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Decarboxylative Fluorination Strategies for Accessing Medicinally-relevant Products

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Abstract

Fluorinated organic compounds have a long history in medicinal chemistry, and synthetic methods to access target fluorinated compounds are undergoing a revolution. One powerful strategy for the installation of fluorine-containing functional groups includes decarboxylative reactions. Benefits of decarboxylative approaches potentially include: 1) readily available substrates or reagents 2) mild reaction conditions; 3) simplified purification. This focus review highlights the applications of decarboxylation strategies for fluorination reactions to access compounds with biomedical potential. The manuscript highlights on two general strategies, fluorination by decarboxylative reagents and by decarboxylation of substrates. Where relevant, examples of medicinally useful compounds that can be accessed using these strategies are highlighted.

Keywords

decarboxylation; fluorination; difluoromethylation; trifluoromethylation; copper

1) Introduction

Synthetic methods for the efficient incorporation of fluorinated functional groups enable the rapid construction of biologically interesting molecules and therefore, are important for medicinal chemistry [1–2]. Although many creative and elegant fluorination strategies have recently been developed [3–6], a need remains for new transformations that grant access to unique products and that rely on principles of green chemistry [7]. One emerging approach that has gained appreciation in non-fluorine chemistry involves decarboxylative coupling [8–9]. This strategy typically exhibits several appealing features, including the: 1) use of inexpensive and readily accessible starting materials; 2) ability to selectively generate reactive species under mild reaction conditions; 3) release of CO_2 as a benign and easily removed by-product [9]. Given these benefits, decarboxylative coupling represents an attractive approach for the installation of fluorine and fluorinated functional groups into organic compounds. The following manuscript discusses historical strategies for

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CONFLICT OF INTEREST
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decarboxylative fluorination to provide a framework for presenting recent developments in the field. The discussion is divided into two general sections: 1) decarboxylation of reagents to generate reactive fluorinated species; 2) decarboxylation of substrates to generate reactive species that can be converted to fluorinated functional groups. Within these two topics, only reactions that utilize decarboxylation to form new C–F or C–$C(F)_n$ bonds are considered.

2) Fluorination by Decarboxylative Reagents

2.1 Introduction to Reagents

The development of reactions that utilize inexpensive, atom-economical reagents represents a goal of green chemistry [7]. Halodifluoroacetic acids represent an attractive class of reagents that undergo decarboxylation to release reactive fluorinated species. While trifluoroacetic acid is the least expensive and most desirable reagent in this class, it decarboxylates slowly, and has an estimated half-life of 40,000 years at 15 °C in aqueous solution [10]. Trifluoroacetates have found synthetic utility as fluorinating reagents and will be discussed later in this section; however, decarboxylation typically requires stoichiometric Cu and reaction temperatures >150 °C [11–13]. Other halodifluoroacetic acids decarboxylate more rapidly (Fig. 1); however, metal catalysts, other reagents, and/or high temperatures are required to facilitate synthetically useful transformations.

In contrast, halodifluoroacetates decarboxylate to generate both $:CF_2$, and in the presence of F^-, $^-CF_3$, which can be utilized in a variety of synthetic transformations. The reactivity trend of halodifluoroacetic acids is consistent for both catalyzed and non-catalyzed conditions. Bromo-and chlorodifluoroacetates decarboxylate at lower temperatures (50–130 °C), and therefore, are more commonly employed than trifluoroacetates. These milder conditions allow for increased functional group compatibility, which in turn enables the installation of fluorinated groups into a broader array of molecules.

The present section focuses on reactions involving the use of halodifluoroacetates as sources of $:CF_2$ and $^-CF_3$, and concludes with discussion of other decarboxylative fluorination reagents closely related to halodifluoroacetates.

2.2 Decarboxylative Trifluoromethylation of Halodifluoroacetate Esters

Activated alcohols have been converted to trifluoromethanes *via* a two-step procedure involving formation of a halodifluoroacetic ester followed by reaction with stoichiometric CuI in the presence of fluoride (Fig. 2) [14]. Substrates were limited to simple primary allylic, benzylic, and propargylic alcohols. Allylic and benzylic halodifluoroacetates underwent formal S_N2 substitution, while propargylic chlorodifluoroacetates underwent formal S_N2' substitution to yield trifluoromethylallenes [14]. Bromodifluoroacetic esters displayed greater reactivity than chlorodifluoroacetic esters, and produced higher yields (ca. 10%) at 20–30 °C lower reaction temperatures [14]. Most commonly, a two-step procedure was employed in which an activated alcohol was converted to a halodifluoroacetate, purified, and then subjected to stoichiometric CuI and KF. A two-step, one-pot procedure was also developed that utilized ethyl halodifluoroacetates and afforded the product in moderate to low yield [14].

The mechanism of Cu-mediated decarboxylative trifluoromethylation was proposed to proceed by a multi-step process that involves both Cu^{I} and the I^{-} counterion (Fig. 3) [14]. Initially, the halodifluoroacetic ester reacted with CuI to yield an organic iodide and CuO_2CCF_2X (Fig. 3A). Next, CuO_2CCF_2X decarboxylated to generate CuX, CO_2, and $:CF_2$ (Fig. 3B). In the presence of KF, an equilibrium was established that formed $^{-}CF_3$ (Fig. 3C). CuI subsequently reacted with $^{-}CF_3$ to form $Cu–CF_3$ (Fig. 3D). Finally, $Cu–CF_3$ reacted with the organic iodide to yield the trifluoromethyl product (Fig. 3E). Product was not formed in the absence of either CuI or KF [14].

This procedure has been employed to access an allylic trifluoromethyl building block, as a precursor to biologically relevant molecules. In one example, a one-pot, two-step conversion of an allylic alcohol to an allylic trifluoromethane was employed for the synthesis of the COX-2 inhibitor, L-784,512 (Fig. 4) [15]. Initial treatment of alcohol **1** with chlorodifluoroacetic anhydride in the presence of *N*,*N*-diisopropylethylamine (DIPEA) yielded intermediate ester **2**. Addition of KF and stoichiometric CuI and heating at 90 °C for 1 h, provided the product trifluoromethane **3** in high yield. Interestingly, DIPEA was critical for the reaction, as the use of NEt_3, pyridine, or K_2CO_3 resulted in formation of the corresponding allylic chloride, and 30–60% lower yield of desired product. The one-pot procedure was more efficient than a two-step procedure in which alcohol **1** was first converted to an allylic iodide, and subsequently treated with CuI and MeO_2CCF_2Cl. Subjection of trifluoromethane **3** to Sharpless asymmetric dihydroxylation, alcohol oxidation, and coupling/cyclization reactions afforded L-784,512 [15].

Recent research has focused on the development of more green reaction sequences that utilize catalytic quantities of Cu. Towards this end, the decarboxylative trifluoromethylation of primary allylic bromodifluoroacetates was conducted in the presence of catalytic CuI (Fig. 5) [16]. A variety of functional groups were tolerated, including aryl halides, N- and O-containing functional groups, and a variety of substitution patterns on the alkene. The system benefited from the use of *N*,*N*'-dimethylethylenediamine (DMEDA) as a ligand, and a catalyst activation procedure in which a solution of CuI, DMEDA, and NaO_2CCF_2Br were heated before the addition of substrate. The procedure presumably generated a DMEDA–$Cu–CF_3$ species that facilitated entry into the catalytic cycle (Fig. 5). The $Cu–CF_3$ species generated during activation presumably underwent substitution with allylic bromodifluoroacetate, resulting in the formation of product and DMEDA–$Cu–O_2CCF_2Br$. Decarboxylation and formal halogen exchange allowed catalyst turnover and regeneration of a DMEDA–$Cu–CF_3$ species. Unlike the proposed mechanism for the Cu-mediated allylic trifluoromethylation, the mechanism of the Cu-catalyzed reaction did not invoke an allylic iodide intermediate; control reactions provided comparable yields in the presence and absence of iodide. For substrates containing *Z*-alkenes, isomerization to more stable *E*-alkene products was observed (Fig. 5). Therefore, this allylic substitution might proceed *via* a π–allyl intermediate, which has been invoked to explain substitution reactions of allylic halides and trifluoroacetates from well defined $(PPh_3)_3Cu–CF_3$ complexes [17] and $Cu–CF_3$ complexes generated *in situ* [18].

2.3 Aromatic Trifluoromethylation

A series of trifluoromethylating reagents, including halodifluoroacetate salts and esters, and fluorosulfonyldifluoroacetate salts and esters were developed [19–27], and have been applied to the trifluoromethylation of aryl and heteroaryl halides (Fig. 6) [19–30]. Generally, these reagents undergo Cu-mediated decarboxylation of the reagent *in situ* to release :CF_2, and then react with F^- to generate $^-CF_3$. Most of these reagents are commercially available, and those that are not, such as $KO_2CCF_2SO_2F$, are easily accessible [26]. Historically, aryl trifluoromethylation reactions with these reagents required high temperatures, stoichiometric CuI, and polar solvents such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMAc). For these reactions, reactivity trends of aryl and heteroaryl halides mimic trends of other Cu-based coupling reactions (Ar–I > Ar–Br ≫ Ar–Cl) [31]. The introduction of electron-withdrawing groups, such as NO_2, to the aromatic ring can improve the reactivity of aryl halides, especially aryl chlorides.

Traditionally, decarboxylative aromatic trifluoromethylation required stoichiometric CuI; however recently, reactions utilizing catalytic Cu^I were reported [29–30]. In one example, the Weinreb amide derived from a 5-bromo-2-iodobenzoic acid underwent trifluoromethylation in the presence of $MeO_2CCF_2SO_2F$ and catalytic CuBr (Fig. 7) [29]. In this unique example, the amide may have served as a directing group to help facilitate the reaction. For substrates lacking directing groups, Cu-catalyzed reactions have been achieved through the use of 1,10-phenanthroline as a ligand (Fig. 7) [30]. Unfortunately, when this Cu-catalyzed reaction was conducted on a multi-kilogram scale, the formation and separation of $Ar(CF_2)_nCF_3$ side products proved problematic [30]. These byproducts resulted from insertion of :CF_2 into Cu–CF_3, and were suppressed by reverting to the use of stoichiometric CuI.

Fluorine-18-labelled organic molecules are used for positron emission tomography (PET) [32]. Recently, a method of decarboxylative trifluoromethylation enabled the preparation of Ar–CF_3[^{18}F] based PET imaging agents (Fig. 8) [32]. This procedure generated radiolabeled Cu–[^{18}F]CF_3 *in situ* from MeO_2CCF_2Cl, CuI, *N*,*N*,*N’*,*N’*-tetramethylethylenediamine (TMEDA), and [^{18}F]KF/kryptofix. Under the reaction conditions, a diverse set of aryl and heteroaryl iodides were rapidly trifluoromethylated. While some medicinally important functional groups, such as acids and amines, were not compatible with the reaction conditions, an example of a successful protection strategy was demonstrated by synthesis of [^{18}F]fluoxetine (selective serotonin reuptake inhibitor) (Fig. 8). Due to the large scope of substrates and operational simplicity, this transformation should facilitate the drug discovery process. For more details on PET imaging agents, the reader is referred to an alternate article [33].

Compared to halodifluoroacetates, trifluoroacetic acid derivatives represent more ideal reagents for trifluoromethylation, because they are less expensive and do not require the addition of fluoride to generate $^-CF_3$. To this end MeO_2CCF_3 has served as a trifluoromethylating reagent in the presence of stoichiometric CuI and promoters, such as CsF or CsCl [34]. The trifluoromethylation of aryl and heteroaryl halides (the reactivity: ArI > ArBr ≫ ArCl) using MeO_2CCF_3 provided the corresponding benzotrifluorides in 42–79%

yield, using DMF at 180 °C or sulfolane at 140–180 °C. However, the use of stoichiometric Cu limits the economic value of the transformation, and the development of a method that employs only catalytic quantities of a Cu salt represents a desirable target. The CuI-catalyzed decarboxylative trifluoromethylation of aryl and heteroaryl halides with MeO_2CCF_3 using CsF as initiator provided products in 47–95% yield (Fig. 9). To achieve the catalytic variant, MeO_2CCF_3 was added at a rate so that the slow decarboxylation step (k_1) matched the consumption of $CuCF_3$ in the aromatic trifluoromethylation step (k_2). For some less active aryl bromides, the use of 1,10-phenanthroline as ligand proved helpful for the trifluoromethylation reactions [35].

Alkali trifluoroacetate salts are also inexpensive and readily available, and represent attractive sources of CF_3 for large-scale processes. As early as 1981, the decarboxylative trifluoromethylation of aryl iodides and bromides occurred using NaO_2CCF_3 in the presence of CuI [36]. Further investigations confirmed the reactivity of a cuprate, $[F_3CCuI]^-$, with aryl halides to deliver the trifluoromethylated products (Fig. 10A) [11]. Although the use of the trifluoroacetate salts makes this a desirable protocol for trifluoromethylation, the use of stoichiometric CuI and high reaction temperature to promote decarboxylation (160–180 °C) limited the method to reactions of stable substrates. To address this problem, the use of Ag_2O as an additive (30–40 mol%) allowed the analogous CuI-catalyzed reaction of aryl iodides to occur using NaO_2CCF_3 at reduced temperature (130 °C) [37]. For this reaction, the Ag_2O was essential, and might lower the activation energy of decarboxylation of sodium trifluoroacetate to generate $AgCF_3$ *in situ* (Fig. 10B).

Another commercially available trifluoroacetate salt, KO_2CCF_3, can also be used in the trifluoromethylation of aryl and heteroaryl halides. The CuI-mediated trifluoromethylation of a bromotetrahydronaphthalene with KO_2CCF_3 afforded the product in 35% yield [38], and the CuI-mediated trifluoromethylation of *N*-protected 5-bromoisoindoline with KO_2CCF_3, using toluene as co-solvent, provided the desired product in 90% yield [39]. However, the reaction time of the latter was far less than the former (1.5 h *vs.* 2 d), which may be attributed to the electron-withdrawing group at the *meta*-position of the bromide or the coordinating ability of the –OMe group (Fig. 11).

Chemical reactions conducted in flow microreactors have several advantages over traditional reaction vessels including: 1) precise control of reaction variables, such as temperature and rates of mixing; 2) increased safety profiles; 3) the ability to perform multiple transformations without isolating potentially reactive species [40]. Flow chemistry has facilitated various fluorination reactions, and recently, enabled the rapid and efficient trifluoromethylation of aryl and heteroaryl iodides using KO_2CCF_3 [41]. In the flow reactor, a solution of KO_2CCF_3, CuI and pyridine in NMP was mixed with a solution of aryl or heteroaryl iodides, and the mixture was introduced into a stainless steel tube reactor submerged in a preheated 200 °C bath using an optimized 16 minutes residence time (Fig. 12). At this point, the mixture was diluted with a stream of ethyl acetate (controlled with a back regulator), and the resulting mixture was collected and purified to afford trifluoromethylated arenes in good to excellent yields [41].

In addition to the systems described above, trifluoromethylation of aryl halides has been accomplished using well-defined NHC–Cu–O_2CCF_3 and –O_2CCF_2Cl complexes. Upon heating, the complexes released CO_2 and generated NHC–Cu–CF_3, which reacted with aryl electrophiles [42]. When aryl halide was used as the solvent, the ligated copper complex provided trifluoromethylated products in higher yields than “ligandless” CuI. However, when the aryl halide was used as only a co-solvent with DMAc, the copper complexes did not perform superior to reaction of CuI with MO_2CCF_3 and MO_2CCF_2Cl (Fig. 13).

2.4 Difluoroolefination

Halodifluoroacetate salts can also serve as regents for difluoroolefination reactions (Fig. 14). An early one-step synthesis of l,l-difluoroolefins involved heating a solution of an aldehyde, PPh_3 and NaO_2CCF_2Cl [43].

Three mechanisms were proposed for the conversion of carbonyl compounds to difluoroolefins (Fig. 15) [44]. Mechanism A would involve the decomposition of NaO_2CCF_2Cl to generate :CF_2, which would then react with PPh_3 to form a phosphonium ylide. In the presence of a carbonyl compound, the phosphonium ylide could then react *via* a Wittig mechanism to form product [43]. Mechanism B involved initial reaction of NaO_2CCF_2Cl and PPh_3 to generate $Ph_3P^+CF_2CO_2^-$. This species would then decarboxylate to form the common phosphonium ylide species. Finally, mechanism C would involve a reaction between NaO_2CCF_2Cl and PPh_3 to form an enolate and a phosphonium species, which would decompose to form a phosphonium ylide.

In order to distinguish between these potential reaction pathways, a series of experiments were conducted. First, NaO_2CCF_2Cl and PPh_3 were heated in the presence of two :CF_2-trapping reagents, tetramethylethylene and isopropyl alcohol. Formation of difluorocyclopropane was not observed, which suggested that free :CF_2 was not present in solution [45]. A second experiment monitored the evolution of CO_2, when NaO_2CCF_2Cl was heated in the presence and absence of PPh_3 [45]. The decomposition of the salt was accelerated in the presence of PPh_3, and required only 4–6 h to evolve 70% of the theoretical amount of CO_2. In contrast, the decomposition of the salt in the absence of PPh_3 was slow, and required 17 h to achieve a comparable result. These data were able to discount mechanism A; however, could not be used to differentiate mechanisms B and C.

The difluoroolefination reaction was later applied to various classes of ketones. For activated ketones (Fig. 16A), good to excellent yields of difluoroalkenes were obtained using the standard reaction conditions (PPh_3, NaO_2CCF_2Cl, diglyme, 105 °C) [46]; however, non-activated substrates did not provide substantial quantities of products. Replacement of PPh_3 and diglyme with $P(^nBu)_3$ and *N*-methylpyrrolidone (NMP) (Fig. 16B) allowed for the extension of the difluoromethylation reaction to some non-activated ketones [47]; however in some cases, transfer of a butylidine group to the ketone formed a butylidine side product [48]. Formation of this butylidene product occurred during the reaction with various electrophilic substrates, including cyclohexanone, heptanal, and trifluoroacetophenone. In the latter case, only the butylidene product was isolated from the reaction mixture [48].

A rearrangement mechanism was proposed to explain the formation of butylidene product (Fig. 17) [48]. However, further studies revealed that the butylidene product was directly formed *via* reaction of $P(^nBu)_3$ and trifluoroacetophenone (Fig. 18) [49].

While earlier researchers favored mechanism B (Fig. 15) (formation of Ph $P_3P^+CF_2CO^-2$, decarboxylation to provide $Ph_3P{=}CF_2$, then Wittig difluoromethylenation), they were unable to isolate the key intermediate, $Ph_3P^+CF_2CO_2^-$. Recently, the synthesis and characterization of the key difluoromethylene phosphobetaine provided direct evidence for this reaction mechanism [50]. To identify the proposed intermediate, PPh_3 was reacted with KO_2CCF_2Br instead of NaO_2CCF_2Cl, which allowed for the substitution reaction to proceed under mild conditions, which allowed for the isolation of $Ph_3P^+CF_2CO_2^-$ in good yield (Fig. 19). $Ph_3P^+CF_2CO_2^-$ was stable to storage in under ambient conditions, and provided a convenient new reagent for the difluoromethylenation of aldehydes. Moreover, replacement of PPh_3 with $P(NMe_2)_3$ provided an alternate reagent, $(Me_2N)_3P^+CF_2CO_2^-$ that reacted well with non-activated ketones [50].

2.5 Cyclopropanation

Decarboxylative strategies have also been employed for the preparation of fluorinated cyclopropanes. Early studies showed that thermolysis of NaO_2CCF_2Cl generated $:CF_2$, which reacted with cyclohexene to provide 60–65% of the theoretical amount of CO_2 in addition to 22% of difluoronorcarane (Fig. 20) [51].

Later, this strategy was applied to the difluorocyclopropanation of conjugated steroidal dienes [52]. Both di- and tri-substituted alkenes reacted with $:CF_2$ to provide a mixture of isomeric adducts (Fig. 21). In addition, the conjugated double bond of an enone system was also underwent difluorocyclopropanation [53]. However, high temperature 165–225 °C and large amount of NaO_2CCF_2Cl (20–50 equiv) were required. Control studies showed that cyclopropanation did not occur below 150 °C, even though decomposition of the salt occurred at 125 °C.

This strategy was also applied for difluorocyclopropanation of other nonsteroidal alkenes, including (*Z*)-4-(benzyloxy)-2-butenylacetate [54]. However, high temperature (190 °C) and excesses NaO_2CCF_2Cl (11 equiv) were required to obtain reasonable yields. Subsequent Zemplén deacetylation and Mitsunobu reactions allowed for the preparation of a large number of nucleoside analogues as potential chemotherapeutic agents (Fig. 22A). This strategy was also amenable to the stereospecific preparation of boron-substituted *gem*-difluorocyclopropanes [55], which could be rapidly transformed to afford functionalized *gem*-difluorocyclopropanes *via* lithium carbenoids or by subsequent oxidation (Fig. 22B). Moreover, this strategy was used to synthesize *cis*- or *trans*-4,5-difluoromethanoproline through difluorocyclopropanation of the aminoacyl derivatives of 4,5-dehydroproline [56]. The two building blocks were stable and could be easily incorporated into the proline-rich SAP peptide (Fig. 22C). Subsequently, a convenient synthesis of fluorinated cyclopropanes and cyclopropenes was developed using NaO_2CCF_2Br as a source of $:CF_2$ [57]. Compared to NaO_2CCF_2Cl, NaO_2CCF_2Br was less hygroscopic at room temperature, and thus, easier to handle. Further reactions using NaO_2CCF_2Br were more efficient, and tolerated the presence of electron-deficient substrates (Fig. 22D).

The use of an alternative source of $:CF_2$, trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), provided access to difluorocyclopropanes under more mild conditions [58] (Fig. 23A). In the presence of catalytic fluoride, TFDA easily decomposed to generate $:CF_2$ (105 °C), and difluorocyclopropanes were obtained in high yields. The moisture-sensitive nature of TFDA provided a poor shelf life, and made the reagent relatively challenging to handle. Therefore, a more stable and convenient reagent was designed [59]. This new reagent, $MeO_2CCF_2SO_2F$, in combination with KI and TMSCl exhibited comparable reactivity as TFDA at high concentration and high temperature [60]. Using $MeO_2CCF_2SO_2F$, a broad range of alkenes was converted into the corresponding difluorocyclopropanes, even including unreactive *n*-butyl acrylate (Fig. 23B). To contrast the usage of $MeO_2CCF_2SO_2F$ and TFDA, sodium trifluoroacetate can also serve as a precursor to $:CF_2$ [61]. NaO_2CCF_3 decomposed at 170 °C in the presence of AIBN to form $:CF_2$, which then reacted with a variety of alkenes. Given the inexpensive nature of NaO_2CCF_3, this procedure provided an economical method for difluorocyclopropanation of robust substrates.

Historically, little overlap existed between reactions that generate $:CF_2$ and difluoromethylene phosponium ylides. MO_2CCF_2X-based reagents decarboxylated to form reactive $:CF_2$ species that were used to generate difluorocyclopropanes. In contrast, regents derived from MO_2CCF_2X and PPh_3 generated difluoromethylene phosphonium ylides for difluoroolefination reactions. However recently, the interconversion between difluoromethylene ylide and $:CF_2$ was successfully achieved [62]. By changing the solvent from DMF to less-polar *p*-xylene, $Ph_3P^+CF_2CO_2^-$ was converted from a precursor of difluoromethylene phosphonium ylide to an efficient precursor of $:CF_2$ (Fig. 19 and 24A). In contrast, under the corresponding reaction conditions, other reagents only generated the difluoromethylene phosphonium ylide (Fig. 24B and C). Therefore, $Ph_3P^+CF_2CO_2^-$ holds unique status as a reagent that can generate reactive species for both difluoroolefination or difluorocyclopropanation reactions.

The reactive $:CF_2$ intermediate has also undergone cycloadditions with alkynes to access strained difluorocyclopropenes. Using this strategy, a number of difluorocyclopropenyl steroids were synthesized (Fig. 25A) [63]. Difluorocylopropenes were also used as precursors to biologically active compounds that showed potent insecticidal activities (Fig. 25B) [64]. Using the same strategy, a simple and efficient method for the preparation of 3,3-difluoroiodocyclopropenes provided access to interesting fluorinated building blocks [65]. In this case, the combination of TDFA and NaF (10 mol%) generated $:CF_2$, which subsequently reacted with the alkynyl iodide. These new iodides were further functionalized by: 1) Heck type cross-coupling reactions with α,β-unsaturated compounds; 2) trifluoromethylation using CuI and TFDA; 3) hydrolysis under acidic conditions to provide ring opened β-alkyl-β-iodoacrylic acids with exclusive *Z*-configuration (Fig. 25C).

2.6 Heteroatom Difluoromethylation

Reactive $:CF_2$ intermediates, generated from NaO_2CCF_2Cl, have also inserted into heteroatom–H bonds to provide difluoromethylated ethers and amines. At only 95 °C, NaO_2CCF_2Cl decarboxylated in the absence of any transition metal catalyst to afford $:CF_2$, which was directly trapped with a variety of aromatic and heteroaromatic thiols [66].

Further, the difluoromethylation of nitrogenous heterocycles and phenylselenol were also successful (Fig. 26).

3) Fluorination and Trifluoromethylation of Substrates that Undergo Decarboxylation

3.1 Decarboxylation of Acrylic Acid Derivatives

In the preceding section, trifluoromethylation and difluoromethylenation reactions were realized by decarboxylation of fluorine-based reagents to generate CF_3^-, $:CF_2$ or $F_2C{=}PR_3$. Contrary to this strategy, fluoroalkylation and fluorination can also involve decarboxylation of the substrate in the presence of fluoroalkylating or fluorinating reagents. This developing strategy already provides medicinal chemists facile access fluoroalkyl-substituted alkenes, α-trifluoromethyl ketones, alkyl fluorides, and [^{18}F]-labeled di- and tri-fluoromethylated arenes directly from a vast number of carboxylic acids that already exist in pharmaceutically important building blocks [67–75].

A series of Cu-mediated decarboxylative fluoroalkylation reactions were developed that converted α,β-unsaturated [67], β,γ-unsaturated [68], and propargylic [69] carboxylic acids to fluorinated species using Togni-type electrophilic fluoroalkylating reagents (Fig. 27) [76–77]. Using the combination of catalytic CuF_2 and I^{III}–CF_3 reagents, a variety of α,β-unsaturated acids were stereoselectively converted to *E*-vinyl trifluoromethanes [67] (Fig. 27A). Similarly, *E*-vinyl difluoromethylsulfones could be accessed using a DMEDA–Cu^{II} catalyst system, and an I^{III}–CF_2SO_2Ph reagent (Fig. 27B). Allylic difluoromethylsulfones could also be formed in regioselective fashion from β,γ-unsaturated carboxylic acids (Fig. 27C) [68]. Representative difluoromethylsulfone products could be subjected to reducing conditions and converted to allylic difluoromethanes, which are difficult to selectively access using other methods. Finally, propargylic alcohols were converted to trifluoroethylketones using stoichiometric $Cu(OAc)_2$, DMEDA, and a Togni trifluoromethylating reagent (Fig. 27D) [69]. This unique result, in which an oxygen atom originating from water was incorporated into the product, was rationalized by considering inherent differences in substrate reactivity in the context of the proposed mechanisms.

While the mechanisms of the above decarboxylative fluoroalkylation reactions might share similar intermediates, distinct properties of the substrates provided discrete products. According to the proposed mechanisms for both substrates, Cu^{II} served as a Lewis acid, and facilitated the reaction by; 1) increasing the electrophilicity of the Togni-type reagents; 2) promoting decarboxylation; 3) coordinating substrates and reagents to bring reactive centers into close proximity. The following mechanism was proposed for the decarboxylative difluoromethylsulfonylation of α,β-unsaturated acids (Fig. 27E) [67]. DMEDA–CuF_2 underwent ligand exchange to form a highly electrophilic species **I**. Another ligand exchange would form ternary complex **II**, thus placing the π–system of the alkene in close proximity to the iodonium group. Nucleophilic attack by the alkene would generate carbocationic intermediate **III**, which could decarboxylate to form vinyl–I^{III} species **IV**. Reductive eliminate would provide product, and a series of ligand exchanges would regenerate the DMEDA–CuF_2 catalyst. When propargylic carboxylic acids were used as

substrates, the initial steps of the proposed mechanism would be identical, and intermediate **VI** would form (analogous to **II**) [69]. The more difficult nucleophilic attack of the alkyne in **VI** towards the iodonium could alter the mechanism (Fig. 27F). In one case, attack of the iodonium by π–electrons of the alkyne would provide a high-energy vinyl cation (Path 1). This species could be quenched with water to form intermediate **VII**, which would eventually provide product. An alternate mechanism involved the iodonium acting as a π–acid to activate the alkyne for nucleophilic attack by H_2O (Path 2). Intermediate **VII** would then undergo subsequent tautomerization, decarboxylation, and reductive elimination to form the trifluoroethylketone product [69].

Several complementary decarboxylative methods for the construction of *E*-configured C_{vinyl}–CF_3 and C_{vinyl}–CF_2 bonds *via* radical addition–elimination processes were recently developed [70–71]. A variety of (heteroaryl)cinnamic acids were converted to vinyl trifluoromethanes using catalytic $CuSO_4{\cdot}5H_2O$, stoichiometric TBHP, and $NaSO_2CF_3$ as a source of $\cdot CF_3$ (Fig. 28A). An alternative procedure enabled the conversion of electron-rich cinnamic acids to difluoromethanes using Fe-catalysis with $(CF_2HSO_2)_2Zn$ (DFMS) as a source of $\cdot CF_2H$. While both of these methods utilized mild reaction conditions, the substrate scope was limited to (heteroaryl)cinnamic acids. Alkyl-substituted acrylic acids failed to give the desired products, which might arise from the instability of a radical intermediate. Subsequently, a similar strategy was applied to the $FeCl_3$-mediated decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids [71]. A variety of (heteroaryl)cinnamic acids were compatible with the reaction conditions (Fig. 28B). More importantly, the reaction could be conducted under an open atmosphere. Decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids was also accomplished by photoredox catalysis [72]. *fac*-$Ir(ppy)_3$ served as a photocatalyst and generated CF_3 from Togni reagent. The mild reaction conditions provided excellent functional group compatibility, and moderate to high yields of products were obtained (Fig. 28C).

3.2 Decarboxylation of Aromatic and Aliphatic Acid Derivatives

Recently, the selective fluorination of organic compounds *via* a radical mechanism was successfully achieved [73]. In this reaction, decomposition of diacylperoxies or *tert*-butylperoxiacids generated organic radicals, which reacted with *N*-fluorobenzenesulfonimide (NFSI) to afford alkyl fluorides. This procedure demonstrated that alkyl radicals could undergo fluorine atom transfer to from alkyl fluorides. A broad range of alkyl radicals, including primary, secondary, tertiary, benzylic, and heteroatom-stabilized radicals underwent fluorination. In some cases, the products of the reactions would have been difficult to access using electrophilic or nucleophilic fluorination procedures.

Ag-catalyzed decarboxylative fluorinations of carboxylic acids have recently been developed [74–75]. Aliphatic carboxylic acids were converted to the corresponding alkyl fluorides using $AgNO_3$ and Selectfluor® in aqueous acetone [74]. A catalytic cycle invoking Ag^I, Ag^{II}, and Ag^{III} was proposed (Fig. 30A). The mechanism initiated with the reaction of Ag^I and Selectfluor® to provide Ag^{III}–F. Single electron transfer then generated Ag^{II}–F and a carboxyl radical, which decarboxylated to form the corresponding alkyl radical. Reaction

of Ag^{II}–F with the organic radical then provided the fluorinated product [74]. Under similar reaction conditions, di- and trifluoromethylated arenes were synthesized from readily available α, α-difluoro- and α-fluoroarylacetic acids (Fig. 30B) [75]. Adaptation of this system to the usage of [^{18}F]Selectfluor bis(triflate) provided access to ^{18}F-radiolabeled products. Compared to the usage of [^{18}F]F_2, the $AgNO_3$/[^{18}F]Selectfluor bis(triflate) system offered an expanded scope of substrates and in several examples, provided higher radiochemical yields.

CONCLUSION

Methods for the synthesis of fluorinated organic compounds are important for medicinal chemistry as they enable the facile construction of biologically interesting molecules. In recent years, new methods for the installation of fluorine-containing functional groups have been developed that utilize powerful strategies, including decarboxylative coupling. As the field of synthetic organofluorine chemistry continues to advance, decarboxylative coupling should play an important role in the development of more general, functional-group tolerant, and practical synthetic methods for the synthesis of fluorinated compounds.

Acknowledgments

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LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMAc	Dimethylacetamide
DMEDA	*N N'*-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
NFSI	*N*-Fluorobenzenesulfonimide
NMP	*N*-Methyl-2-pyrrolidone
MDFA	Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate
TBHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetic acid
TFDA	Trimethylsilyl fluorosulfonyldifluoroacetate

TMEDA	*N*,*N*,*N*’,*N*’-Tetramethylethylenediamine
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

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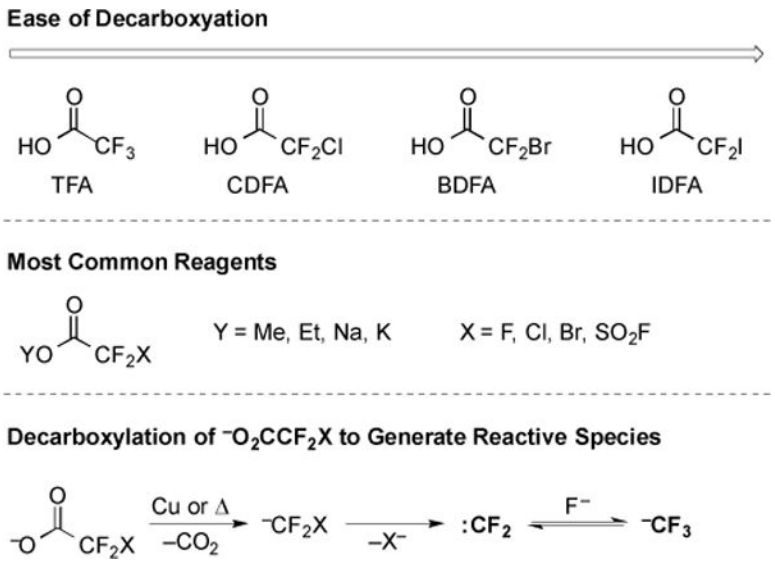

Fig. (1).
Reactivity of halodifluoroacetates.

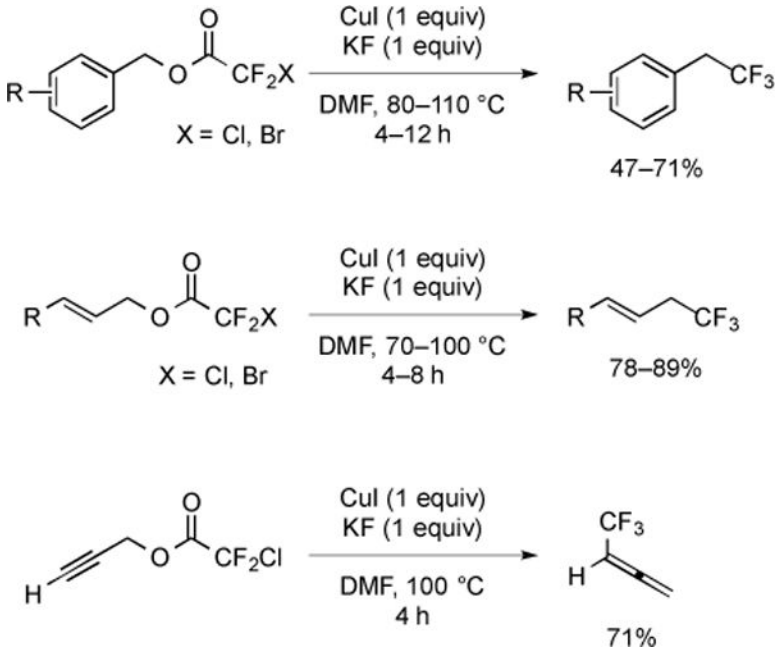

Fig. (2).
Decarboxylative trifluoromethylation of activated halodifluoroacetates.

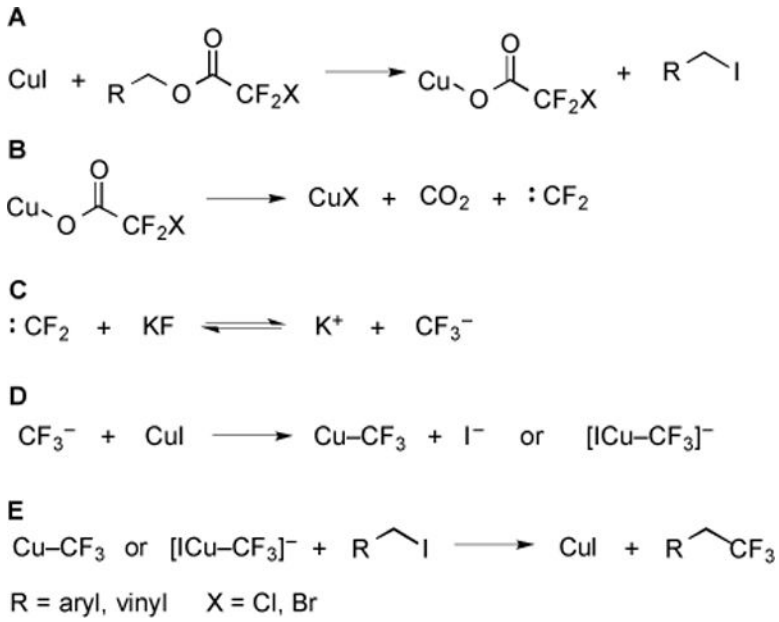

Fig. (3).

Proposed mechanism for CuI-mediated conversion of halodifluoroacetic esters to trifluoromethanes.

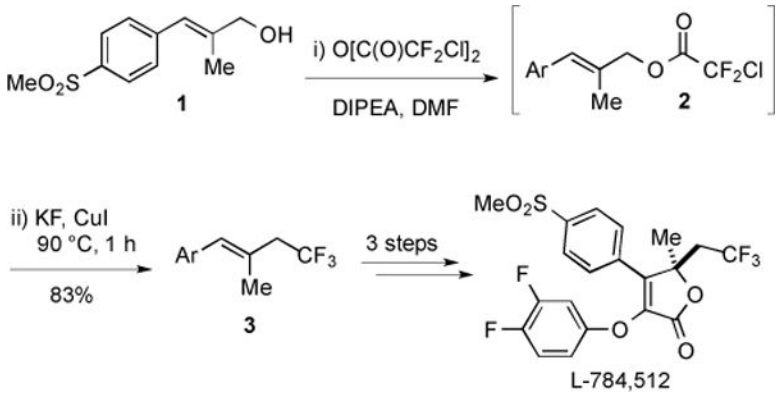

Fig. (4).

Decarboxylative trifluoromethylation employed in the synthesis of L-784,512.

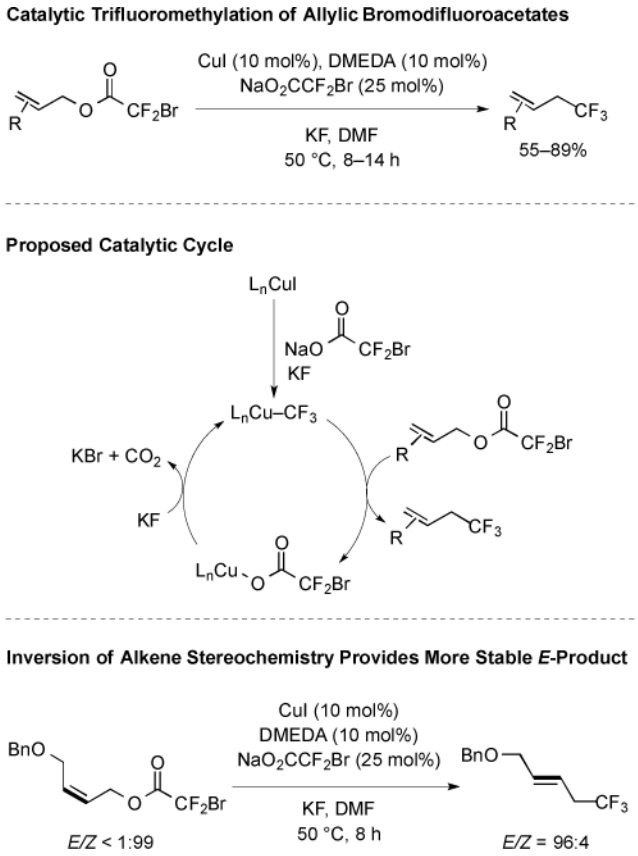

Fig. (5).
Cu-catalyzed decarboxylative trifluoromethylation.

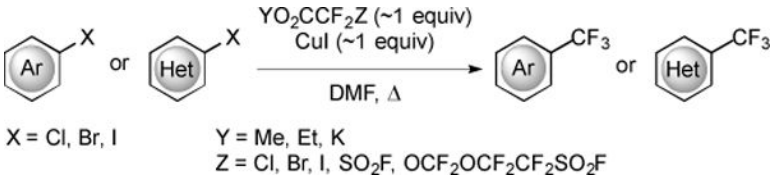

Fig. (6).
Trifluoromethylation of aromatic halides.

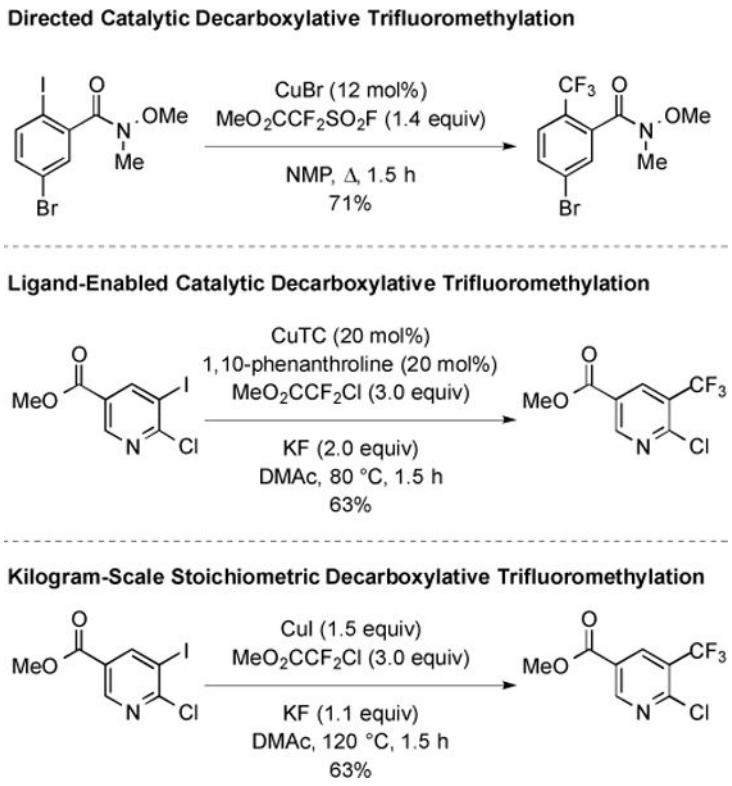

Fig. (7).
Recent developments in decarboxylative aromatic trifluoromethylation.

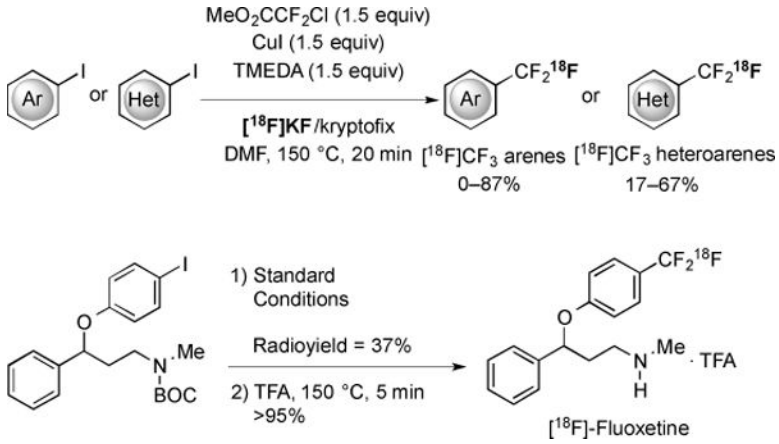

Fig. (8).

The synthesis of ^{18}F-labelled trifluoromethylated arenes.

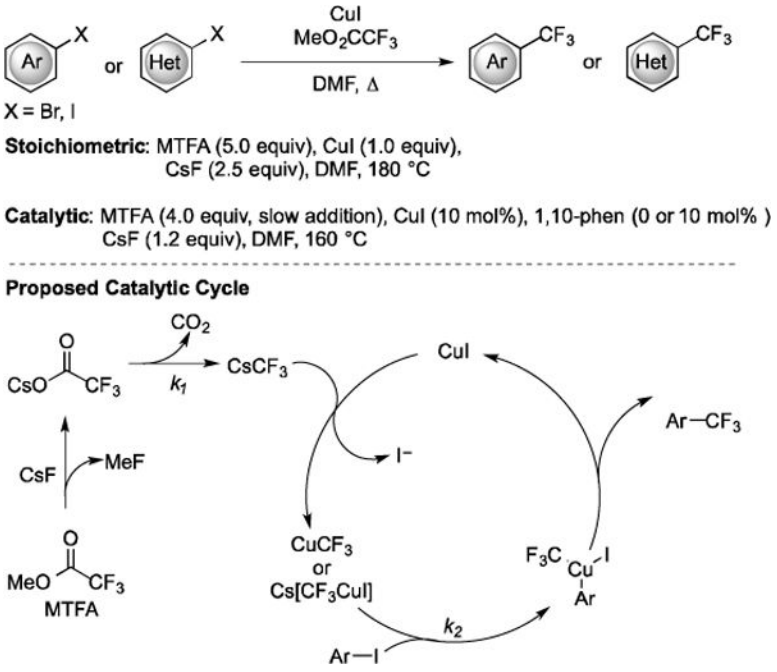

Fig. (9).

The stoichiometric and catalytic decarboxylative trifluoromethylation of aryl halides using MeO_2CCF_3.

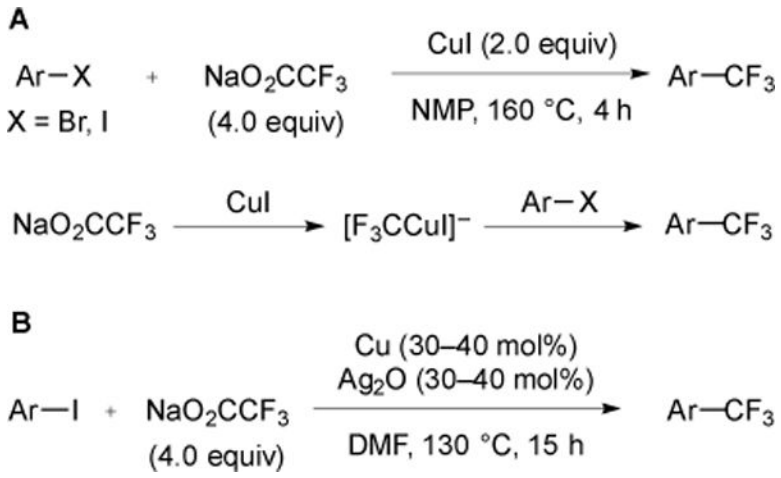

Fig. (10).

The stoichiometric (A) and catalytic (B) decarboxylative trifluoromethylation of aryl halides using NaO_2CCF_3.

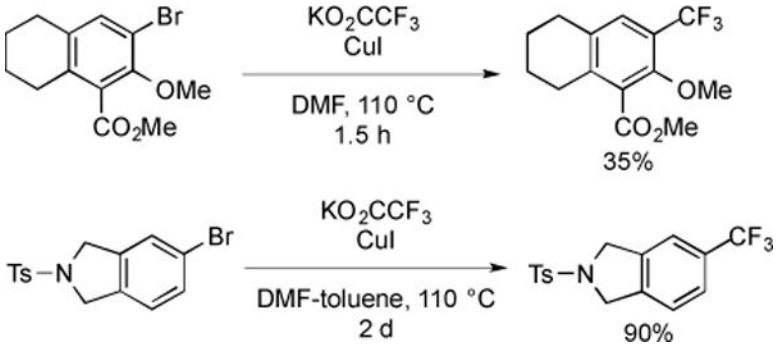

Fig. (11).
The decarboxylative trifluoromethylation of aryl bromides using KO_2CCF_3.

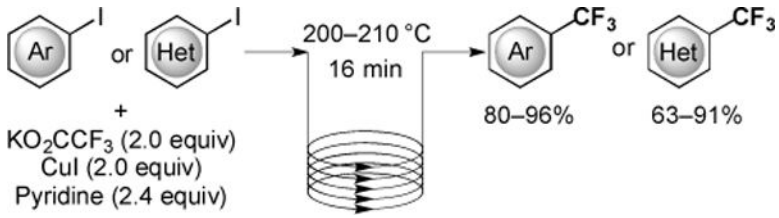

Fig. (12).

The decarboxylative trifluoromethylation of aromatic halides using KO_2CCF_3 in a flow reactor.

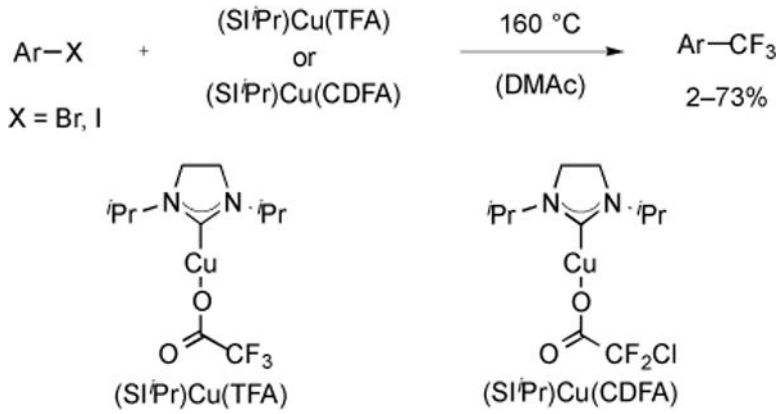

Fig. (13).
Decarboxylative trifluoromethylation of aryl halides using well-defined copper complexes.

Fig. (14).
General strategy of difluoroolefination.

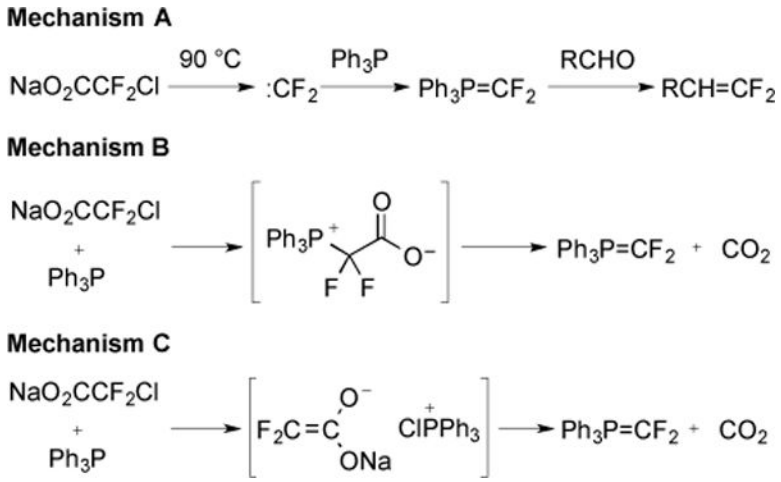

Fig. (15).
Mechanisms for the formation of l, l-difluoroolefins.

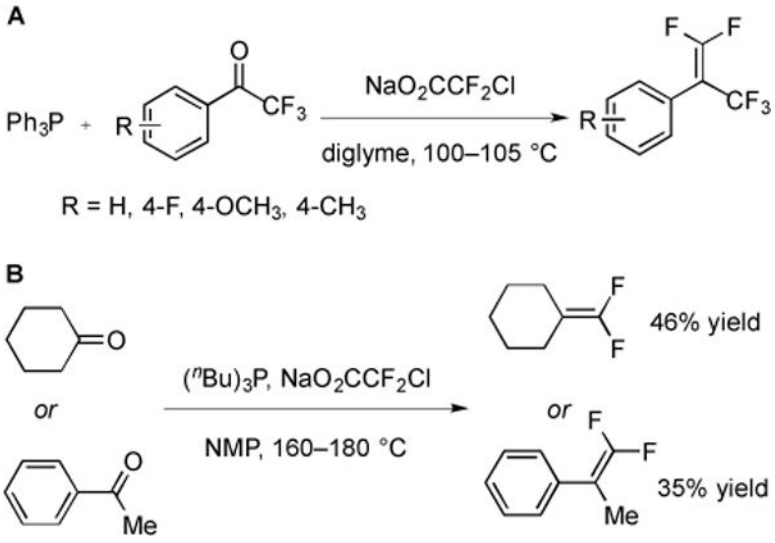

Fig. (16).
Synthesis of 1,l-difluoroolefins from ketones.

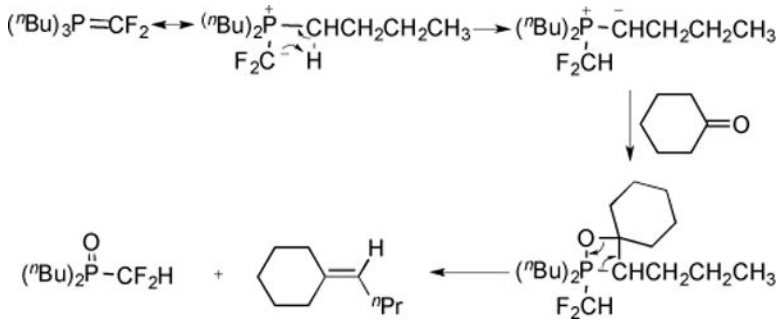

Fig. (17).
Mechanism for the formation of butylidenecyclohexane.

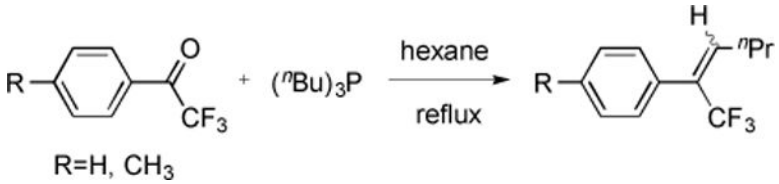

Fig. (18).
Olefination of aryl trifluoromethyl ketones with *n*-trialkylphosphines.

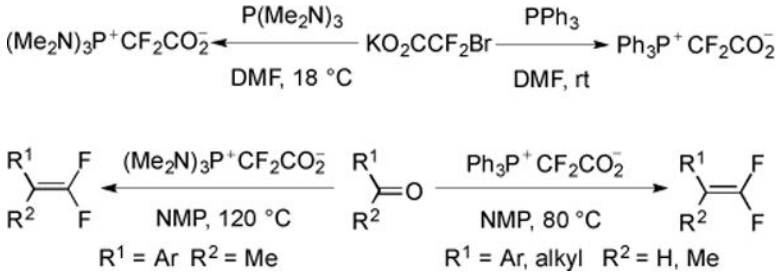

Fig. (19).
gem-Difluoroolefination of aldehydes and ketones.

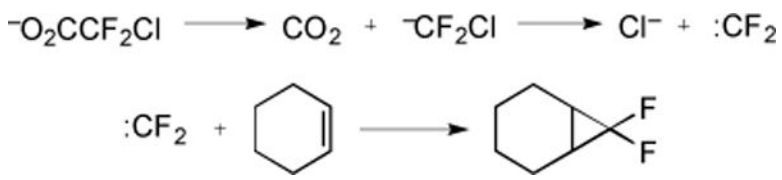

Fig. (20).
Synthesis of difluoronorcarane *via* :CF_2 intermediate.

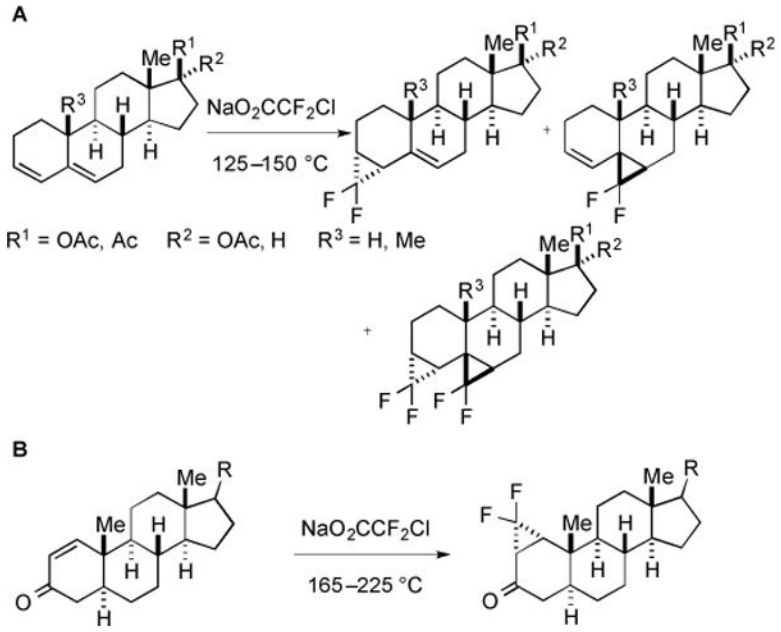

Fig. (21).
Addition of :CF_2 to conjugated dienes and enones.

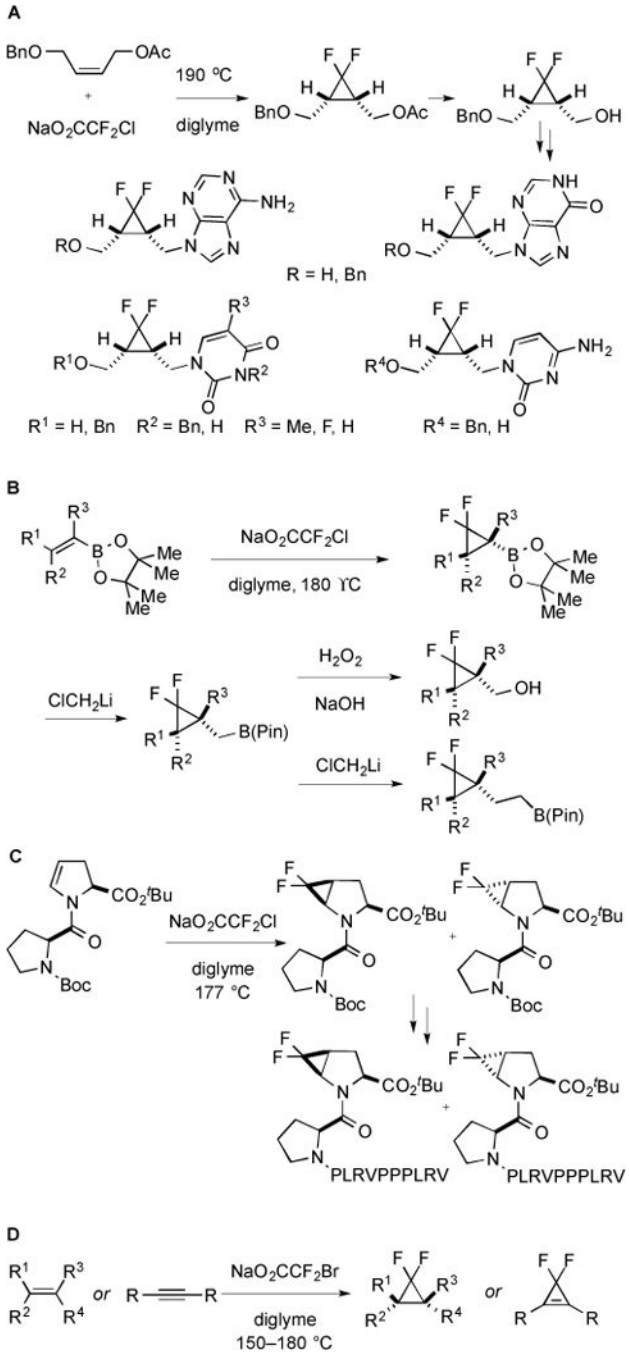

Fig. (22).
Synthesis derivatives of difluorocyclopropanes.

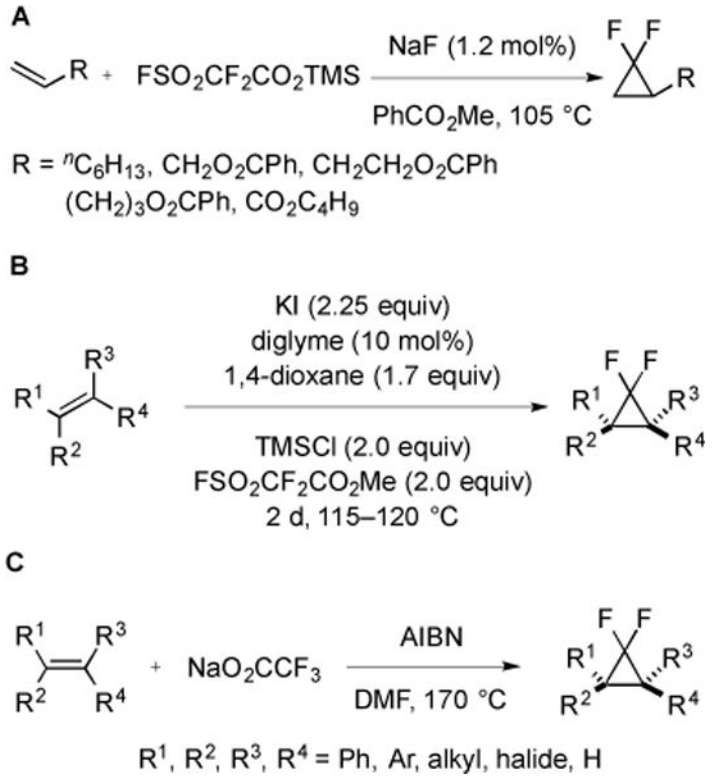

Fig. (23).

Synthesis of *gem*-difluorocyclopropanes using TFDA, $MeO_2CCF_2SO_2F$, and NaO_2CCF_3 as sources of $:CF_2$.

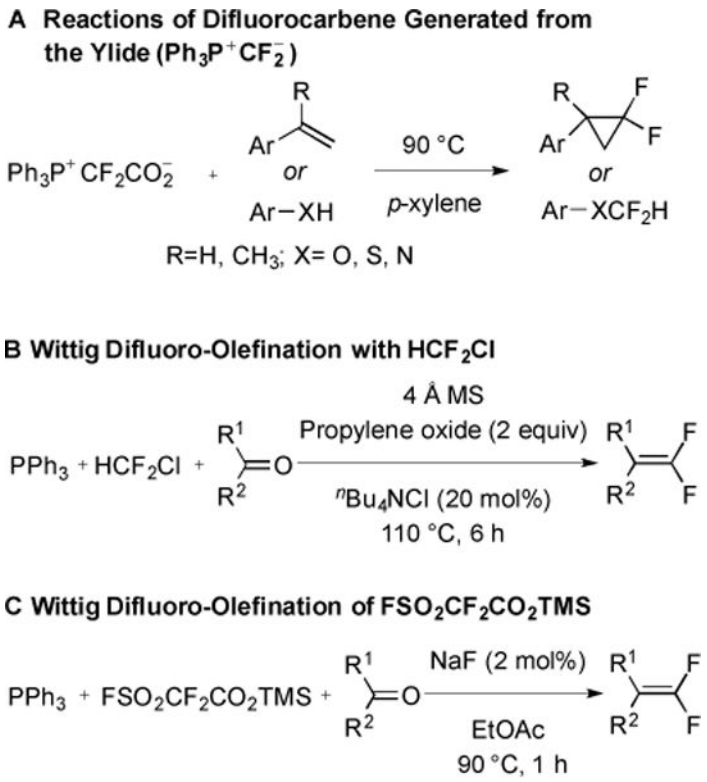

Fig. (24).

Conversion between :CF_2 and difluoromethylene ylide.

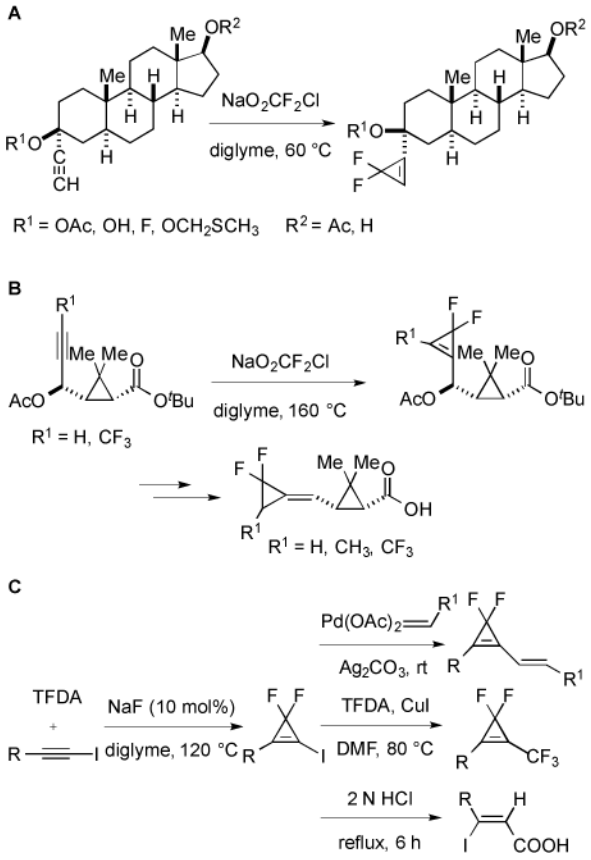

Fig. (25).
Synthesis of different difluorocyclopropene derivatives.

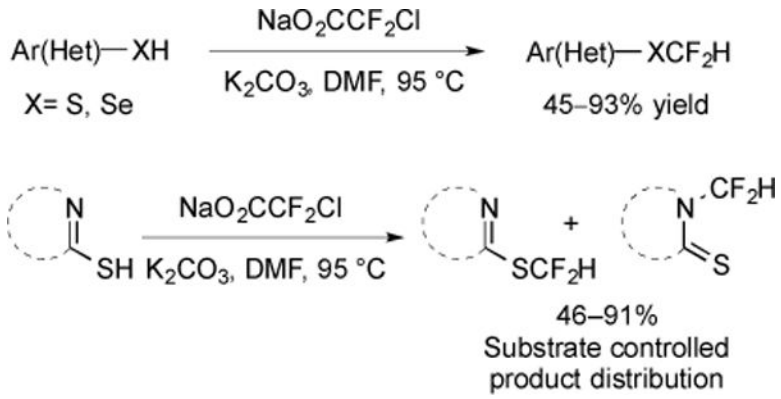

Fig. (26).
Difluoromethylation of thiophenols, nitrogenous heterocycles and phenylselenols.

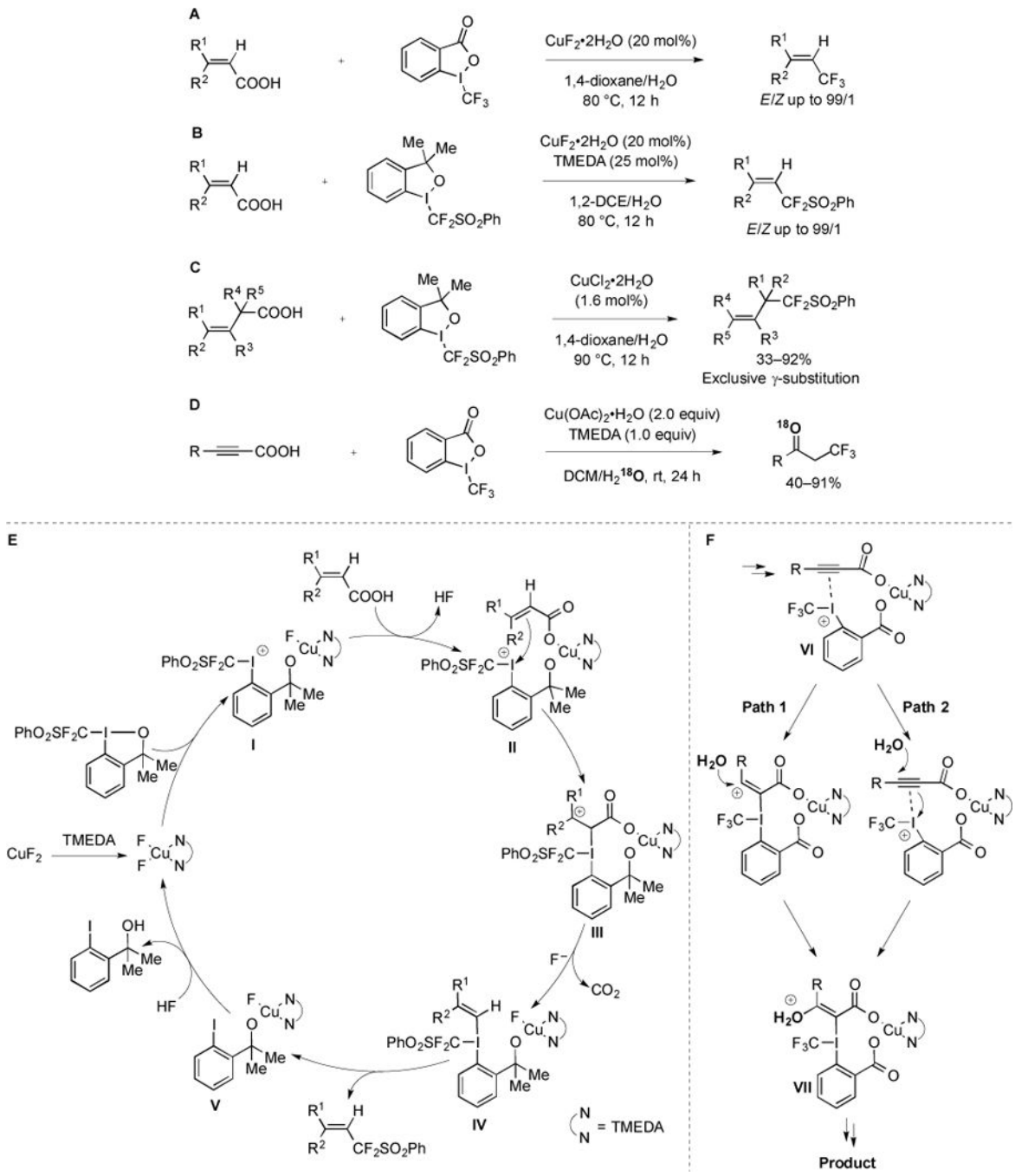

Fig. (27).
Difluoromethylation and trifluoromethylation of unsaturated carboxylic acids.

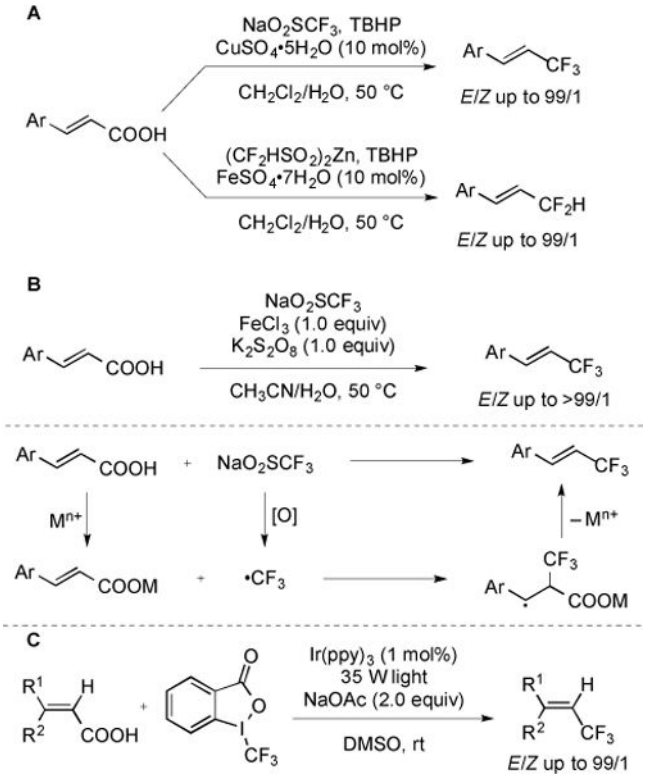

Fig. (28).

Decarboxylative trifluoromethylation of α,β-unsaturated unsaturated carboxylic acids *via* radical processes.

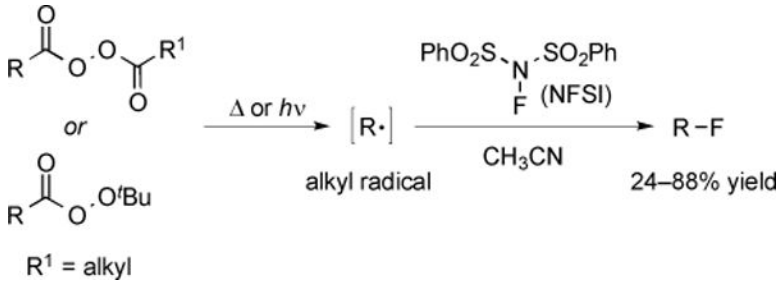

Fig. (29).

Decarboxyaltive radical fluorination of diacylperxoides and peroxides using *N*-fluorobenzenesulfonimide.

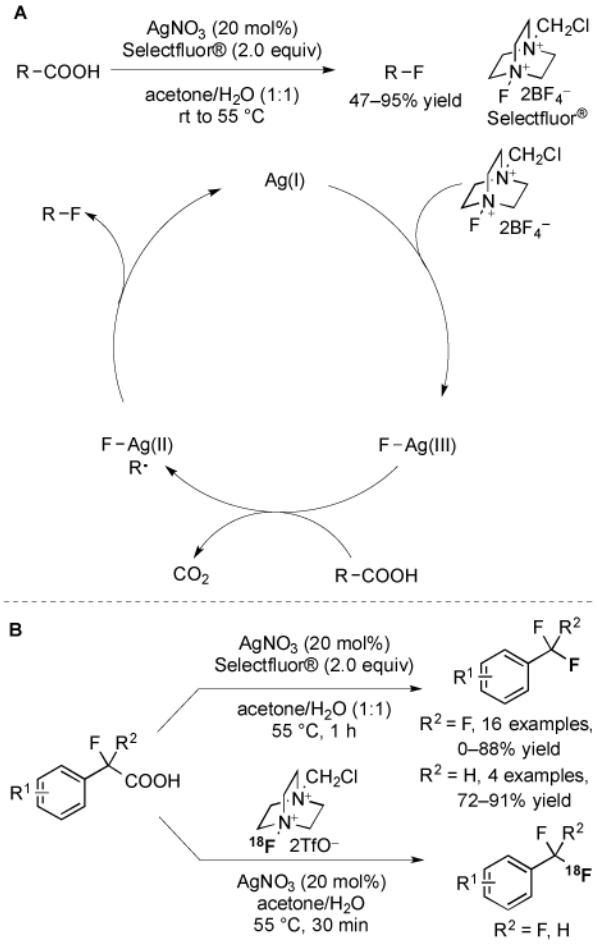

Fig. (30).
Fluorination of carboxylic acids *via* radical mechanisms.