# Aryl Sulfonium Salts for Site-Selective Late-Stage Trifluoromethylation

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***Abstract:*** *Incorporation of the $CF_3$ group into arenes has found increasing importance in drug discovery. Herein, we report the first photoredox-catalyzed cross-coupling of aryl thianthrenium salts with a copper-based trifluoromethyl reagent, which enables a site-selective late-stage trifluoromethylation of arenes. The reaction proceeds with broad functional group tolerance, even for complex small molecules on gram scale. The method was further extended to produce pentafluoroethylated derivatives.*

$T$he first mention of $CF_3$-containing molecules to impact pharmacology dates back as far as 1928.[1] Today, trifluoromethyl groups are often used advantageously in drug discovery[2] because they can substantially alter the lipophilicity of small molecules and increase their ability to penetrate the blood–brain barrier,[3] which can result in better in vivo uptake and more desirable transport.[4] The trifluoromethyl substituent is unknown in nature, and conventionally prepared by halogen exchange,[5] the Halex reaction, with harsh reaction conditions. Cross-coupling approaches from aryl bromides or aryl boronic acid derivatives are much more functional-group-tolerant but also require pre-functionalized arenes, and late-stage halogenation and borylation, if successful, often provide constitutional isomers that must be separated.[6] Direct C−H trifluoromethylation does not require pre-functionalization but cannot generally afford the products regioselectively.[7] Herein, we report the first cross-coupling of aryl thianthrenium salts to introduce trifluoromethyl groups. The two-step reaction sequence, thianthrenation followed by cross-coupling, enables a site-selective trifluoromethylation of arenes, even for complex small molecules, which currently cannot be accomplished by other methods. The reaction proceeds well with broad functional

group tolerance, can be performed on gram scale, and was extended to pentafluoroethylation.

Industrial syntheses of simple benzotrifluoride building blocks are typically executed by radical chlorination of toluene derivatives followed by fluorine–chlorine exchange (Swarts reaction).[5] The method has low functional group tolerance and is therefore not appropriate for late-stage functionalization. Several useful and practical functional group interconversion reactions have been developed successfully, such as the trifluoromethylation of aryl halides,[8] boronic acids,[9] and aniline derivatives,[10] but such starting materials are often not accessible at a late stage in a selective fashion unless the functional groups are already present in the molecule. Additionally, trifluoromethylation of aryl iodonium salts is well established, but introduction of hypervalent iodine at a late stage is not.[11] Direct trifluoromethylation of aromatic C−H bonds avoids the necessity for pre-functionalization, and appropriate directing groups, if present, can effectively control the regioselectivity.[12] For example, *ortho*-selective aryl trifluoromethylations were reported by Yu and Bräse with pyridine, amide, or triazene directing groups.[13] C−H bond trifluoromethylation of arenes by $CF_3$ radical addition does not require the presence of directing groups and typically affords mixtures of constitutional isomers. For example, MacMillan and Nagib employed $CF_3SO_2Cl$ as a $CF_3$ radical precursor for photoredox catalysis.[14] The Langlois reagent ($CF_3SO_2Na$) combined with an oxidant was utilized by Baran and co-workers as a $CF_3$ radical precursor to accomplish C−H trifluoromethylations of heterocycles.[15a] Subsequently, zinc sulfinates ($Zn(SO_2CF_3)_2$) were developed as practical trifluoromethylating reagents with improved reactivity.[15b,c]

Furthermore, other reagents such as $Tf_2O$, $C_6F_5I$-$(OCOCF_3)_2$, Togni's reagent, $CF_3$-containing sulfones, and $CF_3X$ (X = I, Br) can be used for aromatic trifluoromethylation.[16] Our group developed an easily handled liquid source of $CF_3I$ based on halogen bonding for direct aromatic trifluoromethylation.[17] With so many new modern methods, trifluoromethylation chemistry has become more reliable than ever, but one important challenge remains: No process is available to generally introduce trifluoromethyl substituents selectively at a late stage in the absence of specific substituents or directing groups. To fill this gap, we present here the first cross-coupling of a trifluoromethyl nucleophile with aryl thianthrenium salts, which can be accessed site-selectively, even for complex small molecules (Scheme 1). For example, the trifluoromethyl derivative of flurbiprofen methyl ester (**2**) was obtained in 81 % yield on gram scale over two steps from flurbiprofen methyl ester. In this case, the reactive position,

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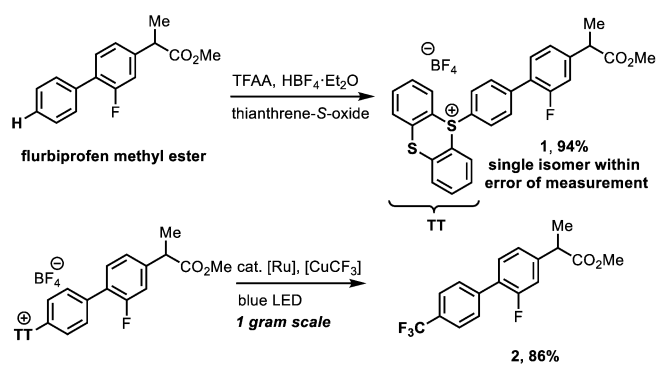
**Scheme 1.** Site-selective C−H thianthrenation followed by trifluoro-methylation.

which is susceptible to metabolic oxidation, can be selectively blocked by a $CF_3$ group with our new method.[18]

Despite the success of aryl–$CF_3$ bond formation through Pd catalysis,[19] aryl thianthrenium salts were not competent coupling partners to efficiently obtain $CF_3$-containing arenes when using literature-reported conditions. Yet, we rationalized that photoredox catalysis, in conjunction with copper complexes, was a promising approach for the desired chemistry, as facile reductive elimination from $Cu^{III}$ complexes that could be accessed from aryl thianthrenium salts could enable the otherwise challenging C−$CF_3$ bond formation (Figure 1).[20] Although oxidative addition to $Cu^I$ is slow,
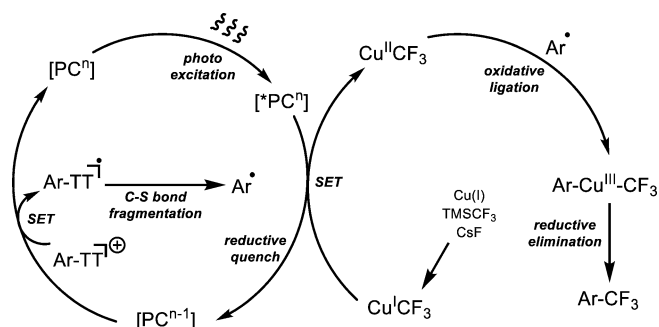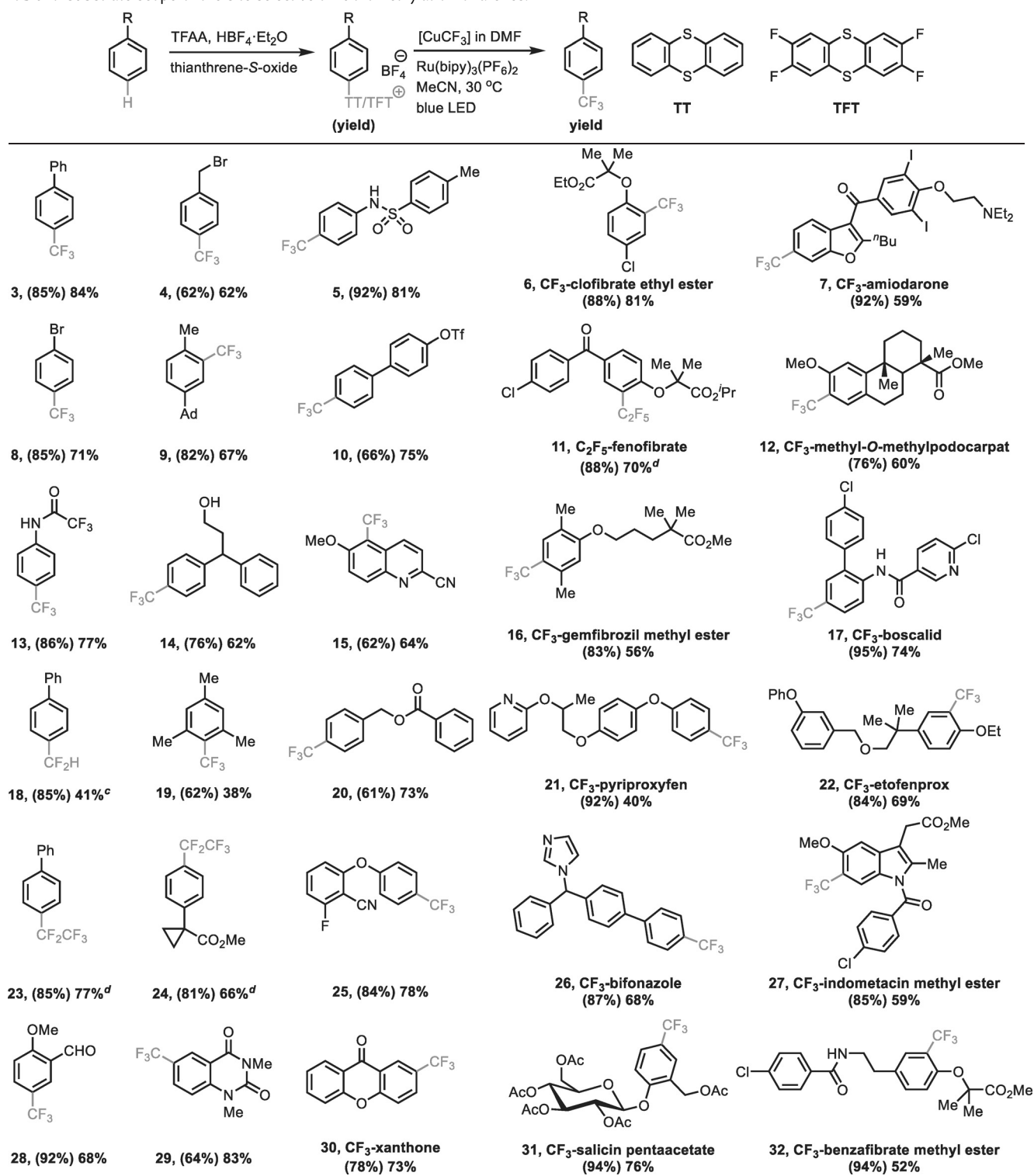


**Figure 1.** Reaction design.

oxidative ligation of aryl radicals to a $Cu^{II}$ species could produce $Cu^{III}$ complexes,[8p,20] while the $Cu^{II}$ species is available from oxidation of [$Cu^ICF_3$] reagents. Trifluoromethyl copper species have been widely used as trifluoromethylation reagents since they were first discovered by Mcloughlin and Thrower in 1969.[21] Moreover, aryl sulfonium salts can likely generate aryl radicals through single electron transfer pathways and C−S bond fragmentation.[22] We thus anticipated a photoredox process as shown in Figure 1. Reductive quenching of the excited photoredox catalyst by the [$CuCF_3$] reagent followed by single electron transfer to the aryl thianthrenium salt would generate an Ar−TT radical. After C−S bond fragmentation, the ensuing Ar radical could ligate to $Cu^{II}$ to form an aryl−$Cu^{III}$−$CF_3$ intermediate, from which reductive elimination could occur to furnish the trifluoromethylated arene.[23]

C−H functionalization proceeds regioselectively: In no example of those shown in Table 1 were we able to isolate any other constitutional isomer for any of the compounds shown. Optimization of the trifluoromethylation (see the Supporting Information, Table S1) revealed that it proceeds equally well with thianthrenium and tetrafluorothianthrenium salts (see the Supporting Information, Figure S1). Ru(bipy)$_3$(PF$_6$)$_2$ was identified as the best photoredox catalyst of those evaluated. The $CuCF_3$ reagent has to be prepared by mixing CuSCN, CsF, and TMSCF$_3$ at 23°C in DMF prior to addition of the $Ru^{II}$ catalyst and the aryl thianthrenium salt for best results. Otherwise, the yield of trifluoromethylated product is substantially lower because of the formation of undesired side products such as hydrodefunctionalized arene. A higher reaction temperature gave rise to the formation of pentafluoroethylated side products, presumably due to the formation of the [$CuC_2F_5$] reagent from [$CuCF_3$].[24] Trifluoromethylation of aryl thianthrenium salts is successful on arenes bearing electron-withdrawing (**8**), -neutral (**3, 4, 9, 10, 14, 20**), and -donating (**5, 13, 25, 28**) groups, as well as substrates bearing heterocycles (**7, 15, 17, 21, 26, 27, 29, 30**) as displayed in Table 1. The reaction is tolerant towards electrophilic functional groups, such as aldehydes (**8**), ketones (**7, 30**), and esters (**6, 12, 16, 27, 32**), and also tolerates protic groups such as alcohols (**14**). All halides (**6, 7, 8, 25**) and evaluated pseudohalides (**10, 15**) are tolerated in both thianthrenation and subsequent trifluoromethylation, which enables late-stage introduction of trifluoromethyl groups even in the presence of aryl iodides as illustrated for amiodarone (**7**). Tertiary amines (**7**), amides (**13, 17, 29, 32**), and sulfonamides (**5**) are compatible as well. Copper-mediated cross-coupling reactions can be sensitive to bulky substituents.[25] Yet, for the trifluoromethylation reported here, *ortho* substituents are generally tolerated (**6, 9, 12, 15, 16, 22, 27, 32**). Even for mesitylene, the trifluoromethylated product was obtained in 38% yield (**19**).[26] Phenols and free carboxylic acid derivatives only deliver the $CF_3$ derivatives in less than 5% yield; nitro groups are not tolerated in the transformation, most likely because of reduction by the $Ru^I$ intermediate. As late-stage aromatic trifluoromethylation is desirable in drug discovery, site-selective trifluoromethylation of a number of pharmaceuticals was evaluated successfully, also on gram scale. The protocol could be extended to the pentafluoro-ethylation of arenes, as shown for **11, 23**, and **24**, by using TMSC$_2$F$_5$ as the pentafluoroethyl source. Furthermore, we obtained a promising result towards the extension of this chemistry to difluoromethylarenes: Difluoromethylbiphenyl **18** was obtained in 41% yield. As [$CuCF_2H$] is less stable than [$CuCF_3$],[27] the difluoromethylation reaction is less powerful than the trifluoromethylation reaction described above.

Preliminary experiments with respect to the mechanism of the photoredox trifluoromethylation are consistent with our design (Figure 1). A Stern–Volmer analysis revealed that the photoexcited $Ru^{II}$ catalyst is quenched faster by the [$CuCF_3$] reagent than the aryl thianthrenium salt and tetrafluorothianthrene (Figure 2). In the presence of 0.5 equiv of TEMPO, the yield of 4-$CF_3$-chlorobenzene (**33**) was only 6% lower than that without the addition of TEMPO, and TEMPO-$CF_3$ (**34**) was detected in less than 5% (Figure 3a). Together with the

**Table 1:** Substrate scope of the site-selective trifluoromethylation of arenes.[a,b]



**3, (85%) 84%**

**4, (62%) 62%**

**5, (92%) 81%**

**6, CF₃-clofibrate ethyl ester**
**(88%) 81%**

**7, CF₃-amiodarone**
**(92%) 59%**

**8, (85%) 71%**

**9, (82%) 67%**

**10, (66%) 75%**

**11, C₂F₅-fenofibrate**
**(88%) 70%ᵈ**

**12, CF₃-methyl-O-methylpodocarpat**
**(76%) 60%**

**13, (86%) 77%**

**14, (76%) 62%**

**15, (62%) 64%**

**16, CF₃-gemfibrozil methyl ester**
**(83%) 56%**

**17, CF₃-boscalid**
**(95%) 74%**

**18, (85%) 41%ᶜ**

**19, (62%) 38%**

**20, (61%) 73%**

**21, CF₃-pyriproxyfen**
**(92%) 40%**

**22, CF₃-etofenprox**
**(84%) 69%**

**23, (85%) 77%ᵈ**

**24, (81%) 66%ᵈ**

**25, (84%) 78%**

**26, CF₃-bifonazole**
**(87%) 68%**

**27, CF₃-indometacin methyl ester**
**(85%) 59%**

**28, (92%) 68%**

**29, (64%) 83%**

**30, CF₃-xanthone**
**(78%) 73%**

**31, CF₃-salicin pentaacetate**
**(94%) 76%**

**32, CF₃-benzafibrate methyl ester**
**(94%) 52%**

[a] Reaction conditions for the first step: Arene (1.0 equiv), trifluoroacetic anhydride (3.0 equiv), HBF₄·Et₂O or triflic acid or BF₃·Et₂O or TMSOTf (1.2 equiv), (tetrafluoro)thianthrene S-oxide (1.0 equiv) in MeCN (0.4 M to 1.0 M), 0°C to 23°C, 3 h to 12 h. Reaction conditions for the second step: CuSCN (1.5 equiv), CsF (2.0 equiv), TMSCF₃ (1.5 equiv) in DMF (c = 0.3 M) at 23°C for 30 min, followed by addition of aryl (tetrafluoro)thianthrenium salts (0.2–0.3 mmol), Ru(bipy)₃(PF₆)₂ (2 mol%) in MeCN (c = 0.2 M), blue LED (34 W), 30°C, 3 h. [b] Yield of isolated product; yield in parentheses for the first step. [c] TMSCF₂H (1.5 equiv) instead of TMSCF₃. [d] TMSC₂F₅ (1.5 equiv) instead of TMSCF₃.

observation of 40% remaining [CuCF₃] reagent after the reaction, these results indicate that a CF₃ radical may not be

involved in the trifluoromethylation pathway.[10a,b, 16c] We also observed biaryl formation (**36**) under the standard conditions
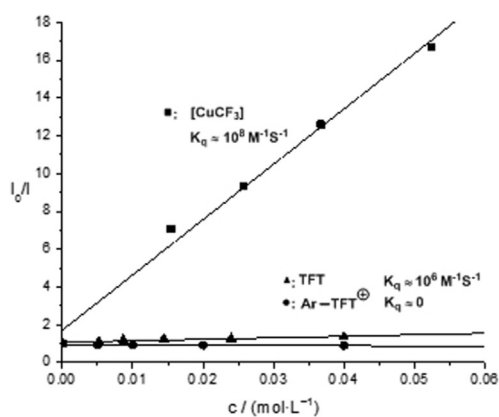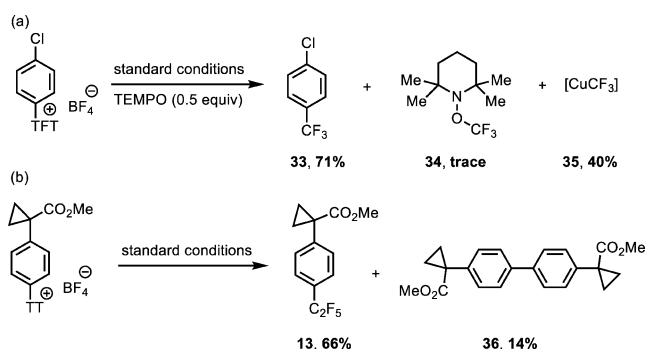
**Figure 2.** Stern–Volmer analysis.



**Figure 3.** Control experiments. [a] TEMPO trapping experiments for possible Radical intermediates. Yields determined by $^{19}F$ NMR analysis. [b] Biaryl formation from aryl thianthrenium salt.

(Figure 3b), which could be derived from reductive elimination from Ar–Cu$^{III}$–Ar after oxidative ligation of two aryl radicals to Cu$^{I}$.

In conclusion, we have reported a site-selective late-stage introduction of trifluoromethyl groups into arenes. The two-step procedure entails exquisitely selective thianthrenation followed by chemoselective photoredox-mediated trifluoromethylation of the aryl thianthrenium salts. Mechanistically, the reaction can take advantage of the interplay between facile bond formation mediated by copper complexes and facile photoredox catalysis of aryl thianthrenium salts. Preliminary results indicate that the approach may be more general for the introduction of other fluoroalkyl groups such as difluoromethyl or pentafluoroethyl groups.

### Conflict of interest

A patent application (country of application: Germany, application number: EP18204755.5) dealing with the use of thianthrene and its derivatives for C−H functionalization, and tetrafluorothianthren-S-oxide, has been filed. T.R. and F.B. may benefit from thianthrene S-oxide sales.

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[27] The freshly prepared [CuCF₃] reagent is a yellowish DMF solution and stable over 3 h (Ref. [24c]). The [CuCF₂H] reagent prepared with the same method formed visible black precipitate.