Advances in trifluoromethylation or trifluoromethylthiolation with copper CF₃ or SCF₃ complexes

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Abstract. The copper CF₃ or SCF₃ complexes as the fluoride sources for the synthesis of trifluoromethylated or trifluoromethylthiolated compounds are reviewed. Compared with the ordinary fluoride reagents, the addition of reactant species in the reaction systems of copper trifluoromethyl or trifluoromethylthio complexes were less, so the reaction systems are relatively simple and easy to operate. In most cases, the trifluoromethylated or trifluoromethylthiolated products were obtained in moderate to excellent yields.

Keywords. Trifluoromethylation; trifluoromethylthiolation; copper complexes; aryl halides; heteroaryl bromides.

1. Introduction

In recent years, the organic compounds containing a trifluoromethyl or trifluoromethylthio group, have been extensively studied in many fields, such as pharmaceuticals and agrochemicals, as the fluorine groups have the potential to improve the biological activity of these compounds. A large number of nonmetallic fluorine reagents, such as NaSO₂CF₃, CF₃SiMe₃, Umemoto’s reagents, Togni’s reagents, difluorinated phosphonium salts, or PhNHSCF₃, have been developed for trifluoromethylation or trifluoromethylthiolation of organic molecules. However, in most cases, these transformations of the fluorine functional groups would suffer from an oxidation or catalytic process in the presence of tert-butyl hydroperoxide (TBHP), hypervalent iodoses, copper catalysts [Cu(I) or Cu(II)], or Ru(bpy)₃(PF₆)₂. With the continuous development of organic fluorine chemistry, some metallic fluorine reagents, such as AgCF₃, AgSCF₃, and Zn(CF₃)₂(DMPU)₂, have also emerged for these transformations. In these metallic fluoride reagents, CuCF₃ and CuSCF₃ derived from HCF₃ and CF₃SiMe₃ respectively, also play an important role in the trifluoromethylation or trifluoromethylthiolation reactions in the effect of B(OMe)₃, Et₃N, tetrakis(tetramethylenediamine) (TMEDA), hexamethylphosphoramide (HMPA) or N-methyl pyrrolidone (NMP) as base.

In less than ten years, some copper trifluoromethyl and trifluoromethylthio complexes, such as compounds (phen)CuCF₃, (phen)Cu(CF₃)₃, (bpy)Cu(CF₃)₃, (Ph₃P)₂CuCF₃, and (bpy)CuSCF₃ (Figure 1), derived from CuSCF₃ or CF₃SiMe₃, have been employed for the direct trifluoromethylation and trifluoromethylthiolation in the absence of oxidants, bases or catalysts in the vast majority of cases. Compared with the above mentioned fluorine reagents, due to the addition of reactant species in the reaction systems being less, the reaction systems are relatively simple, and the reaction conditions are mild and easy to operate. However, the reports on the application of complexes 1–5 in trifluoromethylation and trifluoromethylthiolation reactions are really rare. This review provides an overview of trifluoromethylation and trifluoromethylthiolation using complexes 1–5 over the period from 2011 to the present (Scheme 1). Seven approaches will be reviewed and divided into (i) trifluoromethylation or trifluoromethylthiolation of arenes, aryl halides, heteroaryl bromides, (ii) trifluoromethylation of arylboronic acids, (iii) trifluoromethylation of arylsilanes and heteroarylsilanes, (iv) trifluoromethylthiolation or trifluoromethylthiolation of benzyl bromides, propargylic and allylic halides or trifluoroacetates, (v) trifluoromethylthiolation of vinyl...
1. Trifluoromethylthiolation with copper CF$_3$ or SCF$_3$ complexes.

A series of synthetic methods of complexes 1–5 have been described in the literature, as shown in Scheme 2.

In 2011, Hartwig and co-workers showed that CuO$\text{Bu}$ can react with 1,10-phenanthroline (phen) in benzene as solvent, followed by TMSCF$_3$ at room temperature to afford the complex (phen)CuCF$_3$ 1 in 96% yield. In 2016, Zhang et al. reported that the complexes 2 or 3 can be obtained in 63% or 71% yield by the reaction of CuI with TMSCF$_3$ in the presence of 1,10-phenanthroline (phen) or 2,2'-bipyridine (bpy) as complexing agent and AgF as oxidant at room temperature. The compound CuSCF$_3$, arising from the reaction between TMSCF$_3$ with S$_8$, AgSCF$_3$ with CuBr, or CF$_3$SO$_2$Na with CuCl, reacted with 2,2'-bipyridine to produce the complex 4 in 57% yield. [((Ph$_3$P)$_3$CuF) · 2MeOH obtained from the reaction of CuF$_3$ with PPh$_3$ in MeOH reacted with Me$_3$SiCF$_3$ to afford (Ph$_3$P)$_3$CuCF$_3$ 5 in 97% yield.

2. Trifluoromethylation or trifluoromethylthiolation of arenes, aryl halides, heteroaryl bromides

2.1 Trifluoromethylation of arenes

In 2012, the groups of Hartwig and Qing reported an effective method for the synthesis of trifluoromethyl arenes 7 and 9 employing arenes 6, 8 as substrates and complex 1 as CF$_3$ source (Scheme 3). A large number of arenes 6 containing either electron-withdrawing groups or electron-donating groups, such as methyl, methoxy, dimethylamino, tert-butyl or esters, bromine and trifluoromethyl, were all tested for the trifluoromethylation in the presence of (phen)CuCF$_3$ as CF$_3$ source, [Ir(cod)(OMe)$_2$]$_2$ (cod = cyclooctadiene) and 4,4'-di-tert-butyl-2,2'-bipyridyl (dbpy) as catalysts, and afforded the target compounds 7 in 50–80% yields. The compound 8 reacted with (phen)CuCF$_3$ in the effect of $t$-BuONa to give the trifluoromethylated arene 9 in 43% yield.
2.2 Trifluoromethylation of aryl halides and heteroaryl bromides

In 2011, 2012, 2014 and 2015, a simple synthetic procedure for the generation of trifluoromethylated products 7, 13 and 15 from the reactions of (phen)CuCF3 or (Ph3P)3CuCF3 with aryl iodides 10, aryl bromides 11, heteroaryl bromides 12 or compound 14 in DMF or NMP as solvent was developed by the research groups of Hartwig, Weng, Gade and Grushin (Scheme 4). These research groups showed that the trifluoromethylation reactions were performed well in the presence of (phen)CuCF3 or (Ph3P)3CuCF3 to afford the desired products 7 in high yields ((phen)CuCF3: 68%-quant., (Ph3P)3CuCF3: 50–90%), when aryl iodides 10 containing not only electron-withdrawing groups but also electron-donating groups were used as the starting materials. However, when the aryl bromides 11 were employed as substrates under the conditions of 110 °C or in the effect of PdCl2(dppf) [Dichloro(1,1′-bis(diphenylphosphino)ferrocene)palladium] as catalyst, the reactions gave 60–66% or 53–88% yields of the products 7. Heteroaryl bromides 12 bearing a substituent, such as methyl, CH3O, NO2, aldehyde, ester, cyano, ketone, Cl, or amide, afforded the desired products 13 in moderate to excellent yields (32–99%) within 8 h. The trifluoromethylated product 15 can be obtained in 63% yield, when the substrate 14 was treated with (phen)CuCF3 in DMF as solvent within 12 h.

Scheme 4. Trifluoromethylation of aryl halides and heteroaryl bromides.

2.3 Trifluoromethylthiolation of aryl halides and heteroaryl bromides

In 2013 and 2016, a wide range of aryl halides 16 (aryl iodides and aryl bromides) or heteroaryl bromides 12, reacting with (bpy)CuSCF3 to produce the aryl or heteroaryl trifluoromethyl thioethers 17 or 18 in 57–90% or 4–99% yields was developed by Weng’s group (Scheme 5). In general, the substrates 16 bearing an electron-donating group (CH3, t-Bu, CH3O, Ph) afforded the target products 17 in higher yields than that containing an electron-withdrawing group (CH3CO, CN, CH3OCO, NO2, Cl). The experimental results of this research group showed that a small number of heteroaryl bromides 12, such as 3-bromobenzofuran, 3-bromobenzothiophene, 2-ester substituted 3-bromothiophene and 5-bromopyrimidine gave only 4%, 8%, 17% and 19% yields of the corresponding products 18. The other substrates such as bromopyridines, bromooxazole, bromoquino林, bromoquinoxalines, bromopyrimidines and bromoimidazole afforded the target compounds 18 in modest to excellent yields (21–99%). On the trifluoromethylthiolation of aryl halides, Huang, Weng and co-workers proposed four possible reaction mechanisms, such as σ-bond metathesis, oxidative addition/reductive elimination, iodine atom transfer, and single electron transfer. However, we only give one specific reaction mechanism, as shown in Scheme 6. Firstly, addition reaction of (bpy)CuSCF3 with iodobenzene generated the transition state A, which experienced C-H bond breaking to afford the Cu(III) complexe B. Then, the recombination of chemical bonds of the Cu(III) complexe B was carried out to give the intermediate C, which was decomposed into the product PhSCF3 and compound D.

Scheme 5. Trifluoromethylthiolation of aryl halides and heteroaryl bromides.

3. Trifluoromethylation of arylboronic acids

In 2016, Zhang and Bie reported an effective trifluoromethylation of arylboronic acids in the presence of (phen)Cu(CF3)3 or (bpy)Cu(CF3)3 as CF3 source (Scheme 7). In general, the arylboronic acids 19 containing electron-donating groups afforded the target...
Proposed mechanistic for the trifluoromethylthiolation of iodobenzene.

Scheme 6.

Scheme 7.

Trifluoromethylation of arylboronic acids.

products in higher yields than that having electron-withdrawing groups. In addition, the para-substituted boronic acids are generally more reactive than meta- and ortho-substituted substrates. However, 2-boronoanisole gave only trace yield of the product.

A plausible mechanism for the trifluoromethylation was proposed by Zhang and Bie, as depicted in Scheme 8. In the presence of KF or AgF, (phen)Cu(CF$_3$)$_3$ reacted with ArB(OH)$_2$ to produce the key Cu(III) intermediate A, which would undergo a reductive elimination process to afford the desired product ArCF$_3$ and intermediate B or C. Then, the intermediate B or C can be oxidized by oxygen in the presence of water to give the Cu(III) complexe D, which reacted with ArB(OH)$_2$ to generate the intermediate E, followed by reductive elimination to afford the intermediate F and the product ArCF$_3$.

4. Trifluoromethylation of arylsilanes and heteroarylsilanes

In 2016, an approach for the trifluoromethylation of arylsilanes 21 and heteroarylsilanes 23 using (phen)CuCF$_3$ as CF$_3$ source to synthesize the corresponding trifluoromethylated products 22 and 24 was reported by Hartwig and co-workers (Scheme 9). Arylsilanes 21a–f containing some substituents, such as Cl, CO$_2$Me, CONEt$_2$, MeO, COMe, CN, NH$_2$ and CF$_3$, afforded the trifluoromethylarenes 22a–f in 59–88% yields. However, the substrate 21g and 3,4-dimethylphenylsilane 21h reacted with (phen)CuCF$_3$ to give only moderate yields of the products 22g and 22h (22g: 39%, 22h: 34%). In addition, five and six-membered ring heteroarylsilanes 23a–i derived from pyrrole, furan, indole, pyridine, pyrazine and quinoline, also occurred in the transformation of these fluorine functional groups, and generated the desired products 24a–i in good to excellent yields (51–96%).

5. Trifluoromethylthiolation or trifluoromethylation of benzyl bromides, propargylic and allylic halides or trifluoroacetates

5.1 Trifluoromethylthiolation of benzyl bromides

In 2013, Jiang, Weng and co-workers described an effective and operative nucleophilic trifluoromethylthiolation of benzyl bromides 25 in situ to afford the desired products 26 in good to excellent yields (89–98%), employing (bpy)Cu(SCF$_3$)$_3$ as SCF$_3$ source in CH$_3$CN as solvent (Scheme 10). Under the optimized reaction condition, all reactions proceeded very smoothly, regardless of the substrates 25 containing an electron-withdrawing or electron-donating group, such as alkyl, alkoxy, phenyl, or cyano, halide, nitro and ester.

5.2 Trifluoromethylation of propargylic and allylic halides or trifluoroacetates

In 2012 and 2013, a copper-mediated trifluoromethylation of propargylic and allylic halides or trifluoroacetates employing (Ph$_3$P)$_3$CuCF$_3$ in THF or CDCl$_3$ as solvent was reported by Szabó and co-workers (Scheme 11). The branched propargylic chlorides or trifluoroacetates 29 or 30 reacted with (Ph$_3$P)$_3$CuCF$_3$ in THF at room temperature or 50$^\circ$C to give 58–92% yields of the linear allenyl trifluoromethyl derivatives 31, in the majority of cases. Under the optimized reaction condition, the substituted linear propargylic chlorides or bromides 27 gave the main products of trifluoromethylated alkynes 28 at room temperature. In general, the cinnamyl chlorides 32 having an electron-donating group gave higher yields than that with an electron-withdrawing group. Both linear and branched cinnamyl chlorides or trifluoroacetates 33 afforded the same terminal substituted olefins 34 in moderate to good yields (30–85%) (Scheme 11).

A plausible mechanism for the trifluoromethylation of allylic halides using (Ph$_3$P)$_3$CuCF$_3$ as CF$_3$ source
was proposed by Szabó and co-workers, as shown in Scheme 12. The reaction of allylic halides with \((\text{Ph}_3\text{P})_3\text{CuCF}_3\) formed the allyl copper intermediates A, which may rearrange to afford the intermediates B. Then, the products were obtained by reductive elimination of the intermediates B.

### 6. Trifluoromethylthiolation of vinyl bromides and iodopyridinones

#### 6.1 Trifluoromethylthiolation of vinyl bromides

In 2014 and 2015, Weng and co-workers developed an efficient and convenient trifluoromethylthiolation of α-bromo-α,β-unsaturated carbonyl compounds, β-bromo-α,β-unsaturated ketones, and vinyl bromides to give the corresponding trifluoromethylthiolated products in moderate to good yields with \((\text{bpy})\text{CuSCF}_3\) as SCF₃ source (Scheme 13). When MeCN and xylene were used as solvent, under the conditions of 140°C, the substrates, whether they are α-bromo-α,β-unsaturated aldehydes, ketone, esters, or β-bromo-α,β-unsaturated ketones, were shown to be well tolerated, and afforded the desired products in 53–69% and 44–87% yields, respectively. Vinyl trifluoromethyl thiocarboxylic acids can be obtained in 23–93% yields by the reactions of vinyl bromides with \((\text{bpy})\text{Cu(SCF}_3\text{)}\) in the presence of diglyme as solvent. A plausible mechanism for the trifluoromethylthiolation of β-bromo-α,β-unsaturated ketones was proposed by Weng and co-workers, as shown in Scheme 14. First of all, the 1, 4-addition of \((\text{bpy})\text{CuSCF}_3\) to β-bromo-α,β-unsaturated ketones generated the intermediates A or B. Then, the intermediates A or B underwent a process of \((\text{bpy})\text{CuBr}\) elimination to afford the desired products.

#### 6.2 Trifluoromethylthiolation of iodopyridinones

Recently, some fluorine reagents, such as \text{FSO}_2\text{CF}_2\text{CO}_2\text{CH}_3\) and \text{Me}_3\text{SiCF}_3\) were applied to the
trifluoromethylthiolation of iodopyridinones are rare. In 2016, Weng, You and co-workers described an efficient protocol for the copper-mediated trifluoromethylthiolation of iodopyridinones with (bpy)Cu(SCF₃) in diglyme (Scheme 15). Under the optimized condition, a large number of iodopyridinones containing a substituted phenyl modified by methyl, phenyl, tert-butyl, cyano, aldehyde, ketone, ester, amide, methoxy, chloro, or fluoro at the N atom of the pyridin-2(1H)-one ring were all tested for the trifluoromethylthiolation reactions to afford the corresponding products in moderate to excellent yields.

Scheme 9. Trifluoromethylthiolation of arylsilanes.

Scheme 10. Trifluoromethylthiolation of benzyl bromides.
Trifluoromethylation or trifluoromethylthiolation with copper

Scheme 11. Trifluoromethylation of propargylic and allylic halides or trifluoroacetates.

Scheme 12. Suggested mechanism for the trifluoromethylation.

Scheme 13. Trifluoromethylthiolation of vinyl bromides.

7. Trifluoromethylthiolation of α-bromo ketones

In 2014, an effective protocol for the synthesis of α-trifluoromethylthio-substituted ketones 44 in the presence of α-bromo ketones 43 as substrates and (phen) CuCF3 as SCF3 source was also reported by Weng and Li’s group (Scheme 16). In general, the α-bromo ketones bearing an electron-withdrawing or electron-donating group in the para, meta or ortho position of the benzene ring, such as CN, NO2, CF3, CO2Me, Cl, Br, CH3O, and amino were well tolerated to afford corresponding products 44 in good yields (electron-withdrawing group: 60–83%, electron-donating group: 82–93%, respectively). However, when 2-bromo-4'-hydroxyacetophenone was employed as substrate for the trifluoromethylthiolation, only 32% yield of 1-(4-hydroxyphenyl)-2-(trifluoromethylthio) ethanone was obtained.

8. Trifluoromethylthiolation of acid chlorides

In 2016, a mild and efficient trifluoromethylthiolation of acid chlorides 45 with (bpy)CuSCF3 in dioxane at room temperature to afford the S-trifluoromethyl esters 46 in good to excellent yields (66-99%) was reported by Weng, Chen and co-workers (Scheme 17). From the experimental results, the electronic effect has no significant effect on the yields of the products. The substrates having an electron-withdrawing group (NO2, CN, CF3, CH3CO2, F, Cl, Br) in the position of the benzene ring, were all well tolerated to afford the corresponding products 46 in good to excellent yields (electron-withdrawing group: 60–83%, electron-donating group: 82–93%, respectively). However, when 2-bromo-4'-hydroxyacetophenone was employed as substrate for the trifluoromethylthiolation, only 32% yield of 1-(4-hydroxyphenyl)-2-(trifluoromethylthio) ethanone was obtained.

yields (41–92%). When the R group was naphthyl, pyridine, methyl, or 4-MeC6H4CH2, the reaction can still be performed to give 52–85% yields of the products 42u-y. In addition, other two substituted compounds iodopyridinones 41z, 41aa-ac were also employed for these transformations of fluorine functional groups to afford the corresponding products 42z, 42aa-ac in good to excellent yields (42z: 60%, 42aa: 94%, 42ab: 95%, 42ac: 68%).
Scheme 15. Trifluoromethylthiolation of iodopyridinones.

42a, R = C_6H_5, 73%
42b, R = 4-MeC_6H_4, 72%
42c, R = 4-t-BuC_6H_4, 82%
42d, R = 4-PhC_6H_4, 63%
42e, R = 4-CNC_6H_4, 41%
42f, R = 4-OHCC_6H_4, 56%
42g, R = 4-MeOCC_6H_4, 53%
42h, R = 4-MeO_2CC_6H_4, 52%
42i, R = 4-EtO_2CC_6H_4, 55%
42j, R = 4-Me_2NOCC_6H_4, 71%
42k, R = 4-MeOC_6H_4, 71%
42l, R = 4-CIC_6H_4, 50%
42m, R = 4-FC_6H_4, 92%
42n, R = 3-PhC_6H_4, 47%
42o, R = 3-NO_2C_6H_4, 42%
42p, R = 3-MeO_2CC_6H_4, 45%
42q, R = 3-EtO_2CC_6H_4, 62%
42r, R = 3-MeOC_6H_4, 71%
42s, R = 3-MeCONHC_6H_4, 57%
42t, R = 3,4-Cl_2C_6H_3, 55%
42u, R = 1-naphthyl, 52%
42v, R = 2-pyridyl, 55%
42w, R = 4-pyridyl, 52%
42x, R = Me, 85%
42y, R = 4-MeC_6H_4CH_2, 72%

Scheme 16. Trifluoromethylthiolation of α-bromo ketones.

from the reaction of (bpy)CuSCF_3 with the substrate 45e or 45f (46e: 94%, 46f: 98%).

9. Conclusion

In summary, recent developments in trifluoromethylation or trifluoromethylthiolation reactions by use of copper trifluoromethyl or trifluoromethylthio complexes are presented. Compared with the ordinary fluoride reagents, such as NaSO_2CF_3, CF_3SiMe_3, Umemoto’s reagents, Togni’s reagents, PhNHSCF_3, AgCF_3, AgSCF_3, Zn(CF_3)_2(DMPU)_2 and CuCF_3, the addition of reactant species in the reaction systems of copper trifluoromethyl or trifluoromethylthio complexes was less, so the reaction systems are relatively simple and easy to
operate. In this review, we classified trifluoromethylation and trifluoromethylthiolation reactions under seven headings: (i) trifluoromethylation or trifluoromethylthiolation of arenes, aryl halides, heteroaryl bromides, (ii) trifluoromethylation of arylboronic acids, (iii) trifluoromethylation of arylsilanes and heteroarylsilanes, (iv) trifluoromethylthiolation or trifluoromethylation of benzyl bromides, propargylic and allylic halides or trifluorooacetates, (v) trifluoromethylthiolation of vinyl bromides and iodopyridinones, (vi) trifluoromethylthiolation of α-bromo ketones, (vii) trifluoromethylthiolation of acid chlorides. In the vast majority of cases, the trifluoromethylated or trifluoromethylthiolated products were obtained in moderate to excellent yields. We also expect the copper trifluromethyl and trifluromethylthio complexes to be more widely used in industrial production of trifluoromethylated and trifluoromethylthiolated compounds.

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References

9. (a) Hang Z, Li Z and Liu Z Q 2014 Iodotrifluoromethylation of alkenes and alkynes with sodium trifluoromethanesulfinate and iodine pentoxide Org. Lett. 16 3648; (b) Wang Q, Dong X, Xiao T and Zhou L 2013 Phl(OAc)$_2$-mediated synthesis of 6-(trifluoromethyl)phenanthridines by oxidative cycliza-


19. Zhang S L and Bie W F 2016 Isolation and characterization of copper(III) trifluoromethyl complexes and reactivity studies of aerobic trifluoromethylation of arylboronic acids RSC Adv. 6 70902


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32. Zhao T S N and Szabó K J 2012 Trifluoromethylation of propargylic halides and trifluoroacetates using (Ph₃P)₃Cu(CF₃) reagent Org. Lett. 14 3966


34. Zhu P, He X, Chen X, You Y, Yuan Y and Weng Z 2014 Copper-mediated synthesis of α-trifluoromethylthio- and seleno-α,β-unsaturated carbonyl compounds Tetrahedron 70 672


38. Takasuka T K and Yamazaki T 2015 The modified trifluoromethylation protocol applicable to electronically deficient iodopyridinones Tetrahedron 71 6824


41. Zhang M, Chen J, Chen Z and Weng Z 2016 Copper-mediated effective synthesis of S-trifluoromethyl esters by trifluoromethylthiolation of acid chlorides Tetrahedron 72 3525