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An overview of reductive trifluoromethylation reactions using electrophilic '$^{+}CF_3$' reagents

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Contents

1. Introduction

The era of fluorine chemistry began with the synthesis and successful isolation of elemental fluorine (F_2) by Henri Moissan in 1886.[1] Within more than a century's development, especially in the past few decades, a large number of effective approaches for the introduction of fluorine atoms into widely used synthetic frameworks have been extensively exploited.[1,2] Fluorine has the strongest electronegativity (4.0 in Pauling scale) and a small atomic size (r_v=1.47 Å).[1] The C–F bond formed between fluorine and carbon is slightly longer than the C–H bond, but the bond energy of the former is much higher than that of the latter.[3] Fluorine is more similar to oxygen than to hydrogen in terms of electronic properties;[1,3] it can be used as a functional bioisostere of oxygen.[1a,4a] These unique 'fluorine effects' render enhanced biological activities of fluorinated bioactive molecules and fabulous physicochemical properties of fluorine-containing materials.[1]

Among fluorine-containing functional groups, the trifluoromethyl moiety (CF_3) is one of the most prevalent groups in

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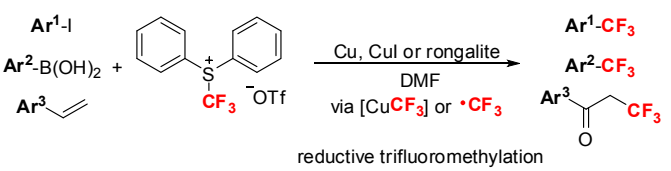
design of new pharmaceuticals and agrochemicals because its incorporation into drug candidates can dramatically change their metabolic stability, lipophilicity, bioavailability, and the protein bind affinity.[1] The CF_3 group is an electron-withdrawing group and has a significant influence on the p*K*a values of the neighboring functional groups, such as alcohols, carboxylic acids, and amines, which result in 'special' properties.[1,4a] Despite fluorine is the most abundant halogen and ranks the 13th most abundant element in the earth's crust, there are no naturally occurring CF_3-substituted compounds and all the target CF_3-containing compounds are without exception artificially synthesized. Therefore, the development of efficient methods to introduce CF_3 group into organic scaffolds has become one of the hottest topics in organic synthesis today.[2,4,5]

The direct trifluoromethylation reactions have been confirmed to be the most important and promising methods to construct C–CF_3 bonds among the widely used approaches.[1,2,4,5] Traditionally, the direct trifluoromethylation includes the reactions of electrophiles with nucleophilic CF_3 reagents, nucleophiles with electrophilic CF_3 species, and radical acceptors with CF_3 radical precursors. It is remarkable that the direct trifluoromethylation of nucleophiles with nucleophilic CF_3 reagents and electrophiles with electrophilic CF_3 sources have also been accomplished. The reactions proceed through oxidative-trifluoromethylation mechanism[5g] and reductive-trifluoromethylation pathways,[6] respectively. The early examples of reductive trifluoromethylation showed that electrophiles, such as disulfides and aldehydes, can be readily trifluoromethylated by CF_3X (X=I, Br) or $PhSO_2CF_3$ in the presence of reductants like Na, Mg, Zn, and TDAE ([tetrakis(dimethylamino) ethylene]).[6] Although the nomenclature of reductive trifluoromethylation is known,[6] to our knowledge, its definition has never been made. To differentiate these transformations from other types of reactions, we tentatively propose a conceptual model of reductive trifluoromethylation in this report: electrophiles or nucleophiles are trifluoromethylated by CF_3 reagents in the presence of reductants, wherein the reactions start with the reduction of CF_3 sources.

The first metal-mediated reductive trifluoromethylation with electrophilic '$^{+}CF_3$' reagent was reported in 2011.[7] The reaction of aryl iodides (electrophiles) with electrophilic $[Ph_2SCF_3][OTf]$ salt in the presence of copper powder gave the corresponding trifluoromethylated products in almost quantitative yields; the $CuCF_3$ intermediate was determined in the reaction by ^{19}F NMR and mass spectrometric analysis of the reaction mixture.[7a] Later, Cu(I)-mediated reductive trifluoromethylation of arylboronic acids (nucleophiles) with $[Ph_2SCF_3][OTf]$ was performed, and the $CuCF_3$ species was observed similarly.[8a] The rongalite-initiated bifunctional trifluoromethylation of styrenes (nucleophiles) with $[Ph_2SCF_3][OTf]$ was harnessed, as well, and the CF_3 radical intermediate was captured by styrenes.[9] Since then, more trifluoromethylation reactions involving reductive transformation of electrophilic '$^{+}CF_3$' reagents have been reported.



reductive trifluoromethylation

In this review, we summarize the rapid progress of the reductive trifluoromethylation reactions with electrophilic '$^{+}CF_3$' reagents in the past few years, in which either electrophiles or nucleophiles are trifluoromethylated by '$^{+}CF_3$' sources in the presence of proper reductants. The reactions should involve CF_3 radicals, CF_3 anions or related intermediates, which are derived from the reduction of '$^{+}CF_3$' reagents by transition-metals, inorganic salts, photoredox catalysts or even substrates via single electron transfer processes. The reduction of '$^{+}CF_3$' sources is the initial step that triggers the entire reaction. Although numerous mechanistic discussions and debates have been commenced, the whole mechanisms of the reductive trifluoromethylation with '$^{+}CF_3$' reagents are still unclear (see Sections 2 and 3).

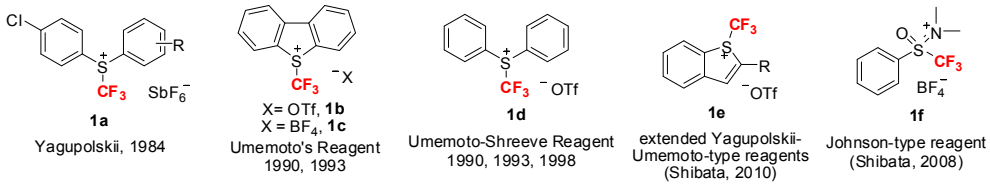
Our report will mainly focus on the transition-metal mediated/catalyzed trifluoromethylation of electrophiles/nucleophiles with electrophilic '$^{+}CF_3$' sources, which comprises CF_3 radicals or metal-CF_3 species, or undergoes other reductive transformation of '$^{+}CF_3$' reagents. The reactions of perfluoroalkyl halides ($R_{fn}X$, e.g., CF_3I) with reductants (such as $Na_2S_2O_4$ and Zn) and radical initiators (like Bz_2O_2 (benzoyl peroxide) and AIBN (azobisisobutyronitrile)), which give, respectively, the sulfinatodehalogenated products, the hydrodehalogenated products, the homo-coupling products, and the perfluoroalkylated products via radical or nucleophilic processes,[4b,10] represent a broader concept of reductive perfluoroalkylation reactions and will not be included in this report. We simply classify reductive trifluoromethylation reactions with electrophilic '$^{+}CF_3$' reagents, according to the type of CF_3 reagents, into two parts (see Sections 2 and 3). In each part, the debates related to the transformations are also described.

2. Reductive trifluoromethylation reactions with Umemoto's reagents and their analogs

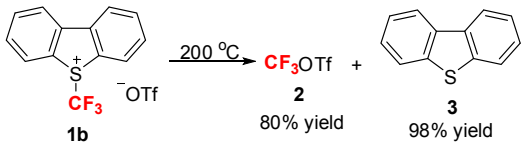
2.1. Electrophilic Umemoto's reagents and their analogs

Because of the strong electronegativities of R_{fn} groups (e.g., CF_3: 3.45 in Pauling scale), $R_{fn}X$ (R_{fn}=perfluoroalkyl, X=I, Br, Cl) and even $R_{fn}OTf$ (OTf=OSO_2CF_3) do not undergo electrophilic perfluoroalkylation; the nucleophiles attack the halogen atoms (X) of $R_{fn}X$ or the sulfur center of OTf group rather than the R_{fn} groups.[11a-b] Significantly, in the 1970s and 1980s Yagupolskii and co-workers synthesized (perfluoroalkyl)-aryliodonium salts and (perfluoroalkyl)chalcogen salts (including '$^{+}CF_3$' salts), and found that these compounds can be used as electrophilic perfluoroalkylation reagents.[11c–e] Since this pioneering work, the design and synthesis of novel electrophilic '$^{+}CF_3$' reagents have been widely investigated (Scheme 1).[11a,b] *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate and triflate (Umemoto's reagent, **1b**–**c**) and *S*-(Trifluoromethyl)diarylsulfonium triflate (Umemoto-Shreeve reagent, **1d**), developed by Umemoto, Shreeve, and so on, are the most widely used chalcogenium salts for effective electrophilic trifluoromethylation of a wide range of nucleophiles.[1,2,4,5,11,12] *S*-(Trifluoromethyl)thiophenium salts (expanded Yagupolskii-Umemoto-type reagents or Shibata's reagents, **1e**), prepared from triflic acid-catalyzed intramolecular cyclization of *o*-ethynylaryltrifluoromethylsulfanes, have also demonstrated to be promising trifluoromethylation reagents for *β*-ketoesters and dicyanoal kylidenes.[13]

The Umemoto's reagent (**1b**) was initially described as a pure electrophilic '$^{+}CF_3$' source since it could form $CF_3SO_3CF_3$ (**2**) in high yield by pyrolysis (Scheme 2).[14] However, in the same article, the authors recognized that the reaction may occur via a bimolecular ionic substitution and/or a free radical chain mechanism, which is dependent upon the nature of the nucleophiles.[14] The kinetic study later disclosed that the cyclic Umemoto's reagent (**1b**) has higher reactivity than the non-cyclic Umemoto-Shreeve reagent (**1d**).[15] The critical difference in chemoselectivity of reactions between *S*-(methyl)dibenzothiophenium salt (**6**) and **1b** with aniline (N-methylation vs C-trifluoromethylation, Scheme 3) was indicative of a mechanism different from a classical S_N2 process, despite their respective CH_3 and CF_3 groups adopting similar orientations in the crystal structures.[15,16a] The Mulliken population analysis of *S*-(trifluoromethyl)dibenzothiophenium cation (**8**) indicated a positive

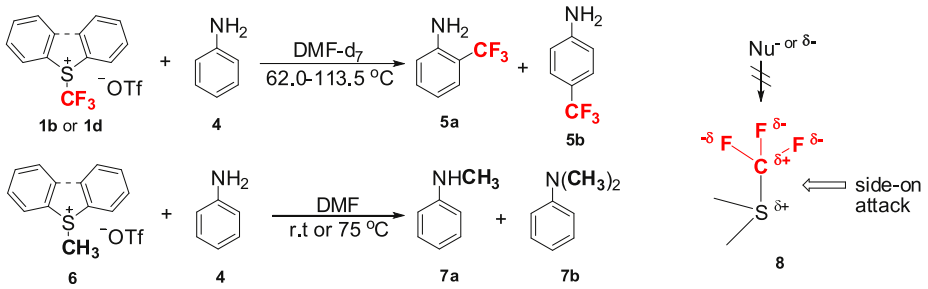


Scheme 1. The commonly used Umemoto's reagents and their analogs.



Scheme 2. The pyrolysis of **1b** at high reaction temperature.

radical pathways in the trifluoromethylation. Magnier and co-workers envisioned that, if the reaction follows a pure ionic route, **10** would be the sole product. Otherwise, the intermediate **12** from the oxidation of **9** by sulfonium salts gives rise to **10** via homo-coupling (path a, Scheme 4) and/or **11** via a 5-*exo-trig* cyclization (path b, Scheme 4). The single product (**11**) isolated from reaction of **9** and **1b** under ultraviolet irradiation provided an unambiguous



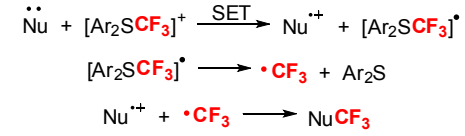
Scheme 3. The critical difference in chemoselectivity of the reactions between **6** and **1b** with aniline.

CF_3 carbon binding to a positive S atom (Scheme 3).[15] Considering the thermodynamic and electronic properties of **1b** and **1d**, Umemoto and co-worker proposed a 'side-on' attack of aniline (*ortho*- or *para*-position, Scheme 3) to S–CF_3 bond, which might be accompanied by a one- or two-electron exchange process.[15]

Moreover, the electron-exchange hypothesis can be partially supported by the research work of Magnier and co-workers, which disclosed a big yield improvement in the preparation of trifluoromethyl estradiol when silyl enol was treated with **1b** under UV-irradiation.[16] In light of the results from $R_{fn}X$'s perfluoroalkylation,[4b,10] they postulated a single electron transfer (SET) mechanism for the formation of trifluoromethyl ketones from enol derivatives, which is analogous to that observed for the reaction of similar nucleophiles with trifluoromethyl halides.[16a]

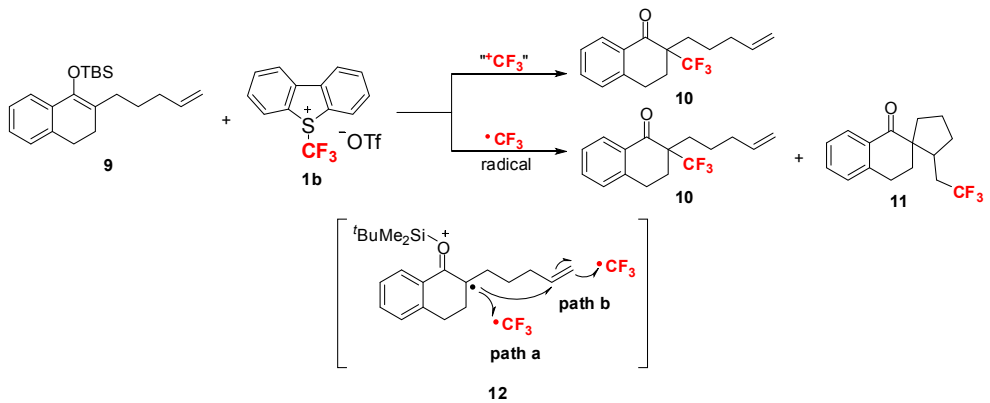
To demonstrate the SET mechanism, the reaction of silyl enol with Umemoto's reagent (**1b**) was further investigated (Scheme 4).[16a] Compound **9** bearing a $(CH_2)_3CH{=}CH_2$ group was chosen as the model substrate to distinguish the electrophilic and

proof of the radical character of the reaction mechanism (Scheme 5).[16a]



Scheme 5. The radical mechanism of the reaction of $[Ar_2SCF_3]^+$ reagent and nucleophiles.

First, nucleophiles (Nu) behave as the SET reducing agents towards Umemoto's reagents and their analogs in the reactions, leading to the generation of radical cations ($Nu^{\cdot+}$) and radical intermediates ($[Ar_2SCF_3]^{\bullet}$) (Scheme 5). Then $[Ar_2SCF_3]^{\bullet}$ fragment into neutral sulfur derivatives (Ar_2S) and a trifluoromethyl radical ($^{\bullet}CF_3$).[16a] The combination of $Nu^{\cdot+}$ and $^{\bullet}CF_3$ finally produces the trifluoromethylated products. In the case of **9**, the intramolecular



Scheme 4. The reaction of silyl enol bearing a $(CH_2)_3CH{=}CH_2$ group with Umemoto's reagent (**1b**) to understand the possible reaction mechanism.

cyclization of the radical cation (**12**) appears to be more rapid than the production of CF_3 radical, thus leading to **11** as the exclusive product.

Umemoto and co-worker excluded the free radical mechanism of the electrophilic trifluoromethylsulfonium salts at the beginning because 1) these reagents could trifluoromethylate *p*-hydroquinone, an effective free radical scavenger, to form 2-(trifluoromethyl)-*p*-hydroquinone, and 2) the addition of *p*-dinitrobenzene, another well-known radical inhibitor, did not affect the trifluoromethylation of aniline with Umemoto's reagent.[14] These results, however, can only refute a radical chain process. Magnier and co-workers later suggested that the trifluoromethylation reaction may occur in the solvent cage, thus it cannot be inhibited by a radical scavenger. And the SET mechanism is not only suitable for the reactions of Umemoto's reagents and analogs with silyloxanes but also for those with other nucleophiles like β-ketoesters, ketones, enamines, and thiolates. Even though a pure ionic mechanism cannot be totally excluded, the radical pathway is presumably the predominant route in the reactions. Nevertheless, the applications of this mechanistic study for synthetic purposes were not implemented.

2.2. Cu-mediated reductive trifluoromethylation with Umemoto's reagents and their analogs

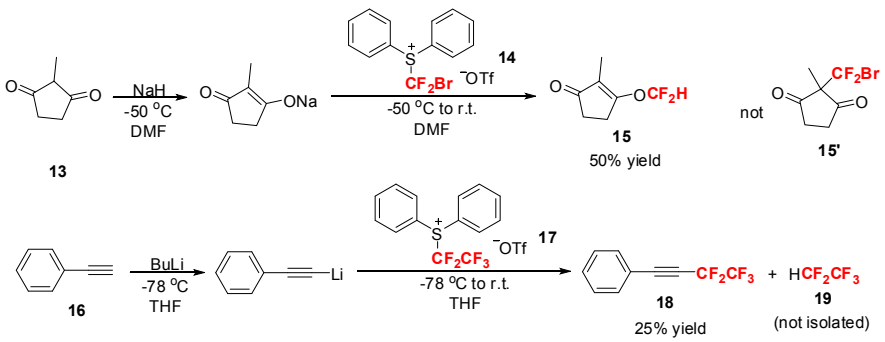
Almost at the same time we separately found a similar redox process in the reaction of *S*-(fluoroalkyl)diphenylsulfonium salts (expanded Umemoto-Shreeve type reagents) with *C*-nucleophiles (Scheme 6).[17a] The reaction of 2-methylcyclopentane-1,3-dione anion with *S*-(bromodifluoromethyl)diphenylsulfonium triflate (**14**) yielded 3-(difluoromethoxy)-2-methyl-cyclopent-2-enone (**15**) rather than **15′**, as the sole major product. This abnormal result indicated a halogenophilic mechanism, which led to a difluorocarbene ($:CF_2$) intermediate.[17] Moreover, ^{19}F NMR measurement of the reaction course of *S*-(pentafluoroethyl)diphenylsulfonium triflate (**17**) with phenylacetylene anion or ethyl 2-methyl-3-oxobutanoate anion showed the simultaneous formation of undesired 1*H*-pentafluoroethanes (**19**), suggesting that the $\bullet CF_2CF_3$ radical is generated in the reactions.[17a] The: CF_2 species and $\bullet CF_2CF_3$ intermediate involved in these reactions are most likely from the reduction of *S*-(fluoroalkyl)diphenylsulfonium triflates by *C*-nucleophiles.[17a,b]

trifluoromethylated by other commonly used approaches, was developed (Scheme 7).[7a] Heteroaromatic systems (**20**) containing nitrogen, oxygen, and/or sulfur and substituted with iodine were all effectively functionalized in the Cu(0)-mediated reductive trifluoromethylation reactions.

The ^{19}F NMR analysis of the reaction mixture showed that $CuCF_3$ was produced under the reaction conditions (δ=−33.9 ppm).[7a] As the reaction proceeded, $CuCF_3$ was consumed and the concentration of the trifluoromethylated product gradually increased. Analysis of the reaction mixture by ESI-MS methods also indicated the formation of $CuCF_3$ (*m*/*z* 131.9). The $CuCF_3$ intermediate may be generated by the pathway shown in Scheme 7. The *S*-(trifluoromethyl)diphenylsulfonium triflate (**1d**) is first reduced by copper via a single electron transfer (SET). Intermediate **22** then decomposes rapidly to produce the CF_3 radical, which generates $CuCF_3$ with another equivalent of Cu. The cross-coupling reaction of $CuCF_3$ and ArI finally yields the trifluoromethylated products. The byproduct diphenyl sulfide was isolated by column chromatography after workup, which can support the proposed mechanism.

Shortly after, Shibata and co-workers reported a Cu(0)-mediated trifluoromethylation of benzylic bromides (**23**) with **1d** under mild conditions (Scheme 8).[19a] The reaction is amenable to a wide variety of benzyl bromides, and can facilitate the rapid construction of structural diversity in drug discovery. Likewise, benzyl bromides were trifluoromethylated by $CuCF_3$ species, which is also produced by the reduction of **1d** via single electron transfer processes. The mechanism of the electrophilic trifluoromethylation of Cu-benzyl spices with **1d** can be ruled out in this reaction.[19a]

Moreover, the reductive trifluoromethylation of benzylic xanthates (**25**) using **1b** as the CF_3 source in the presence of copper was described by Altman and co-workers (Scheme 9).[19b] It is interesting that when xanthate (**25a**, R=H, Ar=C_6H_4Ph in **25**) was treated with either Cu in the absence **1b** or with **1b** in the absence of Cu, no reaction happened and the majority of the starting material was recovered. Treatment of **25a** with $CuCF_3$ (formed by reaction of CuI and $TMSCF_3$ (TMS=trimethylsilyl) in the presence of CsF) provided **26a** (R=H, Ar=C_6H_4Ph in **26**) in 20% ^{19}F NMR yield, while the addition of CuOTf to the reaction mixture improved the yield of the product to 43%. According to these, a redox process was postulated, which involves the reaction of Cu with **1b** to generate CuOTf and $CuCF_3$. In the sequence, CuOTf activates the xanthate towards trifluoromethylation by $CuCF_3$ via a radical cation intermediate. This



Scheme 6. The discovery of a redox process in the reaction of **14** or **17** and *C*-nucleophiles.

Based on this, we continued to investigate the reaction of sulfonium salts and metals (Scheme 7).[7a] It was found that **1d**[18] could be successfully reduced by metals like Fe, $[Pd(PPh_3)_4]$, Zn, Ag, Cu, and CuI.[7a] Using copper powder as a reductant, the reaction of **1d** with iodobenzene (**20a**) provided trifluoromethylbenzene (**21a**) in high yield. Consequently, an efficient method for the late-stage trifluoromethylation of potentially bioactive heteroaromatic compounds (**20**), which cannot be or are difficult to be

method is compatible with an array of benzylic xanthates bearing useful functional groups.

Remarkably, the reductive Sandmeyer trifluoromethylation reaction for the conversion of aromatic amines (**27-S**) to trifluoromethylated products (**27-P**) using **1c**/Cu(0) system was developed by Fu and co-workers (Scheme 10).[19c] This operationally simple transformation proceeded smoothly under mild conditions and exhibited good tolerance of various functional groups,

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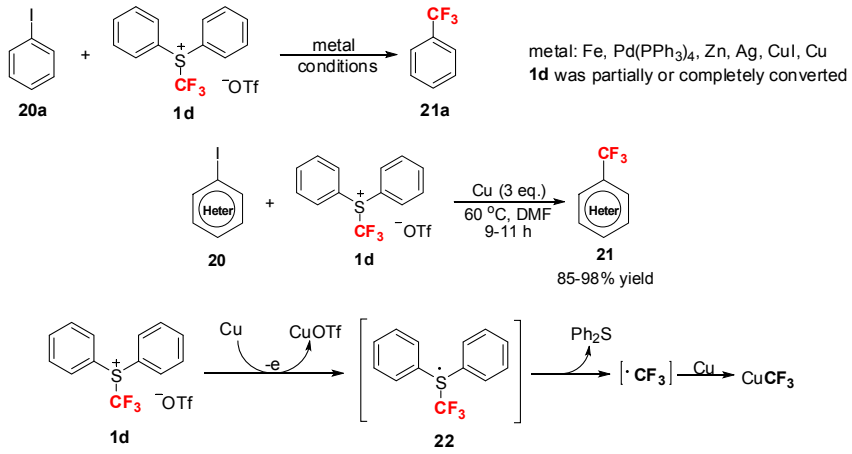
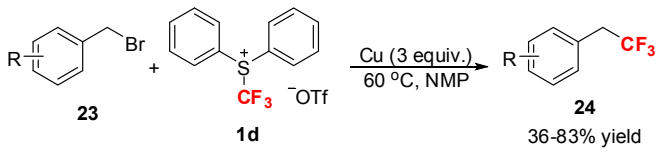
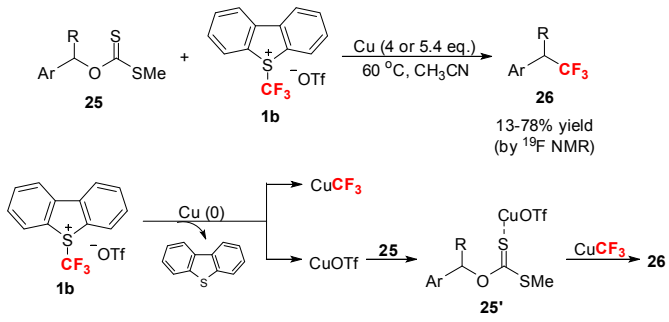


Scheme 7. Reductive trifluoromethylation of heteroaromatic iodides by **1d**/Cu(0) reagents and a reasonable mechanism for the generation of $CuCF_3$ intermediate.



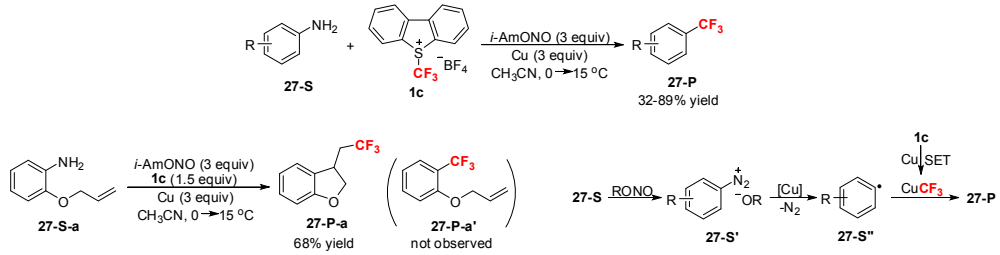
Scheme 8. Cu(0)-mediated reductive trifluoromethylation of benzylic bromides with **1d**.



Scheme 9. Trifluoromethylation of benzylic xanthates (**25**) with **1b**/Cu(0) via a $CuCF_3$ intermediate.

providing an alternative approach for the synthesis of trifluoromethyl arenes and heteroarenes. To understand the reaction mechanism, the reaction of **1c** and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) in the presence of copper was tested (Scheme 10).[19c] When **1c** and copper were mixed with a solution of TEMPO, the ESR signal of TEMPO significantly decreased and TEMPO-CF_3 adduct was identified. This implies the generation of a CF_3 radical. When **1c** was treated with copper without TEMPO, however, a new product with ^{19}F NMR chemical shift of −34.72 ppm was observed, which is assigned to a $CuCF_3$ intermediate. On the other hand, the reaction of 2-(allyloxy)aniline (**27-S-a**) with *i*-AmONO/**1c**/Cu (*i*-AmONO=isoamyl nitrite) gave the cyclized product (**27-P-a**, 68% yield) rather than the acyclic product (**27-P-a′**), indicating that an aryl radical species is formed in the reaction, as well (Scheme 10). Based on these results, the reaction mechanism of Cu-promoted reductive Sandmeyer trifluoromethylation is proposed (Scheme 10).[19c] Likewise, a single electron transfer (SET) from copper to **1c** generates the CF_3 radical, which reacts with second copper to produce $CuCF_3$. Then $CuCF_3$ reacts with the aryl radical, generated from the aryldiazonium ion (derived in situ from **27-S** and *i*-AmONO), to afford the final product.

Recently, the copper-mediated reductive trifluoromethylation of propargyl acetates (**28**) with **1d** under mild conditions was reported, leading to trifluoromethyl allenes (**28-P**) in moderate to excellent yields (Scheme 11).[20a] The studies show that the aryl substituents (Ar) with electron-rich groups on phenyl rings in **28** are favorable for the trifluoromethylation, and that the substrate bearing a weak electron-withdrawing group in Ar can also be transformed to the expected product (in good yield). When a strong electron-withdrawing group (e.g., NO_2) introduced in Ar, however, the desired conversion is greatly suppressed (16% yield). The reaction mechanism may involve an oxidative addition of propargyl



Scheme 10. Cu(0)-mediated reductive Sandmeyer trifluoromethylation of aromatic amines with **1c**.

acetate to the $CuCF_3$ intermediate, which is generated from the reaction of **1d** with copper powder (Scheme 11). Propargyl acetate (**28**) acts as a bidentate ligand in this case and its coordination to $CuCF_3$ favors the oxidative addition to give intermediate **28-S**. The reductive elimination of **28-S** finally gives the desired product (**28-P**). It should be mentioned that Szabó and Nishibayashi have independently achieved the trifluoromethylation of propargyl trifluoroacetates and chlorides[20b,c]; their reaction systems, however, are not effective for propargyl acetates (Szabó: $(Ph_3P)_3CuCF_3$/THF/22 °C, Nishibayashi: CuTc/KF/Me_3SiCF_3/THF/60 °C).[20a]

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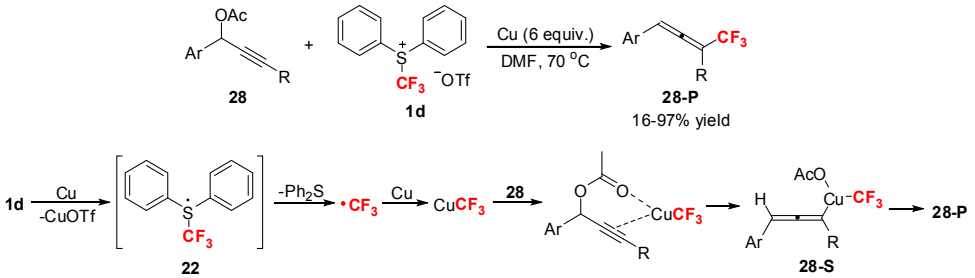
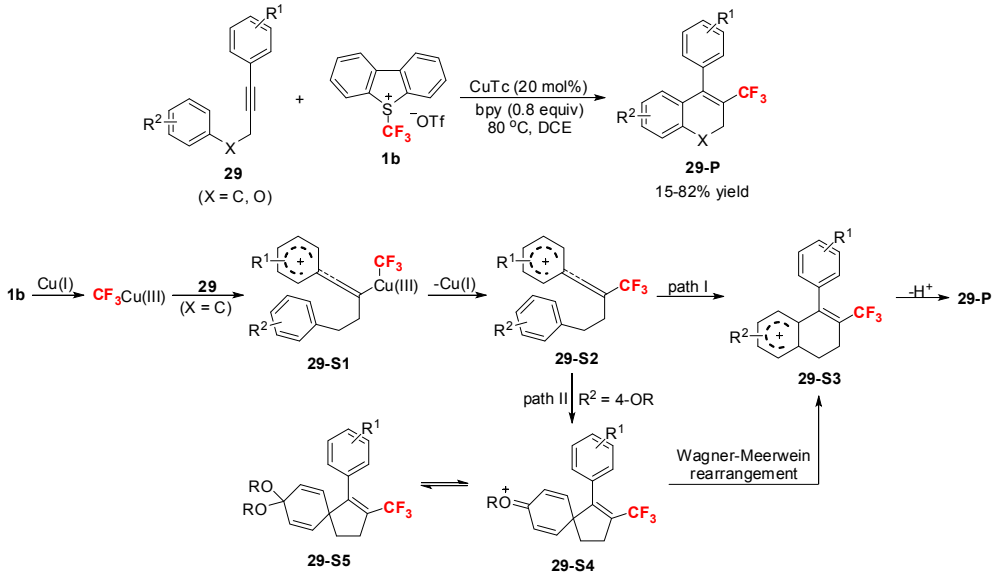


Scheme 11. Cu(0)-mediated reductive trifluoromethylation of **28** with **1d** and the proposed reaction mechanism.

The Cu(I)-catalyzed tandem reductive trifluoromethylation/cyclization of internal alkynes (**29**) with **1b** was disclosed, which provided 3-trifluoromethyl-1,2-dihydronaphthalene derivatives (**29-P**) in moderate to good yields (Scheme 12).[20d] Oxidation or reduction of **29-P** gave naphthalenes or tetrahydronaphthalenes, respectively. A plausible reaction mechanism was proposed, which is different from that for **28**.[20d] First, the oxidation of Cu(I) by **1b** produces $CF_3Cu(III)$, the electrophilic attack of which to **29** generates **29-S1**. Reductive elimination of **29-S1** forms **29-S2** and regenerates Cu(I). Then the intramolecular cyclization of **29-S2** gives **29-S3** (path I), which releases proton to furnish the final product (**29-P**). If the homopropargylic benzene ring is substituted by a 4-RO group, intermediate **29-S2** might also undergo *ipso* Friedel–Crafts reaction to form **29-S4** (path II). The use of alcohol as an additive can stabilize **29-S4** by converting this intermediate to **29-S5**. The Wagner-Meerwein rearrangement of **29-S4** produces **29-S3**, and, after aromatization, it affords **29-P**.

then undergoes transmetallation with the arylboronic acid (**30**) to provide an aryl-Cu(II)–CF_3 or aryl-Cu(III)–CF_3 intermediate, which goes on to produce the trifluoromethylated product by facile reductive elimination. Likewise, the Cu(I)-catalyzed trifluoromethylation of aryl- and vinylboronic acids by **1e** (R=cyclopropyl) was explored at room temperature; the reaction gave the CF_3-products in good to high yields under mild conditions.[8b]

The Cu(I)-mediated reductive trifluoromethylation of terminal alkynes with **1d** was disclosed, which afforded trifluoromethylated acetylenes in moderate to good yields.[21a] One of the possible reaction mechanisms indicated that the reaction may form a Halo-Cu(III)CF_3 complex, leading to the key RC≡C–Cu(III)CF_3 intermediates for the final products. The Cu(I)-catalyzed reductive trifluoromethylation of terminal alkenes with **1b** was reported by Liu et al. The reaction comprises a Cu(III)CF_3 intermediate, as well, which is likely first generated from the oxidative addition of **1b** to CuTc.[21b] Both experimental and theoretical analyses indicated that



Scheme 12. Cu(I)-catalyzed tandem reductive trifluoromethylation/cyclization of **29** with **1b**.

Furthermore, the ligand-free reductive trifluoromethylation of arylboronic acids with **1d**/Cu(0) system was investigated (Scheme 13).[8a] Aryl-, alkenyl- and heteroarylboronic acids with a variety of functional groups were readily transformed in the reaction. The $CuCF_3$ intermediate is suggested for the reaction, which was similarly determined by analysis of the ^{19}F NMR and MS spectra of the reaction mixtures. In contrast to that from ArI/**1d**/Cu system, the $CuCF_3$ intermediate from $ArB(OH)_2$/**1d**/Cu mixture is probably oxidized by another equivalent of **1d** to form a Cu(II)–CF_3 or Cu(III)–CF_3 complex (Scheme 13). The Cu(II)–CF_3 or Cu(III)–CF_3 complex the trifluoromethylation may occur via a Heck-like four-membered-ring transition state.

Besides, the reaction of **1d** with $Na_2S_2O_4$ and $HOCH_2SO_2Na$ under suitable conditions was implemented.[9] The *S*-(trifluoromethyl) diphenylsulfonium triflate is first reduced by $Na_2S_2O_4$ or $HOCH_2SO_2Na$ to form **22** via a SET mechanism, which decomposes rapidly to CF_3 radical. The CF_3 radical is the key intermediate, which reacts with styrene to produce, after oxidation, α-trifluoromethylated ketones. This reaction allows for a convenient synthesis of α-trifluoromethylated ketones.

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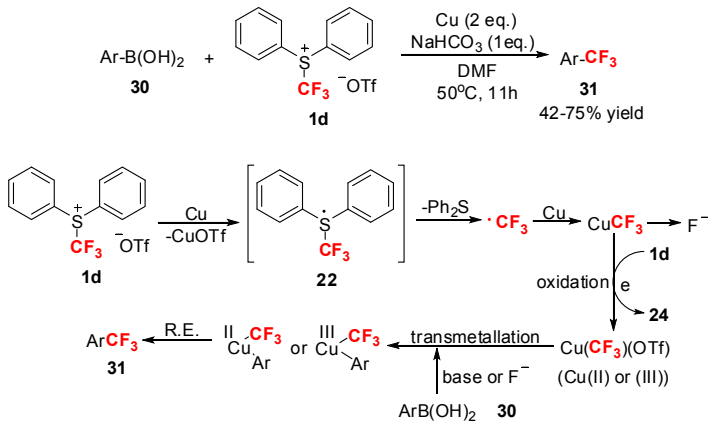
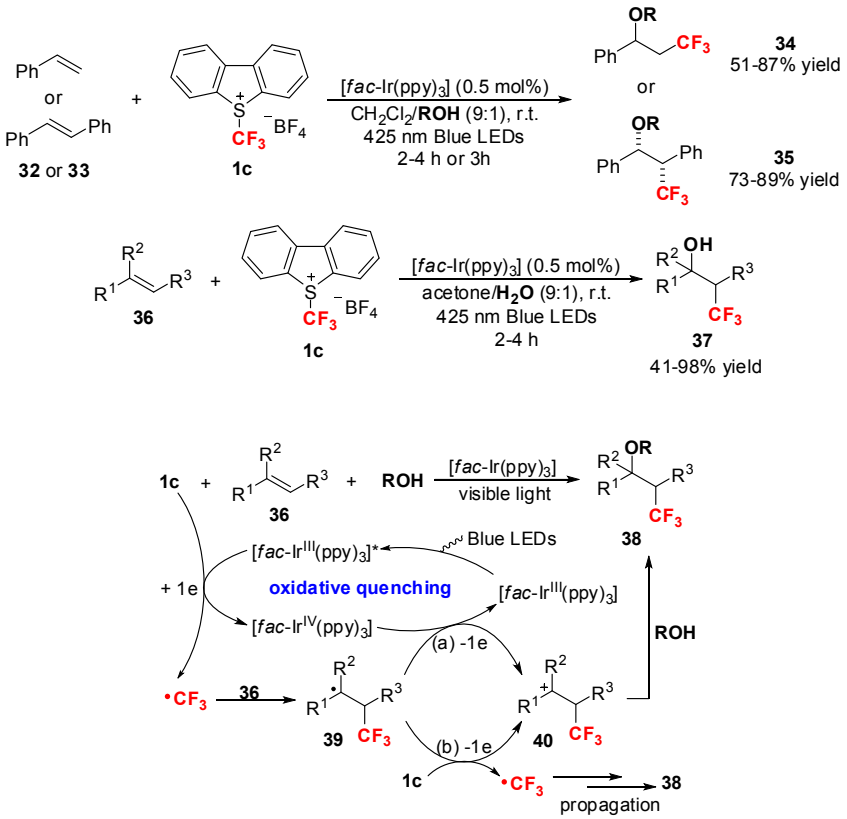


Scheme 13. The ligand-free reductive trifluoromethylation of arylboronic acids with **1d**/Cu(0) system.

2.3. Reductive trifluoromethylation with Umemoto's reagents under photoredox catalysis

Photoredox catalytic systems can trigger the reductive trifluoromethylation of Umemoto's reagents. The first visible-light driven three-component oxytrifluoromethylation of alkenes using Umemoto's reagent and photoredox catalyst ([*fac*-Ir(ppy)$_3$], ppy=2-phenylpyridine) was reported by Koike and Akita (Scheme 14).[22] This highly efficient and regioselective radical transformation of alkenes proceeded at room temperature under sunlight with a broad range of *O*-nucleophiles, such as alcohols, carboxylic acids, and water. This protocol was also available in the synthesis of the panomifene (antiestrogen drug) from the corresponding triarylalkene. The choice of the CF_3 source has influence on the reaction; using Togni's reagent instead of **1c** leads to loses in efficiency and selectivity of the reaction. The cyclic voltammetry investigation indicated that **1c** is reduced more easily than others, which provides a reasonable explanation to the different efficiency of the reagents.[22]

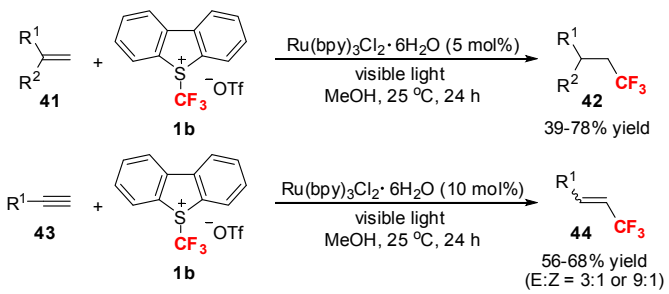
A plausible redox reaction mechanism is proposed (Scheme 14, bottom).[22] First, the visible-light irradiation excites [*fac*-Ir^{III}(ppy)$_3$] to [*fac*-Ir^{III}(ppy)$_3$]*, which reacts with **1c** to afford •CF_3 via a SET process (supported by luminescence quenching experiments). Then addition of •CF_3 to alkene (**36**) gives the alkyl radical intermediate (**39**), which is oxidized by [*fac*-Ir^{IV}(ppy)$_3$] formed in the SET process (path a in Scheme 14). Finally, the reaction of **ROH** with the carbocation intermediate (**40**) produces the three-component coupled product **38**. Although the radical chain propagation



Scheme 14. Visible-light driven three-component oxytrifluoromethylation of alkenes with **1c** and [*fac*-Ir(ppy)$_3$] and the possible radical reaction mechanism.

mechanism (path b) cannot be ruled out, the present reaction requiring continuous irradiation of visible light suggests that chain propagation is not a main mechanistic component.

Later, a visible-light mediated hydrotrifluoromethylation of unactivated alkenes that uses the Umemoto's reagent and $Ru(bpy)_3Cl_2·6H_2O$ (bpy=2,2′-bipyridine) catalyst was disclosed by Gouverneur and co-workers (Scheme 15).[23] The reaction performed effectively at room temperature and showed good operational simplicity and functional group tolerance, which resulted in a novel method of net fluoroform addition across alkenes (**41**) and alkynes (**43**) in a regioselective manner under mild conditions. Diene **45** reacting with **1b** under the standard conditions gave cyclized product **46a** (41% yield) along with cyclized byproduct **46b** (8% yield) (Scheme 16). This cyclization event is consistent with the presence of a CF_3 radical intermediate, which strongly suggests a radical-based mechanism of the hydrotrifluoromethylation reaction (Scheme 16).[23] Initially, irradiation of $Ru(bpy)_3Cl_2$ with visible light (452 nm) leads to the excited-state species $[Ru(bpy)_3]^*Cl_2$, which enters an oxidative quenching cycle. Since the reduction potential of **1b** (−0.25 V vs SCE in CH_3CN) is compatible with the reduction step using excited-state $[Ru(bpy)_3]^*Cl_2$, the single electron transfer (SET) reduction of **1b** is most likely concurrent with the oxidation of $[Ru(bpy)_3]^*Cl_2$ to $[Ru(bpy)_3]^{3+}$ (−0.81 V vs SCE in CH_3CN).[23] The resulting Umemoto radical intermediate then decomposes to an electrophilic $•CF_3$ species, which regioselectively adds to the alkene substrate and is subsequently converted to the hydrotrifluoromethylation product. In this case, methanol behaves as the hydrogen atom donor.[23] Upon oxidation of methanol by the strong oxidative $[Ru(bpy)_3]^{3+}$ (+1.29 V vs SCE in CH_3CN), $[Ru(bpy)_3]^{3+}$ is converted into the ground-state photocatalyst $[Ru(bpy)_3]^{2+}$. The reductive quenching pathway is dismissed because oxidation of CH_3OH occurs at potentials greater than +1.5 V (vs SCE) on a glassy carbon electrode and that $[Ru(bpy)_3]^{2+}$ (+0.77 V vs SCE in CH_3CN) is a weaker oxidant than $[Ru(bpy)_3]^{3+}$.

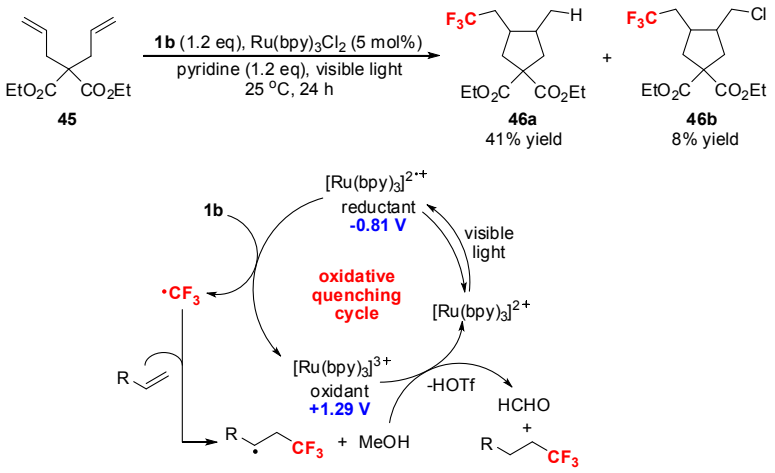


Scheme 15. Visible-light mediated hydrotrifluoromethylation of alkenes with **1b** and $Ru(bpy)_3Cl_2·6H_2O$.

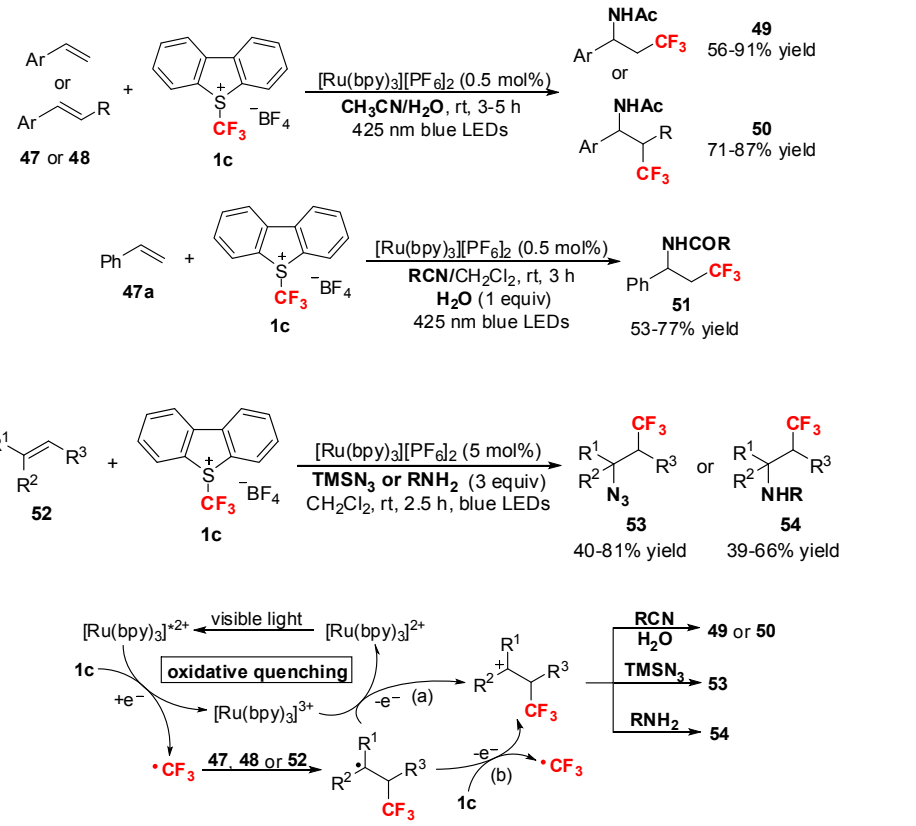
Shortly after, the intermolecular aminotrifluoromethylation of alkenes (**47** and **48**) with Umemoto's reagent (**1c**) and $[Ru(bpy)_3][PF_6]_2$ catalyst under visible-light irradiation was explored (Scheme 17).[24] The transformation afforded an efficient protocol for regioselective difunctionalization of C=C bonds, leading to a variety of β-trifluoromethyl amines bearing numerous functional groups. The reaction could be applied to 'late-stage' aminotrifluoromethylation of steroid and amino acid scaffolds. Analogously, a complete regioselective three-component azido- and amino-trifluoromethylation of alkenes (**52**) under mild conditions was developed by using visible-light-driven photoredox catalyst $[Ru(bpy)_3][PF_6]_2$ and electrophilic '$^+CF_3$' reagent (**1c**).[25] Various substituted styrenes as well as activated and non-activated alkenes are readily difunctionalized, affording β-trifluoromethylated azides (**53**) and amines (**54**) in good yields. Reaction mechanisms similar to that of the previously reported oxytrifluoromethylation of alkenes are suggested, in which $•CF_3$ is generated from the reduction of **1c** by activated $[Ru(bpy)_3]^*[PF_6]_2$ via a SET process. Addition of $•CF_3$ to alkene yields the radical intermediate, which is oxidized by $[Ru(bpy)_3]^{3+}$ (formed in the SET process). The resulting β-trifluoromethylated carbocation species then reacts with **RCN** followed by hydrolysis or with $\mathbf{TMSN_3}$ and $\mathbf{RNH_2}$ to afford β-trifluoromethylated amines and azides (**49**–**51** or **53**–**54**).

Koike, Akita and co-workers recently reported the trifluoromethylative lactonization of both terminal and internal alkenoic acids (**55**) by Umemoto's reagent and Ru photocatalyst (Scheme 18).[26] This operationally easy trifluoromethylation protocol provided a very useful access to a variety of CF_3-substituted five-, six- and seven-membered ring *endo*-lactones (**56** and **57**). Later, they discovered that the photoredox reaction of di- and trisubstituted alkenes (**58**) with **1c** in the presence of $[Ru(bpy)_3][PF_6]_2$ under visible-light irradiation afforded CF_3-substituted alkenes in good yields (Scheme 18).[27] These reactions are also supposed to proceed through a mechanism similar to that of the previously reported oxy- and aminotrifluoromethylation of alkenes by photoredox catalysis (Scheme 19).

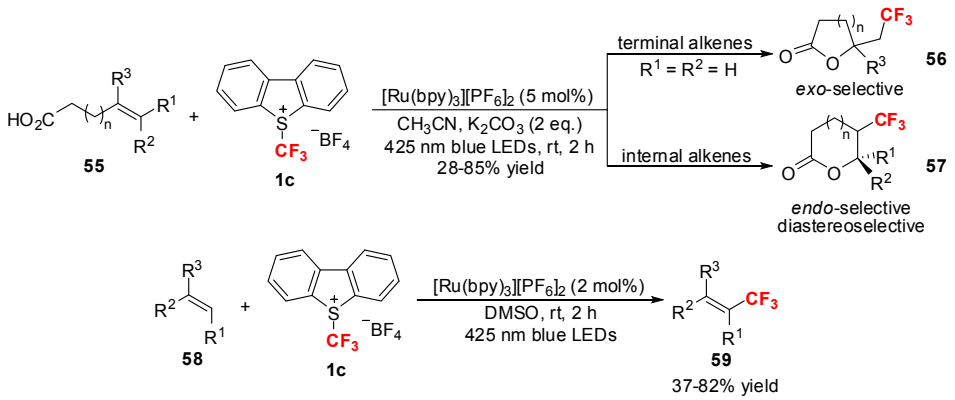
The visible-light promoted biaryl isocyanide insertion reaction was explored for the synthesis of phenanthridine derivatives (Scheme 20).[28a] Under standard reaction conditions, various 6-trifluoromethylated phenanthridine derivatives (**61**) were produced in good to excellent yields without any external oxidant. The insertion reaction goes through a radical mechanism. The CF_3



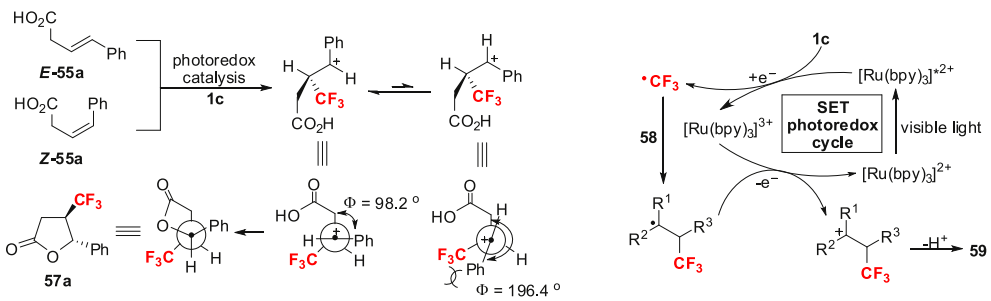
Scheme 16. A proposed pathway for visible-light mediated hydrotrifluoromethylation of alkenes with **1b** in the presence of $Ru(bpy)_3Cl_2·6H_2O$.



Scheme 17. Visible-light initiated intermolecular aminotrifluoromethylation of alkenes with **1c** and catalytic amounts of $[Ru(bpy)_3][PF_6]_2$.



Scheme 18. Reductive trifluoromethyl functionalization of alkenoic acids and multi-substituted alkenes by **1c** in the presence of Ru photocatalyst.



Scheme 19. Proposed pathways to illustrate the high diastereoselectivity of **57** and the production of **59**.

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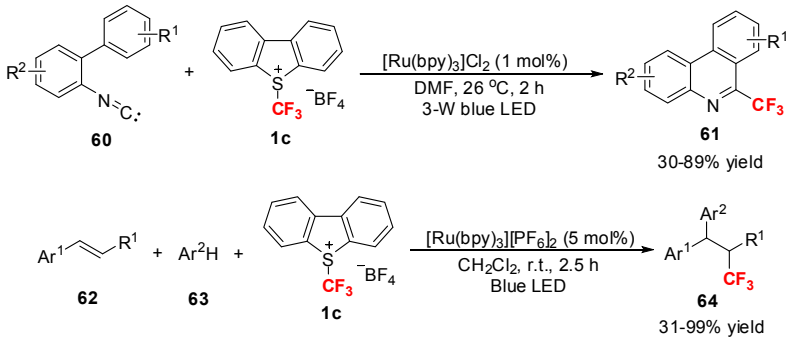


Scheme 20. Visible-light promoted intra- and intermolecular aryltrifluoromethylation of biaryl isocyanide and styrenes with **1c**/$[Ru(bpy)_3]^{2+}$ system.

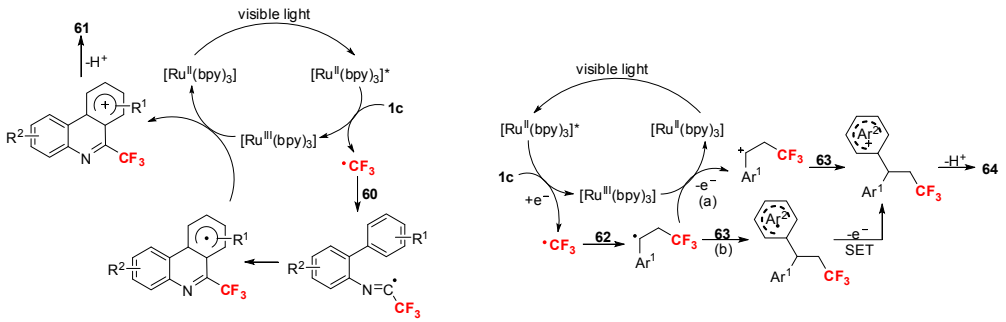
radical, generated from the reduction of **1c** by visible-light excited $[Ru(bpy)_3]^*Cl_2$, is captured by **60** to give the corresponding radical, which undergoes an intramolecular cyclization and subsequent oxidation to provide **61**. With an analogous strategy, the synthesis of 1-trifluoromethylisoquinoline derivatives was enabled by a photoredox vinyl isocyanide insertion using $Ir(ppy)_2(dtbbpy)$ (dtbbpy=4,4′-di-*tert*-butyl-2,2′-bipyridine) as catalyst and **1c** as CF_3 reagent.[28b] The trapping experiments and theoretical calculations indicated that CF_3 radical is formed in the reaction, which is derived from **1c** probably via several possible pathways including the homolytic cleavage of the S–CF_3 bond of **1c** by visible light, the formation of electron donor-acceptor complexes between **1c** and isocyanides, and the reduction of **1c** by excited state Ir(III)* complexes.

In addition, the intermolecular aryltrifluoromethylation of styrenes using **1c** and visible-light-driven photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ under mild conditions was reported by Masson and co-workers (Scheme 20).[29] This transformation is suitable for the complete regioselective synthesis of a wide range of α-aryl β-trifluoromethyl products (**64**) with good functional group compatibility. The control experiments suggested a radical/cationic process of the reaction.[29] Likewise, the CF_3 radical, derived from **1c** by treatment with $[Ru(bpy)_3]^*[PF_6]_2$ via a single electron transfer process, adds to styrene **62** furnishing the benzylic radical (Scheme 21). The latter oxidized by $[Ru(bpy)_3]^{3+}$, with subsequent Friedel–Crafts-type alkylation, ultimately affords the desired α-(hetero)aryl β-trifluoromethyl adduct **64**. Oxidation of the benzylic radical species by **1c** to regenerate the CF_3 radical (radical chain propagation) is excluded, as the reaction requires continuous irradiation.[29]

and the less thermodynamically stable *Z*-trifluoromethylated alkenes are produced by employing Umemoto's reagent and photocatalyst $Ir(ppy)_3$. The former transformation is via direct C–H trifluoromethylation of styrenes promoted by Ru-catalyzed SET mechanism, while the latter synthesis is by a one-pot Ir-catalyzed tandem SET/TTET (TTET=triplet–triplet energy transfer) process.[30]

The electrochemical behavior of Umemoto's reagent (**1b**, **1c**) and the expanded Yagupolskii-Umemoto-type reagents (**1e**, R=cyclopropyl, phenyl, 2,4-difluorophenyl, 4-methoxyphenyl) was investigated in anhydrous CH_3CN, DMF (*N*,*N*-dimethylformamide), and CH_3OH by Médebielle and co-workers using cyclic voltammetry.[31] The results showed that electrophilic trifluoromethylsulfonium salts can be reduced under electrochemical conditions. In CH_3CN, these reagents are reduced in two steps with the first irreversible reduction occurring at low cathodic potentials between −0.49 and −0.72 V (vs Ag/Ag^+) on a glassy carbon electrode, implying that they are good electron-acceptors. This irreversible reduction is probably caused by the cleavage of the S–CF_3 bond with formation of CF_3 radical.[31] In addition, the Togni's reagent **65b** is the most difficult to reduce at −1.82 V (vs Ag/Ag^+) and the Togni's reagent **65a** reduced at −1.10 V (vs Ag/Ag^+) has therefore an electron-accepting ability positioned in between the sulfonium reagents and **65b**.[31] These valuable data are of great interest for the development of trifluoromethylation reactions under photoredox, electrochemical and other reductive conditions.

By the way, fluorinated methylsulfoxinium tetrafluoroborate (**1f**), a trifluorinated version of a Johnson-type methyl-transfer reagent, was developed by Shibata and co-workers for the purpose of electrophilic trifluoromethylation of *C*-nucleophiles.[5c,32a] The computational studies on the C/O regioselectivity of the reaction of



Scheme 21. The possible radical reaction mechanism for intra- and intermolecular aryltrifluoromethylation of biaryl isocyanide and styrenes.

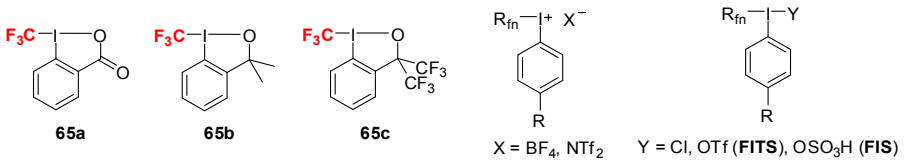
Very recently, Qing and co-workers developed a tunable and chemo-, regio-, and stereoselective photocatalytic trifluoromethylation of styrenes.[30] The thermodynamically stable *E*-trifluoromethylated alkenes are constructed with Togni's reagent in the presence of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ under visible-light irradiation, β-ketoesters with **1f** disclosed that the trifluoromethylation involves a cationic species ($^+CF_3$), which affords *C*-alkylated products. In other cases, monofluoromethylation of β-ketoesters with monofluoromethylsulfoxinium salt possibly contains a radical-like intermediate (such as $\cdot CFH_2$ produced via a SET process), which

yields *O*-alkylated products, and difluoromethylation with difluoromethylsulfoxinium tetrafluoroborate possesses both cationic and radical species that provide a mixture of *C*- and *O*-isomers.[5c,32b]

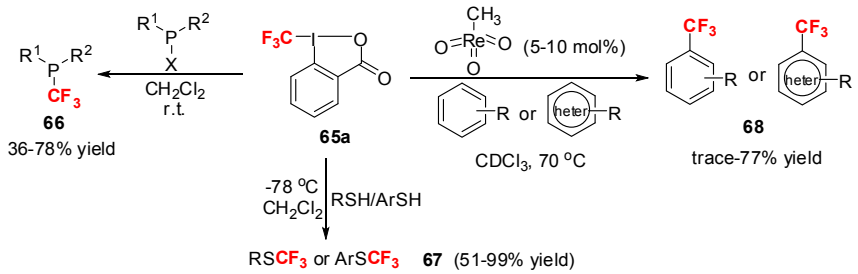
To date, various transition-metal-mediated and visible-light/photoredox-catalyzed trifluoromethylation reactions with Umemoto's reagents and their analogs have been reported. Although the possible reductive reaction mechanisms have been carefully studied by control experiments, the whole processes of the mechanisms remain unclear and more details are still necessary for better insights into these transformations.

3. Reductive trifluoromethylation reactions with Togni's reagents

Togni's reagents represent some of the most important electrophilic '$^{+}CF_3$' reagents (Scheme 22), which, first reported by Togni and co-workers in 2006,[33] have been widely utilized as the CF_3 radical precursors for the reductive bi-functional trifluoromethylations of alkenes in the presence of certain reductants.[5a,d,e,11b,12b] Before Togni's reagents, to our knowledge, there were no stable I(III)-trifluoromethylated hypervalent iodine compounds that are suitable for CF_3 transfer reactions. Umemoto and co-workers once attempted to prepare an acylic hypervalent I(III)-trifluoromethylated structure by following their general procedure to **FITS** and **FIS** reagents (Scheme 22).[11a,33] However, the desired product was not obtained due to the lack of stability of the starting material and presumably of the target molecule under the reaction conditions.[11a,33] Gratefully, Yagupolskii and Umemoto investigated the electrophilic reactions of acylic arylperfluoroalkyliodonium(III) reagents with nucleophiles such as alkenes, enolates or enol ethers, alkynes, arenes, Grignard reagents, thiophenolates, nitrite, and thiocyanate.[11c,d,f–h] The results indicated that perfluoroalkylations with '$^{+}R_{fn}$' sources ($R_{fn} \neq CF_3$) proceed through cationic mechanisms and/or radical pathways, which are greatly dependent upon the nature of substrates and the solvents. These works have offered significant reference to the exploration of Togni's reagents in the past several years.



Scheme 22. Togni's reagents, the most important electrophilic '$^{+}CF_3$' reagents.



Scheme 23. Examples of using Togni's reagents as CF_3 radical precursors towards nucleophiles.

At the beginning, Togni's reagents were limited to the reactions with carbonyl compounds such as β-ketoesters and α-nitro esters, and some types of sulfur-, phosphorus and oxygen-centered nucleophiles.[11b] In the last few years, in particular during the last four to five years, the reactions of Togni's reagents with arenes, alkenes and alkynes have been extensively investigated.[5a,d,e,11b,12b] These reagents have attracted great attention of numerous research groups worldwide, which are most prominently active in area of organofluorine chemistry and homogeneous catalysis to the development of new synthetic methods.[5a]

3.1. Reductive trifluoromethylation reactions with Togni's reagents in the presence of nucleophiles and reductive inorganic additives

Togni's reagents were generally thought as the pure electrophilic $^{+}CF_3$ sources at the early stage in the reactions with carbon- and oxygen-centered nucleophiles. In some cases, however, they were CF_3 radical precursors (Scheme 23 and **24**).[5a,11b] For instance, the reaction of **65a** or **65b** with primary and secondary phosphines gave secondary and tertiary CF_3—P(III) compounds (**66**) in good yields, which was assumed to proceed via a CF_3-radical process (Scheme 23).[34] This claim is based upon the observation that the reaction of Cy_2PH (Cy=cyclohexyl) with **65b** provided $CyP(CF_3)_2$ and $CyP(CF_3)H$ together with $Cy_2P(CF_3)$, indicating a homolytic cleavage of the C—P bond of P-Cy, instead of the P—H bond cleavage, after attack of Cy_2PH by the CF_3 radical. In addition, treatment of aromatic and aliphatic mercaptans with **65a** or **65b** provided the corresponding trifluoromethylated products (**67**) in moderate to excellent yields (Scheme 23).[35] The byproducts of the reaction, disulfide and CF_3H, hint toward a radical-based mechanism. Nitrone spin trapping experiment followed by EPR detection also confirms the hypothesis. It appears that **65a** or **65b** is readily reduced by the nucleophilic substrates to form a CF_3 radical and the corresponding $[NuH]^{\bullet+}$ (**69**) (Scheme 24).[5a] After recombination, the highly acidic intermediate **70** is produced, which ultimately affords the desired product (**71**).

The direct trifluoromethylation of both activated and inactivated arenes and heteroarenes using hypervalent iodine(III) trifluoromethylating reagent (**65a**) and 5—10 mol % of methyltrioxorhenium (MTO) catalyst was disclosed by Togni and co-workers (Scheme 23).[36] This reaction showed a broad substrate scope, despite the low yields of the products (**68**) bearing electron-withdrawing substituents. A radical chain mechanism is proposed for the transformation (Scheme 25).[36] In the first stage of the reaction, **65a** is coordinated by MTO, making the hypervalent iodine reagent more electrophilic and thus promoting the single electron

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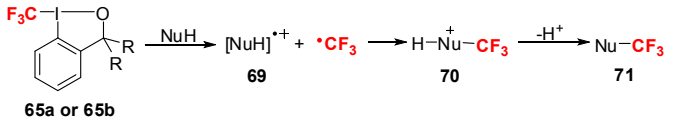
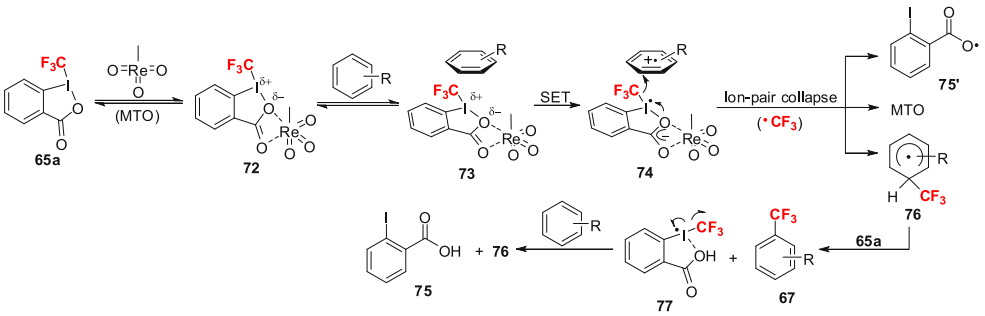


Scheme 24. The proposed SET process for the reaction of Togni's reagents with nucleophiles.

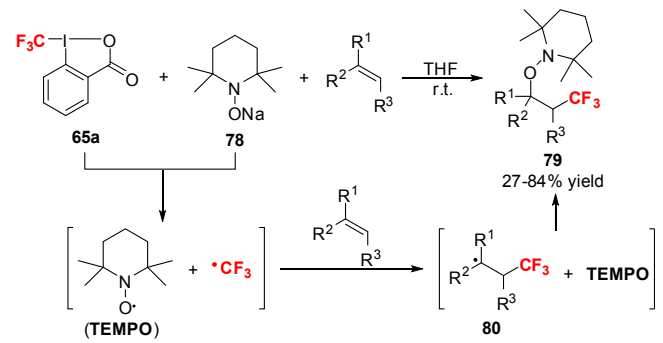
the reductive radical initiator. Unlike the direct arene trifluoromethylation occurring at an intact arene ring, this method comprises a trifluoromethylation with concomitant arene formation. Later, the preparation of 2-trifluoromethylindoles (**84**, **85**) from readily available isonitriles **83** and **65a** in the presence of Bu_4NI was accomplished by the same research group (Scheme



Scheme 25. A plausible radical chain mechanism for the trifluoromethylation reaction of arenes and heteroarenes with **65a** in the presence of catalytic amounts of MTO.

transfer from arene. This generates an aromatic cation radical species (**74**) antiferromagnetically coupled with the reduced Togni's reagent, which is subsequently converted to a CF_3-aromatic radical intermediate (**76**) via ion-pair collapse.[36] The propagation step starts with the slow deprotonation of **76**, probably by **65a**, providing **67** and the reactive **77**; the latter transfers a $•CF_3$ unit to the substrate again affording **76**. The termination step would be the decomposition of **76** after consumption of **65a**.

The radical trifluoromethylation of alkenes with **65a** in the presence of TEMPONa (**78**) was explored by Studer and co-workers (Scheme 26).[37] TEMPONa is a useful SET reagent for the production of CF_3 radical from **65a**. It acts as a mild organic reducing reagent for the generation of *C*-radicals along with formation of the TEMPO radical (2,2,6,6-tetramethylpiperidine-1-oxyl), which then works as an oxidant to trap the *C*-radicals.[37] The in situ generation of TEMPO ensures its low concentration during the reaction, which is the key for the success of the CF_3 radical addition and TEMPO-trapping reactions. The TEMPONa-initiated trifluoromethylation is easy to conduct, occurs under mild conditions, and shows a broad substrate scope.[37] The product (**79**) can be reduced under mild conditions to give the corresponding β-trifluoromethylated secondary alcohols. This method is also applicable to the pentafluoroethylation of alkenes.



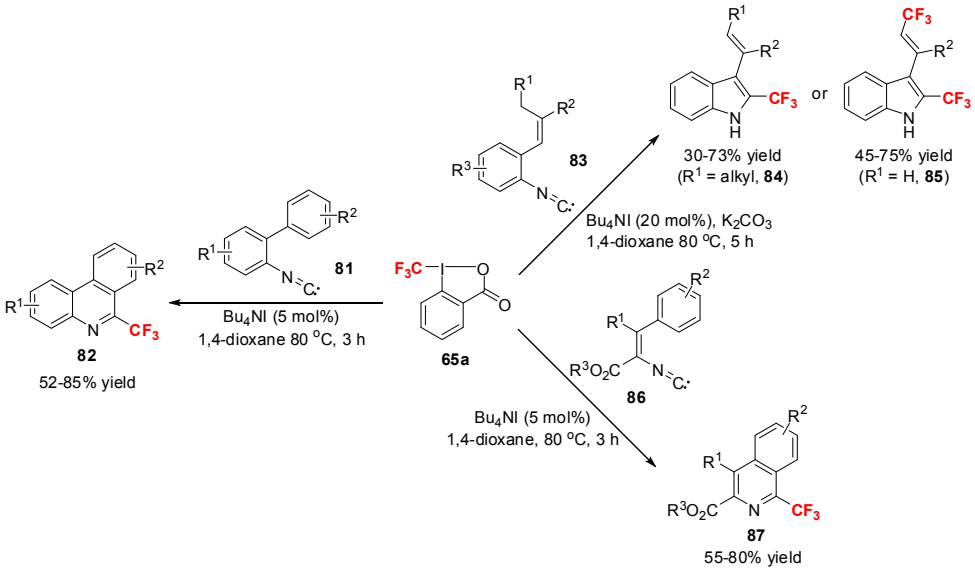
Scheme 26. TEMPONa-mediated radical trifluoromethylation of alkenes with **65a**.

The iodide-initiated radical reaction of **65a** with isonitriles **81** to the synthesis of 6-trifluoromethylated phenanthridines (**82**) was reported by Studer and co-workers (Scheme 27).[38] The reaction employs Togni's reagent as the CF_3 radical precursor and Bu_4NI as

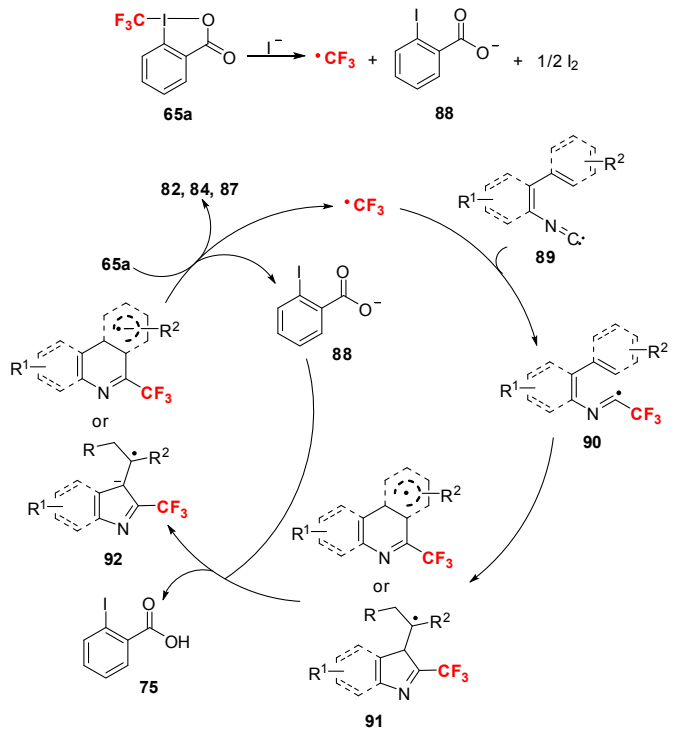
27).[39] In contrast to the direct indole trifluoromethylations at an intact indole ring, the present process consists of a trifluoromethylation with concomitant indole framework and C=C bond formation. Mono- or bistrifluoromethylated products are obtained dependent upon the substituents of the alkene acceptors. In addition, a simple approach to biologically important 1-trifluoromethylated isoquinolines (**87**) starting with β-aryl-α-isocyano-acrylates (**86**) and commercially available Togni's reagent was described recently (Scheme 27).[40] All these transformations occur in the absence of transition metal and afford products in moderate to good yields.

The reaction mechanism of the phenanthridine formation is presumed (Scheme 28).[38–40] In the initiation step, the iodide reacts with **65a** to give 2-iodobenzoate (**88**), the CF_3 radical, and iodine via a single electron transfer (SET). The addition of CF_3 radical to isonitrile functionality in **89** generates imidoyl radical (**90**), which cyclizes to arene or alkene giving the radical intermediate **91**. Then **91** is deprotonated by **88** to produce the radical anion **92**, which further reacts with **65a** through a single electron transfer to form $•CF_3$ and phenanthridine **82**, **84** or **87**, thereby sustaining the radical chain reaction. **92** can also react with I_2 (from the initiation step) to provide iodide and **82**, **84** or **87**. This allows the regeneration of the initiator (iodide). However, because of the low concentration of I_2 compared to **65a**, this process is likely a minor reaction pathway. The mechanism for the formation of CF_3 radical can be further supported by the fact that in the presence of TEMPO radical, the reaction affords TEMPO-CF_3 rather than phenanthridines.

On the other hand, Nevado and co-workers reported an iodide-induced metal-free non-radical aryltrifluoromethylation of alkenes with **65a**.[41a] They assumed that **65a** reacting with iodide forms an iodonium complex rather than the CF_3 radical, which is in line with the species determined by HRMS-ESI and NMR spectroscopies.[41a] Moreover, the reactions of methacryloyl benzamide in the presence of BHT (di-*tert*-butylated hydroxytoluene) and TEMPO gave the desired products in yields comparable to those obtained under the standard conditions, and, notably, no TEMPO-CF_3 adducts was detected. These results indicate a non-radical mechanism for the reaction, which is in contrast to the radical trifluoromethylation of isonitriles developed by Studer under similar conditions.[38–40] Very recently, Tan and Liu disclosed a direct C–H β-trifluoromethylation of α,β-unsaturated carbonyl compounds under iodide-induced metal-free conditions, where they also suggested an ionic reaction mechanism, which is similar to that described by Nevado.[41b] In addition to the ionic process, they announced that an alternative



Scheme 27. Iodide-initiated radical trifluoromethylation of isonitriles with **65a** as the CF_3 source.



Scheme 28. The proposed radical mechanism for iodide-initiated phenanthridine formation.

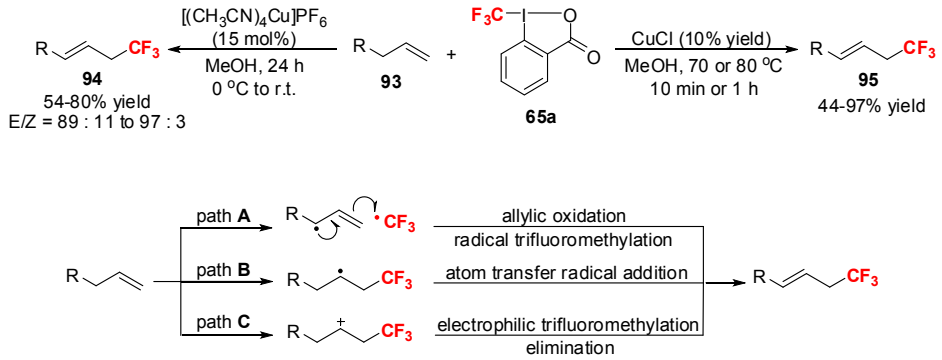
mechanism involving the CF_3 radical cannot be ruled out. Nevertheless, no supportive evidences are given in their experimental section. Thus, more mechanistic studies on these reactions are indispensable in the near future.

3.2. Metal-mediated/catalyzed reductive trifluoromethylation reactions with Togni's reagents

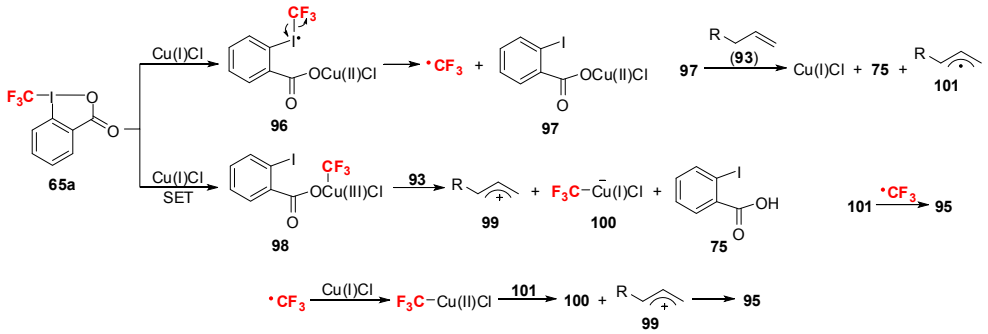
The copper-catalyzed reductive trifluoromethylation of unactivated olefins using **65a** as the CF_3 reagent were developed independently by Buchwald and Wang (Scheme 29).[42] These reactions supply general and straightforward ways to construct allylic trifluoromethylated compounds under mild conditions with a wide range of functional group tolerance. The hypervalent iodine(III) reagent (**65a**) is employed as both the oxidant and the CF_3 source in the reactions. Buchwald and co-workers hypothesized that the reactions might involve an allylic oxidation with subsequent radical trifluoromethylation (path A, Scheme 29), an atom transfer radical addition by a $^{\bullet}CF_3$ species (path B, Scheme 29), or an electrophilic trifluoromethylation via a cationic intermediate (path C, Scheme 29).[42a] Their preliminary results indicated that the reaction mechanism is complex and multiple path-ways to the allyl-CF_3 products may be operating.

On the other hand, Wang and co-workers envisioned that the CF_3 radical is likely the reactive species in the transformation (Scheme 30).[42b] This is supported by the truth that, when TEMPO was added into the standard reaction, the trifluoromethylation was totally shut down and TEMPO-CF_3 adduct was formed (79% yield) without producing allyl-TEMPO (determined by GC–MS and ^{19}F NMR spectroscopy). Based on these, the possible mechanistic pathways are outlined (Scheme 30).[42b] Initially, Cu(I)Cl reduces **65a** to form **96**, which decomposes to produce **97** with simultaneous release of a CF_3 radical. Then alkene (**93**) undergoes copper-assisted single-electron-transfer (SET) oxidation with **97** generating the allyl radical (**101**), which can be further oxidized by CF_3–Cu(II)Cl to afford **99** and **100**. It is also possible that Cu(I)Cl is directly oxidized by **65a** to form Cu(III) species **98**, which oxidizes **93** to produce **99** and **100**. Subsequently, **99** is attacked by nucleophilic Cu-(I)CF_3 species (**100**), affording the final product **95**. However, the radical process involving the coupling of **101** and the CF_3 radical cannot be ruled out.[42b]

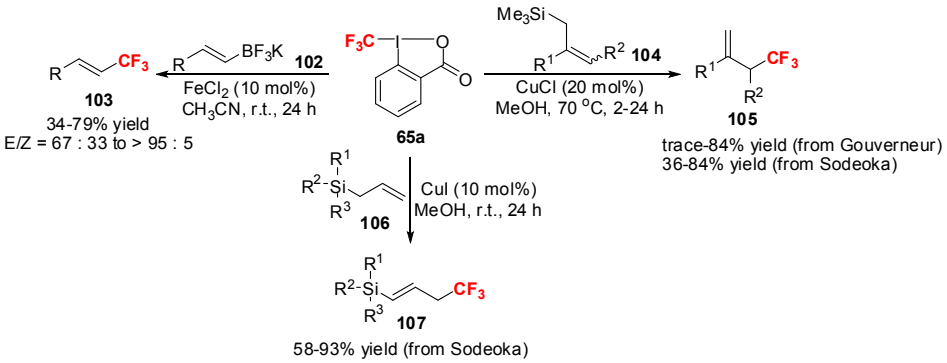
Later, Buchwald and co-workers reported an Fe(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates (**102**) (Scheme 31).[43a] The reaction is amenable to a bench top set-up and proceeds under exceedingly mild conditions. Preliminary analyses suggest the reaction runs through a carbocationic intermediate by Lewis acid catalysis, but the radical-type mechanism including CF_3 radical cannot be ruled out (Scheme 32). Then Gouverneur and co-workers disclosed a Cu(I)-catalyzed allylic trifluoromethylation of allylsilanes (**104**), which furnished various branched cyclic and acyclic allylic-CF_3 products including compounds featuring Csp^3-CF_3 stereogenicity (Scheme 31).[43b] Further investigation reveals that the mechanism of the reaction is complex and may comprise



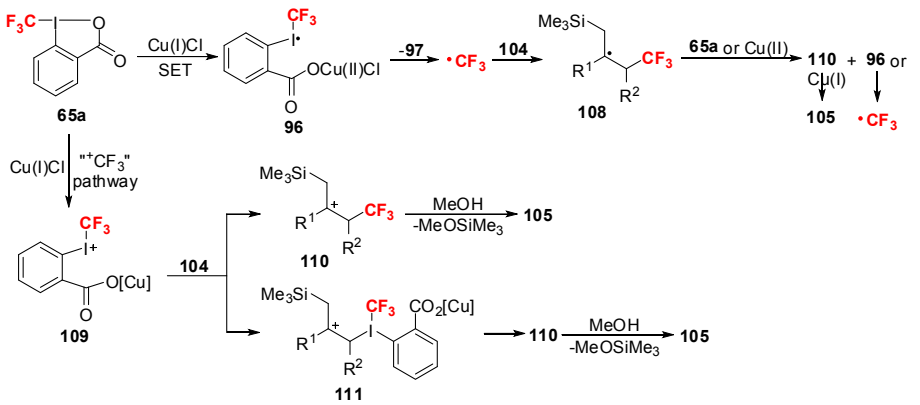
Scheme 29. Cu-catalyzed reductive trifluoromethylation of olefins with **65a** and the possible mechanistic pathways.



Scheme 30. The CF_3-radical-based process envisioned by Wang for the Cu-catalyzed reaction of alkenes with **65a**.



Scheme 31. Fe(II)- and Cu(I)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates and allylsilanes by **65a**.



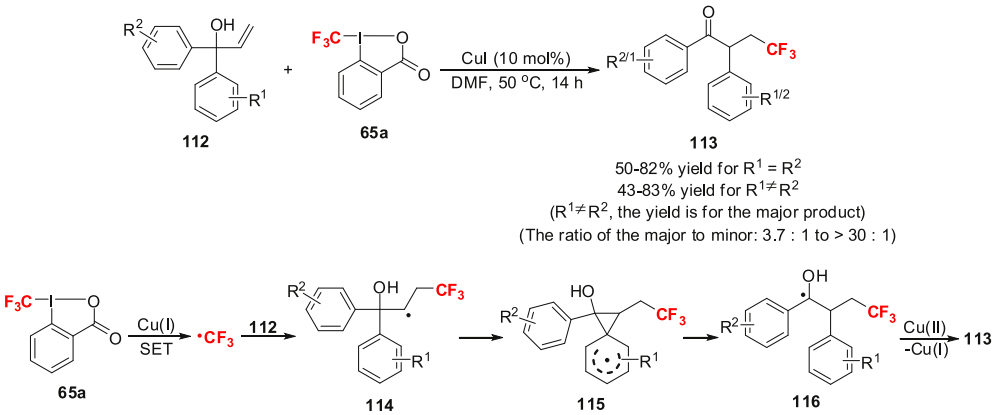
Scheme 32. The proposed pathways involving CF_3 radical and/or cationic intermediates in Fe(II)- and Cu(I)-catalyzed reactions.

multiple pathways involving CF_3 radical and/or cationic intermediates (**109**); the CF_3 radical is derived from **65a** via a single electron transfer process, as well (Scheme 32). Similar reaction was also harnessed by Sodeoka and co-workers (earlier than Gouverneur's report).[43c] They discovered that when 2-substituted allylsilanes (**104**) was treated with CuI (10 mol%) and **65a**, the desilylated products (**105**) bearing a CF_3 group at the allylic position were obtained (Scheme 31). In the case of non-substituted allylsilanes (**106**), however, the CF_3-vinyl silane derivatives (**107**) were produced. In the end, the authors speculated that the transformations involve cationic intermediates (Scheme 32), such as **98** (Scheme 30) and **109**; the former is probably generated by the redox reaction of copper catalyst with **65a**.

The Cu(I)-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration in α,α-diaryl allylic alcohols was explored by Li and Wu (Scheme 33).[44] Various β-trifluoromethyl α-aryl ketones are readily prepared under mild conditions. Notably, the aryl groups bearing more electron-deficient substitutions at *meta*- or *para*-position migrate preferentially over those with relatively electron-rich ones. And *ortho*-substituted aryl groups are reluctant to migrate. The experimental results, in combination with the DFT calculations, indicate that this rearrangement occurs through a radical 1,2-aryl migration, which is initiated by the addition of CF_3 radical to alkene. The CF_3 radical is presumably derived from the reduction of **65a** by CuI via a SET process under the reaction conditions.[44]

preliminary studies that TEMPO inhibits the addition of **65a** to C–C multiple bonds and that only *trans*-addition of **65a** across the triple bond of alkynes is observed. Later, the Cu(I)-catalyzed trifluoromethylation of alkenes using **65a** as the CF_3 reagent in the presence of DBU (2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine) was described (Scheme 34).[45b] The reaction provides a versatile approach for the construction of Cvinyl-CF_3 bonds (**119**) without using prefunctionalized substrates. The pathway involving CF_3 radical and the related species, analogous to the previous reports,[42] is postulated for the transformation, since the desired trifluoromethylation was completely suppressed when TEMPO, the well-known radical scavenger, was added into the reaction of 4-vinylbiphenyl with **65a** in the presence of $[(MeCN)_4Cu]PF_6$.[45b]

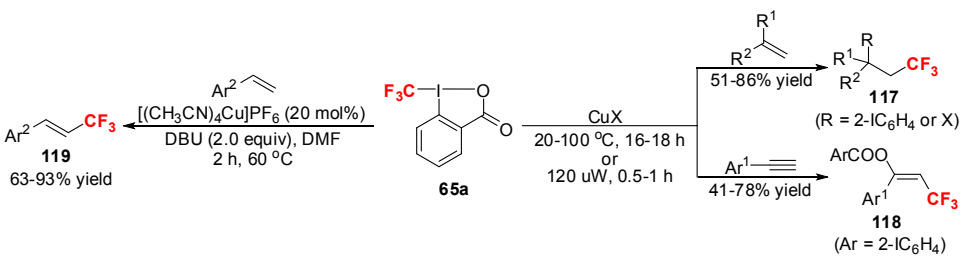
The copper(I)-catalyzed, regioselective C–H α-trifluoro methylation of α,β-unsaturated carbonyl compounds using **65a** as the CF_3 source was developed by Bi and co-workers (Scheme 35).[46a] Substrates like enones as well as α,β-unsaturated esters, thioesters, and amides are stereospecifically converted to the corresponding (*E*)-α-trifluoromethylated products (**120**) in moderate to high yields. The reaction can also be applied to the C–H trifluoromethylation of drugs. Shortly after, the Cu(I)-catalyzed direct β-trifluoromethylation of α,β-unsaturated aldehyde *N,N*-dibenzylhydrazones with **65a** was reported by Monteiro and Bouyssi (Scheme 35).[46b] The reaction constructs the stereodefined CF_3-alkenyl derivatives (**121**, **122**) in good yields under mild conditions.



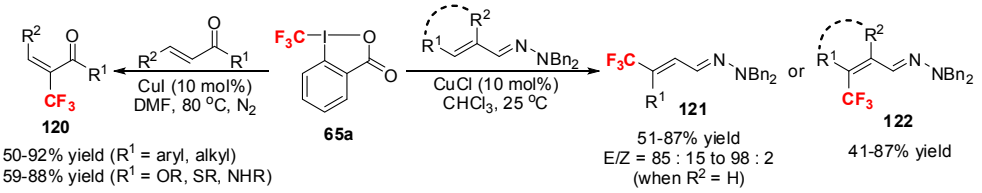
Scheme 33. Cu(I)-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration of α,α-diaryl allylic alcohols with **65a**.

The regio- and stereoselective Cu(I)-catalyzed reductive addition of the hypervalent iodine(III) reagent **65a** to alkynes and alkenes was investigated (Scheme 34).[45a] The reaction favorably performs the trifluoromethyl-benzoyloxylation and trifluoro methyl-halogenation of alkenes and alkynes (**117** and **118**), especially the substrates with electron-donating substituents, in the presence of CuI. Alkenes are transformed faster than alkynes under identical reaction conditions. It is hypothesized that the reaction happens via a radical process similar to that suggested in the allylic C–H trifluoromethylation with **65a**. This can be supported by the

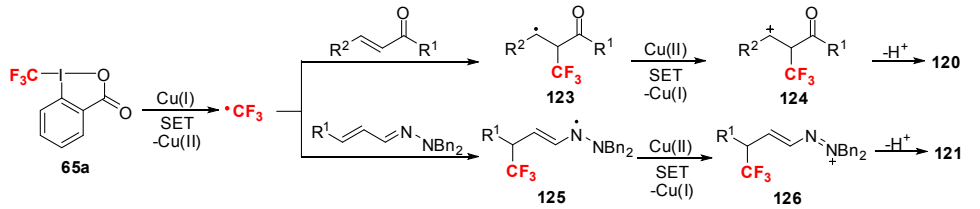
The deuterium labeling studies[46a] and the radical trapping experiments[46a,b] clearly indicate that these reactions proceed via a radical mechanism (Scheme 36). The reactions begin with the reduction of **65a** by Cu(I) via a single electron transfer (SET) to generate the CF_3 radical and a Cu(II) species. Reaction of the CF_3 radical and the α,β-unsaturated carbonyl substrates produces the trifluoromethylated radical intermediates (**123**, **125**). Then another SET process affords the cationic intermediates (**124**, **126**) and regenerate the active Cu(I) catalyst. Finally, H-elimination of **124** (or **126**) gives the desired products (**120** or **121**).[46]



Scheme 34. Cu(I)-catalyzed reductive addition of **65a** to alkynes and alkenes, and the trifluoromethylation of styrenes in the presence of DBU.



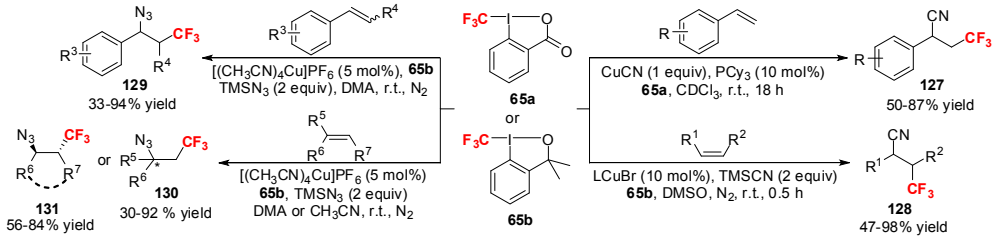
Scheme 35. Cu(I)-catalyzed α- and β-trifluoromethylation of α,β-unsaturated carbonyl derivatives using **65a** as the CF_3 reagent.



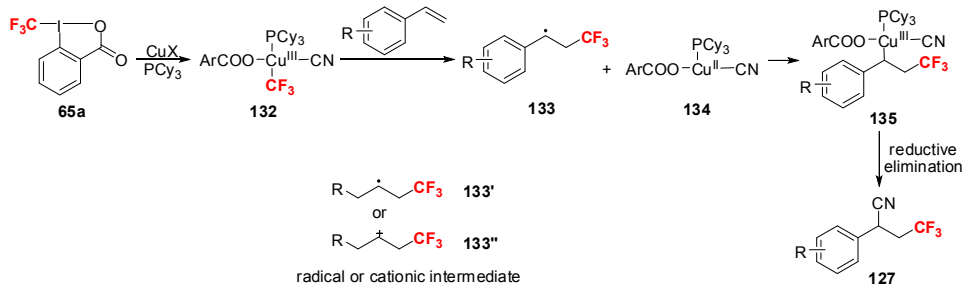
Scheme 36. The plausible mechanisms for Cu(I)-catalyzed α- and β-trifluoromethylation of α,β-unsaturated carbonyl derivatives with **65a**.

The reductive cyanotrifluoromethylation of various styrene derivatives with **65a** and equal equivalent of CuCN was disclosed by Szabó and co-workers (Scheme 37).[47a] The reaction is suitable for the bifunctionalization of styrenes with high regioselectivity at late stage in the presence of bulky phosphines or B_2pin_2 (bis(pinacolato)diboron) additives under mild conditions. It is interesting that, using *para*-methoxy substituted styrene as the substrate, the reaction affords the oxytrifluoromethylation product rather than the cyanotrifluoromethylation product. Furthermore, the Cu(I)-catalyzed intermolecular cyanotrifluoromethylation of alkenes with less reactive **65b** as the CF_3 source and TMSCN as the cyano source was discussed by Liu and co-workers (Scheme 37).[47b] Both activated and unactivated alkenes are available for the transformation, showing good functional group tolerance. The reaction affords a convenient way to trifluoromethylated nitriles for medicinal chemistry. Similarly, the Cu(I)-catalyzed intermolecular trifluoromethylazidation of alkenes with **65b** as oxidant and CF_3 source was developed (Scheme 37).[47c] The resultant CF_3-containing organoazides can be easily converted into the corresponding amine derivatives, which provides an efficient method to synthesize trifluoromethyl amino acids.

The exact reaction mechanism of the cyanotrifluoromethylation is not clear. However, the outcome of the control experiments hints a plausible radical pathway shown in Scheme 38.[47a] The initial steps of the reaction are assumed to be identical to those of the previously reported Cu-catalyzed oxytrifluoromethylation reactions[48] and the closely related allylic/vinylic C–H activation reactions[42,45] by using **65a** as the CF_3 source. Thus, in these cases, **65a** undergoes oxidative addition to CuCN to generate **132**, in which the Cu–CF_3 bond is homolytically cleaved to give the CF_3 radical and Cu(II) complex (**134**) in a doublet electronic state. The PCy_3 ligand may facilitate this process by increasing the electron density on Cu. The CF_3 radical then adds to the C=C bond of styrenes to give radical **133**. Recombination of **133** with **134** affords complex **135**. The unique electrosteric nature of the ligand and the substituents on styrenes in **135** finally determines the type and geometry of the product.[47a] Unlike the pathway in Scheme 38, the mechanistic process in Liu's reports suggests that Togni reagent **65b** is activated by TMS group and Cu(I) to give a CF_3 radical. Then •CF_3 reacting with alkene affords the carbon radical (**133′**) or carbon cation intermediate (**133″**), which is trapped by TMSCN or $TMSN_3$ to yield the final products.[47b,c]



Scheme 37. Cu-mediated reductive trifluoromethyl difuctionalization of styrene derivatives with **65a** and nucleophiles.

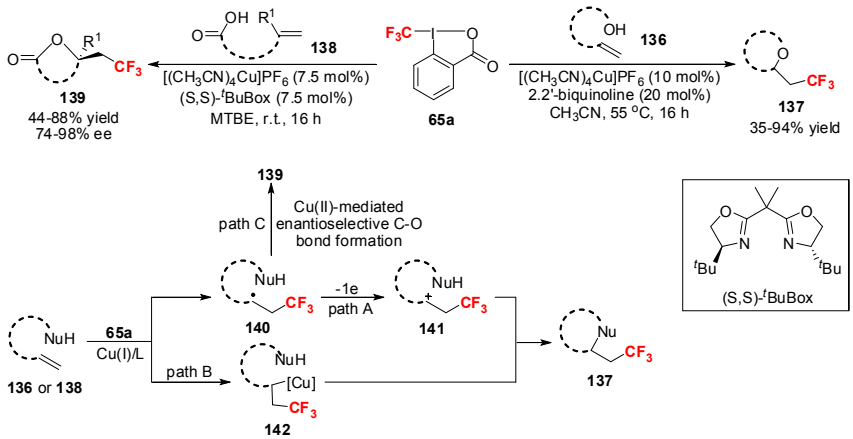


Scheme 38. The proposed reaction mechanism for Cu-mediated cyanotrifluoromethylation.

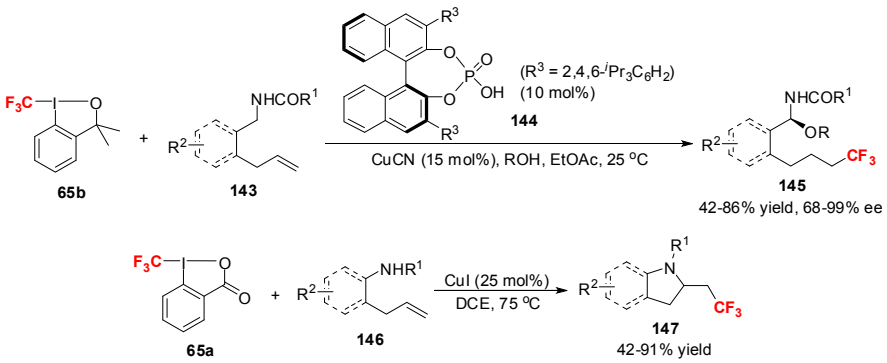
In addition, Buchwald and co-worker developed a mild and efficient intramolecular radical/ionic oxytrifluoromethylation of unactivated alkenes based on a **65a**/Cu(I)/2,2′-biquinoline system (Scheme 39).[48a] The reaction is appropriate for diverse nucleophiles, such as carboxylic acids, alcohols, and phenols, and is compatible with a range of functional groups including amides, β-lactones, epoxides, and aryl bromides, allowing for a rapid access to a variety of synthetically useful building blocks, such as CF_3-containing lactones, cyclic ethers, and epoxides, from simple starting materials. Interestingly, the reaction can be completely inhibited by the addition of TEMPO. While the mechanistic details of the reaction remain unclear, the use of a Cu(I)/pyridine-based bidentate ligand system and the outcome of the inhibition experiment are suggestive of an atom transfer-type CF_3 radical addition pathway (path A, Scheme 39).[42a,48a] Later, the same research group reported an enantioselective oxytrifluoromethylation of alkenes using a **65a**/Cu(I)/(*S*,*S*)-^{t}BuBox system, which delivers a set of enantioenriched CF_3-containing lactones with good functional-group compatibility (Scheme 39).[48b] Evidences from the reactions with the cyclopropane radical clock, the diallyl malonate, and the radical scavenger TEMPO support a redox radical addition mechanism.[48b] It seems that a single-electron transfer between **65a** and the Cu(I) catalyst generates a CF_3 radical and a Cu(II) complex. The CF_3 radical then adds to alkene giving the radical intermediate **139**, which undergoes Cu(II)-catalyzed enantioselective C–O bond formation to afford the lactone product and regenerate the Cu(I) catalyst (path C, Scheme 39). This novel enantioselective C–O bond construction can potentially be applied to a range of metal-catalyzed radical difunctionalization reactions.[48b]

The asymmetric alkene/C–H bond difunctionalization reaction for the concomitant construction of C–CF_3 and C–O bonds was realized by using a **65b**/Cu(I)/Brønsted acid cooperative system, which provides a facile access to valuable chiral CF_3-containing *N*,*O*-aminals (**145**) with excellent regio-, chemo-, and enantioselectivity (Scheme 40).[49a] The control experiments suggest that chiral Brønsted acid not only determines the stereoselectivity but also increases the reaction rate through activation of **65b**. Further mechanistic studies reveal that this reaction may proceed through an unprecedented 1,5-hydride shift involving activation of alkenes and a radical trifluoromethylation to initiate subsequent enantioselective functionalization of the C–H bonds. In addition, the mild and step-economical ligand-free intramolecular aminotrifluoromethylation of unactivated alkenes with a variety of nitrogen-based nucleophiles (**146**) in the presence of **65a** and a simple copper catalyst was described (Scheme 40).[49b] Nucleophiles, such as basic primary aliphatic and aromatic amines, sulfonamides, carbamates, and ureas, can be employed in this aminotrifluoromethylation reaction, which allows for a straightforward access to diversely substituted CF_3-containing pyrrolidines or indolines (**147**), in good to excellent yields, through a direct radical/ionic difunctionalization strategy from the respective acyclic starting materials.

The plausible mechanistic processes for these transformations are proposed (Scheme 41).[49] First, the reaction of **65a** or **65b** with Cu(I) generates the CF_3 radical, via a single electron transfer, which adds to alkenes to afford the α-CF_3-alkyl radical intermediates (**148**, **151**). Second, **148** abstracts a proximal hydrogen atom adjacent to the nitrogen atom of the amide to generate **149**, which is further



Scheme 39. Cu(I)-catalyzed intramolecular radical/ionic oxytrifluoromethylation of alkenes by using **65a** as the CF_3 reagent.



Scheme 40. Cu-catalyzed trifluoromethylative bifunctionalization of alkenes with Togni's reagents.

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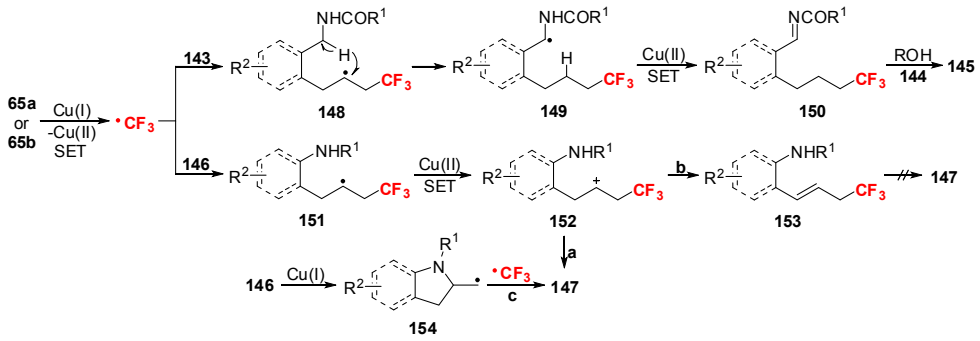


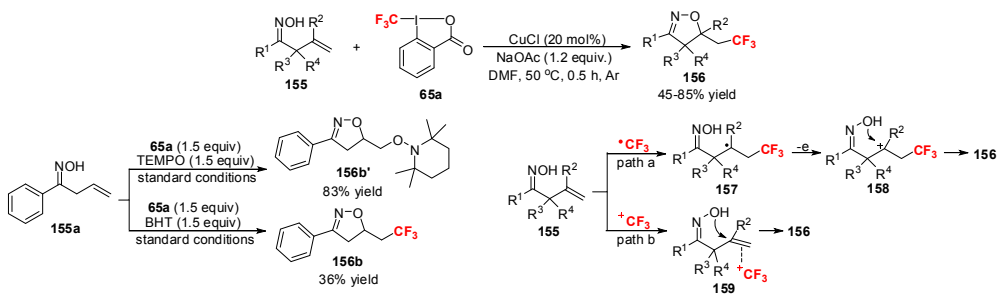
Scheme 41. The plausible pathways for Cu-catalyzed trifluoromethylative bifunctionalization of **143** and **146** with Togni's reagents.

oxidized by Cu(II) to afford **150**. Finally, the attack of an alcohol nucleophile on **150**, catalyzed by chiral Brønsted acids, furnishes the final product (**145**) with excellent enantioselectivity. In other case, the radical intermediate **151** is oxidized to cation **152**, which is trapped by the nitrogen nucleophile, leading to the desired product **147**. Because no cyclization reaction of **153** (R^1=Ts, R^2=H) in the presence of CuI (25 mol%) under the standard conditions occurs, a mechanism that involves copper-catalyzed intramolecular hydroamination of **153** to give the final product can be excluded. An alternative catalytic mechanism, that is, the formation of a primary carbon radical (**154**), through an aminocupration followed by homolysis of the C–Cu bond, and subsequent coupling of this intermediate and a CF_3 radical, cannot be ruled out. The exact mechanism for the aminotrifluoromethylation reaction remains unclear at present and deserves further studies.

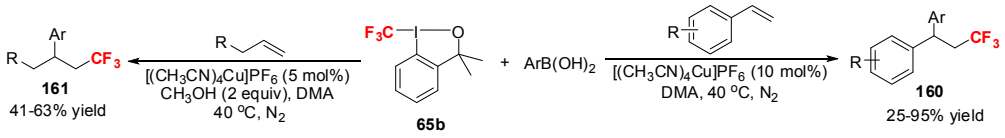
The Cu(I)-catalyzed trifluoromethylation reaction, which involves the cyclization of oximes to construct a C–CF_3 bond and a C–O bond in one step with **65a** was developed by Liang and co-workers (Scheme 42).[50] This reaction afforded a convenient and straightforward method to prepare a variety of useful trifluoromethyl-substituted isoxazolines (**156**). To gain some mechanistic insights into the transformation, inhibition experiments were conducted. When TEMPO radical was added to the reaction mixture, the trifluoromethylation reaction was completely inhibited, and, instead, the TEMPO-trapped 4,5-dihydroisoxazole **156b′** was obtained in 83% yield. However, when BHT was added to the standard conditions, surprisingly, the desired product was obtained in a low yield (36%), and the BHT-CF_3 adduct was detected by GC–MS. These experimental results provide evidence that the reaction mechanism might involve both the CF_3 radical and the CF_3 cation. Thus, two plausible mechanisms for the transformation are proposed (Scheme 42).[50] In path A, a single-electron oxidation occurs between copper catalyst and Togni's reagent, resulting in the formation of a radical intermediate (**157**), which could be further trapped by the oxygen atom to generate the cyclization product. In path B, the reaction of Cu(I) with Togni's reagent would provide $^+CF_3$, then the alkene is activated by $^+CF_3$ (**159**), and the oxygen atom of oxime attacks the activated alkene to give 4,5-dihydroisoxazole.

Moreover, the Cu(I)-catalyzed intermolecular trifluoromethylarylation of alkenes was developed under mild conditions by using less active **65b** as the CF_3 source (Scheme 43).[51] Various alkenes and diverse arylboronic acids are suitable substrates in the reaction. Preliminary mechanistic studies indicate that a mutual activation between arylboronic acid and **65b** is essential at the early stage of the transformation. The addition of TEMPO radical can significantly inhibit the trifluoro methylarylation. Both the reactions of *Z*- and *E*-isomers of alkene under standard conditions afford the product with the same diastereoselectivity. These results suggest a CF_3 radical involved in the reaction, and a benzyl radical species (**164**) generated through the addition of CF_3 radical to alkenes. A plausible pathway consisting of a $•CF_3$ and an ArCu(II) species is proposed (Scheme 44). First, the reaction of activated **162** with Cu(I) catalyst generates a CF_3 radical, a new activated arylboronic acid (**163**), and a Cu(II) intermediate; the latter two undergo transmetalation to give a ArCu(II) species. Then ArCu(II) is oxidized by benzyl radical **164** to yield a Cu(III) species **165**, which delivers the final product (**160**) through reductive elimination (path a, Scheme 44). Another possible mechanism comprises an initial transmetalation, which gives ArCu(I) and **166**. Subsequent redox reaction between ArCu(I) and **166** affords ArCu(II) with release of CF_3 radical (path b, Scheme 44). However, the competing experiments show no significant difference in reaction rate for electron-poor arylboronic acids and electron-rich arylboronic acids; this result is more consistent with path a and against path b, since the latter path should favor the electron-rich substrates.[51] Besides, paths c and d in Scheme 44 are less likely because they are opposite the results from the dynamic experiments with both electron-poor and electron-rich arylboronic acids.[51]

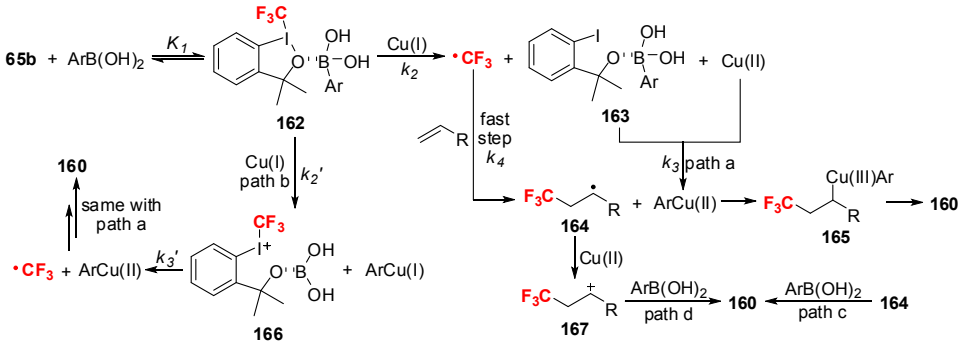
The Cu(I)-catalyzed one-pot trifluoromethylation/aryl migration/desulfonylation/sp^2C–N bond formation of conjugated tosyl amides with **65a** was disclosed by Nevado and co-workers (Scheme 45).[52] The reaction regioselectively furnishes



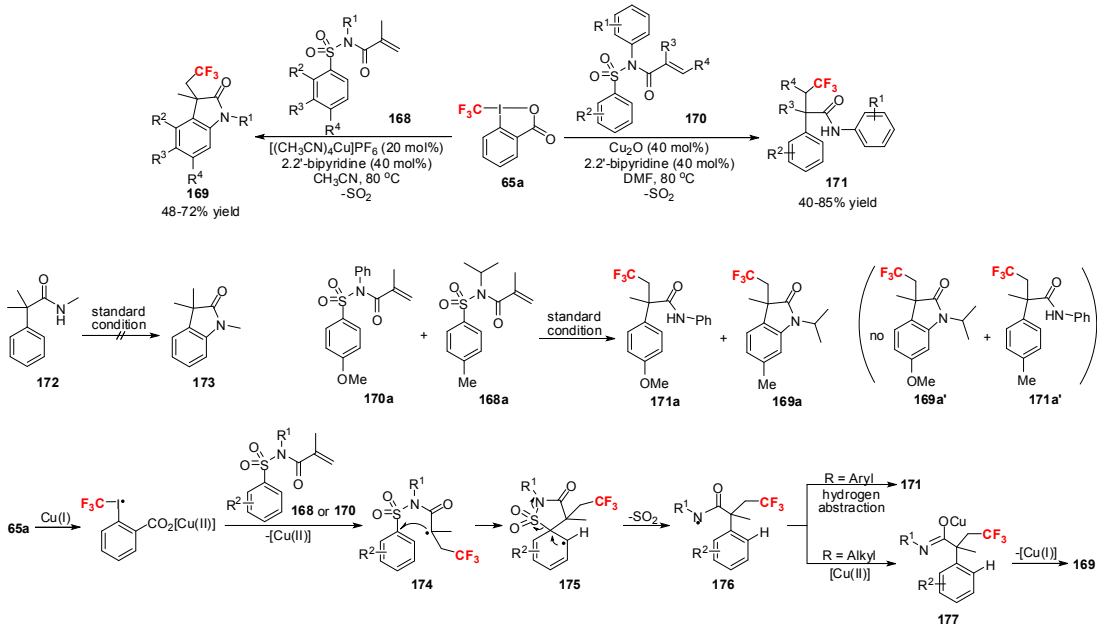
Scheme 42. Copper-catalyzed synthesis of trifluoromethyl-substituted isoxazolines with **65a**.



Scheme 43. Cu(I)-catalyzed intermolecular trifluoromethylarylation of alkenes with **65b**.



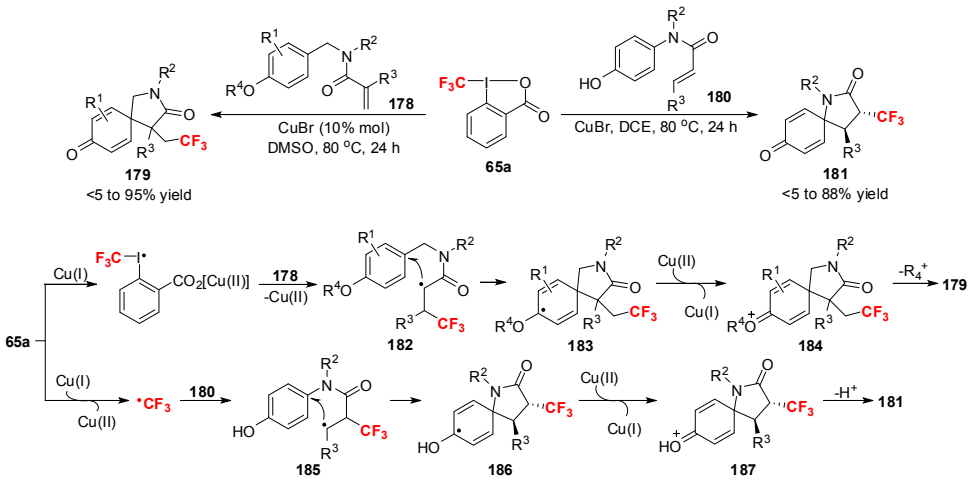
Scheme 44. A plausible mechanism for Cu(I)-catalyzed trifluoromethylarylation involving CF_3 radical and ArCu(II) species.



Scheme 45. Cu(I)-catalyzed one-pot trifluoromethylative transformation of conjugated tosyl amides with **65a** and the possible reaction mechanisms.

trifluoromethylated oxindoles (**169**) or α-aryl-β-trifluoromethyl amides bearing quaternary stereocenters (**171**) in good yields. The results from control experiments in the presence of BHT and TEMPO point toward a radical reaction mechanism. Employing amide **172** as substrate under standard conditions didn't afford **173**, suggesting that amide is not the intermediate in the formation of oxindoles **169**. When a mixture of **168a** and **170a** (1:1) was used in the standard reaction, a 1:1 ratio of both oxindole **169a** and amide **171a** was obtained, and no crossover products were detected, indicating an intramolecular aryl migration for the transformation. Based on these, the possible reaction mechanism is proposed (Scheme 45).[52] In the first step, the copper catalyst reacts with **65a** generating a CF_3—I-$ArCO_2$[Cu(II)] radical, which interacts with alkene to give the trifluoromethyl α-alkyl radical intermediate (**174**). A 5-*ipso* cyclization then takes place on the sulfonyl aromatic ring producing **175**, which undergoes rapid desulfonylation to form **176**. The key amidyl radical (**176**) can undergo hydrogen abstraction from the medium to give the trifluoromethylated amides (**171**) when the substituent R^1 on the N atom is an aryl group. In contrast, the presence of a more electron donating alkyl moiety triggers the oxidation of **176** to give the copper enolate **177**, which is finally trapped by the aromatic ring to afford **169**.[52]

Likewise, the copper-catalyzed reductive intramolecular trifluoromethylation of *N*-benzylacrylamides (**178**) and *N*-phenylcinnamamides (**180**) coupled with 5-*exo* cyclization and dearomatization in the presence of **65a** was achieved by Wang and co-workers (Scheme 46).[53] The reactions allowed for region- and/or diastereospecific construction of a variety of trifluoromethylated 2-azaspiro[4.5]decanes (**179**) and trifluoromethylated 1-azaspiro[4.5]decanes (**181**), respectively, under mild conditions in moderate to high yields. The trifluoromethylation reaction under the standard conditions in the presence of either TEMPO or BHT was severely inhibited, pointing toward a radical mechanism.[53a] However, when the reaction was run with TEMPO, no TEMPO-CF_3



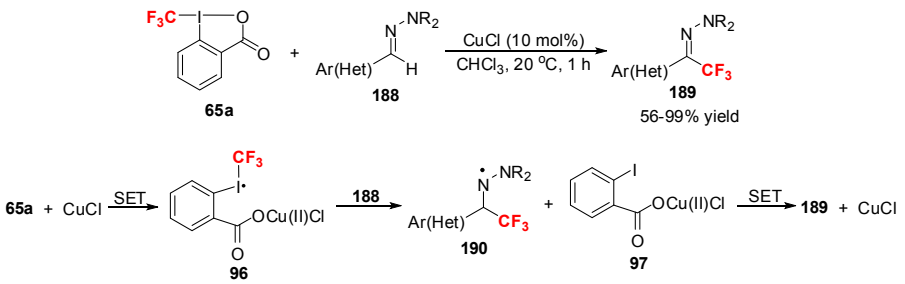
Scheme 46. Cu(I)-catalyzed reductive intramolecular trifluoromethylation of **178** and **180** with **65a** and the possible mechanistic pathways.

adduct was not detected, suggesting that some species other than CF_3 radical might be formed at the outset of the process.[53a] Thus, plausible mechanisms are proposed for these reactions (Scheme 46).[53] First, Togni's reagent **65a** is reduced by Cu(I) to afford a CF_3–I-ArCO_2[Cu(II)] radical or a CF_3 radical, which reacts with **178** (at the β-position) or **180** (at the α-position) to form radical species **182** or **185**, respectively. Then **182** or **185** undergoes thermodynamically controlled 5-*exo* cyclization onto the phenol ring to give spiro intermediate **183** or **186**. Oxidation of **183** or **186** by Cu(II) affords oxonium ion **184** or the corresponding protonated species **187**, which is transformed into **179** or **181** either in the reaction medium or during workup, and Cu(I) is released to participate in the next reaction cycle. The steric bulk of the trifluoromethyl and phenyl groups in **181** favors the *trans* configuration.

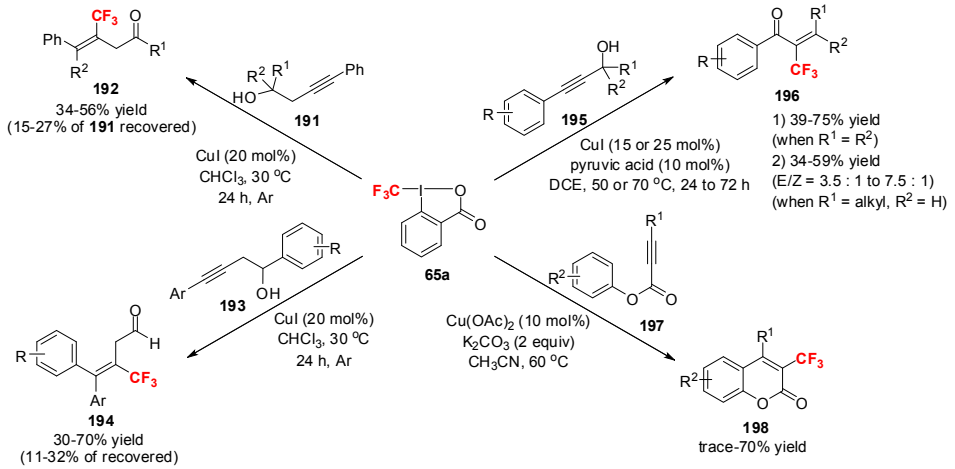
Furthermore, Bouyssi and Baudoin developed a practical procedure for the reductive trifluoromethylation of (hetero)aromatic aldehyde *N*,*N*-dialkylhydrazones with **65a** and CuCl catalyst (Scheme 47).[54] To gain an insight into the possible mechanism of the reaction, the radical-trapping experiment was performed with TEMPO, in which the formation of the desired trifluoromethylated product was almost completely inhibited, and instead the TEMPO-CF_3 adduct was formed in almost quantitative yield, suggesting a radical process (Scheme 47). The reaction pathway may begin with the reduction of **65a** by CuI via a single electron transfer (SET) to generate **96**, which acts as a CF_3 radical donor. Reaction of **96** with **188** produces **97** and **190**; the latter is stabilized by the lone pair of the adjacent nitrogen atom. Finally, oxidation of **190** by **97** restores the hydrazone functional group and CuCl. 2-iodobenzoic acid is isolated quantitatively as a co-product of the reaction by standard aqueous extraction, thus supporting the above process.

Liu and Liang described a Cu(I)-catalyzed one-pot functionalization of homopropargylic alcohols (**191** and **193**) with **65a** that includes trifluoromethylation, aryl migration, and carbonyl moiety formation (Scheme 48).[55a] This reaction constitutes the direct conversion of homopropargylic alcohols into CF_3-substituted 3-buten-1-one or 3-butenal derivatives (**192** or **194**) in a regioselective manner. The control experiment, ESR studies and DFT calculation indicated that the reaction is initiated by the addition of CF_3 radical to alkyne (Mechanism A, Scheme 49). Likewise, the CF_3 radical is generated from **65a** and CuI via a redox process. The aryl migration proceeds through a 5-*ipso* cyclization, which leads to high regioselectivity. The 5-*ipso* cyclization product **200** undergoes intramolecular 1,4-aryl migration (ring opening) to form **201**, which is oxidized by Cu(II) to give **194** and to release the Cu(I) catalyst. **200** can also undergo 1,2-migration to afford **202**, which would give the side products (**203**) through a SET process.

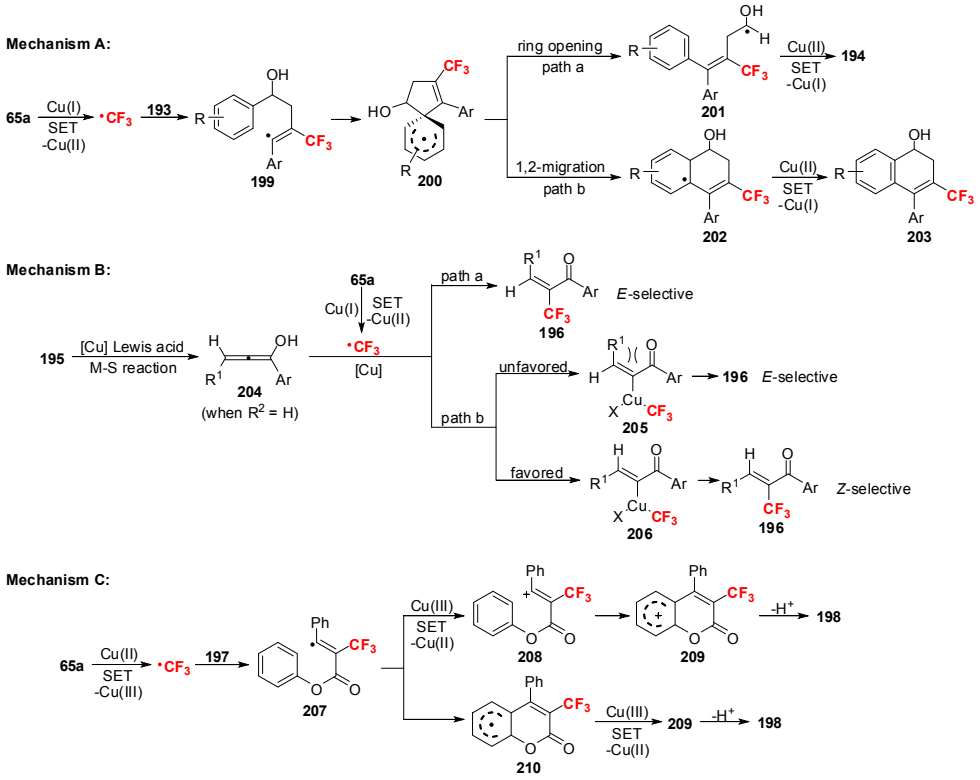
Later, Tan and Liu disclosed an approach to transform readily accessible propargylic alcohols (**195**) into α-CF_3 enones by using **65a** reagent and Cu(I) catalyst (Scheme 48).[55b] This Cu(I)-catalyzed trifluoromethyl Meyer-Schuster rearrangement (M–S reaction) protocol affords a broad scope of the desired α-CF_3 enone products (**196**) in moderate to good yields with good *E*-isomeric selectivity. On the basis of the control experimental results, a tentative redox reaction mechanism is proposed, as well (Mechanism B, Scheme 49). Since the *E*-isomer is the major product, path a may be predominant in the reaction system. The exact mechanism for the domino process is still unclear and needs further investigation.[55b] Very Recently, the Au(I)/Cu(I)-cocatalyzed tandem 1,3-acyloxy migration/trifluoromethylation of 1-arylpropargyl esters with **65a** was described.[55c] The reaction gave α-trifluoromethyl enones in



Scheme 47. Cu-catalyzed reductive trifluoromethylation of (hetero)aromatic aldehyde *N*,*N*-dialkylhydrazones by **65a**.



Scheme 48. Cu(I)-catalyzed one-pot trifluoromethylative functionalization of **191**, **193**, **195**, and **197** using **65a** as the CF_3 source.

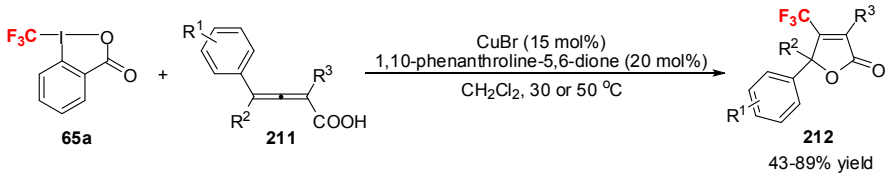


Scheme 49. The proposed radical mechanism for Cu(I)-catalyzed one-pot trifluoromethylation.

moderate yields with excellent stereoselectivity. This transformation may also involve a radical process since the radical scavenger (TEMPO) can completely suppress the desired trifluoromethylation. The CF_3 radical, that is, derived from the reduction of **65a** by Cu(I) salt is also the key intermediate in the reaction. In addition, Lu and Ding reported a Cu(II)-catalyzed direct reductive trifluoromethylation of internal alkynes (**197**) by using **65a** as the CF_3 reagent (Scheme 48).[55d] The reaction provided a rapid access to trifluoromethylated coumarins (**198**) in good yields with good functional group tolerance. Similar control experiments with TEMPO indicated that the reaction proceeds through a CF_3 radical mechanism; the $\cdot CF_3$ adds to activated alkynes, followed by sequential oxidation/cyclization or cyclization/oxidation, to furnish the target products (Mechanism C, Scheme 49). The CF_3 radical is produced under the reaction conditions from **65a** in the presence of Cu(II) salt.

Besides, Ma and co-workers developed a Cu(I)-catalyzed cyclic oxytrifluoromethylation of 2,3-allenoic acids (**211**) with **65a** in an analogous manner, which affords a straightforward way to β-trifluoromethylated butenolides (**212**) (Scheme 50).[56] This reaction is of interest to organic and medicinal chemists. The authors ruled out the direct electrophilic trifluoromethylation of 2,3-allenoic acid (**187**) with **65a** since the reaction didn't yield product in the absence of copper catalyst. Instead, they propose a mechanism that involves a CF_3 radical, which is generated from the reduction of **65a** by Cu(I) salt, as well.

The synthesis of trifluoromethylated quinones (**214**) by employing cheap CuI as the catalyst and **65a** as both the oxidant

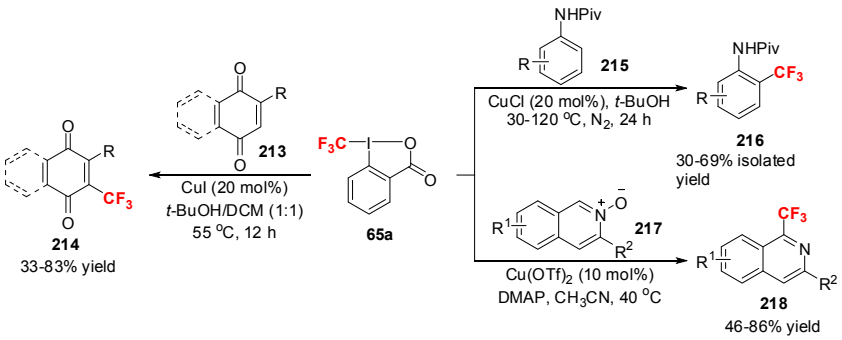


Scheme 50. Cu(I)-catalyzed cyclic oxytrifluoromethylation of 2,3-allenoic acids with **65a**.

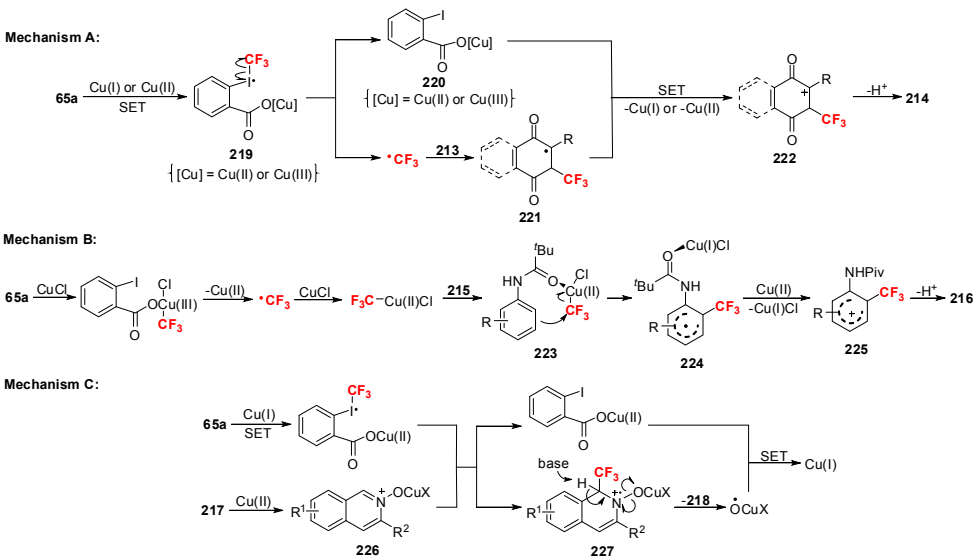
and CF_3 source was reported by Zhang and Wang (Scheme 51).[57a] In due course, the sp^2C-CF_3 bond was formed on an electron deficient π-system under mild conditions. Since other substrates bearing electron-deficient C=C bonds didn't afford the expected trifluoromethylation product, the success of the quinone trifluoromethylation method is largely attributed to its unique nature of the structure. On the basis of a series of experimental results, the authors considered that the CF_3 radical is involved in the reaction (Mechanism A, Scheme 52). At first, **65a** is activated by CuI generating **219**, which decomposes to afford **220** and simultaneous release of the CF_3 radical. It is possible that the Cu(II) species (**220**) reduces **65a** to form **219** (Cu(III)) via a second SET process. This putative pathway is consistent with the fact that the reaction is not quenched by catalytic TEMPO and that Cu(II) salt can also catalyze the conversion. Then CF_3 radical adds to quinone (**213**) to give **221**, which is oxidized by **220** to regenerate Cu(I) or Cu(II) species and to form **222**. Finally, deprotonation of **222** yields the desired products (**214**).

Similarly, the CuCl-catalyzed direct trifluoromethylation of sp^2C–H bonds of anilines (**215**) using Togni's reagent as the CF_3 source was realized (Scheme 51).[57b] The reaction can regioselectively convert C–H into C–CF_3 with ecological and readily available starting materials. The results from inhibition experiments and EPR analysis clearly indicate a radical pathway of the reaction. Thus, the possible reaction mechanism is proposed (Mechanism B, Scheme 52), in which the CF_3 radical is the key intermediate derived from CuCl and **65a** via a redox process, as well. Recently, the Cu(II)-catalyzed reaction of isoquinoline-*N*-oxides (**217**) with **65a** was described, which afforded 1-(trifluoromethyl) isoquinolines (**218**) in good yields (Scheme 51).[57c] The trifluoromethyl group can be easily introduced at the 1-position of isoquinoline under mild conditions. An analogous SET processes involving CF_3 radical is hypothesized to illustrate the synthesis of the final products (Mechanism C, Scheme 52).

It should be mentioned again that the transition-metal-mediated/catalyzed trifluoromethylation reactions with Togni's



Scheme 51. Cu-catalyzed reductive trifluoromethylation of quinones, anilines, and isoquinoline-*N*-oxides with **65a**.



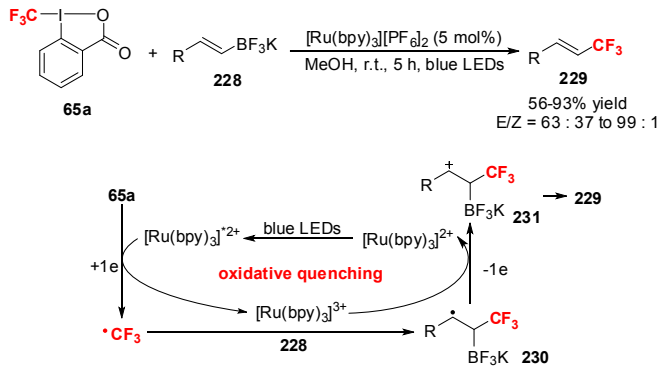
Scheme 52. The possible reaction mechanisms involving CF_3 radical intermediates for Cu-catalyzed trifluoromethylation of **213**, **215**, and **217**.

reagents via '$^{+}CF_3$' intermediates or pure ionic pathways is not included in this section. The interested readers can find these reactions beyond radical or redox processes in the recent reviews.[4a,5a]

3.3. Reductive trifluoromethylation reactions with Togni's reagents under photoredox catalysis

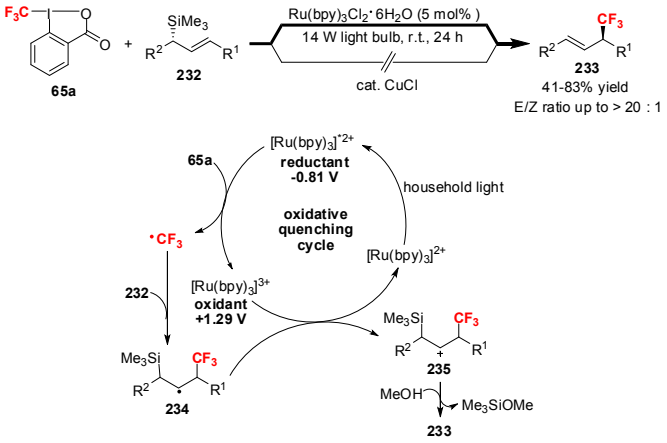
Over the past few years, a large number of catalytic methods for construction of $sp^2C–CF_3$ bonds with Togni's reagents have been disclosed, among, which several approaches have been reported on radical trifluoromethylation by photoredox catalysis. The '$^{+}CF_3$' reagents in these cases serve as CF_3 precursors, which can be reduced by the well-defined photoredox catalysts (e.g., $[Ru(bpy)_3]^{2+}$ and $Ir^{III}(ppy)_3$) under visible-light irradiation. This is a useful redox tool for trifluoromethylation of organic compounds via single electron transfer (SET) under mild conditions. In this part, we summarize the recent reductive trifluoromethylation reactions with commercially available and air-stable Togni's reagents by visible-light-driven photoredox catalysis.

Initially, Koike and Akita developed a radical trifluoromethylation of vinyltrifluoroborates (**228**) with Togni's reagent (**65a**), allowing for an easy access to *E*-trifluoromethylated alkenes bearing electron-deficient moieties, which are difficult to achieve by previous catalytic systems (Scheme 53).[58] **65a** behaves as both the oxidant and CF_3 source in the reaction in the presence of photoredox catalyst $[Ru(bpy)_3][PF_6]_2$ under visible light irradiation. The authors suggested a plausible mechanism based on a SET photoredox process (oxidative quenching), as shown in Scheme 53. First, the $•CF_3$ is generated from the single electron reduction of **65a**, which reacts with vinylborates **228** to give **230** in a regioselective manner. Subsequent single electron oxidation of **230** by $[Ru(bpy)_3]^{3+}$ produces **231**. Finally predominant Peterson elimination of the BF_3K group with *trans*-selectivity provides *E*-trifluoromethylated alkenes (**229**) in good yields. However, a possible radical chain propagation process for the above transformation cannot be ruled out.[58]



Scheme 53. Photoredox-catalyzed radical trifluoromethylation of vinyltrifluoroborates with Togni's reagent via a SET process.

Almost simultaneously, Gouverneur and co-workers described a similar photoredox catalytic method for the synthesis of enantioenriched branched allylic CF_3 products (**233**) with **65a** (Scheme 54).[59] These reactions used the visible light excited $Ru(bpy)_3Cl_2$ $6H_2O$ catalyst and delivered enantioenriched allylic trifluoromethylated products that are not accessible under Cu(I) catalysis. The silyl group in **232** is an important entity to control the regioselectivity of the products. The results from cyclic voltammetry analysis indicated a catalytic oxidative quenching cycle in the reaction (Scheme 54). The reduction potential of **65a** (−0.68 V vs SCE in CH_3CN) is compatible with the reduction step using excited-state $[Ru(bpy)_3]^{*2+}$; this implies that single electron transfer (SET)

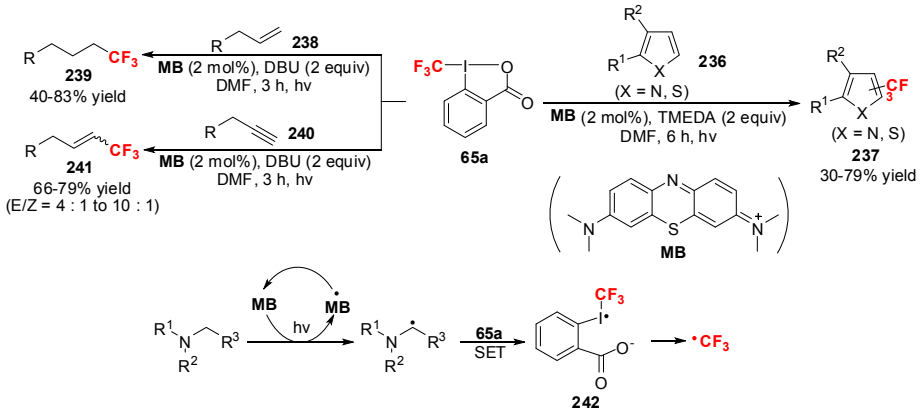


Scheme 54. Photoredox-catalyzed radical trifluoromethylation of allylsilanes with **65a** in the presence of $Ru(bpy)_3Cl_2$ $6H_2O$.

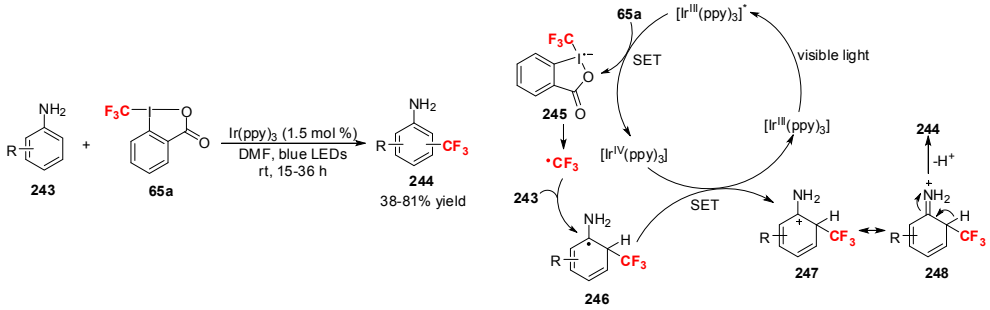
reduction of **65a** is concurrent with the oxidation of $[Ru(bpy)_3]^{*2+}$ to $[Ru(bpy)_3]^{3+}$ (−0.81 V vs SCE in CH_3CN). The resultant radical anion collapses to generate $•CF_3$, which adds regio- and stereoselectively to **232** to afford **234**. Intermediate **234** then undergoes a second SET with $[Ru(bpy)_3]^{3+}$ (+1.29 V vs SCE in CH_3CN) to form **235** and to regenerate the ground state photocatalyst $[Ru(bpy)_3]^{2+}$. Desilylation of **235** with methanol provides the desired products (**233**). The proposal of an alternative reductive quenching cycle for the reaction is excluded based on the high oxidation potential of allylsilane **232** (above +1.8 V vs SCE in CH_3CN), which makes the formation of the radical cation thermodynamically quite challenging. Moreover, the 'light/dark' control experiments verify the necessity of light and are not supportive of a radical chain propagation mechanism.

Recently, the use of methylene blue (**MB**) as a photosensitizer and **65a** as a CF_3 reagent for the catalytic radical trifluoro- and hydrotrifluoromethylation of electron-rich heterocycles (**236**), terminal alkenes (**238**), and alkynes (**240**) under visible-light irradiation was reported by Scaiano and co-workers (Scheme 55).[60] These reactions gave the desirable trifluoromethylated products (**237**, **239**, **241**) in moderate to good yields with low catalyst loadings and short irradiation times in the absence of expensive transition-metal complexes. When the reaction was performed with TEMPO radical, TEMPO-CF_3 was obtained in good yield, confirming the formation of CF_3 radicals. Thus, a possible mechanism for the catalytic generation of CF_3 radicals is depicted (Scheme 55). The triplet state **MB** upon visible-light irradiation is quenched by either TMEDA (*N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine) or DBU to form the semireduced **MB** radical and an α-amino radical. Both of these species can in turn reduce **65a**, resulting in the release of a CF_3 radical and the formation of 2-iodobenzoate.

Zhu and Ma developed a visible-light induced radical trifluoromethylation of free anilines (**243**) with **65a** and $Ir^{III}(ppy)_3$ at room temperature, leading to an economical and powerful access to trifluoromethylated free anilines (**244**) that are of high synthetic and biological value (Scheme 56).[61] The products are not only bioactive compounds but also versatile organic intermediates and building blocks to a variety of valuable fluorine-containing molecules and heterocyclic compounds. The kinetic isotope effect measurement, radical trapping experiments, and theoretical calculations hint a possible mechanism, as shown in Scheme 56. First, the single electron transfer (SET) from excited-state $[Ir^{III}(ppy)_3]^*$ to **65a** generates $[Ir^{IV}(ppy)_3]$ and **245**, which rapidly collapses to $•CF_3$. Second, the electron-deficient CF_3 radical is added to the most electron-rich position of aniline to form cyclohexadienyl radical (**246**). Single electron oxidation of **246** by $[Ir^{IV}(ppy)_3]$ gives the



Scheme 55. Photoredox-catalyzed radical trifluoro- and hydrotrifluoromethylation of electron-rich heterocycles, terminal alkenes and alkynes in the presence of **MB**.

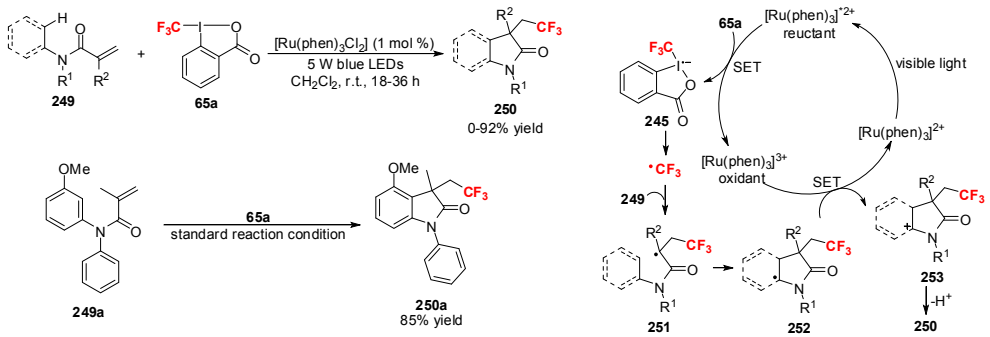


Scheme 56. Visible-light induced radical trifluoromethylation of anilines with **65a** and $Ir(ppy)_3$.

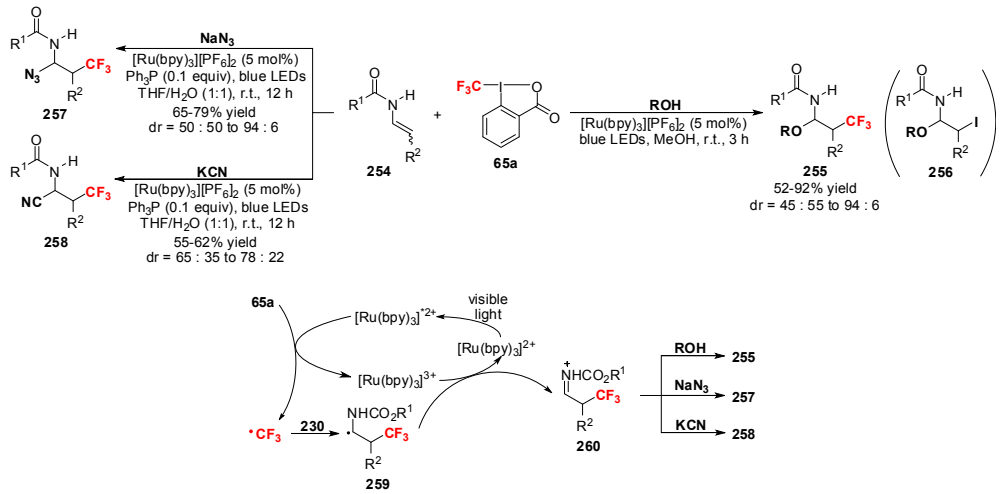
cyclohexadienyl cation species **247**. Finally, deprotonation of **248** affords the desired product **244**.

The visible-light induced tandem trifluoromethylation/arylation of electron-deficient alkenes (**249**) with **65a** and $Ru(phen)_3Cl_2$ (phen=phenanthroline) was disclosed by Zhu and co-workers, which affords an effective method to synthesize a variety of CF_3-containing oxindoles (**250**) bearing a quaternary carbon center (Scheme 57).[62] This is an improvement over the previous protocols for the introduction of a CF_3 group through visible-light-induced radical addition to alkenes, because it is performed at room temperature with a low catalyst loading and without additives. The result of inhibition experiment with TEMPO (the radical inhibitor) is supportive of a radical process for the reaction. The regioselectivity of the cyclization of the *meso* methoxy-substituted aromatic substrate (**249a**) suggests that the catalytic cycle may involve a cationic intermediate, whose stability is greatly affected by the substituents on the aromatic ring, and that the process of generating this cationic intermediate may be the rate limiting step. Accordingly, a possible reaction mechanism is postulated in Scheme 57, which is analogous to the previous reports. First, the excited-state $[Ru(phen)_3]^{*2+}$, formed under the irradiation by visible light, reduces Togni's reagent (**65a**) to **245**, which rapidly collapses to CF_3 radical. Subsequently, the CF_3 radical undergoes a radical C–H functionalization cascade, forming **252**, which is ultimately oxidized by $[Ru(phen)_3]^{3+}$ to give **253** through a single electron transfer (SET) process. Finally, deprotonation of **253** by 2-iodobenzoate gives the trifluoromethylation/arylation product (**250**). Since the transformation requires continuous irradiation of visible light, the radical chain propagation may be not a mechanistic pathway.

The photoredox-induced three-component synthesis of β-trifluoromethyl amines was explored by Magnier and Masson (Scheme 58).[63] The reaction employs **65a** as the CF_3 source and $[Ru(bpy)_3][PF_6]_2$ as the photocatalyst. Under the optimized conditions (see the equations in Scheme 58), a wide range of substituted enecarbamates (**254**) are readily difunctionalized by means of various *O*-, *N*-, and *C*-nucleophiles, which produces numerous difunctionalized trifluoromethyl carbamates (**255, 257, 258**) in



Scheme 57. Visible-light induced tandem trifluoromethylation/arylation of electron-deficient alkenes (**249**) with **65a** in the presence of $Ru(phen)_3Cl_2$.



Scheme 58. Photoredox induced three-component synthesis of β-trifluoromethyl amines by employing **65a** and [Ru(bpy)$_3$][PF$_6$]2 catalyst.

good yields. The control experiments suggested a radical/cationic process in the reaction (Scheme 58), although the mechanism of the transformation is not completely clear yet. First, irradiation with visible light excites $[Ru(bpy)_3]^{2+}$ into a strong reductant species $[Ru(bpy)_3]^{*2+}$, which performs a single electron transfer (SET) to **65a** generating $^{\bullet}CF_3$. Subsequent regioselective addition of $^{\bullet}CF_3$ to enecarbamate (**254**) leads to the α-amido radical **259** that can be rapidly oxidized to Nacyliminium cation **260** by $[Ru(bpy)_3]^{3+}$ via a SET process. Finally, nucleophilic addition by alcohol (ROH), NaN_3, or KCN affords the corresponding trifluoromethylated adducts **255**, **257**, or **258**.

In a word, the use of organofluorine compounds with an incorporated CF_3 moiety has increased dramatically in both the pharmaceutical and agrochemical industry. The mild and efficient photoredox-catalyzed trifluoromethylation methodology using Togni's reagents as $^{\bullet}CF_3$ precursors has become the important and versatile approaches to introduction of CF_3 groups into conventional organic compounds. We believe that, in the near future, more reaction methodologies and mechanistic studies based on the reductive transformation of '$^{+}CF_3$' reagents will be disclosed by a wider range of research groups around the world.

4. Conclusions

Since the initial report of trifluoromethylsulfonium reagents in 1984 and Togni's reagents in 2006, the electrophilic '$^{+}CF_3$' sources have been thoroughly investigated. A large amount of mechanistic studies with appropriate analytical tools have been harnessed to understand the CF_3 transfer processes. At the early stage, bimolecular nucleophilic substitution, the S_N2 type mechanism, was often suggested, although the single electron transfer pathway couldn't be ruled out. In the past four to five years, increasing evidences of the single electron transfer processes from metals, inorganic salts, photoredox catalysts, and even substrates to '$^{+}CF_3$' reagents to generate CF_3 radical, CF_3 anion, or related reduced intermediates, aiming for versatile reductive trifluoromethylation reactions, have been exceedingly disclosed.[64]

This review highlights the recent achievements of the reductive trifluoromethylation with electrophilic '$^{+}CF_3$' reagents. In the first section, the reductive trifluoromethylation reactions with Umemoto's reagents and their analogs are discussed, which employ transition metals or photoredox catalysts as single electron donors to form CF_3 radical or $CuCF_3$ intermediates (by second SET). In the second section, the reductive transformation of Togni's reagents to CF_3 intermediate or related $[Cu^{II}CF_3]/[Cu^{III}CF_3]$ species is described, which trifluoromethylate alkenes, alkynes, and arenes via radical or metal-mediated cross-coupling processes. The trifluoromethylation reactions with Umemoto's reagents and Togni's reagents performed through '$^{+}CF_3$' pathway are not included in this report. Although the complete reaction mechanisms remain unclear, the readers can find proofs of the formation of CF_3 radicals or the related reductive species from '$^{+}CF_3$' reagents that initiate the aforementioned trifluoromethylation reactions. It's notable that the radical and cationic pathways sometimes coexist in these reactions, which is largely dependent upon the substrates, the catalysts, and the reaction conditions.[65]

The reductive trifluoromethylation reactions with electrophilic '$^{+}CF_3$' reagents allow for efficient construction of various C(sp^2, sp^3)–CF_3 bonds, leading to diverse trifluoromethylated alkenes, arenes and heteroarenes, and bifunctional products in moderate to excellent yields. Nevertheless, these reactions have several disadvantages. The recent study reveals that Togni's reagent **65a** has explosive properties.[66] So laboratory work with this type of reagents should be carefully done behind safety shields with small amounts, and soft and polished tools are necessary for manipulations avoiding fierce friction.[66] Considering the high cost of the reagents, the requirement of an excess of **1b**–**d** and **65a**–**b** in most cases is severely against the practicability of the reactions on large scales. On the other hand, the poor atom utilization of '$^{+}CF_3$' reagents makes the trifluoromethylation reactions less economical. We hope that this review can stimulate chemists to implement more research work on the design of new reagents and the utilization of the old ones to develop greener, more economical, and more useful reductive trifluoromethylation reactions with a wider range of substrate scopes. Because of the importance of the CF_3 moieties in pharmaceuticals and agrochemicals, the reductive trifluoromethylation reactions and the relevant promising strategies will find more applications in areas of medicinal chemistry and pesticide science in the coming decades.

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References and notes

1. (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley: Chichester, UK, 2009; (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2004.

2. (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214–8264; (b) Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051–3069; (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477; (d) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521; (e) Zhang, C. P.; Chen, Q. Y.; Guo, Y.; Xiao, J. C.; Gu, Y. C. *Coord. Chem. Rev.* **2014**, *261*, 28–72.
3. (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319; (b) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
4. (a) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294–8308; (b) Zhang, C. P.; Chen, Q. Y.; Guo, Y.; Xiao, J. C.; Gu, Y. C. *Chem. Soc. Rev.* **2012**, *41*, 4536–4559; (c) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950–8958.
5. (a) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650–682; (b) Xu, X. H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731–764; (c) Bizet, V.; Kowalczyk, R.; Bolm, C. *Chem. Soc. Rev.* **2014**, *43*, 2426–2438; (d) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598–6608; (e) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765–825; (f) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683–730; (g) Chu, L.; Qing, F. L. *Acc. Chem. Res.* **2014**, *47*, 1513–1522.
6. (a) Yasui, H.; Yamamoto, T.; Tokunaga, E.; Shibata, N. *J. Fluorine Chem.* **2011**, *132*, 186–189; (b) Zhao, Y.; Zhu, J.; Ni, C.; Hu, J. *Synthesis* **2010**, 1899–1904; (c) Requirand, N.; Andrieu, A.; Blancou, H.; Commeyras, A. *J. Fluorine Chem.* **1994**, *69*, 57–59; (d) Pawelke, G. *J. Fluorine Chem.* **1989**, *42*, 429–433.
7. (a) Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Gu, Y. C.; Xiao, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1896–1900; (b) References: Wang, X.; Truesdale, L.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649 and Allen, A.; MacMillan, W. C. J. Am. Chem. Soc. 2010, 132, 4986–4987 pioneeringly employed Umemoto's reagents and Togni's reagent in transition-metal mediated trifluoromethylations. However, according their mechanistic study, they are ruled out as the "reductive trifluoromethylation". The plausible reaction pathways from Yu showed that the production of $ArCF_3$ is possible via either the nucleophilic attack of ArPd(II) to $^{+}CF_3$ or the oxidation of ArPd(II) by $^{+}CF_3$ followed by reductive elimination. The reduction of $^{+}CF_3$ is not the initiation step of trifluoromethylation but the formation of ArPd(II) via C–H activation. The proposed mechanism from MacMillan indicated no reduction of Togni's reagent for their transformations. Although they initially envisioned an alternate mechanism wherein Togni's reagent might participate in a redox one-electron alkylation pathway, they finally excluded this hyperthesis. Based on these, to our knowledge, we believe that the Cu(0)-mediated reaction between ArI and $^{+}CF_3$ reagent is the *first* metal mediated reductive trifluoromethylation.
8. (a) Zhang, C. P.; Cai, J.; Zhou, C. B.; Wang, X. P.; Zheng, X.; Gu, Y. C.; Xiao, J. C. *Chem. Commun.* **2011**, 9516–9518; (b) Arimori, S.; Shibata, N. *Org. Lett.* **2015**, *17*, 1632–1635.
9. Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Gu, Y. C.; Xiao, J. C. *Chem. Commun.* **2011**, *47*, 6632–6634.
10. Zhang, C. P.; Chen, Q. Y.; Guo, Y.; Xiao, J. C. *Tetrahedron* **2013**, *69*, 10955–10989.
11. (a) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777; (b) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, http://dx.doi.org/10.3762/bjoc.6.65; (c) Yagupolskii, L M.; Maletina, I. I.; Kondratenko, N. V.; Orda, V. V. *Synthesis* **1978**, 835–837; (d) Yagupolskii, L. M.; Mironova, A. A.; Maletina, I. I.; Orda, V. V. *Zh. Org. Khim.* **1980**, *16*, 232–233; (e) Yagupolskii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 103–106; (f) Umemoto, T.; Kuriu, Y.; Nakayama, S. I. *Tetrahedron Lett.* **1982**, *23*, 1169–1172; (g) Umemoto, T.; Kuriu, Y.; Nakayama, S. I.; Miyano, O. *Tetrahedron Lett.* **1982**, *23*, 1471–1474; (h) Umemoto, T.; Kuriu, Y.; Miyano, O. *Tetrahedron Lett.* **1982**, *23*, 3579–3582; (i) Liu, Y.; Shao, X.; Zhang, P.; Lu, L.; Shen, Q. *Org. Lett.* **2015**, http://dx.doi.org/10.1021/acs.orglett.5b01170
12. (a) Zhang, C. *Org. Biomol. Chem.* **2014**, *12*, 6580–6589; (b) Koike, T.; Akita, M. *J. Fluorine Chem.* **2014**, *167*, 30–36.
13. Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 572–576.
14. Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164.
15. Ono, T.; Umemoto, T. *J. Fluorine Chem.* **1996**, *80*, 163–166.
16. (a) Macé, Y.; Pradet, C.; Popkin, M.; Blazejewski, J. C.; Magnier, E. *Tetrahedron Lett.* **2010**, *51*, 5388–5391; (b) Blazejewski, J. C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H. S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335–345.
17. (a) Zhang, C. P.; Cao, H. P.; Wang, Z. L.; Zhang, C. T.; Chen, Q. Y.; Xiao, J. C. *Synlett* **2010**, 1089–1092; (b) Liu, G.; Wang, X.; Xu, X. H.; Lu, X.; Tokunaga, E.; Tsuzuki, S.; Shibata, N. *Org. Lett.* **2013**, *15*, 1044–1047.
18. Magnier, E.; Blazejewski, J. C.; Tordeux, M.; Wakselman, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1279–1282.
19. (a) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596–3599; (b) Zhu, L.; Liu, S.; Douglas, J. T.; Altman, R. A. *Chem.—Eur. J.* **2013**, *19*, 12800–12805; (c) Dai, J. J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z. J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436–8439.
20. (a) Ji, Y. L.; Kong, J. J.; Lin, J. H.; Xiao, J. C.; Gu, Y. C. *Org. Biomol. Chem.* **2014**, *12*, 2903–2906; (b) Zhao, T.; Szabó, K. *Org. Lett.* **2012**, *14*, 3966–3969; (c) Miyake, Y.; Ota, S. I.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, 7809–7811; (d) Ji, Y. L.; Lin, J. H.; Xiao, J. C.; Gu, Y. C. *Org. Chem. Front.* **2014**, *1*, 1280–1284.
21. (a) Wang, X. P.; Lin, J. H.; Zhang, C. P.; Xiao, J. C.; Zheng, X. *Chin. J. Chem.* **2013**, *31*, 915–920; (b) Xu, J.; Fu, Y.; Luo, D. F.; Jiang, Y. Y.; Xiao, B.; Liu, Z. J.; Gong, T. J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300–15303.
22. Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567–9571.
23. Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Medebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505–2508.
24. Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136–2139.
25. Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 4340–4343.
26. Yasu, Y.; Arai, Y.; Tomita, R.; Koike, T.; Akita, M. *Org. Lett.* **2014**, *16*, 780–783.
27. Tomita, R.; Yasu, Y.; Koike, T.; Akita, M. *Beilstein J. Org. Chem.* **2014**, *10*, 1099–1106.
28. (a) Wang, R.; Jiang, H.; Cheng, Y.; Kadi, A. A.; Fun, H. K.; Zhang, Y.; Yu, S. *Synthesis* **2014**, *6*, 2711–2726; (b) Cheng, Y.; Yuan, X.; Jiang, H.; Wang, R.; Ma, J.; Zhang, Y.; Yu, S. *Adv. Synth. Catal.* **2014**, *356*, 2859–2866.
29. Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Chem. Commun.* **2014**, *50*, 14197–14200.
30. Lin, Q. Y.; Xu, X. H.; Qing, F. L. *J. Org. Chem.* **2014**, *79*, 10434–10446.
31. Mizuta, S.; Verhoog, S.; Wang, X.; Shibata, N.; Gouverneur, V.; Médebielle, M. *J. Fluorine Chem.* **2013**, *155*, 124–131 and the literatures therein.
32. (a) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465–3468; (b) Yang, Y. D.; Lu, X.; Liu, G.; Tokunaga, E.; Tsuzuki, S.; Shibata, N. *ChemistryOpen* **2012**, *1*, 221–226.
33. (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579–2586; (b) Niedermann, K.; Welch, J. M.; Koller, R.; Cvengroš, J.; Santschi, N.; Battaglia, P.; Togni, A. *Tetrahedron* **2010**, *66*, 5753–5761.
34. Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575–1577.
35. Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754–757.
36. Mejía, E.; Togni, A. *ACS Catal.* **2012**, *2*, 521–527.
37. Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221–8224.
38. Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792–10795.
39. Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1216–1219.
40. Zhang, B.; Studer, A. *Org. Biomol. Chem.* **2014**, *12*, 9895–9898.
41. (a) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086–13090; (b) Li, L.; Guo, J. Y.; Liu, X. G.; Chen, S.; Wang, Y.; Tan, B.; Liu, X. Y. *Org. Lett.* **2014**, *16*, 6032–6035.
42. (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120–9123; (b) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413.
43. (a) Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2947–2950; (b) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem.—Eur. J.* **2012**, *18*, 8583–8587; (c) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577–4580.
44. Liu, X.; Xiong, F.; Huang, X.; Xu, L.; Li, P.; Wu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6962–6966.
45. (a) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882–2885; (b) Wang, X. P.; Lin, J. H.; Zhang, C. P.; Xiao, J. C.; Zheng, X. *Beilstein J. Org. Chem.* **2013**, *9*, 2635–2640.
46. (a) Fang, Z.; Ning, Y.; Mi, P.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 1522–1525; (b) Prieto, A.; Jeamet, E.; Monteiro, N.; Bouyssi, D.; Baudoin, O. *Org. Lett.* **2014**, *16*, 4770–4773.
47. (a) Ilchenko, N. O.; Janson, P. G.; Szabó, K. J. *J. Org. Chem.* **2013**, *78*, 11087–11091; (b) Liang, Z.; Wang, F.; Chen, P.; Liu, G. *J. Fluorine Chem.* **2014**, *167*, 55–60; (c) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881–1886.
48. (a) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462–12465; (b) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655–12658.
49. (a) Yu, P.; Lin, J. S.; Li, L.; Zheng, S. C.; Xiong, Y. P.; Zhao, L. J.; Tan, B.; Liu, X. Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11890–11894; (b) Lin, J. S.; Xiong, Y. P.; Ma, C. L.; Zhao, L. J.; Tan, B.; Liu, X. Y. *Chem.—Eur. J.* **2014**, *20*, 1332–1340; (c) Example using phosphine as catalyst: Yu, P.; Zheng, S. C.; Yang, N. Y.; Tan, B.; Liu, X. Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4041–4045.
50. He, Y. T.; Li, L. H.; Yang, Y. F.; Wang, Y. Q.; Luo, J. Y.; Liu, X. Y.; Liang, Y. M. *Chem. Commun.* **2013**, *49*, 5687–5689.
51. Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202–10205.
52. Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480–14483.
53. (a) Han, G.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, *16*, 3188–3191; (b) Han, G.; Wang, Q.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, *16*, 5914–5917.
54. Pair, E.; Monteiro, N.; Bouyssi, D.; Baudoin, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 5346–5349.
55. (a) Gao, P.; Shen, Y. W.; Fang, R.; Hao, X. H.; Qiu, Z. H.; Yang, F.; Yan, X. B.; Wang, Q.; Gong, X. J.; Liu, X. Y.; Liang, Y. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7629–7633; (b) Xiong, Y. P.; Wu, M. Y.; Zhang, X. Y.; Ma, C. L.; Huang, L.; Zhao, L. J.; Tan, B.; Liu, X. Y. *Org. Lett.* **2014**, *16*, 1000–1003; (c) Ji, Y. L.; Lin, J. H.; Xiao, J. C.; Gu, Y. C. *Eur. J. Org. Chem.* **2014**, 7948–7954; (d) Li, Y.; Lu, Y.; Qiu, G.; Ding, Q. *Org. Lett.* **2014**, *16*, 4240–4243.
56. Yu, Q.; Ma, S. *Chem.—Eur. J.* **2013**, *19*, 13304–13308.
57. (a) Wang, X.; Ye, Y.; Ji, G.; Xu, Y.; Zhang, S.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 3730–3733; (b) Cai, S.; Chen, C.; Sun, Z.; Xi, C. *Chem. Commun.* **2013**, 4552–4554; (c) Fan, C.; Song, J.; Qiu, G.; Liu, G.; Wu, J. *Org. Chem. Front.* **2014**, *1*, 924–928.
58. Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 2037–2039.
59. Mizuta, S.; Engle, K. M.; Verhoog, S.; Galicia-López, O.; O'Duill, M.; Médebielle, M.; Wheelhouse, K.; Rassias, G.; Thompson, A. L.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 1250–1253.
60. Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *ACS Catal.* **2014**, *4*, 2530–2535.

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61. Xie, J.; Yuan, X.; Abdukader, A.; Zhu, C.; Ma, J. *Org. Lett.* **2014**, *16*, 1768–1771.
62. Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem.—Eur. J.* **2013**, *19*, 14039–14042.
63. Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240–1243.
64. The use of "$^{+}CF_3$" reagents as both oxidants and CF_3 sources to construct CF_3-containing organometallic complexes or intermediates are also reported, in which the low-valent transition-metals are oxidized by "$+CF_3$" reagents to form hypervalent metal-CF_3 species. See representative examples below: (a) Wilbuer, A.; Vlecken, D. H.; Schmitz, D. J.; Krling, K.; Harms, K.; Bagowski, C. P.; Meggers, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3839–3842; (b) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682–14687; (c) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002–12009; (d) Zhang, X. G.; Dai, H. X.; Wasa, M.; Yu, J. Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948–11951; (e) Zhang, L. S.; Chen, K.; Chen, G.; Li, B. J.; Luo, S.; Guo, Q. Y.; Wei, J. B.; Shi, Z. J. *Org. Lett.* **2013**, *15*, 10–13; (f) Xu, J.; Luo, D. F.; Xiao, B.; Liu, Z. J.; Gong, T. J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, 4300–4302; (g) Luo, D. F.; Xu, J.; Fu, Y.; Guo, Q. X. *Tetrahedron Lett.* **2012**, *53*, 2769–2772; (h) Ge, G.; Huang, X.; Ding, C.; Li, H.; Wan, S.; Hou, X. *Chin. J. Chem.* **2014**, *32*, 727–733 (In these cases, the aryl-Pd(II) or aryl-Cu(I) complexes trigger the whole reactions. The reduction of $^{+}CF_3$ species is not the initial step of the reaction, which does not qualify "reductive trifluoromethylation".).
65. Ling, L.; Liu, K.; Li, X.; Li, Y. *ACS Catal.* **2015**, *5*, 2458–2468.
66. Fiederling, N.; Haller, J.; Schramm, H. *Org. Process Res. Dev.* **2013**, *17*, 318–319.

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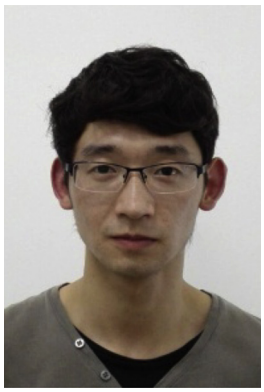
Biographical sketch

Shi-Meng Wang is currently a master student in the research group of Prof. Cheng-Pan Zhang at Wuhan University of Technology. She obtained her B.S. in applied chemistry from Quanzhou Normal University in 2014. Her research interests are the synthesis and reactivities of fluorinated phosphonium salts and sulfonium salts.



Jia-Bin Han is a master student in the research group of Prof. Cheng-Pan Zhang at Wuhan University of Technology. He obtained his B.S. in pharmaceutical engineering from Wuhan University of Technology. His research interests focus on transition-metal-mediated difluoromethylthiolation and trifluoromethylsulfonylation.

Cheng-Pan Zhang obtained his B.S. in pharmacy from Chongqing Medical University in 2005. He joined Prof. Ji-Chang Xiao's group in 2006 for Ph.D. study and received his Ph.D. degree from Shanghai Institute of Organic Chemistry (SIOC), in 2011. From 2011 to 2012, he was a postdoctoral fellow in the research group of Prof. David A. Vicic at the University of Hawai'i. Then he worked in Prof. John A. Gladysz's group at Texas A&M University for two years. Since the end of 2014, he joined the faculty of Wuhan University of Technology as a full professor. His research interests are the synthesis and reactivities of fluorine-containing metal complexes and the development of metal-mediated fluorination and fluoroalkylation reactions.

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