# Fluoroform ($CF_3H$): An Industrial Waste or a Useful Raw Material?

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**Abstract:** Trifluoromethylated compounds have received great attention in organofluorine chemistry because of a variety of applications in the fields of drug discovery, material chemistry and polymer chemistry. There are many available reagents (electrophilic, nucleophilic and radical- based), which can be used to introduce trifluoromethyl group in a given molecule. Fluoroform ($CF_3H$) is one the most simple and cheap sources of trifluoromethyl group. In this review, we briefly summarize some important research and development efforts in past two decades where chemists have used fluoroform as a source of trifluoromethyl group to synthesize a variety of trifluoromethylated products.

Fluoroform ($CF_3H$) can be considered as a fluorine analog of a well-known compound, chloroform ($CCl_3H$ or $CHCl_3$). Fluoroform, (trifluoromethane, HFC-23, FE-13 or R23), is a potent green house gas with a global warming potential that is 11700 times greater than $CO_2$.(1) It is a colorless, odorless gas with a boiling point of -84 °C and melting point of -160 °C . It is a very less reactive weak acid (pKa = 28 in DMSO) and hence practically a non-toxic gas. (2)

Fluoroform is produced as an inevitable by-product during the production of chlorodifluoromethane ($HCClF_2$, HCFC-22, R-22) by exhaustive fluorination of chloroform. (3) Trifluoromethane can also be produced by chlorofluorination of methane in high yields using chromium-based catalyst. (4) Chlorodifluoromethane ($HCClF_2$, R-22) is used as a refrigerant and for air-conditioning applications, however, its main application has been as a raw material for the synthesis of fluoropolymers such as Teflon® (a product produced in large tonnage). In 1990, it was estimated that about 4% of fluoroform is produced as a by-product of the total chlorodifluoromethane produced. With no significant applications, fluoroform was being released to the atmosphere at that time. In 1995, cumulative emissions of fluoroform were equivalent to 1.6 billion tons of $CO_2$. (3) The concentration of fluoroform is steadily increasing since 1978 at the rate of 5% per year. Unfortunately, the atmospheric life-time of fluoroform is close to 264 years because of the slow reactions of fluoroform with stratospheric OH radicals. (3) The mean rate of global emission of fluoroform was about 50% higher between 2006 and 2008 as compared to 1990's. While it may be possible to optimize the process of fluorination of chloroform so as to produce less fluoroform (as a by-product), the optimized process is known to reduce the plant capacity and will have economic consequences. (1)

**Abatement of fluoroform**

Disposal by destruction (incineration) is the most common way for the abatement of fluoroform. This is usually carried in the following three ways, thermal oxidation,

catalytic hydrolysis and plasma destruction. In thermal oxidation, liquid petroleum gas (LPG), air (from combustion air fan) and a stream of fluoroform are combined to form a flame at a very high temperature (1473 K in a burner). During this process, fluoroform is oxidized to $CO_2$, HF and HCl. However there are serious limitations to this process because of the formation of very corrosive HF during the process. Another main challenge is to find materials which can function at that high temperature (1473K) and in presence of corrosive HF. Formation of dioxins (a toxic substance) during this process is another concern.

Catalytic hydrolysis method was introduced to overcome the high temperature issues associated with thermal oxidation of fluoroform. Zirconium ($ZrO_2$/ $ZrO_2$-$SO_4$), Alumina ($AlPO_4$-$Al_2O_3$) and Ni-Mg P2 based catalytic systems were developed for this process and destruction of fluoroform was achieved at much lower temperature (573-773 K for Zr-based and 773 K for Ni-Mg based catalysts) than thermal oxidation processes. However, the catalyst poisoning due to corrosive HF by-product was still a problem. The major limitation of this method is the requirement of noble metals such as Au, Pt, Pd and Ti or other metals such as Ni and Ga to convert the carbon monoxide (CO) formed during the reaction to $CO_2$. In addition to this, the whole process was only effective when fluoroform concentration was lower than 5000 ppm in the stream. At higher concentration, catalyst life was an issue.

A commercially available method of fluoroform abatement is a plasma destruction method. This is typically performed by pyrolysis of fluoroform in plasma arc at very high temperatures such as 10,000 and 30,000 K. The products obtained after pyrolysis include HF, $F_2$ and an extremely toxic gas $COF_2$ (fluorophosgene), all of these can pose significant threat to the environment. In addition, operating cost of plasma destruction method can be very high. There are other methods that can utilize fluoroform as a feedstock to make other value added compounds such as $CH_2F_2$, $C_2F_4$ (tetrafluoroethylene, TFE), $C_3F_6$ (hexafluoropropene, HFP) and $CF_3I$ (iodotrifluoromethane). (1)

From the above discussion, it is clear that with the exception of $CF_3I$ or $CF_3Br$, most of the chemicals synthesized do *not* use trifluoromethane as a source of trifluoromethyl ($CF_3$) group and require higher temperatures for the reaction to take place. While $CF_3I$ and $CF_3Br$ both use fluoroform as a source of $CF_3$ group, their synthesis and use is highly regulated due to Montreal protocol for environmental concerns related to ozone destruction. So there is a great opportunity for chemists to develop milder methods to use fluoroform as a source of trifluoromethyl group to synthesize a variety of organic molecules and commercially important chemicals. If this can be successful, potentially in the long run, fluoroform can actually be considered as a useful feedstock (raw material) rather than an industrial waste.

This mini-review, thus, focuses primarily on only those methods that have been developed over the past 30 years or so, where researchers have used trifluoromethane as a source of trifluoromethyl group to synthesize trifluoromethylated organic compounds or commercially important chemicals more or less in one or two steps. It is by no means a complete compilation of fluoroform research activities over three decades but a short discussion about the use of fluoroform in organic synthetic methodology development research. In short, this is a brief overview of trifluoromethylations of small organic molecules using fluoroform as a source of the trifluoromethyl group.

Trifluoromethylation reactions using trifluoromethyl lithium or trifluoromethyl Grignard reagents were reported in early 1950's. (5-6) However, both the reagents were made from trifluoromethyl iodide ($CF_3I$). Based on these studies, it was reported that trifluoromethyl anion is very unstable even at low temperatures. It was believed that upon formation, trifluoromethyl anion ($CF_3^-$) spontaneously decomposes to give singlet difluoromethylene ($:CF_2$ carbene) and fluoride ion ($F^-$). This happens due to concentrated negative charge on the carbon atom of $CF_3$ anion, which results in an increased repulsion between electron pairs on three fluorine atoms and anionic carbon.

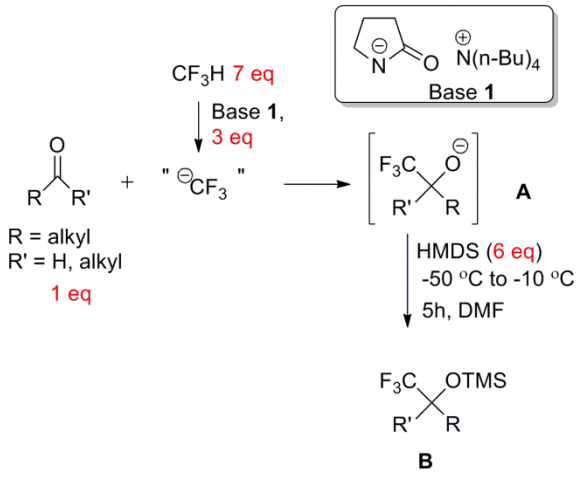
$$^{\ominus}CF_3 \rightleftharpoons :CF_2 + F^{\ominus}$$

Difluoromethylene carbene

However, later on, taking advantage of the unique reactivity of electrogenerated bases, Shono et al. (7) showed for the first time that fluoroform ($CF_3H$) can be deprotonated under electrochemical conditions using electrochemical bases (derived from 2-pyrrolidone) to generate trifluoromethyl anion equivalent. In presence of excess of fluoroform ($CF_3H$, 7 equivalents), a variety of aldehydes and ketones were trifluoromethylated (23-92% yield) under electrochemical conditions to give corresponding trifluoromethyl carbinols (Scheme 1).

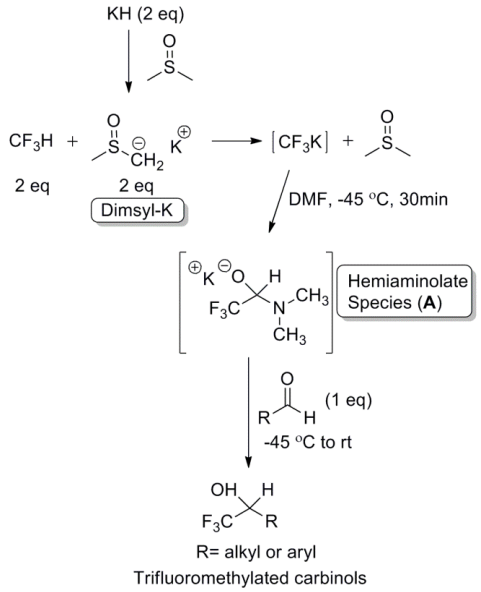
Interestingly, presence of hexamethyldisilazide (HMDS) in the reaction mixture as an additive increased the percent conversion substantially. It was assumed that HMDS silylates the intermediate **A** to give **B** and thus promotes the reaction towards completion. It was not clear at that time as to why electrogenerated bases were successful in deprotonation and subsequent reactions of fluoroform. Presence of tetraalkylammonium counterion and aprotic solvent were thought to be important factors for the success of this chemistry.

**Scheme 1**




Intrigued by the results obtained by Shono et al using electrogenerated bases to deprotonate fluoroform, Folleas (8) and others decided to investigate this reaction further. They attempted deprotonation of fluoroform using common organic bases such as potassium *tert*-butoxide, KH, *n*-BuLi, NaH, LDA, etc. in THF as a solvent but were not successful. This result suggested that the presence of DMF as a reaction solvent in the deprotonation of fluoroform is important. Based on some interesting experiments, authors proposed that trifluoromethyl anion generated after deprotonation of fluoroform is trapped efficiently by DMF to generate trifluoromethylhemiaminolate species (**A**, Scheme 2). This species acts as a reservoir of trifluoromethyl anion and reacts as a source of trifluoromethyl anion during the trifluoromethylation of aldehydes to give the corresponding trifluoromethyl carbinols. Using excess of fluoroform and base combination (2 eq each), trifluoromethylation of aldehydes (1 eq) was carried out in DMF as a solvent in 20-60% yield; however, the substrate scope of this chemistry was limited.

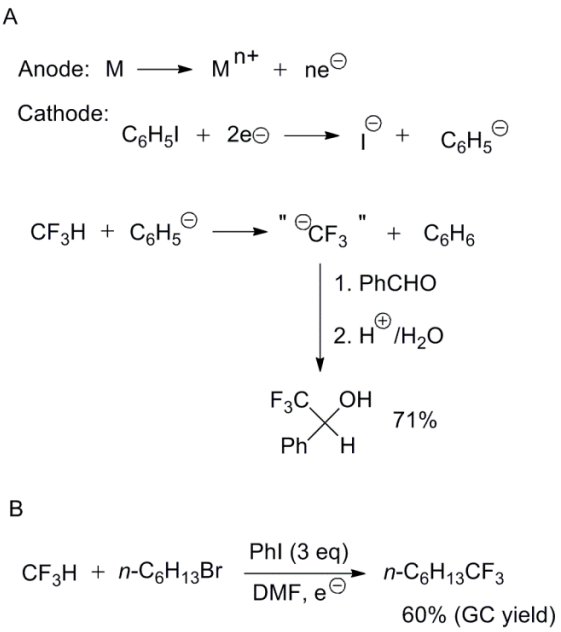
**Scheme 2**




In 1998, Barhdadi et al (9) reported a new type of electrogenerated base, which was generated using iodobenzene at cathode (covered by electrolytic deposit of cadmium) and a sacrificial anode of magnesium or aluminum in DMF. Using this type of electrolytic system, authors were able to show that various aldehydes can be trifluoromethylated under continuous stream of fluoroform under atmospheric pressure in moderate yields (12-76%, Scheme 3a). Interestingly, authors also report one example of trifluoromethylation of alkyl halide (*n*-hexyl bromide) in 60% GC conversion (Scheme 3b).

A more in-depth study of nucleophilic trifluoromethylations using fluoroform and common organic bases appeared later. In these papers, Roques et al (10) and Normant et al (11), studied variety of aspects of fluoroform/base/DMF combination in achieving trifluoromethylations. They showed that using the correct stoichiometry of aldehyde and base (1:1), one can obtain trifluoromethylated carbinols in good conversion (67% from benzaldehyde) along with better selectivity (only 2% of benzyl alcohol as a side product).

**Scheme 3**



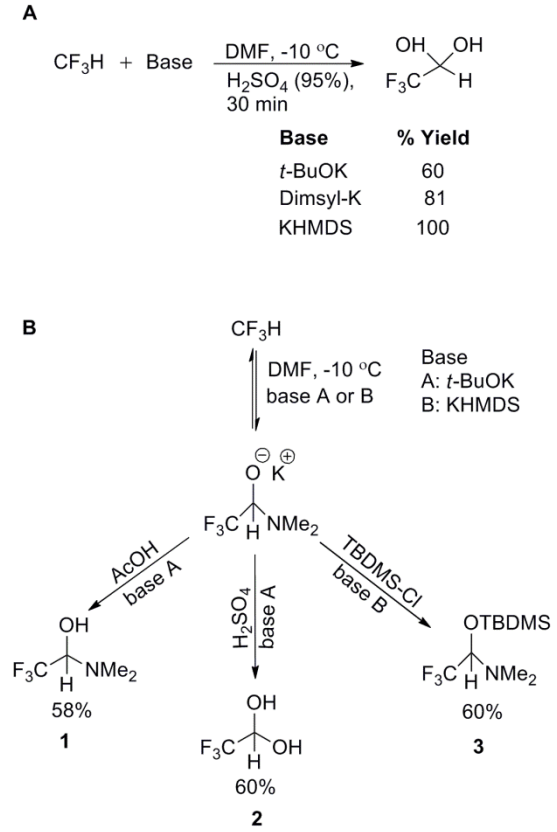

Taking synthesis of fluoral hydrate as an example, they were able to show that with a strong base like potassium hexamethyldisilazide (KHMDS) fluoral hydrate was produced quantitatively (100%), where as with weaker bases such as potassium *tert*-butoxide (*t*-BuOK), or Dimsyl-K the % conversion were 60% and 81%, respectively (Scheme 4). Recently, even fluoral hydrate was used by Prakash et al as a source of trifluoromethyl anion. (12)

In order to be able to observe the actual trifluoromethylating species obtained from fluoroform, a low temperature (-45 °C) NMR study was performed. When *t*-BuOK was added to an NMR tube which had fluoroform in anhydrous DMF, a *new* peak was observed in $^{19}F$ NMR. Benzaldehyde addition to this NMR tube then resulted in disappearance of this peak and appearance of the corresponding trifluoromethylated product peak.

In order to characterize the hemiaminolate species (an intermediate that is formed after the reaction between trifluoromethyl anion and DMF), authors (10) performed three quenching

experiments. After mixing fluoroform and base (*t*-BuOK or KHMDS) at -10 °C, they used three different reagents to quench the expected hemiaminolate intermediate. When the reaction was quenched with acetic acid, trifluoromethylated DMF was formed (Scheme 4B, **1**) as a product, with sulfuric acid, fluoral hydrate was observed (Scheme 4B, **2**). Very interestingly though, with KHMDS as a base and *tert*-butyldimethylchlorosilane (TBDMS-Cl) as a quenching agent, they observed formation of compound **3** (Scheme 4B) without any mention of other possible products such as TBDMS-$CF_3$. This suggests that hemiaminolate species formed in DMF is incapable of trifluoromethylating silyl chlorides.

**Scheme 4**




The role of DMF, specifically the carbonyl moiety of DMF, was better understood by another experiment. In this experiment, authors took dimethyl acetal of DMF as a solvent instead of DMF. Dimethyl acetal is a compound where the carbonyl moiety of DMF is masked. With this dimethyl acetal of DMF as a solvent authors observed that at low temperatures, fluoroform showed rapid exothermic violent reaction with reaction mixture turning black in color (indication of carbenoid degradation) and a complete absence of the desired product. This clearly demonstrated that carbonyl moiety in DMF is very important for the success of trifluoromethylation reactions using DMF as a solvent.

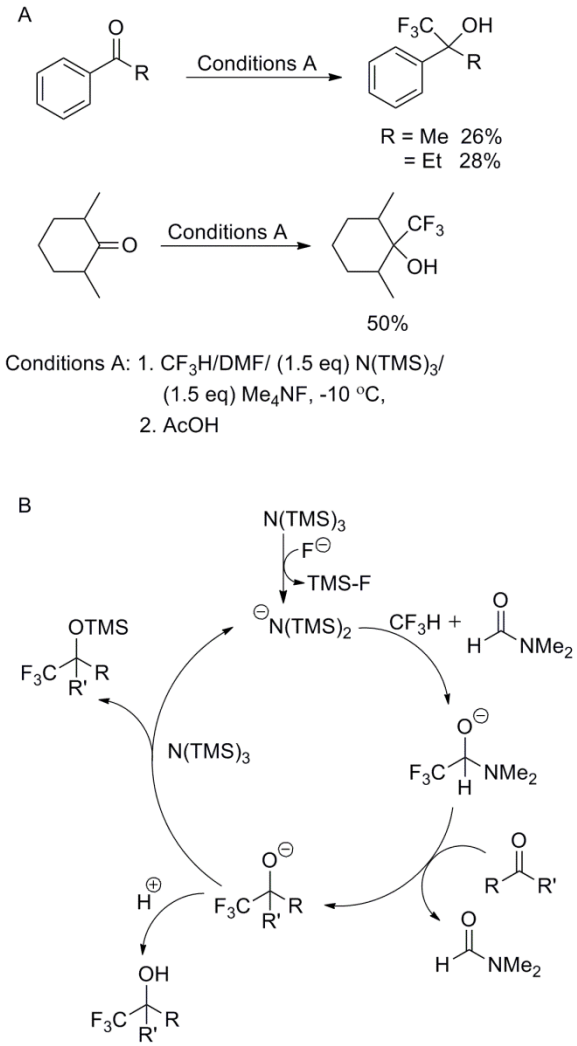
In order to expand the scope of this trifluoromethylation system ($CF_3H$/base/DMF), authors also studied trifluoromethylation of aromatic esters and sulfur derivatives. Under unoptimized reaction conditions, authors conclude that trifluoromethylation of methyl benzoate can be achieved in 70% yield using Dimsyl-K as a base in DMF with excess of fluoroform. For trifluoromethylation of aryl disulfides, aryl sulfinyl chlorides and aryl thiosulfonates, excess fluoroform (4 eq)/*t*-BuOK/DMF system proved to be better giving 60-90% yields of corresponding trifluoromethylated products.

All the work so far discussed used some sort of base or basic reaction conditions to facilitate deprotonation of fluoroform. This could however be detrimental if a substrate is base sensitive and can undergo side reactions under the reaction conditions. For example, with enolizable carbonyl compounds, enolization can prevail over trifluoromethylation and indeed this was observed when acetophenone (an enolizable carbonyl compound) was used as a substrate for the trifluoromethylation reaction using fluoroform and base. In order to solve this problem, Langlois and others, (13) introduced a new system for the trifluoromethylation of carbonyl compounds using fluoroform. The idea was to generate base *in situ* in low

concentrations and at slow rates to prevent its reaction with the substrate prior to its reaction with fluoroform. They used a three-component system [(tristrimethylsilyl)amine (1.5 eq), $CF_3H$ (excess) and $F^-$ source (1.5 eq)] in DMF at -10 °C to carry out trifluoromethylation of enolizable carbonyl compounds. Unfortunately, the reported substrates (acetophenone (26%) and 1-phenyl-1-propanone (phenylethyl ketone) (28%)) gave low conversions to the corresponding trifluoromethylated products using this system. The conversion was slightly improved when enolization was disfavored due to steric effects as in the case of 2,6-dimethylcyclohexanone (50%) (Scheme 5 **A**). Authors proposed following mechanism for this trifluoromethylation using three-component system. It was thought that, initial activation of tris(trimethylsilyl)amine with $F^-$ source would produce TMS-F and $^-N(SiMe_3)_2$ ("in situ" slowly generated base). This after deprotonation of fluoroform would generate hemiaminolate species (with DMF as discussed earlier). This hemiaminolate species then would trifluoromethylate carbonyl substrate followed by regeneration of DMF as shown in Scheme 5 **B**.

For optimization of reaction conditions, authors studied trifluoromethylation of benzophenone (a non-enolizable ketone) and results of that study actually resulted in two important observations. First, other amides such as *N*,*N*-dimethylethyleneurea (DMEU) or *N*,*N*-dimethylpropyleneurea (DMPU) can also be used instead of DMF as a solvent and second, that the reaction gives excellent conversion to product even when DMF is present in the reaction medium in *catalytic* amount with THF as the main solvent of the reaction. It was also reported that trifluoromethylation of other carbonyl compounds such as chalcones and 4-methoxy-4-methyl-2,5-cyclohexadiene-1-ones and obtained the respective trifluoromethylated products in good yields (62-83% for chalcones) and moderate selectivities (cis:trans ratios with cis favored in most cases for cyclohexadiene-1-ones). Unfortunately, this three-component system was not successful with esters as substrates and surprisingly, benzaldehyde gave *N*-trimethylsilylimine.

**Scheme 5**

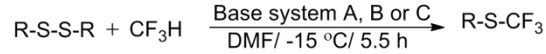



Extending the scope of this three-component trifluoromethylating system, authors reported trifluoromethylation of disulfides using this system. For aliphatic disulfides, a binary system of [(tristrimethylsilylamine (1.5 eq)/ $F^-$ source (1.5 eq)] gave better results whereas for aromatic disulfides use of only single base *t*-

BuOK was more productive. Stoichiometric amount of $F^-$ source was required for this transformation (compared to 0.2 eq required for benzophenone). This could be due to the inability of thiolates produced in the reaction to desilylate tris(trimethylsilyl)amine. The most intriguing result of this work was that the chemistry was successful even in neat THF [neat (DMF (73%) vs neat THF (66%)]. It was proposed that the desilylation of tristrimethylsilylamine was so slow in THF that the $CF_3$ anion was produced in very low concentrations, which was trapped immediately by the sulfide before it underwent any decomposition. It was also thought that this efficient trapping of $CF_3$ anion with sulfide could be a result of favorable soft electrophile-soft nucleophile interaction between the two reacting partners (Scheme 6).

In prior studies, it was shown that the hemiaminolate species which forms after the trapping of trifluoromethyl anion with DMF as a solvent (or as a catalyst) acts as a reservoir of trifluoromethyl anion, which trifluoromethylates carbonyl species.

**Scheme 6**

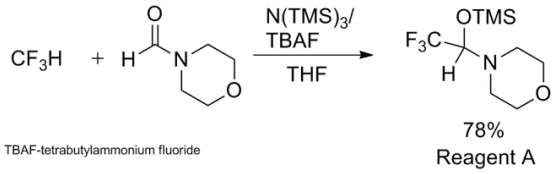


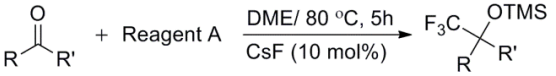

Base system: A- LiHMDS (1.1 eq)/ $HN(TMS)_2$ (0.2 eq)
B- $N(TMS)_3$ (1.5 eq)/ $Me_4NF$ (1.5 eq)
C- *t*-BuOK (1.1 eq)

| Disulfide | Base system | % Conversion based on $^{19}F$ NMR |
|---|---|---|
| $(C_8H_{17}S)_2$ | A | 51 |
| | B | 73 |
| | C | 54 |
| $(c\text{-}C_6H_{11}S)_2$ | A | 2 |
| | B | 54 |
| | C | 45 |
| PhSSPh | A | 4 |
| | B | 6 |
| | C | 82 |

Based on this concept, Langlois and others (14) designed new stable reagents, which were prepared by the reaction of fluoroform, base and an appropriate amide. While DMF, *N*-formylpiperidine, *N*-pyrrolidine and *N*,*N*-dibutylamine all failed to give stable and isolable species, *N*-formylmorpholine gave Reagent **A** in 78% yield as shown in Scheme 7.

**Scheme 7**




R = Ph, R' = Ph - 75%
R = Ph, R' = H - 95%

This "reagent" was then tested for its ability to trifluoromethylate carbonyl compounds under conditions similar to (trifluoromethyl)trimethylsilane (TMS-$CF_3$, the Ruppert-Prakash reagent), most common nucleophilic trifluoromethylating reagent. (15) With benzophenone, this reagent gave good yields of the trifluoromethylated product (75%) only when the reagent was used in excess (2 eq) and at high temperature (80 °C) while benzaldehyde gave 95% yield of the product under similar reaction conditions.

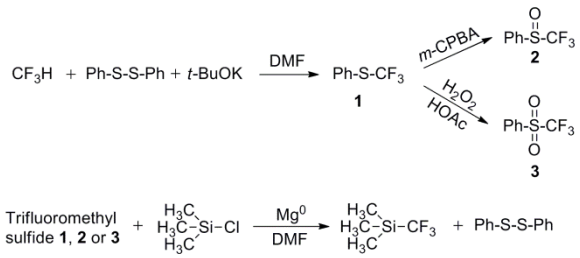
There were other stable nucleophilic trifluoromethylating reagents developed using this concept of amides trapping trifluoromethyl anion. (16) These reagents include, piperazinohemiaminal (hemiaminal of fluoral) and showed some promise in achieving nucleophilic trifluoromethylations of carbonyl compounds, however these reagents were not synthesized directly from fluoroform and so will not be discussed here.

After 2001, research area of nucleophilic trifluoromethylation of carbonyl compounds using fluoroform and base became sort of dormant. This could possibly be due to some limitations in the chemistry, which was developed before. These limitations could be due to any of the following such as the need of excess of fluoroform for the reaction, mandatory presence of DMF (or any related amide) in the reaction medium, limited solvent scope for the transformation or more importantly, trifluoromethylations of only carbon centers (and sulfur and selenium to some extent) were studied.

Fluoroform can be considered to be the most abundant and cheap source of trifluoromethyl group and ideally it would be a very practical and economical approach to be synthesize to make the most versatile, commercially available nucleophilic trifluoromethylating reagent (trifluoromethyl)trimethylsilane (TMS-$CF_3$, the Ruppert-Prakash reagent) directly from fluoroform. However, no such method was available (*vide supra*), in spite of severe limitations imposed on $CF_3Br$ (after Montreal Protocol, its use being banned in the US), a key starting material for the industrial synthesis of TMS-$CF_3$ known back then.

In 2003, Prakash and coworkers (17), reported first synthesis of TMS-$CF_3$ starting from fluoroform in two steps. The idea here was to use trifluoromethyl sulfides (or its higher oxides such as sulfoxide and sulfones) as intermediate compounds. The sulfur compounds were synthesized using fluoroform and base using the conditions reported earlier by Langlois and others (13) (Scheme 8). These sulfur compounds, especially sulfoxides and sulfones, when reacted with chlorosilanes under magnesium-mediated reductive reaction conditions gave excellent yields of corresponding trifluoromethylsilanes. (Scheme 8). This was the first report of synthesis of TMS-$CF_3$ where the actual source of $CF_3$ group was fluoroform. These trifluoromethylated sulfides (**1**, **2** and **3**) were used to synthesize a variety of other trifluoromethylated silanes.

**Scheme 8**

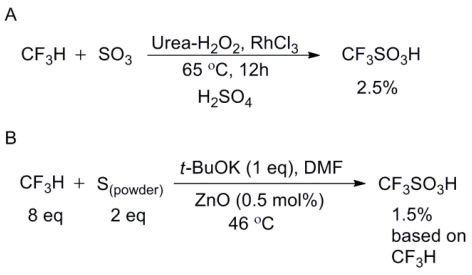



| Sulfide | % Yield |
|---|---|
| **1** | 45 |
| **2** | 100 (81) |
| **3** | 100 (83) |

( )- Isolated yields

In a different area of research, Bell and others (18) subsequently published an interesting article, where authors reacted fluoroform under very acidic as well as very basic conditions using Rh-chloride as a catalyst to synthesize trifluoromethanesulfonic acid (triflic acid, $CF_3SO_3H$), one of the widely used Bronsted superacid. (19) They also reported a reaction between fluoroform with sulfur powder in the presence of ZnO/MgO to synthesize trifluoromethyl sulfur species followed by oxidation using $HCl/H_2O_2$ to obtain triflic acid. Unfortunately, however, after over 400 experiments, the highest yield (based on GC conversion) reported using any of these processes was not greater than 2.5% (Scheme 9).

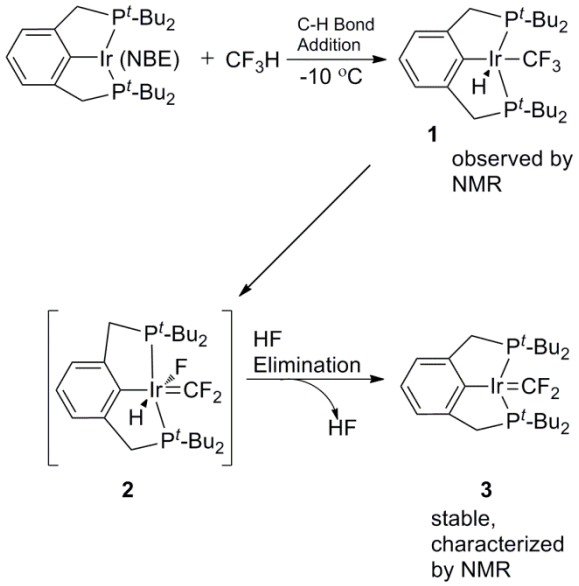
**Scheme 9**



Over the years, what became increasingly important is the introduction of $CF_3$ group into aromatic and heteroaromatic systems. This research is driven by the fact that about 20-25% of the active pharmaceutical entities developed till to date contain fluorine atoms, mostly either as a fluoride or as a trifluoromethyl group. (20)

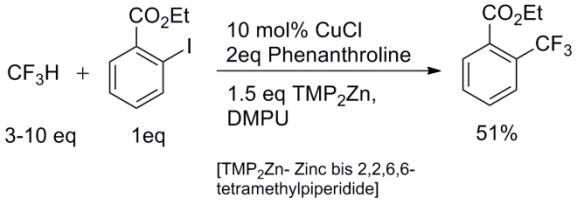
It is well-known that carbon-fluorine (C-F) bond is one of the strongest known chemical bonds. In 2011, Goldman and others (21) developed a new strategy to break this C-F bond in a given compound. Their strategy was to first achieve initial C-H activation of the carbon attached to fluorine C(F)-H and then subsequently effect C-F bond cleavage. They developed iridium-based catalysts and showed that fluoroform can be converted into metal-carbenoid species [(L)Ir=$CF_2$)]. Unfortunately, they were not able to isolate the [(L)Ir=$CF_2$)] species (species **3**, Scheme 10). However, species **3** was characterized by NMR Spectroscopy. In this chemistry, initial C-H bond activation of fluoroform results in formation of **1** at -10 °C, which upon warming (20 °C) undergoes a-fluorine migration to give **2**. This then undergoes HF elimination to give species **3**.

**Scheme 10**




Aromatic trifluoromethylation using $CuCF_3$ as a $CF_3$ source has been known for a long time and there are many papers published regarding the synthesis of $CuCF_3$ reagents, (22) their stability, reactivity and overall stoichiometry (catalytic or stoichiometric) of the aromatic trifluoromethylation reaction. However, formation of $CuCF_3$ based reagent directly from fluoroform was not much discussed. In early 2011, Daugulis and others (23) reported for the first time that fluoroform (excess) can be used to trifluoromethylate ethyl-2-iodobenzoate using catalytic CuI/phenanthroline and Zn-based base in 51% yield in DMPU (an-amide based compound) as a solvent (Scheme 11). Although the substrate scope was limited and the yield was moderate, this study was an important step towards using fluoroform to achieve direct trifluoromethylation of aryl iodides mediated by Cu.

**Scheme 11**

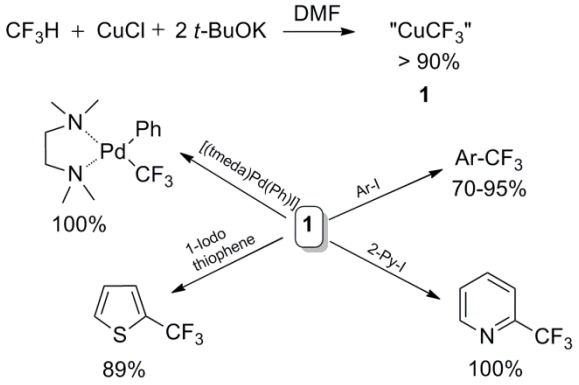



Later on, in the same year, 2011, Grushin et al, (24) reported a direct cupration of fluoroform. By using precise combination of CuCl:*t*-BuOK (1:2) in DMF, authors were able to generate $CF_3Cu$ species quantitatively (based on $^{19}F$ NMR), directly from fluoroform (excess) within minutes. Interestingly, this result was obtained in absence of any ligand. To gain more insight into the mechanism of the reaction, authors used styrene or α-methylstyrene as a trapping agent to detect any formation of $CF_3^-$ or $CF_2$ carbene (difluoromethylene, :$CF_2$). Since there was no indication of formation of *gem*-difluorocyclopropane, a product of difluoromethylene insertion, in both the reactions, authors concluded that both $CF_3^-$ and

$CF_2$ carbene are not involved as a reactive intermediate during the cupration of fluoroform. $CuCF_3$ derived from fluoroform under these conditions proved to be a good source of $CF_3$ group for the trifluoromethylation of aromatic iodides, some heteroaromatic iodides and trifluoromethyl palladium aryl complexes (Scheme 12). However, as expected, without any stabilization, $CuCF_3$ derived from fluoroform decomposed rapidly.

This problem was solved by addition of TREAT-HF ($Et_3N$-HF) complex to acidify the reaction mixture containing $CuCF_3$ that resulted in a more "stable" $CuCF_3$ reagent that permitted its wide use in solution for further synthetic transformations. Using this stabilized $CuCF_3$ reagent solution, authors subsequently reported synthesis of trifluoromethylated arenes from aromatic boronic acids (25) in presence of air.

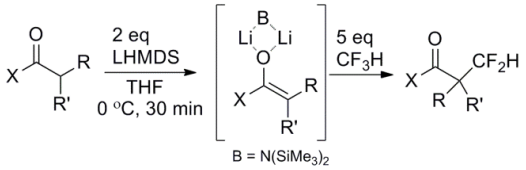
**Scheme 12**

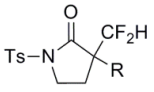



Both the substrate scope and percent yields of the products from boronic acid derivatives were excellent for this transformation. The same research group also reported trifluoromethylation of α-haloketones (26) from this fluoroform-derived $CuCF_3$ reagent in excellent substrate scope and yields. However, both of these transformations were not achieved in a single step, "directly" from fluoroform.

In 2012, a completely different approach of using fluoroform in organic synthesis was reported by Mikami and others. (27) Their approach was based on the "hydrodefluorination" of chlorofluorocarbons (an approach reported earlier by Douris and Ozarov (28) to tackle the environmental issues posed by the chlorofluorocarbons in the atmosphere). In their paper, Mikami and others report that fluoroform can undergo C-F bond activation in the presence of excess of lithium enolates to produce synthetically useful, $CF_2H$ (difluoromethyl) carbocation equivalent. Using this methodology they introduced difluoromethyl group in carbonyl lithium enolates in moderate to good yields (Scheme 13). Although the reaction was performed in pure THF, excess (5 eq) of fluoroform was used for this transformation. Interestingly authors showed synthesis of difluoromethyl analog of ibuprofen using their developed methodology.

**Scheme 13**



| R | % Yield[a] |
|---|---|
| Bn | 69 |
| allyl | 45 |
| H | 0 |

[a]- based on $^{19}F$ NMR conversions

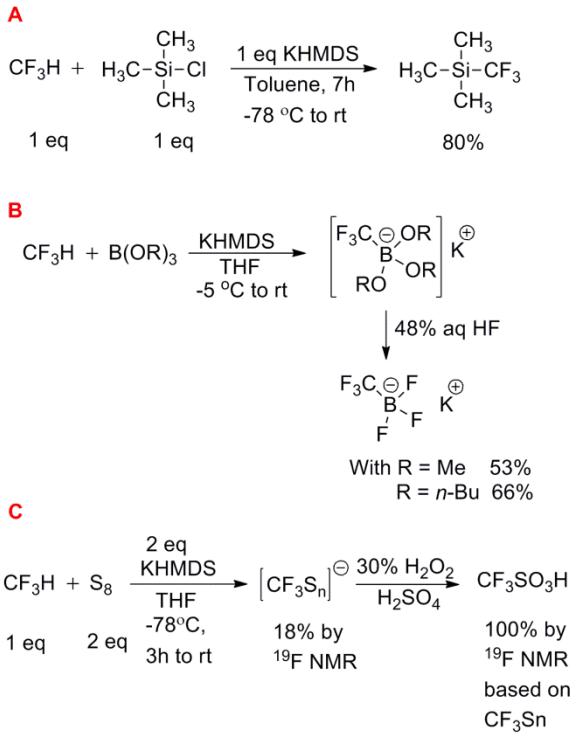
In 2012, our group reported (29,30) major breakthroughs related to direct trifluoromethylations using fluoroform. Under simple but unique reaction conditions, we were able to tame fluoroform to synthesize the Ruppert-Prakash reagent in excellent yield directly from fluoroform in one single step. We used potassium hexamethyldisilazide (KHMDS) as a base and chlorotrimethylsilane to achieve this synthesis. We extended the scope of the reaction to other chlorosilanes and even were

able to synthesize (bis)trifluoromethyldiethylsilane. The important aspects of this study are that all the reactions were performed either in ether or toluene (hydrocarbon) as a solvent and in complete absence of DMF and stoichiometric (only 1 eq) amount of fluoroform was used for all the reactions (Scheme 14 A).

We were also able to show that boron compounds (borates) can also be trifluoromethylated directly from fluoroform (again using 1 eq) in THF to give corresponding trifluoromethylated borates, which were converted directly (without isolation) to trifluoromethylated tetrafluoroborates ($CF_3BF_3K$) (using 48% aq HF) in overall two steps in good preparative yields. This is the first report of synthesizing $CF_3BF_3K$ compounds directly from fluoroform (Scheme 14 B). Going further, we also reported a reaction between fluoroform and elemental sulfur, $S_8$ (the most abundant and cheapest resources available for trifluoromethyl group and sulfur, respectively) to produce trifluoromethylated sulfide species ($CF_3S^-$) which upon complete oxidation with $H_2SO_4/H_2O_2$ gave trifluoromethanesulfonic acid ($CF_3SO_3H$, triflic acid) in 18% overall conversion (Scheme 14 **C**). Although the reaction conditions are still under optimization, the reported conversion is still better than the one previously reported by Bell and others.(18) Again the reaction was performed with only stoichiometric amount of fluoroform and in THF (in complete absence of DMF).

Based on our studies where presence of DMF (or any related amide) did not seem to have any effect on the trifluoromethylation of silicon, boron and sulfur centers, we decided to revisit the direct trifluoromethylation of carbonyl substrates using a stoichiometric amount of fluoroform in complete absence of DMF.

**Scheme 14**

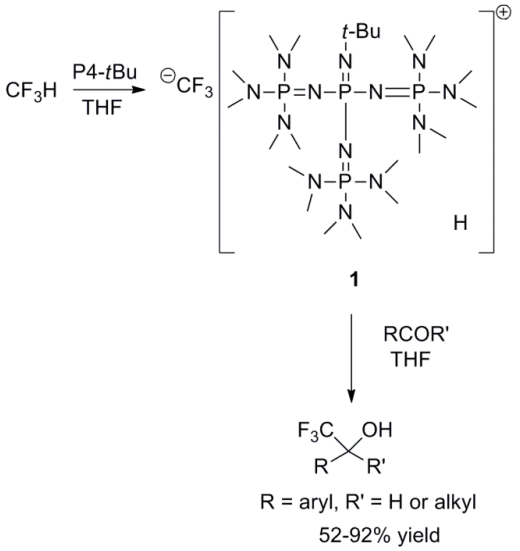



As expected, we were able to obtain trifluoromethylated carbinols from aldehydes, non-enolizable ketones and even chalcones in moderate to good yields in either THF or ether without any co-solvent or additives. We further extended this study to show direct trifluoromethylations of alkyl formates, alkyl halide and even aromatic esters although reactions with these substrates are still under study to improve their conversions.

Just after our work was published, Shibata and others (31) reported their findings about direct trifluoromethylations of aldehydes, ketones and some chalcones from fluoroform in pure THF (in complete absence of DMF). They achieved this by using a very sterically hindered base *t*-Bu-P4, which according to authors help stabilize naked $CF_3$ anion and prevent it from collapsing to fluoride ion and difluorocarbene (Scheme 15). Although useful in general, this method suffers from disadvantages such as requirement of excess (1.5 eq) uncommon and

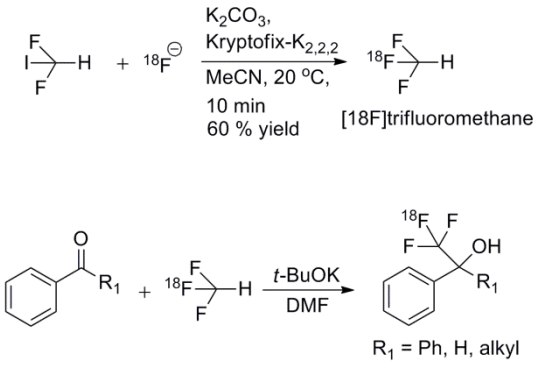
expensive base, excess fluoroform and limited substrate scope (only carbon electrophiles).

**Scheme 15**




In 2013, Vugts and others (32) reported a very interesting paper where they synthesized [$^{18}$F] trifluoromethane from difluoroiodomethane ($ICF_2H$) and $^{18}F^-$ in acetonitrile using $K_2CO_3$ as a base in about 60% yield in 10 minutes at room temperature. Using this [$^{18}$F]trifluoromethane, authors were able to achieve nucleophilic trifluoromethylation of benzophenones (>99 %), acetophenones (22-41%) and benzaldehydes (31-98 %) in good yields (Scheme 16).

**Scheme 16**




## Conclusions

In conclusion, it is evident from the recent studies that "direct" trifluoromethylations using fluoroform is becoming an active area of research and will continue to be so for some time. New and exciting discoveries are being made that will help us understand the structure, existence and stability of the elusive "trifluoromethyl anion ($CF_3^-$)" species.

Further research work is being pursued to observe this species by low temperature NMR experiments. This will help chemists to understand the trifluoromethylation reaction in detail and may narrow down the ideal reaction conditions for the trifluoromethylation of a particular substrate in less time. This kind of research will be advantageous to pharmaceutical and agrochemical industry where introduction of $CF_3$ group at a later stage in a synthetic scheme could have a profound effect on structure and function of a biologically active molecule.

Broadly speaking, there are two main areas of research that can have significant impact of using fluoroform as a "direct" source of trifluoromethyl group. One would be, new and efficient synthesis of trifluoromethylated chemicals, both specialty and commodity chemicals and second, development of stereoselective synthetic methods to achieve enantioselective or diastereoselective trifluoromethylations using fluoroform.

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