Title

Sequential Xanthalation and O-Trifluoromethylation of Phenols: A Procedure for the Synthesis of Aryl Trifluoromethyl Ethers

Journal

The Journal of Organic Chemistry, 84(24)

ISSN

0022-3263

Authors

Yoritate, Makoto
Londregan, Allyn T
Lian, Yajing
et al.

Publication Date

2019-12-20

DOI

10.1021/acs.joc.9b02717

Peer reviewed

HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2020 November 12.

Published in final edited form as:

J Org Chem. 2019 December 20; 84(24): 15767–15776. doi:10.1021/acs.joc.9b02717.

Sequential Xanthalation and *O*-Trifluoromethylation of Phenols: A Procedure for the Synthesis of Aryl Trifluoromethyl Ethers

Makoto Yoritate[†,‡], **Allyn T. Londregan**[*,§], **Yajing Lian**[§], **John F. Hartwig**[*,†]

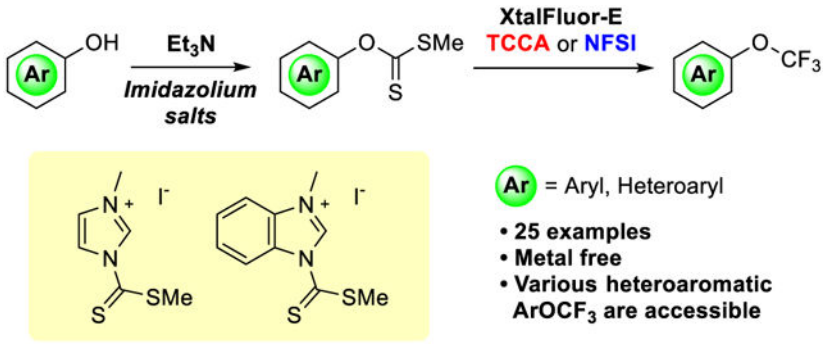
[†]Department of Chemistry, University of California, Berkeley, California 94720, United States

[§]Medicine Design, Pfizer Inc., Groton, Connecticut 06340, United States

Abstract

Molecules containing trifluoromethoxyaryl groups are of interest in pharmaceutical, agrochemical, and materials science research, due to their unique physical and electronic properties. Many of the known methods to synthesize aryl trifluoromethyl ethers require harsh reagents and highly controlled reaction conditions and rarely occur when heteroaromatic units are present. The two-step *O*-trifluoromethylation of phenols via aryl xanthates is one such method that suffers from these drawbacks. Herein, we report a method for the synthesis of aryl trifluoromethyl ethers from phenols by the facile conversion of the phenol to the corresponding aryl and heteroaryl xanthates with newly synthesized imidazolium methylthiocarbonothioyl salts and conversion of these xanthates to the trifluoromethyl ethers under mild reaction conditions.

Graphical Abstract



INTRODUCTION

Organic molecules containing fluorine are common in pharmaceutical, agrochemical, and materials science, due to their unique physical properties and bioactivities.[1] Therefore, new

[*]**Corresponding Authors**: jhartwig@berkeley.edu., allyn.t.londregan@p fi zer.com.

[‡]**Present Address**: M.Y.: Graduate School of Pharmaceutical Science, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02717.

Additional experimental procedures and original spectral data (PDF)

The authors declare no competing financial interest.

synthetic methodologies to introduce fluorine into organic molecules have been studied extensively in recent years.[2] The OCF_3 group is of particular interest to pharmaceutical research, owing to its high electronegativity (χ = 3.7), unique orthogonal conformation relative to the aromatic ring,[3] high lipophilicity,[4] and high metabolic stability. Although the OCF_3 group possesses an intriguing combination of properties, few pharmaceuticals exist that contain the moiety. The absence of such structures is due, in part, to the relatively harsh and toxic reaction conditions needed for their synthesis and lack of existing methods that tolerate heterocyclic diversity, both of which are important considerations in pharmaceutical research.

Known methods to form aryl trifluoromethyl ethers include silver-mediated direct trifluoromethylation of phenols with the Ruppert-Prakash reagent,[5] silver-mediated trifluoromethoxylation of arylstannanes[6a] and aryldiazonium salts,[6b] C–H trifluoromethoxylation via redox-active catalysis or trifluoromethoxy migration,[7] and fluorodecarboxylation of aryloxydi-fluoroacetic acids.[8] Other useful methods[9–11] have been reported, but many of them rely on harsh fluorinating reagents or are of narrow substrate scope.

In this work, we focused our efforts on utilizing readily available aromatic and heteroaromatic alcohols as precursors for the synthesis of aryl trifluoromethyl ethers via aryl and heteroaryl xanthates (Scheme 1). In their pioneering work on the subject, Hiyama and co-workers reported the conversion of phenols to trifluoromethoxy arenes via methylxanthates.[9c,e] The trifluoromethylation reactions, however, only proceeded with an exceptionally large excess of highly toxic HF-pyridine. Leroux and co-workers[9f] investigated this transformation further and determined that heterocyclic functionality, with the exception of 2-halo-azines, was not tolerated. (See the Supporting Information.) Some operational improvements to this procedure were made by Umemoto et al.,[9g] using FluoLead in combination with antimony trichloride, but the reported substrate scope for aryl xanthates was limited to a single unisolated example. Finally, to the best of our knowledge, there have been few advancements on the synthesis of aryl xanthates. Most preparations use a two-step protocol consisting of alcohol deprotonation with a strong base followed by condensation and alkylation with CS_2 and MeI, respectively. In our experience, this reaction is highly sensitive to the steric and electronic properties of the phenol. (See the Supporting Information.)

RESULTS AND DISCUSSION

We began our investigation by first developing a robust method to form xanthates from aromatic and heteroaromatic alcohols. Under standard conditions with NaH, CS_2, and MeI, 4-dimethylaminocarboxy phenol **1a** (Table 1) reacted to low conversion, likely due to the low nucleophilicity of **1a**. To improve this transformation, we evaluated several potential reagents that could form xanthates. The reaction of **1a** with commercially available imidazole carbodithioate **4**,[12] which is reported to be more reactive than CS_2, did not proceed in appreciable yield (entry 1). The same reaction with benzotriazole analog **5** was much more effective and afforded **2a** in 70% yield, along with unreacted starting material (entry 2). Therefore, we designed imidazolium and benzimidazolium analogs **6** and **7**,[13]

which we expected to be more electrophilic than **5**.[14] After investigating the effects of added base, we found that the combination of imidazolium **6** and triethylamine formed xanthate **2a** in 99% yield (entry 3). The analogous reaction with benzimidazolium salt **7** afforded **2a** in lower yield (entry 4, **2a**: 79%), due to a side reaction, which was later determined to be thiocarbonylation of the aromatic ring, owing to the stronger electrophilicity of **7** than of **6**. The conversion of phenol **1a** to the corresponding xanthate with **6** in MeCN was as effective as that in DMF (entry 5, **2a**: 98%). The analogous reaction of the 4-alkoxycarbonyl-substituted phenol **1b** with **6** and **7** also formed the xanthate in a high yield (91% and 99%, entries 6 and 7). The reactions with these reagents to form aromatic xanthates are operationally simple and convenient.

Having established reliable conditions for the formation of aromatic and heteroaromatic xanthates from phenols, we investigated the conversion of 4-dimethylaminocarbonyl phenoxyxanthate **2a** to the corresponding aryl trifluoromethyl ether (Table 2). XtalFluor-E, a commercially available, free-flowing solid, was chosen as a fluoride source due to its good stability under air and low proclivity for thermal degradation.[15] Control investigations with other potential fluoride sources, including PyFluor, HF/KF, HF/Pyr, DeoxoFluor, DAST, XtalFluor-M, and XtalFluor-E with TCCA showed that the yield of the trifluoromethyl ether from xanthate **2a** was the highest with XtalFluor-E as the source of fluoride. (See the Supporting Information.)

To optimize the formation of trifluoromethyl ether **3a** from xanthate **2a** with XtalFluor-E, we tested a series of reactions with various halonium oxidants as soft Lewis acids. Previous computational studies by Kepp[16] showed that halogen atoms have a relatively high thiophilicity and are particularly useful Lewis acids toward thiocarboyls. Hiyama and co-workers[9c,e] demonstrated this principal when they utilized various sources of electrophilic bromides (i.e., NBS or DBH) to accelerate the fluorination of xanthates in the presence of HF-pyridine. Under our conditions, the yields of the reactions with fluorinating, brominating, and iodinating reagents as Lewis acid were low (entries 1–6); in contrast, the yield of the aryl trifluoromethyl ether from the reaction with trichloroisocyanuric acid (TCCA) was high (entry 6, **3a**: 78%). The same reaction conducted in a glovebox gave **2a** in a significantly lower 32% yield (entry 7). On the basis of the hypothesis that water in the air facilitates the reaction, we found that reactions with added water (1.0 equiv) were reproducible and scalable (entry 8, **3a**: 76%).[17]

The reaction of the more electron-deficient 4-ethoxycarbonyl phenoxyxanthate **2b** occurred in high yield under slightly different conditions. We found that the reaction of 4-ethoxycarbonyl phenoxyxanthate **2b** with XtalFluor-E and TCCA afforded a difluorochloromethyl ether ($ArOCF_2Cl$; 18%) side product, in addition to the desired trifluoromethyl ether (entry 9, **2b**: 56%). In light of this result, fluoronium reagents, such as *N*-fluorobenzenesulfoneiminde (NFSI) and Selectfluor, were investigated as alternative halonium Lewis acid sources. Although reactions were slower (24 h), the treatment of **2b** with 3 equiv of NFSI and XtalFluor-E afforded trifluoromethyl ether **3b** in a high 75% yield (entry 10). Under these conditions with XtalFluor-E, the yield of the reaction was the same with or without 1 equiv of added water (entry 11, **2b**: 70%). The reaction of the more electron-rich 4-adamantyl phenoxyxanthate **2c** was similar to that of **2b**. The reaction of **2c**

with XtalFluor-E and TCCA formed both the difluorochloromethyl ether and the trifluoromethyl ether (Table 2; entry 12, **2c**: 56%), whereas the reaction of **2c** with NFSI led to the desired **3c** without the chlorinated side product (Table 2; entry 13, **2c**: 80%).

The scope of the conversion of aromatic and heteroaromatic alcohols to the corresponding aryl trifluoromethyl ethers under the conditions discovered for the two-step trifluoromethoxylation of phenols is shown in Table 3. This operationally simple method allowed for the facile formation of a broad range of xanthates from the corresponding phenols, using a minimal amount of reagent **6** or **7** (1 equiv) and mild base (1.1 equiv) in MeCN. Phenols **1a**–**1w** were converted to the corresponding xanthates **2a**–**2w** in over 90% yield with reagent **6**, with a few exceptions. The formation of xanthates from electron-poor phenols, such as ethylbenzoate **2c**, chromenone **2h**, and hydroxypyrazole **2w**, proceeded in higher yield with the more electrophilic benzimidazole-derived reagent **7**. The formation of the xanthate from 2,4-di-*t*-butylphenol **1f** with either reagent **6** or **7** resulted in poor yield, because decomposition of the xanthalating reagents is faster than the desired xanthate formation. (See the Supporting Information.) Instead, formation of **2f** occurred quantitatively with the less electrophilic benzotriazole **5**.

The conversion of the xanthates produced by this method to the corresponding aryl trifluoromethyl ethers was performed under one of two conditions: condition A, with XtalFluor-E (5 equiv), TCCA (1 equiv), and H_2O (1 equiv) in 1,2-dichloroethane at 80 °C for 3–12 h, or condition B, with XtalFluor-E (3 equiv) and NFSI (3 equiv) in 1,2-dichloroethane at 80 °C for 12–48 h. All the reactions were performed under atmospheric conditions with no added controls. Generally, the reactions with substrates containing Lewis-basic functional groups, such as amides, nitriles, or nitrogen-containing heteroaromatic rings, occurred in higher yield under condition A than under condition B. Reactions of substrates lacking Lewis basic functionality occurred in higher yield under condition B than under condition A.

Using condition A or B, we synthesized a variety of aryl trifluoromethyl ethers from the corresponding xanthates in modest to excellent yields. In several cases, the isolated yields were lower than the yields determined by NMR spectroscopy because of the low boiling point of the product or the necessity for preparative SFC or both. Both electron-poor and electron-rich xanthates readily reacted to yield the desired aryl trifluoromethyl ethers. For certain substrates containing electron-rich aromatic rings, electrophilic chlorination reactions were observed as side processes from the reaction with TCCA. This side reaction could be avoided by utilizing condition B, with NFSI in place of TCCA (for example: **3f**, 56%; **3g**: 65%). Trifluoromethoxylation of more electron-neutral 4-bromophenol and 4-iodophenol also reacted smoothly to afford useful building blocks **3k** and **3l** in 66% and 67% yield, respectively.

A few examples of the conversion of aromatic alcohols containing heterocyclic substituents or heteroaromatic alcohols to the corresponding trifluoromethyl ethers have been reported.[5,11] We found that the conversion of xanthates derived from these classes of alcohols to the corresponding trifluoromethyl ether occurred under both conditions A and B. The reactions of **2m**–**2q**, in which the aryl xanthate is substituted with a heteroaromatic substituent,

afforded the corresponding trifluoromethyl ethers. Likewise, xanthates derived from phenols substituted with six-membered heteroarenes, such as **2o**, **2p**, and **2q**, formed the corresponding heteroaryl trifluoromethyl ethers in good yield.

Heteroaromatic xanthates, in which the xanthyl group is connected directly to a heteroaromatic ring, such as a pyridine or quinoline, also formed the corresponding trifluoromethyl ethers. Although yields were modest in most cases, these reactions enabled the conversions of heteroaromatic alcohols to several previously unknown trifluoromethoxy heteroarenes (**3r**, **3u**–**3w**). In certain instances, such as compound **3s**, the volatility prevented complete isolation, even though the product was formed in substantial yield, as determined by ^{1}H and ^{19}F NMR spectroscopy. Perhaps most notable product from reaction of a heteroaromatic xanthate is example **3w**. To the best of our knowledge, this example represents the first known preparation of a five-membered, nitrogen-containing heterocycle containing an OCF_3 group derived from the corresponding alcohol.

Observations made during the fluorination reactions of xanthates provided insight into a potential reaction mechanism. For example, reactions under condition A gave Ar-OCF_2Cl as a byproduct in certain cases.[18] In addition, under condition A, the reactions with one equivalent of water occurred in higher yields than those lacking added water. These data suggest that the reactions conducted under conditions A and B proceed through slightly different pathways (Scheme 2).

The first step of the mechanism is likely coordination of the thiocarbonyl group of the xanthates to TCCA or NFSI to form activated species **9**. Nucleophilic addition of fluoride then would yield monofluoro intermediate **10**. Two additional substitutions of fluoride would ultimately afford the desired trifluoromethyl ether **3**. It is possible in the last step involving difluoro intermediate **11** that homolytic cleavage of the C–S bond and trapping with a source of Cl· occurs in competition with nucleophilic substitution by fluoride. Consistent with the possibility of these two parallel pathways for the final step, no byproduct **8** was observed in the presence of BHT.

Further analysis of the reaction mixture with xanthate **2a** revealed the presence of carbamothioate byproduct **12a** (Scheme 3). The formation of **12a** can be attributed to the liberation of diethylamine from the degradation of XtalFluor-E, followed by a Newman-Kwart-type rearrangement.[19] Indeed, a control experiment conducted with **2a**, Et_2NH, and TCCA produced the byproduct **12a**, along with the hydrolyzed product **1a**. From the water present in condition A, a small amount of HF is likely generated, and this HF would protonate the diethylamine to suppress this side reaction. It is uncertain why added water does not have the same effect on the reaction by path B, but it is possible that the smaller amount of XtalFluor-E and lower Lewis acidity of NFSI causes the competing Newman-Kwart-type rearrangement to be slower.

In summary, we have described an improved, two-step trifluoromethoxylation of phenols via xanthate intermediates by simple procedures and easily-handled reagents. In the first step, phenols or heteroaryl alcohols react with imidazolium salt **6** or benzimidazolium salt **7** to form xanthates in high yield. In the second step, XtalFluor-E reacts with xanthate in the

presence of trichloroisocyanuric acid (TCCA) or *N*-fluorosulfonimide (NFSI) to form a range of aryl and heteroaryl trifluoromethyl ethers from common phenols and heteroaromatic alcohols. All reactions were performed under atmospheric conditions with no added controls. This methodology should be useful for pharmaceutical, agrochemical, and materials science research in which aromatic and heteroaromatic trifluoromethyl ethers are highly desired.

EXPERIMENTAL SECTION

General Remarks.

All xanthate formations were conducted with N_2-flushed round-bottom flasks. The trifluoromethylation was conducted with 20 mL screw cap vials in air. All the solvents for the reactions were purchased from Sigma-Aldrich (anhydrous grade equipped sure seal) and used as received. Unless otherwise stated, the reaction temperatures above 23 °C refer to the temperatures of an aluminum heating block, which were controlled by an electronic temperature modulator. NMR spectra were recorded on Bruker AVQ-400 and AV-600 instruments at UC Berkeley and a 500 MHz Bruker Avance III with a CryoProbe at Kyushu University. Chemical shifts (δ) are reported in ppm, relative to the residual solvent signal. Data from 1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and bs (broadening singlet). All ^{13}C NMR spectra were proton-decoupled. GC-MS data were obtained on an Agilent 6890-N GC system containing an Alltech EC-1 capillary column and an Agilent 5973 mass-selective detector. High-resolution electron impact (EI) mass spectral data were obtained from the University of California, Berkeley Mass Spectrometry Laboratory. High-resolution electron spray ionization (ESI) TOF-MS and atmospheric pressure chemical ionization (APCI) TOF-MS were obtained from the Lawrence-Berkeley National Laboratory Catalysis Center.

Synthesis of Phenols.

1a, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**, **1l**, **1m**, **1n**, **1q**, **1s**, **1t**, **1u**, and **1v** were commercially available. The syntheses of **1o**, **1p**, **1r**, and **1w** are described below.

3-Hydroxy-6-dimethylaminocarbonylpyridine (1r).—Ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI, 2.11 g, 11.0 mmol, 1.1 equiv) was added to a solution of 5-hydroxypicolinic acid (1.39 g, 10.0 mmol, 1.0 equiv), dimethylamine hydrochloride (897 mg, 11.0 mmol, 1.1 equiv), 4-dimethylaminopyridine (DMAP, 1.22 g, 10.0 mmol, 1.0 equiv), and diisopropylethylamine (3.8 mL, 22 mmol, 2.2 equiv) in CH_2Cl_2 (20 mL) at room temperature. After stirring at room temperature for 12 h, the solution was directly poured onto a silica gel column and purified (EtOAc/MeOH 100:0 to 80:20) to give 1.00 g of **1r** (61%); white crystal; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.38 (bs, 1H), 8.09 (d, J = 2.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.9 Hz, 1H), 3.00 (bs, 3H), 2.96 (bs, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 154.3, 145.1, 135.9, 124.7, 122.6, 38.6, 35.2; HRMS (ESI), calcd for $C_8H_{11}N_2O_2^+$ $(M + H)^+$ 167.0815, found 167.0818.

4-(6-Chloropyridin-3-yl)phenol (1o).—Procedure A: To a 100 mL single-neck round-bottom flask, 4-hydroxyphenylboronic acid (690 mg, 6.00 mmol, 1.2 equiv), 2-chloro-5-bromopyridine (962 mg, 5.00 mmol, 1.0 equiv), sodium carbonate (1.59 g, 15.0 mmol, 3.0 equiv), 1,4-dioxane (19 mL), and H_2O (6 mL) were added. The mixture was degassed by bubbling with nitrogen for 30 min. [1,1′-Bis-(diphenylphosphino)ferrocene]dichloropalladium ($PdCl_2$(dppf), 73.2 mg, 2 mol %) was added to the mixture at room temperature. The mixture was warmed at 80 °C, stirred for 24 h, and then cooled to room temperature. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 50:50 to 100:0) to give 905 mg of phenol **1o** (88%); white crystal; 1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.76 (s, 1H), 8.64 (d, J = 2.5 Hz, 1H), 8.05 (dd, J = 8.2, 2.5 Hz, 1H), 7.58–7.54 (m, 2H), 7.52 (d, J = 8.2 Hz, 1H), 6.90–6.86 (m, 2H); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 158.1, 148.1, 147.0, 136.9, 135.0, 128.1, 126.2, 124.2, 116.0; HRMS (ESI), calcd for $C_{11}H_9ClNO^+$ $(M + H)^+$ 206.0367, found 206.0368.

4-(Pyridin-3-yl)phenol (1p).—Procedure A was followed for the reaction of 3-bromopyridine (790 mg, 5.00 mmol). The title compound **1p** was obtained in 94% yield; white crystal; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.69 (s, 1H), 8.81 (d, J = 1.9 Hz, 1H), 6.98 (dd, J = 4.7, 1.3 Hz, 1H), 7.97 (ddd, J = 7.9, 1.9, 1.3 Hz, 1H), 7.57–7.53 (m, 2H), 7.42 (dd, J = 7.9, 4.7 Hz, 1H), 6.90–6.86 (m, 2H); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 157.6, 147.4, 147.0, 135.6, 133.1, 128.0, 127.7, 123.8, 115.9; HRMS (ESI), calcd for $C_{11}H_{10}NO^+$ $(M + H)^+$ 172.0757, found 172.0756.

1-(4-Chlorophenyl)-1H-pyrazol-4-ol (1w).—Ethyl-4-chloroacetoacetate (2.7 m L, 20 mmol) was added to aqueous conc. HCl (5 mL) at room temperature. After stirring at room temperature for 24 h, the solution was poured into ice and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under high vacuum at 0 °C to give 4-chloroacetoacetic acid, which was diluted with 6 mL of water (solution A).

Sodium nitrite (1.38 g, 20.0 mmol, 1.0 equiv) was added dropwise to a solution of *p*-chloroaniline (2.52 g, 20.0 mmol, 1.0 equiv), conc. HCl (5 mL), and H_2O (20 mL) at 0 °C (solution B). After maintaining solution B for 30 min at 0 °C, this solution was transferred into solution A by pipet and then stirred for 10 min. An aqueous 6 M solution of sodium acetate (10 mL) was added to the resulting solution dropwise. *(CAUTION: CO_2 bubbles violently.)* After stirring for 1 h, the precipitate in the mixture was collected by filtration, washed with H_2O, and dried under high vacuum to give 2.02 g of (*E*)-1-chloro-3-(2-(4-chlorophenyl)hydrazineylidene)-propan-2-one (**13**) (58%); yellow powder; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.67 (bs, 1H), 7.38–7.35 (m, 2H), 7.31 (d, J = 1.3 Hz, 1H), 7.25–7.22 (m, 2H), 4.87 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 189.2, 141.8, 132.6, 129.3, 125.7, 115.4, 45.2; HRMS (ESI), calcd for $C_9H_8Cl_2N_2ONa^+$ $(M + Na)^+$ 252.9906, found 252.9900.

Sodium hydroxide (1.00 g, 25.0 mmol, 3.2 equiv) was added to a solution of **13** (1.82 g, 7.88 mmol, 1.0 equiv) and MeOH (50 mL) at room temperature, causing the temperature rise to

approximately 40 °C. After stirring for 1 h at room temperature, the mixture was concentrated and diluted with water (10 mL). Insoluble material was removed by filtration. The solution then was neutralized with conc. HCl. The resulting precipitate was filtered, washed with water, and dried under high vacuum to give 1.51 g of 4-hydroxylpyrrazole **1w** (99%); pale-yellow powder; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.38–7.35 (m, 2H), 7.53–7.48 (m, 2H), 7.41 (s, 2H), 7.40–7.36 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.1, 138.8, 131.9, 131.6, 129.7, 119.9, 114.0; HRMS (ESI), calcd for $C_9H_8ClN_2O^+$ $(M + H)^+$ 195.0320, found 195.0319.

Synthesis of Xanthate Forming Reagents.

Reagent **4** is commercially available. *N*-(Methylthiothiocarbonyl)benzotriazole **5** was synthesized following a reported procedure.[20] The methods to synthesize imidazolium reagent **6** and benzimidazolium reagent **7** are described below.

Imidazolium Salt (6).—A 250 mL single-neck-shield flask equipped with a stir bar and septum was purged with nitrogen. Methylthio-(thiocarbonyl)imidazole **4** (7.09 g, 44.9 mmol, 1.0 equiv)[21] in benzene (120 mL) was transferred to the flask via cannula. Iodomethane (28 mL, 450 mmol, 10 equiv) was added to the mixture. The septum was replaced with a screw cap quickly. The resulting mixture was warmed to 80 °C with an oil bath. While stirring for 3 h, an orange precipitate formed. The precipitate was filtered, washed with anhydrous benzene (100 mL), and dried under high vacuum to give 6.44 g of imidazolium reagent **6** (48%); a bright orange solid; mp. 89 °C; ^{1}H NMR (600 MHz, $(CD_3)_2SO$), δ 10.14 (bs, 1H), 8.50 (dd, J = 2.2, 1.5 Hz, 1H), 7.97 (dd, J = 2.2, 1.5 Hz, 1H), 3.94 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (151 MHz, $(CD_3)_2SO$) δ 197.6, 136.3, 125.1, 119.5, 36.7, 21.2; HRMS (ESI), calcd for $C_6H_9N_2S_2^+$ $(M + H)^+$ 173.0202, found 173.0208.

Benzimidazolium Salt (7).—A 250 mL single-neck-shield flask equipped with a stir bar and septum was purged with nitrogen. *N*-Methylthio(thiocarbonyl)-benzimidazole (9.00 g, 43.2 mmol, 1.0 equiv)[22] in MeCN (90 mL) was transferred to the flask via cannula. Iodomethane (22 mL, 350 mmol, 8.0 equiv) was added to the mixture. The septum was replaced with a screw cap quickly. The resulting mixture was warmed to 80 °C with an oil bath. While stirring for 4.5 h, a bright orange precipitate was generated. The precipitate was filtered, washed with EtOAc/hexane 3:1 (100 mL), and dried under high vacuum to give 10.9 g of benzimidazolium reagent **7** (72%) as a yellowish orange solid; mp. 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$, rotamer was observed) δ 10.629 (bs, 1/2H), 10.627 (bs, 1/2H), 8.59–8.54 (m, 1H), 8.17–8.12 (m, 1H), 7.84–7.79 (m, 2H), 4.182 (s, 3/2H), 4.181 (s, 3/2H), 3.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 143.0, 132.7, 129.4, 128.5, 127.8, 116.0, 114.5, 34.0, 21.5; HRMS (ESI), calcd for $C_{10}H_{11}N_2S_2^+$ $(M + H)^+$ 223.0358, found 223.0355.

General Procedure B for the Formation of Xanthates.

Reagent **6** or **7** (2.00 mmol, 1.0 equiv) was added to a solution of the phenol **1a**–**1w** (2.00 mmol, 1.0 equiv), triethylamine (330 μL, 2.2 mmol, 1.1 equiv), and MeCN (10 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over

Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography or recrystallization to give xanthates **2a**–**2w**.

4-Dimethylaminocarbonylphenoxy Xanthate (2a).—General Procedure B was followed for the reaction of 4-dimethylaminocarbonyl phenol **1a** (330 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:1) to give the product as a white solid (510 mg, >99%). **2a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 3.10 (bs, 3H), 3.01 (bs, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.4, 170.7, 155.3, 134.6, 128.8, 122.3, 39.8, 35.6, 20.2; HRMS (ESI), calcd for $C_{11}H_{14}NO_2S_2^+$ $(M + H)^+$ 256.0460, found 256.0464.

4-Ethoxycarbonylphenoxy Xanthate (2b).—General Procedure B was followed for the reaction of 4-ethoxycarbonylphenol **1b** (332 mg, 2.00 mmol) and benzimidazolium reagent **7** (700 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give the product as a white solid (510 mg, 99%). **2b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H), 7.19–7.15 (m, 2H), 4.39 (q, J = 6.9, 2H), 2.68 (s, 3H), 1.39 (t, J = 6.9, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.3, 165.8, 158.0, 131.3, 128.9, 122.4, 61.3, 20.2, 14.5; HRMS (ESI), calcd for $C_{11}H_{12}O_3S_2Na^+$ $(M + Na)^+$ 279.0120, found 279.0115.

4-Adamantylphenoxy Xanthate (2c).—General Procedure B was followed for the reaction of 4-adamantylphenol **1c** (456 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 0:1 to 1:100) to give the product as a white solid (598 mg, 94%). **2c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.05–7.02 (m, 2H), 2.67 (s, 3H), 2.12–2.08 (m, 3H), 1.92 (d, J = 2.2 Hz, 6H), 1.82–1.72 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.0, 152.5, 149.8, 126.2, 121.4, 43.4, 36.9, 36.3, 29.1, 20.1; HRMS (ESI), calcd for $C_{18}H_{23}OS_2^+$ $(M + H)^+$ 319.1185, found 319.1186.

4-Cyanophenoxy Xanthate (2d).—General Procedure B was followed for the reaction of 4-cyanophenol **1d** (238 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:1) to give the product as a white solid (351 mg, 84%). **2d**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H), 7.25–7.22 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 214.9, 157.6, 133.9, 123.7, 118.2, 110.7, 20.3; HRMS (ESI), calcd for $C_9H_7NOS_2Na^+$ $(M + Na)^+$ 231.9861, found 231.9854.

Phenoxy Xanthate (2e).—General Procedure B was followed for the reaction of phenol **1e** (376 mg, 4.00 mmol) and imidazolium reagent **6** (1.20 g, 4.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a pale-yellow oil (676 mg, 92%). **2e**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.30 (tt, J = 7.7, 1.1 Hz, 1H), 7.13–7.09 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.9, 154.8, 129.7, 126.7, 122.2, 20.1; HRMS (EI), calcd for $C_8H_8OS_2^+$ $(M)^+$ 184.0017, found 184.0015.

2,4-Di-t-butylphenoxy Xanthate (2f).—Cesium carbonate (1.30 g, 4.00 mmol, 2.0 equiv) was added to a single-neck flask, dried by heat gun under vacuum, cooled, and filled back with nitrogen. 2,4-Di-*t*-butyl-phenol **1f** (413 mg, 2.00 mmol, 1.0 equiv) and DMF (20 mL) were added to the flask. The resulting mixture was cooled to 0 °C, and benzotriazole reagent **5** (628 mg, 3.00 mmol, 1.5 equiv) was added. After stirring for 3 h at 0 °C, the mixture was treated with saturated aqueous $NaHCO_3$ and extracted with hexane (20 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 0:100) to give the product as a white solid (587 mg, 99%). **2f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1H), 7.26–7.23 (m, 1H), 7.01–6.98 (m, 1H), 2.70 (s, 3H), 1.38 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.5, 151.0, 149.0, 140.4, 124.6, 123.69, 123.68, 34.91, 34.88, 31.6, 30.6, 20.1; HRMS (ESI), calcd for $C_{16}H_{24}OS_2Na^+$ $(M + Na)^+$ 319.1161, found 319.1170.

4-(Methoxycarbonylethyl)phenoxy Xanthate (2g).—General Procedure B was followed for the reaction of methyl 3-(4-hydroxyphenyl)propanoate **1g** (360 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give the product as a white solid (524 mg, 97%). **2g**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.04–7.00 (m, 2H), 3.67 (s, 3H), 2.97 (t, J = 7.7 Hz, 2H), 2.66 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.0, 173.2, 153.2, 139.0, 129.5, 122.1, 51.8, 35.6, 34.88, 31.6, 30.6, 20.1; HRMS (ESI), calcd for $C_{12}H_{14}O_3S_2Na^+$ $(M + Na)^+$ 293.0277, found 293.0278.

O-Methylthiocarbonyl-7-hydroxycoumarin (2h).—General Procedure B was followed for the reaction of 7-hydroxycoumarin (umbelliferone) **1h** (324 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:3) to give the product as a white solid (490 mg, 97%). **2h**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, J = 9.5 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.43 (d, J = 9.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.1, 160.3, 156.8, 154.9, 142.9, 128.8, 119.2, 117.4, 116.6, 111.4, 20.3; HRMS (ESI), calcd for $C_{11}H_9O_3S_2^+$ $(M + H)^+$ 252.9988, found 252.9982.

4-Benzoylphenoxy Xanthate (2i).—General Procedure B was followed for the reaction of 4-benzoylphenol **1i** (396 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2) to give the product as a white solid (538 mg, 93%). **2i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91–7.88 (m, 2H), 7.81 (dd, J = 8.4, 1.4 Hz, 2H), 7.60 (tt, J = 7.4, 1.4 Hz, 1H), 7.49 (dd, J = 8.4, 7.4 Hz, 1H), 7.24–7.21 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.2, 195.5, 157.7, 137.5, 135.7, 132.6, 131.8, 130.0, 128.5, 122.3, 20.2; HRMS (ESI), calcd for $C_{15}H_{12}O_2S_2Na^+$ $(M + Na)^+$ 311.0171, found 311.0168.

4-Trifluoromethylphenoxy Xanthate (2j).—General Procedure B was followed for the reaction of 4-trifluoromethylphenol **1j** (324 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column

chromatography (hexane) to give the product as a pale-yellow oil (475 mg, 94%). **2j**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 156.9, 128.9 (q, J = 33 Hz, C), 127.1 (q, J = 3.6 Hz, CH), 123.9 (q, J = 272 Hz, CF_3), 123.0 20.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ 62.3 (s); HRMS (EI), calcd for $C_9H_7F_3OS_2$ 251.9890, found 251.9894.

4-Bromophenoxy Xanthate (2k).—General Procedure B was followed for the reaction of 4-bromophenol **1k** (346 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a pale-yellow oil (525 mg, >99%). **2k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.01–6.97 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.6, 153.7, 132.8, 124.1, 120.0, 20.2; HRMS (EI), calcd for $C_8H_7BrOS_2$ 261.9122, found 261.9124.

4-Iodophenoxy Xanthate (2l).—General Procedure B was followed for the reaction of 4-iodophenol **1l** (440 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a white solid (602 mg, 97%). **2l**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H), 6.89–6.85 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.5, 154.5, 138.8, 124.5, 91.0, 20.2; HRMS (EI), calcd for $C_8H_7IOS_2$ 309.8983, found 309.8988.

4-(1H-Imidazol-1-yl)phenoxy Xanthate (2m).—General Procedure B was followed for the reaction of 4-(1*H*-imidazol-1-yl)phenol **1m** (320 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:1) to give the product as a white solid (500 mg, >99%). **2m**: ^{1}H NMR (600 MHz, $CDCl_3$), δ 7.86 (dd, J = 1.2, 1.2 Hz, 1H), 7.47–7.42 (m, 2H), 7.28 (dd, J = 1.2, 1.2 Hz, 1H), 7.25–7.21 (m, 3H), 2.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.8, 153.4, 135.7, 135.6, 130.7, 123.8, 122.7, 118.4, 20.2; HRMS (ESI), calcd for $C_{11}H_{11}N_2OS_2^+$ $(M + H)^+$ 251.0307, found 251.0304.

4-(Benzothiazole-2-yl)phenoxy Xanthate (2n).—General Procedure B was followed for the reaction of 4-(benzothiazole-2-yl)phenol **1n** (422 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:20 to 1:10) to give the product as a white solid (549 mg, 91%). **2n**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18–8.15 (m, 2H), 8.08 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.51 (dd, J = 8.1, 7.3 Hz, 1H), 7.40 (dd, J = 8.1, 7.3 Hz, 1H), 7.27–7.23 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.5, 166.8, 156.6, 154.2, 135.3, 129.0, 126.6, 125.5, 123.5, 123.1, 121.8, 20.2; HRMS (ESI), calcd for $C_{15}H_{12}NOS_3^+$ $(M + H)^+$ 318.0076, found 318.0081.

4-(6-Chloropyridine-3-yl)phenoxy Xanthate (2o).—General Procedure B was followed for the reaction of 4-(6-chloropyridine-3-yl)phenol **1o** (411 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 1:2) to give the product as a white solid (575 mg, 97%). **2o**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (dd, J = 2.6, 0.7 Hz, 1H), 7.84

(dd, J = 8.4, 2.6 Hz, 1H), 7.61–7.58 (m, 2H), 7.41 (dd, J = 8.4, 0.7 Hz, 1H), 7.24–7.21 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.9, 155.0, 150.8, 148.1, 137.3, 135.0, 134.8, 128.4, 124.4, 123.2, 20.2; HRMS (ESI), calcd for $C_{13}H_{11}ClNOS_2^+$ $(M + H)^+$ 295.9965, found 295.9961.

4-(Pyridine-3-yl)phenoxy Xanthate (2p).—General Procedure B was followed for the reaction of 4-(pyridine-3-yl)phenol **1p** (342 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 1:2) to give the product as a yellow oil (499 mg, 95%). **2p**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (d, J = 2.2 Hz, 1H), 8.61 (dd, J = 4.8, 1.5 Hz, 1H), 7.88 (ddd, J = 7.7, 2.2, 1.8 Hz, 1H), 7.65–7.61 (m, 2H), 7.38 (dd, J = 7.7, 4.8 Hz, 1H), 7.24–7.21 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.9, 154.8, 148.7, 148.3, 136.3, 135.8, 134.6, 128.4, 123.8, 123.0, 20.2; HRMS (ESI), calcd for $C_{13}H_{12}NOS_2^+$ $(M + H)^+$ 262.0355, found 262.0361.

4-(Pyrimidine-5-yl)phenoxy Xanthate (2q).—General Procedure B was followed for the reaction of 4-(pyrimidine-5-yl)phenol **1q** (344 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:4) to give the product as a white solid (445 mg, 85%). **2q**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.97 (s, 2H), 7.66–7.62 (m, 2H), 7.29–7.25 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.8, 157.7, 155.4, 155.0, 133.6, 132.7, 128.4, 123.5, 20.2; HRMS (ESI), calcd for $C_{12}H_{11}N_2OS_2^+$ $(M + H)^+$ 263.0307, found 263.0308.

O-(6-(Dimethylcarbamoyl)pyridin-3-yl) S-Methyl Carbonodithioate (2r).—General Procedure B was followed for the reaction of 6-carboxyamide-3-hydroxypyridine **1r** (332 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:4) to give the product as a white solid (445 mg, 87%). **2r**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, J = 2.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 8.4, 2.6 Hz, 1H), 3.14 (s, 3H), 3.12 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.2, 168.1, 152.2, 151.4, 142.4, 131.1, 124.9, 39.3, 36.1, 20.2; HRMS (ESI), calcd for $C_{10}H_{13}N_2O_2S_2^+$ $(M + H)^+$ 257.0413, found 257.0410.

O-(6-Chloropyridin-3-yl) S-Methyl Carbonodithioate (2s).—General Procedure B was followed for the reaction of 6-chloro-3-hydroxypyridine **1s** (220 mg, 2.00 mmol) and imidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give the product as a pale-yellow solid (352 mg, 94%). **2s**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 2.9 Hz, 1H), 7.44 (dd, J = 8.4, 2.9 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.4, 150.2, 148.7, 143.8, 133.2, 124.9, 20.4; HRMS (ESI), calcd for $C_7H_7ClNOS_2^+$ $(M + H)^+$ 219.9652, found 219.9648.

O-(Quinoline-3-yl) S-Methyl Carbonodithioate (2t).—General Procedure B was followed for the reaction of 3-hydroxyquinoline **1t** (290 mg, 2.00 mmol) and imidazolium

reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 0:1 to 1:9) to give the product as a brown oil (395 mg, 84%). **2t**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.72 (dd, J = 8.4, 7.3 Hz, 1H), 7.57 (dd, J = 8.1, 7.3 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.8, 148.0, 146.3, 146.1, 129.6, 129.5, 128.2, 127.8, 127.5, 127.1, 20.3; HRMS (ESI), calcd for $C_{11}H_{10}NOS_2^+$ $(M + H)^+$ 236.0198, found 236.0196.

O-(Quinoline-7-yl) S-Methyl Carbonodithioate (2u).—General Procedure B was followed for the reaction of 3-hydroxyquinoline **1u** (290 mg, 2.00 mmol) and benzimidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give the product as a white solid (459 mg, 98%). **2u**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (dd, J = 4.4, 1.5 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.15 (dd, J = 8.4, 1.5 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.50 (dd, J = 9.2, 2.6 Hz, 1H), 7.43 (dd, J = 8.4, 4.4 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.6, 152.4, 150.7, 146.7, 136.1, 131.3, 128.7, 125.2, 121.8, 119.2, 20.4; HRMS (ESI), calcd for $C_{11}H_{10}NOS_2^+$ $(M + H)^+$ 236.0198, found 236.0195.

O-(Pyridine-3-yl) S-Methyl Carbonodithioate (2v).—General Procedure B was followed for the reaction of 4-ethoxycarbonyl phenol **1v** (185 mg, 2.00 mmol) and benzimidazolium reagent **6** (600 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 3:1) to give the product as a yellow oil (353 mg, 98%). **2v**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.8, 1.1 Hz, 1H), 8.42 (d, J = 2.6 Hz, 1H), 7.46 (ddd, J = 8.4, 2.6, 1.1 Hz, 1H), 7.37 (dd, J = 8.4, 4.8 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 215.6, 151.3, 147.6, 144.1, 136.1, 131.3, 128.7, 125.2, 121.8, 119.2, 20.4; HRMS (ESI), calcd for $C_{11}H_{10}NOS_2^+$ $(M + H)^+$ 236.0198, found 236.0195.

O-(1-(4-Chlorophenyl)-1H-pyrazol-4-yl) S-Methyl Carbonodithioate (2w).—General Procedure B was followed for the reaction of 4-hydroxypyrazole **1w** (389 mg, 2.00 mmol) and benzimidazolium reagent **7** (700 mg, 2.00 mmol). The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:9) to give the product as a white solid (563 mg, 99%). **2w**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.68 (s, 1H), 7.62–7.59 (m, 2H), 7.44–7.41 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 214.5, 140.1, 138.7 134.2, 132.5, 129.7, 120.2, 118.9, 20.4; HRMS (ESI), calcd for $C_{11}H_9ClN_2OS_2^+$ $(M + Na)^+$ 306.9737, found 306.9740.

General Procedures for the Synthesis of Aryltrifluoromethyl Ethers ($ArOCF_3$) 3a–3w.

General Procedure C (Reaction Conditions with TCCA).—A 20 mL vial was charged with xanthate **2** (0.5 mmol, 1.0 equiv), TCCA (116 mg, 0.5 mmol, 1.0 equiv), and XtalFluor-E (573 mg, 2.5 mmol, 5.0 equiv) in air. Then, anhydrous dichloroethane (5 or 10 mL) and water (9.0 mg, 0.5 mmol, 1.0 equiv) were added to the vial. (*One equivalent of water was weighed into a pipet, and the water was transferred to the flask by forced air.) The resulting mixture was stirred at 80 °C for the reported reaction time. After cooling to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), stirred for

30 min, and filtered through a pad of Celite. The filtrate was extracted with EtOAc (2 × 10 mL). Activated charcoal powder (ca. 1 g) and silica gel (ca. 1 g) were added to the combined organic layer. (Note: Charcoal helps to remove brown byproducts derived from XtalFluor-E.) After stirring for 1 min, the mixture was filtered with Celite and washed with EtOAc. The filtrate was concentrated and purified by silica gel column chromatography to give $ArOCF_3$ (**3**).

General Procedure D (Reaction Conditions with NFSI).—A 20 mL vial was charged with xanthates **2** (0.5 mmol, 1.0 equiv), NFSI (473 mg, 1.5 mmol, 3.0 equiv), and XtalFluor-E (343 mg, 1.5 mmol, 3.0 equiv) under air. Then, anhydrous dichloroethane (2 or 5 mL) was added to the vial. The resulting mixture was stirred at 80 °C for desired reaction time. After cooling to room temperature, the mixture was quenched with saturated aqueous NaHCO3 (5 mL), stirred for 30 min, and filtered through a pad of Celite. The filtrate was extracted with EtOAc (2 × 10 mL). Activated carbon powder (ca. 1 g) and silica gel (ca. 1 g) were added to the combined organic layer. After stirring for 1 min, the mixture was filtered with Celite and washed with EtOAc. The filtrate was concentrated and purified by silica gel column chromatography to give $ArOCF_3$ (**3**).

4-(Dimethylaminocarbonyl)trifluoromethoxybenzene (3a).—General Procedure C was followed for the reaction of xanthate **2a** (128 mg, 0.50 mmol). The reaction was conducted with dichloroethane (10 mL) for 3 h. The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to give a mixture of 3a (65.0 mg, 56%) and $ArOCF_2Cl$ byproduct (1.9 mg, 1.5%). **3a**: a pale-yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.26–7.22 (m, 2H), 3.11 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 149.9, 134.9, 129.0, 120.8, 120.4 (q, J = 258.7, CF_3), 39.6, 35.5; ^{19}F (376 MHz, $CDCl_3$) δ −59.0 (s); HRMS (ESI), calcd for $C_{10}H_{11}F_3NO_2^+$ $(M + H)^+$ 234.0736, found 234.0742.

4-(Ethoxycarbonyl)trifluoromethoxybenzene (3b).—General Procedure D was followed for the reaction of xanthate **2b** (128 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a pale-yellow oil (56.0 mg, 48%). **3b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H), 7.26–7.22 (m, 2H), 3.11 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 149.9, 134.9, 129.0, 120.8, 120.4 (q, J = 258.7, CF_3), 39.6, 35.5; ^{19}F (376 MHz, $CDCl_3$) δ −59.0 (s); HRMS (EI), calcd for $C_{10}H_9F_3O_3^+$ $(M)^+$ 234.0504, found 234.0507.

4-(Adamantyl)trifluoromethoxybenzene (3c).—General Procedure D was followed for the reaction of xanthate **2c** (159 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a white solid (118 mg, 80%). **3c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H), 7.17–7.13 (m, 2H), 2.13–2.09 (m, 3H), 1.90 (d, J = 2.2, 6H), 1.82–1.72 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.1, 147.2, 126.4, 120.7 (q, J = 257, CF_3), 120.6, 43.4, 36.8, 36.2, 29.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.1 (s), HRMS (EI), calcd for $C_{17}H_{19}F_3O^+$ $(M)^+$ 296.1388, found 296.1392.

2,4-(Di-t-butyl)trifluoromethoxybenzene (3f).—General Procedure D was followed for the reaction of xanthate **2f** (148 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a colorless oil (77.1 mg, 56%). **3f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 2.6 Hz, 1H), 7.22 (dd, J = 8.4, 2.6 Hz, 2H), 7.18–7.14 (m, 1H), 1.41 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.5, 146.6, 139.9, 124.9, 124.1, 120.9 (q, J = 258, CF_3), 118.4, 35.1, 34.8, 31.6, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.8 (s), HRMS (EI), calcd for $C_{15}H_{21}F_3O^+$ $(M)^+$ 274.1544, found 274.1549.

4-(Methoxycarbonylethyl)trifluoromethoxybenzene (3g).—General Procedure D was followed for the reaction of xanthate **2g** (135 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a pale-yellow oil (81.1 mg, 65%). **3g**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23–7.20 (m, 2H), 7.15–7.11 (m, 2H), 3.67 (s, 3H), 2.95 (t, J = 7.7 Hz, 2H), 2.95 (t, J = 7.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 147.8, 139.4, 129.7, 121.2, 120.6 (q, J = 258, CF_3), 51.8, 35.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.9 (s), HRMS (EI), calcd for $C_{11}H_{11}F_3O_3^+$ $(M)^+$ 248.0660, found 248.0662.

7-Trifluoromethoxy Coumarin (3h).—General Procedure D was followed for the reaction of xanthate **2g** (126 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 6 h. The crude reaction mixture was filtered through a pad of silica gel (EtOAc/hexane 3:1) and then purified by preparative SFC to remove $(PhSO_2)_2NH$ as a main contaminant (95% CO_2/40% MeOH; flow: 3.0 mL/min; Princeton PPU 250 mm × 10.0 mm 5 mm) to give the product as a white solid (25.0 mg, 22%). **3h**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 9.8 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.22 (s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.45 (d, J = 9.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 154.8, 151.3, 142.4, 129.1, 120.3 (q, J = 256, CF_3), 117.3, 116.9, 116.9, 109.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.9 (s); HRMS (APCI) Calculated for $C_{10}H_6F_3O_3^+$ $(M + H)^+$ 231.0260, found 231.0261.

4-(Benzoyl)trifluoromethoxybenzene (3i).—General Procedure D was followed for the reaction of xanthate **2i** (144 mg, 0.50 mmol). The reaction was conducted with dichloroethane (2 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography (hexane) to give the product as a colorless oil (68.3 mg, 51%). **3i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.79 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.34–7.30 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.2, 152.2, 137.2, 136.0, 132.8, 132.1, 130.0, 128.5, 120.5 (q, J = 259, CF), 120.3; ^{19}3 F NMR (376 MHz, $CDCl_3$) δ −58.8 (s); HRMS (EI), calcd for $C_{14}H_9O_2F_3^+$ $(M)^+$ 266.0555, found 266.0558.

4-(1H-Imidazol-1-yl)trifluoromethoxybenzene (3m).—General Procedure C was followed for the reaction of xanthate **2m** (125 mg, 0.50 mmol). The reaction was conducted with dichloroethane (10 mL) for 12 h. The crude reaction mixture was filtered through a pad

of silica gel (EtOAc) and then purified by preparative SFC to remove byproducts derived from XtalFluor-E (85% CO_2/15% MeOH (0.2% 7 M NH_3 in MeOH); flow: 3.0 mL/min; Princeton PPU 250 mm × 10.0 mm 5 mm) to give the product as a white solid (41.0 mg, 36%). **3q**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (s, 1H), 7.30–7.26 (m, 2H), 7.22–7.18 (m, 2H), 7.11–7.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 154.9, 149.9, 133.9, 133.2, 128.6, 121.9, 120.5 (q, J = 258, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0 (s); HRMS (APCI) calcd for $C_{11}H_8F_3N_2O^+$ $(M + H)^+$ 241.0583, found 241.0586.

4-(Benzothiazole-2-yl)trifluoromethoxybenzene (3n).—General Procedure C was followed for the reaction of xanthate **2n** (151 mg, 0.50 mmol). The reaction was conducted with dichloroethane (10 mL) for 3 h. The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 0:1 to 1:100) to give a mixture of **3n** (53.6 mg, 38%), $ArOCF_2Cl$ byproduct (5.9 mg, 3.8%), and $ArOCFCl_2$ byproduct (3.6 mg, 2.2%).[23] **3n**: pale-yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16–8.12 (m, 2H), 8.08 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.52 (dd, J = 8.1, 7.3 Hz, 1H), 7.41 (dd, J = 8.1, 7.3 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 154.2, 151.2, 135.3, 132.3, 129.2, 126.7, 125.6, 123.5, 121.8, 121.3, 120.5 (q, J = 259, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.1 (s); HRMS (ESI), calcd for $C_{14}H_9F_3NOS^+$ $(M + H)^+$ 296.0351, found 296.0347.

4-(6-Chloropyridine-3-yl)trifluoromethoxybenzene (3o).—General Procedure C was followed for the reaction of xanthate **2o** (148 mg, 0.50 mmol). The reaction was conducted with dichloroethane (5 mL) for 12 h. The crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 9:1 to 3:1) to give a mixture of **3o** (68.5 mg, 50%), $ArOCF_2Cl$ byproduct (2.7 mg, 1.9%), and $ArOCFCl_2$ byproduct (2.5 mg, 1.6%).[23] **3o**: pale-yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.58 (d, J = 2.6 Hz, 1H), 7.81 (dd, J = 8.4, 2.6 Hz, 1H), 7.58–7.55 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.9, 149.6, 147.9, 137.2, 135.3, 134.4, 128.6, 124.5, 121.7, 120.5 (q, J = 257, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.0 (s); HRMS (APCI) calcd for $C_{12}H_8ClF_3NO^+$ $(M + H)^+$ 274.0241, found 274.0240.

4-(Pyridine-3-yl)trifluoromethoxybenzene (3p).—General Procedure D was followed for the reaction of xanthate **2p** (131 mg, 0.50 mmol) with the exception adding Selectfluor (117 mg, 0.50 mmol, 1.0 equiv). The reaction was conducted with dichloroethane (2 mL) for 12 h. The crude reaction mixture was filtered through a pad of silica gel (EtOAc/hexane 3:1) and then purified by preparative SFC to remove $(PhSO_2)_2NH$ as a main contaminant (95% CO_2/5% MeOH (0.2% 7 M NH_3 in MeOH); flow: 3.0 mL/min; Princeton PPU 250 mm × 10.0 mm 5 mm) to give the product as a colorless oil (55.0 mg, 46%). **3p**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90–8.79 (m, 1H), 8.63 (d, J = 4.8 Hz, 1H), 7.87 (t, J = 5.6 Hz, 1H), 7.66–7.57 (m, 2H), 7.43–7.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 148.8, 148.1, 136.5, 136.0, 134.5, 128.6, 123.7, 121.6, 120.5 (q, J = 258, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.8 (s); HRMS (APCI) calcd for $C_{12}H_9F_3NO^+$ $(M + H)^+$ 240.0631, found 240.0624.

4-(Pyrimidine-3-yl)trifluoromethoxybenzene (3q).—General Procedure D was followed for the reaction of xanthate **2q** (131 mg, 0.50 mmol) with the exception adding

Selectfluor (354 mg, 1.00 mmol, 2.0 equiv). The reaction was conducted with dichloroethane (2 mL) for 12 h. The crude reaction mixture was filtered through a pad of silica gel (EtOAc/hexane 1:1) and then purified by preparative SFC to remove $(PhSO_2)_2NH$ as a main contaminant (95% CO_2/5% MeOH (0.2% 7 M NH_3 in MeOH); flow: 3.0 mL/min; Princeton PPU 250 mm × 10.0 mm 5 mm) to give the product as a white solid (35.0 mg, 29%). **3q**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.25 (s, 1H), 8.95 (s, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 154.9, 149.9, 133.9, 133.2, 128.6, 121.9, 120.5 (q, J = 258, CF); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0 (s); HRMS (APCI) calcd for $C_{11}H_8F_3N_2O^+$ $(M + H)^+$ 241.0583, found 241.0586.

5-Dimethylaminocarbonyl-3-trifluoromethoxypyridine (3r).—General Procedure C was followed for the reaction of xanthate **2r** (128 mg, 0.50 mmol). The reaction was conducted with dichloroethane (5 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography to give a mixture of **3q** (19.2 mg, 16%), $ArOCF_2Cl$ (0.6 mg, 0.5%), and $ArOCFCl_2$ (0.6 mg, 0.4%). Brown oil; **3q**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.49 (d, J = 2.6 Hz 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.8, 2.6 Hz, 1H), 3.14 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.7, 152.9, 146.3, 141.0, 129.1, 125.2, 120.4 (q, J = 260 Hz, CF_3), 39.2, 36.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0 (s); HRMS (APCI) calcd for $C_9H_{10}F_3N_2O_2^+$ $(M + H)^+$ 235.0689, found 235.0691.

3-Trifluoromethoxyquinoline (3t).—General Procedure C was followed for the reaction of xanthate **2t** (118 mg, 0.50 mmol). The reaction was conducted with dichloroethane (5 mL) for 24 h. The crude reaction mixture was purified by silica gel column chromatography to give a mixture of **3q** (11.7 mg, 11%) and $ArOCF_2Cl$ byproduct (0.3 mg, 0.3%). **3q**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.84 (d, J = 2.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.88–7.86 (m, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.77 (ddd, J = 8.4, 6.6, 1.1 Hz, 1H), 7.64 (ddd, J = 8.1, 6.6, 1.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.0, 144.6, 142.9, 130.3, 129.3, 128.3, 128.0, 127.9, 126.2, 120.7 (q, J = 260, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.1 (s); HRMS (EI) calcd for $C_{10}H_6F_3NO^+$ $(M)^+$ 213.0401, found 213.0404.

7-Trifluoromethoxyquinoline (3u).—General Procedure C was followed for the reaction of xanthate **2u** (118 mg, 0.50 mmol). The reaction was conducted with dichloroethane (5 mL) for 6 h. The crude reaction mixture was purified by silica gel column chromatography to give the product as a brown oil (41.6 mg, 39%). **3u**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.95 (dd, J = 4.0, 1.8 Hz, 1H), 8.18–8.15 (m, 2H), 7.65 (d, J = 2.6 Hz, 1H), 7.58 (dd, J = 9.2, 2.6 Hz, 1H), 7.47 (dd, J = 8.4, 4.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.9, 147.1, 146.5, 136.2, 131.8, 128.6, 123.8, 122.2, 120.7 (q, J = 258, CF_3), 117.9 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.7 (s); HRMS (APCI) calcd for $C_{10}H_7F_3NO^+$ $(M + H)^+$ 214.0474, found 214.0467.

1-(4-Chlorophenyl)-4-(trifluoromethoxy)-1H-pyrazole (3w).—General Procedure C was followed for the reaction of xanthate **2w** (142 mg, 0.50 mmol). The reaction was conducted with dichloroethane (5 mL) for 3 h. The crude reaction mixture was purified by silica gel column chromatography to give a mixture of **3w** (39.4 mg, 30%) and $ArOCF_2Cl$ byproduct (1.8 mg, 1.3%). Brown oil; **3w**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.89 (s, 1H), 7.66

(s, 1H), 7.61–7.58 (m, 2H), 7.45–7.42 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.5, 135.6, 133.3, 132.9, 129.8, 129.3, 120.6 (q, J = 258 Hz, CF_3), 118.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.7 (s); HRMS (EI) calcd for $C_{10}H_6ClF_3N_2O^+$ $(M)^+$262.0121, found 262.0125.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We are thankful for support from Pfizer and the NIH (1R35GM130387). We also thank Dr. Vincent Mascitti for his helpful insight into this research.

REFERENCES

(1). (a)Betageri R; Zhang Y; Zindell RM; Kuzmich D; Kirrane TM; Bentzien J; Cardozo M; Capolino AJ; Fadra TN; Nelson RM; Paw Z; Shih D-T; Shih C-K; Zuvela-Jelaska L; Nabozny G; Thomson DS Trifluoromethyl group as a pharmacophore: Effect of replacing a CF3 group on binding and agonist activity of a glucocorticoid receptor ligand. Bioorg. Med. Chem. Lett 2005, 15, 4761–4769. [PubMed: 16112571] (b)Wang J; Sánchez-Roselló M; Aceña J; del Pozo C; Sorochinsky AE; Fustero S; Soloshonok VA; Liu H Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). Chem. Rev 2014, 114, 2432–2506. [PubMed: 24299176] (c)Gillis EP; Eastman KJ; Hill MD; Donnelly DJ; Meanwell NA Applications of Fluorine in Medicinal Chemistry. J. Med. Chem 2015, 58, 8315–8359. [PubMed: 26200936] (d)Swallow S Fluorine in Medicinal Chemistry In Progress in Medicinal Chemistry; Elsevier: Amsterdam, Netherlands, 2015; Vol. 54, pp 65–133. [PubMed: 25727703]

(2). (a)For reviews of fluorinations, see:Liang T; Neumann CN; Ritter T Introduction of Fluorine and Fluorine-Containing Functional Groups. Angew. Chem., Int. Ed 2013, 52, 8214–8264.(b)Zhu Y; Han J; Wang J; Shibata N; Sodeoka M; Soloshonok VA; Coelho JAS; Toste FD Modern Approaches for Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. Chem. Rev 2018, 118, 3887–3964. [PubMed: 29608052] (c)Remete AM; Nonn M; Fustero S; Fülöp F; Kiss L Synthesis of fluorinated amino acid derivatives through late-stagedeoxyfluorinations. Tetrahedron 2018, 74, 6367–6418 (and references cited therein).

(3). (a)Serfaty I; Hodgins T; McBee E Halogen-containing substituents. II. Methoxy system. Reactivity parameters. Charge distribution and conformation of the anisoles. J. Org. Chem 1972, 37, 2651–2655.(b)Herkes FE Halogenation of trifluoromethoxy and bis(trifluoromethoxy)benzene. J. Fluorine Chem 1977, 9, 113–126.(c)Rose-Munch F; Khourzom R; Djukic J-P; Rose E; Langlois B; Vaisserman J Etude conformationnelle du complexe η6-(4-(trifluorométhoxy)aniline)tricarbonylchrome. J. Organomet. Chem 1994, 470, 131–135. (d)Federsel D; Herrmann A; Christen D; Sander S; Willner H; Oberhammer H Structure and conformation of α,α,α-trifluoroanisol, $C_6H_5OCF_3$. J. Mol. Struct 2001, 567, 127–136.(e)Leroux FR; Manteau B; Vors J-P; Pazenok S Trifluoromethyl ethers – synthesis and properties of an unusual substituent. Beilstein J. Org. Chem 2008, 4, 13. [PubMed: 18941485] (f)Iijima A; Amii H Selective aromatic carbon–oxygen bond cleavage of trifluoromethoxyarenes: a trifluoromethoxy group as a convertible directing group. Tetrahedron Lett. 2008, 49, 6013–6015.

(4). For example, $OCF_3\Pi_x$ = 1.04, CF_3 = 0.88, CH_3 = 0.56, and OCH_3 = −0.02. See: Hansch C; Leo A Substituent Constants for Correlation Analysis in Chemistry and Biology; Wiley: New York, 1979; part VII 339.

(5). Liu J; Chen C; Chu L; Chen Z; Xu X; Qing F Silver-Mediated Oxidative Trifluoromethylation of Phenols: Direct Synthesis of Aryl Trifluoromethyl Ethers. Angew. Chem., Int. Ed 2015, 54, 11839–11842.

(6). (a)Huang C; Liang T; Harada S; Lee E; Ritter T Silver-Mediated Trifluoromethoxylation of Aryl Stannanes and Arylboronic Acids. J. Am. Chem. Soc 2011, 133, 13308–13310. [PubMed: 21827148] (b)Yang Y-M; Yao J-F; Yan W; Luo Z; Tang Z-Y Silver-Mediated

Trifluoromethoxylation of (Hetero)aryldiazonium Tetrafluoroborates. Org. Lett 2019, 21, 8003–8007. [PubMed: 31524411]

(7). (a)Hojczyk KN; Feng P; Zhan C; Ngai M Trifluoromethoxylation of Arenes: Synthesis of ortho-Trifluoromethoxylated Aniline Derivatives by OCF_3 Migration. Angew. Chem., Int. Ed 2014, 53, 14559–14563.(b)Lee K; Lee J; Ngai M-Y Synlett 2016, 27, 313–319. [PubMed: 27872511] (c)Zheng W; Morales-Rivera CA; Lee JW; Liu P; Ngai M Catalytic C-H Trifluoromethoxylation of Arenes and Heteroarenes. Angew. Chem., Int. Ed 2018, 57, 9645–9649.(d)Jelier BJ; Tripet PF; Pietrasiak E; Franzoni I; Jeschke G; Togni A Angew. Chem., Int. Ed 2018, 57, 13784–13789. (e)Yang S; Chen M; Tang P Visible-Light Photoredox-Catalyzed and Copper-Promoted Trifluoromethoxylation of Arenediazonium Tetrafluoroborates. Angew. Chem., Int. Ed 2019, 58, 7840–7844.

(8). (a)Zhang Q; Brusoe AT; Mascitti V; Hesp KD; Blakemore DC; Kohrt JT; Hartwig JF Fluorodecarboxylation for the Synthesis of Trifluoromethyl Aryl Ethers. Angew. Chem., Int. Ed 2016, 55, 9758–9762;Angew. Chem 2016, 128, 9910–9914.(b)Zhou M; Ni C; He Z; Hu J Synthesis of Trifluoromethoxylated (Hetero) Arenes via OCF_3 Migration. Org. Lett 2016, 18, 3754–3757. [PubMed: 27440264] (c)Chatalova-Sazepin C; Binayeva M; Epifanov M; Zhang W; Foth P; Amador C; Jagdeo M; Boswell BR; Sammis GM Xenon Difluoride Mediated Fluorodecarboxylations for the Syntheses of Di- and Trifluoromethoxyarenes. Org. Lett 2016, 18, 4570–4573. [PubMed: 27560791]

(9). (a)For classical examples of synthetic methods of ArOCF3 using fluoride substitution, see:Sheppard WA α-Fluorinated Ethers. I. Aryl Fluoroalkyl Ethers. J. Org. Chem 1964, 29, 1–11. (b)Feiring AE Chemistry in hydrogen fluoride. 7. A novel synthesis of aryl trifluoromethyl ethers. J. Org. Chem 1979, 44, 2907–2910.(c)Kuroboshi M; Suzuki K; Hiyama T Oxidative desulfurization-fluorination of xanthates. A convenient synthesis of trifluoromethyl ethers and difluoro(methylthio)methyl ethers. Tetrahedron Lett. 1992, 33, 4173–4176.(d)Kanie K; Tanaka Y; Suzuki K; Kuroboshi M; Hiyama T A Convenient Synthesis of Trifluoromethyl Ethers by Oxidative Desulfurization-Fluorination of Dithiocarbonates. Bull. Chem. Soc. Jpn 2000, 73, 471–484.(e)Kuroboshi M; Kanie K; Hiyama T Oxidative Desulfurization-Fluorination: A Facile Entry to a Wide Variety of Organofluorine Compounds Leading to Novel Liquid-Crystalline Materials. Adv. Synth. Catal 2001, 343, 235–250.(f)Manteau B; Genix P; Brelot L; Vors J-P; Pazenok S; Giornal F; Leuenberger C; Leroux FR A General Approach to (Trifluoromethoxy)pyridines: First X-ray Structure Determinations and Quantum Chemistry Studies. Eur. J. Org. Chem 2010, 2010, 6043–6066.(g)Umemoto T; Singh RP; Xu Y; Saito N Discovery of 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity. J. Am. Chem. Soc 2010, 132, 18199–18205. [PubMed: 21125999]

(10). (a)For selected reviews of fluoroalkylation of alcohols and phenols, see:Tlili A; Toulgoat F; Billard T Synthetic Approaches to Trifluoromethoxy-Substituted Compounds. Angew. Chem., Int. Ed 2016, 55, 11726–11735;Angew. Chem 2016, 128, 11900–11909.(b)Lee KN; Lee JW; Ngai M-Y Catalytic trifluoromethoxylation reactions. Tetrahedron 2018, 74, 7127–7135. [PubMed: 30906076] (c)Zhang XT; Tang P Recent advances in new trifluoromethoxylation reagents. Sci. China: Chem 2019, 62, 525–532.(d)Lee JW; Lee KN; Ngai M-Y Synthesis of Tri- and Difluoromethoxylated Compounds by Visible-Light Photoredox Catalysis. Angew. Chem., Int. Ed 2019, 58, 11171–11181 (and references cited therein).

(11). (a)For synthetic examples of synthesizing hetero $ArOCF_3$, see:Liang A; Han S; Liu Z; Wang L; Li J; Zou D; Wu Y; Wu Y Regioselective Synthesis of N-Heteroaromatic Trifluoromethoxy Compounds by Direct O-CF_3 Bond Formation. Chem. - Eur. J 2016, 22, 5102–5106. [PubMed: 26791812] (b)Zhang Q-W; Hartwig JF Synthesis of heteroaromatic trifluoromethyl ethers with trifluoromethyl triflate as the source of the trifluoromethoxy group. Chem. Commun 2018, 54, 10124–10127.Refs 5 and 7 also showed several examples of heteroaryl trifluoromethyl ethers. Although trifluoromethylation of 2-hydroxypyridine derivatives has been demonstrated in ref 11a, the trifluoromethylation of phenols by the Togni reagent usually proceeds at the carbon atom instead of the oxygen atom; see:(c)Stanek K; Koller R; Togni A Reactivity of a 10-I-3 Hypervalent Iodine Trifluoromethylation Reagent With Phenols. J. Org. Chem 2008, 73, 7678–7685. [PubMed: 18771328]

(12). Sun W; Hu J; Shi Y 1-(Methyldithiocarbonyl)imidazole: A Reagent of S-Methyldithiocarbonylation. Synlett 1997, 1997, 1279–1280.

(13). Mohanta PK; Dhar S; Samal SK; Ila H; Junjappa H 1-(Methyldithiocarbonyl)imidazole: a Useful Thiocarbonyl Transfer Reagent for Synthesis of Substituted Thioureas. Tetrahedron 2000, 56, 629–637.

(14). The pK_a values of the conjugate acid of the leaving groups of **5**, **6**, and **7** are 8.4, 6.0, and 4.6, respectively. See: Buncel E; Joly HA; Jones JR Proton transfer from imidazole, benzimidazole, and their 1-alkyl derivatives. FMO analysis of the effect of methyl and benzo substitution. Can. J. Chem 1986, 64, 1240–1245.

(15). (a)Beaulieu F; Beauregard L-P; Courchesne G; Couturier M; LaFlamme F; L'Heureux A Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents. Org. Lett 2009, 11, 5050–5053. [PubMed: 19799406] (b)L'Heureux A; Beaulieu F; Bennett C; Bill DR; Clayton S; LaFlamme F; Mirmehrabi M; Tadayon S; Tovell D; Couturier M Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling. J. Org. Chem 2010, 75, 3401–3411. [PubMed: 20405933]

(16). Kepp KP A Quantitative Scale of Oxophilicity and Thiophilicity. Inorg. Chem 2016, 55, 9461–9470. [PubMed: 27580183]

(17). The addition of 2 or more equivalents of water totally prevented the desired trifluoromethylation and caused hydrolysis of xanthate to form the corresponding phenols. Since all the reactions were conducted under air, catalytic water is present. In the case of condition A, 1 equiv of water resulted in better reproducibility than the catalytic amount.

(18). $ArOCF_2Cl$ and $ArOCFCl_2$ byproducts have been obtained from several substrates. According to ref 11a, the chlorinated products might be converted to the corresponding trifluoromethyl ether by treatment of SbF_3 and the catalytic amount of $SbCl_5$[22][35].

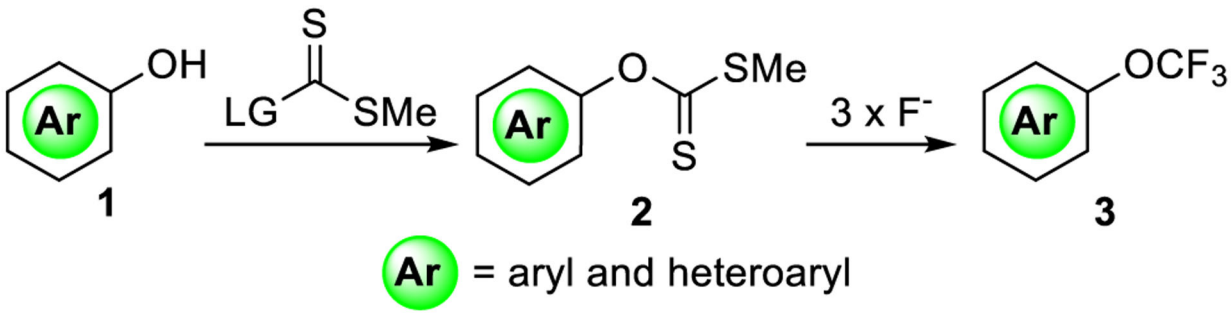
(19). (a)Moseley JD; Sankey RF; Tang ON; Gilday JP The Newman–Kwart rearrangement re-evaluated by microwave synthesis. Tetrahedron 2006, 62, 4685–4689.(b)Lloyd-Jones G; Moseley J; Renny J Mechanism and Application of the Newman-Kwart *O*→*S* Rearrangement of *O*-Aryl Thiocarbamates. Synthesis 2008, 2008, 661–689.(c)Burns M; Lloyd-Jones GC; Moseley JD; Renny JS The Molecularity of the Newman-Kwart Rearrangement. J. Org. Chem 2010, 75, 6347–6353. [PubMed: 20812755]

(20). Wang Y-Q; Ge Z-M; Hou X-L; Cheng T-M; Li R-T A Mild and Efficient Procedure for the Synthesis of 1-(Alkyldithiocarbonyl)-imidazoles. Synthesis 2004, 2004, 675–678.

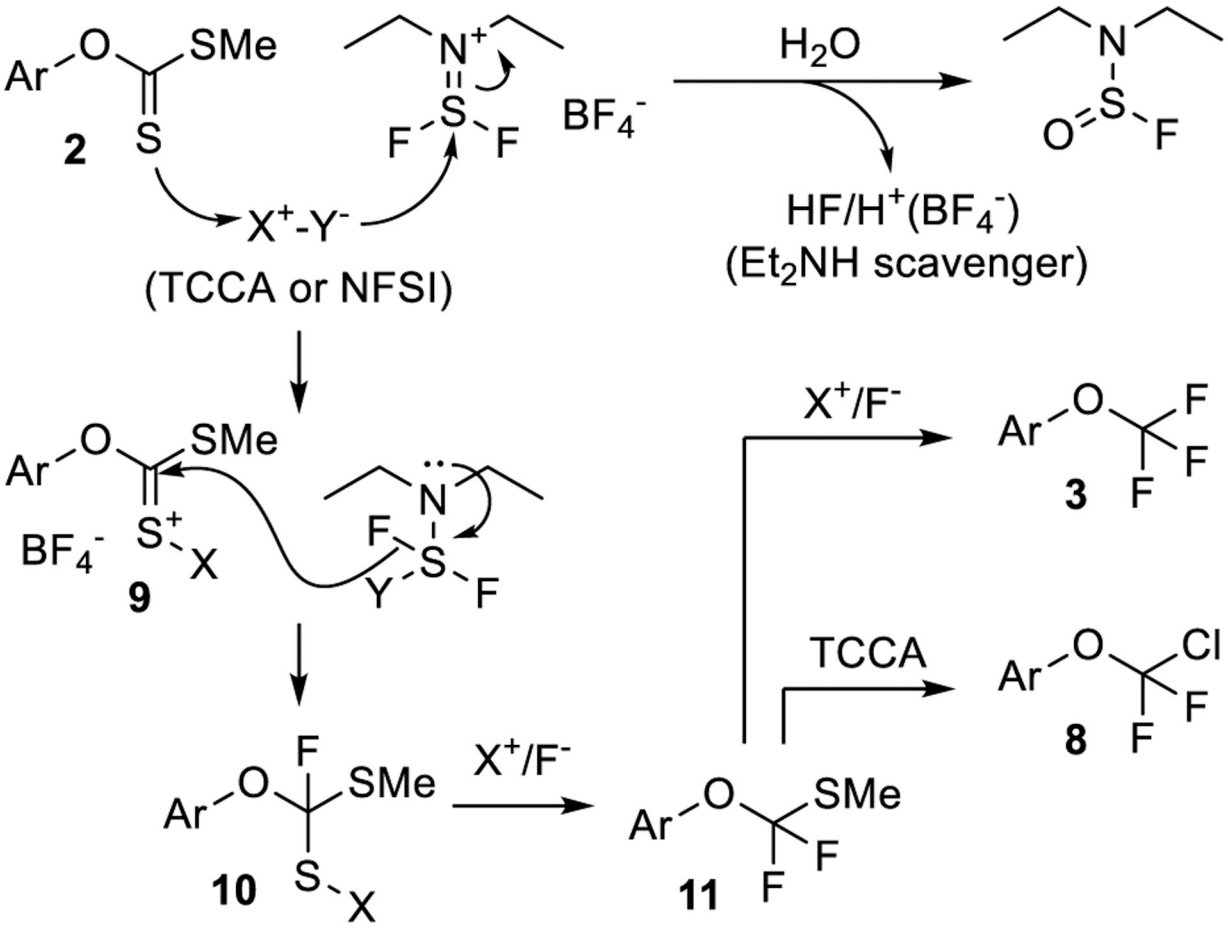
(21). Sun W; Hu J; Shi Y 1-(Methyldithiocarbonyl)imidazole: A Reagent of *S*-Methyldithiocarbonylation. Synlett 1997, 1997, 1279–1280.

(22). Pedras MSC; Sarma-Mamillapalle VK Metabolism and Metabolites of Dithiocarbamates in the Plant Pathogenic Fungus Leptosphaeria maculans. J. Agric. Food Chem 2012, 60, 7792–7798. [PubMed: 22823278]

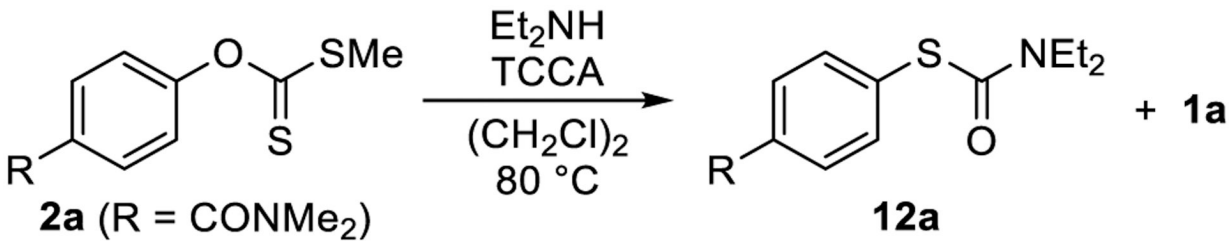
(23). The ratio of $ArOCF_2Cl$ and $ArOCFCl_2$ byproducts in the isolated mixture was increased from that of the crude mixture. This indicates that the boiling point of the desired product **3n**/**3o** would be significantly lower than that of the byproducts[22]**3n3o**.



Scheme 1.
Two-Step Trifluoromethoxylation of Phenol



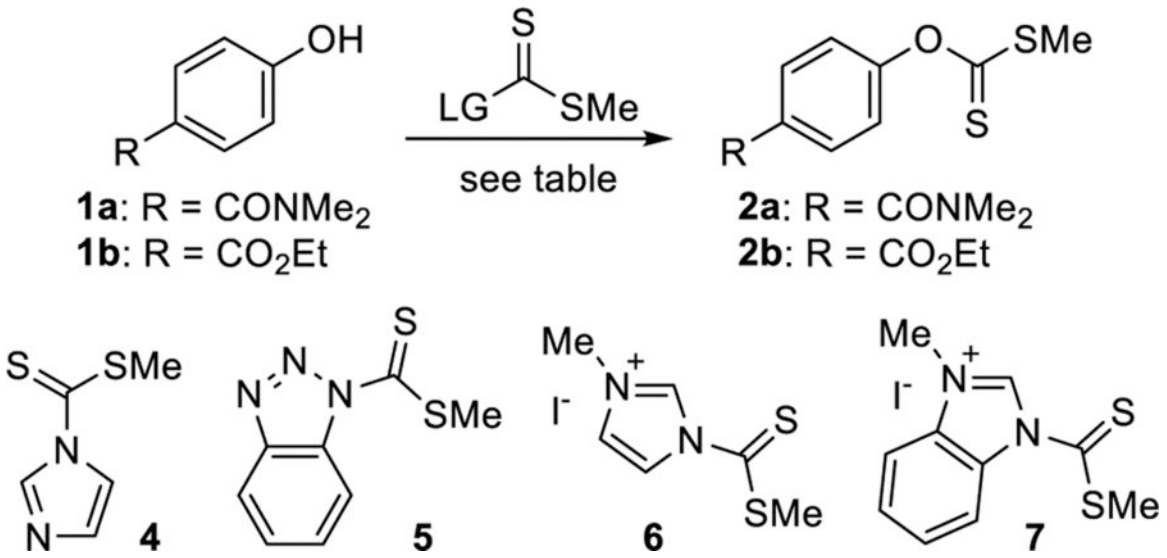
Scheme 2.
Likely Mechanism for Conversion of Aryl Xanthate to Aryl Trifluoromethyl Ether



Scheme 3.
Control Experiment with Diethylamine

Table 1.

Reactions of Phenols with a Series of Xanthalating Reagents[a]



entry[b]	phenol	reagent	base	solvent	yield[c]
1	**1a**	**4**	NaH	DMF	**2a**: 5%[d]
2	**1a**	**5**	NaH	DMF	**2a**: 70%
3	**1a**	**6**	Et_3N	DMF	**2a**: 99%
4	**1a**	**7**	Et_3N	DMF	**2a**: 79%
5	**1a**	**6**	Et_3N	MeCN	**2a**: 98%
6	**1b**	**6**	Et_3N	MeCN	**2b**: 91%
7	**1b**	**7**	Et_3N	MeCN	**2b**: 99%

[a] LG: leaving group.

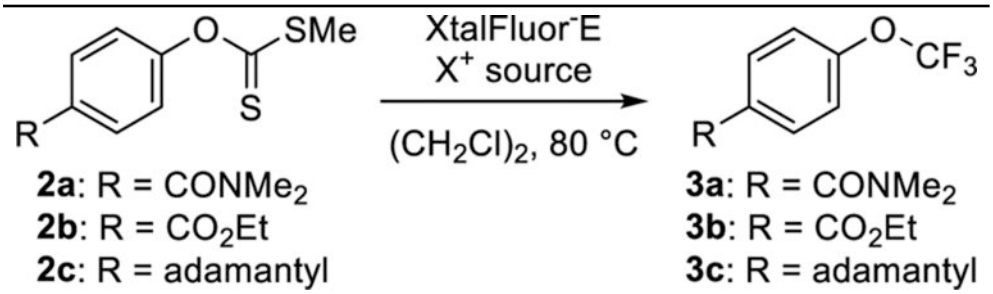
[b] Standard reaction conditions: **1** (0.5 mmol), xanthate-forming reagent (0.5 mmol), base (0.6 mmol), and solvent (5 mL).

[c] Isolated yields.

[d] Yield was determined by ^1H NMR using Me_2SO_2 as an internal standard instead of isolated yield.

Table 2.

Development of Conditions for the Conversion of Aryl Xanthates to Aryl Trifluoromethyl Ether



entry[a]	xanthate	X+ source (equiv)	additive (equiv)	yield[b]
1	**2a**	I_2 (3.0)	none	**3a**: 0%
2	**2a**	NBS (3.0)	none	**3a**: 4%
3	**2a**	DBH (1.5)	none	**3a**: 6%
4	**2a**	DBCA (1.5)	none	**3a**: 13%
5	**2a**	NFSI (3.0)	none	**3a**: 9%
6	**2a**[d]	TCCA (1.0)	none	**3a**: 78%
7[c]	**2a**[d]	TCCA (1.0)	none	**3a**: 32%
8	**2a**	TCCA (1.0)	H_2O (1.0)	**3a**: 76%
9	**2b**[d]	TCCA (1.0)	none	**3b**: 56%
10	**2b**[d,e]	NFSI (3.0)	none	**3b**: 75%
11	**2b**[d,e]	NFSI (3.0)	H_2O (1.0)	**3b**: 70%
12	**2c**[d]	TCCA (1.0)	none	**3c**: 56%
13	**2c**[d,e]	NFSI (3.0)	none	**3c**: 80%
14	**2c**[d,e]	NFSI (3.0)	H_2O (1.0)	**3c**: 75%

[a]Standard conditions: **2** (50 mmol, 1.0 equiv), XtalFluor-E (250 mmol, 5.0 equiv), X^+ source (50–150 mmol, 1–3 equiv), additives, $(CH_2Cl)_2$ (1 mL), 80 °C, 3 h.

[b]Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

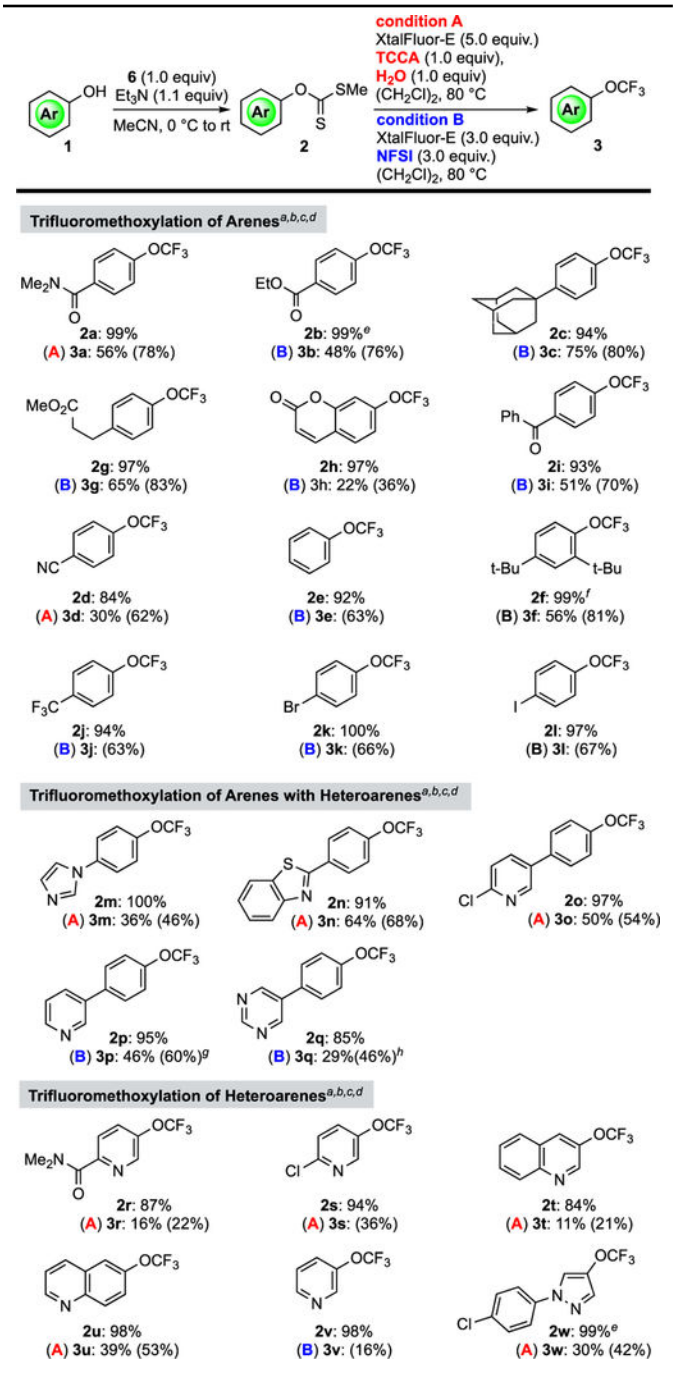
[c]The reaction was conducted in a glovebox.

[d]0.5 mmol of **2** was used.

[e]3.0 equiv of XtalFluor-E was used.

Table 3.

Substrate Scope of Two-Step Trifluoromethylation of Phenol



[a]Standard condition of xanthate formation: **1** (2.0 mmol), **6** (2.0 mmol), Et_3N (2.0 mmol), MeCN (10 mL), 0 °C, 1 h.

[b]Condition A: **2** (0.5 mmol), XtalFluor-E (2.5 mmol), TCCA (0.5 mmol), H_2O (0.5 mmol), and $(CH_2Cl)_2$ (10 mL), 80 °C.

[c] Condition B: **2** (0.5 mmol), XtalFluor-E (1.5 mmol), NFSI (1.5 mmol), and $(CH_2Cl)_2$ (10 mL), 80 °C.

[d] NMR yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard were reported in the parentheses.

[e] Reagent **7** was used instead of **6**.

[f] Reagent **5** (1.5 equiv), Cs_2CO_3 (2.0 equiv), and DMF (0.1 M) were used instead of the standard conditions.

[g] Selectfluor (0.5 mmol, 1.0 equiv) was added.

[h] Selectfluor (1.0 mmol, 2.0 equiv) was added.