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RESEARCH ARTICLE

Trifluoromethyl Nonaflate: A New and Practical Trifluoromethoxylating Reagent and its Application to the Regio- and Stereoselective Synthesis of Trifluoromethoxylated Alkenes

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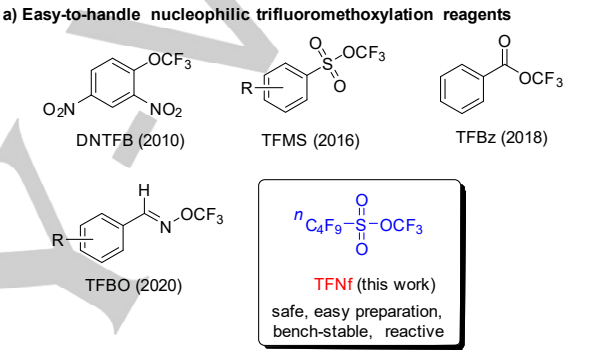
Abstract: The trifluoromethoxy group has elicited much interest among drug and agrochemical discovery teams because of its unique properties. We developed trifluoromethyl nonafluorobutanesulfonate (nonaflate), TFNf, an easy-to-handle, bench-stable, reactive, and scalable trifluoromethoxylating reagent. TFNf is easily and safely prepared in a simple process in large scale and the nonaflyl part of TFNf can easily be recovered as nonaflyl fluoride after usage and recycled. The synthetic potency of TFNf was showcased with the underexplored synthesis of various trifluoromethoxylated alkenes, through a high regio- and stereoselective hydro(halo)trifluoromethoxylation of alkyne derivatives such as haloalkynes, alkynyl esters and alkynyl sulfones. The synthetic merits of TFNf were further underscored with a high yielding and smooth nucleophilic trifluoromethoxylation of alkyl triflates/bromides and primary/secondary alcohols.

The trifluoromethoxy (CF_3O) group has become a prominent motif in pharmaceuticals, agrochemicals, and organic materials because of its distinctive properties,[1] chiefly among them, its high lipophilicity and electron-withdrawing effect, which improve the permeability and metabolic stability of organic compounds considerably.[2] Despite its potential, current methods for the syntheses of the trifluoromethyl ether motif, either through indirect or direct trifluoromethoxylation leave room for improvement. Indirect trifluoromethoxylation, such as trifluoromethylation of alcohols or phenols,[3] fluorodecarboxylation of aryloxydifluoroacetic acids,[4] fluorodesulfurization of xanthates,[5] deoxofluorination of aryl fluoroformates with SF_4,[6] and chlorination/fluorination of anisoles with Cl_2/HF[7] suffer from long steps for their preparation, use of toxic, explosive, or expensive reagents, poor substrate scope, or harsh reaction conditions. In theory, direct trifluoromethoxylation is the ideal method for the preparation of trifluoromethyl ether-containing compounds but despite the tremendous effort devoted to the development of nucleophilic trifluoromethoxylation reagents, the reported nucleophilic trifluoromethoxylating reagents have shortcomings. Among earlier reports, sulfurane and its oxide, $(CF_3)_2S(O)_n(OCF_3)_2$ (n = 0, 1), converted phenols to (trifluoromethoxy)benzenes via nucleophilic attack of the CF_3O moiety.[8] However, the preparation of sulfuranes required a special technique that used very toxic and explosive compounds.[9] More recently, trifluoromethyl triflate (TFMT)[10] was employed as a nucleophilic reagent with fluoride to prepare alkyl and aryl trifluoromethyl ethers.[11] However, the high volatility of TFMT (bp 19 °C) is a serious disadvantage.



Scheme 1. Trifluoromethyl Nonaflate (TFNf) as a New Nucleophilic Trifluoromethoxylation Reagent and Its Application

To address these issues, easy-to-handle nucleophilic trifluoromethoxylating reagents such as 2,4-dinitro(trifluoromethoxy)benzene (DNTFB),[12] trifluoromethyl arylsulfonates (TFMS),[13] trifluoromethyl benzoate (TFBz)[14] and (*E*)-*O*-trifluoromethyl-benzaldoximes (TFBO)[15] were developed (Scheme 1a). These reagents have been explored[16] in the reactions with alkyl derivatives,[11b,11c,11g,11k,12,13b,13e-h,14-15,17] olefins,[11f,13i,18] and (hetero)aromatic substrates.[11a,11h,13c,19] However, trifluoromethoxylation of alkynes has been scarcely reported to date[20] except for a reactive benzyne

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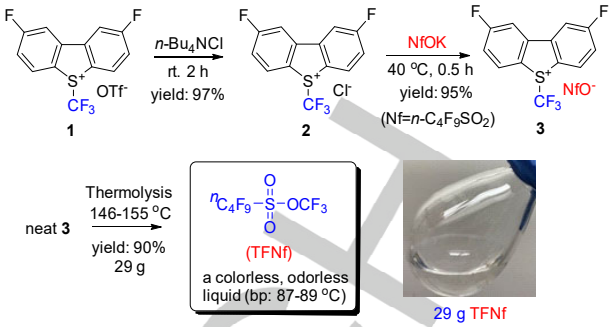
species[11c,14](Scheme 1b) (during our manuscript's first review process, a paper on dibromotrifluoromethoxylation of terminal alkynes with TFMS appeared.[21])

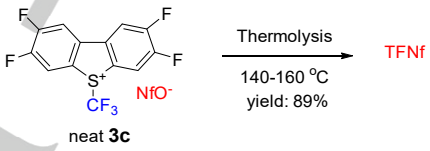
Despite their effectiveness in straightforward trifluoromethoxylation reactions, DNTFB showed low reactivity and very limited scope; TFMS and TFBO were prepared with Togni's reagent, whose suspected explosiveness raises safety concerns in large-scale synthesis; and the synthesis of TFBz required stringent reaction conditions because of the hygroscopic nature of the reagents required for its preparation as well as the generation of toxic fluorophosgene during the reaction. Recently, it was reported that R_4NOCF_3[17] was prepared by the reaction of CF_3OCH_3 with tertiary amines. But CF_3OCH_3 is a gas and the resulting hygroscopic CF_3O^- ammonium salts showed low reactivity. Also, $AgOCF_3$ generated from triphosgene and AgF,[22] was reported, but triphosgene is hazardous; the reaction scope was narrow too. In sum, the search for a safe, practical, and versatile trifluoromethoxylating agent is still an unmet challenge. We are now pleased to introduce trifluoromethyl nonafluorobutanesulfonate (nonaflate) (TFNf), an easy-to-prepare, easy-to-handle, stable yet reactive, and scalable trifluoromethoxylating agent whose nonaflyl part can be easily recovered after use and recycled. The synthetic potency of TFNf was underscored with the synthesis of various new trifluoromethoxylated alkenes through a highly regio- and stereoselective hydro(halo)trifluoromethoxylation of alkyne derivatives in addition to high-yield preparation of CF_3O-compounds from alkyl halides and alcohols.

Although there have been two reports[23] on the synthesis of TFNf, these methods are cumbersome and not suitable for scale-up preparation. One method needed dangerous F_2 and FCl,[23a] and the other was haunted by expensive $^nC_4F_9SO_3Ag$, gaseous CF_3I, low yield as well as difficult purification from solvent (benzene).[23b] Consequently, the application of TFNf, especially as a trifluoromethoxylation reagent, has never been reported. Our new method for TFNf preparation is safe, easy, efficient, and scalable (for details, see Supporting Information, SI). As shown in Scheme 2, starting from 2,8-difluoro-*S*-(trifluoromethyl)dibenzothiophenium triflate **1** (Umemoto reagent II),[24] TFNf reagent was prepared in high yield following two simple anion exchange steps and subsequent thermolysis of neat nonaflate **3**. TFNf was easily collected in a condenser vessel from the thermolysis reaction. The easy and effective thermolysis of nonaflate **3** was possible because of its low melting and decomposition point (133-135 °C), compared to triflate **1**, which has a high decomposition point of 204 °C. This unique property of **3** was further underscored by thermolysis of methanesulfonate **3a** ($CH_3SO_3^-$ counter-anion) and benzenesulfonate **3b** ($PhSO_3^-$ counter-anion). These provided poor thermolysis outcomes (see SI, section 2.1c, d for details).



Scheme 2. Preparation of TFNf

Since 2,3,7,8-tetrafluoro-*S*-(trifluoromethyl)dibenzothiophenium nonaflate **3c** also exhibited a low decomposition point (156.9 °C), we chose to prepare TFNf by thermolysis of nonaflate **3c** (Scheme 3). Indeed, TFNf was prepared smoothly and in high yield by thermolysis of neat **3c**, which was prepared from the corresponding triflate[24-25] using simple anion exchange steps analogous to **3** (see SI).



Scheme 3. Thermolysis of tetrafluoro analog **3c**

Thus, the whole process of preparing TFNf in high yield from **1** encompassed a simple reaction setup and an easy workup procedure (just filtration for the first two steps and distillation for the last step). It should be noted that Umemoto reagent II (**1**) is commercially available and can be prepared effectively in large scale, in one-pot and using a water-washing workup process.[24] TFNf is an odorless, thermally stable, and non-flammable liquid with a boiling point 87-89 °C; this convenient boiling point allows for easy distillation in the production process as well as its handling, storage, and transportation. TFNf can withstand a 3 M HCl solution for 150 hours without decomposition and 40% of TFNf was still intact after being treated with 3M KOH solution for 150 hours (see SI). In sum, the preparation of TFNf does not employ any explosive chemicals or toxic gaseous chemicals and is purifiable by simple distillation. Therefore, our process can be carried out in large scale in industrial settings without safety or separation concerns. These properties are in sharp contrast to the previously reported trifluoromethoxylating agents that use explosive or toxic chemicals in their productions and had to be purified by costly column chromatography. Moreover, the nonaflyl fluoride (NfF), generated from the TFNf activation by fluoride, can be easily recovered by simple pipetting from acetonitrile after the reaction is complete (see SI, section 2.3). This easy and economically advantageous recovery is due to the poor solubility of NfF in acetonitrile and its spontaneous partition from the reaction mixture. The recovered NfF can be reused for the synthesis of TFNf through hydrolysis and anion exchange reaction with **2** (see SI, section 2.3). The significant merits of TFNf

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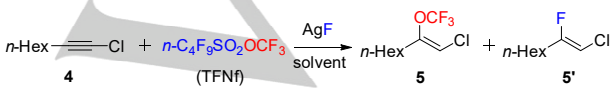
(i.e. smooth thermolysis of nonaflate **3**, suitable boiling point of TFNf for easy separation and handling, and easy recovery of NfF from organic solvent) are brought about by the unique properties of the perfluoroalkyl chain in TFNf, namely its very low surface energies, low intermolecular interaction, and water and oil-repulsion effect.[26]

Using TFNf, in conjunction with AgF, for the trifluoromethoxylation of alkynes, we discovered that simple alkynes were too inert and thus alkyne derivatives were explored (see SI). We found that haloalkynes afforded satisfactory results. The reaction with 1-iodooctyne furnished 11% of the expected hydrotrifluoromethoxylation product along with iodotrifluoromethoxylation and iodofluorination by-products (48% and 25%, respectively). These iodo by-products implied that additional intermolecular reactions occurred due to the presence of reactive iodoalkynes. The reaction with 1-bromooctyne afforded 75% yield of the expected product, but 24% of the hydrofluorination by-product was also found (see SI). The best result was obtained with 1-chloroalkynes.1-Chlorooctyne was then selected as a model substrate for the reaction optimization (Table 1). AgF was an excellent activator and it played a dual role in that F^- activated TFNf and Ag^+ activated the alkyne triple bond. The reaction was conducted in a sealed ampoule to inhibit the decomposition of the CF_3O^- to fluorophosgene and fluoride anion, which is detrimental to the reaction.[13h,16a,27] To our delight, 86% of hydrotrifluoromethoxylation product **5** was found when acetonitrile was used as solvent (entry 2). However, hydrofluorination also occurred and formed **6** as a side product (14%). Less polar solvents gave low conversion of the starting material (entry 3). More polar solvents, on the other hand, converted more starting material but also produced more hydrofluorination side product (entry 4). This phenomenon could be explained by the solubility of AgF in different solvents as more AgF dissolved in polar solvents and hence promoted the reaction. The polar solvents also increased the fluoride concentration in the reaction, which then competed with the CF_3O^- to generate more side product **5'**. A CH_3CN/DME solvent system proved beneficial (entry 1 vs entries 2 and 3) and a AgF/TFNf ratio screening led to the optimal amount of both reagents (entries 5, 6 and 7). The activation time at room temperature was critical because too long or short activation times impaired the reaction outcome (entries 8, 9). Heating was still required after activation (entries 10, 11). Additives played a key role: The reaction yield decreased dramatically without them. Various quaternary ammonium salt additives improved the AgF solubility and helped to stabilize the CF_3O^-.[13h,17] The reaction yield was further improved when 0.2 mmol of chloroalkyne **4** was employed, due to scale merit (entry 17). After thorough reaction condition screenings (see SI for more details), we found that reacting 0.2 mmol of chloroalkyne **4** with 2 equiv of AgF, 3.0 equiv of TFNf, and 0.5 equiv of TMABr in 1:2 (v/v) CH_3CN/DME in a sealed ampoule gave the best yield of the desired product **5**.

Table 1. Reaction Condition Optimization for Hydrotrifluoromethoxylation of Chloroalkynes[a]



Entry	Deviation	Yield (**5**, %)[b]	Yield (**5'**, %)[b]
1	no	84	5
2	0.3 mL CH_3CN as solvent	86	14
3	0.3 mL DME as solvent	4	3
4	0.3 mL DMF as solvent	54	27
5	1.5 eq AgF	81	6
6	2.5 eq AgF	78	9
7	2 eq TFNf	61	15
8	activation at rt for 3h	76	8
9	no activation at rt	75	6
10	rt for 48 h, no heating	42	1
11	rt for 2 h, then heating to 80 °C	78	20
12	no additive	58	6
13[c]	0.5 eq TMAI as additive	73	5
14[c]	0.5 eq TMACl as additive	81	8
15[d]	0.5 eq TBABr as additive	71	5
16[e]	0.5 eq TOABr as additive	61	12
17[f]	0.2 mmol **4**	88	7

[a]Conditions: Unless otherwise noted, reactions were conducted as follows: A 2-mL amber ampoule was loaded with 4 (0.1 mmol), tetramethylammonium bromide (TMABr) (additive) (0.5 equiv), AgF (2 equiv) and 0.3 mL mixed solvent (CH_3CN/DME = 1/2) sequentially. TFNf (3 equiv) was then added and the ampoule was sealed immediately. The reaction was activated (stirred) at rt for 1h and then stirred at 65 °C for 48h. [b]Yields were determined by GC. [c]TMAI, TMACl: tetramethylammonium iodide, chloride. [d]TBABr: tetrabutylammonium bromide. [e]TOABr: tetraoctylammonium bromide. [f]Optimized condition.

With the optimized reaction conditions in hand, we explored the reaction scope of this hydrotrifluoromethoxylation. As shown in

Table 2 **Table 2**, all reactions gave regio- and stereoselective hydrotrifluoromethoxylation products in good to excellent yields. Chloroalkynes with diverse functionalities such as esters (**5a**-**5f**, **5t**-**5w**, **5y**, **5z**, **5aa**, **5cc**, **5dd**), ethers (**5k**-**5q**, **5bb**), nitro (**5e**), nitriles (**5j**, **5dd**), aldehyde (**5p**), ketones (**5m**, **5bb**), amides (**5r**, **5s**, **5y**, **5z**, **5aa**), sulfonates (**5g**, **5h**), and sulfonamides (**5i**, **5cc**) were well-tolerated using our protocol. Acceptable to high yields were also obtained with heterocyclic substrates including pyridine (**5t**), thiazole (**5u**), furan (**5v**), thiophene (**5w**), triazole (**5x**), pyrrolidine (**5y**), and piperidine (**5z**). Impressively, some "vulnerable" substituents such as 2-tetrahydropyranyl (**5k**) and cyclopropyl (**5o**) proved to be suitable substrates. These results underscored the mild conditions and excellent functional group tolerance of our methodology. The absolute configuration of the double bond was determined to be cis by single-crystal X-ray diffraction analysis of **5s**.[28] We then explored late-stage regio- and stereoselective hydrotrifluoromethoxylation of natural products (**5aa**, **5bb**) and biologically active molecule derivatives (**5cc**, **5dd**). Both hydrotrifluoromethoxylation reactions of L-phenylalanine and estrone derivatives proceeded smoothly to provide the corresponding **5aa** and **5bb** in good isolated yields.

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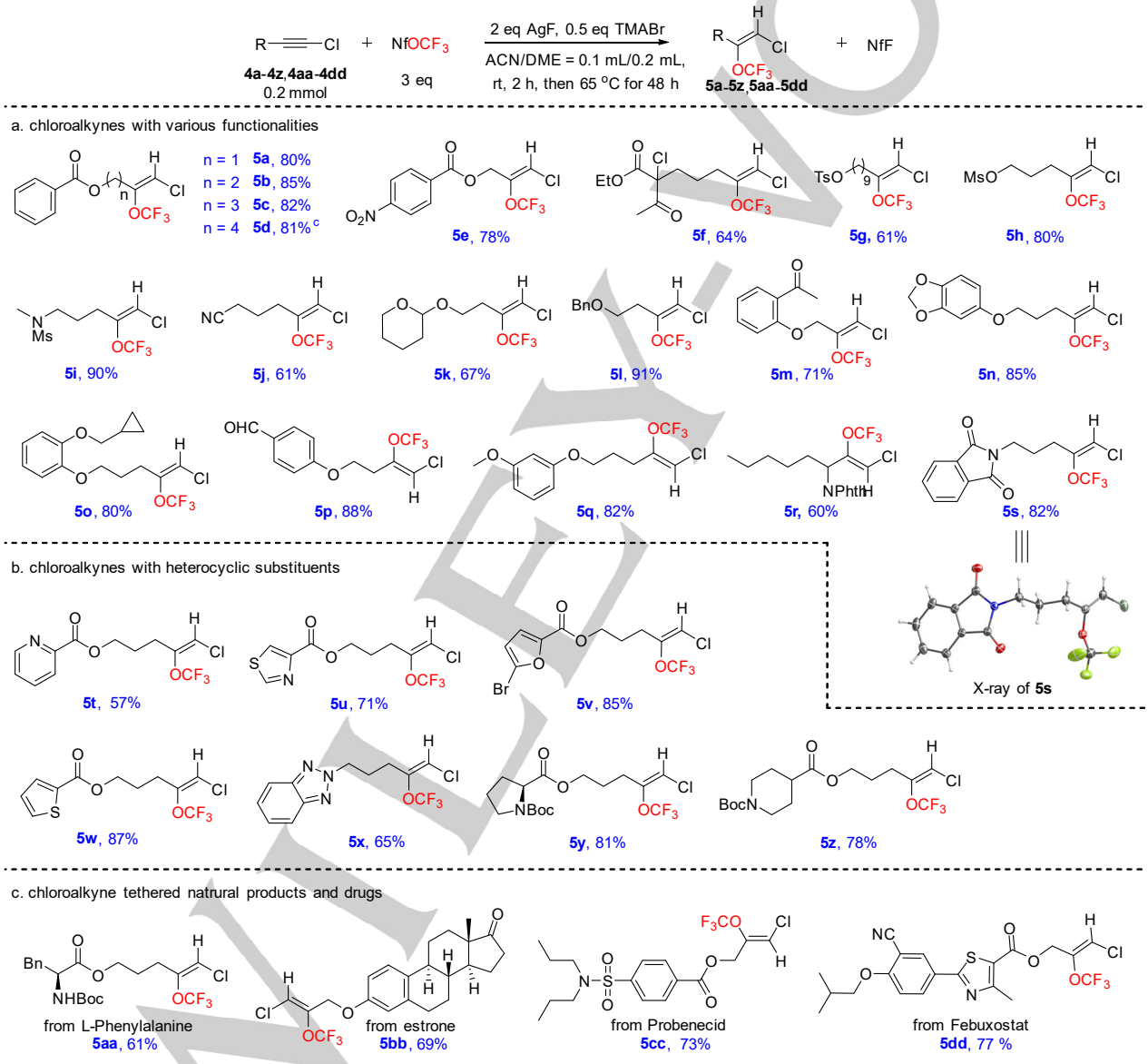
Our protocol provides an easy-to-use synthetic tool for the modification of drug molecules. For example, we obtained a derivative of Probenecid (**5cc**) in 73% yield. Probenecid is a prototypical uricosuric agent used to treat patients with renal impairment. On the other hand, a Febuxostat-tethered chloroalkyne was converted to the hydrotrifluoromethoxylated product in 77% yield. Febuxostat is a xanthine oxidase inhibitor for the treatment of gout. It possesses various functionalities like ester, nitrile, ether, and a thiazole ring which remained intact using our mild protocol. These examples further demonstrate that our hydrotrifluoromethoxylation protocol is suitable for the late-stage, protecting-group-free modification of biologically interesting molecules. In addition, we prepared **5d** on a gram scale under standard reaction conditions in 82% isolated yield, which demonstrated both the scalability and practicality of this method. It should also be noted that the chlorine atoms on the double bonds of these products are potential versatile handles for further functionalization through transition metal-catalysed coupling reactions.

Table 2. Substrates Scope of Hydrotrifluoromethoxylation of Chloroalkynes[a,b]



[a]Reaction Conditions: Unless otherwise noted, reactions were conducted as follows: Starting material **4** (0.2 mmol), TMABr (0.5 equiv), AgF (2 equiv), and 0.3 mL mixed solvent (CH_3CN/DME = 1/2) were added to a 2-mL amber ampoule sequentially. TFNf (3 equiv) was then added and the ampoule was sealed immediately. The reaction mixture was stirred at rt for 2h and then stirred at 65 °C for 48h. [b]Isolated yields. [c]82% isolated yield was obtained when 1.01 g of **4d** was applied.

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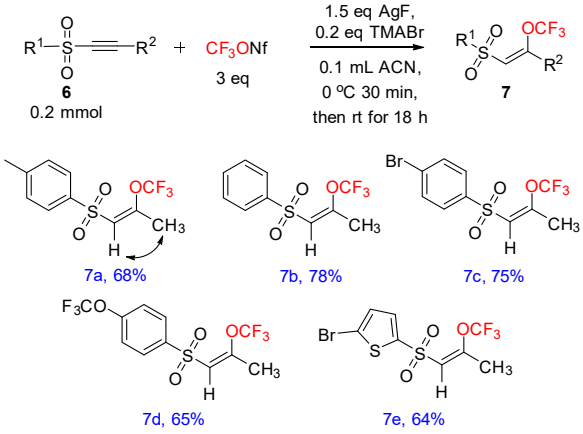
Our hydrotrifluoromethoxylation protocol also works with alkynyl sulfones. As shown in Table 3, various alkynyl sulfones (**7a-7e**) can be converted to the corresponding hydrotrifluoromethoxylation products in good yields and high regio- and stereoselectivity. The *Z*-configuration of the products was determined by observation of the NOE interactions between the CH_3 group and the proton as shown by the double-headed arrow in **7a** (see SI for more details).

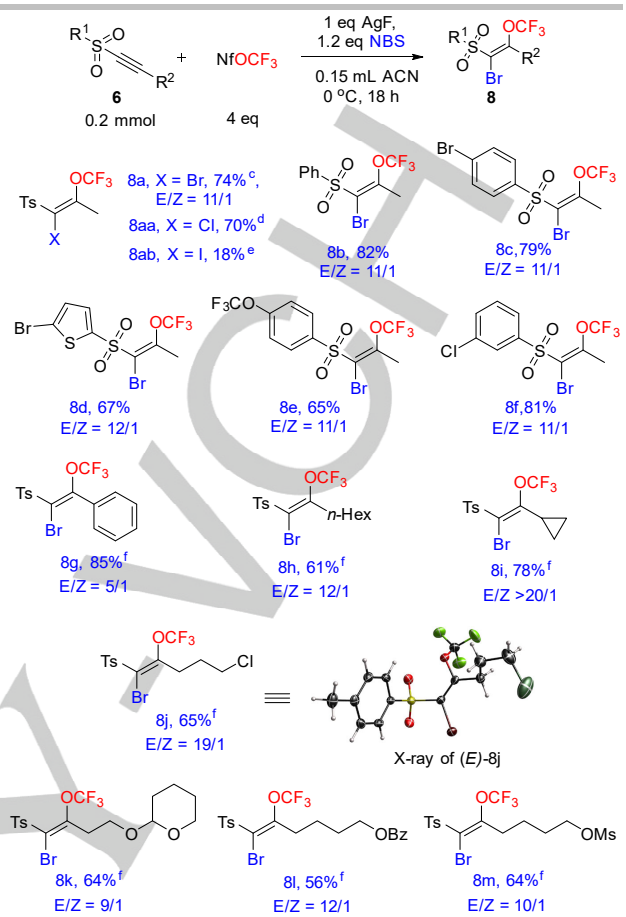
Table 3. Hydrotrifluoromethoxylation of Alkynyl Sulfones[a,b]



[a]Reaction Conditions: Reactions were conducted as follows: Starting material **6** (0.2 mmol), TMABr (0.2 equiv), AgF (1.5 equiv), and 0.1 mL CH_3CN were added to a 1-mL amber ampoule sequentially. TFNf (3 equiv) was then added and the ampoule was sealed immediately. The reaction mixture was stirred at 0 °C for 0.5 hour and then stirred at rt for 18 hours. [b]Isolated yields.

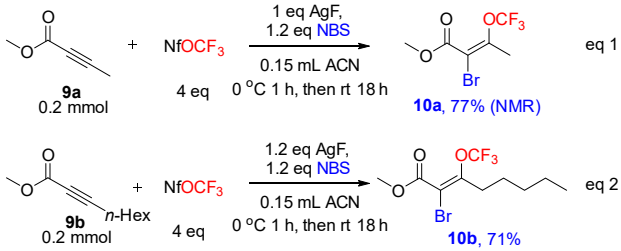
We also found that alkynyl sulfones easily underwent halotrifluoromethoxylation when an electrophilic halogenating reagent was added with our protocol. The reaction delivered the tetrasubstituted alkene, a highly functionalized trifluoromethoxylated alkene tethered with a halogen, which could be further converted to other trifluoromethoxylated derivatives by coupling reactions. As shown in Table 4, all reactions gave highly regio- and stereoselective bromotrifluoromethoxylated alkenes in good to excellent yields, with *E*-configuration as the major product. Alkynyl sulfones with diverse functionalities such as esters (**8l**), ethers (**8k**), sulfonates (**8m**), and halide (**8j**) were well-tolerated with our protocol. Chlorotrifluoromethoxylated alkene (**8aa**) and Iodotrifluoromethoxylated alkene (**8ab**) could also be obtained when trichloroisocyanuric acid or *N*-iodosuccinimide was used as the halogenating reagent instead of *N*-bromosuccinimide. Various aryl sulfones with different substituents on the aromatic ring (**8a-8f**) were screened and all showed good yields. Alkynyl sulfones with either aryl (**8g**) or alkyl (**8a-8f**, **8h-8m**) substituents (R^2) worked well with our protocol. It should be noted that substrates with "vulnerable" substituents such as cyclopropyl (**8i**) and 2-tetrahydropyranyl (**8k**) are also compatible with our halotrifluoromethoxylation protocol. When the reaction with **6a** was scaled up to 3 mmol, a good isolated yield (72%) was obtained. The absolute configuration of the major product was determined by single-crystal X-ray diffraction analysis of **8j** as a *E*-configuration.[29]

Table 4. Halotrifluoromethoxylation of Alkynyl Sulfones[a,b]



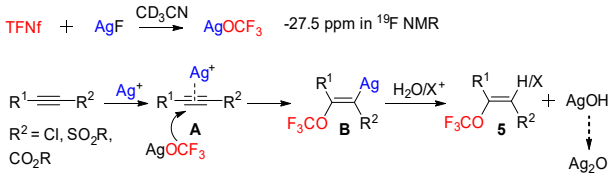
[a]Reaction Conditions: Unless otherwise noted, reactions were conducted as follows: Starting material **6** (0.2 mmol), AgF (1 equiv), NBS (1.2 equiv) and 0.15 mL CH_3CN were added to a 1-mL amber ampoule sequentially. TFNf (4 equiv) was then added and the ampoule was sealed immediately. The reaction mixture was stirred at 0 °C for 18 hours. [b]Isolated yields. [c]72% isolated yield was obtained when 3 mmol (583 mg) of **6a** was applied. [d]1.2 equiv trichloroisocyanuric acid was applied instead of NBS. [e]1.2 equiv *N*-iodosuccinimide was applied instead of NBS. [f]The reaction mixture was stirred at 0 °C for 1 hour and then stirred at rt for 18 hours.

We found that alkynyl ester substrates also work with our bromotrifluoromethoxylation protocol. As shown in the equations 1 and 2, alkynoates **9a** and **9b** can be converted to bromotrifluoromethoxylated alkenoate **10a** and **10b** respectively in good yields.



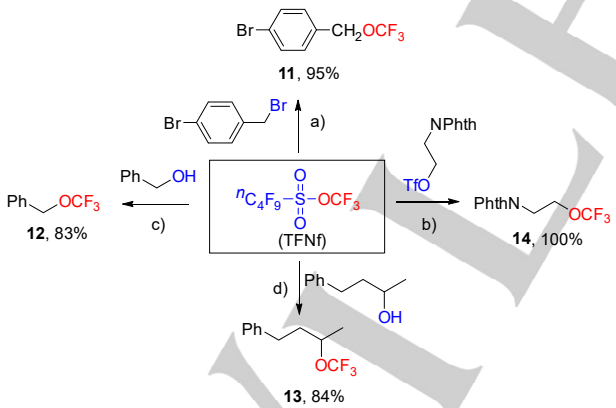
To gain an insight on the reaction mechanism, we monitored the reaction between TFNf and AgF by ^{19}F NMR spectroscopy. It showed that $AgOCF_3$ (–27.5 ppm) and NfF were generated in the reaction (see SI), which confirmed that $AgOCF_3$ was generated *in situ* during the reaction. Cationic silver species are well-known effective catalysts for the electrophilic activation of alkynes towards nucleophiles,[30] so it is not unrealistic to expect that the alkyne moiety coordinates with the silver cation to form π-complex

A, which is subsequently converted to the corresponding vinyl-silver intermediate **B** by *trans*-addition of $AgOCF_3$. Protonation/halogenation of the vinyl-silver intermediate **B** by moisture/halogenating reagent yielded trifluoromethoxylated alkene as the product, plus silver oxide as a black precipitate observed in the reaction (Scheme 4).[30a] The protonation process was further proved by adding D_2O to the reaction (see SI). We ascribed the high regio- and stereoselectivity of the product to the back-side attack of trifluoromethoxide anion (**A** to **B**)[30a] with the electron-withdrawing R^2 group serving as an activating and regio-directing group for the weakly nucleophilic CF_3O anion.[30a]



Scheme 4. Plausible Mechanism for the Regio- and Stereoselective Hydrotrifluoromethoxylation of Alkynes Derivatives

To demonstrate the synthetic prowess of TFNf, we carried the synthesis of trifluoromethyl ethers under various protocols (Scheme 5). The AgF-activated TFNf converted benzyl bromide and alkyl triflate to the alkyl trifluoromethyl ethers **11** and **14** in excellent yields. Furthermore, TFNf was an excellent vehicle for the one-pot synthesis of trifluoromethyl ethers **12** and **13** from primary and secondary alcohols in high yields. We also compared our reagent with TFMS ($TsOCF_3$ was used in this case) in the hydrotrifluoromethoxylation of chloroalkyne **4d** and alkynyl sulfone **6a,** our TFNf showed slightly better yields than TFMS in both reactions (see SI, section 6 for details).



[a]Reaction Conditions (see SI for more details): (a) 4-bromobenzyl bromide, AgF, CH_3CN, rt, 10 min. (b) R-OTf, AgF, CH_3CN, rt, 40 min. (c) and (d) i) ROH, Tf_2O, DIPEA, DCM, -78 °C, 30 min; ii) TFNf, AgF, CH_3CN, -40 °C, 1h.

Scheme 5. Application of TFNf in Other Trifluoromethoxylation Reactions.[a]

In conclusion, we have developed trifluoromethyl nonaflate (TFNf), a user-friendly, thermally stable, and reactive trifluoromethoxylating reagent. TFNf has a suitable boiling point (87-89 °C) for handling and can easily be prepared in high yield by smooth thermolysis of **3** at large scale. In addition, the nonaflyl portion of TFNf can easily be recovered and recycled. The significant merits of TFNf are brought about by the fluorine effect of the long perfluoroalkyl chain of TFNf. The high synthetic potential of TFNf was demonstrated with the regio- and stereoselective hydro(halo)trifluoromethoxylation of various alkyne derivatives. This synthetic protocol is characterized by wide functional group compatibility, good yields, and accessible gram-scale synthesis, all of which may elicit broader applications in pharmaceutical and agrochemical research and development. Other trifluoromethoxylation reactions, including nucleophilic substitution of alkyl (pseudo)halides and one-pot trifluoromethoxylation of primary/secondary alcohols via triflates, were effectively achieved with TFNf. Further applications and commercialization of this reagent are currently underway in our laboratory.

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[29] Crystallographic data for (***E*)-8j**: deposition Number 2084183 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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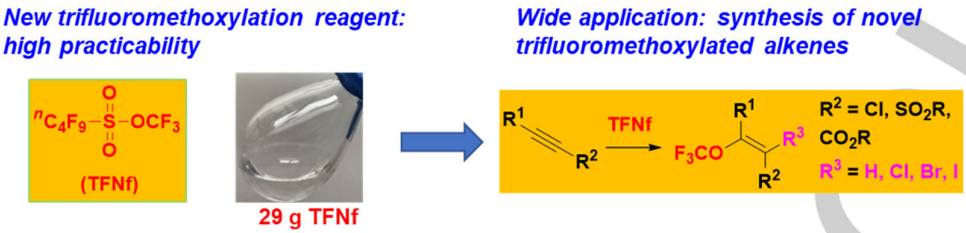

Trifluoromethyl nonaflate (TFNf), an odorless liquid (bp 87-89 °C), was developed as an easy-to-handle, bench-stable, and reactive trifluoromethoxylating reagent which can be easily and safely prepared in large scale. The synthetic potency of TFNf was demonstrated with the underexplored synthesis of various trifluoromethoxylated alkenes, through a highly regio- and stereoselective direct hydro(halo)trifluoromethoxylation of various alkyne derivatives. The reactions showed wide functional group compatibility, good yields, and gram-scale synthesis.