Research progress on trifluoromethyl-based radical reaction process

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Abstract. Due to the unique properties imparted by the trifluoromethyl group, such as high electron density and strong lipotropy, which effectively improve acidity, lipophilicity and metabolic stability of the molecule itself, trifluoromethyl-substituted organic compounds are becoming increasingly important as structural motifs in pharmaceuticals, agrochemicals and organic materials. In this review, we present several methods developed for the direct introduction of a trifluoromethyl group, beginning with its rich and storied history. Then the present article addresses mechanism and process in carbon-carbon bond forming reaction based on radical process which is divided into three parts according to the way of CF3 radical generation. Finally, challenges and opportunities of researches on trifluoromethylation reactions facing are prospected.

1. Introduction

It is well-known that organofluorine compounds are extremely rare in nature despite the relatively high abundance of fluorine in our earth’s crust. The seeds of researches on fluorinated compounds were firstly planted in 1764, however, seeds didn't sprout until 1896 when Swarts successfully synthesized ethyl fluorooacetate [1]. And then the ingenious Balz-schiemann reaction moved the fluoro-organic chemistry field into a brand new stage with a better comprehension of the specific fluorine factors on the outcome of organic reactions [2].

Psychotropic drugs containing F atom such as Fluphenazine was discovered in 1956 and 5-Fluorouracil in 1957 [3], brought greater hopes for cancer therapy as well as more attention on the application of fluorinated compounds. (Hetero)arenes bearing CF3 groups constitute an indispensable part of numerous important drugs, including celecoxib, fluoxetine and fluazinam. Currently, the interest in fluoro-organic chemistry is at an all-time high.

It is therefore apparent that the development of new methods for trifluoromethylation, especially in an efficient, mild and green way, is essential and necessary. It is noteworthy that new discoveries and developments of trifluoromethylation reactions are built on the researches on Trifluoromethyl reagents. Mechanisms corresponding to their regents' properties which are electrophilic, nucleophilic, or radical, can be divided into electrophilic trifluoromethylation; nucleophilic and radical. In this review, we 1) Categorize types of trifluoromethylation with presentation of the reagents in each section. 2) Introduce some recent examples of C-C bond formation based on radical way, which have appeared in the primary literature. Important earlier work in this field is also covered. 3) Focus our attention on summarizing the mechanism and propose the problems hindering the evolving chemical landscape that has engaged trifluoromethylation reactions.

2. Trifluoromethyl-introducing methods
Three main trifluoromethyl-introducing methods include (a) Electrophilic trifluoromethylation; (b) Nucleophilic trifluoromethylation; and (c) Radical trifluoromethylation. The general equations of reactions are shown respectively:

(a) Electrophilic trifluoromethylation:
\[ \text{Nu}^+ + [\text{CF}_3]^+ \rightarrow \text{Nu-CF}_3 \]

(b) Nucleophilic trifluoromethylation:
\[ E^+ + [\text{CF}_3]^+ \rightarrow E-\text{CF}_3 \]

(c) Radical trifluoromethylation:
\[ \text{R} \cdot + [\text{CF}_3] \rightarrow R-\text{CF}_3 \]

2.1. Electrophilic trifluoromethylation

Because it is extremely difficult to generate the trifluoromethyl cation \( \text{CF}_3^+ \) which is in low stability by chemical reaction, electrophilic trifluoromethylation does not mean utilizing \( \text{CF}_3^+ \) ion directly. Here it means using \( \text{CF}_3 \) group connected with and polarized by high electronegativity atoms as electrophilic reagents. Essentially, two classes of reagents for utilizing \( \text{CF}_3^+ \) have been developed: the trifluoromethylchalcogen salts (Umemoto's reagents) and the hypervalent iodine(III)-\( \text{CF}_3 \) reagents (Togni's reagents). Here we review the interesting stories about discoveries of them.

2.1.1 Trifluoromethylchalcogen salts (Umemoto's reagents)

In 1984, Yagupolskii and co-workers firstly described the first electrophilic trifluoromethylating agents (Figure 1(1a, 1b)) [4]. Based on this pioneering work, the group of Umemoto reported a series of power-variable trifluoromethylating agents named Umemoto's reagents later (Figure 1(2, 3)) [5-8]. Although these are effective for transfer of the \( \text{CF}_3 \) group, drawbacks are also apparent: long synthetic steps and their poor enantioselection.

2.1.2 Hypervalent iodine (III)-\( \text{CF}_3 \) reagents (Togni's reagents)

Due to the drawbacks of Umemoto's reagents mentioned above, Togni and co-workers designed a new family of electrophilic trifluoromethylating reagent called Togni's reagents (Figure 1(4, 5)) [9,10]. Experiments had shown that these reagents have broad substrates scope (\( \beta \)-keto esters, silyl enol ethers and \( \alpha \)-nitro esters, as well as to thiols).

Although Umemoto's reagents and Togni's reagents can react directly, current methods either require the use of harsh reaction conditions or suffer from a limited substrate scope. In order to avoid these, recently, researchers develop a new type of radical trifluoromethylation via electrophilic trifluoromethylating reagents as \( \text{CF}_3 \) source in the presence of metal or photoredox catalysts. Besides, scientists lay emphasis on synthesis of easier control reagents with better stereoselectivity and higher reactivity [11]. These spectacular discoveries will continue to be monumental in the chemical sciences.
2.2. Nucleophilic trifluoromethylation
Among the strategies for the direct introduction of a CF₃ group into organic molecules, nucleophilic trifluoromethylation has been the most attractive approach during the last few decades. The key to these nucleophilic regents preparation is to the formation of CF₃⁻ with metal catalyzed. In the early stage, trifluoromethyl metal species (Hg, Cu, Zn, and Cd) have been extensively investigated [12].

At the first begin, trifluoromethylation reactions involved with copper had been extensively studied. McLoughlin [13] and Kumadaki [14] reported independently, with copper powder, that CF₃I can react with Ar-I to form Ar-CF₃. Gradually, metal-catalyzed trifluoromethylation has been the most frequently-used method, however, several drawbacks limited their utility. For an instance, many of these reactions under thermal activation, suffer from low yields and numerous fluorinated side products. These regents are considered as sluggish ones. Thanks to the advent of Ruppert-Prakash reagent (Me₃SiCF₃), now a tame nucleophilic trifluoromethylation is not a dream.

2.3. Radical trifluoromethylation
CF₃ radicals can easily generate under light, heat or chemical reaction, and then it can reacts with olefins and aromatic rings. Based on ESR, IR, MW and other analysis methods as well as molecule orbital theoretical calculation, researchers have found that the stability of the CF₃ radical is strongly influenced by stereoelectronic effects. The geometry of methyl radical changes from near-planar to trigonal pyramidal as each hydrogen is successively replaced by F atom (Figure 3) [19].

Recent advanced researches focus on and have developed radical trifluoromethylation reactions under mild condition, which pave a more convenient way for the synthesis of fluorinated compounds. Detailed trifluoromethylation based on radical process will be put into emphasis in the next part.

3. Carbon-Carbon bond formation involved with trifluoromethyl radical
The strategies for producing trifluoromethyl radicals and trifluoromethylation of compounds such as olefins, aromatics and the like have been studied for decades. The production of trifluoromethyl
radicals (·CF₃) can be divided into three main types in theory: (1) Trifluoromethylated agents are homogenized to produce trifluoromethyl radicals; (2) Reduction of trifluoromethyl reagents to produce trifluoromethyl radicals; (3) Oxidation of trifluoromethyl reagents to produce trifluoromethyl radicals.

### 3.1. Trifluoromethylated agents are homogenized to produce trifluoromethyl radicals

The study of radical trifluoromethylation is kicked off by CF₃I. Haszeldine reported already in the late 1940s that CF₃ radicals are generated from CF₃I through C-I bond homolysis upon irradiation or heating. In the presence of ethene, he observed the formation of 3-iodo-1,1,1-trifluoropropane as the major product resulting from a radical addition/iodine transfer reaction [20](Figure 4).

![Figure 4. Radical trifluoromethylation of ethene with CF₃I [20].](image)

It is obvious that cheap and readily available reagent (CF₃I) as radical precursor holds the advantages of easy generation of ·CF₃. But from a practical point of view, experiments with gaseous CF₃I are not convenient to use and store. What's more, it is not easy to control the concentration, in particular when the reactions are conducted at higher temperature. Therefore, scientists have been looking for more convenient alternatives and have found that the electrochemical oxidation of trifluoroacetic acid cleanly generates CF₃ radicals. The scope of radical precursors was appreciably expanded toward the begin of the 1980s. With great effort, new trifluoromethyl radical precursors including CF₃SO₂X [21], Te(CF₃)₂ [22], trifluoroacetic anhydride [23], TFA under electrolysis [34] have developed.

In the nutshell, it can be seen that direct homogenization of radicals is mostly unsatisfactory due to the relatively active radicals themselves, in the stereoselectivity and yield. So the follow-up work focused on and gradually developed new approaches that utilizing moderate reduction or oxidation system to trigger and use ·CF₃ indirectly.

### 3.2. Reduction of trifluoromethyl reagents to produce trifluoromethyl radicals

Electrophilic trifluoromethylating agents (such as Togni’s reagent, Umemoto’s reagent) are equivalent to the use of CF₃⁺, usually with proton acids or Lewis acids activation to enhance their electrophilic properties. They can play a dual role of trifluoromethyl source and oxidant. Based on the single electron transfer (SET) and the changes of the valence state of the transition metal, the trifluoromethyl radicals are produced by the reduction of the trifluoromethyl reagents with the transition metal, and the catalytic cycle can be achieved. The reducing agent is the catalytic amount and the trifluoromethyl radical efficiency and reactivity are relatively high, and the selection of electrophilic trifluoromethylated reagents and transition metals is the key to such reactions.

In this part, due to the wide range of applications of the metal catalyst system causing increasing number of reactions in recent years, so only a few representatives of the work are shown in the table, and some of the special reactions are to a detailed analysis.

| ·CF₃ source | Reductants | Inventors | Year | Reference |
|-------------|------------|-----------|------|-----------|
| CF₃Br       | Zn and SO₂ | Wakselman | 1987 | [24]      |
| CF₃I        | Ir(ppy)₂(dtb-bpy)PF₆ | MacMillan | 2009 | [26]      |
| CF₃I        | H₂O₂, FeSO₄, DMSO | Yamakawa | 2010 | [27]      |
| CF₃I        | RuCl₂(PPh₃)₃ | Zakarian | 2012 | [28]      |
The presence of trifluoromethyl radicals initiated by the earliest reduction system was reported by Wakselman in 1987 with zinc and sulfur dioxide as complex reductants to produce ·CF₃ and then reacted with the substrate aniline [24]. With the gradual progress of the trifluoromethylation reaction, a variety of methods have been developed to install trifluoromethyl group into organic molecules, however, as mentioned above, these reaction conditions are often very intense, the stereoselectivity of the product is also unsatisfactory. Therefore, researchers in the later study, pay more attention to the development of the mild reduction system under with high yield, especially the better stereoselectivity. A "rational" new era of radical chemistry began.

Among the first reported investigations of a catalytic enantioselective electrophilic trifluoromethylation reaction was that of Ma and Cahard. They examined the use of chiral ammonium salts acting as phase-transfer catalysts for trifluoromethylation of β-ketoester, although the highest enantiomeric excess recorded was only 19% [25]. Enantioselective trifluoromethylation was not improved until MacMillan outstanding disclosure in 2009 of the asymmetric α-trifluoromethylation of aldehydes via the successful merger of organometallic photoredox catalysis 11 and enamine 12 [26]. MacMillan hypothesized that the enantioselective α-trifluoromethylation of aldehydes should also be possible by the marriage of two similar activation pathways (Figure 5).

In addition, a class of development is the use of commercial Umemoto reagent or Togni reagents, a new comers in the important field of trifluoromethylation chemistry, to avoid using toxic (CF₃I, a gas), ozone-depleting (CF₃Br, a gas), or corrosive (CF₃SO₂Cl, a low-boiling liquid) as a trifluoromethyl radical precursor. The Gouverneur group used the Umemoto's reagent as a precursor of trifluoromethyl radicals in 2013 (Figure 6) [30]. The hydrogenated radical trifluoromethylation of unactivated olefins in the presence of photocatalyst was reported for the first time by the ruthenium catalyst which catalyzed in the single electron reduction of electrophilic Umemoto reagent to generate CF₃ radicals. In the same year, the group also reported the ruthenium-catalyzed radical trifluoromethylation of allyl silanes with Togni reagents (Figure 6) [31].
In addition to the above-mentioned reaction to produce trifluoromethyl radicals, in recent years, trifluoromethyl precursors in the reduction system to produce trifluoromethylcarbene (CF₃CH₂) can also be seen as a further reduction of free radicals, through the C-H bond insertion reaction to generate C-C bond, which becomes a new type of powerful method for introducing trifluoromethyl group. Ma and co-workers have proposed to prepare CF₃CH₂NH₂ by CF₃CH₂NH₂·HCl in 2012 [33], introducing the
trifluoromethyl group into the alkyne under mild conditions with Cul as a catalyst. The reaction has a wide range of substrates, and the yield is high as well (Figure 7).

![Figure 7. Cu-catalyzed trifluoroethylation of terminal alkynes with CF₃CHN₂][33].

The above results show that the yield of this reaction to some extent depends on the activity of active hydrogen. As we know, the activity of hydrogen in benzyl and even in naphthenes is relatively low, so the yield of this reaction is only low to moderate as shown in the experiences. Nevertheless, this research provides a broader idea for the later development of this approach. As Langlois reagent, originally used in the benzene ring but shown unsatisfactory activity, finally developed into the heterocyclic ring which surprisingly shows a broad substrate range.

3.3. Oxidation of trifluoromethyl reagents to produce trifluoromethyl radicals.

This type of reaction mainly utilizes the oxidation system to achieve the trifluoromethylation reaction, and the most typical of which is the Langlois reagent. Story of this part will focus on this reagent.

The Langlois reagent is a mean of trifluoromethylation via using the CF₃SO₂Na/t-BuOOH system. Compared with CF₃I (gas) and CF₃SO₂Cl (liquid), Langlois reagent is the most preferable as it is inexpensive and easy to handle. Therefore, this excellent reagent is profound in the development of trifluoromethylation. This reagent's first appearance on the stage was in the work of the Langlois's group in 1991, with the following mechanism: in the absent of Cu(II), trifluoromethyl radicals can be generated from sodium trifluoromethanesulfinate (CF₃SO₂Na) with t-butylhydroperoxide (TBHP) as oxidant. However, the suitability and selectivity of the reaction substrate such as electron-rich benzene are not satisfactory (Figure 8) [35]. Indeed, Langlois et al. original report have specifically stated that productive reactions were only possible "provided that the substrates were substituted by mesomeric electron-releasing groups."

![Figure 8. Generation of the CF₃ trifluoromethanesulfinate][35, 36].
Due to the unsatisfactory yield, Langlois reagent wasn't regarded as a potential one and used widely at that time. Fortunately, however, a story of Bologna showed up in 2011. Baran et al. showed an elegant study that radical trifluoromethylation of arenes with sodium trifluoromethanesulfinate can be a excellent one (Figure 8) [36]. Unlike others, Baran held a novel view that Langlois reagent might have capacity in reactions with other substrates although its poor performance with benzene. Finally, he figured it out that various heteroarenes such as pyridines, pyrroles, indoles, pyrimidines, pyrazines, phthalazines, quinoxalines, deazapurines, thiadiazoles, uracils, xanthines and so on were successfully trifluoromethylated using this procedure in moderate to good yields (33-96%). As this reagent can efficiently trifluoromethylate in absence of any transition metal, especially in the scale of gram, CF₃SO₂Na now come back to the stage of trifluoromethylation of a series of drug molecules.

From then on, trifluoromethylation based on radical intermediates, as a valuable alternative transformation using the inexpensive and stable solid sodium trifluoromethanesulfinate (CF₃SO₂Na; Langlois reagent), has attracted much attention and has become a hot research field. The scope of the substrate from the original benzene, heterocyclic and other aromatic system extended to the olefins and so forth, and the reaction conditions become milder and greener. In 2014, Fennewald et al. developed a new trifluoromethylation reaction of hetero-cyclic compounds using CF₃SO₂Na (Figure 9) [37]. The catalyst TPGS-750-M and the oxidant TBHP were used for the first time to react with the water system at room temperature and a series of trifluoromethyl-substituted heterocyclic compounds were obtained in medium to excellent yield successfully. The advantage of this method is that the catalyst can be recycled several times and definitely environmentally friendly.

![Figure 9. Trifluoromethylation of heterocycles in water at room temperature [37].](image)

Now, through a series of reactions to build a ring system become increasingly important, and our CF₃SO₂Na also have a place in such construction. In 2016 the Maruokai group reported that CF₃SO₂Na was used in the improved oxidative agent PIFA (hypervalent iodine (III) oxidants) under mild conditions, with no metal involved in the construction of heterozygous systems of N-arylacrylamide in high yield [38].

4. Conclusions and perspectives
Progress in so many areas of societal need, from agrochemical to drug, relies on advances in the development of a new mild and environmental friendly C-CF₃ bond formation reaction. As shown in this review, methods for radical trifluoromethylation thrive on increasing molecular complexity. But there are still some unavoidable problems and challenges: firstly, the free radical reaction itself is poorly selective, as well as the product corresponding to poor selectivity, and some radicals generation need harsh reaction conditions. In addition, despite the development of various metal catalyzed reactions, now blind spots still exist. Correspondingly, the future prospects of the trifluoromethylation will focus on the development of new trifluoromethyl reagents, more efficient catalysts, and the expansion of the substrate structure scope. Indeed, the enantioselective trifluoromethylation is also at the forefront of researches in fluorine chemistry. Of special interests are low-cost and mild reaction conditions such as asymmetric trifluoromethylation reaction (enantioselective, regional selectivity) to synthesize a series of trifluoromethyl-containing chiral drug molecules providing chiral fluoride drugs convenient synthesis method. One thing is clear: the potential of trifluoromethylation reaction under the process of radicals is great, and it still has a long way to go.
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