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,¹ as the fluorine groups have the potential to improve the biological activity of these compounds. A large number of nonmetallic fluorine reagents, such as NaSO₂CF₃,² CF₃SiMe₃,³ Umemoto's reagents,⁴ Togni's reagents,⁵ difluorinated phosphonium salts,⁶ or PhNHSCF₃,⁷ 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),⁸ hypervalent iodines,⁹ copper catalysts [Cu(I) or Cu(II)],^{3c,10} or Ru(bpy)₃(PF₆)₂.¹¹ With the continuous development of organic fluorine chemistry, some metallic fluorine reagents, such as AgCF₃,¹² AgSCF₃,¹³ and Zn(CF₃)₂(DMPU)₂,¹⁴ have also emerged for these transformations. In these metallic fluorine reagents, CuCF₃ and CuSCF₃ derived from HCF₃¹⁵ and CF₃SiMe₃¹⁶ respectively, also play an important role in the trifluoromethylation or trifluoromethylthiolation

reactions in the effect of B(OMe)₃, Et₃N, tetramethylethylenediamine (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)₃CuCF₃, and (bpy)CuSCF₃ (Figure 1), derived from CuSCF₃¹⁶ or CF₃SiMe₃¹⁷, 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 trifluoromethylation of benzyl bromides, propargylic and allylic halides or trifluoroacetates, (v) trifluoromethylthiolation of vinyl

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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).^{18,22,23,25–27} 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.^{18,22,26} However, when the aryl bromides **11** were employed as substrates under the conditions of 110 °C or in the effect of PdCl₂dppf [Dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium] as catalyst, the reactions gave 60–66% or 53–88% yields of the products **7**.^{18,23} 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.²⁷ 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.²⁵

Scheme 4. Trifluoromethylation of aryl halides and heteroaryl bromides.

Scheme 5. Trifluoromethylthiolation 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).^{28,29} 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).²⁸ The experimental results of this research group showed that a small number of heteroaryl bromides **12**, such as 3-bromobenzofuran, 3-bromobenzo[*b*]thiophene, 2-ester substituted 3-bromothiophene and 5-bromopyrimidine gave only 4%, 8%, 17% and 19% yields of the corresponding products **18**.²⁹ The other substrates such as bromopyridines, bromooxazole, bromoquinolines, bromoquinoxalines, bromopyrimidines and bromoimidazole afforded the target compounds **18** in modest to excellent yields (21–99%).²⁹

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.²⁸ However, we only give one specific reaction mechanism, as shown in Scheme 6.²⁸ Firstly, addition reaction of (bpy)CuSCF₃ with iodobenzene generated the transition state **A**, which experienced C–H bond breaking to afford the Cu(III) complex **B**. Then, the recombination of chemical bonds of the Cu(III) complex **B** was carried out to give the intermediate **C**, which was decomposed into the product PhSCF₃ and compound **D**.

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).¹⁹ In general, the arylboronic acids **19** containing electron-donating groups afforded the target

Scheme 6. Proposed mechanistic for the trifluoromethylthiolation of iodobenzene.

Scheme 7. Trifluoromethylation of arylboronic acids.

products **20** 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 8.¹⁹ In the presence of KF or AgF, (phen)Cu(CF₃)₃ **2** 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 ArCF₃ 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) complex **D**, which reacted with ArB(OH)₂ to generate the intermediate **E**, followed by reductive elimination to afford the intermediate **F** and the product ArCF₃.

4. Trifluoromethylation of arylsilanes and heteroarylsilanes

In 2016, an approach for the trifluoromethylation of arylsilanes **21** and heteroarylsilanes **23** using (phen)CuCF₃ as CF₃ source to synthesize the corresponding trifluoromethylated products **22** and **24** was reported by Hartwig and co-workers (Scheme 9).³⁰ Arylsilanes **21a–f** containing some substituents, such as Cl, CO₂Me, CONEt₂, MeO, COMe, CN, NH₂ and CF₃, afforded the

trifluoromethylarenes **22a–f** in 59–88% yields. However, the substrate **21g** and 3,4-dimethylphenylsilane **21h** reacted with (phen)CuCF₃ 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(SCF₃) as SCF₃ source in CH₃CN as solvent (Scheme 10).³¹ 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 (Ph₃P)₃CuCF₃ **5** in THF or CDCl₃ as solvent was reported by Szabó and co-workers (Scheme 11).^{32,33} The branched propargylic chlorides or trifluoroacetates **29** or **30** reacted with (Ph₃P)₃CuCF₃ **5** in THF at room temperature or 50 °C to give 58–92% yields of the linear allenyl trifluoromethyl derivatives **31**, in the majority of cases.³² Under the optimized reaction condition, the substituted linear propargylic chlorides or bromides **27** gave the main products of trifluoromethylated alkynes **28** at room temperature.³² In general, the cinnamyl chlorides **32** having an electron-donating group gave higher yields than that with an electron-withdrawing group.³³ 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).³³

A plausible mechanism for the trifluoromethylation of allylic halides using (Ph₃P)₃CuCF₃ as CF₃ source

Scheme 8. Proposed mechanism for the trifluoromethylation of arylboronic acids.

was proposed by Szabó and co-workers, as shown in Scheme 12.³³ The reaction of allylic halides with (Ph₃P)₃CuCF₃ formed the allyl copper intermediates **A**, which may rearrange to afford the intermediates **B**. Then, the products **34** 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 **35**, β -bromo- α,β -unsaturated ketones **37**, and vinyl bromides **39** to give the corresponding trifluoromethylthiolated products **36**, **38** and **40** in moderate to good yields with (bpy)CuSCF₃ as SCF₃ source (Scheme 13).^{34–36} When MeCN and xylene were used as solvent, under the conditions of 140°C, the substrates **35** and **37**, 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 **36** and **38** in 53–69% and 44–87% yields, respectively.^{34,35} Vinyl trifluoromethyl thioethers **40** can be obtained in 23–93% yields by the reactions of vinyl bromides **39** with (bpy)Cu(SCF₃) in the presence of diglyme as solvent.³⁶

A plausible mechanism for the trifluoromethylthiolation of β -bromo- α,β -unsaturated ketones was proposed by Weng and co-workers,³⁵ as shown in Scheme 14. First of all, the 1, 4-addition of (bpy) CuSCF₃ to β -bromo- α,β -unsaturated ketones **37** generated the intermediates **A** or **B**. Then, the intermediates **A** or **B** underwent a process of (bpy) CuBr elimination to afford the desired products **38**.

6.2 Trifluoromethylthiolation of iodopyridinones

Recently, some fluorine reagents, such as FSO₂CF₂CO₂CH₃ and Me₃SiCF₃ were applied to the

Scheme 9. Trifluoromethylthiolation of arylsilanes.

Scheme 10. Trifluoromethylthiolation of benzyl bromides.

trifluoromethylation of iodopyridinones for accessing 3-(trifluoromethyl) pyridin-2(1*H*)-one derivatives.^{37,38} However, the reports on the trifluoromethylthiolation of

iodopyridinones are rare. In 2016, Weng, You and co-workers described an efficient protocol for the copper-mediated trifluoromethylthiolation of iodopyridinones **41** with (bpy)Cu(SCF₃) in diglyme (Scheme 15).³⁹ Under the optimized condition, a large number of iodopyridinones **41a-t** 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(1*H*)-one ring were all tested for the trifluoromethylthiolation reactions to afford the corresponding products **42a-t** in moderate to excellent

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

Scheme 12. Suggested mechanism for the trifluoromethylation.

Scheme 13. Trifluoromethylthiolation of vinyl bromides.

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 14. Proposed mechanistic for formation of β -trifluoromethylthio- α , β -unsaturated ketones.

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).⁴⁰ 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).⁴¹ 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 66–99% yields. In addition, naphthoyl chlorides or heteroaryl acid chlorides reacted with (bpy)CuSCF₃ to give the expected products in good to excellent yields (**46a**: 90%, **46b**: 99%, **46c**: 70%, **46d**: 76%). An excellent yield of **46e** or **46f** was also obtained

42a , R = C ₆ H ₅ , 73%	42n , R = 3-PhC ₆ H ₄ , 47%
42b , R = 4-MeC ₆ H ₄ , 72%	42o , R = 3-NO ₂ C ₆ H ₄ , 42%
42c , R = 4- <i>t</i> -BuC ₆ H ₄ , 82%	42p , R = 3-MeO ₂ CC ₆ H ₄ , 45%
42d , R = 4-PhC ₆ H ₄ , 63%	42q , R = 3-EtO ₂ CC ₆ H ₄ , 62%
42e , R = 4-CNC ₆ H ₄ , 41%	42r , R = 3-MeOC ₆ H ₄ , 71%
42f , R = 4-OHCC ₆ H ₄ , 56%	42s , R = 3-MeCONHC ₆ H ₄ , 57%
42g , R = 4-MeOCC ₆ H ₄ , 53%	42t , R = 3,4-Cl ₂ C ₆ H ₃ , 55%
42h , R = 4-MeO ₂ CC ₆ H ₄ , 52%	42u , R = 1-naphthoyl, 52%
42i , R = 4-EtO ₂ CC ₆ H ₄ , 55%	42v , R = 2-pyridyl, 55%
42j , R = 4-Me ₂ NOCC ₆ H ₄ , 71%	42w , R = 4-pyridyl, 52%
42k , R = 4-MeOC ₆ H ₄ , 71%	42x , R = Me, 85%
42l , R = 4-ClC ₆ H ₄ , 50%	42y , R = 4-MeC ₆ H ₄ CH ₂ , 72%
42m , R = 4-FC ₆ H ₄ , 92%	

Scheme 15. Trifluoromethylthiolation of iodopyridinones.

Scheme 16. Trifluoromethylthiolation of α -bromo ketones.

from the reaction of (bpy)CuSCF₃ 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 NaSO₂CF₃, CF₃SiMe₃, Umemoto's reagents, Togni's reagents, PhNHSCF₃, AgCF₃, AgSCF₃, Zn(CF₃)₂(DMPU)₂ and CuCF₃, the addition

Scheme 17. Trifluoromethylthiolation of acid chlorides.

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 trifluoroacetates, (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 trifluoromethyl and trifluoromethylthio complexes to be more widely used in industrial production of trifluoromethylated and trifluoromethylthiolated compounds.

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