Photoredox Catalytic Trifluoromethylation and Perfluoroalkylation of (Hetero)arenes Using Trifluoroacetic and Related Carboxylic Acids

Dehang Yin,‡ Dengquan Su,‡ and Jian Jin*

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ABSTRACT: A mild and practical method has been achieved that allows for the direct C–H trifluoromethylation, perfuoroalkylation and chlorodifluoromethylation of (hetero)arenes using inexpensive and abundant trifluoroacetic acid and the corresponding carboxylic acids. A diverse array of arenes and heteroarenes were successfully transformed into valuable fluoroalkylated compounds. The combination of photoredox catalysis and a diaryl sulfoxide provides a platform for the facile generation of fluoroalkyl radicals from the corresponding fluoroalkyl carboxylic acids under mild conditions.

Fluorine is the most electronegative element, which results in two facts just like two sides of the same coin. In general, fluorinated drugs have better membrane permeability and increased bioavailability compared with their non-fluorinated analogues because of the changes in the physical and chemical properties.[1] On the other hand, the uniqueness of fluorine renders the installation of itself a challenging task.[2] Trifluoromethyl group is one of the privileged moieties in modern drug discovery. Among the top 200 small molecule pharmaceuticals by retail sales in 2018, there were 15 drugs containing at least one trifluoromethyl group, mostly (12 out of 15) on their aryl or heteroaryl scaffolds. Therefore, simple methodologies for the incorporation of trifluoromethyl and fluoroalkyl groups into arenes and heteroarenes are highly desirable.[3] While cross-coupling approaches from aryl halides,[4] boronic acids,[5] silanes,[6] and aniline derivatives[7] have facilitated the CF_3 introduction, the direct aromatic C–H trifluoromethylation represents a straight manner not requiring pre-functionalization. Recently, transition metal-catalyzed C–H activation has emerged as an effective strategy for the construction of CF_3-containing (hetero)arenes.[8] Very recently, Ritter reported a site-selective late-stage trifluoromethylation of arenes via the aryl sulfonium salt intermediates.[9] Moreover, there is a renaissance in aromatic C–H trifluoromethylation by the CF_3 radical addition mechanism.[10] A variety of reagents have been extensively used as CF_3 radical precursors, including CF_3I,[11] CF_3Br,[12] CF_3SO_2Cl,[13] $(CF_3SO_2)_2O$,[14] $CF_3SO_2CH(Me)COPh$,[15] Togni reagent,[16] Umemoto reagent,[17] $TMSCF_3$,[18] Langlois reagent $NaSO_2CF_3$,[19] and $Zn(SO_2CF_3)_2$.[20] Nevertheless, the high cost, environmental impact, and multistep preparation of these reagents hamper their further application on large scales. In this regard, it is a long-term interest for chemists to develop new trifluoromethylation reactions with inexpensive and easy-to-handle CF_3 sources.

Trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) are among the most attractive trifluoromethylation reagents with respect of their low prices, ease of handling, and availability in large quantities. The major challenge associated with this type of transformations is to produce the trifluoroacetate radical under mild conditions, which after prompt CO_2 extrusion affords the desired CF_3 radical. Yoshida and subsequently Bräse disclosed that bis(trifluoroacetyl)peroxide (BTFAP) generated from TFAA and hydrogen peroxide could undergo a homolytic cleavage, followed by the release of CO_2 to yield the CF_3 radical.[21] Remarkably, Stephenson reported that the adducts of TFAA and pyridine *N*-oxide derivatives were ready to be reduced via a single-electron transfer pathway to furnish the CF_3 radical effectively.[22] Very recently, Qing developed a hypervalent iodine reagent $C_6F_5I(OCOCF_3)_2$ easily accessible from C_6F_5I and TFA by an oxidation procedure, which could provide the CF_3 radical under reductive conditions as well.[23] TFA and its salts are commercially abundant and low priced. However, because of their exceedingly high oxidation potentials, the direct oxidation of TFA and its salts to the trifluoroacetate radical requires harsh conditions (Figure 1, oxidative pathway), for instance, strong oxidants,[24] electrolysis with forcing potentials,[25] high temperatures,[26] and ultraviolet irradiation.[27] In addition, a large excess of TFA or its salts was usually necessary in these reactions. For all these reasons, mild and efficient protocols for the direct conversion of TFA to CF_3 radical are still in high demand.

Herein, we present a new strategy for the use of TFA as a trifluoromethylation reagent via visible light photoredox catalysis. The working hypothesis is outlined in Figure 1. We envisioned that TFA would condense with a sulfoxide to form the sulfonium intermediate, followed by a single-electron transfer event with the photo-excited $*Ru(bpy)_3^{2+}$ to afford $Ru(bpy)_3^{3+}$,[28] a sulfide, and trifluoroacetate radical after fragmentation. The resultant radical should rapidly collapse to generate the CF_3 radical, which would add to the arene to form the radical adduct. Finally, the radical adduct could be oxidized by $Ru(bpy)_3^{3+}$, and then deprotonated to furnish the trifluoromethylated arene, while regenerating the photocatalyst $Ru(bpy)_3^{2+}$.

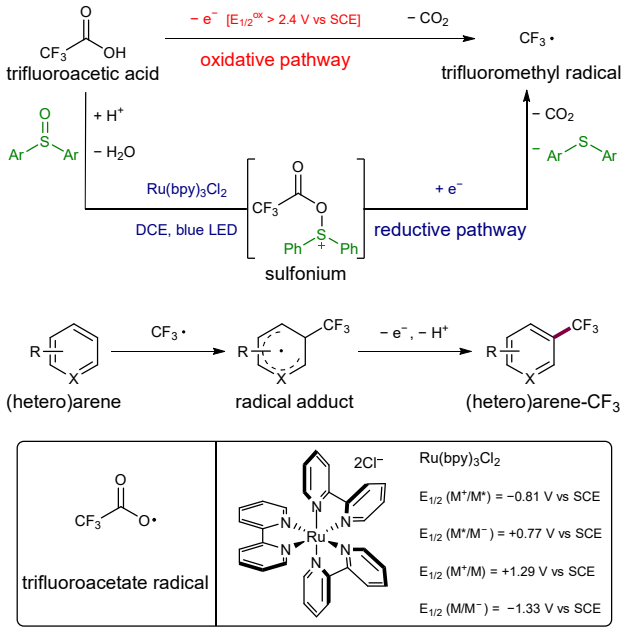
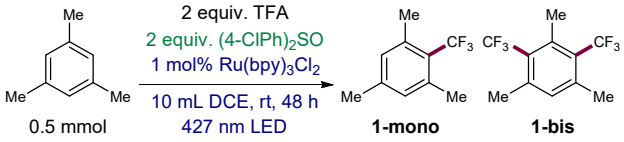


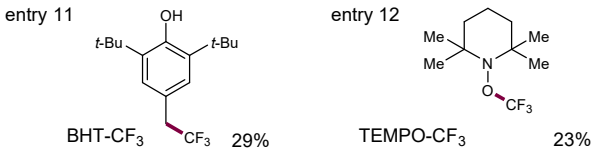
Figure 1. Working hypothesis for the trifluoromethylation.

To explore the proposed aromatic C–H trifluoromethylation with TFA, mesitylene was chosen as the model substrate (Table 1). Our initial experimental results showed that DMSO was not a capable activator as compared to diaryl sulfoxides. After careful investigation of various reaction parameters, the trifluoromethylation products **1-mono** and **1-bis** were obtained in a total yield of 76% (mono:bis = 6:1) with bis(4-chlorophenyl) sulfoxide as the activator (entry 1). This sulfoxide is commercially available and inexpensive, and could be recycled quantitatively in the forms of sulfoxide and thioether. Besides, other sulfoxides were also evaluated for this reaction. While bis(4-bromophenyl) sulfoxide exhibited a comparable efficiency, the electron-richer sulfoxides were less reactive (entries 2–4). Moreover, replacement of the solvent with CH_2Cl_2 resulted in a decreased total yield (62%, entry 5). To our delight, the switch of irradiation wavelength from 427 nm to 390 nm rendered an improved outcome (80%, entry 6). When both TFA and sulfoxide were reduced to 1 equivalent each, it still afforded the products in 59% combined yield (entry 7). Control experiments indicated that the sulfoxide, photocatalyst and light were all essential to this transformation (entries 8–10). Finally, by the addition of free radical scavengers, the aromatic C–H trifluoromethylation was severely inhibited with BHT (entry 11) and even shut down (entry 12) in the presence of TEMPO along with the formation of BHT-CF_3 and TEMPO-CF_3 adducts, respectively, supporting a radical mechanism in these transformations.

Table 1. Optimization for the Trifluoromethylation[a]



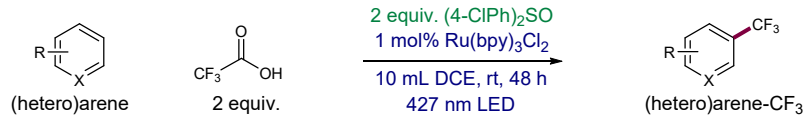
Entry	Variation from standard conditions	1-mono/1-bis, % Yield
1	none	65/11
2	$(4\text{-BrPh})_2SO$ instead of $(4\text{-ClPh})_2SO$	60/13
3	Ph_2SO instead of $(4\text{-ClPh})_2SO$	55/5
4	$(4\text{-MePh})_2SO$ instead of $(4\text{-ClPh})_2SO$	57/5
5	CH_2Cl_2 instead of DCE	57/5
6	390 nm instead of 427 nm	68/12
7	1 equiv. TFA and 1 equiv. $(4\text{-ClPh})_2SO$	54/5
8	without sulfoxide	0/0
9	without photocatalyst	0/0
10	without light	0/0
11	2 equiv. BHT	37/1
12	2 equiv. TEMPO	0/0

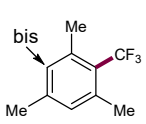


[a]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. BHT = 3,5-di-tert-butyl-4-hydroxytoluene. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

With the established optimal conditions, we began to examine the substrate scope of the decarboxylative trifluoromethylation protocol by employing structurally diverse arenes and heteroarenes. As shown in Scheme 1, a variety of aromatic compounds could be transformed into the valuable trifluoromethylated products in moderate to excellent isolated yields. Electron-enrichment favors the electrophilic trifluoromethylation. Benzene derivatives bearing electron-donating alkyl or alkoxy substituents were amenable to the protocol (**1**–**12**). It is of note that the liable boronate group was tolerated under the reaction conditions, and could be utilized for further transformations (**2**). To our delight, the trifluoromethylation of naphthalene proceeded well with a preference at the α position (**13**). The introduction of methoxy groups also rendered quinone and pyridine good substrates for the protocol (**14** and **15**). A series of pyridinones and coumarins reacted selectively at the α positions (**16**–**22**). Moreover, five-membered heteroarenes proved suitable substrates for the radical trifluoromethylation, including pyrroles, indoles, furans, benzofurans, thiophens, and benzothiophens (**23**–**51**). For this type of heteroarenes, the 2-positions if available were preferentially trifluoromethylated. Gratifyingly, the acid-sensitive Boc protecting group survived from the reaction (**24** and **32**). Notably, the compatibility with boronate and bromide groups illustrated an orthogonal reactivity to the transition metal-catalyzed C–X trifluoromethylation (**2**, **17**, **31** and **46**). Then, the more complex, biologically active heteroarenes, caffeine and pentoxifylline, were also functionalized (**52** and **53**), as well as the electron-deficient oxazole substrate (**54**).

Scheme 1. Scope of the arenes and heteroarenes for trifluoromethylation[a]





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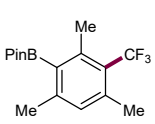

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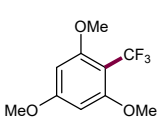

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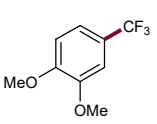

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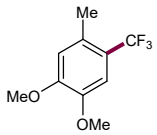

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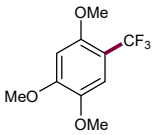

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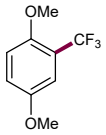

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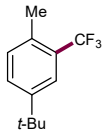

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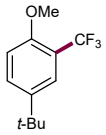

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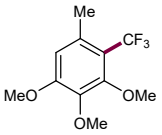

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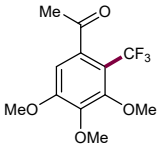

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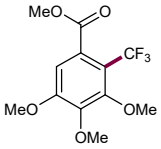

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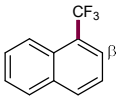

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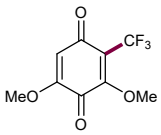

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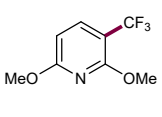

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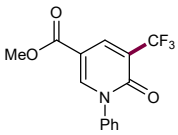

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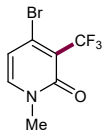

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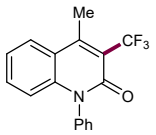

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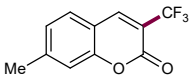

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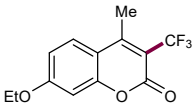

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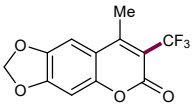

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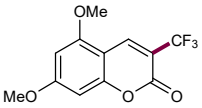

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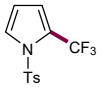

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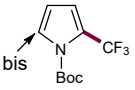

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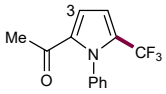

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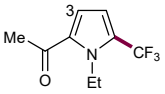

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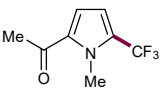

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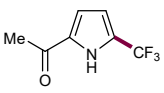

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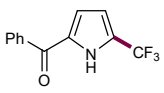

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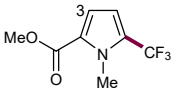

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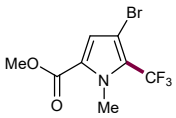

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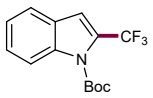

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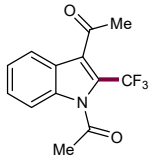

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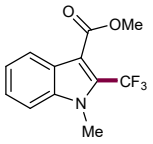

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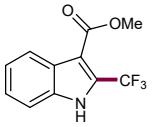

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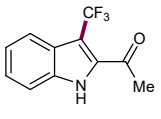

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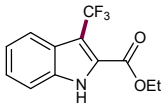
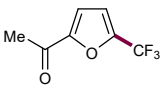
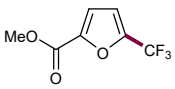


37, 45%



38, 62%



39, 59%

40, 58%

41, 43%

42, 59%

43, 44%

44, 31%

45, 44%

46, 56%

47, 60%

48, 58% (1.8:1)

49, 64%

50, 65%

51, 52%

52, 35%

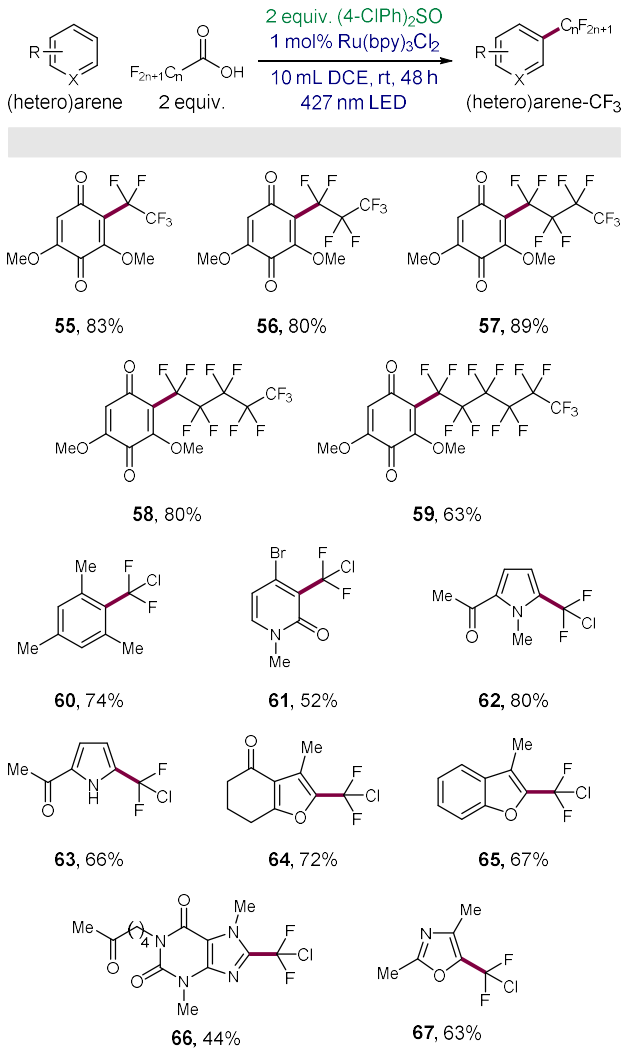
53, 30%

54, 67%

[a]Isolated yields. [b]390 nm LED used. [c]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard.

While a great deal of efforts has been devoted to the CF_3 introduction, synthetic procedures for incorporating other fluoroalkyl (Rf) groups are relatively limited. To this end, we decided to investigate the scope of fluoroalkyl carboxylic acids, which resulted in the extension of the current protocol to efficient C–H perfuoroalkyaltion and chlorodifluoromethylation[29] (Scheme 2). We were pleased to find with the corresponding perfluoroalkyl carboxylic acids, the C_2F_5, C_3F_7, C_4F_9 and C_5H_{11} groups were successfully installed onto the arene ring without loss of reactivity as the chain goes longer (**55**–**58**). Until the case of C_6F_{13}, a diminished yield was observed perhaps because of the poor solubility of $C_6F_{13}CO_2H$ (**59**). Furthermore, the chlorodifluoromethylation proceeded smoothly with a broad range of arenes and heteroarenes (**60**–**67**).

Scheme 2. Scope of the fluoroalkyl carboxylic acids



[a]Isolated yields. [b]390 nm LED used. [c]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard.

In summary, we have developed a mild and practical method that allows for the decarboxylative radical trifluoromethylation, perfuoroalkylation and chlorodifluoromethylation of (hetero)arenes using inexpensive and abundant trifluoracetic acid and the related carboxylic acids. A diverse array of arenes and heteroarenes were successfully transformed into valued fluoroalkylated compounds. The combination of photoredox catalysis and a diarylsulfoxide provides a platform for the facile generation of fluoroalkyl radicals from the corresponding fluoroalkyl carboxylic acids under mild conditions. Further development of our described protocol in terms of easy removal the sulfide byproduct as well as possible use of the sulfoxide activator in a catalytic amount is under active investigation in our lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

Experimental procedures; spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

*jjin@sioc.ac.cn.

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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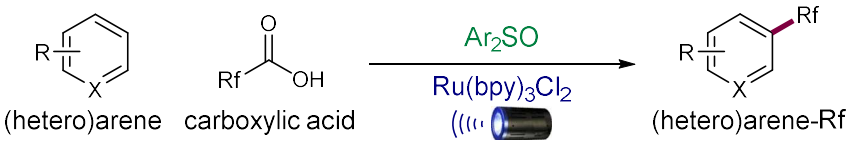

(hetero)arene carboxylic acid (hetero)arene-Rf

Rf = CF_3, C_2F_5, C_3F_7, C_4F_9, C_5F_{11}, C_6F_{13}, CF_2Cl