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Trifluoromethyl Benzoate: A Versatile Trifluoromethoxylation Reagent

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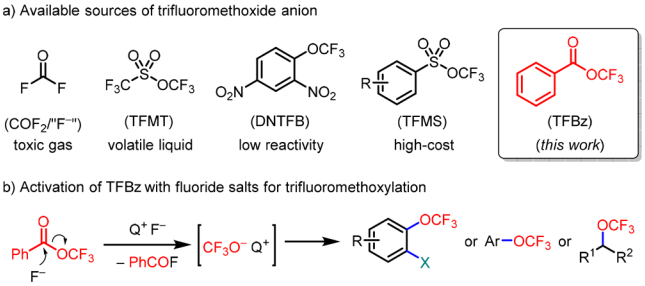
Supporting Information

ABSTRACT: Trifluoromethyl benzoate (TFBz) is developed as a new shelf-stable trifluoromethoxylation reagent, which can be easily prepared from inexpensive starting materials using KF as the only fluorine source. The synthetic potency of TFBz is demonstrated by trifluoromethoxylation−halogenation of arynes, nucleophilic substitution of alkyl (pseudo)halides, cross-coupling with aryl stannanes, and asymmetric difunctionalization of alkenes. The unprecedented trifluoromethoxylation−halogenation of arynes proceeds smoothly at room temperature with the aid of a crown ether-complexed potassium cation, which significantly stabilizes the trifluoromethoxide anion derived from TFBz.

The trifluoromethoxy (CF_3O) group has increasingly become a prominent structural motif in pharmaceuticals, agrochemicals, and organic materials owing to its unique characteristics.[1,2] Indeed, many CF_3O-containing compounds are of vital importance because they possess increased biological potency, often coupled with reduced side effects.[1a−c] However, despite their great potentials, there are few methods to access the trifluoromethyl ether motif,[3] which rely on either fluorination,[4] trifluoromethylation[5] or trifluoromethoxylation.[6−10] From a viewpoint of synthetic chemistry, trifluoromethoxylation is the most ideal approach, albeit still in its infancy, as it has the capability to directly introduce a CF_3O group into structurally diverse molecules.[3f] In this context, recently, most efforts have been devoted to direct trifluoromethoxylation with various trifluoromethoxide salts.[3e,f,7−10]

However, available trifluoromethoxide anion (CF_3O^-) sources are limited and usually suffer from disadvantages (Scheme 1a).[7−10] The trifluoromethyl triflate (TFMT) can readily release CF_3O^- under the activation of a fluoride salt, and is a commonly employed precursor to prepare both alkyl and aryl trifluoromethyl ethers[7] and to develop novel transition-metal-promoted trifluoromethoxylations, including silver-mediated oxidative trifluoromethoxylation of aryl stannanes/boronic acids [via tris(dimethylamino)sulfonium trifluoromethoxide ($TASOCF_3$)],[7e] palladium-catalyzed trifluoromethoxylation of alkenes (via CF_3OAg or CF_3OCs),[7f−h] and silver-mediated trifluoromethoxylation of diazo compounds (via CF_3OAg).[7i] Moreover, a structurally well-defined Ag(I) trifluoromethoxide complex has been prepared from TFMT and applied in nucleophilic substitution reactions.[7k] Although TFMT is commercially available, it is a volatile liquid (bp 19 °C) and of high cost, which impede its wide applications. Additionally, the combination of difluorophosgene (COF_2) and a fluoride anion has been applied to prepare trifluoromethoxide salts and alkyl trifluoromethyl ethers ($ROCF_3$),[8] but the toxic and gaseous natures of COF_2 restrict its laboratory application. To address the problems associated with COF_2 and TFMT, 2,4-dinitro(trifluoromethoxy)benzene (DNTFB)[9] and trifluoromethyl aryl sulfonates (TFMS)[10] have been elegantly developed as CF_3O^- sources. Nevertheless, the former showed low reactivity and suffered from limited substrate scope, whereas the latter has to be prepared from Togni's reagent, a susceptible explosive that is difficult to use in large scale.[11] Therefore, it is still of great demand to develop a practical and efficient nucleophilic trifluoromethoxylation reagent.

Scheme 1. Development of TFBz Reagent and Its Applications



We envisioned that a new trifluoromethoxylation reagent should fulfill the following requirements: (1) it should be a high-boiling liquid or a solid, (2) it should be easily prepared from inexpensive starting materials, and suitable for large-scale preparation, and (3) it should be stable enough for storage, but active enough to readily release CF_3O^-. Herein, we report the development of trifluoromethyl benzoate (TFBz), a shelf−stable liquid, as a new trifluoromethoxylation reagent, which can be readily prepared from triphosgene/KF/benzoyl bromide, using KF as the only fluorine source. TFBz can be easily activated by fluoride anion to release CF_3O^- species (Scheme 1b). The synthetic potency of TFBz is demonstrated by its various aromatic and aliphatic trifluoromethoxylation reactions.

Our investigation began with the preparation of TFBz (**1a**) from COF_2 (Scheme 2a). To address the safety issues associated with the storage and transportation of COF_2 in academic laboratories, we prepared it by treating triphosgene

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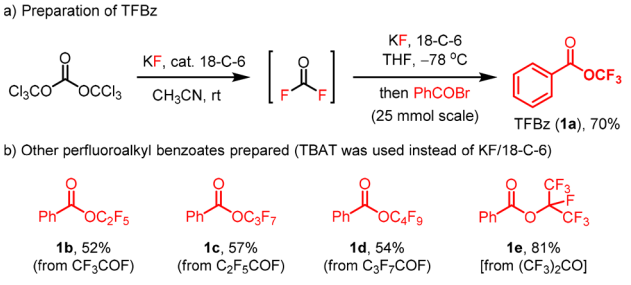
Scheme 2. Preparation of TFBz and Other Perfluoroalkyl Benzoates

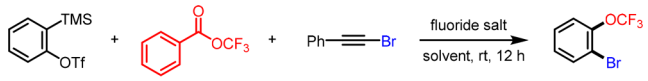


with KF and catalytic amount of 18-crown-6 (18-C-6) in acetonitrile.[12] The capture of the *ex situ* generated COF_2 with KF/18-C-6 in THF, followed by addition of benzoyl bromide, afforded **1a**[7d] as a stable liquid in 70% yield (for details, see the Supporting Information, SI). For industrial production, the bulk fluorochemical COF_2 can be used directly. Notably, perfluoroalkyl benzoates **1b**-**1e** could be prepared similarly as stable liquids from the corresponding perfluoroalkanoyl fluorides or perfluoroalkyl ketones (Scheme 2b, see SI).

With TFBz (**1a**) in hand, we set out to explore its application in the synthesis of aryl trifluoromethyl ethers ($ArOCF_3$) that are usually obtained via fluorination and trifluoromethylation.[3−5] Arynes are highly reactive and versatile intermediates,[13] which not only provide a unique probe to test the generation of CF_3O^- from TFBz (**1a**) but also constitute a universal platform for rapid construction of *ortho*-functionalized aryl trifluoromethyl ethers. To our knowledge, there has been no report on trifluoromethoxylation-involved difunctionalization of arynes.[14]

First, we chose the trifluoromethoxylation−bromination of benzyne [*in situ* generated from 2-trimethylsilylphenyl triflate (**2a**)][15] to investigate the activation of TFBz and the transfer of CF_3O^- (Table 1). Initially, inspired by our previous reports on silver-mediated fluoro-difuctionalization of arynes,[16] we tried the reaction between CF_3OAg (*in situ* generated from **1a** and AgF), **2a**, and phenylethynyl bromide (**3a**)[17] under the action of CsF (to activate **2a**) in acetonitrile (Table 1, entry 1). Although CF_3OAg was formed quantitatively, the ready precipitation of CF_3OCs precluded the trifluoromethoxylation of benzyne, and no desired product was detected. To our delight, when tetrabutylammonium difluorotriphenylsilicate (TBAT) was used, the desired product **4a** was observed in 9% yield (Table 1, entry 2). Preliminary screening results showed that the yield of **4a** was largely influenced by the solvent and countercation effects. Among several organic fluoride salts and solvents examined (Table 1, entries 2−7), the combination of TBAT/THF was found to be the most effective, giving **4a** in 39% yield without any fluorination−bromination or trifluoromethoxylation−protonation product (Table 1, entry 5). However, the trifluoromethoxylation−protonation was severe when toluene or dichloromethane were used as solvent (Table 1, entries 3 and 4), and fluorination predominated when tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) was used (Table 1, entry 6). It is worthwhile noting that in all cases, the formation of the trifluoromethoxide salts from **1a** was much faster than the release of benzyne, but the result varied case by case, suggesting that the stabilization of CF_3O^- should be beneficial for the desired reaction. Thus, we made a thorough survey on the fluoride salts and solvents (Table 1, entries 8−15; for details, see SI). Although CsF/Ph_2IOTf[18] or CsF/15-crown-5 (15-C-5) failed to activate **2a** in THF (Table 1, entries 8 and 9), the use of KF/18-C-6 and an oxygen-containing solvent was rewarding (Table 1, entries 10−13). Changing 18-C-6 to the bulkier ether *cis*-dicyclohexano-18-C-6 (*cis*-DCy-18-C-6, a mixture of *cis-syn-cis*- and *cis-anti-cis*-isomers) improved the yield of **4a** to 76% (Table 1, entry 14). Finally, the highest yield (81%) was obtained after an exhaustive optimization of the molar ratio and concentration of the reactants (Table 1, entry 15; for details, see SI). Note that $C_6F_{13}Br$ (**3b**) and C_6F_5Br (**3c**) also worked well as electrophilic bromination reagents (see SI).

Table 1. Survey of Reaction Conditions[a]



Entry	Fluoride salt	Solvent	Conv. (**2a**, %)[b]	Yield (**4a**, %)[b]
1[c]	CsF	CH_3CN	100	0
2	TBAT	CH_3CN	19	9
3	TBAT	Toluene	100	7 (21)
4	TBAT	CH_2Cl_2	49	2 (7)
5	TBAT	THF	100	39
6	TASF	THF	100	0
7	TBAF	THF	100	0
8	CsF/Ph_2IOTf (1:1)	THF	3	0
9	CsF/15-C-5 (1:1)	THF	14	0
10	KF/18-C-6 (1:1)	THF	100	49
11	KF/18-C-6 (1:1)	DME	100	51
12	KF/18-C-6 (1:1)	Diglyme	100	64
13	KF/18-C-6 (1:1)	EtOAc	100	67
14	KF/*cis*-DCy-18-C-6 (1:1)	EtOAc	100	76
15[d]	KF/*cis*-DCy-18-C-6 (1:1)	EtOAc	100	81

[a]Conditions: **2a** (0.05 mmol), **1a** (0.125 mmol), **3a** (0.2 mmol), fluoride salt (0.2 mmol), solvent (2.0 mL), rt, 12 h. [b]Yields and conversions were determined by ^{19}F NMR with $PhCF_3$ as internal standard. In all cases, the conversion of **1a** was 100%. The yield of $PhOCF_3$ is given in the parentheses. [c]CF_3OAg was *in situ* generated from **1a**/AgF. [d]Optimized conditions: **2a** (0.05 mmol), **1a** (0.15 mmol), **3a** (0.2 mmol), KF (0.225 mmol), *cis*-DCy-18-C-6 (0.225 mmol), EtOAc (1.0 mL), rt, 12 h.

Having the optimized reaction conditions in hand, we then explored the scope of this protocol (Table 2). Both substituted benzynes (**4a**−**4p**) and indolynes (**4q**−**4u**) smoothly underwent trifluoromethoxylation−bromination to give the corresponding products in moderate to good yields.[19] In all cases, no fluorination− or trifluoromethoxylation−protonation product was observed. The 3-substituted unsymmetrical arynes gave moderate to excellent regioselectivity, probably owing to the steric hindrance (**4i**, **4k**). In cases of unsymmetrical arynes with only 4-substituents, low to moderate regioselectivities were observed, which seems to be dependent on the electronic nature of the substituents (**4l**−**4p**). Functional groups such as allyl (**4h**), fluoride (**4f**, **4o**), chloride (**4p**), bromide (**4k**), acetal (**4e**), acetyl (**4q**, **4r**), and *tert*-butyloxycarbonyl (**4t**) are well tolerated in this reaction. Of note, indolynes are also suitable substrates for this reaction, which could be useful for life sciences-related applications (**4q**−**4u**). Moreover, this protocol was applicable to the trifluoromethoxylation−iodination and −chlorination of arynes when C_6F_5I (**3d**) and CCl_4 (**3e**) were used as the halogenation reagents, respectively (Table 2b,c). All the arynes were converted to *o*-CF_3O-iodoarenes (**5d**, **5e**, **5g**,

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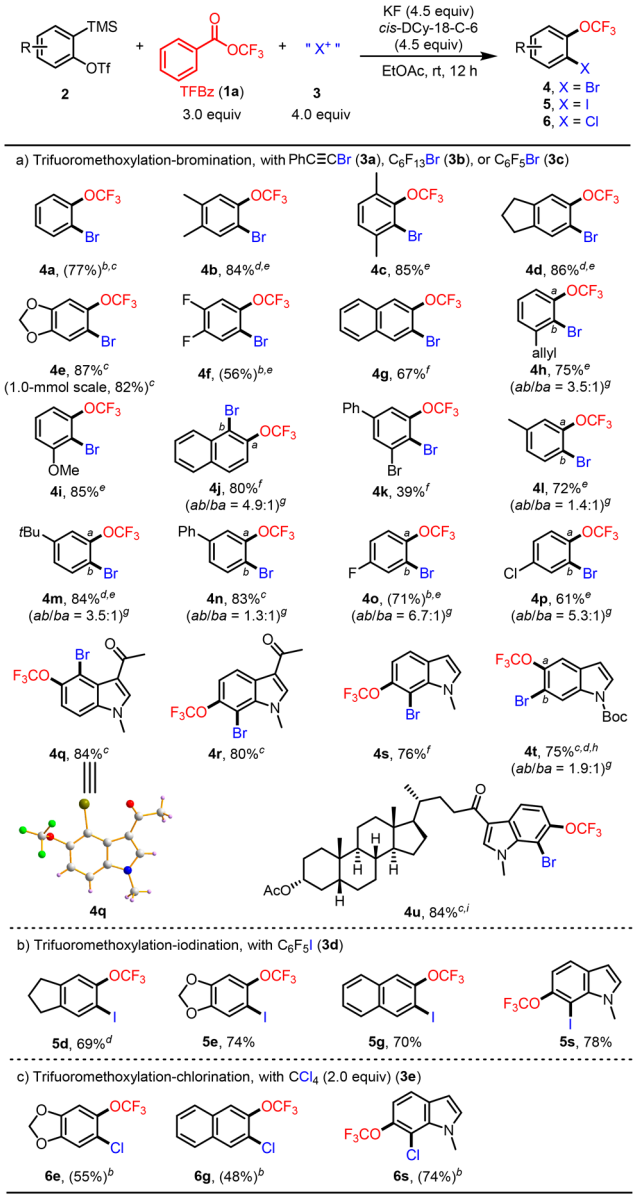
Table 2. Trifluoromethoxylation–Halogenation of Arynes[a]

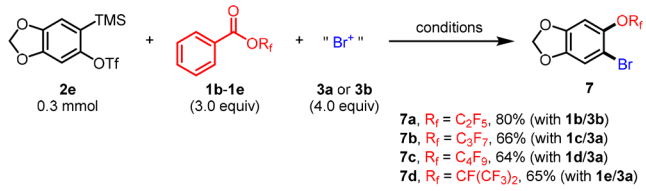


[a]Reactions were conducted on 0.3 mmol scale. Unless otherwise noted, isolated yields are given. For details on the structure of **2**, see SI. [b]^{19}F NMR yield with $PhCF_3$ as an internal standard. [c]**3a** was used. [d]KF (6.0 equiv), *cis*-DCy-18-C-6 (6.0 equiv), 48 h. [e]**3b** was used. [f]**3c** was used. [g]The ratio of regioisomers was determined by ^{19}F NMR spectroscopy prior to isolation. [h]24 h. [i]Reaction was conducted on 0.2 mmol scale.

5s) or -chloroarenes (**6e**, **6g**, **6s**) in moderate to good yields; however, in cases of using CCl_4, *o*-dichloroarenes were formed as the main side-products. The synesthetic utility of the so-obtained products was demonstrated by the conversion of **4d** and **4e** into various trifluoromethoxylated complex molecules (see SI).

This protocol can also be extended to other perfluoroalkoxylation reactions. As shown in Scheme 3, treating aryne precursor **2e** with perfluoroalkyl benzoates **1b–1e** and bromination reagents **3a** or **3b** under aforementioned standard conditions afforded *o*-perfluoroalkoxyl-bromoarenes **7** in 64–80% yields.

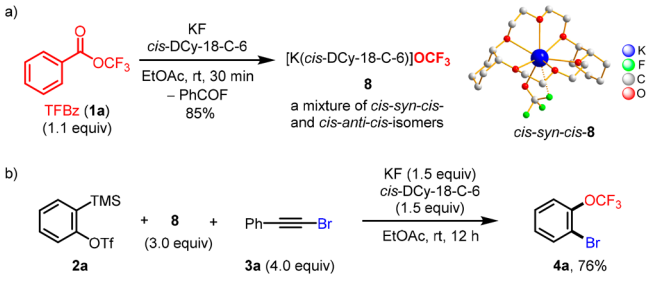
Scheme 3. Perfluoroalkoxylation–Bromination of Arynes[a]



[a]Conditions: KF (4.5 equiv), *cis*-DCy-18-C-6 (4.5 equiv), EtOAc, rt, 12 h. Isolated yields are given.

To gain more insights into the present trifluoromethoxylation reaction, we carried out preliminary mechanistic studies (Scheme 4). As aforementioned, the generation of CF_3O^- is a

Scheme 4. Mechanistic Investigations



fast process, so we first monitored the reaction between **1a** and KF/*cis*-DCy-18-C-6 in EtOAc by using ^{19}F NMR spectroscopy (see SI). It was found that **1a** was consumed within 15 min, affording a clear solution of trifluoromethoxide salt with the signal of CF_3O^- at δ −23 ppm, and the signal remained even after stirring at room temperature for 48 h (see SI). After recrystallization, $[K(cis\text{-DCy-18-C-6})]^+$ CF_3O^- (**8**) was obtained as a white solid in 85% yield, which could be kept at room temperature in the glovebox for 2 days without significant decomposition. The X-ray structure of one isomer of **8** is given in Scheme 4a. Thereafter, we examined the reactivity of the isolated salt **8**. As shown in Scheme 4b, the replacement of **1a** with **8** afforded **4a** in similar yield, supporting that CF_3O^- is the reactive species toward arynes.

To further demonstrate the synthetic utility of TFBz (**1a**), we applied it to the synthesis of other trifluoromethyl ethers by using different trifluoromethoxylation protocols (Scheme 5). In the presence of **1a**/AgF, simple alkyl halides[7b] such as primary alkyl iodide and benzyl bromide were converted to alkyl trifluoromethyl ethers in good yields via *in situ* generated CF_3OAg (**9** and **10**). This protocol is also applicable for the efficient trifluoromethoxylation of *N*-bromoacetyl (+)-camphorsultam and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[7d] (**11** and **12**). By using $[K(cis\text{-DCy-18-C-6})]^+$ CF_3O^- *in situ* generated from **1a**/KF/*cis*-DCy-18-C-6, trifluoromethoxylated glucuronolactone **13** was prepared from the corresponding triflate[7b] in 62% yield. By using **1a**, silver-catalyzed asymmetric bromtrifluoromethoxylation of an alkene[10a] also proceeded smoothly in good yield and enantioselectivity (**14**). Of note silver-mediated oxidative trifluoromethoxylation of aryl stannanes[7e] could be modified by using **1a** via the reaction of the relatively stable $[K(cis\text{-DCy-18-C-6})]^+CF_3O^-$ (**15**). We also found that **1a** is a good reagent for trifluoromethoxylation–protonation of arynes, thus treating **2s** and **1a** with KF/*cis*-DCy-18-C-6 in EtOAc/MeCN in the absence of a halogenation

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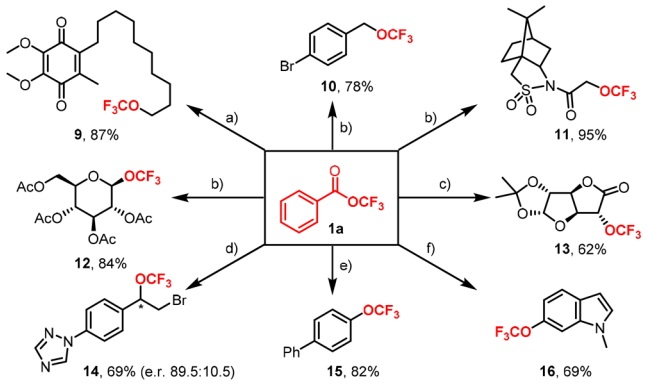
Scheme 5. Versatile Trifluoromethoxylations with TFBz[a]



[a]Conditions (for details, see SI): (a) R-I, AgF, CH_3CN, rt. (b) R-Br, AgF, CH_3CN, rt. (c) (i) KF/*cis*-DCy-18-C-6, EtOAc, rt; (ii) R-OTf, −30 °C to rt. (d) alkene, cat. AgF, cat. $(DHQD)_2PHAL$, DBDMH, CsF, $MeCN/CH_2Cl_2$, rt to −20 °C. (e) (i) KF/*cis*-DCy-18-C-6, THF, rt; (ii) Ar-$SnBu_3$, $AgPF_6$, F-TDAE-PF_6, $NaHCO_3$, acetone/THF, −30 °C. (f) **2s**, KF/*cis*-DCy-18-C-6, EtOAc/MeCN, rt. Reactions were conducted on 0.3 mmol scale. Isolated yields are given.

reagent afforded **16** in 69% yield. Additionally, the commonly used trifluoromethoxide salts $CsOCF_3$ and $AgOCF_3$[7f−j] could be preprepared from **1a** (see SI).

In conclusion, we have developed trifluoromethyl benzoate (TFBz) as a new, easy-to-prepare, and practical reagent for various aromatic and aliphatic trifluoromethoxylation reactions. The unprecedented trifluoromethoxylation−halogenation of arynes with TFBz via thermally stable trifluoromethoxide salt $[K(cis\text{-dicyclohexano-18-crown-6})]^+$ CF_3O^- provides a useful synthetic tool for the one-pot synthesis of *o*-haloaryl trifluoromethyl ethers with an excellent handle (the halogen atom) for further functionalization. Other trifluoromethoxylation reactions, including nucleophilic substitution of alkyl (pseudo)halides, cross-coupling with aryl stannanes, and asymmetric difunctionalization of alkenes, can also be effectively accomplished by using TFBz reagent.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04000.

Experimental procedures and characterization data (PDF)
Data for $C_{12}H_9BrF_3NO_2$ (CIF)
Data for $C_{21}H_{36}F_3KO_7$ (CIF)
Data for $C_{15}H_{19}F_3O_{10}$ (CIF)

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Notes

The authors declare the following competing financial interest(s): J.H., M.Z and C.N. are inventors on a pending patent application related to this work.

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