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Oxidative Trifluoromethylation and Trifluoromethylthiolation Reactions Using (Trifluoromethyl)trimethylsilane as a Nucleophilic CF_3 Source

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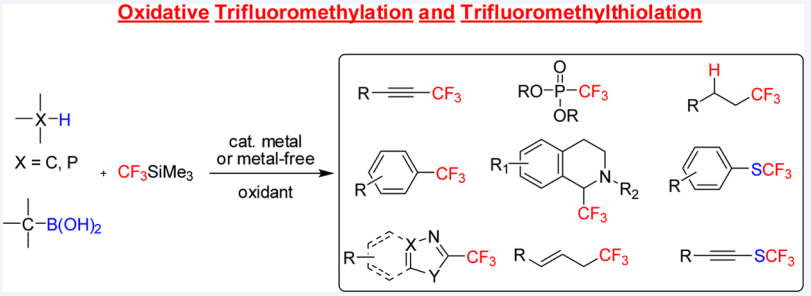

CONSPECTUS: The trifluoromethyl group is widely prevalent in many pharmaceuticals and agrochemicals because its incorporation into drug candidates could enhance chemical and metabolic stability, improve lipophilicity and bioavailability, and increase the protein bind affinity. Consequently, extensive attention has been devoted toward the development of efficient and versatile methods for introducing the CF_3 group into various organic molecules. Direct trifluoromethylation reaction has become one of the most efficient and important approaches for constructing carbon−CF_3 bonds. Traditionally, the nucleophilic trifluoromethylation reaction involves an electrophile and the CF_3 anion, while the electrophilic trifluoromethylation reaction involves a nucleophile and the CF_3 cation. In 2010, we proposed the concept of oxidative trifluoromethylation: the reaction of nucleophilic substrates and nucleophilic trifluoromethylation reagents in the presence of oxidants.

In this Account, we describe our recent studies of oxidative trifluoromethylation reactions of various nucleophiles with CF_3SiMe_3 in the presence of oxidants. We have focused most of our efforts on constructing carbon−CF_3 bonds via direct trifluoromethylation of various C−H bonds. We have demonstrated copper-mediated or -catalyzed or metal-free oxidative C−H trifluoromethylation of terminal alkynes, tertiary amines, arenes and heteroarenes, and terminal alkenes. Besides various C−H bonds, aryl boronic acids proved to be viable nucleophilic coupling partners for copper-mediated or -catalyzed cross-coupling reactions with CF_3SiMe_3. To further expand the reaction scope, we also applied H-phosphonates to the oxidative trifluoromethylation system to construct P−CF_3 bonds. Most recently, we developed silver-catalyzed hydrotrifluoromethylation of unactivated olefins. These studies explore boronic acids, C−H bonds, and P−H bonds as novel nucleophiles in transition-metal-mediated or -catalyzed cross-coupling reactions with CF_3SiMe_3, opening new viewpoints for future trifluoromethylation reactions. Furthermore, we also achieved the oxidative trifluoromethylthiolation reactions of aryl boronic acids and terminal alkynes to construct carbon−SCF_3 bonds by using CF_3SiMe_3 and elemental sulfur as the nucleophilic trifluoromethylthiolating reagent. These oxidative trifluoromethylation and trifluoromethylthiolation reactions tolerate a wide range of functional groups, affording a diverse array of CF_3- and CF_3S-containing compounds with high efficiencies, and provide elegant and complementary alternatives to classical trifluoromethylation and trifluoromethylthiolation reactions. Because of the importance of the CF_3 and SCF_3 moieties in pharmaceuticals and agrochemicals, these reactions would have potential applications in the life science fields.

1. INTRODUCTION

The trifluoromethyl group (CF_3-) has a privileged role in pharmaceuticals and agrochemicals because its incorporation into drug candidates could enhance chemical and metabolic stability, improve lipophilicity and bioavailability, and increase protein binding affinity.[1] Additionally, trifluoromethylated organic compounds are widely applied in materials such as liquid crystals.[2] While there are no naturally occurring CF_3-containing compounds, it is not surprising that numerous efforts have been devoted to the development of new methodologies for the preparation of these compounds. Direct trifluoromethylations,[3] especially transition-metal-mediated or -catalyzed trifluoromethylation reactions,[4] are the most

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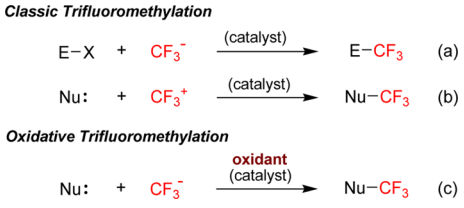
promising and efficient route to access a wide range of CF_3-containing molecules. Methods for the incorporation of the trifluoromethyl group into organic molecules may be considered as nucleophilic, electrophilic, or free radical processes. Traditionally, a nucleophilic trifluoromethylation reaction involves an electrophile and the CF_3 anion (Scheme 1a), while an electrophilic trifluoromethylation reaction

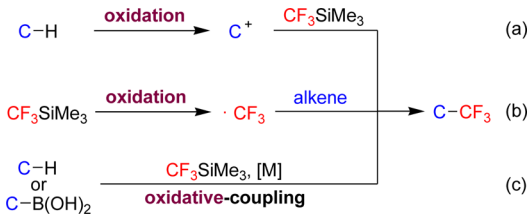
Scheme 1. Trifluoromethylation Reactions



involves a nucleophile and the CF_3 cation (Scheme 1b). Inspired by the Glaser−Hay coupling[5] and Chan−Lam reaction,[6] where two nucleophiles underwent cross coupling in the presence of oxidants (termed "oxidative cross-coupling reactions"),[7] we recently questioned whether it might be possible to enable direct trifluoromethylation via the reaction of a nucleophile and a nucleophilic trifluoromethylating agent in the presence of an exogenous oxidant. Given the variability of nucleophiles (including organometallic reagents and hydrocarbons) and tunability of exogenous oxidants (including oxygen and inorganic and organic oxidants), we expected that the new mode of trifluoromethylation, termed "oxidative trifluoromethylation", could extend the capability to access a diverse range of trifluoromethylated molecules (Scheme 1c). With regard to the nucleophilic trifluoromethylating agent, we selected (trifluoromethyl)trimethylsilane (CF_3SiMe_3, or Me_3SiCF_3),[8] known as Ruppert reagent or Ruppert−Prakash reagent) as a CF_3 source, due to its stability, ready availability, easy handling and storage (bp 54−55 °C), relatively low cost,[9] and wide applications in the areas of traditional nucleophilic trifluoromethylation[3] and transition-metal-mediated trifluoromethyl coupling reactions.[4] In 2010, three examples of oxidative trifluoromethylation reactions of nucleophilic substrates using CF_3SiMe_3 were reported by our group.[10−12] Since then, more and more oxidative trifluoromethylation reactions have been developed by our group, as well as other groups. This Account describes the recent development of oxidative trifluoromethylation reactions of nucleophiles with CF_3SiMe_3, mostly from our laboratory. Many salient reports from Yu,[13] Sanford,[14] and other research groups[15] have developed the transition-metal-mediated trifluoromethylation of various nucleophiles with electrophilic CF_3 sources (such as Umemoto's reagent and Togni's reagent, also demonstrated to be oxidants), which belong to a broader definition of oxidative trifluoromethylation and are not included in this Account.

It should be mentioned that the mechanisms of these oxidative trifluoromethylation reactions are still unclear and remain to be elucidated. We simply classify these reactions, according to the role of oxidant, into three types: oxidation of substrates (Scheme 2a, C−H oxidative activation followed by trifluoromethylation), oxidation of trifluoromethylation reagent (Scheme 2b, oxidation of CF_3SiMe_3 to generate CF_3 radical for further transformation), and transition-metal-mediated or -catalyzed oxidative-coupling reaction (Scheme 2c). In the last part of this Account, oxidative trifluoromethylthiolation using CF_3SiMe_3 will be discussed.

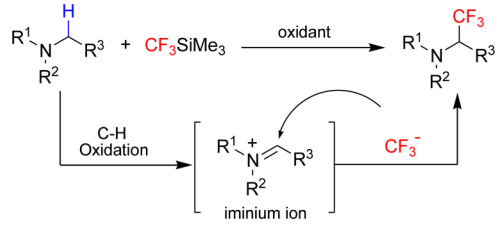
Scheme 2. Oxidative Trifluoromethylation Reactions with CF_3SiMe_3



2. OXIDATIVE TRIFLUOROMETHYLATION VIA OXIDATION OF SUBSTRATES

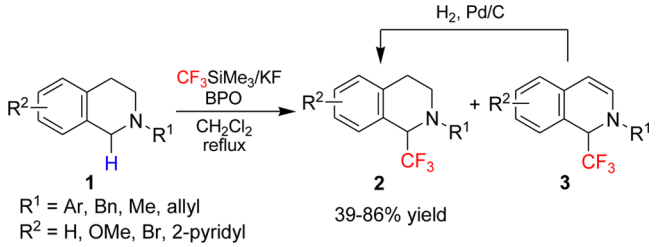
It is well-known that oxidation of the sp^3 C−H bond adjacent to the nitrogen atom in tertiary amine, followed by attack of a nucleophile, is a powerful strategy for the synthesis of functionalized amines.[7] So we chose tertiary amines as the substrates to achieve oxidative trifluoromethylation. The proposed pathway is shown in Scheme 3.

Scheme 3. Proposed Pathway for Oxidative Trifluoromethylation of Tertiary Amines



Because tetrahydroisoquinoline derivatives are important structural features of pharmaceutical and natural products, we focused on the direct oxidative trifluoromethylation of tetrahydroisoquinoline derivatives **1**. As shown in Scheme 4,

Scheme 4. Benzoyl Peroxide (BPO)-Promoted Oxidative Trifluoromethylation of Tetrahydroisoquinolines



various 1-trifluoromethylated tetrahydroisoquinoline derivatives **2** were prepared under benzoyl peroxide (BPO)-promoted oxidative trifluoromethylation conditions.[10] In most cases, overoxidation could be observed, producing the corresponding 1,2-dihydro analogues **3**, which can be easily converted to the desired products **2** via hydrogenation in the presence of Pd/C. Notably, this transformation represents the first example of direct trifluoromethylation of sp^3 C−H bonds via C−H activation. Similar oxidative trifluoromethylation of tetrahydroisoquinoline derivatives was reported by other groups

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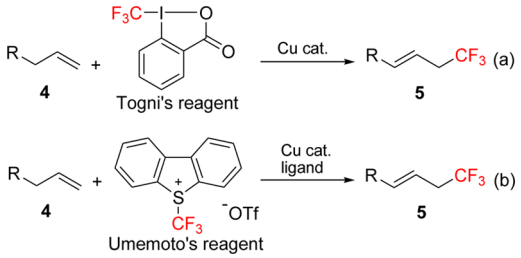
promoted by CuI/2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[16] or Rose Bengal (RB)/visible light.[17]

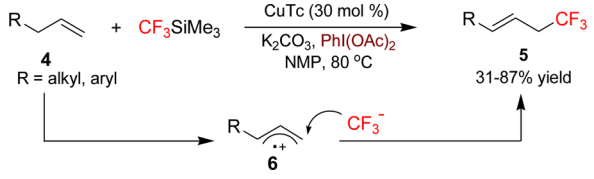
In 2011, the groups of Buchwald,[18a] Liu,[18b] and Wang[18c] independently reported Cu-catalyzed direct trifluoromethylation of terminal alkenes **4** for the preparation of trifluoromethylated allylic compounds **5** using expensive electrophilic trifluoromethylating reagents (Togni's reagent and Umemoto's reagent, Scheme 5).

Scheme 5. Trifluoromethylation of Terminal Alkenes



We developed Cu-catalyzed oxidative trifluoromethylation of terminal alkenes using nucleophilic CF_3SiMe_3 as the trifluoromethylating reagent in 2012 (Scheme 6).[19] This method

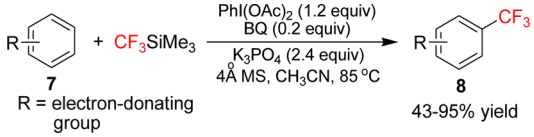
Scheme 6. Oxidative Trifluoromethylation of Terminal Alkenes



allows access to a variety of trifluoromethylated allylic compounds and provides a complementary method to direct trifluoromethylation of terminal alkenes. Preliminary mechanism investigations precluded the involvement of a CF_3 radical or an allylic radical in this process. We surmised that this transformation occurred via $PhI(OAc)_2$-induced oxidation of terminal alkene and then formation of the radical cation intermediate **6** as a key intermediate.

From the radical cation **6** in Scheme 6, we envisaged that a $PhI(OAc)_2$-induced aromatic cation radical[20] would undergo a similar nucleophilic attack by the CF_3 anion, generating the trifluoromethylated arenes. As expected, a series of electron-rich arenes **7** indeed underwent the $PhI(OAc)_2$-induced oxidative trifluoromethylation reactions to give trifluoromethylated products **8** in good to excellent yields (Scheme 7).[21] What was more, the heteroarenes such as indole and pyrrole derivatives were also amenable to this reaction system, and high yields were obtained under the standard reaction conditions. The oxidative trifluoromethylation of furan and benzofuran gave traces of the desired products. This protocol

Scheme 7. $PhI(OAc)_2$-Induced Oxidative Trifluoromethylation of Arenes

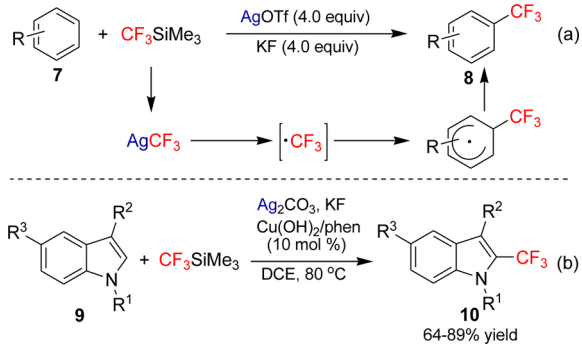


precludes the need for substrate prefunctionalization and metal catalysts. The addition of a catalytic amount of benzoquinonine (BQ) was necessary to achieve high yield, although the role of BQ remains to be elucidated. In the same year, the group of Shibata developed direct oxidative trifluoromethylation of unsymmetrical biaryls by the combination of CF_3SO_2Na (Langlois' reagent) and phenyliodine bis(trifluoroacetate) (PIFA).[22]

3. OXIDATIVE TRIFLUOROMETHYLATION VIA OXIDATION OF CF_3SIME_3

The use of CF_3SiMe_3, the well-known nucleophilic trifluoromethylating agent, as a source of CF_3 radical has been rarely reported. In 2011, the Sanford group reported a Ag-mediated trifluoromethylation of arenes 7 with CF_3SiMe_3 (Scheme 8a).[23]

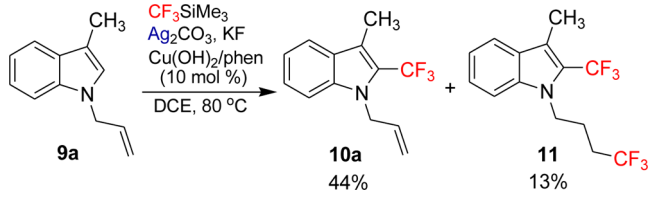
Scheme 8. Oxidative Trifluoromethylation of Arenes and Indoles



They proposed that the reaction proceeded via a $AgCF_3$[24] intermediate and CF_3 radical might be involved for the further transformation. At that time, we also found the generation of CF_3 radical from CF_3SiMe_3 in our copper-catalyzed direct C–H oxidative trifluoromethylation reactions of indoles **9** with Ag_2CO_3/KF (Scheme 8b).[25] Our reaction being different from Sanford's system, both copper and 1,10-phenanthroline (phen) were essential for the oxidative trifluoromethylation of indoles.

To probe the reaction mechanism, *N*-allyl-3-methylindole **9a** was chosen as the test substrate in our oxidative trifluoromethylation reaction, and the ditrifluoromethylated product **11** was obtained in low yield (Scheme 9). The transformation of terminal alkene suggested that a CF_3 radical probably was involved in this reaction system.

Scheme 9. Oxidative Trifluoromethylation of *N*-Allyl-3-Methylindole



The result in Scheme 9 prompted us to explore the oxidative hydrotrifluoromethylation of alkenes using CF_3SiMe_3 as the CF_3 radical source. With much effort, we ultimately developed the hydrotrifluoromethylation of unactivated alkenes with CF_3SiMe_3 under silver catalysis.[26] Addition of 1.0 equiv of 1,4-cyclohexadiene (1,4-CHD) as the H-donor was essential to

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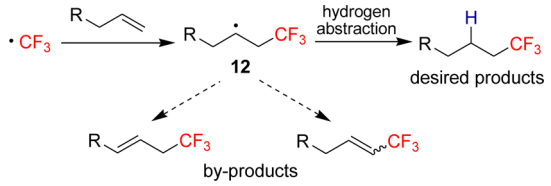
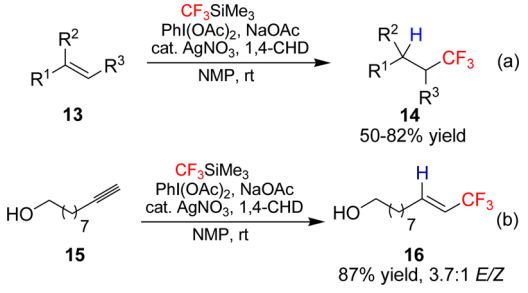
inhibit the competitive reactions from intermediate **12** (Scheme 10).

Scheme 10. Competitive Reactions



Various unactivated alkenes **13** with a wide range of functional groups underwent the hydrotrifluoromethylation reaction smoothly to afford the corresponding products **14** in moderate to excellent yields (Scheme 11a). To our delight, the

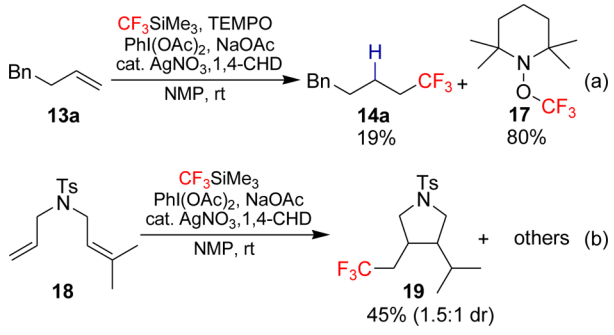
Scheme 11. Hydrotrifluoromethylation of Unactivated Alkenes and Terminal Alkyne



hydrotrifluoromethylation protocol was also suitable for terminal alkyne **15**, producing the trifluoromethylated alkenes **16** in high yields and moderate *E*/*Z* ratio (Scheme 11b).

Preliminary mechanistic experiments are shown in Scheme 12. The inhibition experiment of olefin **13a** was conducted with

Scheme 12. Mechanistic Experiments



the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1.0 equiv), and the desired product **14a** was obtained in only 19% yield together with the TEMPO adduct **17** in 80% yield (Scheme 12a). Furthermore, the reaction of **18**, a radical clock, with CF_3SiMe_3 under the standard reaction conditions gave the trifluoromethylated pyrrolidine **19** in 45% yield (Scheme 12b). These results strongly supported the generation of a CF_3 radical intermediate. This mechanism involving a CF_3 radical intermediate is consistent with the one proposed in Gouverneur's hydrotrifluoromethylation reaction system using electrophilic Umemoto's reagent as the CF_3 source.[27]

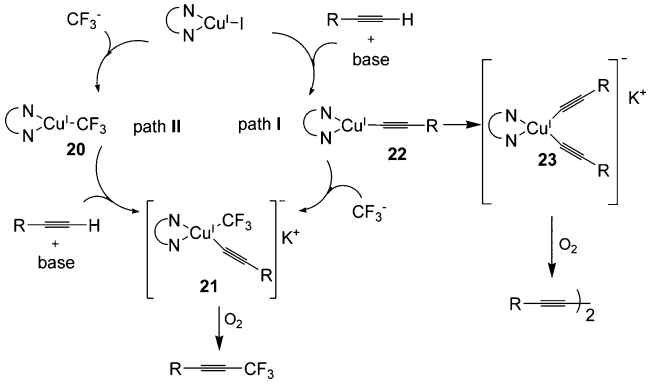
The oxidative trifluoromethylation method via oxidation of $TMSCF_3$ to generate CF_3 radical recently has also been reported by different groups in the synthesis of other CF_3-containing compounds (arenes,[28] heteroarenes,[29] and ketones[30]). It was noteworthy that Wang and Liu reported that a new trifluoromethylating reagent, PhI^+CF_3, was generated by simply mixing $PhI(OAc)_2$, Me_3SiCF_3, and KF.[31] With this reagent, the direct sp^2 C–H trifluoromethylation of ketene dithioacetals and indoles was successfully achieved.

4. TRANSITION-METAL-MEDIATED OR -CATALYZED OXIDATIVE TRIFLUOROMETHYLATION

In the past decades, transition-metal-catalyzed oxidative-coupling reactions have emerged as an attractive and viable alternative to classical cross-coupling reactions.[7] These methods definitely broaden the substrate scope of cross couplings. However, the analogous oxidative cross-coupling reactions between CF_3 anion and nucleophiles to construct carbon–CF_3 bonds have not been reported. The achievement of oxidative trifluoromethylation with the CF_3 anion is a conspicuous challenge due to the inherent instability of the CF_3 anion, especially under the oxidative conditions.

Initially, we focused on the Cu-mediated oxidative trifluoromethylation of terminal alkynes since the C–H bonds of terminal alkynes are highly active. We expected that $CuCF_3$ species **20** or Cu(alkynyl) complex **22** would undergo transmetalation to give the key intermediate Cu(alkynyl)(CF_3) **21**, which would eventually deliver the desired trifluoromethylated product (Scheme 13).

Scheme 13. Possible Reaction Pathway for Oxidative Trifluoromethylation of Terminal Alkynes



Due to the undesired homocoupling of terminal alkynes under oxidative conditions, however, our initial attempt to achieve this oxidative trifluoromethylation reaction by simply mixing the substrate, reagents, and copper catalyst together in one pot under an air atmosphere was completely unsuccessful. This result implied that the formation of Cu(alkynyl)(CF_3)-complex **21** via path I was impossible because of the competitive formation of Cu–alkynyl complex **22** and subsequently bialkynyl–Cu complex **23**. To solve this problem, we hypothesized that the pregenerated $CuCF_3$ species might preferentially afford intermediate **21** and drive the reaction to proceed via path II. Gratifyingly, we found that changing the addition mode, in which terminal alkyne was added slowly by a syringe pump to a premixed CuI/CF_3SiMe_3/KF in *N*,*N*-dimethylformamide (DMF), was actually capable of promoting the formation of the desired trifluoromethylated product, albeit

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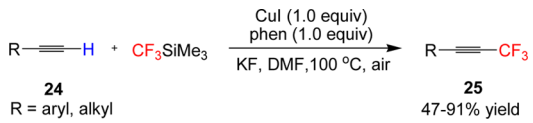
with a low efficiency. Considering the fact that the $CuCF_3$ species was unstable under oxidative conditions, we speculated that use of ligands to enhance the stability of the pregenerated $CuCF_3$ species or employment of excess CF_3SiMe_3 to offset the decomposition of $CuCF_3$ species would raise the active concentration of $CuCF_3$ in the system. To our delight, we found that with the combination of employing 1,10-phenanthroline (phen) as a ligand and increasing the amount of CF_3SiMe_3 to 5 equiv, Cu-mediated oxidative trifluoromethylation of terminal alkynes **24** proceeded smoothly.[11] A variety of functionalized trifluoromethylated acetylenes **25**, which are versatile building blocks for the preparation of other CF_3-containing compounds, were obtained in moderate to excellent yields (Scheme 14).

Scheme 14. Oxidative Trifluoromethylation of Terminal Alkynes



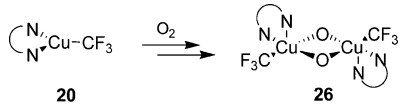
Notably, this reaction represents the first example of oxidative cross-coupling of a nucleophile and CF_3SiMe_3, and the first example of Cu-mediated cross-coupling protocol for the construction of C(sp)−CF_3 bonds. It opens up a new viewpoint to introduce the CF_3 groups into organic molecules.

Our later investigations indicated that the catalytic process could be achieved when CF_3SiMe_3 was slowly added via a syringe pump, rather than in one pot, to the reaction mixture (Scheme 15a).[32] We reasoned that the slow addition of CF_3SiMe_3 could avoid the quick decomposition of the CF_3 anion under the oxidative conditions such that there was sufficient amount of active CF_3 anion to capture the regenerated copper catalyst, affording the key intermediate $CuCF_3$ to continue the catalytic cycle.

On the other hand, we surmised that high temperature required in the stiochiometric and catalytic systems would exacerbate the decomposition of the CF_3 anion, so that large excessive loadings of CF_3SiMe_3 (5 equiv) were required. To reduce the loadings of CF_3SiMe_3, a new system (CuCl/phen/*t*-BuOK/CF_3SiMe_3) developed by Hartwig was used.[33] The oxidative trifluoromethylation was conducted with only 2.0 equiv of CF_3SiMe_3 at room temperature (Scheme 15b).[34]

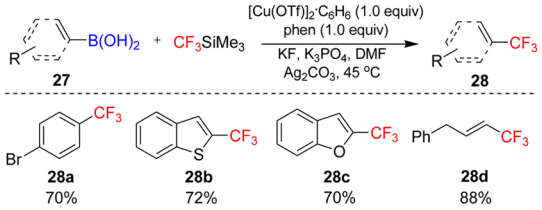
Maseras and Jover proposed that dinuclear Cu species, such as compound **26**, were probably involved in the Cu-catalyzed aerobic oxidative trifluoromethylation of terminal alkynes by computational study (Scheme 16).[35]

Scheme 16. Dinuclear Cu intermediate 26



After the success of Cu-mediated oxidative trifluoromethylation of terminal alkynes, we turned our attention to the oxidative trifluoromethylation of aryl boronic acids. Because of the ease of handling, commercial availability, and stability to heat, air, and water of boronic acid derivatives, we expected that oxidative trifluoromethylation of boronic acids would serve as an attractive alternative to the classical trifluoromethylation of aryl halides. Under the optimal conditions of Cu-mediated oxidative trifluoromethylation of terminal alkynes, however, oxidative trifluoromethylation of aryl boronic acids failed. Using K_3PO_4 as a cobase, the desired transformation could be triggered. Some side products, such as aryl halides and diaryl ethers, were also formed. To inhibit these side products, we chose $[Cu(OTf)]_2{\cdot}C_6H_6$ as the optimal catalyst and Ag_2CO_3 as the new oxidant and carried out the reaction at a lower temperature (45 °C).[12] In contrast to the classical Cu-mediated trifluoromethylation of aryl iodides where electron-deficient substrates exhibit higher reactivity, both electron-deficient and electron-rich aryl boronic acids worked well, providing the desired trifluoromethylated arenes in good to excellent yields (Scheme 17). It was noteworthy that a bromo substituent

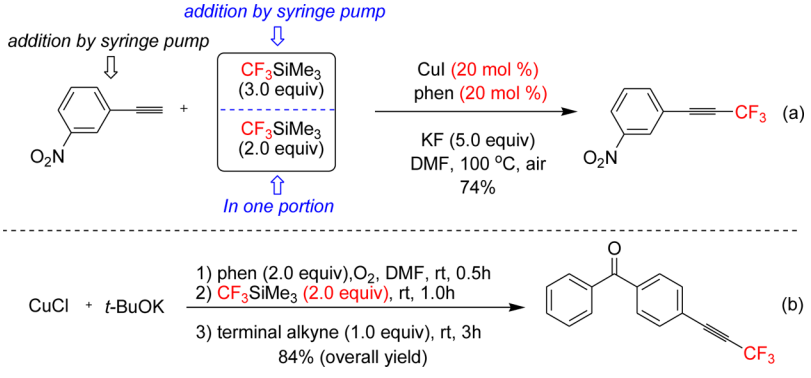
Scheme 17. Representative Products of Oxidative Trifluoromethylation of Boronic Acids



(**27a**) was tolerated. In addition, heteroaryl and alkenyl boronic acids (**27b−d**) could also be trifluoromethylated smoothly under the optimal conditions.

Following the same logic for the achievement of Cu-catalyzed oxidative trifluoromethylation of terminal alkynes, we

Scheme 15. Modified Procedures for Oxidative Trifluoromethylation



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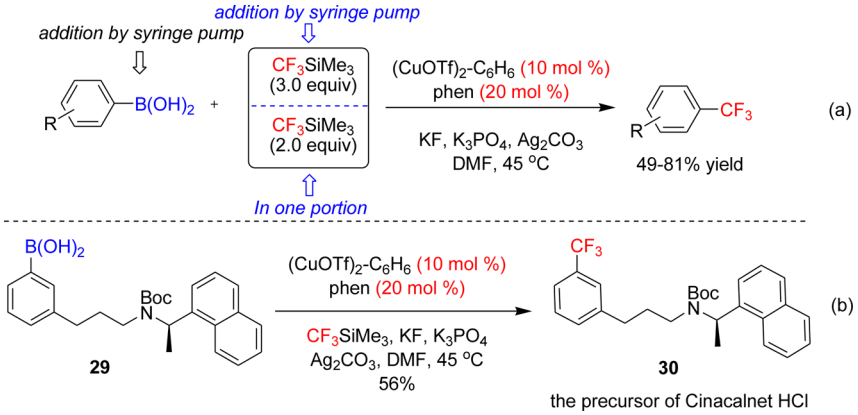
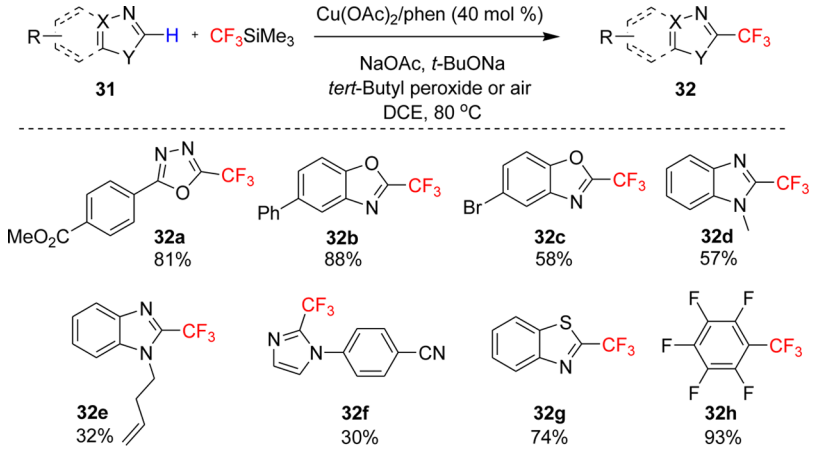
Scheme 18. Cu-Catalyzed Oxidative Trifluoromethylation of Boronic Acids



Scheme 19. Representative Products of Cu-Catalyzed Oxidative Trifluoromethylation of Heteroarenes



also successfully developed the catalytic process for the oxidative trifluoromethylation of aryl boronic acids by simply changing the addition mode of CF_3SiMe_3 (Scheme 18a).[32] Notably, the important precursor **30** for the synthesis of cinacalcet, a calcimimetic agent, could be obtained in 56% yield using the Cu-catalyzed oxidative trifluoromethylation of aryl boronic acid **29** (Scheme 18b).

After our work on the oxidative trifluoromethylation of boronic acids, Buchwald and co-workers also reported a similar but more economical one-pot protocol that employed $Cu(OAc)_2$ as the catalyst and dry O_2 as the oxidant.[36] Hartwig[37] and Gooßen[38] successively developed oxidative trifluoromethylation of aryl boronates using preprepared $[(phen)CuCF_3]$ or potassium (trifluoromethyl)trimethoxyborate, $K[CF_3B(OMe)_3]$. Remarkably, a ligand-free oxidative trifluoromethylation of aryl boronic acids with fluoroform-derived $CuCF_3$ reagent in the atmosphere of air has been disclosed by Grushin.[39] Furthermore, Fu successfully extended our oxidative protocol to alkyl boronic acids.[40]

Although much progress has been made in the transition-metal-mediated or -catalyzed trifluoromethylation of aryl halides and boronic acids, these substrates require prefunctionalizations prior to the trifluoromethylation reactions and thereby lower the step and atom economy. Undoubtedly, the direct trifluoromethylation of aryl C−H bonds would be the most attractive and ideal route to construct aryl−CF_3 bonds. We chose C−H bonds of heteroarenes as the platform for the investigation of direct oxidative trifluoromethylation of aryl C−H bonds since heteroarenes bear similar acidic C−H bonds[41] as those of terminal alkynes and Cu-catalyzed functionalization of heteroaryl C−H bonds has been studied extensively.[42] A catalytic system composed of $Cu(OAc)_2$ and phen with the combination of NaOAc and *t*-BuONa was found to be highly efficient, allowing the direct C−H oxidative trifluoromethylation to proceed smoothly at 80 °C. Various functionalized heteroarenes including 1,3,4-oxadiazole (**31a**), benzo[*d*]-oxazoles (**31b** and **31c**), benzo[*d*]imidazoles (**31d** and **31e**), imidazole (**31f**), and benzo[*d*]thiazole (**31g**), as well as electron-deficient polyfluoroarene (**31h**), could be regioselectively trifluoromethylated, affording the corresponding trifluoromethylated heteroarenes and arenes in moderate to excellent yields (Scheme 19).[25] The efficiency of this transformation is highly dependent on the pK_a of the C−H bond to be trifluoromethylated. For some substrates such as benzo[*d*]-imidazoles and imidazoles that are less acidic, rather low conversions could be observed. Interestingly, when air rather than *tert*-butyl peroxide was used as an oxidant, 1,3,4-oxadiazoles could undergo the desired transformations without any loss of reaction efficiency.

After the success of Cu-mediated or -catalyzed oxidative trifluoromethylation reactions with C-based nucleophiles, we further explored heteroatom-based nucleophiles as the coupling partners to construct heteroatom−CF_3 bonds. After some survey of reaction conditions, we found that several H-phosphonates **33** could be trifluoromethylated in the presence

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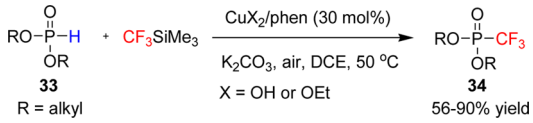
of catalytic amounts of Cu(II) catalyst and phen under an air atmosphere (Scheme 20).[43]

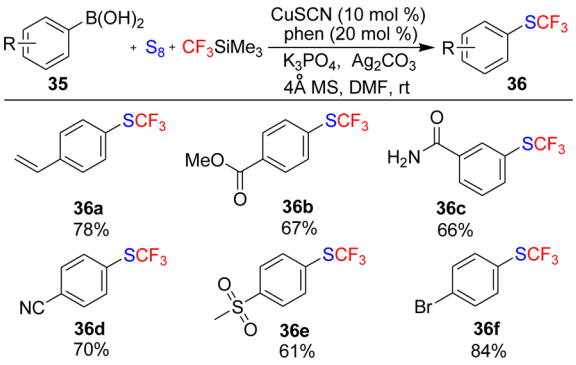
Scheme 20. Oxidative Trifluoromethylation of H-Phosphonates



5. OXIDATIVE TRIFLUOROMETHYLTHIOLATION

Aryl trifluoromethyl sulfides ($ArSCF_3$) are important structural units found in various pharmaceuticals and agrochemicals.[44] Transition metal-mediated or -catalyzed cross-coupling of aryl halides with trifluoromethanethiolates has been proven to be an efficient method for the preparation of $ArSCF_3$ compounds.[45] Given our success in the oxidative trifluoromethylation of aryl boronic acids, we were keen to explore the possibility of achieving the oxidative trifluoromethylthiolation of aryl boronic acids by simply adding elemental sulfur into the previously developed oxidative trifluoromethylation system. Initially, we were afraid that it would be difficult to inhibit the competitive oxidative trifluoromethylation process. Surprisingly, it turned out that only a trace of trifluoromethylated byproducts were observed in the presence of elemental sulfur. With some modifications of reaction conditions, we gratifyingly found that the desired oxidative trifluoromethylthiolation reaction proceeded smoothly in the presence of catalytic amounts of CuSCN and phen at room temperature.[46] The mild conditions allowed for the efficient trifluoromethylthiolation of aryl boronic aicds **35** containing a wide range of functional groups including ester (**35a**), ketone (**35b**), unprotected amide (**35c**), nitrile (**35d**), sulfone (**35e**), and even bromide (**35f**) (Scheme 21). The tolerance of bromides is particularly striking, because

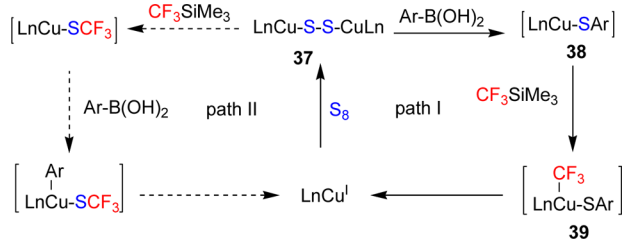
Scheme 21. Representative Products of Oxidative Trifluoromethylthiolation of Aryl Boronic Acids



aryl bromides are highly reactive in the transition metal-mediated or -catalyzed trifluoromethylthiolation reactions. This work also represents an important step forward in the development of the trifluoromethylthiolation reactions.

Mechanistic studies indicated that in the two possible pathways that we initially proposed, the one involving intermediate LnCu(SAr) **38** followed by the formation of intermediate $LnCu(CF_3)(SAr)$ **39** would be more reasonable (Scheme 22, path I). Further oxidation of intermediate **39** and subsequent reductive elimination would give rise to the

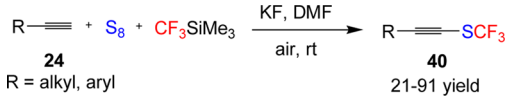
Scheme 22. Proposed Mechanism



expected product. Zhang and Vicic also reported similar transformations of aryl and alkenyl boronic acids using $[NMe_4][SCF_3]$ as a nucleophilic trifluoromethylthiolating agent.[47]

Although remarkable advances have been made in construction of sp^2 C–SCF_3 bonds through transition-metal catalysis, similar cross-coupling processes that facilitate the generation of sp C–SCF_3 bonds have not been explored. On the basis of oxidative trifluoromethylation of terminal alkynes, we sought to develop oxidative trifluoromethylthiolation of terminal alkynes with CF_3SiMe_3 and elemental sulfur. Being different from the case of aryl boronic acids, the desired products were cleanly formed in high yields in the absence of copper catalyst and phen. Interestingly, further investigations showed that oxygen was not required for the oxidative transformation and elemental sulfur did act as a stoichiometric oxidant in the current reaction. This result also explained why this transformation required excessive amounts of elemental sulfur (6.0 equiv). Under the metal-free reaction conditions, the electron-rich and electron-poor aryl and aliphatic alkynes converted cleanly to the corresponding alkynyl trifluoromethyl sulfides in moderate to good yields (Scheme 23).[48] Further investigation revealed that *in situ* generated CF_3S anion species might be the active species in this transformation.

Scheme 23. Oxidative Trifluoromethylthiolation of Terminal Alkynes



6. CONCLUSIONS

Since we proposed the concept of oxidative trifluoromethylation in 2010, oxidative trifluoromethylation reactions have been widely used in the synthesis of various CF_3-containing compounds. This Account summarizes our recent efforts on the development of oxidative trifluoromethylation reactions using widely employed and relatively cheap CF_3SiMe_3 as the nucleophilic CF_3 source from three aspects: via oxidative C–H activation, via generation of CF_3 radical, and via transition-metal catalysis. These new methods allowed novel and efficient constructions of various C(sp, sp^2, sp^3)–CF_3 bonds, and diverse trifluoromethylated alkynes, arenes, and heteroarenes, amines, alkenes, and even phosphonates were easily prepared in moderate to excellent yields under mild conditions. Furthermore, as an extension of the oxidative trifluoromethylation protocols, we also achieved the oxidative trifluoromethylthiolation reactions of aryl boronic acids and terminal alkynes using CF_3SiMe_3 and elemental sulfur as the nucleophilic trifluoromethylthiolating reagent. Due to the importance of the

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CF_3 and SCF_3 moieties in pharmaceuticals and agrochemicals, the present oxidative trifluoromethylation and trifluoromethylthiolation reactions would find wide applications in the pharmaceutical and agrochemical fields.

Of course, several limitations still remain. First, due to the inherent instability of the CF_3 anion, the use of an excess of CF_3SiMe_3 is usually required in most of cases, which decreased the economy and practicability of reactions. Second, the substrate scope and the regioselectivity of the current C−H direct oxidative trifluoromethylathion and trifluoromethylthiolation are significantly limited and poor. Finally, stoichiometric amounts of "un-green" oxidants, such as Ag(I), peroxides, and hypervalent iodines, are required in some cases. Further efforts in out laboratory will focus on the development of more green, economical, and useful oxidative trifluoromethylation and trifluoromethylthiolation reactions.

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Notes

The authors declare no competing financial interest.

Biographies

Lingling Chu received her B.S. degree in engineering from Hefei University of Technology in 2007. In 2012, she received her Ph.D. in organic chemistry from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Professor Feng-Ling Qing. Her doctoral research focuses on the development of oxidative trifluoromethylation reactions. Currently, she is a postdoctoral researcher in David W. C. MacMillan's group at Princeton University.

Feng-Ling Qing received his Ph.D. at the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, under the supervision of Professor Chang-Ming Hu. He was promoted to an Associate Professor at the SIOC in 1992. From 1992 to 1995, he was a postdoctoral fellow at Wyeth Research (Pearl River, New York). He returned to the SIOC in 1995 and became a full Professor in 1997. Since 2001, he has been Cheung Kong Professor at Donghua University. From 2008 to the present, he has been Dean of the College of Chemistry, Chemical Engineering and Biotechnology of Donghua University. He is currently a member of the Editorial Board of *Journal of Fluorine Chemistry*. His research interests include the synthesis and applications of fluorine-containing building blocks, fluorinated bioactive compounds, and fluorinated functional polymers.

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