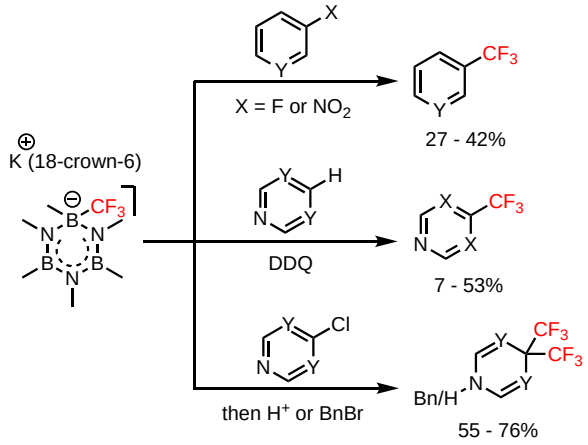
Moreover, the borazine-CF_3 reagent could react with elemental chalcogens to generate F_3CX^- species in good yields, which were then trapped *in situ* by benzyl bromides to give $ArCH_2XCF_3$ products (Scheme 13a). The $ArXCF_3$ products could also be obtained using phenyl dichalcogenides as substrates. Carbonyl compounds, including aldehydes, non-enolizable ketones, acyl chlorides, esters, carbonates and isocyanates, were suitable substrates in the reaction with the borazine-CF_3 reagent without activators (Scheme 13b) [38].



Scheme 13. Reactions of borazine-CF_3 reagent with (a) organic and inorganic chalcogens (b) carbonyl compounds.

Nucleophilic aromatic substitution (S_NAr) was also tested, in which aromatic C-F and C-NO_2 bonds were converted to C-CF_3 without the help of transition metals, albeit in low to moderate yields. Oxidative trifluoromethylation of electron-deficient heteroaryl C-H bonds

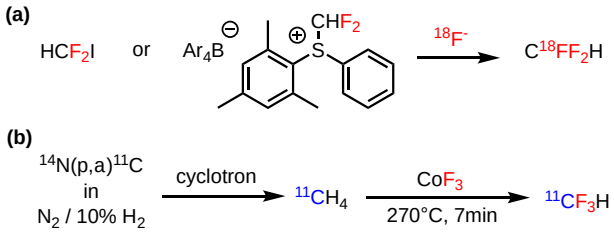
and geminal bis-trifluoromethylation/dearomatization of chloroheteroarenes were also achieved (Scheme 14) [38].



Scheme 14. Reactions of borazine-CF_3 reagent with (hetero)aryl substrates.

5. Radiolabeled fluoroform

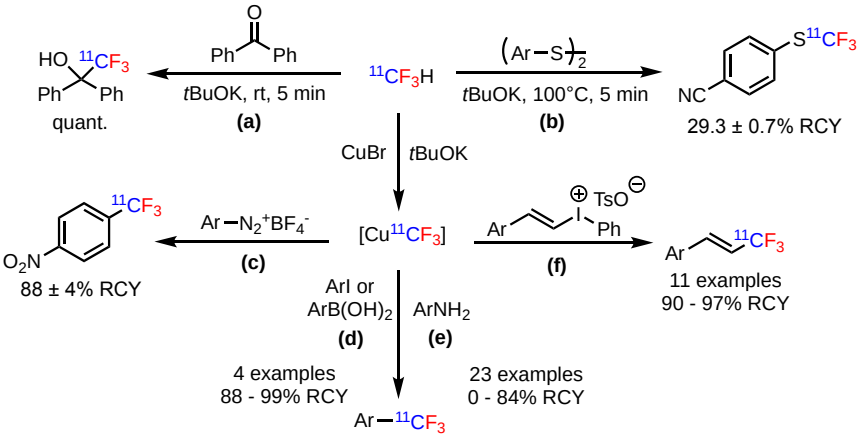
Radiolabelled fluoroform is a versatile reagent for constructing radiolabelled trifluoromethyl compounds, which are widely used in clinical positron emission tomography (PET) imaging applications. While [^{18}F]fluoroform has been well investigated [39], the [^{11}C]fluoroform was less discussed. Despite the shorter half-life of ^{11}C ($t_{1/2}$ = 20 min) compared to ^{18}F ($t_{1/2}$ = 110 min), CF_3-containing compounds labelled by ^{11}C have higher molar activity (>200 GBq/μmol) than those with ^{18}F (<32 GBq/μmol). Unlike those methods using $^{18}F^-$ as radioactivity source through nucleophilic substitution to generate the [^{18}F]fluoroform (Scheme 15a) [40-43], the synthesis of [^{11}C]fluoroform must start from a synthon with ^{11}C as its carbon center. This challenge was overcome by Pike and co-workers in 2017 who developed a synthetic route of [^{11}C]fluoroform from [^{11}C]methane [44]. By controlling the temperature and flow rate of purified [^{11}C]methane in its reaction with CoF_3, [^{11}C]fluoroform could be produced at the yield of 53±4% within only 7 min (Scheme 15b).



Scheme 15. Preparation of [^{18}F] and [^{11}C]fluoroform.

The [^{11}C]fluoroform was used for direct nucleophilic trifluoromethylation upon deprotonation or preparation of Cu[^{11}C]CF_3 towards the synthesis of various [^{11}C]CF_3-containing compounds. For example, ketones and disulfides could react with [^{11}C]CF_3^- generated from [^{11}C]fluoroform under basic conditions rapidly (Scheme 16a,b). Aryl diazonium salts, iodides and boronic acids could be converted to the corresponding [^{11}C]CF_3-containing arenes using Cu[^{11}C]CF_3 (Scheme 16c,d). To avoid the use of unstable diazonium salts, a Sandmeyer-type [^{11}C]trifluoromethylation was achieved with *in situ* generated aryl diazonium from various substituted anilines, which significantly broadened the substrate scope (Scheme 16e) [45]. By employing a stronger nucleophile phenyliodonium tosylate as substrate, β-[^{11}C]CF_3-styrene

could be synthesized in high radiochemical yield (Scheme 16f) [46]. Importantly, all these reactions were completed in relatively short periods of time, thus allowing the products to be applied in PET before losing their radioactivity.



Scheme 16. Applications of [^{11}C]fluoroform.

6. Conclusion

The past decade has witnessed tremendous progress in utilizing fluoroform, an industrial waste and greenhouse gas, for the synthesis of valuable trifluoromethyl compounds in organic transformations. Creative approaches have been developed to activate fluoroform and stabilize the trifluoromethyl species thus generated. The use of organic and inorganic bases with additives allowed the efficient generation of CF_3^- anion from fluoroform towards nucleophilic trifluoromethylation of carbonyl compounds and imines. The preparation of copper-, silver- and borazine-based trifluoromethylation reagents from fluoroform enabled an array of novel trifluoromethylation reactions that were previously impossible with other reagents. Radiolabelled [^{18}F]- or [^{11}C]fluoroform can now be synthesized for the preparation of radiolabelled compounds towards PET applications. The next big challenge would be the "catalytic" activation of fluoroform which is yet to be seen in the future chapters of this important field.

Acknowledgments

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