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Radical C-H Trifluoromethoxylation of (Hetero)arenes with Bis(trifluoromethyl)peroxide

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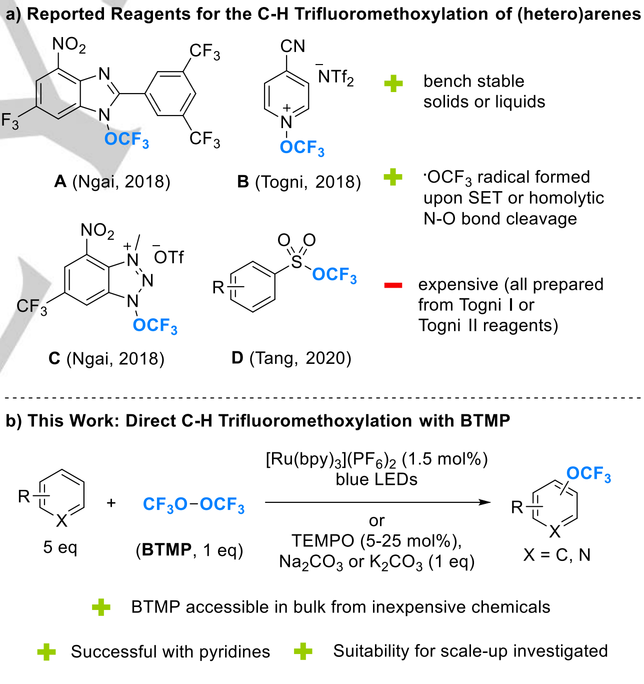
Abstract: Trifluoromethoxylated (hetero)arenes are of great interest for several disciplines, especially in agro- and medicinal chemistry. Radical C-H trifluoromethoxylation of (hetero)arenes represents an attractive approach to prepare such compounds but the high cost and low atom economy of existing •OCF_3 radical sources makes them unsuitable for the large-scale synthesis of trifluoromethoxylated building blocks. Herein, we introduce bis(trifluoromethyl)peroxide (BTMP, CF_3OOCF_3) as a practical and efficient trifluoromethoxylating reagent that is easily accessible from inexpensive bulk chemicals. Using either visible light photoredox or TEMPO catalysis, trifluoromethoxylated arenes could be prepared in good yields under mild conditions directly from unactivated aromatics. Moreover, TEMPO catalysis allowed for the one-step synthesis of valuable pyridine derivatives, which have been previously prepared via multi-step approaches.

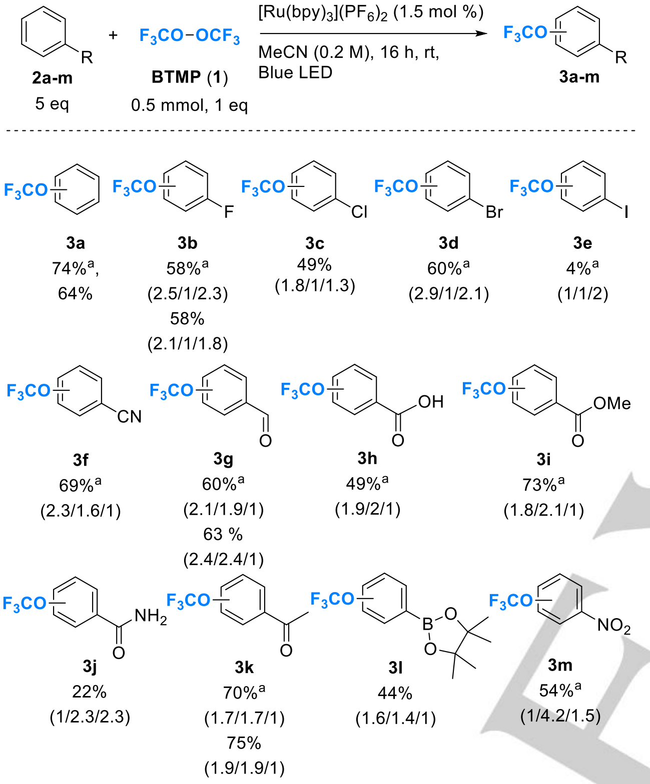
Fluorinated agrochemicals and pharmaceuticals are of great importance due to the beneficial effects fluorine and fluorinated groups can have on a molecule's potency, metabolic stability, selectivity and toxicity.[1] In the last three decades, compounds containing one or more fluorine atoms made up 22% of all globally registered small-molecule drugs[1k] while, in the time period 1998-2020, 53% of all new agrochemicals were organofluorine compounds.[1l] Trifluoromethoxylated arenes and heteroarenes are attracting increasing attention as up-and-coming fluorine-containing moieties. With a Hansch parameter (Π = 1.04) in between that of SCF_3 (1.44) and CF_3 (0.88) and a notably lower electron-withdrawing influence than many other commonly employed fluorinated groups (σ_p = 0.54 (CF_3), 0.50 (SCF_3), 0.35 (OCF_3)),[2] the OCF_3 moiety allows for a fine-tuning of a molecule's biological activity and bioavailability. Furthermore, fluorine-specific stereoelectronic effects result in unconventional conformational preferences not encountered with other substituents.[3] To date, several drugs (eg. Pretomanid, Delamanid, Sonidegib, Riluzol, Celikalim) and agrochemicals (eg. Indoxacarb, Thifluzamide, Flurprimidol) featuring an Ar-OCF_3 moiety have been developed.[4]

Despite this great potential, the study of OCF_3-substituted (hetero)arenes has been hindered by the lack of practical methods to synthesize them.[4] Direct trifluoromethoxylation reactions, wherein the OCF_3 moiety in installed as an intact functional group onto an arene or heteroarene are especially scarce. With no electrophilic sources of the OCF_3 group available and cross-coupling methodologies hampered by the inherent instability of the $^{-}OCF_3$ anion towards β-fluoride elimination, radical trifluoromethoxylation arguably represents the most attractive approach. In 2018, Ngai and co-workers reported a breakthrough in this area by introducing a bench stable reagent **A** (Scheme 1a) that provides the •OCF_3 radical upon photochemical activation.[5] Subsequent reports by the groups of Ngai, Togni and Tang disclosed additional •OCF_3 sources (**B**-**D**), which could be employed in radical C-H trifluoromethoxylation reactions with unactivated arenes.[6] While these reagents are bench stable and convenient on a laboratory scale, each is prepared from either the Togni I or Togni II electrophilic trifluoromethylating reagents. The high cost of these precursors makes large-scale applications unpractical while stoichiometric amounts of organic by-products are produced, which must be separated from the reaction mixture.



Scheme 1. Radical C-H trifluoromethoxylation of (hetero)arenes. a) Previously reported reagents. b) This work: BTMP as a practical •OCF_3 source.

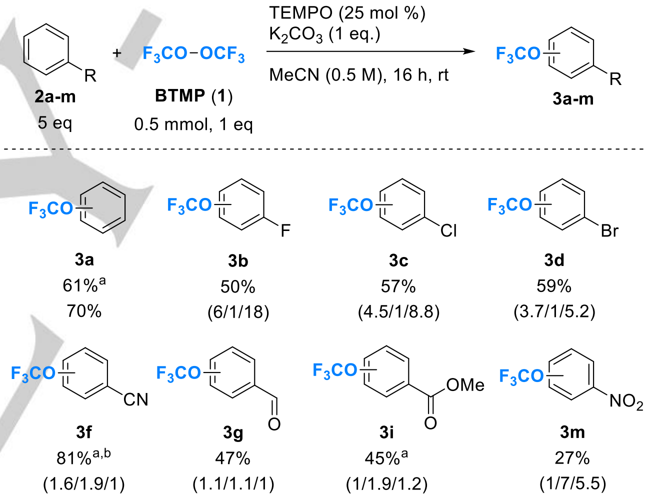
With the aim of developing a practical method suitable for larger scale production of trifluoromethoxylated arene and heteroarene building blocks, our attention was drawn to bis(trifluoromethyl)peroxide (BTMP, **1**) as a potential source of •OCF_3. This compound can be prepared on a large scale from the inexpensive bulk chemicals CO and F_2, and is remarkably stable towards both thermal and photochemical decomposition.[7] A small number of studies demonstrate, however, that BTMP can transfer an OCF_3 group onto organic substrates, although the forcing conditions (high temperature[8], UVA light[9]) employed to activate the peroxide drastically limited the substrate scope and resulted in only low yields and selectivities. Here we report the successful application of BTMP as a practical trifluoromethoxylating reagent under mild conditions employing either visible light photoredox or TEMPO catalysis (Scheme 1b). Using both activation modes, trifluoromethoxylated arenes could be prepared in a single step from simple aromatic feedstocks. The potential of these methods for the production of valuable OCF_3-containing building blocks is further demonstrated by the one-step preparation of (trifluoromethoxy)pyridines, which till now have been prepared via multi-step syntheses.



Scheme 2. Scope of the photocatalytic C-H trifluoromethoxylation of arenes using BTMP. ^{19}F NMR yields using $PhCF_3$ as an internal standard, ratio *ortho-/meta-/para-* determined by ^{19}F NMR shown in brackets. ^{a}With 0.1 equiv KF.

In an initial experiment, BTMP (**1**, 1 eq.) was condensed into an acetonitrile solution containing the photocatalyst $[Ru(bpy)_3](PF_6)_2$ (bpy = 2,2′-bipyridine, 1 mol%) and benzene (**2a**, 10 eq.).[10] After 16 h irradiation with visible light from blue LEDs, we were delighted to observe efficient formation of (trifluoromethoxy)benzene **3a** in 48% ^{19}F NMR yield (internal standard = $PhCF_3$). Working on the hypothesis that single electron transfer from the excited photocatalyst to BTMP followed by mesolysis results in $\bullet OCF_3$ formation, alternative single electron reductants were tested.[11] In addition to light-mediated activation of BTMP by various photocatalysts, the simple metal salt CuCl (1 eq.) also led to the formation **3a** in 50% NMR yield without light irradiation. Photocatalysis with $[Ru(bpy)_3](PF_6)_2$, however, remained the most efficient approach and optimization of the other reaction parameters led to a set of standard conditions that provided **3a** in 74% NMR yield (1.5 mol% $[Ru(bpy)_3](PF_6)_2$, 5 eq. **2a**, 0.1 eq. KF, 0.2 M MeCN, blue LEDs, rt, 16 h).

The scope of the photocatalytic C-H trifluoromethoxylation with a selection of aromatic feedstocks is shown in Scheme 2. A range of diverse substituents on the arene were tolerated with electron-withdrawing groups generally leading to the highest yields. In most cases, BTMP provided similar yields of products **3** to those previously reported using reagents **A**-**D**. Deviations were observed, however, for benzonitrile **2f** and methyl benzoate **2i** with the corresponding trifluoromethoxylated arenes being delivered in significantly higher yields (**3f** = 69%, **3i** = 73%), while iodobenzene **2e** was much less efficiently converted (4%). The successful synthesis of the halogenated arenes **3c** and **3d** as well as the boronic ester species **3l** is particularly noteworthy as these products can serve as OCF_3-containing building blocks for cross-coupling methodologies. The regioselectivity of the photocatalytic trifluoromethoxylation with BTMP also mirrored that obtained using the previously reported reagents **A**-**D** and reflects the inherent electronic properties of the aromatic substrates. In each case, only trace amounts of bis(trifluoromethoxy)arene side-products were observed in the crude reaction mixtures, while waste species derived from the $^{-}OCF_3$ by-product could be readily removed upon aqueous work-up.



Scheme 3. Scope of the TEMPO-catalyzed C-H trifluoromethoxylation of arenes using BTMP. ^{19}F NMR yields using $PhCF_3$ as an internal standard, ratio *ortho-/meta-/para-* determined by ^{19}F NMR shown in brackets. ^{a}TEMPO (5 mol%), no MeCN. ^{b}Arene (10 eq.).

Having developed a set of efficient photocatalytic conditions, we next sought to investigate alternative approaches for activating BTMP, which do not require light irradiation. While initial results had identified metal salts such as CuCl as suitable stoichiometric activators, we were drawn to the recent report from Ngai and co-workers using catalytic amounts of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a single electron shuttle with reagent **C**.[6c] TEMPO is significantly less expensive than $[Ru(bpy)_3](PF_6)_2$ while the avoidance of light irradiation brings practical advantages for potential large scale applications.[12] Benzene (**2a**, 5 eq.) and BTMP (1 eq.) were thus reacted with TEMPO (25 mol%) and inexpensive K_2CO_3 (1 eq.) as a basic additive in MeCN (0.5 M) at rt overnight. Analysis of the reaction mixture by ^{19}F NMR revealed the efficient formation of (trifluoromethoxy)benzene **3a** in 70% yield. Furthermore, the low polarity of TEMPO means that the

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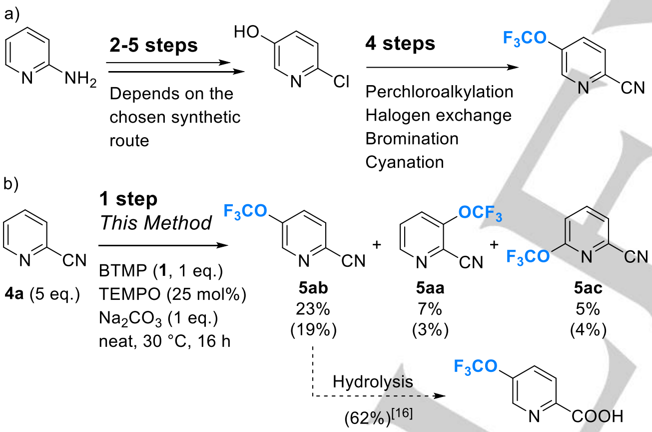
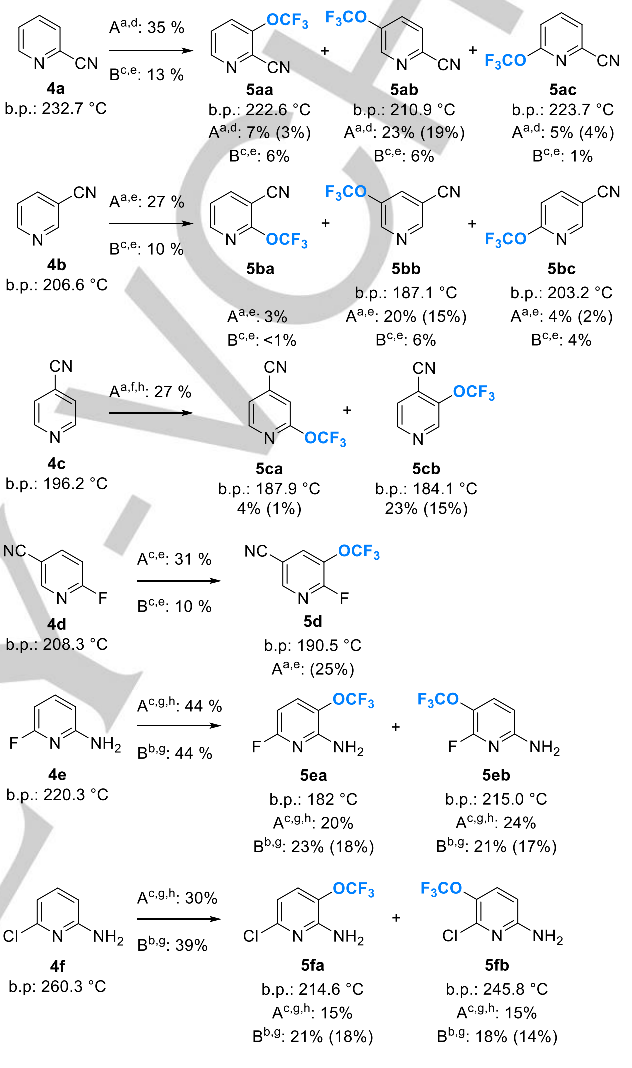
benzene substrate can be used as the only solvent, with **3a** being delivered in 61% ^{19}F NMR yield under neat conditions.

The efficiency of the TEMPO-catalyzed trifluoromethoxylation method with a selection of aromatics is shown in Scheme 3. As for the photocatalytic reaction, a range of electron-poor and electron-neutral examples could be successfully employed in generally moderate to good yields up to 81%. While the cyano- and methyl ester-substituted derivatives **3f** and **3i** could also be prepared in good yields under neat conditions (**3f** = 81%, **3i** = 45%), other examples reacted more efficiently using MeCN as solvent. In most cases, the yields were similar to those obtained under the photocatalytic conditions although nitrobenzene (**2m**) was less efficiently converted using TEMPO (27% vs. 54%). Interestingly, however, significant differences were observed in the regioselectivities of the trifluoromethoxylation reactions under the two sets of conditions. The halogen-substituted arenes **2b**, **2c** and **2d**, for example, exhibited a notably increased preference for the *ortho* and, especially, *para* products under TEMPO catalysis with this preference increasing in the order **3d** < **3c** < **3b** (ie. Br < Cl < F). In fact, while the same broad regioselectivity trends were observed under both sets of conditions, TEMPO catalysis led to a higher selectivity for the *para*-(OCF$_3$)-substituted products with each aromatic substrate tested. The observation that different activation modes lead to different product distributions is both potentially synthetically useful and mechanistically interesting as it implies that the regioselectivity is not simply a reflection of the substrate properties.



Scheme 4. Synthesis of 5-(trifluoromethoxy)picolinonitrile **5ab**. a) Current approach: multi-step indirect synthesis. b) TEMPO-catalyzed trifluoromethoxylation with BTMP. ^{19}F NMR yields (internal standard = PhCF$_3$), isolated yields in parentheses.

At this stage of the study, we sought to explore BTMP as a practical reagent for the direct synthesis of hitherto under-explored OCF$_3$-containing building blocks. Given the importance of nitrogen heterocycles in pharmaceuticals, (trifluoromethoxy)pyridines are highly desirable motifs for incorporation into new drug targets. Currently, however, these species are generally accessed via indirect methods. In comparison to benzene derivatives, such approaches entail additional synthetic steps as the (hydroxy)pyridine starting materials required for *de novo* construction of the OCF$_3$ moiety are not widely available. Furthermore, the key halex step can only be achieved on α-chloropyridine derivatives using the unattractive fluorinating agent SbF$_3$.[13] In 2016, the groups of Zou, Wu and Wu reported a trifluoromethylation approach towards trifluoromethoxylated pyridines and pyrimidines, however the use of the expensive Togni II reagent and the restriction to 2-OCF$_3$-substituted derivatives limits its applicability for the synthesis of diverse building blocks.[14,15]



Scheme 5. C-H Trifluoromethoxylation of pyridines with BTMP. ^{19}F NMR yields, isolated yields in parentheses. A: TEMPO catalysis conditions ((Substrate (5 eq.), BTMP (1 eq., 0.5 mmol), TEMPO (25 mol%), Na$_2$CO$_3$ (1 eq.), 16 h, rt, B: photocatalysis conditions (see Scheme 2). ^{a} 6 mmol scale. ^{b} 3 mmol scale. ^{c} 0.5 mmol scale. ^{d} neat at 30 °C. ^{e} in MeCN (2.0 M). ^{f} in MeCN (0.4 M). ^{g} in MeCN (0.2 M). ^{h} 6 h.

To assess the feasibility of direct C-H trifluoromethoxylation of pyridine building blocks using BTMP, picolinonitrile **4a** was selected as a representative substrate featuring a functional group amenable to subsequent conversion into other useful moieties (eg. through hydrolysis to a carboxylic acid). Reacting **4a** with BTMP under the optimized conditions with TEMPO provided the (trifluoromethoxy)pyridine **5a** in a ^{19}F NMR yield of 35% as a mixture of three regioisomers favouring the 5-(trifluoromethoxy)picolinonitrile (23% of **5ab**, Scheme 4). While the yield is only moderate, the direct synthesis of this species in a single step from **4a** represents a significant improvement on previously reported routes, which involved at least 6 steps from 2-aminopyridine.[16]

A selection of further substrates featuring halogen, cyano and amino substituents were then reacted under both sets of optimized conditions and the product distribution was analyzed by ^{19}F NMR and GC-MS (Scheme 5). In all cases, the desired (trifluoromethoxy)pyridines **5** were obtained in mostly moderate yields with TEMPO catalysis generally proving more efficient. Only with the 2-chloro-5-amino-substituted pyridine **4f** was a higher efficiency observed under photocatalytic conditions with **5f** being produced in 39% ^{19}F NMR yield (cf. 30% using TEMPO). To the best of our knowledge, the successful conversion of substrates **4e** and **4f** represents the first time amino substituents have been tolerated in radical trifluoromethoxylation reactions. The more electron deficient pyridine motif likely inhibits undesired direct electron transfer steps, which are thought to take place between electron rich aromatics and OCF_3 reagents.[17] The product regioisomers could be separated from the unreacted substrate and from each other via normal-phase column chromatography while, in no case, were bis(trifluoromethoxy) side-products resulting from double addition observed by GC-MS.[18] As chromatography is unattractive for large scale applications, differential scanning calorimetry (DSC) analysis was performed to assess the potential isolation of each regioisomer by fractional distillation. As shown in Scheme 5, a significant decrease in the boiling point was observed upon trifluoromethoxylation (up to 45.7 °C for **5fa**), while for most examples, meaningful differences in the boiling points of each product regioisomer were measured (up to 33 °C for **5ea** and **5eb**). These results suggest that radical trifluoromethoxylation with BTMP could prove useful as a practical one-step method for the preparation of (trifluoromethoxy)pyridine building blocks with final product isolation being achieved via well-established and inexpensive distillation techniques.

In conclusion, BTMP has been employed as a source of •OCF_3 radicals in C-H trifluoromethoxylation reactions of aromatic compounds. Using either visible light photoredox catalysis or TEMPO as a catalytic electron shuttle, valuable trifluoromethoxylated arenes could be prepared under mild conditions, while direct radical trifluoromethoxylation of underexplored pyridine derivatives was achieved. Given the ready availability of BTMP from inexpensive bulk compounds, we believe these methods could serve as useful routes to OCF_3-containing building blocks.

Acknowledgements

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Keywords: Trifluoromethoxylation • (Hetero)arenes • TEMPO • Photocatalysis • Fluorine

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[17] This undesired reaction was previously discussed for anisole by Ngai and co-workers, see the SI of ref. [5].
[18] In the reaction of **4c**, 2-fluoro-5-(trifluoromethoxy)isonicotinonitrile was also observed (^{1}H NMR, ^{19}F NMR, GC-MS) as a minor side-product (see the SI).

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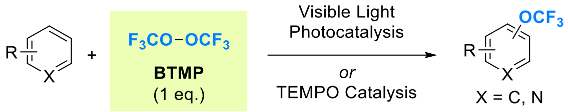
Entry for the Table of Contents



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