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Review

Advances in metal-assisted non-electrophilic fluoroalkylation reactions of organic compounds

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Abbreviations: BHT, butylated hydroxytoluene; Boc, butoxycarbonyl; Boc_2O, butoxycarbonyl anhydride; Bpin, 4,4,5,5-tetramethyl-1,3,2,-dioxaborolane; Bpy, 2,2′-bipyridine; *t*-BuXPhos, 2-di-*t*-butylphosphino-2′,4′,6′-triisopropylbiphenyl; CF_3TMS, trimethylsilyltrifluoromethane; Dabco, 1,4-diazabicyclo[2.2.2]octane; DAST, diethylaminosulfur trifluoride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, dichloroethane; DCM, dichloromethane; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMI, dimethylimidazole; DMSO, dimethylsulfoxide; DPEphos, (bis-[2-(diphenylphosphino)phenyl]ether); dtbbpy, 4,4′-di*t*-butyl-2,2′-bipyridine; ET, electron transfer; HMPA, hexamethylphosphoramide; HR ESI-MS, high resolution electrospray ionization mass spectrometry; NMP, *N*-methyl pyrrolidone; Phen, 9,10-phenanthroline; phenCu(R_f), phenanthroline-copper-R_f complex; ppy, 2-phenylpyridine; PT, proton transfer; r.t., room temperature; R_fX, perfluoroalkyl halide; RuPhos, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; SET, single electron transfer; S_NAr, aromatic nucleophilic substitution; $S_{Ar}H$, homolytic aromatic substitution; $S_{RN}1$, unimolecular radical nucleophilic substitution; TBHP, *t*-butylhydroperoxide; $TESCF_3$, triethylsilyl trifluorometahne; TFA, 2,2,2-trifluoroacetic acid; TIPS, tri*iso*propyl silane; TMEDA, tetramethyl ethylene diamine; TMP, tetramethylpiperidine; TMS, trimethylsilyl; $TMSCF_2H$, trimethylsilyldifluorometahne; T_fO, triflate; TPGS-750-M, DL-α-tocopherol methoxypolyethylene glycol succinate solution; Xantphos, 4,5-*Bis*(diphenylphosphino)-9,9-dimethylxanthene; *p*TSA, *para*-toluensufonic acid.

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ABSTRACT

Metal-assisted trifluoromethylation and perfluoroalkylation reactions are probably one of the first approaches employed to achieve fluoroalkyl-group substitutions of organic substrates through the use of metals such as copper. Fluoroalkylation reactions of both aromatic and aliphatic substrates involving the employment of perfluoroalkyl halides R_fX in conjunction with metallic species, and nucleophilic fluoroalkylating reagents in the presence of metals or organometallic species will be studied. Fluoroalkylation reactions utilizing electrophilic fluoroalkylating reagents in the presence of transition metals or trifluoromethylthiolation reactions will not be the subject of this article. Recently emerging literature (2011–present), with special emphasis on updates from previous review articles on the metal-mediated fluoroalkylation of aromatic substrates will be dealt with.

1. Introduction

Introduction of fluoroalkyl groups into organic substrates is an important transformation on account of the changes that these groups impart to molecules, such as an increase in lipophilicity, resistance to oxidation, bioavailability, increase in bioactivity, water repellent properties, *etc.* Recently, the introduction of trifluoromethyl and perfluoroalkyl groups into aromatic or heteroaromatic substrates has been reinvigorated, as evidenced by the large volume of papers published in the last five years [1–4].

The catalytic aspects of coupling and radical reactions for selective aryl trifluoromethylation and perfluoroalkylation functionalization employing Pd, Ru, Ag, Cu, and Zn organo-catalysts or metals alone is a topic of constant research. The radical nature of some of these metal-assisted transformations has been revisited in recent review articles [5].

The review by Grushin and collaborators [1] summarizes all metal complex-mediated reactions for synthesizing trifluoromethylated and perfluoroalkyl-substituted arenes, with a large variety of Pd(II) trifluoromethyl complexes and Cu-promoted (Cu(I)) trifluoromethyl group *ipso* substitution of haloarenes. Also, the trifluoromethylation of haloarenes in organic solvents catalyzed by Ni was used for the aromatic carbon-halogen bond activation and has been summarized as well [5–8].

Although the involvement of transition metals to effect perfluoroalkylation reactions has relied in the past on the employment of costly organocatalysts and/or harsh reaction conditions, alternative metal-mediated perfluoroalkylation strategies of organic substrates have been sought after.

To this end, the contributions by Baran et al. [9] with the fluoroalkyl sulfinate zinc salts, those from Ritter with the Ni [4,10] and other metals [11] have augmented the repertoire for accomplishing fluorination reactions on organic substrates.

This review intends to be an update of previously published accounts [5], where new approaches and examples on perfluoroalkylation reactions performed through the aid of metals are illustrated, exploring the benefits and advantages of transition metals in polar and radical perfluoroalkylation reactions. These reactions exclude the utilization of electrophilic fluoroalkylating species which encompass an emerging class of reagents that effect both addition and substitution reactions on a large array of organic substrates which have been the subject of a recent review article [12]. The account will make special emphasis on the different classes of organic substrates that can be substituted with trifluoromethyl or perfluoroalkyl moieties with the intervention of metals or metallic organocatalysts rather than the use of a particular metallic species [5].

2. Metal-mediated trifluoromethylation and fluoroalkylation reactions of arenes and heteroarenes

Trifluoromethylated aromatic substrates are widely used as active components of numerous modern pharmaceuticals and agrochemicals (Scheme 1), this being the reason for the continuous search for more and improved protocols into the incorporation of the CF_3 functionality at the last stages of a synthetic approach.

There exists a comprehensive review article on the trifluoromethylation of aromatic compounds with metal complexes by Tomanshenko and Grushin [1] in 2011. Consequently, discussion on these types of substrates will be limited to developments in this expanding area published thereafter. Updates on copper-mediated trifluoromethylation of aromatic compounds have also recently been introduced [13,14].

In the following sections, recent developments on the fluoroalkylation reactions of functionalized arenes such as haloarenes, arylboronic acids, diazobenzenes, and the C_{aryl}-H fluoroalkylation reactions assisted by metals shall be described.

2.1. Fluoroalkylation of aromatic halides [15]

Palladium-catalyzed transmetallation processes afford trifluoromethyl-substituted aromatic substrates from functionalized substituted haloarenes and the nucleophilic CF_3SiMe_3 source [5,16,17a].

2.1.1. Fluoroalkylation of aryl iodides [17b]

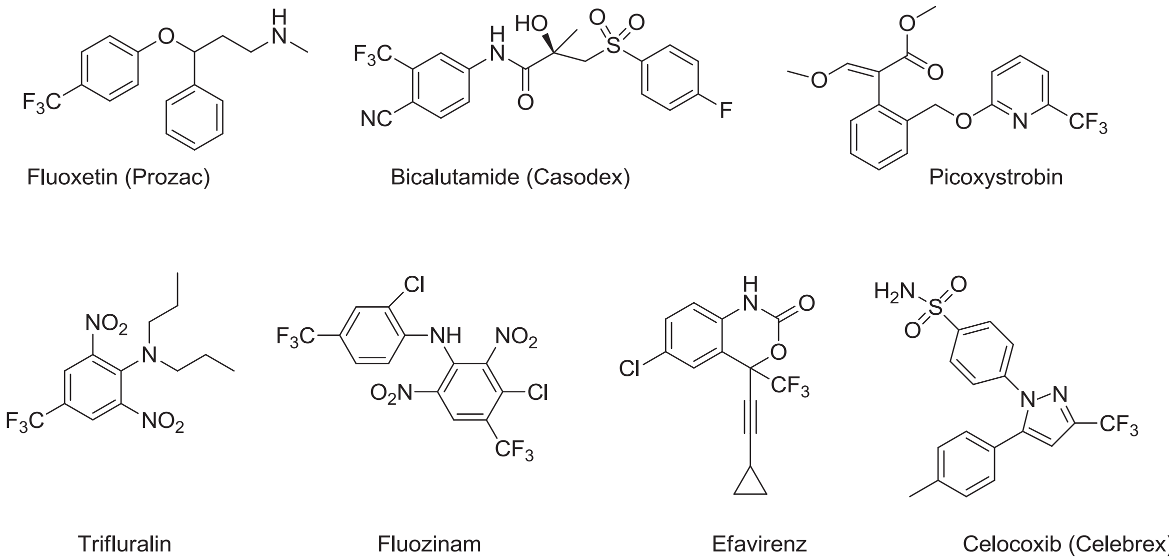
The vast majority of previously reported Cu-mediated/catalyzed trifluoromethylation reactions of aromatic electrophiles occurs efficiently only in the presence of a specifically added ligand, preferentially phenanthroline and a iodoarene [18].

In contrast, Grushin and colleagues have presented a fluoroform-derived $CuCF_3$ [19,20] as being reactive toward iodoarenes in the absence of any added ligands. These and other authors [20–22] have very recently accomplished the trifluoromethylation of aryl and heteroaryl halides through the use of a fluoroform-derived CF_3-copper compound, according to Scheme 2.

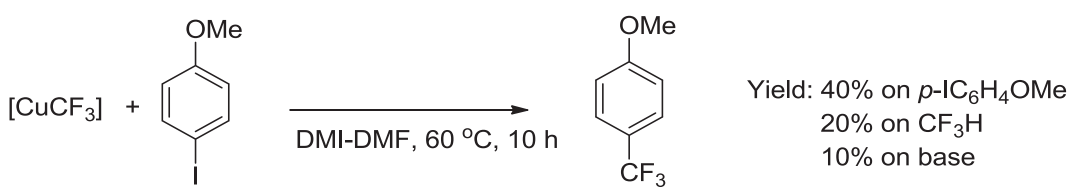
The generation of the $CuCF_3$ complex had previously been carried out employing $MeS(O)CH_2K$, and CuI, which upon decomposition renders the trifluoromethyl cuprate, according to Scheme 3.

However, this methodology (Scheme 3) of generating $CuCF_3$, provides unwanted side products in the trifluoromethylation reaction of aryl iodides, and the stabilization of $CuCF_3$ cannot be attained.

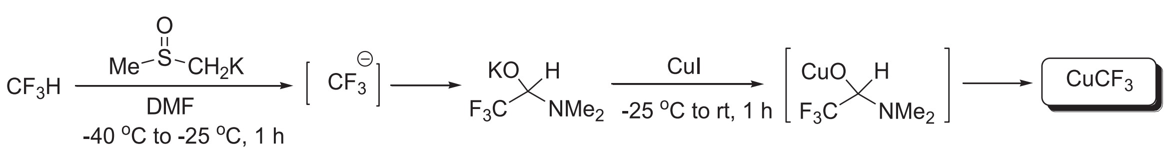
The new method reported by Grushin et al. [20,23] (Scheme 4) is based on a novel *ate* complex reagent, $[K(DMF)][(t\text{-BuO})_2Cu]$, that



Scheme 1. Selective pharmaceuticals and agrochemicals containing a trifluoromethylated moiety.



Scheme 2. Trifluoromethylation of aryl halides with fluoroform-derived $CuCF_3$ [20–22].



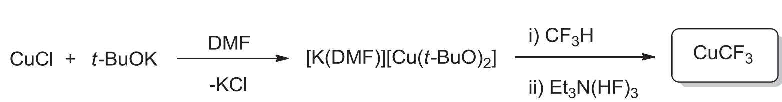
Scheme 3. Generation of complex $CuCF_3$ from fluoroform.

is formed quantitatively upon treatment of CuCl with 2 equiv. of *t*-BuOK. This dialkoxycuprate, generated *in situ* or pre-isolated, reacts with CHF_3 at room temperature and atmospheric pressure within minutes to give rise to $CuCF_3$ in >90% yield. Stabilization of the thus produced trifluoromethyl copper(I) with a source of HF such as $Et_3N{\cdot}3HF$ (*i.e.:* TREAT HF) [19] furnishes the reagent that is stable at room temperature for days (Scheme 4).

This source of $CuCF_3$ (Scheme 4) can be employed to achieve the trifluoromethylation of a variety of aryl iodides. The authors [20] inspected the mechanism of the reaction, and observed a lack of formation of arenes and biaryls as side-products, which indicates that the $S_{RN}1$ mechanism may not be operational to a considerable extent. Moreover, the formation of only small quantities of the *bis*-trifluoromethylated products from *p*- and *o*-BrC_6H_4I is inconsistent with the $S_{RN}1$ mechanism. An independent competition experiment was performed to determine that *p*-nitroiodobenzene is only 22 times more reactive toward the $CuCF_3$ than iodobenzene. This small difference in reactivity rules out the classical S_NAr pathway.

The enhanced reactivity of many *ortho*-substituted haloarene substrates toward the $CuCF_3$ observed in the current work [20] is characteristic of Cu-mediated/catalyzed aromatic substitution reactions in general. This so-called *ortho*-effect, originally discovered by Ullmann himself 110 years ago, was thoroughly studied by the methods of physical organic chemistry in the 1960s and reviewed in the 1970s. The accelerating effect of the nitro group in the *ortho* position reported by Clark et al. [21] for the Cl/CF_3 exchange is yet another example of the general reactivity pattern that has received little study and virtually no understanding in the chemistry of aromatic trifluoromethylation. Clark et al. [21] also reported that this effect was absent in the case of cyano-substituted chloroarenes and therefore concluded that "the correct transition state geometry" was required for the *ortho*-effect to take place (Fig. 1). Only weak activation of the C—Cl bond was observed in Clark's work for carbonyl-containing *ortho*-functionalities CHO, COMe, and CO_2Me.

Further reports by the same authors [24] revealed that the pentafluoroethylation of aryl bromides was also feasible with the employment of C_2F_5H and a copper complex ($[K(DMF)_2][(t\text{-}BuO)Cu(C_2F_5)]$). In another account, the authors [25] attempted the trifluoromethylation of arylboronic acids (*vide*



Scheme 4. Grushin's method for generation of stable $CuCF_3$ complex [20–23].

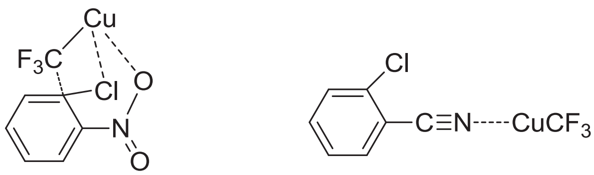


Fig. 1. Proposed correct (*ortho*-NO_2) and incorrect (*ortho*-CN) geometries of transition state structures in Cu-promoted trifluoromethylation of *ortho*-substituted chloroarenes [21].

infra, Section 2.2) through fluoroform-derived $CuCF_3$ in good yields.

Aryl iodides have recently been trifluoromethylated in the presence of $CuCF_3$ prepared from trifluoromethyl phenyl ketone, $K[Cu(t\text{-}BuO)_2]$ in DMF as solvent. The scope of the transformation is shown in Scheme 5 [26].

The reagent $CuCF_3$ was synthesized according to Scheme 6.

The reaction proceeded smoothly when conducted in DMF as solvent with 1,10-phenanthroline as ligand, which was more efficient than TMEDA [26]. With the reaction conditions established, the authors [26] were able to substitute electron-deficient aryl iodides to the corresponding CF_3 products in good-to-excellent yields even at room temperature (Scheme 5). Sterically more demanding *ortho*-substituted derivatives also afforded CF_3-substituted compounds in good yields.

In organic solvents, the fluorosulfonyl difluoromethyliodide FSO_2CF_2I and Cu metal couple has been employed in the *ipso* substitution of iodoarenes with CF_3 group, according to Scheme 7 [5,27].

Mechanistic probes [27] for this reaction include a radical anion scavenger such as *p*-DNB, and a radical inhibitor such as hydroquinone, which suppress partially the reaction. The radical nature of the transformation has been uncovered through trapping of the fluorosulfonyl dimethyl radical with 2,3-dimethyl-2-butene.

Hartwig and colleagues [28a] have recently developed a copper-mediated difluoromethylation [29] method for aryl iodides as well as vinyl iodides in a single step with inexpensive and readily available reagents. The trimethylsilyl difluoromethane ($TMSCF_2H$ [28b]) is the source of the nucleophilic CF_2H group and it is obtained by sodium borohydride reduction of the Ruppert–Prakash reagent (Me_3SiCF_3) as shown in Eq. (1). Noticeable, $TMSCF_2H$ is accessible on multigram scale, a stable reagent and is furnished in good yields.

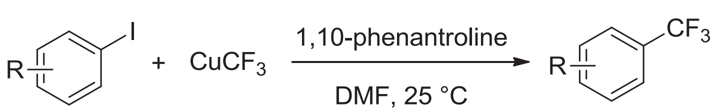
$$Me_3SiCF_3 \xrightarrow[\text{diglyme, 25 °C}]{NaBH_4} Me_3SiCF_2H \quad (1)$$

Substrate scope investigation established that the difluoromethylation procedure was effective for a variety of electron-neutral, electron-rich and sterically hindered aryl and vinyl iodides (Scheme 8). However, the difluoromethylation of electron-deficient aryl iodides formed arene as the major product, along with trace amounts of trifluoromethyl- and tetrafluoroethylarene.

Regarding the reaction mechanism, the authors assessed by ^{19}F NMR the identity of the difluoromethylcopper species whose structure is $Cu(CF_2H)_2^-$. This species acts as a stable reservoir for the neutral $CuCF_2H$ that it is proposed to react with the aryl and vinyl iodides. However, more efforts to shed some light on the mechanism hypothesis are required.

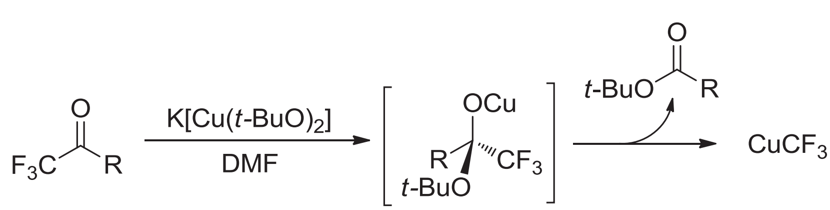
2.1.2. Fluoroalkylation of (hetero)aryl bromides

Although there has been considerable progress in copper-mediated perfluoroalkylation reactions in recent years, these reactions are mostly limited to aryl iodide and arylboron substrates (Section 2.2). Perfluoroalkylation reactions of aryl bromides, which are more commercially and synthetically available than

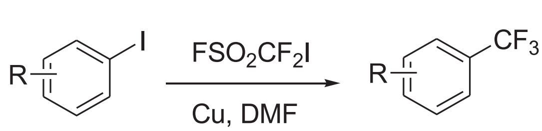


R	Yield (%)
4-NO_2	96
4-COMe	80
4-CF_3	91
3-pyridyl	85
2-CO_2Et	87
2-Br	93
4-OMe	85
4-*t*-Bu	71
1-naphthyl	91

Scheme 5. Scope of the trifluoromethylation of aryl iodides with $CuCF_3$ [26].



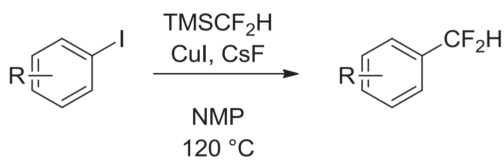
Scheme 6. Preparation of $CuCF_3$ from trifluoromethyl phenyl ketone.



R	Yield (%)
H	80
4-Cl	85
4-NO_2	83

Scheme 7. Trifluoromethylation of iodobenzene derivatives with fluorosulfonyl difluoromethyliodide [5,27].

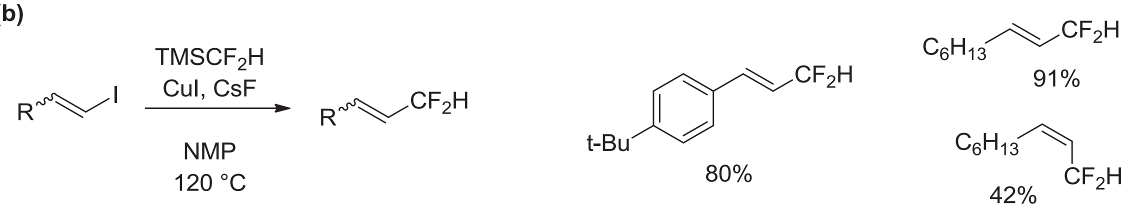
(a)



R	Yield (%)
4-*n*Bu	90
4-*t*Bu	61
4-OBn	87
4-Ph	88
4-CH$_2$NEt$_2$	59

R	Yield (%)
3-OMe	81
2-OMe	30
3,5-diMe	74
2,6-diMe	48

(b)



Scheme 8. Difluoromethylation of aryl and vinyl iodides [28a].

aryl iodides, have been limited to substrates containing electron-withdrawing groups. A single report for the trifluoromethylation of aryl chlorides with Pd has been informed (see Section 2.1.3) [16]. However, these reactions require an expensive palladium pre-catalyst, ligand, and CF_3 source.

More recently, Hartwig and collaborators [30] have accomplished the trifluoromethylation and pentafluoroethylation of aryl bromides with phenCu(R_f) complex in good yields. Later on, this methodology has proved very efficient for the trifluoromethylation of heteroaryl bromides [31]. The scope of the transformation is depicted in Scheme 9.

This thermally stable, commercially available solid reagent PhenCu(CF_3) turned out to be very effective for the trifluoromethylation of bromo(hetero)arenes.

The electron-rich property of five-membered heterocycles could confer low reactivity to this family of substrates toward PhenCu(CF_3). However, complex PhenCu(CF_3) does react with certain five-membered heterocycles containing bromine in the 2-position. 2-Bromoindole, benzimidazole, benzoxazole, and nucleoside derivatives could also be trifluoromethylated under this methodology [31].

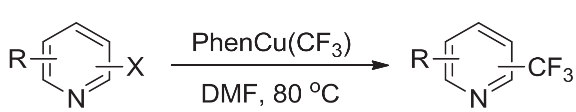
The authors [31] made a good comparison among the methods available for trifluoromethylation of bromopyridines in the light of the methodology they introduced employing PhenCu(CF_3). The results are presented in Scheme 10.

The use of $(PPh_3)_3CuCF_3$/*t*-Bu-bpy in toluene as solvent at 80 °C has been investigated by Grushin and collaborators [32], rendering the trifluoromethylated pyridine in 56% yield (Scheme 10, second row). Gooβen and colleagues [33] employed the complex K[$(MeO)_3BCF_3$], CuI, phenanthroline in DMSO as solvent at 80 °C, obtaining the CF_3-substituted pyridine in 17% yield (Scheme 10, third row). Utilization of Ruppert–Prakash's reagent [34,35] only affords the substituted pyridine in low yields (Scheme 10, rows fourth and fifth). The improved method by Hartwig [31] for the trifluoromethylation of bromopyridines surpasses the reported methods so far (Scheme 10, row 1).

A very recent report by Mikami and colleagues [36a] has demonstrated that pentafluoroethylation with aryl bromides was feasible by reaction of CuC_2F_5 under optimized conditions, providing the pentafluoroethylated aromatic compounds in good-to-excellent yields (Scheme 11). In general, aryl bromides with electron-donating substituents showed lower reactivity than those aryl bromides with electron-withdrawing substituents. Quinoline derivatives [36b] were also successfully pentafluoroethylated by the CuC_2F_5 reagent [36a] (Scheme 11).

The pentafluoro-copper reagent was prepared according to Scheme 12.

CuC_2F_5 reagent from cuprate (K[Cu(*t*-BuO)$_2$]) and pentafluoropropionate derivatives could be prepared under mild conditions in almost quantitative yield [36a]. The noteworthy advantages of this



X = 2-Br

R	Yield (%)
H	94
3-Me	92
6-Me	83
5-NO$_2$	99
3-CO$_2$Me	94
6-COMe	76
6-CO$_2$Me	96

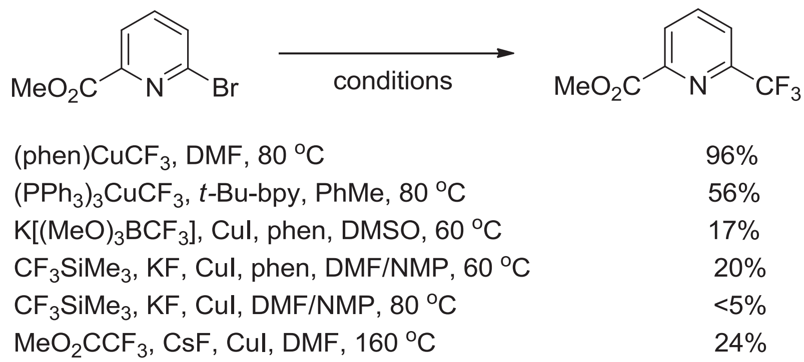
X = 3-Br

R	Yield (%)
H	50
2-Cl	50
4-CO$_2$Me	88
5-CN	66
6-NHBoc	42
6-OMe	32

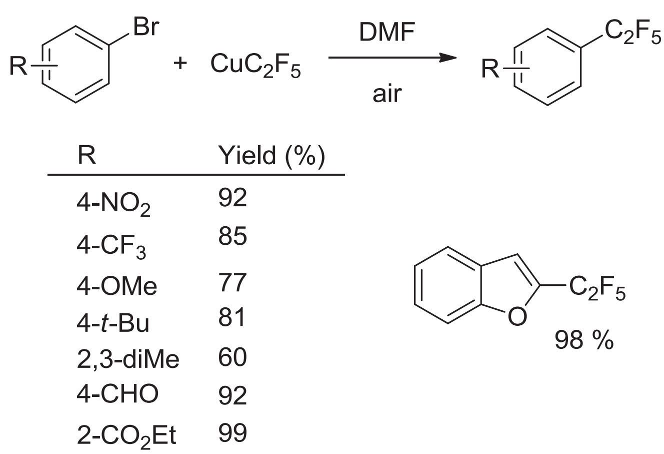
X = 4-Br

R	Yield (%)
H	75
2-Me	59
2-OMe	58
3-CN	92

Scheme 9. Scope of the trifluoromethylation reaction of bromoheteroarenes with PhenCu(CF_3) [31].



Scheme 10. Different methodologies for the reported trifluoromethylation of bromopyridines [31].

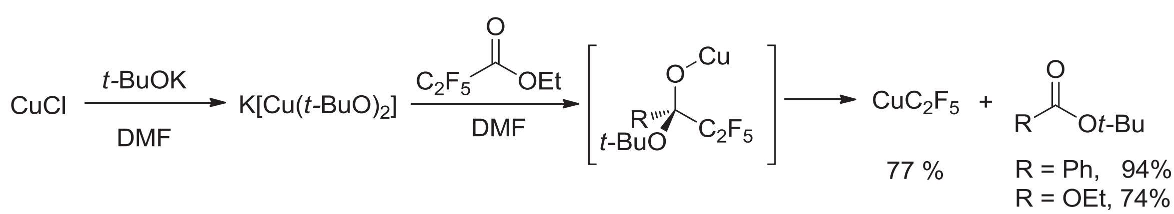


Scheme 11. Pentafluoroethylation of aryl bromides with CuC_2F_5 in DMF as solvent [36a].

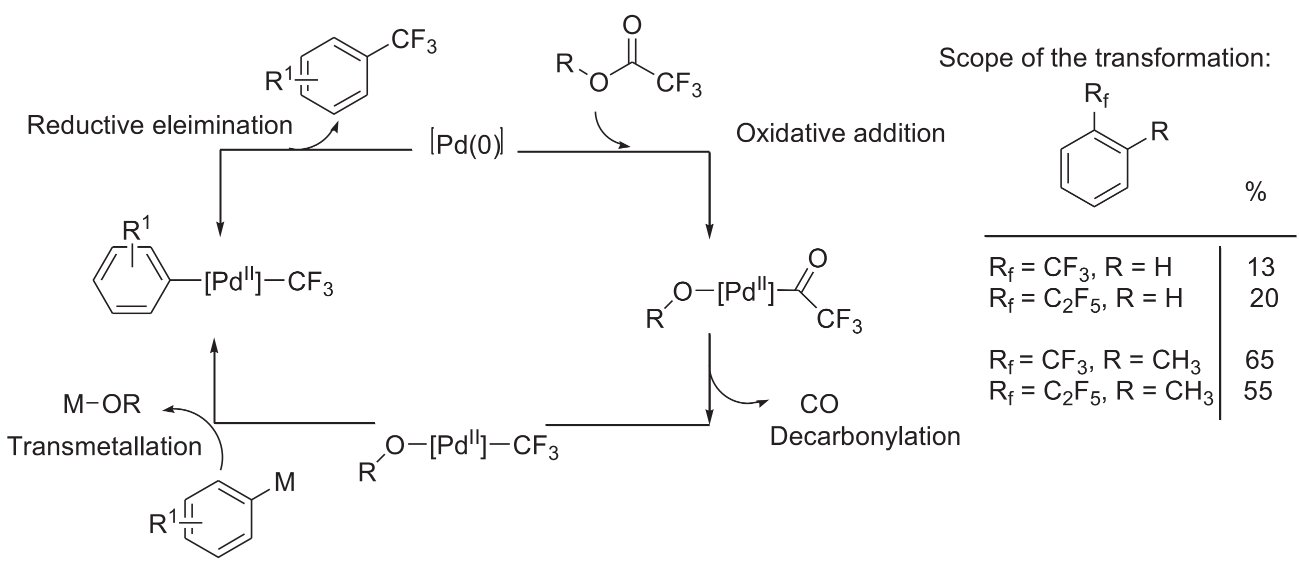
reaction system are a cost-efficient access to the CuC_2F_5 reagent, broad substrate scope, and applicability for large-scale operation [36a].

2.1.3. Fluoroalkylation of aryl chlorides

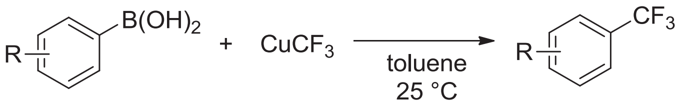
Sanford and colleagues have very recently introduced a synthetic methodology for achieving the fluoroalkylation of aryl chlorides using trifluoroacetic acid esters as CF_3 source in the presence of $Pd(dba)_2$, as catalyst, RuPhos as ligand (a *bis*arylmonophosphine ligand [37]), and KF as additive [38]. Starting from substituted aryl chlorides, up-to 90% yield of CF_3-substituted aryl products can be obtained [38]. The mechanism of the reaction is thought to involve (i) oxidative addition of a trifluoroacetic ester to Pd(0), (ii) CO deinsertion from the resulting trifluoroacyl Pd(I)I complex, (iii) transmetallation of a zinc aryl to Pd(II), and (iv) aryl-CF_3 bond-forming reductive elimination (Scheme 13). The use of RuPhos as the supporting ligand enables each of these steps to proceed under mild conditions (<100 °C).



Scheme 12. Preparation of CuC_2F_5 [36a].



Scheme 13. Proposed catalytic cycle for the trifluoromethylation of aryl chlorides with trifluoroacetates [38].



R	Yield (%)
H	96
4-F	90
4-COMe	94
4-CF3	99
4-OMe	95
4-*t*-Bu	88
3-pyridyl	80
1-naphthyl	90

Scheme 14. Trifluoromethylation of arylboronic acids using $CuCF_3$ [26].

The advantage of this protocol relies on the use of inexpensive trifluoroacetic acid as CF_3 source and commercially available aryl chlorides. The reactions are carried out in THF as solvent under N_2 atmosphere.

2.2. Fluoroalkylation of aryl boronic acids and derivatives

Boronic acids and boronate esters can be replaced effectively by the corresponding organotrifluoroborates in transmetallation reactions.

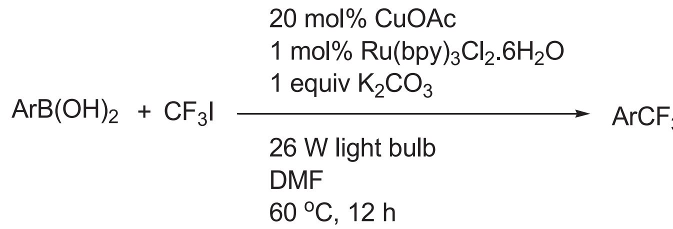
2.2.1. Reaction of aryl boronic acids with prepared CuR_f

Mikami and collaborators [26] have recently accomplished the trifluoromethylation of arylboronic acids through the employment of $CuCF_3$ source in toluene as solvent, with the intervention of 1,10-phennathroline as ligand, according to Scheme 14.

The synthesis of $CuCF_3$ was accomplished as in Scheme 5 (Section 2.1), from phenyl trifluoromethyl ketone and K[Cu(*t*-BuO)$_2$] in DMF as solvent [26].

The reaction by treatment of boronic acids in the presence of the $CuCF_3$ reagent (2 equiv.) proceeded smoothly without any ligands to provide the corresponding products in good-to-excellent yields. In contrast to the oxidative trifluoromethylation of terminal alkynes (*vide infra*, Section 3.3), toluene was the best solvent [26]. Under the optimized reaction conditions [26], aromatic boronic acids bearing both electron-withdrawing and -donating substituents showed high yields of substitution products.

Mikami and collaborators [36a] have very recently accomplished the pentafluoroethylation of arylboronic acids with CuC_2F_5. This latter reagent has been synthesized according to Scheme 12



Scheme 16. Trifluoromethylation of aryl boronic acids with CF_3I, a photoredox catalyst, light, in DMF as solvent [42].

(*vide supra*, Section 2.1). The scope of the transformation is depicted in Scheme 15.

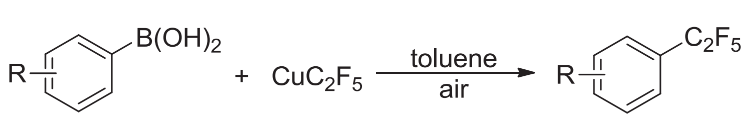
Pentafluoroethylation [36a] of various boronic acids with the CuC_2F_5 reagent without any ligands, such as 1,10-phenantroline or 2,2′-bipyridine, was examined (Scheme 15). A wide range of electronically varied arylboronic acids underwent this oxidative reaction in good-to-excellent yields. A methyl substituent on the *ortho*-position did not interfere with the reaction (Scheme 15, Ar = 2,3-Me_2-C_6H_3). The use of a formyl group (Scheme 15, Ar = 4-CHO-C_6H_4) also led to the corresponding product in high yield but did not afford the pentafluoroethylated alcohol at all. Moreover, the employment of 4-bromo-phenylboronic acid, led to the pentafluoroethylated product with intact bromide in high yield, which could provide a convenient platform for further functionalization [36a].

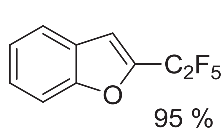
2.2.2. Reaction of aryl boronic acids with R_fX

In an elegant work by Sanford and colleagues, the trifluoromethylation of arylboronic acids has been carried out by the use of CF_3I and the photoredox [39–41] catalyst Ru(bpy)$_3$Cl$_2$.6H$_2$O, a copper salt CuOAc, a conventional light bulb in DMF as solvent, as a means of generating CF_3 radicals [42], according to Scheme 16.

The authors [42] propose a reaction mechanism such as that depicted in Scheme 17.

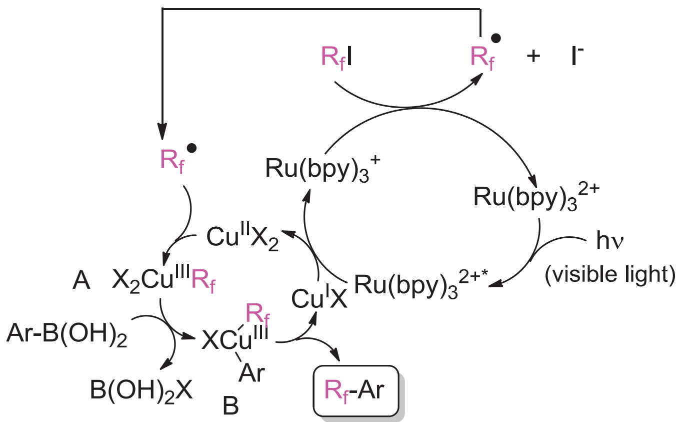
A possible set of catalytic cycles is shown in Scheme 17. In this sequence, photoexcitation of Ru(bpy)$_3^{2+}$ to Ru(bpy)$_3^{2+*}$ is followed by one-electron reduction by Cu(I) to generate Ru(bpy)$_3^{+}$ and Cu(II). Reduction of CF_3I by Ru(bpy)$_3^{+}$ then affords CF_3 radicals and iodide anion. Notably, literature reduction potential data indicate that both of these reactions should be thermodynamically favorable. The $CF_3^{\bullet}$ radical could then react with Cu(II) to generate a Cu(III)(CF_3) intermediate **A** (Scheme 17). Subsequent base-promoted transmetallation between Cu(III) and the arylboronic acid would afford Cu(III)(aryl)(CF_3) (**B**, Scheme 17), which could easily undergo aryl-CF_3 bond-forming reductive elimination to release the organic product and regenerate the CuI catalyst.





R	Yield (%)
4-NO2	81
4-CF3	97
4-OMe	95
4-*t*-Bu	93
2,3-diMe	83
4-CHO	89
4-Br	91

Scheme 15. Pentafluoroethylation of arylboronic acids [36a].



Scheme 17. Photocatalytic cycle for the trifluoromethylation of aryl boronic acids [42].

2.2.3. Reaction of aryl boronic acids with the Ruppert–Prakash reagent

Buchwald and colleagues [43] have recently informed the copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids with the Ruppert–Prakash reagent CF_3SiMe_3 [17a] in DCE as solvent. Addition of 1,10-phenanthroline as a ligand, substantially increased the yield of the trifluoromethylated product. The scope of the transformation is illustrated in Scheme 18.

Electron-rich and electron-deficient aryl boronic acids can be trifluoromethylated in moderate to good yields in small and large scales [43]. Arenes bearing ring substitution in the *ortho* position are difficult substrates for copper-mediated cross-coupling processes. However, under the reaction conditions informed by the authors [43] *ortho*-substituted trifluoromethyl arenes can be obtained in good yields. The authors do not propose a viable reaction mechanism for this transformation [43].

Qing and co-workers have reported the first copper-mediated oxidative trifluoromethylation of aryl- and alkenylboronic acids employing CF_3SiMe_3 as the nucleophilic CF_3 source [44,45]. Advantages of the reaction include mild reaction conditions, high functional group tolerance, and readily availability of boronic acids. The optimal reaction conditions involve $[Cu(OT_f)]_2{}^•C_6H_6$, 1,10-phenanthroline, KF, K_3PO_4 and Ag_2CO_3 in DMF at 45 °C. Applying this optimal condition to benzeneboronic acid in the presence of Me_3SiCF_3 afforded trifluoromethylbenzene in 93% yield. Then, substrate scope of the trifluoromethylation reaction was examined, and the results are summarized in Scheme 19.

The detailed reaction mechanism remains to be elucidated, however, the authors have proposed a plausible sequence as is depicted in Scheme 20.

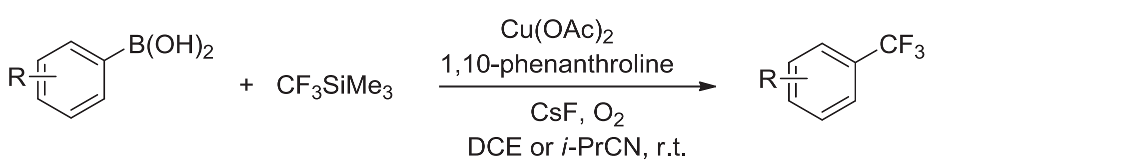
The reaction proceeds by generation of the reactive $CuCF_3$ and followed by transmetallation with arylboronic acid. The presence of a diamine ligand, such as 1,10-phenanthroline, would stabilize the reactive $CuCF_3$ by chelation (intermediate **B**) increasing the electron density on the copper center. Oxidation to complex **C** (Cu(II) or Cu(III) complex) and ulterior reductive elimination delivers the desired product. However, the mechanism for the formation of Cu(II) or Cu(III) complex from **B** is not clear at the moment.

2.2.4. Reaction of aryl boronic acids and aryl trifluoroborates with the Langlois reagent

Recently, Sanford and collaborators have developed a mild protocol for the copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids using $NaSO_2CF_3$ (Langlois reagent) and *t*-butylhydroperoxide (TBHP) as radical initiator [12b]. In this account, arylboronic acids were treated with the Langlois reagent, copper, and TBHP, in aqueous-organic solvent mixtures. The best results for CF_3-substitutions were obtained when using CuCl, in a mixture of MeOH/DCM/water, according to Scheme 21.

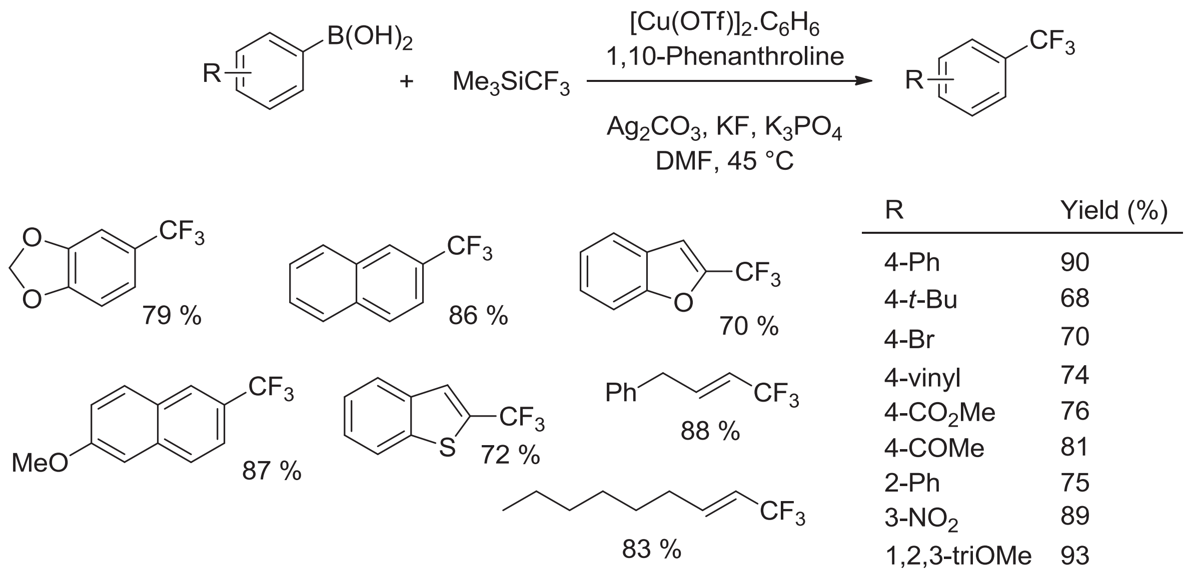
For electron-poor aryl boronic acids such as 4-(cyanophenyl)boronic acid, substitution yields were sluggish. However, replacement of CuCl by $(MeCN)_4CuPF_6$ and $NaHCO_3$ increased the substitution yields substantially [12b].

Dubbaka and colleagues [46] have very recently accomplished the trifluoromethylation of aryl and heteroaryl trifluoroborates in the presence of Langlois reagent $NaSO_2CF_3$, TBHP, in conjunction with CuCl in DCM/H_2O/MeOH as solvent mixture. The scope of the transformation is depicted in Scheme 22.



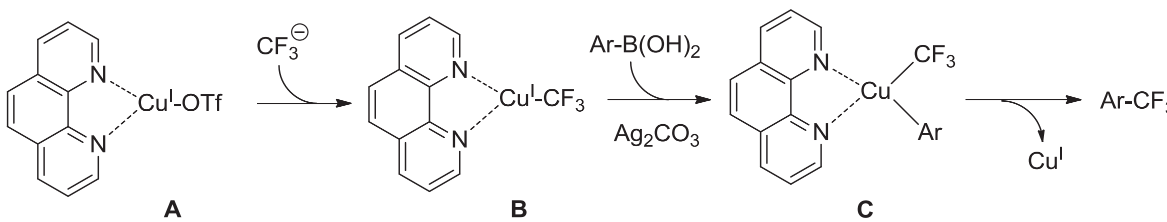
boronic acid	Yield (%)
R = 3-F, 4-BnO, in *i*-PrCN	68%
R = 3-C(O)OMe, 6-Cl, in *i*-PrCN	67%
R = 4-*n*-Bu, in *i*-PrCN	46%
R = 4-CH_2-NHBoc, in *i*-PrCN	34%
2-$B(OH)_2$-6-TBSO-naphthalene, in *i*-PrCN	2-CF_3-6-TBSO-naphthalene, 55%
3-$B(OH)_2$-pyrrol-*N*-TIPS, in DCE	3-CF_3-pyrrol, 48%
2-$B(OH)_2$-benzothiophene, in DCE	2-CF_3-benzothiophene, 45%
4-$B(OH)_2$-phenoxathiiene, in DCE	4-CF_3-phenoxathiine, 64%
3-$B(OH)_2$-quinoline, in *i*-PrCN	3-CF_3-quinoline, 38%
2-$B(OH)_2$-*N*-Boc-indole, in DCE	2-CF_3-*N*-Boc-indole, 61%
5-$B(OH)_2$-*N*-Me-indole, in *i*-PrCN	5-CF_3-*N*-Me-indole, 44%

Scheme 18. Scope of the trifluoromethylation reaction of aryl and heteroaryl boronic acids with CF_3SiMe_3 and $Cu(OAc)_2$ [43].



R	Yield (%)
4-Ph	90
4-*t*-Bu	68
4-Br	70
4-vinyl	74
4-CO_2Me	76
4-COMe	81
2-Ph	75
3-NO_2	89
1,2,3-triOMe	93

Scheme 19. Copper-mediated trifluoromethylation of aryl- and alkenylboronic acids [44,45].



Scheme 20. Trifluoromethylation reaction mechanism [44,45].

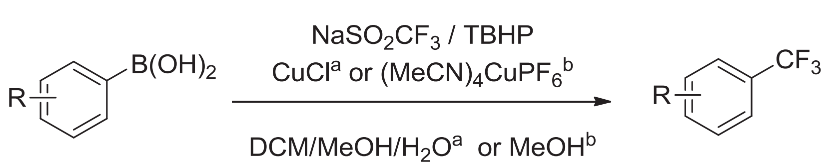
The same authors [46] have also accomplished the trifluoromethylation of benzoheteroarenes trifluoroborates in good yields, according to Scheme 23.

Electron-rich and electron-neutral substrates afforded good yields in most cases whereas electron deficient substrates gave only moderate yields of CF_3-substituted products (Scheme 22) [46]. Interestingly, the reaction of (4-bromophenyl)trifluoroborate resulted in the exclusive formation of 4-trifluoromethyl bromobenzene indicating that the C—Br linkage is inert under the explored reaction conditions [46].

2.2.5. *Difluoromethylation of aryl boronic acids and aryl trifluoroborates*

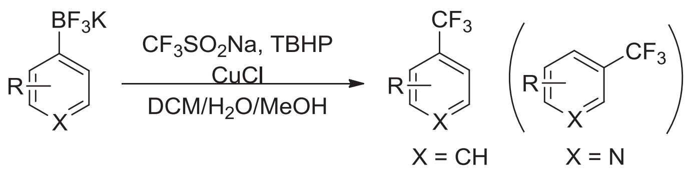
Zhang and colleagues [47–49] have very recently accomplished the Pd-catalyzed difluoroalkylation of aryl boronic acids. The optimum reaction conditions involve the employment of $Pd(PPh_3)_4$, xantphos, K_2CO_3 in dioxane as solvent, and bromodifluoromethylphosphonate $BrCF_2PO(OEt)_2$ according to Scheme 24.

The preparation of aryldifluoroacetates by this strategy [47] was also explored in the presence of a catalytic amounts of CuI (5 mol%) as a co-promoter, and bromodifluoroacetate $BrCF_2CO_2Et$



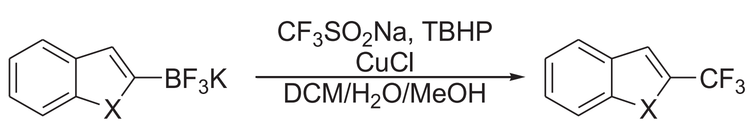
R	Yield (%)	R	Yield (%)
4-H	74[a]	4-F	79[a]
4-Ph	85[a]	4-Cl	68[a]
4-CN	62[b]	4-I	68[a]
4-*t*-Bu	74[a]	4-COMe	67[b]
4-Me	86[a]	4-NHCOMe	80[a]
4-OMe	94[a]	4-CO_2Me	67[b]
4-OPh	88[a]	4-OH	84[a]
4-CF_3	78[a]	2-Me	95[a]
		2,4,6-triMe	70[a]

Scheme 21. Trifluoromethylation of aryl boronic acids [12b].



R (X = CH X = N)	Yield (%)
4-H	80
4-OMe	74
4-Me	79
4-*t*-Bu	77
4-CN	40
4-CO_2Me	41
4-Cl	45
4-Br	57
3-OMe	60
3-Me	51
2-Me	55
2-OMe	85

Scheme 22. Scope of the trifluoromethylation of aryl and heteroaryl trifluoroborates [46].



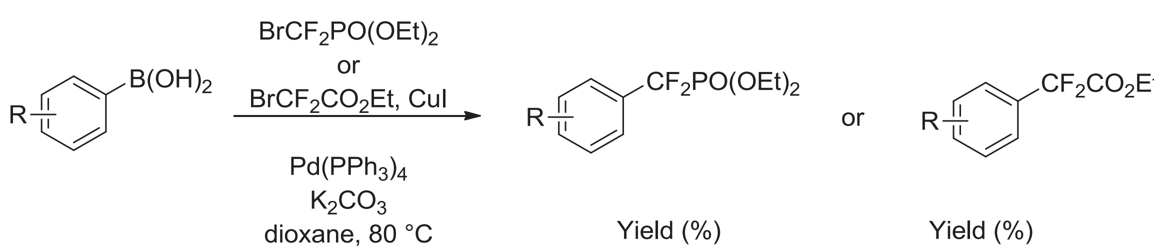
X	Yield (%)
NBoc	55
O	75
S	54

Scheme 23. Trifluoromethylation of benzoheteroarenes trifluoroborates [46].

[47], according to Scheme 24. A large variety of difluoroacetate derivatives could be generated with this method by employing bromodifluoroacetate as the coupling partner (Scheme 24, column 3). Both electron-rich and electron-deficient aryl boronic acids furnished the corresponding difluoroacetates in high efficiency. Many versatile functional groups, such as ester, thioether, were tolerated under the present reaction conditions, which highlights the advantages of the present transformation. The difluoroacetate could also be synthesized on a 1-g scale and was obtained in good yield (69%) [47].

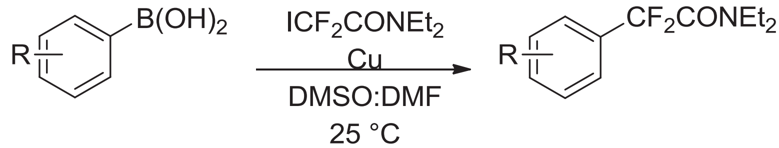
The authors [47] also attempted to investigate the reaction mechanism. It had previously been shown that a [Pd(0)] complex can initiate the generation of radicals from fluoroalkyl halides through single electron transfer (SET) [50]. To identify whether a radical pathway is involved, several radical-inhibition experiments were conducted. Addition of the ET scavenger 1,4-dinitrobenzene or the radical inhibitor hydroquinone to the reaction mixture of phenylboronic acid and $BrCF_2PO(OEt)_2$ in the presence of $[PdCl_2(PPh_3)_2]$ (5 mol%), Xantphos (10 mol%), and K_2CO_3 led to a significant decrease of the reaction efficiency. Thus, these preliminary studies suggested that a SET pathway that proceeds *via* a difluoromethylenephosphonate radical [47].

Shen and Lu [51] have accomplished the fluorobutylation of a series of aryl boronic acids with perfluorobutyl iodide, *N*,*N*-diethyl-2,2-difluoro-2-iodoacetamide ICF_2CONEt_2, and ethyl-2,2-difluoro-2-iodoacetate ICF_2CO_2Et to render the corresponding perfluoroalkyl arenes in moderate-to-good yields. The scope of the transformation is shown in Scheme 25.



R	Yield (%) (with $BrCF_2PO(OEt)_2$)	Yield (%) (with $BrCF_2CO_2Et$)
H	86	88
4-*t*-Bu	81	92
4-Ph	81	74
3-Ph	71	85
3,5-diMe	77	95
4-OMe	60	72
3,5-diOMe	70	77
4-CO_2Et	80	83
4-CF_3	67	75
4-SEt	64	92

Scheme 24. Palladium-catalyzed phosphonyldifluoromethylation of aryl boronic acids with bromodifluoromethylphosphonate or bromodifluoroacetate and CuI [47].



R	Yield (%)
H	65
4-Ph	57
3-OMe	56
3,5-diMe	53
3-Ph	57
4-Cl	60
4-Br	48

R	Yield (%)
4-I	50
3-Br	48
3,5-diCl	62
3-NO_2	43
4-CHO	57
3-COMe	53
4-CO_2Me	51

Scheme 25. Scope of the fluoroalkylation (difluoroalkylation) of aryl boronic acids in the presence of Cu [51].

$$ArB(OH)_2 \xrightarrow[\text{air}]{\text{Cu}} [ArCu] \xrightarrow[\text{- ArI}]{R_fI} [R_fCu] \xrightarrow[\text{air}]{ArB(OH)_2} R_f\text{-}Ar$$

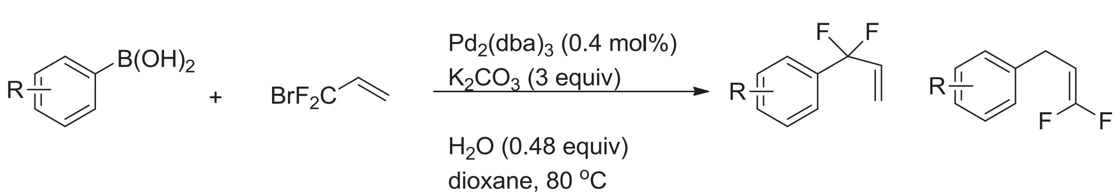
Scheme 26. Proposed mechanism for the fluoroalkylation of arylboronic acids in the presence of Cu [51].

The authors [51] propose a mechanism outlined in Scheme 26. Aryl boronic acids are first converted to [ArCu] in the presence of Cu powder and air. The cuprate then reacts with R_fI by either an oxidative addition/reductive elimination mechanism or nucleophilic substitution *via* a halogen "*ate*" intermediate to form [R_fCu], which suffers oxidative arylation with arylboronic acid in the presence of air to form the perfluoroalkylated product.

Comparison of Zhang's [47] and Shen's [51] methodologies reveal that while that of Zhang's employs a Pd catalyst and K_2CO_3, that of Shen's utilizes Cu metal, in the absence of base. Reaction conditions for the Pd-catalysis necessitates higher temperatures and dioxane as solvent, while that of Shen's can be performed at room temperature in a mixture of DMSO:DMF. Interestingly, when Shen and Lu [51] attempted to carry out the transformation in dioxane as solvent, they observed no trace of product formation.

Organotrifuoroborates are extensively used for C—C (Suzuki–Miyaura coupling), C—N and C—O (Chan–Lam coupling) *etc.* bond formation reactions [52]. Weng et al. have recently reported on the copper-catalyzed trifluoromethylation of potassium aryltrifluoroborates with an electrophilic trifluoromethylating reagent (Togni's reagent). This was followed by the works of Buchwald et al. [37] who reported an iron-catalyzed trifluoromethylation of potassium vinyltrifluoroborates with Togni's reagent. Although these transformations constitute relevant alternative strategies toward the trifluoromethylation of organotrifluoroborates, they employ electrophilic trifluoromethylating reagents, which are outside the scope of the present review article. These strategies have recently been presented in a review article on electrophilic trifluoromethylating reagents [12].

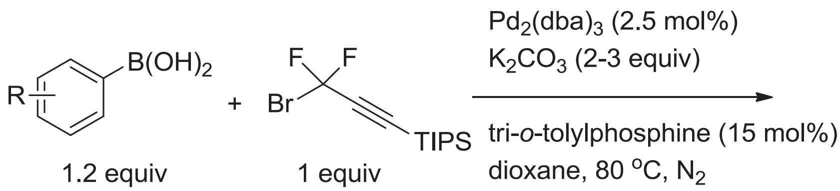
Zhang and collaborators [53] have very recently informed the first example of Pd-catalyzed *gem*difluoroallylation of organoborons using 3-bromo-3,3-difluoropropene in high efficiency. The reaction has broad substrate scope, and excellent functional group compatibility, thus providing a facile route for practical application in drug discovery and development. The scope of the transformation is illustrated in Scheme 27.



	yield % (α : γ ratio)
R = 3,5-diOMe	82 (16:1)
= 3-NO_2	70 (13:1)
= 4-CO_2Et	78 (13:1)
= 4-CHO	60 (10:1)
= 3-CO_2Et	80 (15:1)
= 4-CH_2OH	68 (19:1)
= 3-Br	67 (12:1)
= 4-Br	74 (20:1)

	yield % (α : γ ratio)
R = 4-*t*-Bu	93 (20:1)
= 4-Ph	85 (16:1)
= 3-Ph	87 (16:1)
= 2-Ph	83 (15:1)
= 2,5-Me	92 (18:1)
= 2,4,6-Me_3	78 (17:1)
= 4-OBn	87 (28:1)
= 3,4-diOMe	71 (24:1)

Scheme 27. Scope of the difluoroallylation of aryl boronic acids [53].



	yield%
R = H	91
= 2-Me	77
= 3-Me	85
= 4-Me	82
= 3,5-diOMe	75
= 4-Ph	53
= 3-Ph	58
= 1-naphthyl	79

	yield%
R = 4-COMe	90
= 4-CN	78
= 4-CO_2Et	84
= 4-CHO	70
= 3-NO_2	67
= 3-CF_3	87
= 4-CH_2=CH	56
= 4-CH_2Br	48

Scheme 28. Scope of the *gem*-difluoropropargylation of aryl boronic acids (TIPS = tri*iso*propyl silane) [54].

As observed from Scheme 27, γ-substituted products, albeit in low relative yields, were observed besides linear substituted α-products.

In spite of substantial progress in fluoroalkylation of organic molecules, efficient methods that enable low catalyst loading to practically synthesize fluorinated compounds have received rare attention. In this context, gram-scale synthesis of *gem*difluoroallylated arenes with utilization of 0.1–0.01 mol% of Pd catalyst was conducted by the authors [53] to demonstrate the synthetic utility of the protocol (Scheme 27). The authors [53] achieved the synthesis of the 4-Br-substituted difluoroallyl arene compound in the presence of 0.05 mol% $Pd_2(dba)_3$. Most excitingly, a 10-gram-scale reaction with Pd-catalyst loading as low as 0.01 mol% afforded the difluoroallyl aryl compound substituted with *t*-butyl group at the 4-position of the aryl ring in 80% yield with high regioselectivity ($\alpha/\gamma = 10{:}1$) (Scheme 27). To the best of our knowledge, this is the first example of transition-metal-catalyzed fluoroalkylation of organic molecules by using as low as 0.01 mol% catalyst in a practical manner but no mechanistic information was provided.

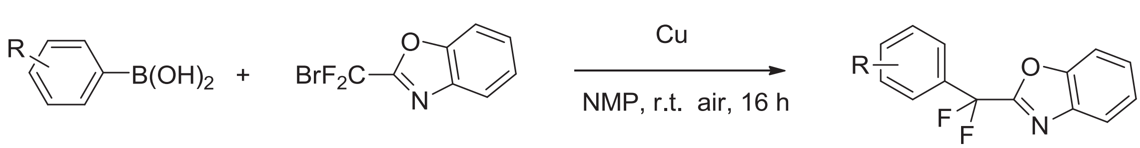
Concomitantly, Zhang and colleagues [54] reported the palladium-catalyzed *gem*-difluoropropargylation of aryl organoboron reagents employing *gem*-difluoropropargyl bromides in very good yields. The scope of the transformation is depicted in Scheme 28.

Hao and collaborators [55] have very recently come up with a protocol for an effective copper-mediated *gem*-difluoromethylenation of aryl boronic acids employing bromodifluoromethylated benzoxazole. The scope of the transformation is represented in Scheme 29.

The addition of ligands was ineffective, and the presence of base shut down the reaction. Importantly, the halogenated arylboronic acids were effectively converted into the corresponding difluoromethylated products, whereas a substitution of the corresponding halide was never or rarely observed. This situation is remarkable, because the most common difluoromethylation reactions substitute halides, especially iodides. Therefore, the new transformation shows a reaction pathway that is orthogonal to common routes [55].

The authors presented a mechanism such as that outlined in Scheme 30.

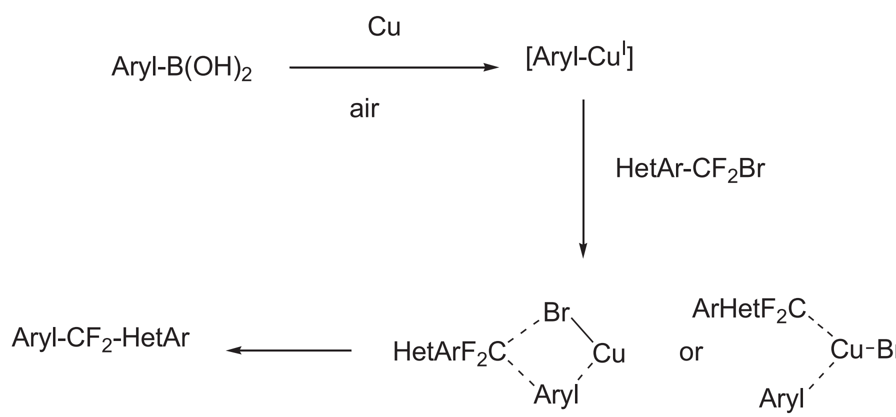
Arylboronic acid is first converted to the [Aryl-Cu^{I}] intermediate in the presence of Cu powder and air. This cuprate of aryl copper species could either react with bromodifluoromethylated benzoxazole by oxidative addition to form a $Cu^{III}(ArCF_2)$(Aryl) species, followed by reductive elimination to give Aryl-CF_2–Ar, or directly



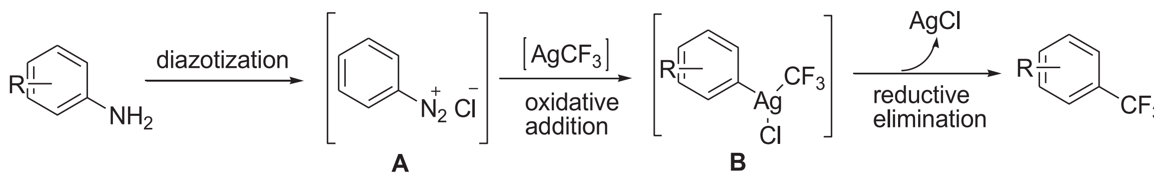
	%yield
R = 4-Cl	88
= 4-Br	70
= 4-I	82
= 4-CF_3	63
= 4-CN	70
= 4-COMe	57
= 4-CHO	46

	%yield
R = H	85
= 4-Ph	62
= 4-OMe	76
= 3-OMe	63
= 2-OMe	88
= 4-OBn	75
= 4-F	87

Scheme 29. Scope of the copper-mediated *gem*-difluoromethylenation of aryl boronic acids employing bromodifluoromethylated benzoxazole [55].



Scheme 30. Proposed mechanism for the copper-mediated *gem*-difluoromethylenation of aryl boronic acids employing bromodifluoromethylated benzoxazole [55].



Scheme 31. Proposed mechanism for the trifluoromethylation of arenes with Ag complex [57].

initiate an S_N2-type substitution (or σ-bond metathesis) reaction at the CF_2 center to release the desired product.

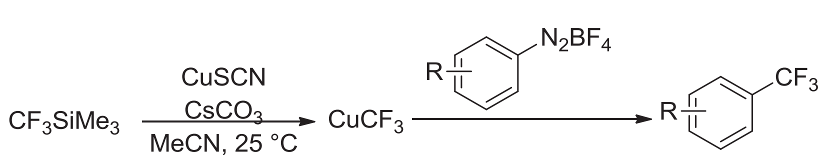
2.3. Trifluoromethylation from aniline precursors. The Sandmeyer trifluoromethylation [56a]

Fu and collaborators [56b] have very recently accomplished the copper-promoted Sandmeyer trifluoromethylation reaction with the Umemoto's reagent in excellent yields. This reaction, however relevant, involves the employment of an electrophilic trifluoromethylating reagent, which is outside the scope of this account and has been recently reviewed [12].

Wang and collaborators [57] have carried out the silver-mediated trifluoromethylation of aryldiazonium salts in good yields employing $AgCF_3$. Based on the oxidizing properties of aryl diazonium salts and the strong σ-donor nature of the trifluoromethyl group in the $[AgCF_3]$ complex and also inspired by Ritter's recent reports on reductive elimination from bimetallic high-valent silver complex to form C_{aryl}—F bonds, [58] the authors [57] proposed that oxidative addition of diazonium salt **A** would be favored at an electron-rich silver center to afford intermediate **B** (Scheme 31).

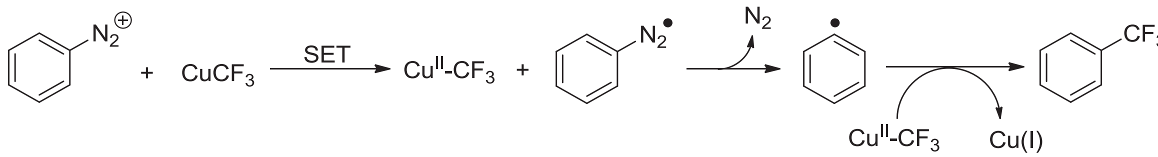
Subsequently, intermediate **B** (Scheme 31) undergoes reductive elimination to form a C_{aryl}—CF_3 bond and a AgCl precipitate. According to this hypothesis, the authors [57] envisioned that conversion of aromatic amines into the corresponding trifluoromethyl arenes (trifluoromethylation variation of the classic Sandmeyer reaction) would be feasible. In general, the aniline derivatives bearing either electron-withdrawing or -donating groups react smoothly to afford the corresponding trifluoromethylation products in moderate to excellent yields. 4-Aminoazobenzene is also a suitable substrate for the reaction, affording the respective 4-azobenzotrifluoride. Remarkably, oxidation sensitive groups, such as vinyl, alkynyl, Bpin, and TMS groups, also tolerate the reaction conditions. The anilines bearing *ortho*-substituents, including ester and bulky *iso*propyl groups, also worked well.

As for the mechanism of the reaction [57] the authors concluded through mechanistic probe-experiments that the CF_3 radical is unlikely involved in the trifluoromethylation pathway. An oxidative addition–reductive elimination mechanism involving high-valent silver species, as shown in Scheme 31, may be participating. However, the authors [57] claimed that rigorous investigations are necessary to unambiguously elucidate the detailed mechanism.



R	Yield (%)
4-MeO	81
4-Ph	78
4-Cl	98
4-I	69
4-CN	68
4-CO_2Me	71
4-NMe_2	95
4-NHCOMe	40
3-COMe	67
3-CO_2H	73
2-OMe	57
2-CO_2H	67

Scheme 32. Sandmeyer trifluoromethylation of arenes [59].



Scheme 33. Postulated reaction mechanism for the Sandmeyer trifluoromethylation [59].

In 2013 Gooßen and colleagues [59] have attempted the trifluoromethylation of arenediazonium tetrafluoroborates employing CF_3SiMe_3 as trifluoromethylating reagent, in the presence of CuSCN, $CsCO_3$ in MeCN as solvent. The scope of the transformation is represented in Scheme 32.

The reaction proceeds analogously to the Sandmeyer halogenations of diazonium salts, which are generally believed to proceed *via* radical intermediates (Scheme 33). It is plausible that the trifluoromethyl copper(I) species, generated from the copper precursor and CF_3SiMe_3 in the presence of the cesium base, transfers one electron to the diazonium salt. The resulting diazo radical releases nitrogen with formation of an aryl radical, which abstracts the trifluoromethyl group from the copper(II) intermediate to form the trifluoromethylated product along with a copper(I) species (Scheme 33).

More recently, Gooßen and co-workers have developed a practical one-pot procedure for the Sandmeyer-type trifluoromethylation. Starting from heteroaromatic amines, heterobenzotrifluorides were synthesized *via in situ* diazotation and copper-mediated trifluoromethylation using the Ruppert–Prakash reagent (Scheme 34) [60].

Recently, Grushin and co-workers have developed a new approach to the preparation of trifluoromethyl arenes in water involving arenediazonium salts and $CuCF_3$, a moisture-sensitive trifluoromethylating reagent [61]. The *in situ* generation of arenediazonium salts is achieved by treatment of anilines with HF (48%), $NaNO_2$ (1.05 equiv.) in water. The aqueous solution is then mixed with acetonitrile and followed by addition of $CuCF_3$ in DMF solution at 0 °C to afford the trifluoromethylated arenes in 70–80% yield. This newly trifluoromethylation protocol is compatible with a broad variety of electron-donating and -withdrawing functional groups as is shown in Scheme 35. Also, 3-amino-pyridine and 8-amino-quinoline have been trifluoromethylated efficiently under this experimental conditions providing the desired CF_3-substituted products in 65% and 73% yields, respectively.

The reaction suffers undesired hydrodediazotation by-products in 3–5% yields, however, minimization of these amounts could be achieved by adjusting the reagent concentration and the amount of the acids used. Also, the protocol is convenient for scaling-up successfully, affording the desired products in good yield and noticeable selectivity. The trifluoromethylation reaction of arenediazonium salts follows a radical pathway within the solvent cage, which is often characteristic of the Sandmeyer-type reactions.

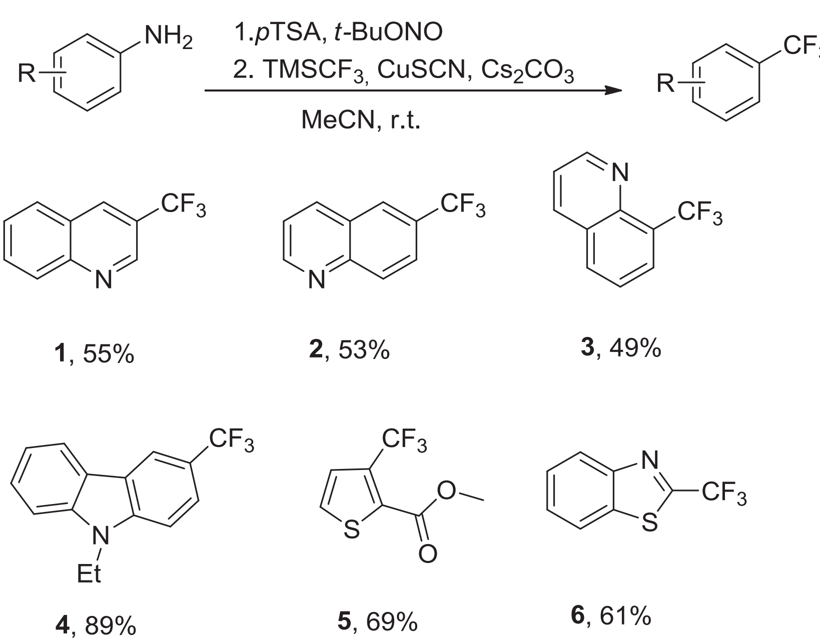
2.4. C—H fluoroalkylation of aromatic compounds

2.4.1. Heteroaromatic compounds and benzene derivatives

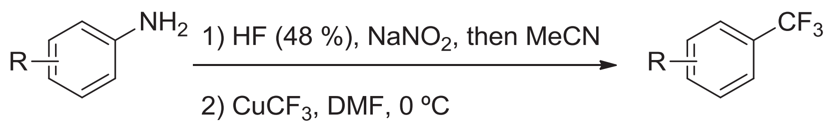
Strategies for the fluoroalkylation of unfunctionalized arene substrates are undoubtedly fundamental since the pharmaceutical industry requires methods for late stage trifluoromethyl and perfluoroalkyl groups incorporation reactions from unfunctionalized substrates [62]. C_{Ar}—H trifluoromethylation of aromatic substrates employing electrophilic trifluoromethylating reagents has recently been reviewed [12a,12c].

2.4.1.1. C_{Ar}—H fluoroalkylation of (hetero)aromatic compounds with R_fX. C_{Ar}—H Pd-catalyzed [63] perfluoroalkylation of arenes has been introduced by Sanford and collaborators [64]. The optimized reaction conditions employ $Pd_2(dba)_3$, BINAP as phosphine ligand, Cs_2CO_3 as base, and a perfluoroalkyl iodide, as indicated in Scheme 36.

The authors [64] postulate a reaction mechanism such as that in Scheme 37.

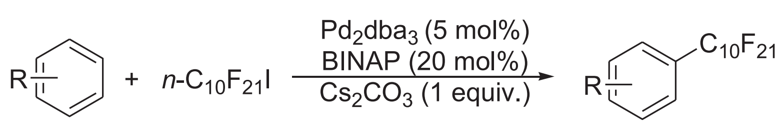


Scheme 34. Trifluoromethylation of aromatic amines with the Rupert–Prakash reagent [60].



R	Yield (%)	R	Yield (%)	R	Yield (%)
4-Me	84	3-NO_2	73	2-CO_2Me	63
4-OMe	81	3-I	50	2,4-diOMe	70
4-NO_2	70	2-OMe	63	2-OMe-4-NO_2	75
4-NHCOMe	80	2-CN	64	3-CF_3-4-CN	60
4-COMe	72	2-I	58	2-CO_2H-4-I	64
4-CO_2H	85	2-F	70	2,6-diF	27
4-CO_2Me	85	2-COMe	75		
4-I	80	2-Cl	69		

Scheme 35. Trifluoromethylation of aniline derivatives [61].



R	Yield (%)
H	60
2,4-diOMe	76
2,6-diOMe	69
2,5-diOMe	69
3,4-diMe	54
2,4-diMe	55
2,5-diMe	52
3,4-diCl	27

Scheme 36. Scope of the Pd-catalyzed perfluorobutylation of arenes [64].

According to this mechanism, the oxidation-addition of R_fI to Pd^0 generates the Pd(II) intermediate **A**, followed by arene activation to form the diorgano Pd(II) species **B**. C—C bond formation coupled with reductive elimination releases the product and regenerates the Pd^0 catalyst (Scheme 37).

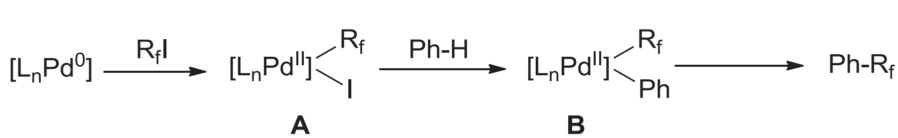
Upon addition of radical scavengers such as BHT, hydroquinone, 1,4-dinitrobenzene, the yields of perfluorodecyl-substituted arenes remain almost identical as compared to the reactions carried out in the absence of such additives [64]. This would indicate that a radical pathway can be ruled out.

Cho and collaborators [65] have informed the trifluoromethylation of heterocycles by visible light photoredox catalysis. TMEDA was chosen as the best electron donor with $Ru(bpy)_3Cl_2$ complex in MeCN as solvent. In general, the use of MeCN as the solvent afforded good results probably due to the greater solubility of the CF_3I in MeCN [65]. A study of reaction concentrations showed that 0.25 M concentration in MeCN afforded the best results. Using a higher equivalent ratio of the base did not affect the reaction efficiency although using less base led to lower trifluoromethylated product yields. Employment of blue LEDs as visible light sources showed higher efficiency. In addition, the reaction required the use of at least 3–4 equiv. CF_3I for reproducible results. The scope of the transformation is illustrated in Scheme 38.

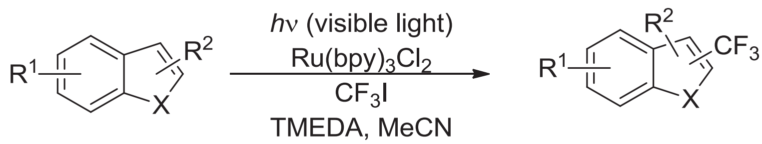
Benzothiazoles and benzofurans also worked well as substrates for the reaction [65]. In addition, electron-deficient heterocycles and unactivated aromatic compounds were not reactive under the reaction conditions. Several functional groups were tolerant including bromide, aldehydes, esters, and amines. Thus this process should be applicable to the late-stage modifications of advanced intermediates in the synthesis of complex molecules [65]. Regarding the regioselectivity, however, a mixture of regioisomers was obtained from the reaction of parent indole. Substitution at the 2-position of indole was preferred over the 3-position due to the formation of a more stable benzylic radical intermediate. In addition, the use of more than 5 equiv. of CF_3I resulted in the formation of multi-trifluoromethylated side products. For example, with 5 equivalents of CF_3I, a 10% yield of 2,5-disubstituted product along with 2-trifluoromethylated *N*-methylpyrrole in the reaction of *N*-methylpyrrole [65] was obtained.

The mechanism of the reaction [65] is proposed in Scheme 39.

In the proposed mechanism, $Ru(bpy)_3{}^{2+}$ is excited generating the oxidizing species $^*Ru(bpy)_3{}^{2+}$, which transfers an electron to the base (NR_3, *i.e.:* TMEDA), and producing the species $Ru(bpy)_3{}^{+}$, which reduces CF_3I into CF_3 radicals (and iodide anion). CF_3 radicals add to the indole, affording a benzyl-type radical intermediate that can be oxidized into a benzyl-type cation intermediate through

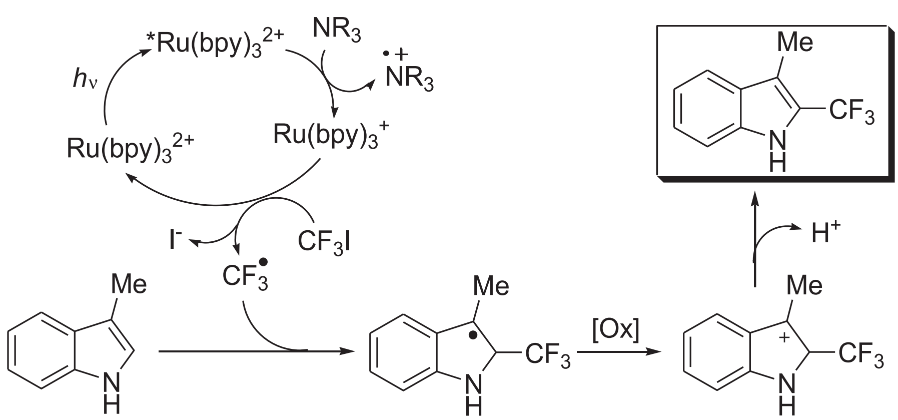


Scheme 37. Postulated reaction mechanism for the Pd-catalyzed perfluoroalkylation of arenes [64].



X = NH, R^1 = H, R^2 = 3-Me	2-CF_3-indole, 90%
X = NMe, R^1 = H, R^2 = 2-Me	3-CF_3-indole, 94%
X = NH, R^1 = H, R^2 = C(O)OEt	3-CF_3-indole, 81%
X = NMe, R^1 = R^2 = H	2-CF_3-indole:3-CF_3-indole, 95%, 1.5:1
X = NMe, R^1 = 5-Br, R^2 = H	2-CF_3-indole:3-CF_3-indole, 86%, 1.3:1
X = NMe, R^2 = H	2-CF_3-pyrrole, 95%
X = NMe, R^2 = 5-CHO	2-CF_3-pyrrole, 71%
X = NMe, R^2 = 5-Et	2-CF_3-pyrrole, 92%

Scheme 38. Photocatalytic trifluoromethylation of indoles and pyrroles [65].



Scheme 39. Proposed reaction mechanism for the photocatalytic trifluoromethylation reaction [65].

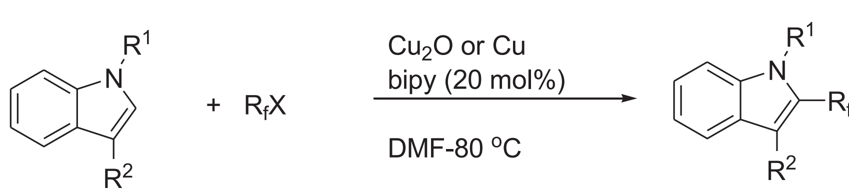
the aid of $Ru(bpy)_3{}^{2+}$. Proton loss affords the trifluoromethylated indole derivative [65]. This mechanism is similar to that postulated in Section 2.2.2 for the photocatalytic trifluoromethylation of aryl boronic acids in the presence of $Ru(bpy)_3{}^{2+}$, CF_3I, K_2CO_3 as base in DMF as solvent [42].

The silver-mediated trifluoromethylation-iodination of arynes has recently been conducted in tetramethylpiperidine (TMP) as solvent [66].

Huang and collaborators [67] have very recently accomplished the direct fluoroalkylation of indoles with Cu and fluoroalkyl halides in DMF as solvent in good yields. The scope of the reaction is shown in Scheme 40.

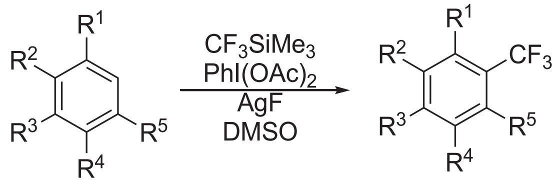
2.4.1.2. C_{Ar}—H fluoroalkylation of (hetero)aromatic compounds with CF_3SiMe_3 [68a]. Greany and colleagues have recently accomplished the C—H silver-catalyzed trifluoromethylation of arenes in reasonably good yields [68b]. The scope of the reaction is depicted in Scheme 41.

Substrate scope investigation established that the procedure was effective for an array of electron-rich arenes. Unsymmetrical substituted substrates (not shown in Scheme 41) give rise to a mixture of trifluoromethylated products, consistent with a $S_{Ar}H$ addition pathway. Interestingly, the reaction was compatible with the presence of halogens on the arene moiety, illustrating the orthogonal reactivity to conventional C—X trifluoromethylations



R^1 = Me, R^2 = H, R_f = C_4F_9	72%
R^1 = Me, R^2 = H, R_f = C_6F_{13}	64%
R^1 = R^2 = Me, R_f = C_6F_{13}	74%
R^1 = CH_2CH_2, R^2 = H, R_f = C_4F_9	55%
R^1 = Me, R^2 = CH_2Ph, R_f = C_4F_9	45%

Scheme 40. Scope of the perfluoroalkylation of indole derivatives [67].



	Yield (%)
$R^1 = R^2 = R^3 = R^4 = R^5 = H$	60
$R^2 = R^3 = OMe$, $R^1 = R^4 = R^5 = H$	55
$R^1 = R^3 = R^5 = OMe$, $R^2 = R^4 = H$	89
$R^1 = R^3 = OMe$, $R^4 = Br$, $R^2 = R^5 = H$	40
$R^1 = Br$, $R^3 = R^4 = R^5 = OMe$, $R^2 = H$	55
$R^1 = I$, $R^3 = R^4 = R^5 = OMe$, $R^2 = H$	51
$R^1 = CHO$, $R^3 = R^4 = R^5 = OMe$, $R^2 = H$	63
$R^1 = COMe$, $R^3 = R^4 = R^5 = OMe$, $R^2 = H$	61
$R^1 = CO_2Me$, $R^3 = R^4 = R^5 = OMe$, $R^2 = H$	54
$R^1 = NMe_2$, $R^4 = Br$, $R^2 = R^3 = R^5 = H$	64
$R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$	67
$R^1 = R^3 = R^5 = Me$, $R^2 = R^4 = H$	71

Scheme 41. Scope of the silver-catalyzed trifluoromethylation reaction of arenes [68b].

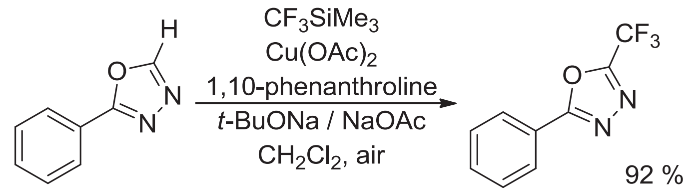
(*vide supra*, Section 2.1) whereby neighboring C—H bonds undergo preferential substitution reaction as opposed to C_{Ar}—X bonds [68b]. Electron-withdrawing groups such as aldehydes, ketones, esters can be tolerated under the reaction conditions [68], likewise *N,N*-dialkylanilines can be trifluoromethylated.

The authors [68b] investigated the reaction mechanism for the silver catalyzed C—H trifluoromethylation reaction employing CF_3SiMe_3 as trifluoromethylating reagent. Radical quenching reactions utilizing TEMPO and galvinoxyl radical, suppressed the trifluoromethylated product formation. A CF_3-TEMPO adduct could be observed by ^{19}F NMR spectroscopy. The proposed reaction pathway is shown in Scheme 42.

The authors [68b] suggested that the combination of $PhI(OAc)_2$ and AgF acted as a sufficiently oxidizing agent to generate CF_3 radicals that add to the arene moiety. Ulterior oxidation (ET) and deprotonation (PT) renders the aromatized substituted product (Scheme 42).

Qing and collaborators have accomplished the oxidative C—H trifluoromethylation of heteroarenes with Me_3SiCF_3, a copper salt ($Cu(OAc)_2$), in the presence of base (NaO*t*-Bu and NaOAc) and an organocatalyst (1,10-phenanthroline) in dichloroethane (DCE) as solvent [69], according to Scheme 43.

The same authors [69] have accomplished the trifluoromethylation of different heteroarenes, such as those illustrated in Scheme 44 in very good yields, employing the Ruppert–Prakash CF_3SiMe_3 reagent, sodium *t*-butoxide as base, and TBHP as radical



Scheme 43. Trifluoromethylation of 1,3,4-oxadiazole derivatives with Me_3SiCF_3 in dichloroethane (DCE) as solvent [69].

initiator, with $Cu(OAc)_2$ and 1,10-phenanthroline as metal- and organocatalysts, respectively.

Next, the same authors [69] have focused on the trifluoromethylation strategies for indole derivatives, and optimized the reaction conditions employing a combination of $Cu(OH)_2$, 1,10-phenanthroline, silver carbonate in conjunction with CF_3SiMe_3 and KF in DME as solvent, according to Scheme 45.

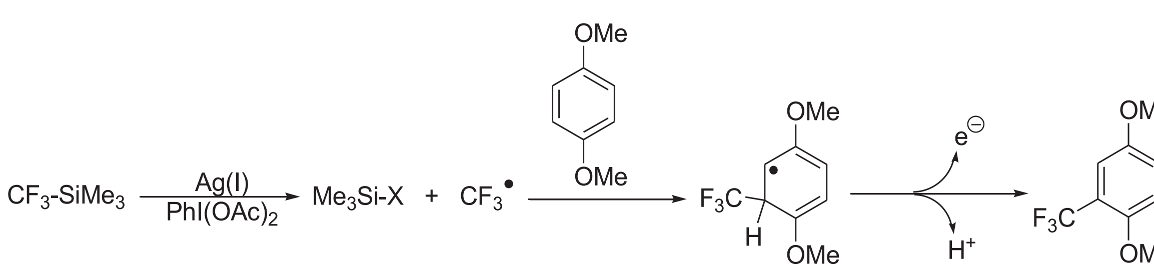
The reaction mechanism is shown in Scheme 46.

First, reduction or disproportionation of a Cu(II) catalyst into a Cu(I) species, followed by reaction with Ruppert's reagent (CF_3SiMe_3) generated *in situ* would afford the $CF_3Cu^IL_n$ species **A** as the key intermediate (Scheme 46). Subsequent transmetallation with activation of Ar—H bond would generate the (aryl)$Cu^I(CF_3)$ species **B**, which might be oxidized to the corresponding (aryl)$Cu^{III}(CF_3)$ intermediate **C**. Finally, reductive elimination of the (aryl)-$Cu^{III}(CF_3)$ intermediate **C** would afford the expected product and regenerate the catalyst to complete the catalytic cycle (Scheme 46, route 1). Alternatively, a catalytic cycle involving the initial generation of the arylcopper complex **D**, which was generally suggested as the key intermediate in the Cu-mediated C—H functionalization of heteroaromatic compounds under basic conditions, might be possible. The transmetallation of arylcopper complex **D** with trifluoromethylsilicate generated *in situ* would lead to the formation of (aryl)$Cu^I(CF_3)$ species **B**, which subsequently would deliver the cross-coupling product (Scheme 46, route 2) [69].

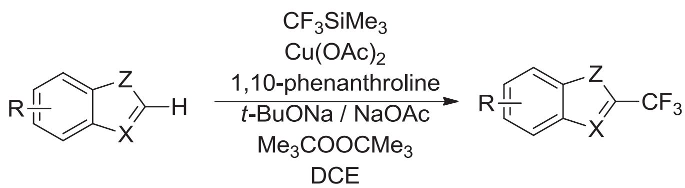
2.4.1.3. C_{Ar}—H fluoroalkylation of (hetero)aromatic compounds with CF_3SO_2Na. Lipshutz and colleagues [70] have very recently accomplished the C-H trifluoromethylation of heteroaromatic compounds [71a] in water in high yields, employing nanoparticles consisting of commercially available TPGS-750-M, a combination of Langlois' reagent ($NaSO_2CF_3$) and *t*-BuOOH (TBHP) to effect the trifluoromethylation reaction. The authors studied the scope of the transformation comparing it with previously reported trifluoromethylation strategies employing the same substrates, the Langlois' reagent and TBHP. The scope of the present reaction is illustrated in Scheme 47.

This procedure [70] constitutes a micellar catalysis amenable to a radical-based methodology of heterocyclic compounds employing nanoreactors composed of surfactants TPGS-750-M.

In an analogous fashion, the trifluoromethylation of coumarins have recently been accomplished by Zou and collaborators [71b].

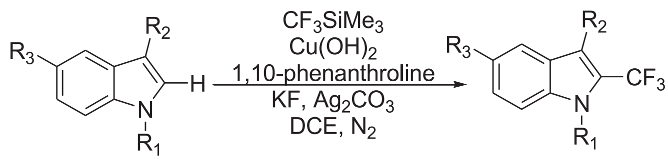


Scheme 42. Proposed reaction mechanism [68b].



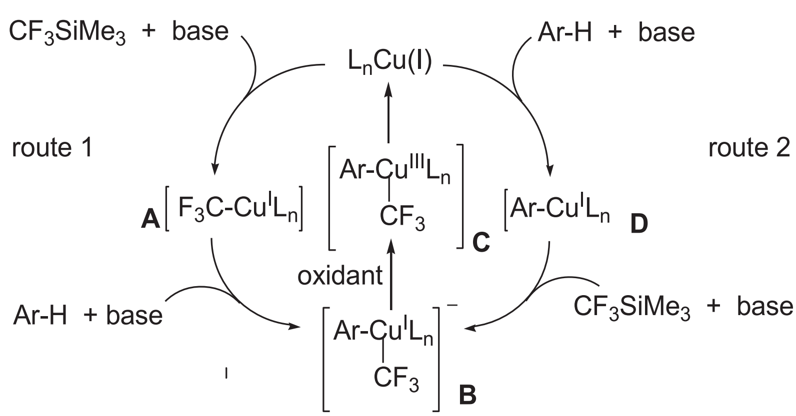
	Yield (%)
Z = O, X = N, R = 5-Me	72
Z = O, X = N, R = 5-Ph	88
Z = O, X = N, R = 5-Br	58
Z = O, X = N, R = 5-Cl	57
Z = NMe, X = N, R = H	32
$Z = NCH_2CH_2CH{=}CH_2$, X = N	74
Z = S, X = N, R = H	72

Scheme 44. Scope of the trifluoromethylation of heterocycles [69].



	Yield (%)
$R_1 = R_2 = Me, R_3 = H$	87
$R_1 = C_2H_5, R_2 = Me, R_3 = H$	80
$R_1 = Ph, R_2 = Me, R_3 = H$	89
$R_1 = Bn, R_2 = Me, R_3 = H$	71
$R_1 = Me, R_2 = C_6H_{11}, R_3 = Cl$	68
$R_1 = Me, R_2 = C_6H_{11}, R_3 = Br$	72
$R_1 = Me, R_2 = C_6H_{11}, R_3 = CO_2Me$	83
$R_1 = Me, R_2 = C_5H_9, R_3 = H$	64
$R_1 = Me, R_2 = i\text{-}Pr, R_3 = H$	82
$R_1 = Ts, R_2 = Me, R_3 = H$	trace
$R_1 = Me, R_2 = CO_2Me, R_3 = H$	0

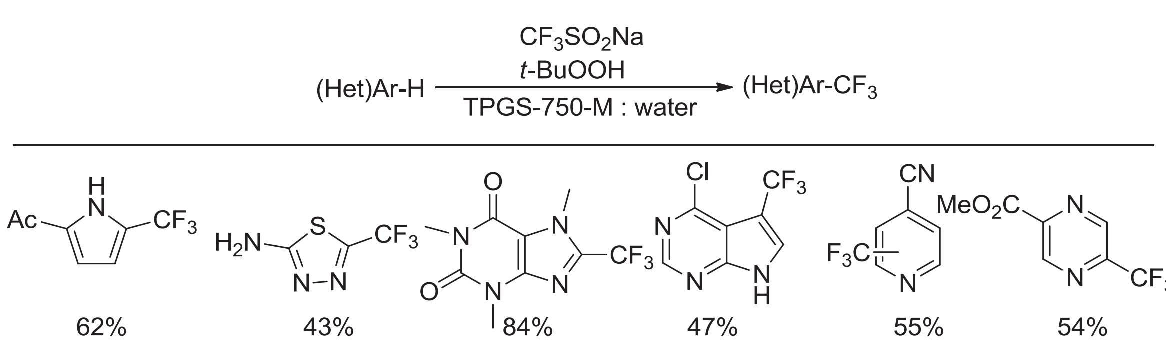
Scheme 45. Trifluoromethylation of *N*-methyl indole, according to Qing's protocol [69].



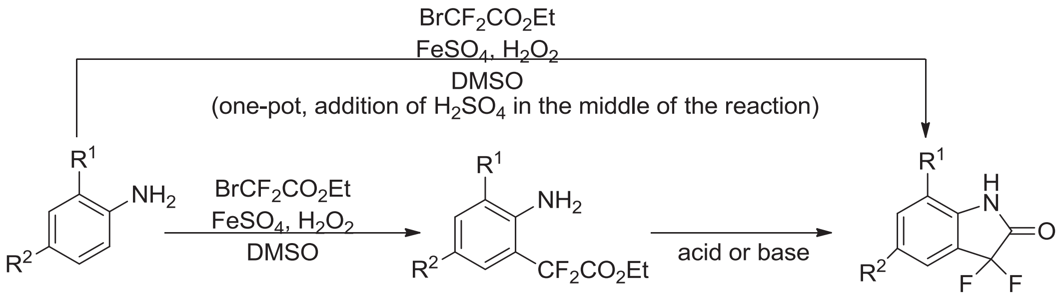
Scheme 46. Proposed reaction mechanism for the copper-catalyzed trifluoromethylation of arenes and heteroarenes in the presence of base [69].

2.4.1.4. C_{Ar}—H difluoromethylation of (hetero)aromatic compounds. In 2010, Yamakawa and colleagues [72] have investigated the fluoroalkylation of aromatic and heteroaromatic substrates employing the Fenton reagent (H_2O_2 and Fe(II), CF_3I in DMSO as solvent). Simple alkyl-substituted arenes, anilines, chloro-substituted anilines and phenols can be fluoroalkylated in yields ranging from 10% to 70%. Simple heteroaromatic compounds such as pyridines, pyrroles, thiophenes, furans, indoles, benzothiophenes, benzofurans, can be fluoroalkylated with this methodology [72].

With regard to the reaction mechanism, the authors [72] considered: (i) a hydroxyl radical is formed through the reduction of H_2O_2 by Fe(II) (Fe(III) is formed simultaneously (Eq. (2))); (ii) the



Scheme 47. Scope of the C—H trifluoromethylation of heteroaromatic compounds in water [70].



R_1	R_2	Yield (%)	Acid or base	Yield (%)	One-pot yield (%)
Cl	Cl	44	Et_3N	99	72
Br	Me	40	Et_3N	71	75
H	CO_2Et	38	H_2SO_4	95	58
H	COMe	31	CF_3COOH	98	43
H	CN	27	CF_3COOH	91	45
H	Cl				50
H	NO_2				13

Scheme 48. Scope of the ethoxycarbonyl difluoromethylation of aniline derivatives [73].

hydroxyl radical is rapidly trapped by DMSO to form a methyl radical (Eq. (3)) and (iii) the reaction of CF_3I and the methyl radical releases a trifluoromethyl radical (Eq. (4)).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\bullet} + HO^{-} \quad (2)$$

$$HO^{\bullet} + DMSO \rightarrow CH_3^{\bullet} + H_3CS(O)\text{-}OH \quad (3)$$

$$CH_3^{\bullet} + CF_3I \rightarrow CF_3^{\bullet} + CH_3I \quad (4)$$

In a more recent work, the main leading author [73] attempted the ethoxycarbonyl difluoromethylation [74] of aromatic compounds using the Fenton reagent in fairly good yields. The scope of the reaction is depicted in Scheme 48.

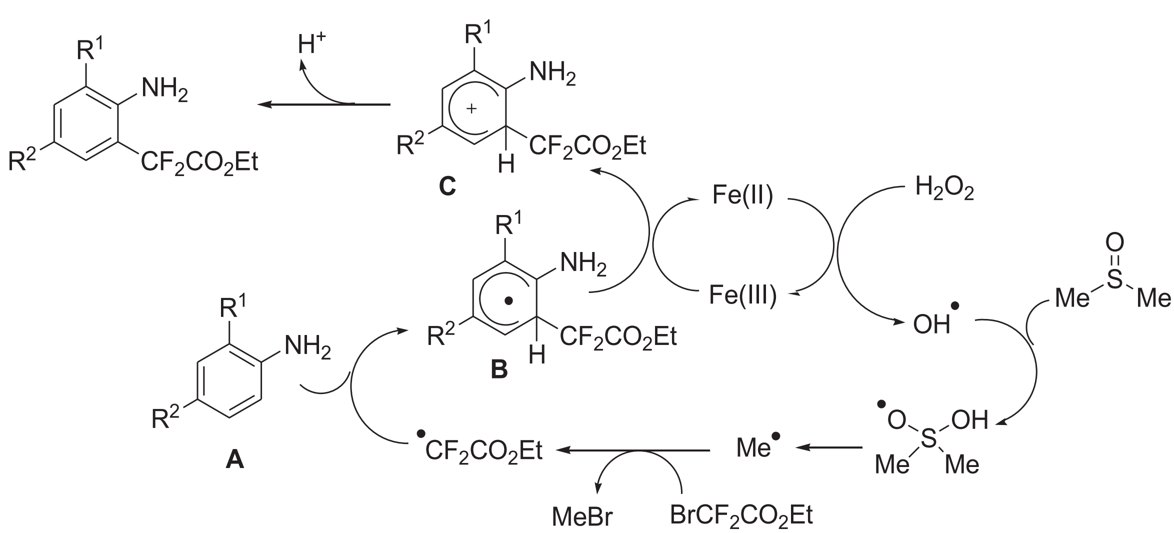
The authors [73] examined the one-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives from *para*-substituted aniline precursors through the ethoxycarbonyldifluoromethylation and the addition of H_2SO_4 in the middle of the reaction. Scheme 48, last column shows the results of the one-pot reactions using various *para*-substituted aniline derivatives as substrates. The authors [73] obtained the products in somewhat low yields. 3,3-Difluoro-2,3-dihydroindole-2-one derivatives are known to be biologically active and are generally synthesized from 1*H*-indole- 2,3-dione derivatives by fluorination with DAST. Since the syntheses of 1*H*-indole-2,3-dione derivatives require several steps from aniline precursors, this methodology [73] is considered superior to other known methods not only based on safety and versatility considerations, but also because of its relative simplicity.

The proposed reaction mechanism is shown in Scheme 49.

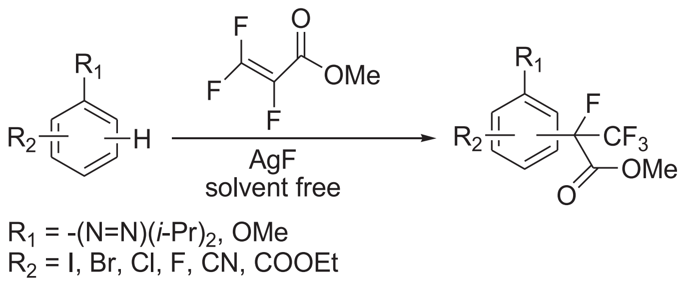
In this mechanism [73], the $^{\bullet}OH$ radicals combine with DMSO and produce Me radicals that abstract the bromine atom from $BrCF_2CO_2Et$ [74], generating $^{\bullet}CF_2CO_2Et$ radicals that add to the aniline derivative **A** and produce a cyclohexadienyl-type radical intermediate **B**, which in turn is oxidized by Fe(III) to produce a Wheland-type intermediate **C**. Proton loss affords the fluorinated product [73] (Scheme 49).

2.4.2. *Methoxycarbonyl tetrafluoroethylation of arenes*

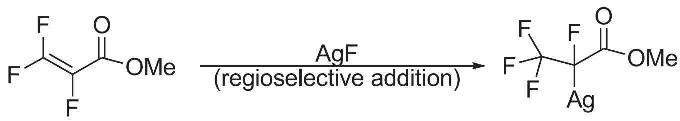
Recently, Bräse and colleagues [75,76] have accomplished the silver-mediated methoxycarbonyl-tetrafluoroethylation of arenes, according to Scheme 50.



Scheme 49. Proposed reaction mechanism [73].



Scheme 50. AgF-mediated methoxycarbonyl tetrafluoroethylation of arenes [75,76].



Scheme 51. Regioselective addition of AgF to olefins [75,76].

Due to the repulsive interactions between the lone electron pairs of the fluorine substituent and the π-orbital of the sp^2-carbon, fluorinated olefins regioselectively add fluoride ions. In donor solvents like acetonitrile, this occurrence can be used to generate silver perfluoroorganyls by adding AgF regioselectively to the fluorinated double bond (Scheme 51).

This regioselective addition is interesting, as it allows rapid access to secondary metal perfluoroalkyl species. The authors [75] further explored the scope of the methoxycarbonyl *tetra*fluoroethylation reaction. Several functionalized aromatic triazenes can be used for this kind of transformation. Most interestingly, this method tolerates various functional groups, *e.g.* iodides, bromides, chlorides, fluorides, nitriles and ethoxycarbonyl moieties. When *para*-substituted aromatic triazenes were used, the *ortho*-methoxycarbonyltetrafluoroethylated triazenes were always the major products [76].

In contrast to these results, the trifluoromethylation reaction showed a high *ortho* selectivity with these substrates. Aromatic triazenes bearing a strong electron-withdrawing group could only be methoxycarbonyltetrafluoroethylated in low yields. This occurrence could also explain why no disubstitution was observed. Thus, the electron-withdrawing effect of the methoxycarbonyltetrafluoroethyl group deactivates the aromatic core for a second substitution [76].

3. Fluoroalkylation of aliphatic systems [77a]

Transition-metal assisted nucleophilic trifluoromethylation of allylic halides, α-haloketones, and propargylic [77b] halides has recently been reviewed by Wang and Liu [35]. These transformations have been accomplished by the employment of CF_3SiMe_3, in the presence of complex CuTc (CuTc: (thiophene-2-carbonyloxy)copper), phosphine- or phenanthroline-stabilized copper reagents $[(Ph_3P)_3CuCF_3]$,and/or $[(phen)CuCF_3]$, in solvents such as THF (CuTc), or DMF ($CuCF_3$).

3.1. Fluoroalkylation of primary and secondary alkyl boronic acids

Primary and secondary alkyl-boronic acids have recently been trifluoromethylated by the Ruppert's reagent (Me_3SiCF_3) in the presence of a copper salt and a ligand in DMF as solvent [78]. The optimized reaction conditions involve CF_3SiMe_3 (3 equiv.), and the conjunction of the following transition metal salts: CuI, AgF, $AgBF_4$, and 3,4,7,8-tetramethyl-*o*-phenanthroline as ligand, in DMF as solvent, according to Scheme 52. The global reaction yields range from 40% to 70% [78,79].

This transformation is particularly interesting from the standpoint of a Csp^3-CF_3 functionalization reaction. Recent metal-mediated trifluoromethylation reactions occur at the sp^2- and sp-hybridized carbon centers. The reaction is a Cu-catalyzed C—C cross coupling reaction of alkyl boronic acid derivatives. The authors do not propose a reaction mechanism for the transformation.

3.2. Trifluoromethylation of alkyl-methanesulfonates, and α-haloketones

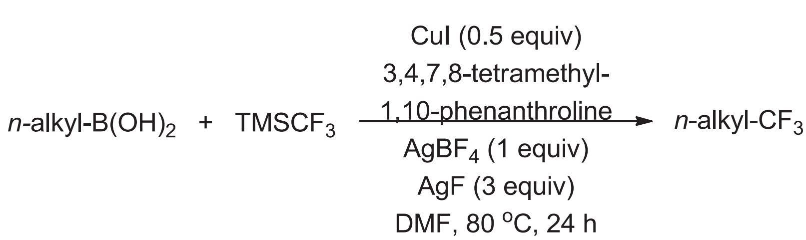
Qing and colleagues [77a] have recently reported the trifluoromethylation of benzyl, allyl and propargyl [80] methanesulfonates with CF_3SiMe_3 in the presence of CuI, KF in DMF/HMPA as solvent mixture. The scope of the transformation is depicted in Scheme 53.

Grushin and co-workers [81] have accomplished the nucleophilic trifluoromethylation of α-haloketones with fluoroform-derived $CuCF_3$ in DMF at room temperature and in 15–120 min. This transformation is regiospecific for the C—X (X = Br, Cl) bond affording 2,2,2-trifluoroethylketones in high yield as depicted in Scheme 54. The reaction applies efficiently to aryl and alkyl α-haloketones and tolerates a wide variety of functional groups. The authors have discovered a new reaction (*vide infra* Scheme 3) for direct cupration of fluoroform [20,23,82] that furnished $CuCF_3$ in nearly quantitative yield (>90%). The $CuCF_3$ reagent is stabilized with $Et_3N\cdot 3HF$ [20,23], easy to handle and can be stored at room temperature for a long period of time.

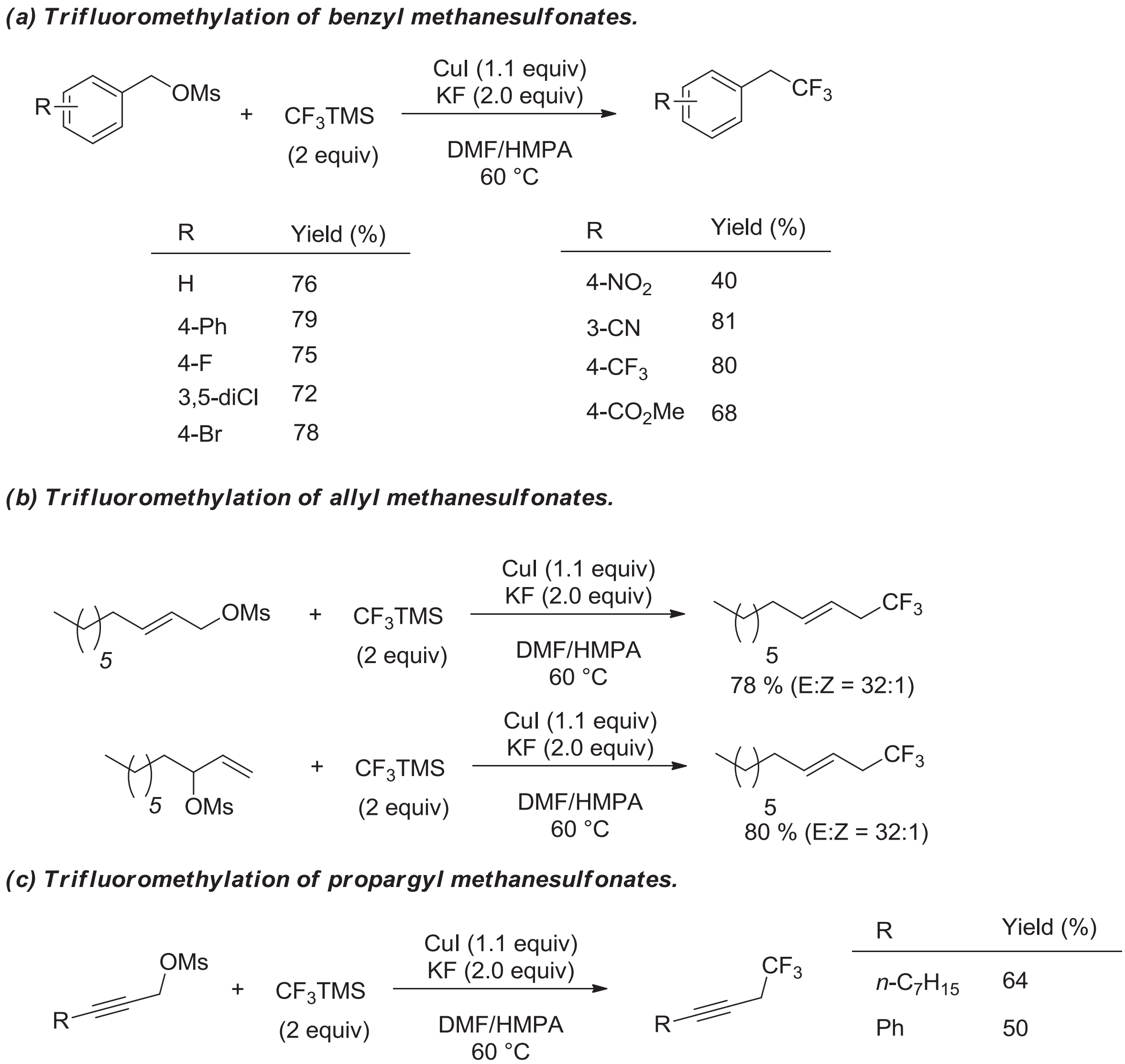
The detailed mechanism of the trifluoromethylation reaction remains to be elucidated, however, the authors propose that coordination of the Cu-atom to the carbonyl group and halide anion facilitates substitution with the CF_3 group, possibly as in the reported Cu-catalyzed cross-coupling of alkylzinc reagents with α-chloroketones [83].

3.3. Alkenes, vinyl sulfonates and alkynes [84a]

A recent review article on the fluoroalkylation of aliphatic unsaturated substrates [5] employing both electrophilic and non-electrophilic fluoroalkylating agents attests to the relevance of the subject. In this latter account [5,84b] a variety of transition



Scheme 52. Trifluoromethylation of alkyl-boronic acids [78].



Scheme 53. Cu-mediated trifluoromethylation of benzyl, allyl and propargyl methanesulfonates [77a].

metals such as Cu, Zn, Pd, Ru, and In are shown to catalyze the fluoroalkylation reaction of olefins and alkynes with R_fX [84b]. Also, photocatalysts derived from Ir and Ru, in conjunction with organocatalysts, fluoroalkylate aldehydes and enolates utilizing R_fX, as fluoroalkylating sources [84b].

Electrophilic and nucleophilic oxidative trifluoromethylation reactions enabling the formation of Csp^3-CF_3, Csp^2-CF_3, and Csp-CF_3 bonds from alkenes and alkynes have recently been reviewed [12,45]. The trifluoromethylation of C—C double bonds from enamines, has recently been informed by MacMillan [85] and has also been reviewed [5].

The trifluoromethylation of alkenes with non-electrophilic trifluoromethylating reagents has been achieved by visible light photoredox catalysis $Ru(Phen)_3Cl_2$, DBU as base in acetonitrile as solvent [86,87], according to Scheme 55.

The optimized reaction conditions [86] involve 0.1 equiv. of $Ru(Phen)_3Cl_2$, 2 equiv. of DBU, 3 equiv. of CF_3I, 0.2 mmol of alkene, in acetonitrile solution. The *E*-selective trifluoromethylated alkenes are obtained in very good yields. Besides high regio- and stereoselectivity, another salient feature of this transformation is the lower reactivity of the trifluoromethylated alkene toward the second trifluoromethylation, resulting in the monotrifluoromethylation product. Although the reactions of terminal alkenes are regio- and stereoselective, those of internal alkenes generated a mixture of isomers [86].

Based on these results, the authors [86] propose a plausible mechanism of the transformation as depicted in Fig. 2. Excitation of $Ru(phen)_3^{2+}$ by visible light provides $Ru(phen)_3^{2+*}$, which

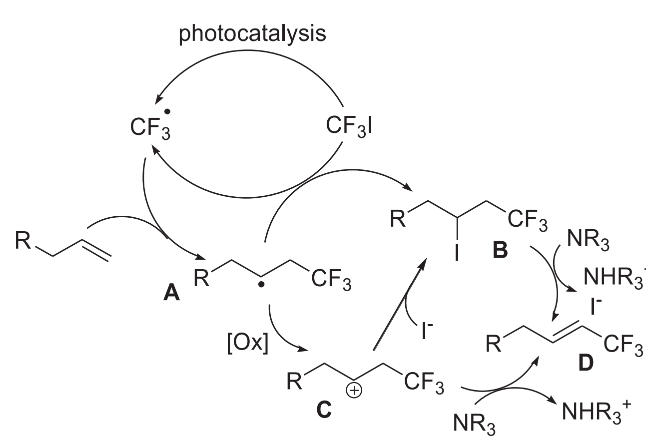
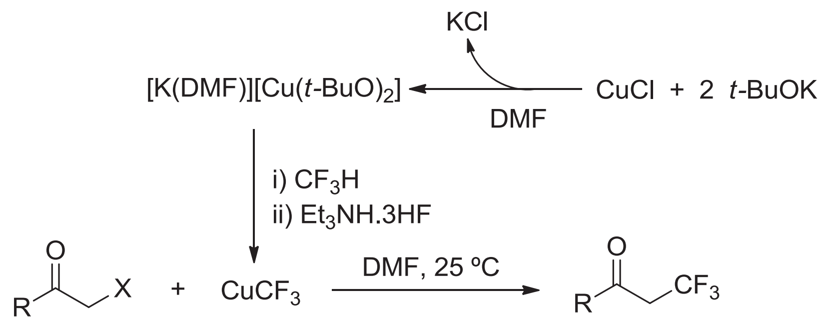


Fig. 2. Photocatalytic cycle for the trifluoromethylation of alkenes [86].

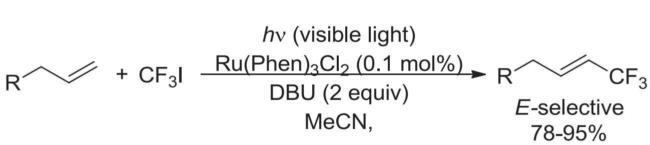


X = Br				X = Cl	
R	Yield (%)	R	Yield (%)	R	Yield (%)
Ph	93	2-ClC_6H_4	84	4-ClC_6H_4	93
4-MeC_6H_4	94	3-$MeOC_6H_4$	95	4-FC_6H_4	89
4-$MeOC_6H_4$	96	3-BrC_6H_4	91	2,4-diClC_6H_3	80
4-PhC_6H_4	95	3,5-di$CF_3C_6H_3$	77		
4-ClC_6H_4	85	2-Naphthyl	95		
4-$NO_2C_6H_4$	83	2-Pirydyl	52		
2,4-diMeC_6H_3	93	2-Thiophenyl	96		
2-$MeOC_6H_4$	94	*t*-Bu	87		
2-$CF_3C_6H_4$	87	Et	86		
		Cyclohexyl	88		

Scheme 54. Trifluoromethylation of α-haloketones [81].

is then reductively quenched by DBU to produce $Ru(phen)_3{}^+$ and the ammonium radical cation. The $Ru(phen)_3{}^+$ in turn performs a single-electron reduction of the F_3C—I bond, regenerating $Ru(phen)_3{}^{2+}$ and forming a carbon-centered $^•CF_3$ radical (and iodide anion). Addition of this electron-deficient radical species to an alkene generates the trifluoromethylated secondary carbon radical **A**. The reaction of this radical can proceed to generate alkenyl-CF_3 products by different possible pathways: (a) oxidation by regenerated $Ru(phen)_3{}^{2+}$, and ulterior deprotonation by base DBU (**C**–**D**) (b) oxidation followed by nucleophilic iodide attack and hydrodehalogenation by base (**B**–**D**). *E*-alkenes seem to be predominantly generated *via* E_2 elimination of HI from trifluoromethylated alkyl iodide intermediates as shown in Fig. 2.

The first example of copper-mediated intramolecular aminotrifluoromethylation of unactivated alkenes using Me_3SiCF_3 as the CF_3 source has recently been developed by Liu and coworkers [88]. This methodology provides a diverse array of valuable trifluoromethylated azaheterocycles under mild conditions. The aminotrifluoromethylation reaction of *gem*-terminal alkenes affords five- and six-membered rings in moderate to good yields when catalytic loadings of $Cu(CH_3CN)_4BF_4$ are used in the presence of $AgNO_3$ as the oxidant and KF as the base or the initiator. The authors assessed the reaction scope of alkenes and found that, regardless of the position and nature of the substituent, a noticeable



Scheme 55. Trifluoromethylation of alkenes *via* photoredox catalysis [86,87].

functional group tolerance was observed as depicted in Scheme 56. Also, the reaction was achieved efficiently when exchanging the phenyl moiety for a naphthyl group in the substrate and further, when substrates that contain *gem*-disubstituted alkenes bearing methyl and phenyl group are employed.

A plausible mechanism was also proposed and is depicted in Scheme 57.

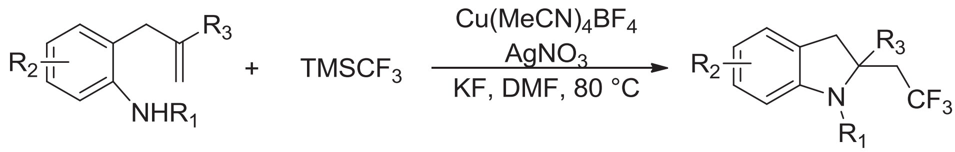
First, outer-sphere attack of the nitrogen atom on the Cu(I)-complex of alkene of **A** is involved to generate the neutral alkyl-copper complex **B**. Second, the reaction of Me_3SiCF_3, $AgNO_3$ and KF *in situ* generates $AgCF_3$, which then reacts with intermediate **B** *via* single-electron transfer to produce the final product and regenerate the cationic copper catalyst and silver.

It has also been reported a convenient Cu-mediated trifluoromethylation of aryl-, heteroaryl, alkenyl and aliphatic alkynyltrifluoroborates using the less expensive and stable Langlois reagent $NaSO_2CF_3$ as CF_3 source by *in situ* generation of $CF_3{}^•$ as the active trifluoromethylating species [89].

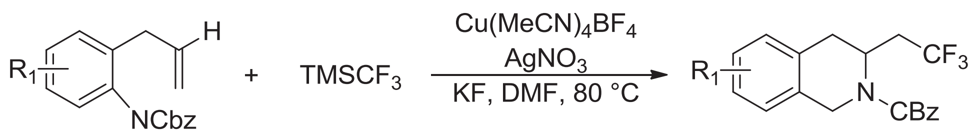
Buchwald and colleagues [90] have reported the trifluoromethylation of vinyl sulfonates employing $Pd(dba)_2$ or $[(allyl)PdCl]_2$ as catalysts and the monodentate biaryl phosphine ligand *t*-BuXPhos (2-di-*t*-butylphosphino-2′,4′,6′-tri*iso*propylbiphenyl). The scope of the transformation is depicted in Scheme 58.

Hu and colleagues [91] have accomplished the Cu-cross-coupled difluoroalkylation of alkenyl iodides with iododifluoroacetamides in fairly good yields, employing DMSO as solvent. The scope of the transformation is illustrated in Scheme 59.

The authors [91] proposed a mechanism as outlined in Scheme 60. A single electron transfer (SET) process between Cu(0) and the iododifluoroacetamides renders a radical anion species, which undergoes elimination of an iodide ion to afford a

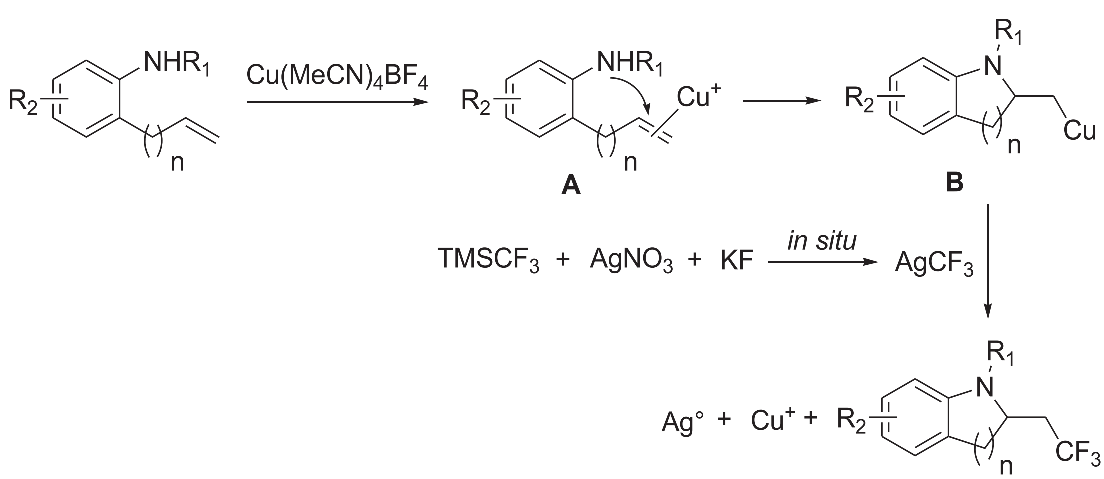


R_1	R_2	R_3	Yield (%)
Cbz	4-Me	H	56
Cbz	2-Me	H	46
Cbz	4-OMe	H	61
Cbz	4-Ph	H	50
Cbz	H	H	59
Cbz	3,5-diMe	H	56
Cbz	4-F	H	58
Cbz	4-Cl	H	58
Boc	4-Me	H	60
Ts	H	H	47

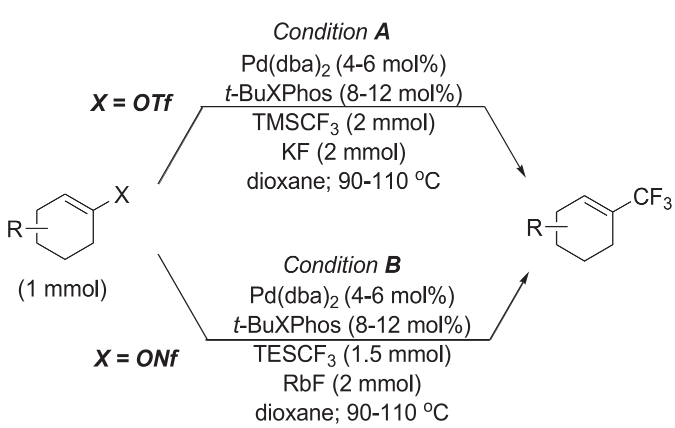


R_1	Yield (%)
H	52
4-Me	60
4-F	45
4-Cl	44

Scheme 56. Aminotrifluoromethylation of unactivated alkenes [88].

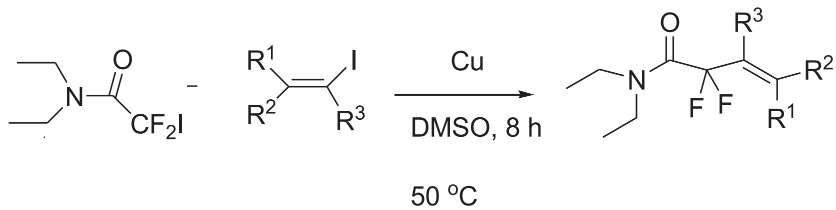


Scheme 57. A plausible reaction mechanism for the aminotrifluoromethylation of unactivated alkenes [88].



R	Condition	Yield (%)
H	A	83
4-Ph	A	81
4-Ph	B	71
4-C_5H_{11}	B	73
3-Ph	A	62
3-Ph	B	76
3-(N-Me-2-indolyl)	A	84

Scheme 58. Trifluoromethylation of vinyl sulfonates [90].



$R^1 = R^3 = H$, $R^2 = Ph$	86%
$R^1 = COOEt$, $R^2 = R^3 = H$	76%
$R^1 = R^3 = H$, $R^2 = n\text{-}Bu$	81%
$R^1 = COOEt$, $R^2 = H$, $R^3 = Me$	60%
$R^1 = R^3 = H$, $R^2 = CH_2CH_2Ph$	83%
$R^1 = COOEt$, $R^2 = H$, $R^3 = n\text{-}Bu$	57%

Scheme 59. Difluoromethylation of iodoalkenes with iododifluoroacetamides [91].

gem-difluoromethyl radical. There are possible pathways for the synthetic utility of difluorinated radical species: copper-mediated cross-coupling reaction with akenyl (or aryl) halides, which is a fast process yielding the difluoroalkylated product, or a homocoupling reaction [91].

Mikami and collaborators [26] have very recently showed the trifluoromethylation of terminal alkynes [92a,92b] with $CuCF_3$ source, according to Scheme 61.

The $CuCF_3$ source was synthesized through reaction of a trifluoromethylketone derivative, according to Scheme 6, Section 2.1.1 [26].

After the optimization of the reaction conditions [26], the use of TMEDA and $Et_3N{\cdot}HCl$ as the ligand and acid, respectively, in the presence of the $CuCF_3$ reagent (2 equiv.) at room temperature in air were required for high product yields. The slow addition of alkynes through a syringe pump was also the key for enhancing the yield. The reaction with both electron-rich and electron-deficient aliphatic alkynes proceeded in more than 88% yield under much milder conditions.

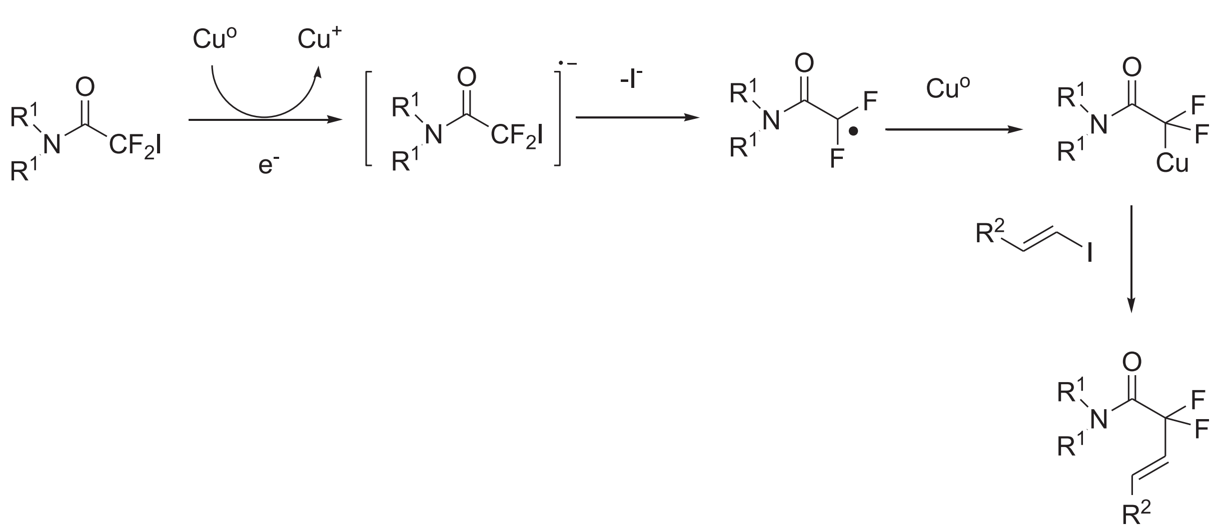
Lee and co-workers [93] have recently studied the palladium-mediated decarboxylative trifluoroethylation of aryl alkynyl carboxylic acids with ICH_2CF_3. Employment of the catalytic systems $[Pd(\eta^3\text{-allyl})Cl]_2$ and XantPhos as the ligand in the presence of Cs_2CO_3 in DMF at 80 °C produce satisfactory results providing the desired products in good yields (Scheme 62). This catalytic system shows high functional group tolerance and it is effective with polycyclic aryls and heteroaryl moieties such as 1-naphthyl, 4′-biphenyl and thiophene-substituted alkynyl carboxylic acids.

The authors also showed that this catalytic methodology applies satisfactorily to the one-pot synthesis of trifluorobutynyl arenes from propiolic acid. Sequential application of Sonogashira coupling of aryl iodides with propiolic acid and decarboxylative coupling with ICH_2CF_3 provides the trifluorobut-1-ynyl arenes in moderate yields (Scheme 62).

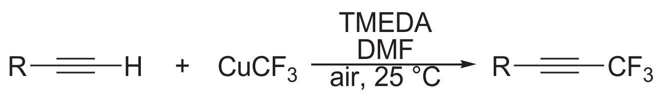
The trifluoroethylation [94a] of terminal alkynes has been attained [94b] through the employment of trifluoroethyl iodide, $Pd_2(dba)_3$ catalyst, DPEphos (bis-[2-(diphenylphosphino)phenyl]ether) as ligand in toluene as solvent. The scope of the reaction is represented in Scheme 63.

The authors proposed a mechanism such as that depicted in Scheme 64.

Initially, the palladium complex **I** [95–97] would be generated by the reaction of the Pd precursor with ligands. Subsequently, the Pd(II) intermediate **II** (Scheme 64) is formed *via* oxidative addition of complex **I** to CF_3CH_2I. Then, ligand dissociation followed by coordination with the alkyne occurs to form the Pd-intermediate complex **III** (η2-RC≡CH)-Pd (CF_3CH_2)XL [95–97]. Deprotonation of the alkyne by the amine (Dabco) renders a new square planar Pd complex **IV** [95–97]. Probably the **III**–**IV** process in the catalytic cycle is relatively facile under Cu-free catalytic Sonogashira reaction

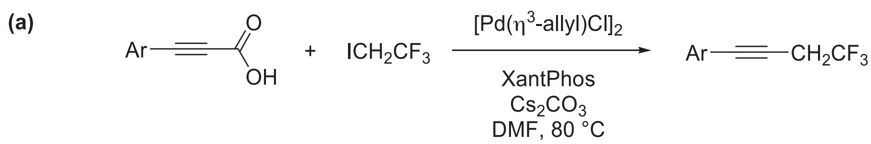


Scheme 60. Proposed mechanism for the difluoromethylation of iodoalkenes with iododifluoroacetamides [91].



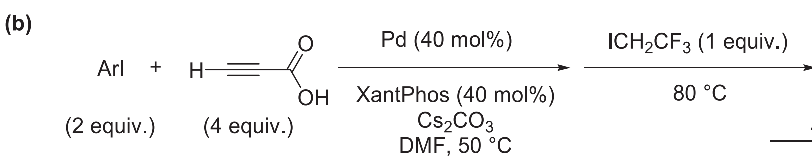
R	Yield (%)
4-F-C_6H_4	91
Ph	91
4-MeO-C_6H_4	89
$4\text{-CF}_3\text{-C}_6H_4$	95
3-pyridyl	95
$CH_3(CH_2)_{12}$	90
$2,4,5\text{-Me}_3\text{-C}_6H_4$	90
2-naphthyl	88
2-Br-C_6H_4	93

Scheme 61. Scope of the trifluoromethylation of alkynes with $CuCF_3$ [26].



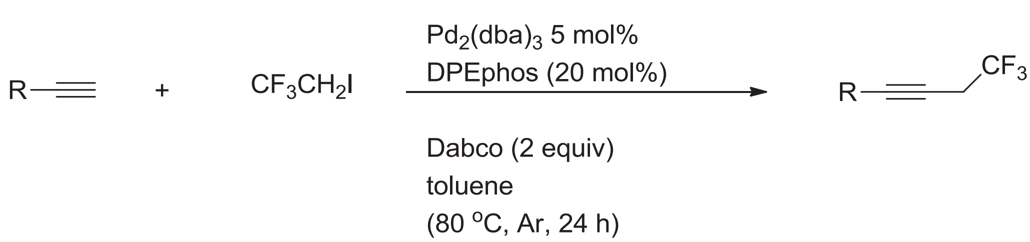
Ar	Yield (%)
Ph	87
2-MeC_6H_4	85
3-MeC_6H_4	65
4-MeC_6H_4	77
$2,4\text{-diMeC}_6H_3$	83
2-MeOC_6H_4	89
$3,4,5\text{-triMeC}_6H_2$	61

Ar	Yield (%)
4-MeCOC_6H_4	65
4-MeOCOC_6H_4	62
4-CNC_6H_4	63
4-FC_6H_4	56
1-Naphthyl	88
4'-biphenyl	64



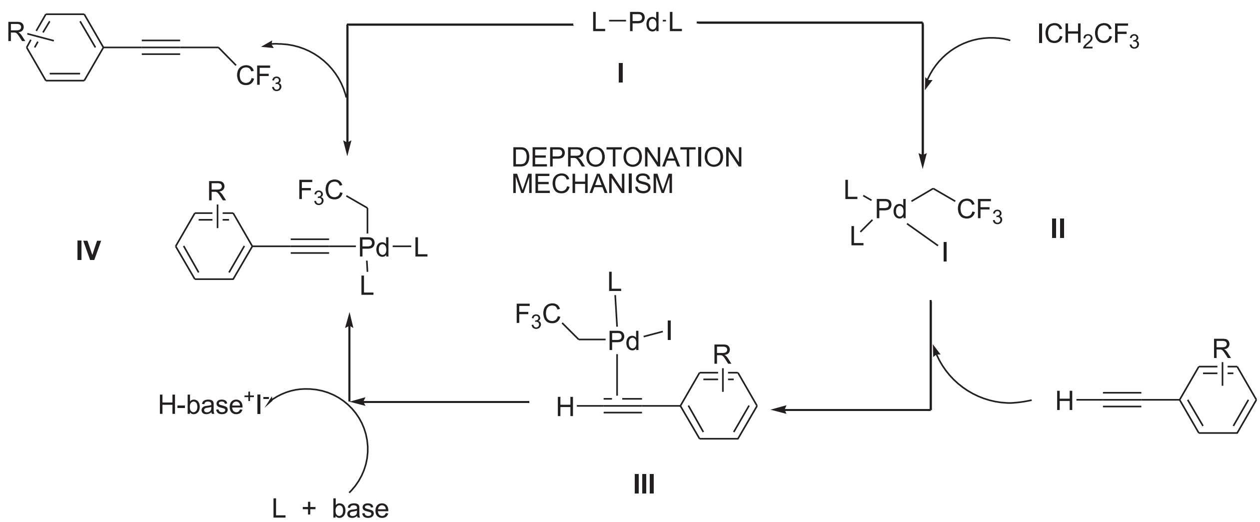
Ar	Yield (%)
Ph	45
2-MeOC_6H_4	43
4-MeC_6H_4	39

Scheme 62. Decarboxylative trifluoroethylation of aryl alkynyl carboxylic acids [93].



R = biphenyl	57%
$= 4\text{-MeO-C}_6H_4$	84%
$= 4\text{-Me-C}_6H_4$	81%
= 1-naphthyl	45%
$= 4\text{-CN-C}_6H_4$	60%
$= 4\text{-CHO-C}_6H_4$	57%
$= 4\text{-NO}_2C_6H_4$	43%
= 4-MeCO	82%
= 3-pyridyl	76%

Scheme 63. Scope of the trifluoroethylation of terminal alkynes [94b].



Scheme 64. Mechanism for the Pd-catalyzed trifluoroethylation of terminal alkynes [94b].

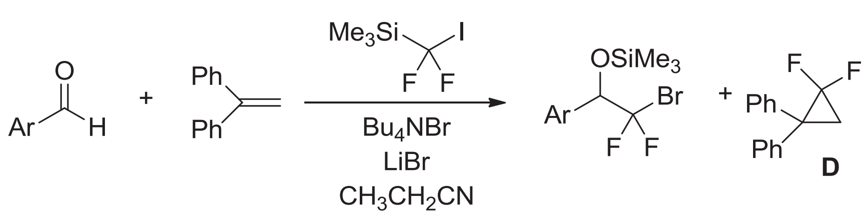
conditions. A reason for this can be the electron-withdrawing nature of the CF_3 group, which is beneficial for formation of complex **IV** from complex **III**. Finally, intermediate **IV** affords the alkynyl-CH_2CF_3 product through reductive elimination [94b].

3.4. Fluoroalkylation of aldehydes

A method for bromo- and iododifluoromethylation of aldehydes using bromo- and iodo-substituted difluoromethyl silicon reagents (Me_3SiCF_2X) has very recently been introduced by Dilman and colleagues [98]. The reaction is performed in the presence of a combination of *tetra*butylammonium and lithium salts Bu_4NX/LiX (X = Br or I) in propionitrile. The authors [98] proposed the intervention of a short-lived halodifluoromethyl carbanion, which serves as nucleophile, which is reversibly generated from difluorocarbene and a halide anion. The scope of the transformation is represented in Scheme 65.

The authors [98] studied the reaction mechanism, and considered two pathways (Scheme 66). In path **I** (Scheme 66), the halide anion reversibly generates a difluorocarbene **A** through the intermediacy of halodifluoromethyl carbanion **B**. Participation of **B** was uncovered through trapping with the appropriate electrophile. A lithium salt that can activate the carbonyl group though some association of the lithium cation with carbanionic species **B** cannot be excluded. In an alternative mechanism, path **II** (Scheme 66), the halodifluoromethyl group can be transferred in a concerted fashion from a pentacoordinate siliconate intermediate **C** (Scheme 66).

When the reaction of difluorocarbene **A**, and iodo-substituted silane ICF_2SiMe_3 was combined with *tetra*butylammonium bromide in the presence of 1,1-diphenylethylene (Eq. (5)), the halogen exchange proceeded rapidly even at room temperature, and in 7 min silane $BrCF_2SiMe_3$ and cyclopropane **D** were detected [98,99]. This evidence was in agreement with path **I**, where the nucleophilic species **B** is converted to difluorocarbene **A** (nucleophilic species **B** is generated from the interaction of difluorocarbene with a halide anion).



(5)

Bromodifluorotrimethylsilane $BrCF_2SiMe_3$ can be obtained from the Ruppert–Prakash reagent [99]. Iododifluorotrimethylsilane ICF_2SiMe_3 was prepared from $BrCF_2SiMe_3$ in 70% yield by the bromine/zinc exchange followed by iodination [98].

Under the optimized conditions, a series of aldehydes were reacted with silane $BrCF_2SiMe_3$. Aromatic aldehydes bearing electron-donating and electron-withdrawing substituents, heterocyclic aldehydes, unsaturated, and non-enolizable aliphatic aldehydes afforded the respected difluoroalkylated products in high yields (Scheme 65). Electron-withdrawing nitro and ester groups accelerated the nucleophilic addition, and the reactions were complete within 2 h. For sterically hindered aldehydes a longer reaction time and 3 equiv. of both ammonium and lithium salts were needed. However, hydroxycinnamaldehyde gave a complex product mixture, presumably, owing to its propensity to aldolization. The ester group is tolerated in this transformation.

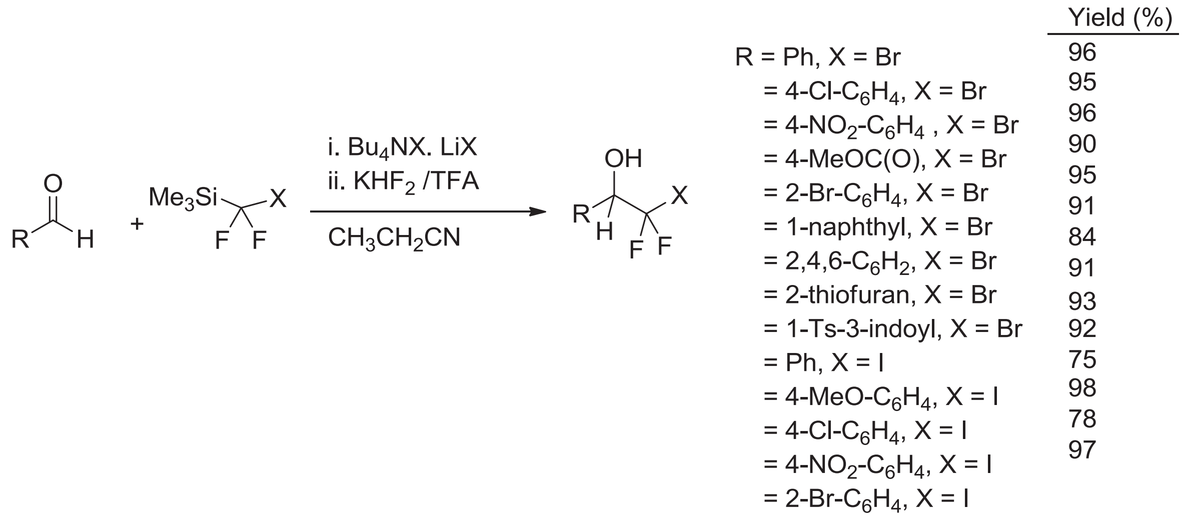
The review by Palacios and collaborators [100] summarizes the main methods for the nucleophilic trifluoromethylation of aldehydes, ketones [101], esters, imines and their analogs published in the literature in the last six years.

3.5. Fluoroalkylation of enols/enolates/enamides

Ando and collaborators [102] have examined the rhodium-catalyzed trifluoromethylation of silyl enol ethers with CF_3I, mediated by Zn, in DME as solvent. The scope of the transformation is depicted in Scheme 67.

In this manner, ketene silyl acetals, have also been trifluoromethylated in fairly good yields [102]. The proposed mechanism for this transformation is illustrated in Scheme 68.

Based on radical trapping experiments, the authors [102] proposed the formation of a highly reactive Rh-Et complex (**I**, Scheme 68), which derived from Rh-X catalyst and Et_2Zn, in the



Scheme 65. Bromo- and iodo-difluoromethylation of aldehydes [98].

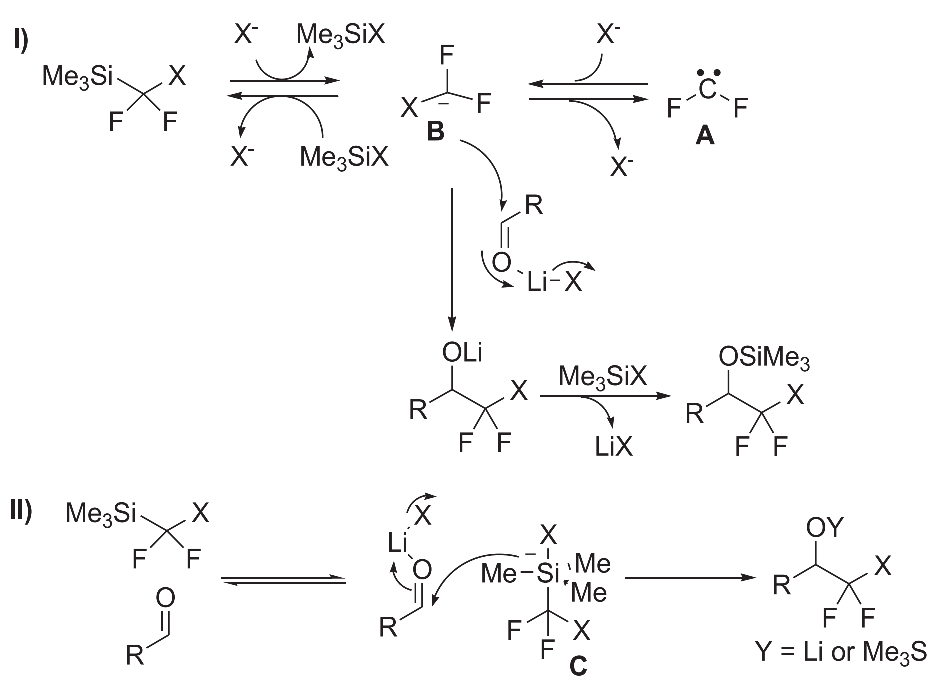
mechanism of α-trifluoromethylation (Scheme 68). Namely, the oxidative addition of CF_3-I onto **I** to form a Rh(III) complex (**II**) was followed by the coordination onto the π-bond of silyl enol ether. On subsequent addition of the CF_3 unit into the olefin, another Rh(III) complex (**III**, Scheme 68) which suffered the reductive elimination was formed to give the desired α-CF_3 product (**IV**, Scheme 68) along with loss of ethyltrimethylsilane (TMS-Et) or trimethylsilane (TMS-H) with ethylene (Scheme 68).

Lu and co-workers [103] have developed an efficient conversion of aryl(heteroaryl) enol acetates to α-CF_3-substituted ketones, using the readily available $NaSO_2CF_3$ (Langlois reagent) catalyzed by Cu(I). The reaction is experimentally simple and is carried out at room temperature, providing good to excellent yields of CF_3-substituted products with wide functional group tolerance. They have investigated the substrate scope as shown in Scheme 69.

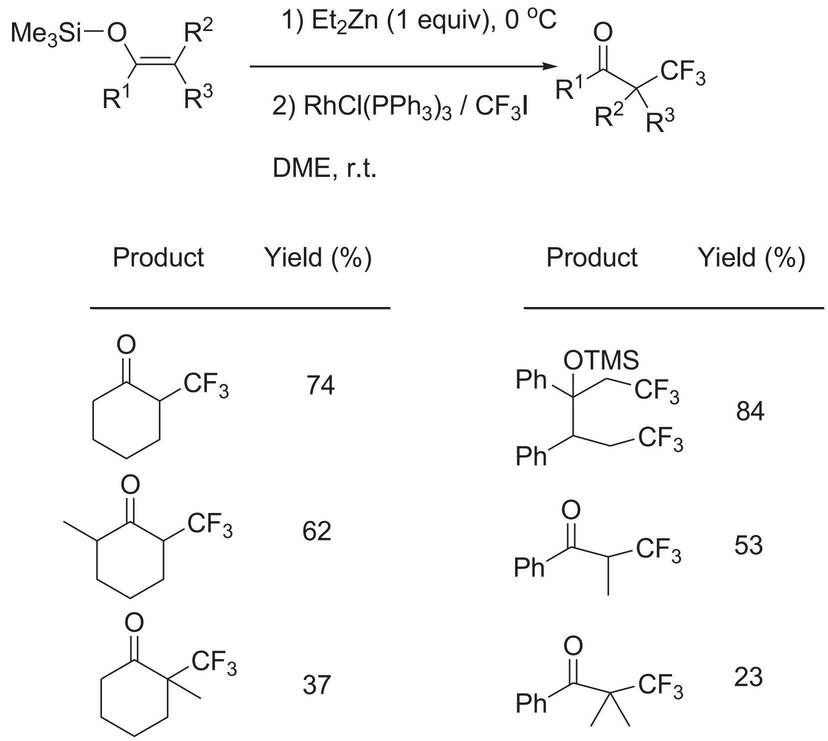
Furthermore, the authors carried out a radical scavenger experiment to confirm the reaction mechanism [103].

Initially, the CF_3·radical is generated *in situ* by the reaction of the *t*-buthylhydroperoxide with $NaSO_2CF_3$ in the presence of catalytic amounts of CuI. Next, addition of the CF_3 radical to the electron-rich α-position of **I** (Scheme 70) results in the radical species **II**. Then the intermediate **II** (Scheme 70) is oxidized by Cu(II) (produced from Cu(I) oxidized by *t*-butylhydroperoxide) to produce the cationic intermediate **III** *via* SET. Finally, cationic intermediate **III** (Scheme 71) loses an acetyl cation to generate the desired product **IV** (Scheme 70) [103].

Zakarian and collaborators [104] have recently developed a Ru-catalyzed direct trifluoromethylation and perfluoroalkylation of *N*-acyloxazolidinones by a radical methodology, and high degree of stereocontrol. This method seemed improved with respect to the photocatalytic method developed by MacMillan (Scheme 25), and employs zirconium enolates. This method proves the formation of soft enolization (Zr) intermediates, which readily accept perfluoroalkyl radicals. Thus, *N*-acyl oxazolidinones obtained from



Scheme 66. Proposed reaction mechanism [98].

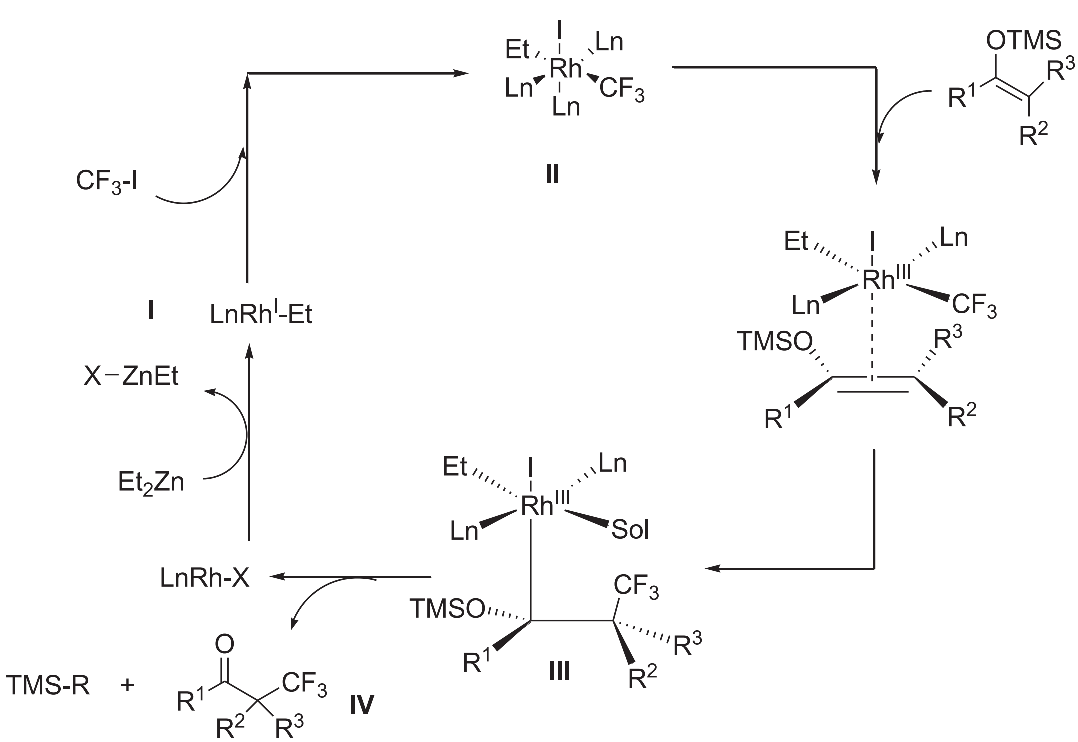


Scheme 67. Scope of the trifluoromethylation of silyl enol ethers [102].

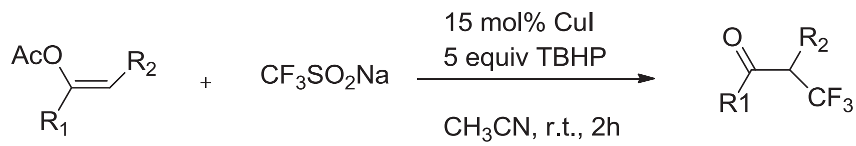
unfunctionalized alkanoic acids undergo efficient and diastereoselective trifluoromethylation, with yields increasing for α-branched substrates. This work has recently been reviewed [5].

Zhang and colleagues [105] have accomplished the trifluoromethylation of enamides employing the photocatalyst $[Ir(ppy)_2(dtbbpy)PF_6]$ with a blue LED, in MeCN as solvent according to Scheme 71.

A possible catalytic cycle was proposed as shown in Scheme 72. The key steps include (i) visible-light excitation of Ir^{3+} complex to generate Ir^{3+*}; (ii) oxidative quenching of Ir^{3+*} by electron-deficient trifluoromethyl sulfonyl chloride **B** to give Ir^{4+} and trifluoromethyl radical respectively (and chloride anion); (iii) radical addition of enamide **A** by trifluoromethyl radical to provide amido radical **C**; (iv) oxidation of amido radical **C** by Ir^{4+} to give *N*-acyliminium



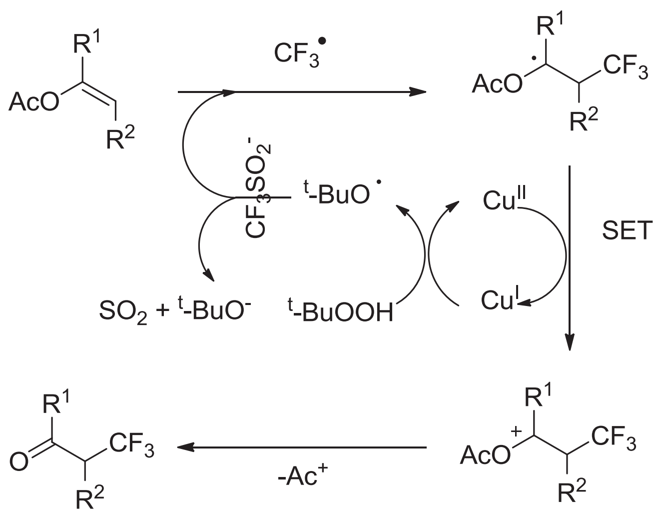
Scheme 68. Reaction mechanism of Zn-mediated Rh-catalyzed α-trifluoromethylation of carbonyl compounds [102].



R1	R2	Yield (%)
Ph	H	93
4-MeO-C_6H_4	H	94
4-Cl-C_6H_4	H	92
2-F-C_6H_4	H	83
3-NO_2-C_6H_4	H	79
3-NHAc-C_6H_4	H	61

R1	R2	Yield (%)
Ph	Me	89
Ph	Ph	64
2-pyr	H	85
2-thiophenyl	H	64
5-Me-furanyl	H	74

Scheme 69. Scope of the α-trifluoromethylation of aryl(heteroaryl) enol acetates [103].



Scheme 70. Proposed mechanism for the trifluoromethylation of enol acetates [103].

cation **D** and regeneration of Ir^{3+} (Path i); and finally (v) deprotonation and then tautomerization of *N*-acyliminium cation **D** to produce functionalized enamide. At this stage, the radical propagation pathway could not be ruled out completely (Path ii). Given that radical species could be generated from trifluoromethanesulfonyl chloride or aryl diazolium salt under visible-light photoredox conditions, it is possible to realize trifluoromethylation and arylation reactions based on the proposed mechanism (Scheme 72). Thus, trifluoromethylation of enamides could be achieved under slightly modified standard conditions.

3.6. Fluoroalkylation of N-arylacrylamides

Tan and co-workers have recently reported a new method for synthesizing trifluoromethyl-substituted oxindoles though silver-catalyzed trifluoromethylation-cyclization reaction of *N*-aryl-acrylamides by using sodium trifluoromethansulfinate ($NaSO_2CF_3$, Langlois reagent) as the trifluoromethyl source [106]. In addition, difluoromethylation and sulfonylation reactions could be achieved through a similar radical procedure when the Langlois reagent was replaced by zinc difluoromethane sulfinate salt ($Zn(SO_2CF_2H)_2$, Baran reagent) and arylsulfinic acid sodium salt (Scheme 73).

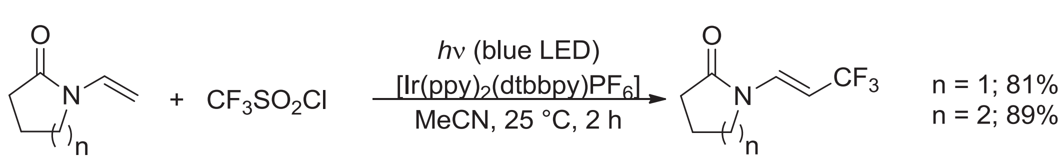
A screening of reaction conditions disclosed that *N*-alkyl or *N*-aryl protecting groups worked well to deliver the desired products in good yields. Both electron-donating and electron-withdrawing groups on the *para*-position of the aromatic ring reacted efficiently with $NaSO_2CF_3$ to render products in 52–79% yields [106]. Furthermore, *ortho*-substituted substrates afforded slightly lower yields (55–40%) of substitution products, which indicated that the transformation was sensitive to steric hindrance. As for *meta*-substituted substrates, the reaction provided a mixture of two products in good yields, albeit low regioselectivity.

The proposed reaction mechanism is depicted in Scheme 74.

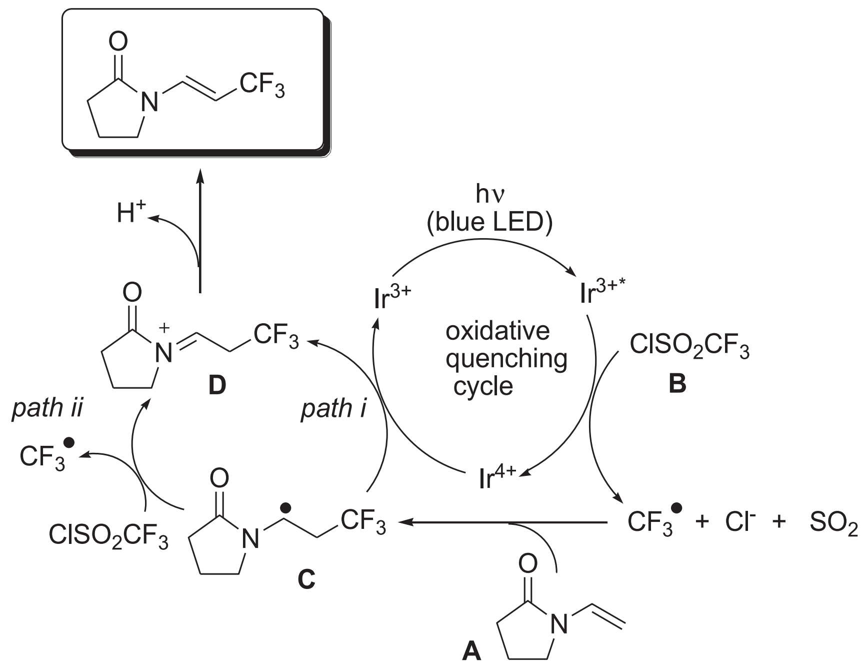
Initially, oxidation of silver(I) to silver(II) is effected by the persulfate anion $S_2O_8^{2-}$, which itself disproportionates into sulfate dianion and sulfate radical anion. In the presence of silver(II) ions, $NaSO_2CF_3$ is oxidized to $CF_3SO_2^{\bullet}$ radical, which subsequently releases one molecule of SO_2 to generate a trifluoromethyl radical. Addition of the *in situ* generated trifluoromethyl radical to the double bond of aryl acrylamides leads to the formation of radical intermediate **A** (Scheme 74), which subsequently undergoes intramolecular cyclization to afford radical intermediate **B**. After being oxidized by the sulfate radical anion and ulterior aromatization, intermediate **B** is transformed into desired trifluoromethylated oxindole product [106].

3.7. Gem-difluoroolefination of diazo compounds [107]

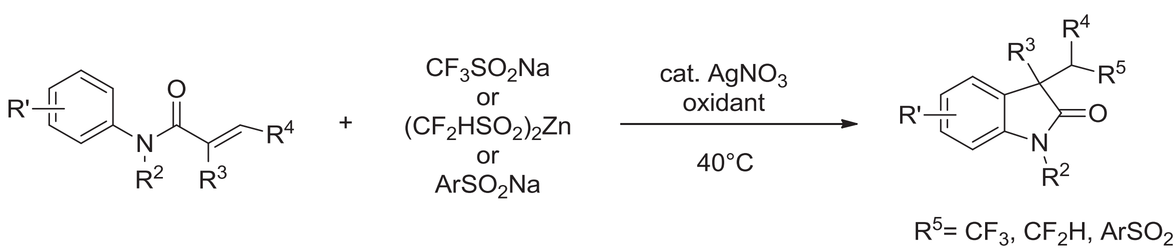
Hu and co-workers [108] have recently introduced the *gem*-difluoroolefination of diazo compounds employing CF_3SiMe_3/CuI/CsF as trifluoromethylating species. The scope of the transformation is depicted in Scheme 75.



Scheme 71. Photocatalytic trifluoromethylation of enamides [105].



Scheme 72. Proposed reaction mechanism for photocatalytic trifluoromethylation of enamides [105].

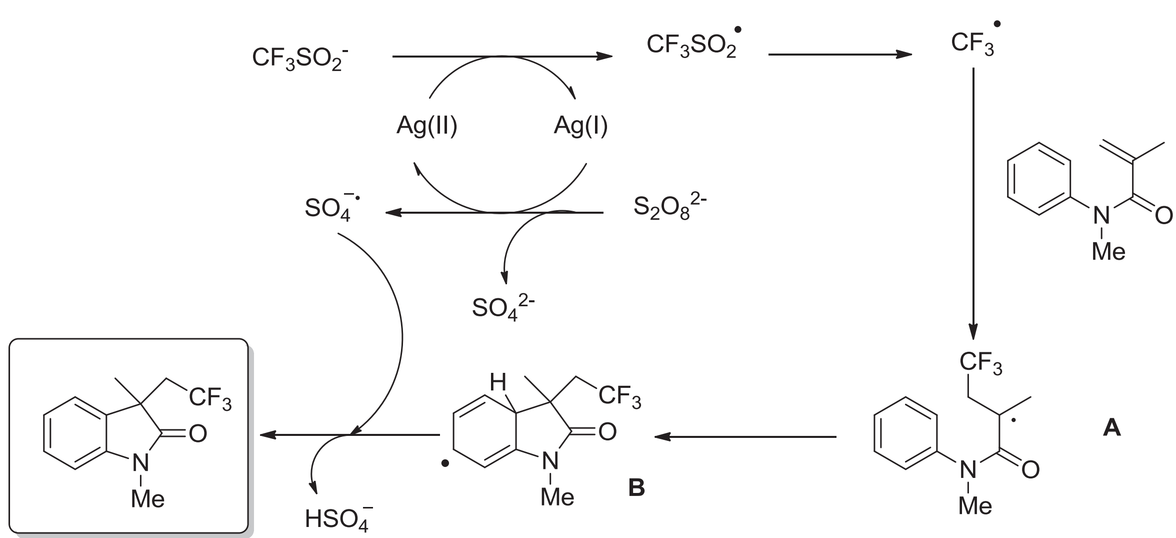


Scheme 73. Silver-catalyzed fluoroalkylation-cyclization reactions of arylacrylamides [106].

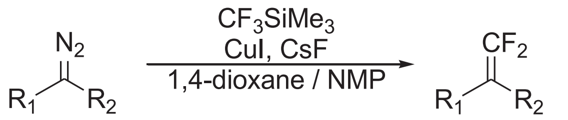
The authors proposed a reaction mechanism such as that shown in Scheme 76.

CF_3SiMe_3 first reacts with CuI and CsF to generate $CuCF_3$ (Scheme 76), and the latter species reacts with diazo compound to form Cu-carbene intermediate **B**. Intermediate **B** undergoes carbene migratory insertion into the Cu—CF_3 single bond to render intermediate **A**. Then, the species **A** suffers a fast β-fluoride elimination to afford the *gem*difluoroolefin product and CuF, which in turn CuF further reacts with CF_3SiMe_3 to regenerate $CuCF_3$ (Scheme 76).

Hu and co-workers [109] have developed a copper-mediated trifluoromethylation of α-diazo esters with the CF_3SiMe_3 reagent as a new method to prepare α-trifluoromethyl esters. This

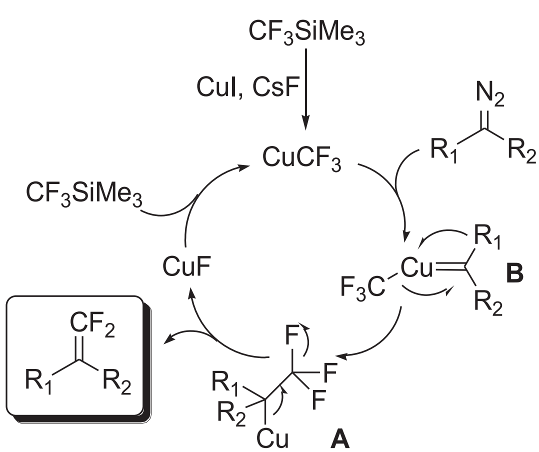


Scheme 74. Proposed mechanism for silver-catalyzed trifluoromethylation-cyclization reactions of arylacrylamides [106].



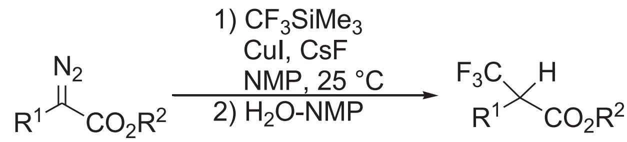
	Yield (%)
$R_1 = R_2 = Ph$	75
R_1 = Naphthyl, R_2 = Ph	74
R_1 = Ph, R_2 = 2-Br-C_6H_4	61
R_1 = 4-Me-C_6H_4, R_2 = Ph	79
R_1 = 3,4-Me_2-C_6H_3, R_2 = Ph	79
R_1 = 4-^{tert}Bu-C_6H_4, R_2 = Ph	49
R_1 = 4-MeO-C_6H_4, R_2 = Ph	50
R_1 = Ph, R_2 = 3-PhO-C_6H_4	54
R_1 = 6-MeO-Naphthyl, R_2 = Ph	48
$R_1 = R_2$ = 4-NMe_2-C_6H_4	0
R_1 = Ph, R_2 = 2-F-C_6H_4	78
R_1 = 4-F-C_6H_4, R_2 = Ph	75
$R_1 = R_2$ = 4-F-C_6H_4	67
R_1 = Ph, R_2 = 2-Cl-C_6H_4	82
R_1 = 3-Cl-C_6H_4, R_2 = Ph	88
R_1 = 3,4-Cl_2-C_6H_4, R_2 = Ph	80
R_1 = 4-NO_2-C_6H_4, R_2 = Ph	86

Scheme 75. Copper-catalyzed *gem*-difluoroolefination of diazo compounds [108].



Scheme 76. Proposed reaction mechanism for the copper-catalyzed *gem*-difluoroolefination of diazo compounds [108].

trifluoromethylation reaction [109] represents the first example of fluoroalkylation of a non-fluorinated carbene precursor. Water plays an important role in promoting the reaction by activating the "$CuCF_3$" species prepared from CuI/Me_3SiCF_3/CsF (1.0:1.1:1.1). The scope of this trifluoromethylation reaction is broad, and its



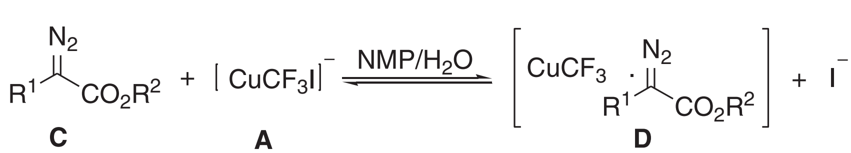
	Yield (%)
R^1 = Ph, R^2 = Et	82
R^1 = naphthyl, R^2 = Et	75
R^1 = 2-Me-C_6H_4, R^2 = Et	85
R^1 = 4-Me-C_6H_4, R^2 = Et	88
R^1 = 4-EtO-C_6H_4, R^2 = Et	94
R^1 = 3,4,$(MeO)_2$-C_6H_4, R^2 = Et	92
R^1 = 4-MeO-C_6H_4, R^2 = Me	96
R^1 = 4-F-C_6H_4, R^2 = Et	82
R^1 = 4-Br-C_6H_4, R^2 = Et	75
R^1 = 4-Cl-C_6H_4, R^2 = Et	78
R^1 = 4-NO_2-C_6H_4, R^2 = Et	81
R^1 = CH_2Ph, R^2 = Et	81
R^1 = CH_2-Naphthyl, R^2 = Et	69

Scheme 77. Scope of the trifluoromethylation of diazoesters [109].

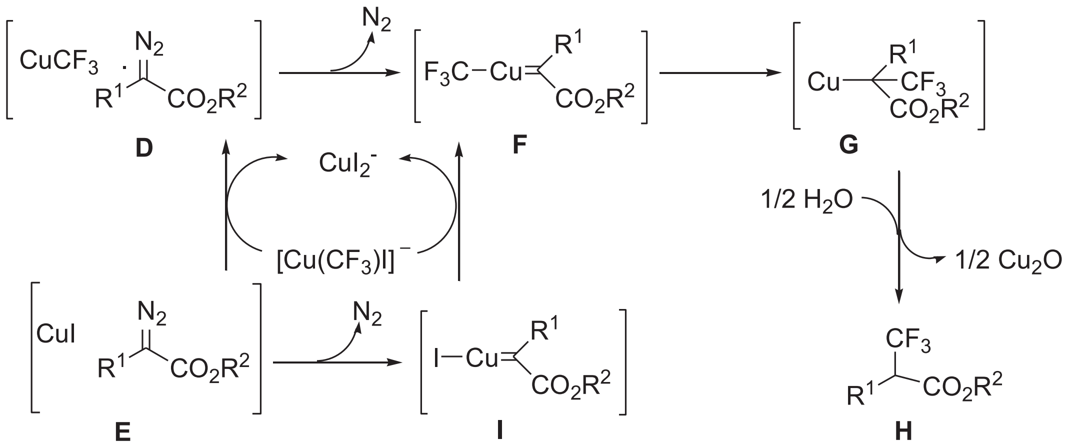
efficiency is demonstrated in the synthesis of a variety of aryl-, benzyl-, and alkyl-substituted 3,3,3-trifluoropropanoates. The utility of the transformation is depicted in Scheme 77.

The authors [109] propose a mechanism for the CuI-mediated, water-promoted trifluoromethylation of diazo esters **C** with CF_3SiMe_3 reagent, according to Scheme 78. Firstly, the reaction of CuI, CF_3SiMe_3 and CsF (in a 1:1.1:1.1 ratio) gives the dicoordinated trifluoromethylcopper species **A**, which is in equilibrium with *bis*(trifluoromethyl)copper species **B** and $[CuI_2]^-$ *via* ligand redistribution on copper (Eq. (6)). After the addition of α-diazo ester **C** and water, a small amount of reactive intermediate complex **D** is formed from **A** by water-promoted α-diazo ester-α-iodide ion exchange reaction (Eq. (7)). The extrusion of N_2 from **D** affords trifluoromethyl copper carbene species **F** (Scheme 78) and the subsequent migration of CF_3 group to the carbenic carbon atom of **F** results in α-CF_3-substituted copper species **G**. The final hydrolysis of **G** by water gives product **H** and the unreactive Cu_2O (Scheme 78). Alternatively, based on the known copper-catalyzed cyclopropanation between diazo compounds and alkenes, the complex **E** generated from $[CuI_2]^-$ by a similar ligand-exchange reaction is also a possible intermediate. The extrusion of N_2 from **E** affords copper carbene species **I**. Both **E** and **I** can undergo ligand redistribution reaction with **A** to give **D** and **F**, respectively. Although the authors could not rule out the formation of complex **E**, **I** is less likely involved in this water-promoted trifluoromethylation reaction as the authors did not observe any intramolecular cyclopropanation byproduct in the case of C=C bond-containing α-diazo ester [109].

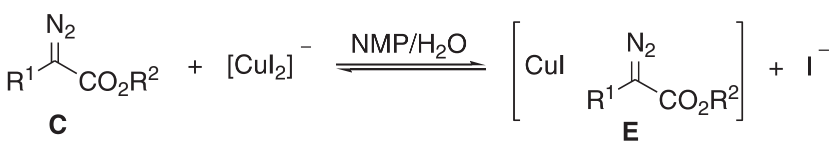
$$\mathrm{CuI} + \mathrm{CF_3SiMe_3} \xrightarrow[\mathrm{NMP}]{\mathrm{F^-}} \underset{\mathbf{A}}{[\mathrm{CuCF_3I}]^-} \rightleftharpoons 1/2\,\underset{\mathbf{B}}{[\mathrm{Cu(CF_3)_2}]^-} + 1/2[\mathrm{CuI_2}]^- \qquad (6)$$



(7)



Scheme 78. Proposed reaction mechanism for the trifluoromethylation of diazoesters [109].



(8)

4. Conclusions

Relevant trifluoromethylation and perfluoroalkylation reactions of organic substrates both aromatic and aliphatic in nature, have recently been accomplished through the employment of metals or metalorganic species, either by thermal methods or photocatalyzed. These reactions are either radical or polar in nature, involving commercially available nucleophilic reagents, such as fluoroform, the Langlois reagent ($NaSO_2CF_3$), the Ruppert–Prakash reagent, or metal-fluoroalkyl species. This wealth of metal-mediated methods has enlarged the Organic Chemist's armamentarium for achieving fluoroalkyl group substitution and addition reactions on a vast array of substrates that are both needed in pharmaceutical and polymer chemistry industries. The investigation into the mechanisms of these reactions has aided in the comprehension of the electron transfer character of many transition metals or metalorganic species for obtaining trifluoromethyl group substitution or addition reactions.

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References

[1] O.A. Tomashenko, V.V. Grushin, Chem. Rev. 111 (2011) 4475.
[2] Y. Ye, M.S. Sanford, Synlett 23 (2012) 2005.
[3] T. Liu, Q. Shen, Eur. J. Org. Chem. 2012 (2012) 6679.
[4] (a) T. Furuya, A.S. Kamlet, T. Ritter, Nature 473 (2011) 470;
(b) T. Liang, C.N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 52 (2013) 8214;
(c) F. O'Hara, R.D. Baxter, A.G. O'Brien, M.R. Collins, J.A. Dixon, T. Fujiwara, Y. Ishihara, P.S. Baran, Nat. Protoc. 8 (2013) 1042.
[5] (a) S. Barata-Vallejo, A. Postigo, Coord. Chem. Rev. 257 (2013) 3051;
(b) P. Chen, G. Liu, Synthesis 45 (2013) 2919.
[6] V.V. Grushin, J.W. Marshall, J. Am. Chem. Soc. 128 (2006) 12644.
[7] A. Bravo, H.R. Borsvik, F. Fontana, L. Liguori, F. Minisci, J. Org. Chem. 62 (1997) 7128.
[8] (a) A. Studer, Angew. Chem. Int. Ed. 51 (2012) 8950;
(b) A. Postigo, Can. J. Chem. 90 (2012) 493.
[9] (a) F. O'Hara, D.G. Blackmond, P.S. Baran, J. Am. Chem. Soc. 135 (2013) 12122;
(b) Y. Fujiwara, J.A. Dixon, F. O'Hara, D.E. Funder, D.D. Dixon, R.A. Rodriguez, R.D. Baxter, B. Herlé, N. Sach, M.R. Collins, Y. Ishihara, P.S. Baran, Nature 492 (2012) 95.
[10] A. Maleckis, M.S. Sanford, Organomet 33 (2014) 3831.
[11] E. Lee, J.M. Hooker, T. Ritter, J. Am. Chem. Soc. 134 (2012) 17456.
[12] (a) S. Barata-Vallejo, B. Lantaño, A. Postigo, Chem. Eur. J. (2014), http://dx.doi.org/10.1002/chem.201404005;
(b) Y. Ye, S.A. Kunzi, M.S. Sanford, Org. Lett. 14 (2012) 4979;
(c) J. Charpentier, N. Früh, A. Togni, Chem. Rev. (2014), http://dx.doi.org/10.1021/cr23h5002.
[13] J. Ullrich, Top. Curr. Chem. 320 (2012) 191.
[14] Z. Jin, G.B. Hammond, B. Xu, Aldrichimica Acta 45 (2012) 66.
[15] A.I. Konovalov, A. Lishchynskyi, V.V. Grushin, J. Am. Chem. Soc. (2014) 64, http://dx.doi.org/10.1021/ja5075.
[16] (a) E.J. Cho, T.D. Senecal, T. Kinzel, Y. Zhang, D.A. Watson, S.L. Buchwald, Science 328 (2010) 1679;
(b) Y. Ye, N.D. Ball, J.W. Kampf, M.S. Sanford, J. Am. Chem. Soc. 132 (2010) 14682;
(c) X. Wang, L. Truesdale, J.-Q. Yu, J. Am. Chem. Soc. 132 (2010) 3648;
(d) X. Mu, S. Chen, X. Zhen, G. Liu, Chem. Eur. J. 17 (2011) 6039;
(e) R.N. Loy, M.S. Sanford, Org. Lett. 13 (2011) 2548;
(f) S. Barata-Vallejo, M. Rosario Torviso, B. Lantaño, S.M. Bonesi, A. Postigo, J. Fluorine Chem. 161 (2014) 134.
[17] (a) L. Xu, H. Jiang, J. Hao, G. Zhao, Tetrahedron 70 (2014) 4373;
(b) Z. Gonda, S. Kovács, C. Wáber, T. Gáti, A. Mászáros, A. Kotschy, Z. Novák, Org. Lett. 16 (2014) 4268.
[18] F. Cerettaa, A. Zaggiaa, L. Contea, B. Ameduri, J. Fluorine Chem. 135 (2012) 220.
[19] Z. Mazloomi, A. Bansode, P. Benavente, A. Lishchynskyi, A. Urakawa, V.V. Grushin, Org. Process Res. Dev. (2014), http://dx.doi.org/10.1021/op09v5001.
[20] A. Lishchynskyi, M.A. Novikov, E. Martin, E.C. Escudero-Adán, P. Novák, V.V. Grushin, J. Org. Chem. 78 (2013) 11126.
[21] J.H. Clark, J.E. Denness, M.A. McClinton, A.J. Wynd, J. Fluorine Chem. 50 (1990) 411.
[22] X.-F. Wu, H. Neumann, M. Beller, Chem. Asian J. 7 (2012) 1744.
[23] A.I. Konovalov, J. Benet-Buchholz, E. Martin, V.V. Grushin, Angew. Chem. Int. Ed. 52 (2013) 11637.
[24] A. Lishchynskyi, V.V. Grushin, J. Am. Chem. Soc. 135 (2013) 12584.
[25] P. Novák, A. Lishchynskyi, V.V. Grushin, Angew. Chem. Int. Ed. 51 (2012) 7767.
[26] H. Serizawa, K. Aikawa, K. Mikami, Chem. Eur. J. 19 (2013) 17692.
[27] Q.-Y. Chen, S.-W. Wu, J. Chem. Soc. Perkin Trans. 1 (1989) 2385.
[28] (a) P.S. Fier, J.F. Hartwig, J. Am. Chem. Soc. 134 (2012) 5524;
(b) G.K.S. Prakash, J. Hu, G.A. Olah, J. Org. Chem. 68 (2003) 4457.
[29] B. Gao, C. Ni, J. Hu, CHIMIA Int. J. Chem. 68 (2014) 414.
[30] N.D. Litvinas, P.S. Fier, J.F. Hartwig, Angew. Chem. Int. Ed. 51 (2012) 563.
[31] M.G. Mormino, P.S. Fier, J.F. Hartwig, Org. Lett. 16 (2014) 1744.
[32] O.A. Tomashenko, E.C. Escudero-Adán, M. Martínez Belmonte, V.V. Grushin, Angew. Chem. Int. Ed. 50 (2011) 7655.
[33] T. Knauber, F. Arikan, G.-V. RÖshenthaler, L.J. Gooßen, Chem. Eur. J. 17 (2011) 2689.
[34] (a) M. Oishi, H. Kondo, H. Amii, Chem. Commun. (2009) 1909;
(b) H. Urata, H. Fuchikami, Tetrahedron Lett. 32 (1991) 91.

[35] X. Liu, C. Xu, M. Wang, Q. Liu, Chem. Rev. (2014) 73a, http://dx.doi.org/10.1021/cr4004.
[36] (a) H. Serizawa, K. Aikawa, K. Mikami, Org. Lett. 16 (2014) 3456;
(b) T. Nishida, H. Ida, Y. Kuninobu, M. Kanai, Nat. Commun. (2014), http://dx.doi.org/10.1038/n.comms4387.
[37] (a) J.E. Milne, S.L. Buchwald, J. Am. Chem. Soc. 126 (2004) 13028;
(b) D.S. Surry, S.L. Buchwald, Angew. Chem. Int. Ed. 47 (2008) 6338;
(c) T.E. Barder, S.L. Buchwald, J. Am. Chem. Soc. 129 (2007) 12003;
(d) M.R. Biscoe, B.P. Fors, S.L. Buchwald, J. Am. Chem. Soc. 130 (2008) 6686.
[38] A. Maleckis, M.S. Sanford, Organomet 33 (2014) 2653.
[39] D.A. Nagib, D.W.C. MacMillan, Nature 480 (2011) 224.
[40] T. Liu, X. Shao, Y. Wu, Q. Shen, Angew. Chem. Int. Ed. 51 (2012) 540.
[41] P. Kirsch, Modern Fluororganic Chemistry. Synthesis, Reactivity and Applications, Wiley-VCH-GmbH, Weinheim, 2004.
[42] Y. Ye, M.S. Sanford, J. Am. Chem. Soc. 134 (2012) 9034.
[43] T.D. Senecal, A.T. Parsons, S.L. Buchwald, J. Org. Chem. 76 (2011) 1174.
[44] (a) L. Chu, F.-L. Qing, Org. Lett. 12 (2010) 5060;
(b) R. Zhu, S.L. Buchwald, J. Am. Chem. Soc. 134 (2012) 12462.
[45] L. Chu, F.-L. Qing, Acc. Chem. Res. 47 (2014) 1513.
[46] S.R. Dubbaka, M. Salla, R. Bolisetti, S. Nizalapur, RSC Adv. 4 (2014) 6496.
[47] Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang, X. Zhang, Angew. Chem. Int. Ed. 53 (2014) 1669.
[48] Z. Feng, F. Chen, X. Zhang, Org. Lett. 14 (2012) 1938.
[49] Y.-L. Xiao, B. Zhang, Z. Feng, X. Zhang, Org. Lett. 16 (2014) 4822.
[50] (a) Q.Y. Chen, Z.Y. Yang, Acta Chim. Sinica 44 (1985) 1118;
(b) Z.-Y. Yang, D.J. Burton, J. Org. Chem. 57 (1992) 4676.
[51] Q. Qi, Q. Shen, L. Lu, J. Am. Chem. Soc. 134 (2012) 6548.
[52] (a) G.A. Molander, T. Ito, Org. Lett. 3 (2001) 393;
(b) G.A. Molander, B.T. Biolatto, J. Org. Chem. 68 (2003) 4302;
(c) G.A. Molander, R. Figueroa, Org. Lett. 8 (2006) 75;
(d) T.D. Quach, R.A. Batey, Org. Lett. 5 (2003) 1381;
(e) T.D. Quach, R.A. Batey, Org. Lett. 5 (2003) 4397;
(f) E.F. Santos-Filho, J.C. Sousa, N.M.M. Bezerra, P.H. Menezes, R.A. Oliveira, Tetrahedron Lett. 52 (2011) 5288.
[53] Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo, X. Zhang, J. Am. Chem. Soc. 136 (2014) 1230.
[54] Y.-B. Yu, G.-Z. He, X. Zhang, Angewandte Chemie 126 (2014) 10625.
[55] G. Ma, W. Wan, Q. Hu, H. Jiang, J. Wang, S. Zhu, J. Hao, Chem. Commun. 50 (2014) 7527.
[56] (a) D.L. Browne, Angew. Chem. Int. Ed. 53 (2014) 1482;
(b) J.-J. Dai, C. Fang, B. Xiao, J. Yi, Z.-J. Liu, X. Lu, Y. Fu, J. Am. Chem. Soc. 135 (2013) 8436.
[57] X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, J. Am. Chem. Soc. 135 (2013) 10330.
[58] (a) T. Furuya, A.E. Strom, T. Ritter, J. Am. Chem. Soc. 131 (2009) 1662;
(b) P. Tang, T. Furuya, T. Ritter, J. Am. Chem. Soc. 132 (2010) 12150;
(c) C. Huang, T. Liang, S. Harada, E. Lee, T. Ritter, J. Am. Chem. Soc. 133 (2011) 13308.
[59] G. Danoun, B. Bayarmagnai, M.F. Grünberg, L.J. Gooßen, Angew. Chem. Int. Ed. 52 (2013) 7972.
[60] B. Bayarmagnai, C. Matheis, E. Risto, L.J. Gooßen, Adv. Synth. Catal. 356 (2014) 2343.
[61] (a) A. Lishchynskyi, G. Berthon, V. Grushin, Chem. Commun. 50 (2014) 10237;
(b) B. Bayarmagnai, C. Matheis, E. Risto, L.J. Goossen, Adv. Synth. Cat. 356 (2014) 2343.
[62] T. Besset, C. Schneider, D. Cahard, Angew. Chem. Int. Ed. 51 (2012) 5048.
[63] X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, J. Am. Chem. Soc. 134 (2012) 11948.
[64] R.N. Loy, M.S. Sanford, Org. Lett. 13 (2010) 2548.
[65] N. Iqbal, S. Choi, E. Ko, E.J. Cho, Tetrahedron Lett. 53 (2012) 2005.
[66] U. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao, J. Hu, J. Am. Chem. Soc. 135 (2013) 2955.
[67] R.-Y. He, H.-T. Zeng, J.-M. Huang, Eur. J. Org. Chem. (2014), http://dx.doi.org/10.1002/ejoc.201402526.
[68] (a) Y.-D. Yang, K. Iwamoto, E. Tokunaga, N. Shibata, Chem. Commun. 49 (2013) 5510;
(b) S. Seo, J.B. Taylor, M.F. Greany, Chem. Commun. 49 (2013) 6385.
[69] L. Chu, F.-L. Qing, J. Am. Chem. Soc. 134 (2012) 1298.
[70] J.C. Fennenwald, B.H. Lipshutz, Green Chem. 16 (2014) 1097.
[71] (a) A.A. Gakh, Y. Shermolovich, Curr. Top. Med. Chem. 14 (2014) 952;
(b) X.-H. Cao, X. Pan, P.-J. Zhou, J. -P- Zou, O.T. Asekun, Chem. Commun. 50 (2014) 3359.
[72] T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa, J. Fluorine Chem. 131 (2010) 98.
[73] Y. Ohtsuka, T. Yamakawa, Tetrahedron 67 (2011) 2323.
[74] X. Sun, S. Yu, Org. Lett. 16 (2014) 2938.
[75] A. Hafner, T.J. Feuerstein, S. Bräse, Org. Lett. 15 (2013) 3468.
[76] A. Hafner, A. Bihlmeier, M. Nieger, W. Klopper, S. Bräse, J. Org. Chem. 78 (2013) 7938.
[77] (a) X. Jiang, F.-L. Qing, Beilstein J. Org. Chem. 9 (2013) 2862;
(b) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F.R. Leroux, Beilstein J. Org. Chem. 9 (2013) 2476.
[78] J. Xu, B. Xiao, C.-Q. Xie, D.-F. Luo, L. Liu, Y. Fu, Angew. Chem. Int. Ed. 51 (2012) 12551.
[79] A.T. Parsons, T.D. Senecal, S.L. Buchwald, Angew. Chem. Int. Ed. 51 (2012) 2947.
[80] J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong, L. Liu, J. Am. Chem. Soc. 133 (2011) 15300.
[81] P. Novak, A. Lishchynskyi, V.V. Grushin, J. Am. Chem. Soc. 134 (2012) 16167.
[82] A. Zanardi, M.A. Novikov, M.E. Benet-Buchholz, V.V. Grushin, J. Am. Chem. Soc. 133 (2011) 20901.
[83] C.F. Malosh, J.M. Ready, J. Am. Chem. Soc. 126 (2004) 10240.
[84] (a) Z. Mao, F. Huang, H. Yu, J. Chen, Z. Yu, Z. Xu, Chem. Eur. J. 20 (2014) 3439;
(b) J. Xu, X. Liu, Y. Fu, Tetrahedron Lett. 55 (2014) 585.
[85] D.A. Nagib, M.E. Scott, D.W.C. MacMillan, J. Am. Chem. Soc. 131 (2009) 10875.
[86] N. Iqbal, S. Choi, E. Kim, E. Jin Cho, J. Org. Chem. 77 (2012) 11383.
[87] E. Merino, C. Nevado, Chem. Soc. Rev. 43 (2014) 6598.
[88] J.-S. Lin, X.-G. Liu, X.-L. Zhu, B. Tan, X.-Y. Liu, J. Org. Chem. 79 (2014) 7084.
[89] S.R. Dubbaka, S. Nizalapur, A.R. Atthunuri, M. Salla, T. Mathew, Tetrahedron 70 (2014) 2118.
[90] E. Jin Cho, S.L. Buchwald, Org. Lett. 13 (2011) 6552.
[91] J. Zhu, W. Zhang, L. Zhang, J. Liu, J. Zheng, J. Hu, J. Org. Chem. 75 (2010) 5505.
[92] (a) L. Chu, F.-L. Qing, J. Am. Chem. Soc. 132 (2010) 7262;
(b) A. Maiji, A. Hazra, D. Maiti, Org. Lett. 16 (2014) 4524.
[93] J. Hwang, K. Park, J. Choe, H. Min, K.H. Song, S. Lee, J. Org. Chem. 79 (2014) 3267.
[94] (a) S. Xu, H.-H. Chen, J.-J. Dai, H.-J. Xu, Org. Lett. 16 (2014) 2306;
(b) Y.-S. Feng, C.-Q. Xie, W.-L. Qiao, H.-J. Xu, Org. Lett. 15 (2013) 936.
[95] R. Chinchilla, C. Najera, Chem. Rev. 107 (2007) 874.
[96] A. Soheili, J. Albaneze-Walker, J.A. Murry, P.G. Dormer, D.L. Hughes, Org. Lett. 5 (2003) 4191.
[97] (a) M. Garcia-Melchor, M.C. Pacheco, C. Najera, A. Lledos, G. Ujaque, ACS Catal. 2 (2012) 135;
(b) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, L. Liu, J. Am. Chem. Soc. 132 (2010) 14391.
[98] M.D. Kosobokov, V.V. Levin, M.I. Struchkova, A.D. Dilman, Org. Lett. 16 (2014) 3784.
[99] L. Li, F. Wang, C. Ni, J. Hu, Angew. Chem. Int. Ed. 52 (2013) 12390.
[100] G. Rubiales, C. Alonso, E. Martínez de Marigorta, F. Palacios, ARKIVOC II (2014) 362.
[101] N. Wakita, S. Hara, Heterocycles 88 (2014) 1201.
[102] K. Sato, T. Yuki, R. Yamaguchi, T. Hamano, A. Tarui, M. Omote, I. Kumadaki, A. Ando, J. Org. Chem. 74 (2009) 3815.
[103] Y. Lu, Y. Li, R. Zhang, K. Jin, C. Duan, J. Fluorine Chem. 161 (2014) 128.
[104] A.T. Herrmann, L.L. Smith, A. Zakarian, J. Am. Chem. Soc. 134 (2012) 6976.
[105] H. Jiang, C. Huang, J. Guo, C. Zeng, Y. Zhang, S. Yu, Chem. Eur. J. 18 (2012) 15158.
[106] J. Liu, S. Zhuang, Q. Gui, X. Chen, Z. Yang, Z. Tan, Eur. J. Org. Chem. (2014), http://dx.doi.org/10.1002/ejoc.201400087.
[107] X. Wang, Y. Xu, Y. Deng, Y. Zhou, J. Feng, G. Ji, Y. Zhang, J. Wang, Chem. Eur. J. 20 (2014) 961.
[108] M. Hu, Z. He, B. Gao, L. Li, C. Ni, J. Hu, J. Am. Chem. Soc. 135 (2013) 17302.
[109] M. Hu, C. Ni, J. Hu, J. Am. Chem. Soc. 134 (2012) 15257.