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Ammonium Chloride-Mediated Trifluoromethylthiolation of *p*-Quinone Methides

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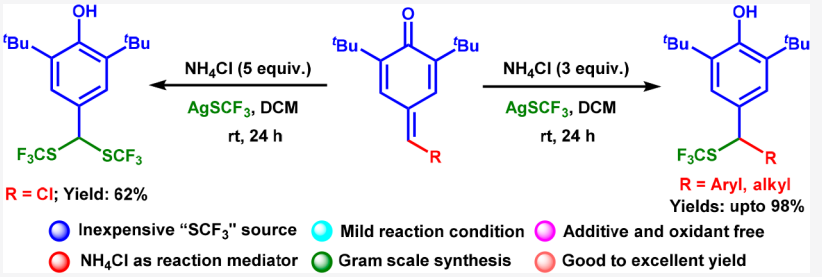

ABSTRACT: Ammonium chloride-mediated trifluoromethylthiolation of *p*-quinone methides is reported using inexpensive and bench stable $AgSCF_3$ as a nucleophilic trifluoromethylthiolating ($-SCF_3$) reagent. This method is an efficient strategy for the construction of the benzylic $C(sp^3)-SCF_3$ bond to synthesize trifluoromethylthio-diarylmethane derivatives by 1,6-conjugate addition/aromatization under mild reaction conditions without any metal catalyst, oxidants, or additives. This is the first report of trifluoromethylthiolation of *p*-quinone methides. In addition, di-trifluoromethylthiolation of δ-chloro-*p*-quinone methide and scalability are demonstrated.

In recent years, fluorinated functionalities (like $-SCF_3$, $-CF_3$, $-CF_2CO_2Et$, etc.) are of considerable interest in pharmaceuticals, agrochemicals, and materials research fields.[1] Being part of bioactive motifs, these groups improve transmembrane permeability and metabolic stability.[2] Also, the presence of a highly electronegative fluorine and a heavy sulfur atom in SCF_3 balance electron-withdrawing (Hammett constants $\sigma_p = 0.50$ and $\sigma_m = 0.40$) and lipophilic (Hansch parameter $\pi = 1.43$) properties.[3] Although there is immense value and interest in trifluoromethylthiolation of organic molecules, a suitable strategy for direct trifluoromethylthiolation under milder reaction conditions with good functional group tolerance is challenging. In the early era of SCF_3 chemistry, trifluoromethylthiolation was carried out either by H−F exchange on thioethers or trifluoromethylation of thiols and disulfides. Recently, direct trifluoromethylthiolation using electrophilic and nucleophilic trifluoromethylthiolating reagents by various activation strategies has been reported.[3,4] However, trifluoromethylthiolation of electron-deficient unsaturated alkene or Michael acceptors has been less explored due a lack of trifluoromethylthiolating reagents.

The 1,4/1,6-conjugate addition of various nucleophiles to an electron-deficient unsaturated alkene or Michael acceptor is one of the most studied, versatile reactions for C−C/C−heteroatom bond construction in organic chemistry.[5] In this respect, *p*-quinone methides (*p*-QMs) are well-known reaction intermediates for the synthesis of diarylmethane derivatives by 1,6-conjugate addition reactions and are also present in various natural products and drug molecules.[6] *p*-QMs consist of a zwitterionic resonance structure of a cyclohexadiene moiety in *para* conjugation with a carbonyl group that enhances the electrophilic character at the δ position and facilitates 1,6-conjugate addition reactions.[7] Different 1,6-conjugate additions of *p*-QMs, for example, transition metal-based Lewis acid-catalyzed borylation, bismuth-catalyzed allylation, and NHC/Lewis acid-catalyzed cyanation of *p*-QMs, have been described.[8] Asymmetric 1,6-conjugate additions of *p*-QM derivatives have also been well studied using various nucleophiles.[5b,6a,9] The Sunliang group demonstrated both transition metal-catalyzed and metal-free approaches for the alkylation of *p*-QM derivatives (Scheme 1).[10]

Liu and our group have successively developed a visible-light-mediated Ir-based and organo-photocatalyst for alkylation and trifluoromethylation of *p*-QMs by a photoredox methodology.[11] Recently, we have reported visible-light-mediated trifluoromethylation of *p*-QMs by 1,6-conjugate addition using a pyrylium salt as the organic photocatalyst (Scheme 1b).[11c]

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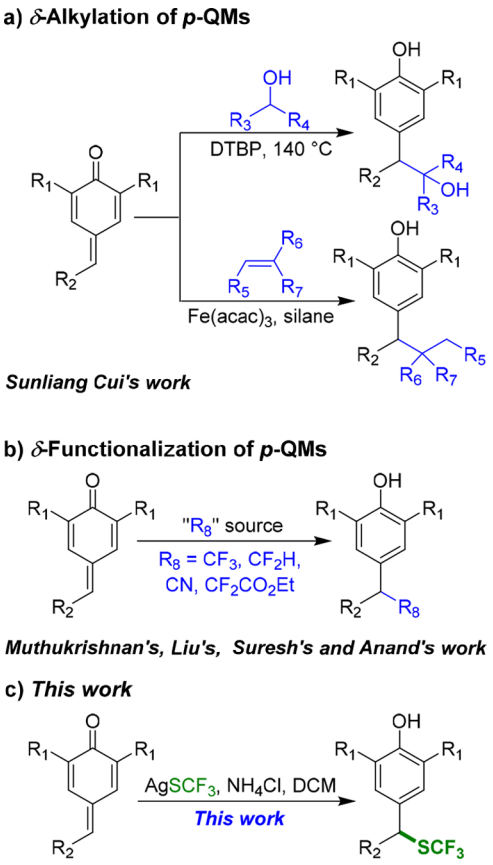
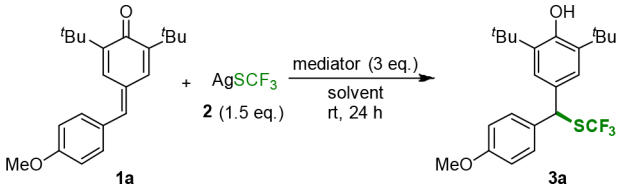
Scheme 1. Different Types of Nucleophilic Addition Reactions of *p*-Quinone Methides



However, to date trifluoromethylthiolation of *p*-QM derivatives has not been described due to challenges associated with the limited trifluoromethylthiolating agents and their stability. Here, we report the first efficient route for direct trifluoromethylthiolation of *p*-QM derivatives using readily available $AgSCF_3$ and very cheap NH_4Cl as reaction mediator under mild and ambient conditions (Scheme 1c).

We began with testing of suitable Lewis acid catalysts to activate the *p*-QMs for trifluoromethylthiolation by 1,6-conjugate addition reaction. For this, *p*-QM derivative **1a** was used as a model substrate and readily available, cheap, bench stable $AgSCF_3$ was employed as the trifluoromethylthiolating agent. Reaction was optimized with screening of different Lewis acids using 1.5 equiv of $AgSCF_3$ in 2 mL of DCM under an aerial atmosphere at room temperature. After screening, Lewis acids such as $CuBr_2$, $AlCl_3$, and $Zn(OTf)_2$ gave trifluoromethylthio-diarylmethane derivative **3a** in 7%, 33%, and 13% yields, respectively, based on ^1H NMR (Table 1, entries 1−3, respectively). The yield increased to 35% when $FeCl_3$ (20 mol %) was used as a catalyst after 24 h. To further improve the yield, we investigated the effect of protic solvents using $FeCl_3$ as a catalyst. Instead of improving the yield of desired product **3a**, protic solvents underwent 1,6-nucleophilic addition/aromatization reactions and furnished solvent-added products. Next, we used 1 equiv of weak Brönsted acid NH_4Cl as an additive with 20 mol % $FeCl_3$ under the same reaction conditions, and this gave desired product **3a** in85% yield. Interestingly, when the reaction was carried out in the absence of Lewis acid $FeCl_3$ using only 1 equiv of NH_4Cl and 1.5 equiv of $AgSCF_3$ in 2 mL of DCM under an aerial atmosphere at rt

Table 1. Optimization of Reaction Conditions[a]



entry	mediator	solvent	yield[b] (%)
1[c]	$CuBr_2$	DCM	7
2[c]	$AlCl_3$	DCM	33
3[c]	$Zn(OTf)_2$	DCM	13
4[c]	$FeCl_3$	DCM	35
5[d]	$FeCl_3$, NH_4Cl	DCM	85
6	NH_4Cl	DCM	98
7	HN_4OAc	DCM	0
8	HCO_2NH_4	DCM	0
9	HCl	DCM	91
10	HNO_3	DCM	0
11	H_2SO_4	DCM	0
12	–	DCM	0
13[e]	NH_4Cl	DCM	82
14[f]	NH_4Cl	DCM	91
15	NMe_4Cl	DCM	0
16	NEt_4Cl	DCM	0
17	NH_4Cl	DCE	85
18	NH_4Cl	toluene	81
19	NH_4Cl	CH_3CN	45
20	NH_4Cl	DME	17
21	NH_4Cl	dioxane	21
22	NH_4Cl	$CHCl_3$	12

[a]Reaction conditions: **1a** (0.15 mmol), **2** (0.23 mmol), solvent (2.0 mL), 0.45 mmol of mediator, room temperature, 24 h. [b]^1H NMR yields using tetrachloroethane as the internal standard. [c]With 20 mol % mediator. [d]With 20 mol % $FeCl_3$ and 0.15 mmol of NH_4Cl. [e]With 0.15 mmol of NH_4Cl. [f]With 0.30 mmol of NH_4Cl.

for 24 h, desired product **3a** was isolated in 82% yield. Next, the required amount of ammonium salts (Table 1, entries 6, 13, and 14), $AgSCF_3$ equivalents (see the Supporting Information), and different solvents (see Table 1 and the Supporting Information) were screened and optimized. The most optimized conditions for this reaction are 0.15 mmol of **1a**, 3 equiv of NH_4Cl, and 1.5 equiv of $AgSCF_3$ in 2 mL of DCM under an aerial atmosphere at rt for 24 h. With these optimized conditions, product **3a** was obtained in 95% yield and confirmed by ^1H NMR, ^{13}C NMR, and ^{19}F NMR.

Next, a wide variety of *p*-QMs were explored for the trifluoromethylthiolation reaction (Scheme 2). The electron-donating substituents on the benzene ring afforded the corresponding trifluoromethylthiolated diarylmethane derivatives (**3a**−**3c**) in excellent isolated yields (79−95%). Simple substituents on the phenyl ring furnished the expected products **3d** and **3e** in good yield of 83% and 87%, respectively. Then, we performed this reaction with different *p*-QMs derived from benzaldehyde, 2-naphthaldehyde, and 1-pyrenecarboxaldehyde, which offered the desired products (**3f**−**3h**, respectively) in moderate to good yields (70−86%). The solid state structure of compound **3h** was confirmed by single-crystal X-ray analysis (see the Supporting Information).

When *p*-QMs with a halogen substitution on the phenyl ring were subjected to this reaction, the respective products (**3i**−**3n**) were isolated (71−87% yields). Electron-withdrawing

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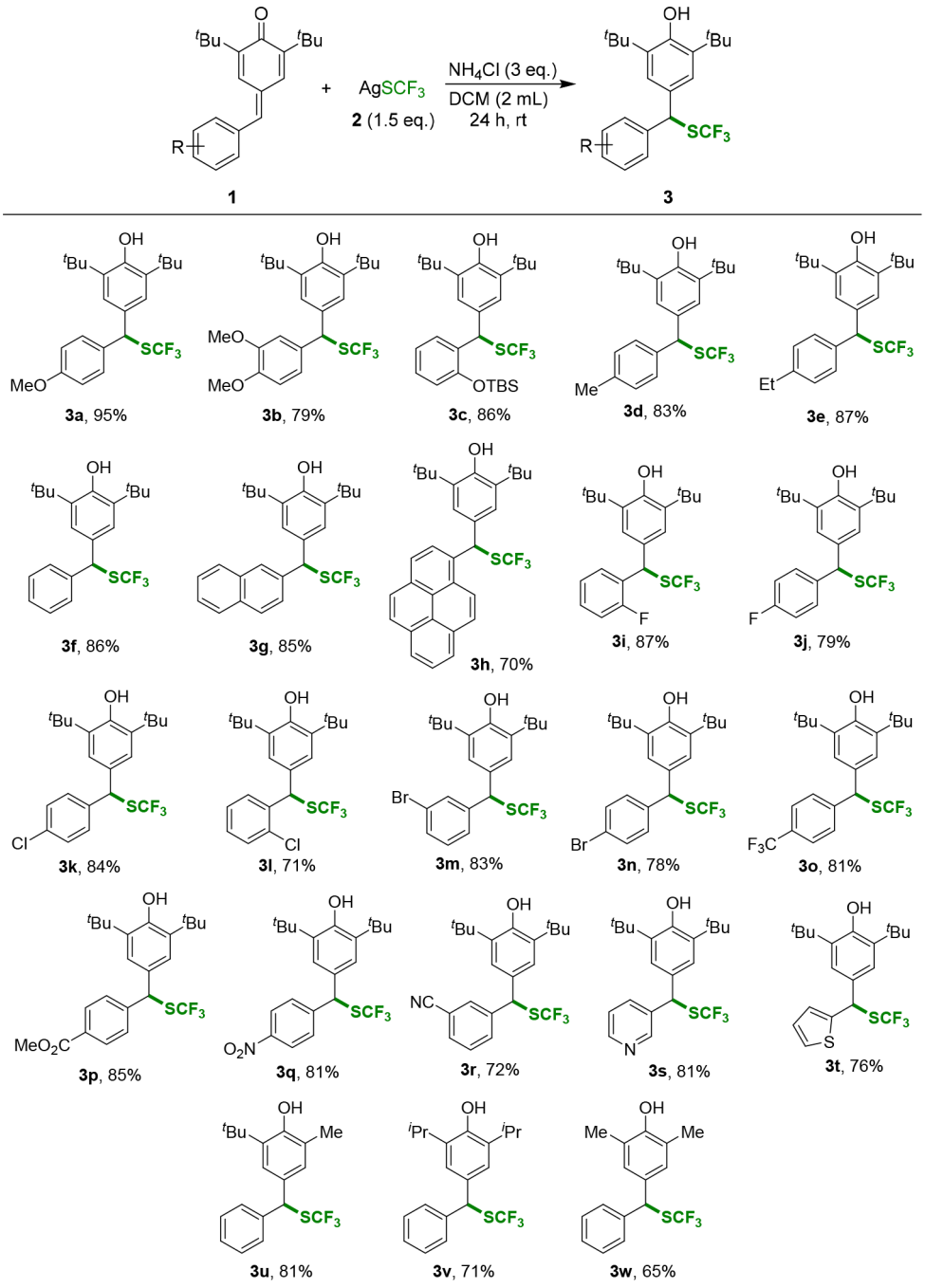
Scheme 2. Substrate Scope for Trifluoromethylthiolation of δ-Aryl-*p*-quinone Methides[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.23 mmol), DCM (2.0 mL), 0.45 mmol of NH_4Cl, room temperature, 24 h.

groups such as *p*-CF_3, *p*-CO_2Me, *p*-NO_2, and *m*-CN on the phenyl ring also yielded the corresponding products in isolated yields of 81%, 85%, 81%, and 72%, respectively (**3o**−**3r**, respectively).

The corresponding *p*-QMs of pyridine-3-carboxaldehyde and thiophane-2-carboxaldehyde produced the expected products (**3s** and **3t**, respectively) with isolated yields of 81% and 76%, respectively. More interestingly, the *p*-QMs derived from 2-*tert*-butyl-6-methyl phenol, 2,6-diisopropyl phenol, and 2,6-dimethyl phenol gave the desired products (**3u**−**3w**, respectively) in moderate to excellent yields (81%, 71%, and 65%, respectively). Next, the scope of δ-alkyl-*p*-QMs was tested. δ-*tert*-Butyl-*p*-QM derived from pivalaldehyde and *p*-QM from isobutyraldehyde offered trifluoromethylthiolated products (**3x** and **3y**, respectively) in 77% and 80% yields, respectively (Scheme 3).

Surprisingly, when δ-chloro-*p*-QM **1aa** was subjected to our optimized reaction conditions, di-trifluoromethylthiolated product **4** was obtained in an isolated yield of 62% (Scheme 4) and the product was characterized by ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR. First, trifluoromethylthiolation of **1aa** generates phenolate intermediate **M**, which loses a chloride anion by an addition−elimination mechanism to form trifluoromethylthio-*p*-QM intermediate **N**. Then, the second trifluoromethylth-

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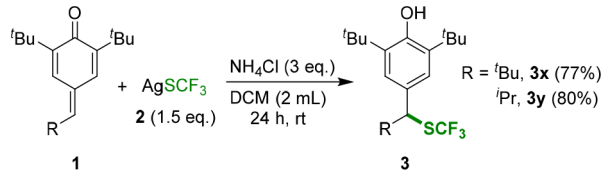
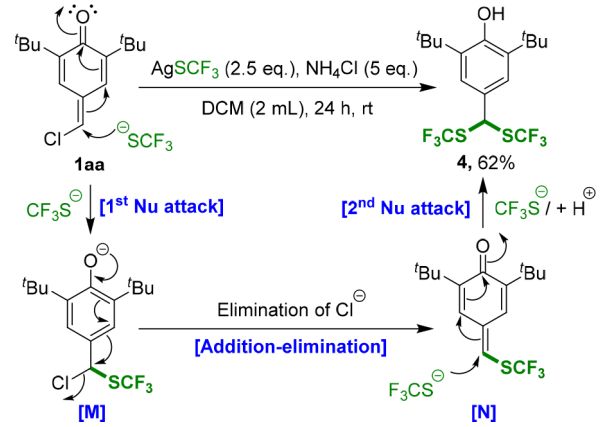
Scheme 3. Substrate Scope for Trifluoromethylthiolation of δ-Alkyl-*p*-quinone Methides[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.23 mmol), DCM (2.0 mL), 0.45 mmol of NH_4Cl, room temperature, 24 h.

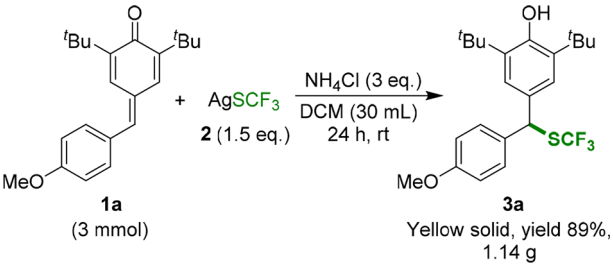
Scheme 4. Di-trifluoromethylthiolation of δ-Chloro-*p*-quinone Methides 1aa[a]



[a]Reaction conditions: **1aa** (0.15 mmol), **2** (0.38 mmol), DCM (2.0 mL), 0.75 mmol of NH_4Cl, room temperature, 24 h.

iolation of intermediate **N** furnished di-trifluoromethylthiolated product **4** in tandem one-pot fashion. To test the scalability of this protocol, a gram-scale synthesis was performed using 3 mmol of **1a**, under our standard optimized conditions. This resulted in **3a** in an 89% isolated yield (Scheme 5).

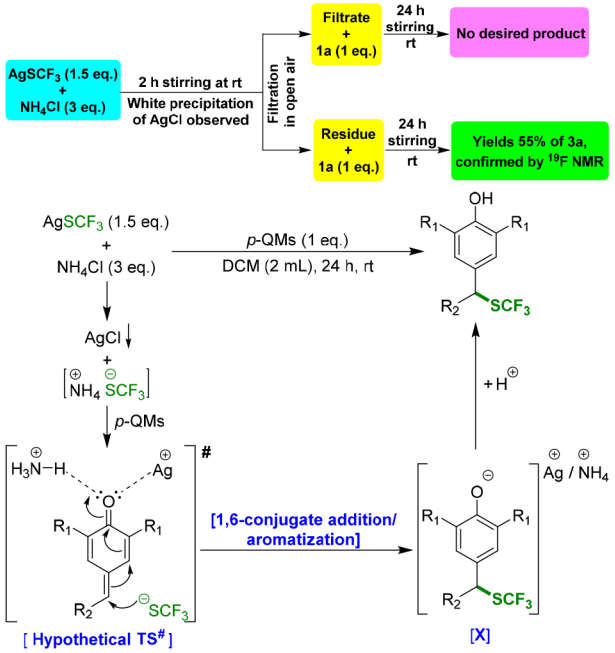
Scheme 5. Gram-Scale Synthesis of 3a[a]



[a]Reaction conditions: **1a** (3 mmol), **2** (4.5 mmol), DCM (30 mL), 9 mmol of NH_4Cl, room temperature, 24 h.

The mechanism of nucleophilic 1,6-conjugate addition to *p*-QM is known;[5−8] here, we aim to understand the reactive nature of both NH_4Cl and $AgSCF_3$ in our reaction. We hypothesized an *in situ* generation of NH_4SCF_3, which reacts with *p*-QM. To test this, we performed a reaction using 0.23 mmol of $AgSCF_3$ and 0.45 mmol of NH_4Cl in 2 mL of DCM at room temperature. As the reaction progressed, we clearly observed formation of the white AgCl precipitate that confirmed the ongoing reaction between NH_4Cl and $AgSCF_3$. After vigorously stirring the mixture for 2 h, we filtered the reaction mixture, and 0.15 mmol of **1a** was added to both the filtrate and the residue (here, an additional 2 mL of DCM was added); the mixture was stirred for 24 h. In the case of the residue, expected product **3a** was obtained and confirmed by ^{19}F NMR whereas the filtrate failed to furnish this product, which clearly indicates that the reactive species NH_4SCF_3 must be insoluble or sparingly soluble in the DCM reaction medium (Scheme 6).

Scheme 6. Probable Mechanism for Trifluoromethylthiolation of *p*-Quinone Methides



Lewis acid-catalyzed 1,6-conjugate addition to *p*-QMs is well-established,[8d,f] and the catalytic behavior of Ag^+ as a Lewis acid has been described in the literature.[12] Here, because Ag^+ is present at levels higher than (~1.5 times) that of the *p*-QM in the reaction medium, its influence should be considered important. Moreover, the involvement of the Lewis acid for enhancing the δ nucleophilicity of *p*-QMs is supported well by previous reports.[5b,6a,7] To deduce *p*-QM's reactivity in our protocol, we consider two simultaneous possibilities, which can enhance its δ nucleophilicity. (a) Participation of a Lewis acidic Ag^+ species: Silver is well-known for its affinity for carbonyl oxygen; as a result, Ag^+ can coordinate with the oxygen atom of the *p*-QM and enhances the δ nucleophilicity.[8f] (b) Participation of NH_4^+: Hydrogen from an ammonium ion is a good hydrogen bond donor, so there is a high likelihood of a successive hydrogen bond formation with the carbonyl oxygen of *p*-QMs. This hydrogen bond formation could enhance the δ nucleophilicity of *p*-QMs. Also, protons from NH_4^+ would furnish the desired product by protonating intermediate **X**.[8f] In addition, another interesting factor that plays a crucial role in this reaction would be the precipitation of AgCl, which provides an entropy boost to generate the reacting nucleophile ($-SCF_3$) or reactive species NH_4SCF_3. On the basis of these preliminary experimental observations, we propose a plausible mechanism for this trifluoromethylthiolation reaction as depicted in Scheme 6.

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In summary, a direct and efficient method for trifluoromethylthiolation of *p*-QMs is demonstrated using cheap ammonium chloride as a reaction mediator and commercially available, bench stable $AgSCF_3$ as a nucleophilic trifluoromethylthiolating reagent. This is the first study of trifluoromethylthiolation of *p*-QMs. Our strategy is benign without the use of any peroxide, while most of the reported nucleophilic trifluoromethylthiolations require sacrificial amounts of peroxides and transition metal catalysts or more equivalents of alkylammonium halides. In addition, this method is successful under ambient reaction conditions and has a good substrate scope with a wide range of functional group tolerance. Given these advantages, this strategy could be applicable in late stage trifluoromethylthiolation for the preparation of biologically active molecules and drugs.

EXPERIMENTAL SECTION

General Information. Commercial reagents and solvents were purified prior to their use following the guidelines of Chai and Armarego.[13a] All NMR spectra were recorded on 400 MHz Jeol and 500 MHz Bruker spectrometers. ^1H, ^{13}C, and ^{19}F NMR spectral data are reported as chemical shifts (δ) in parts per million relative to the solvent residual peak using the Jeol internal referencing procedure (edlock). Chemical shifts (δ) are quoted in parts per million, and coupling constants (J) are measured in hertz. The following abbreviations are used to describe multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; br, broad; m, multiplet; dd, doublet of doublets. High-resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF instrument. IR spectra were recorded on a Bruker ATR spectrometer. All reactions for trifluoromethylthiolation of *p*-QMs were conducted in dried glassware with magnetic stirring under ambient atmosphere, unless otherwise noted. Thin layer chromatography (TLC) was performed using Silica gel 60 F254 and visualized under ultraviolet light and an iodine chamber. Flash column chromatography was performed over Merck silica gel (230−400 mesh). Silver fluoride was purchased from Fluorochem. $AgSCF_3$ was prepared by the reported literature procedure. Other reagents were obtained from commercial suppliers Alfa Aesar, Merck, and Spectrochem and used without further purification, unless otherwise specified.

Synthesis of *p*-Quinone Methides 1. In an oven-dried 250 mL round-bottom flask fitted with a Dean-Stark apparatus, phenol (25 mmol) and the appropriate aldehyde (25 mmol) were placed. To this was added toluene (100 mL), and the mixture was heated using an oil bath to reflux followed by dropwise addition of the piperidine (50 mmol) over a period of 1 h. The reaction mixture was allowed to continue to reflux overnight. After that, it was cooled just below the boiling point of the reaction mixture and acetic anhydride (50 mmol) was added and refluxed for 30 min. It was then poured into 500 mL of ice-cold water and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure using a rotary evaporator. The product was finally purified using column chromatography to afford the corresponding *p*-QMs (**1a**−**1t** and **1v**).[13b]

p-QMs **1u** and **1w** were prepared according to the literature procedure.[8a] *p*-QM **1aa** was also prepared on the basis of the literature.[13c]

Synthesis of $AgSCF_3$. The reagent $AgSCF_3$ was prepared following a previously reported procedure.[14] Briefly, AgF (15 g, 118 mmol) was added under an argon atmosphere followed by CS_2 (15 mL, 248 mmol, 2.1 equiv), and 75 mL of dry acetonitrile and the reaction mixture were refluxed at 80 °C using an oil bath. After 14 h, the reaction mixture was cooled to room temperature and excess CS_2 and solvent were evaporated under reduced pressure in the dark. Then the residue was dissolved in EtOAc and filtered through Celite, and the filtrate was concentrated under reduced pressure in the dark. After that, the yellow residue was dissolved in a minimum amount of dry acetonitrile, and the yellow solution was layered with 60 mL of diethyl ether and kept at −20 °C for crystallization for 24 h by being covered with aluminum foil. Then white crystalline solid was collected by filtration, dried in vacuum, and stored in a refrigerator (7.3 g, 89% yield).

Experimental Procedure for the Synthesis of Compounds 3 and 4. To an oven-dried 20 mL reaction tube equipped with a magnetic stir bar were added *p*-QMs (0.15 mmol, 1.0 equiv), $AgSCF_3$ (0.225 mmol, 1.5 equiv), and NH_4Cl (0.45 mmol, 3.0 equiv). The reaction tube was sealed with a septum. Then, 2 mL of dry DCM was added through the septum using a syringe, and the reaction mixture stirred at room temperature. After 24 h, the reaction mixture was diluted with 15 mL of DCM and dried over Na_2SO_4 and the solvent was removed under reduced pressure at 45 °C in a water bath. To purify the crude product, 230−400 mesh silica gel was used. Before purification, the column was washed with 200 mL of a 2% AcOH/hexane mixture and then the excess of AcOH was washed using 100 mL of hexane. Then, the crude product dissolved in hexane was loaded into the column and purified by flash column chromatography using an EtOAc/hexane mixture as the eluent. Solvent evaporation under reduced pressure at 45 °C afforded product **3**, and compounds **3**(**a**−**y**) and **4** were stored in a refrigerator at 0 °C.

To synthesize **4** from **1aa**, 2.5 equiv of $AgSCF_3$ and 5.0 equiv of NH_4Cl were used, keeping all other conditions the same as mentioned above.

Gram-Scale Synthesis of 3a. To an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar were added *p*-QM **1a** (3 mmol, 1.0 equiv), $AgSCF_3$ (4.5 mmol, 1.5 equiv), and NH_4Cl (9 mmol, 3.0 equiv), and the flask was closed with a septum. Then, 30 mL of dry DCM was added, and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was diluted with 30 mL of DCM and dried over Na_2SO_4 and the solvent was removed under reduced pressure at 45 °C in a water bath. To purify the crude product, 230−400 mesh silica gel was used. First, a 2% AcOH/hexane mixture was passed through the silica gel to make it acidic, and the excess AcOH was washed with 100 mL of hexane. Then, the crude product was dissolved in hexane, applied to the column, and purified by flash column chromatography using hexane as an eluent to afford 1.14 g of yellow solid product **3a** in 89% yield.

Characterization of Compounds 3 and 4. *2,6-Di-tert-butyl-4-{(4-methoxyphenyl)[(trifluoromethyl)thio]methyl}phenol (**3a**).* Compound **3a** was purified by flash column chromatography on silica gel using hexane as the eluent: yellow solid; 95% yield (60.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.6 Hz, 2H), 7.17 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.63 (s, 1H), 5.22 (s, 1H), 3.81 (s, 3H), 1.42 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.2, 153.5, 136.2, 132.2, 130.2 (q, J_{C-F} = 310.0 Hz), 129.7, 129.5, 125.0, 114.1, 55.4, 53.8, 34.6, 30.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −40.73 (s); FT-IR (thin film, neat) 3591, 2919, 2884, 2835, 1592, 1493, 1442, 1415, 1376, 1349, 1303, 1288, 1261, 1237, 1162, 1123, 1089, 1026, 942, 879, 845, 826, 799, 769, 741, 627, 609 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{30}F_3O_2S$ 427.1919, found 427.1936.

*2,6-Di-tert-butyl-4-{(3,4-dimethoxyphenyl)[(trifluoromethyl)-thio]methyl}phenol (**3b**).* Compound **3b** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: orange oil; 79% yield (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H), 7.02−6.96 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 5.62 (s, 1H), 5.22 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 1.41 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.5, 149.1, 148.7, 136.2, 132.5, 130.2 (q, J_{C-F} = 310.0 Hz), 129.5, 125.0, 120.7, 111.6, 111.2, 56.0, 54.0, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.65 (s); FT-IR (thin film, neat) 3586, 2915, 2878, 2828, 1590, 1496, 1432, 1407, 1376, 1351, 1300, 1290, 1252, 1235, 1160, 1118, 1081, 1017, 940, 869, 837, 801, 758, 744, 635, 618 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{24}H_{31}F_3O_3S$ 456.1946, found 456.1946.

*2,6-Di-tert-butyl-4-({2-[(tert-butyldimethylsilyl)oxy]phenyl}-[(trifluoromethyl)thio]methyl)phenol (**3c**).* Compound **3c** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow solid; 86% yield (67.8 mg); ^1H NMR (400

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MHz, $CDCl_3$) δ 7.65 (dd, J = 9.3, 1.5 Hz, 1H), 7.23−7.18 (m, 3H), 7.04 (td, J = 7.6, 1.2 Hz, 1H), 6.89−6.87 (m, 1H), 6.17 (s, 1H), 5.20 (s, 1H), 1.43 (s, 18H), 1.01 (s, 9H), 0.29 (s, 3H), 0.20 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.3, 152.7, 136.0, 130.6, 130.6 (q, J_{C-F} = 308.7 Hz), 130.0, 129.5, 128.7, 125.3, 121.2, 118.5, 47.5, 34.5, 30.3, 25.9, 18.4, −3.9, −4.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.80 (s); FT-IR (thin film, neat) 3572, 2921, 2828, 1463, 1418, 1260, 1243, 1134, 1092, 1036, 996, 909, 876, 822, 793, 796, 741, 695 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{42}F_3O_2SSi$ 527.2627, found 527.2647.

*2,6-Di-tert-butyl-4-{p-tolyl[(trifluoromethyl)thio]methyl}phenol (**3d**).* Compound **3d** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 83% yield (51 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.17 (t, J = 4.0 Hz, 4H), 5.62 (s, 1H), 5.21 (s, 1H), 2.35 (s, 3H), 1.42 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.5, 137.6, 137.3, 136.2, 130.3 (q, J_{C-F} = 308.7 Hz), 129.7, 129.4, 128.2, 125.0, 54.0, 34.6, 30.4, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.64 (s); FT-IR (thin film, neat) 3703, 3628, 3596, 2925, 2886, 2836, 1492, 1415, 1378, 1347, 1298, 1227, 1125, 1091, 1006, 945, 878, 842, 820, 800, 765, 742, 726, 707, 628, 610, 569 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{30}F_3OS$ 411.1969, found 411.1955.

*2,6-Di-tert-butyl-4-{(4-ethylphenyl)[(trifluoromethyl)thio]methyl}phenol (**3e**).* Compound **3e** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 87% yield (55.3 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.8 Hz, 2H), 7.25 (t, J = 3.8 Hz, 4H), 5.70 (s, 1H), 5.28 (s, 1H), 2.71 (q, J = 7.6 Hz, 2H), 1.49 (s, 18H), 1.30 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.5, 143.9, 137.5, 136.2, 130.3 (q, J_{C-F} = 308.7 Hz), 129.8, 128.2, 128.2, 125.1, 54.1, 34.6, 30.4, 28.6, 15.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ −40.20; FT-IR (thin film, neat) 3703, 3543, 2924, 2880, 2839, 1693, 1594, 1417, 1295, 1268, 1226, 1186, 1169, 1134, 1089, 1007, 950, 878, 856, 841, 806, 791, 761, 746, 727, 697, 610 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{32}F_3OS$ 425.2126, found 425.2132.

*2,6-Di-tert-butyl-4-{phenyl[(trifluoromethyl)thio]methyl}phenol (**3f**).* Compound **3f** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 86% yield (51.1 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.19 (s, 2H), 5.69 (s, 1H), 5.25 (s, 1H), 1.44 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.6, 140.2, 136.3, 130.2 (q, J_{C-F} = 310.0 Hz), 129.4, 128.7, 128.3, 127.8, 125.1, 54.2, 34.6, 30.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −40.73 (s); FT-IR (thin film, neat) 3629, 3590, 3569, 2925, 2881, 2834, 1523, 1455, 1434, 1415, 1378, 1348, 1303, 1226, 1186, 1089, 1014, 878, 836, 792, 729, 689, 645, 610 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{28}F_3OS$ 397.1813, found 397.1808.

*2,6-Di-tert-butyl-4-{naphthalen-2-yl[(trifluoromethyl)thio]methyl}phenol (**3g**).* Compound **3g** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: yellow solid; 85% yield (56.8 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 16.6, 8.2 Hz, 4H), 7.65 (d, J = 10.1 Hz, 1H), 7.53−7.48 (m, 2H), 7.24 (s, 2H), 5.85 (s, 1H), 5.25 (s, 1H), 1.43 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.6, 137.6, 136.4, 133.4, 133.0, 130.2 (q, J_{C-F} = 308.7 Hz), 129.3, 128.6, 128.2, 127.8, 127.2, 126.5, 126.4, 126.2, 125.2, 54.4, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.51 (s); FT-IR (thin film, neat) 3851, 3809, 3776, 3756, 3701, 3684, 3648, 3626, 3606, 3575, 3517, 3447, 3183, 2921, 2879, 2851, 2821, 2224, 2002, 1494, 1414, 1347, 1220, 1188, 1128, 1087, 1008, 946, 879, 851, 808,795, 767, 739, 654 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{30}F_3OS$ 447.1969, found 447.1980.

*2,6-Di-tert-butyl-4-{pyren-1-yl[(trifluoromethyl)thio]methyl}phenol (**3h**).* Compound **3h** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: orange solid; 70% yield (54.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 9.3 Hz, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.20 (dd, J = 17.1, 9.7 Hz, 4H), 8.08 (d, J = 2.1 Hz, 2H), 8.02 (t, J = 7.6 Hz, 1H), 7.34 (s, 2H), 6.82 (s, 1H), 5.23 (s, 1H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.5, 136.3, 132.9, 131.5, 131.1, 130.8, 130.3 (q, J_{C-F} = 310.0 Hz), 129.3, 128.4, 128.2, 127.8, 127.6, 126.9, 126.2, 125.7, 125.5, 125.5, 125.3, 125.0, 125.0, 123.8, 122.5, 50.8, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.66 (s); FT-IR (thin film, neat) 3538, 2923, 2875, 2833, 1414, 1299, 1221, 1131, 1090, 959, 831, 746, 703, 671, 639, 615, 561 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{32}F_3OS$ 521.2126, found 521.2138.

*2,6-Di-tert-butyl-4-{(2-fluorophenyl)[(trifluoromethyl)thio]methyl}phenol (**3i**).* Compound **3i** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 87% yield (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (td, J = 7.7, 1.8 Hz, 1H), 7.29−7.24 (m, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.16 (s, 2H), 7.08−7.02 (m, 1H), 5.97 (s, 1H), 5.23 (s, 1H), 1.40 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8 (d, J_{C-F} = 244.4 Hz), 153.7, 136.3, 130.1 (q, J_{C-F} = 310.1 Hz), 129.9 (d, J_{C-F} = 2.0 Hz), 129.5 (q, J_{C-F} = 8.1 Hz), 128.3, 127.8 (d, J_{C-F} = 14.1 Hz), 125.0, 124.4 (d, J_{C-F} = 4.0 Hz), 115.9 (d, J_{C-F} = 22.2 Hz), 46.5, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.99 (s), −117.17 (s); FT-IR (thin film, neat) 3577, 2926, 2881, 2840, 1565, 1468, 1436, 1414, 1380, 1348, 1299, 1262, 1238, 1213, 1191, 1128, 1093, 1020, 947, 922, 878, 839, 785, 746, 638, 599 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}F_4OS$ 415.1719, found 415.1717.

*2,6-Di-tert-butyl-4-{(4-fluorophenyl)[(trifluoromethyl)thio]methyl}phenol (**3j**).* Compound **3j** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow liquid; 79% yield (49 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.7, 5.3 Hz, 2H), 7.12 (s, 2H), 7.06 (t, J = 8.7 Hz, 2H), 5.65 (s, 1H), 5.24 (s, 1H), 1.41 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 247.5 Hz), 153.7, 136.4, 136.0, 130.1 (q, J_{C-F} = 310.1 Hz), 130.0 (d, J_{C-F} = 8.1 Hz), 129.1, 125.0, 115.6 (d, J_{C-F} = 21.2 Hz), 53.4, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.67 (s), −114.44 (s); FT-IR (thin film, neat) 3696, 3575, 2923, 2891, 2827, 1463, 1419, 1262, 1241, 1218, 1133, 1091, 908, 823, 769, 741 cm^{-1}; HRMS (ESI-TOF) m/z $[M + K]^+$ calcd for $C_{22}H_{26}F_4KOS$ 453.1278, found 453.1282.

*2,6-Di-tert-butyl-4-{(4-chlorophenyl)[(trifluoromethyl)thio]methyl}phenol (**3k**).* Compound **3k** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: pale yellow solid; 84% yield (54.2 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.11 (s, 2H), 5.62 (s, 1H), 5.25 (s, 1H), 1.41 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.7, 138.9, 136.4, 133.7, 130.0 (q, J_{C-F} = 310.1 Hz), 129.7, 128.9, 128.8, 125.0, 53.5, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.62 (s); FT-IR (thin film, neat) 3589, 2929, 2882, 2838, 1467, 1416, 1386, 1347, 1306, 1228, 1184, 1131, 1090, 1076, 1000, 945, 883, 842, 826, 801, 775, 741, 711, 679 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}ClF_3OS$ 431.1423, found 431.1437.

*2,6-Di-tert-butyl-4-{(2-chlorophenyl)[(trifluoromethyl)thio]methyl}phenol (**3l**).* Compound **3l** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: pale yellow solid; 71% yield (45.8 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.22 (s, 2H), 6.24 (s, 1H), 5.27 (s, 1H), 1.45 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.7, 138.0, 136.3, 133.2, 130.1, 130.1 (q, J_{C-F} = 308.7 Hz), 130.0, 129.0, 128.1, 127.2, 125.2, 50.0, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.84 (s); FT-IR (thin film, neat) 3854, 3808, 3792, 3772, 3755, 3702, 3690, 3642, 3625, 3606, 3587, 3520, 2923, 2176, 2121, 2004, 1677, 1627, 1490, 1418, 1377, 1222, 1132, 1091, 1024, 823, 791, 740, 715, 685, 635 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}ClF_3OS$ 431.1423, found 431.1415.

*4-{(3-Bromophenyl)[(trifluoromethyl)thio]methyl}-2,6-di-tert-butylphenol (**3m**).* Compound **3m** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: yellow solid; 83% yield (59 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, J = 1.6 Hz, 1H), 7.43 (dd, J = 7.1, 4.9 Hz, 2H), 7.25 (t, J = 7.9 Hz, 1H), 7.13 (s, 2H), 5.60 (s, 1H), 5.27 (s, 1H), 1.42 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.8, 142.6, 136.5, 131.4, 131.0, 130.3, 129.9 (q, J_{C-F} = 310.0 Hz), 128.8, 126.9, 125.0,

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122.8, 53.5, 34.5, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.62 (s); FT-IR (thin film, neat) 3586, 2921, 2877, 2838, 1573, 1546, 1453, 1411, 1377, 1348, 1299, 1223, 1132, 1091, 1013, 983, 878, 841, 792, 761, 741, 690, 660, 641, 602 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}BrF_3OS$ 473.0761, found 473.0754.

*4-{(4-Bromophenyl)[(trifluoromethyl)thio]methyl}-2,6-di-tert-butylphenol (**3n**).* Compound **3n** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: yellow solid; 78% yield (55.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.15 (s, 2H), 5.64 (s, 1H), 5.28 (s, 1H), 1.44 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.8, 139.4, 136.5, 131.9, 130.0 (q, J_{C-F} = 308.7 Hz), 130.0, 128.8, 125.1, 125.0, 121.8, 53.5, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.55 (s); FT-IR (thin film, neat) 3701, 3628, 3591, 3572, 3523, 2925, 2882, 2834, 1462, 1413, 1380, 1349, 1305, 1227, 1185, 1131, 1088, 1055, 994, 945, 881, 839, 822, 801, 775, 738, 709, 662, 608 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{27}BrF_3OS$ 475.0918, found 475.0917.

*2,6-Di-tert-butyl-4-{[4-(trifluoromethyl)phenyl][(trifluoromethyl)-thio]methyl}phenol (**3o**).* Compound **3o** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 81% yield (56.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.59 (m, 4H), 7.12 (s, 2H), 5.68 (s, 1H), 5.27 (s, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.9, 144.4, 136.6, 130.1 (q, J_{C-F} = 32.2 Hz), 130.0 (q, J_{C-F} = 247.5 Hz), 128.7, 128.4, 125.8 (q, J_{C-F} = 3.5 Hz), 125.0, 124.2 (q, J_{C-F} = 272.7 Hz), 53.6, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.63 (s), −62.46 (s); FT-IR (thin film, neat) 3592, 2920, 2889, 2836, 1600, 1417, 1306, 1228, 1151, 1090, 1001, 840, 790, 746 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{27}F_6OS$ 465.1687, found 465.1680.

*4-{(3,5-Di-tert-butyl-4-hydroxyphenyl)[(trifluoromethyl)thio]-methyl}phenylacetate (**3p**).* Compound **3p** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: yellow oil; 85% yield (57.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.14 (s, 2H), 5.71 (s, 1H), 5.30 (s, 1H), 3.93 (s, 3H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.8, 153.8, 145.4, 136.5, 130.1, 130.0 (q, J_{C-F} = 308.7 Hz), 129.7, 128.5, 128.3, 125.1, 53.8, 52.2, 34.5, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.58 (s); FT-IR (thin film, neat) 3695, 3542, 2923, 2881, 2840, 1691, 1593, 1416, 1349, 1268, 1227, 1175, 1131, 1087, 1009, 949, 879, 850, 803, 754, 733, 700 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{30}F_3O_3S$ 455.1867, found 455.1861.

*2,6-Di-tert-butyl-4-{(4-nitrophenyl)[(trifluoromethyl)thio]-methyl}phenol (**3q**).* Compound **3q** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: yellow oil; 81% yield (53.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.07 (s, 2H), 5.70 (s, 1H), 5.28 (s, 1H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.1, 147.7, 147.5, 136.9, 129.8 (q, J_{C-F} = 310.0 Hz), 129.2, 127.7, 125.0, 124.1, 53.4, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.58 (s); FT-IR (thin film, neat) 3575, 2921, 2886, 2819, 1576, 1499, 1417, 1328, 1308, 1241, 1226, 1189, 1161, 1128, 1091, 1002, 878, 848, 824, 785, 737, 693, 669, 608, 578 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{27}F_3NO_3S$ 442.1664, found 442.1679.

*3-{(3,5-Di-tert-butyl-4-hydroxyphenyl)[(trifluoromethyl)thio]-methyl}benzonitrile (**3r**).* Compound **3r** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: yellow oil; 72% yield (45.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.08 (s, 2H), 5.66 (s, 1H), 5.30 (s, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.0, 142.1, 136.8, 132.7, 131.9, 131.5, 129.9 (q, J_{C-F} = 310.0 Hz), 129.6, 127.9, 124.9, 118.6, 113.0, 53.2, 34.6, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.58 (s); FT-IR (thin film, neat) 3559, 2916, 2880, 2209, 1465, 1415, 1377, 1342, 1306, 1242, 1221, 1192, 1126, 1095, 1012, 948, 917, 889, 877, 794, 732, 682, 623, 592 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{27}F_3NOS$ 422.1765, found 422.1758.

*2,6-Di-tert-butyl-4-{pyridin-3-yl[(trifluoromethyl)thio]methyl}-phenol (**3s**).* Compound **3s** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/19) mixture as the eluent: pale yellow oil; 81% yield (48.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (d, J = 3.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.34−7.30 (m, 1H), 7.10 (s, 2H), 5.64 (s, 1H), 5.29 (s, 1H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.9, 149.6, 149.1, 136.7, 136.2, 135.8, 129.9 (q, J_{C-F} = 308.7 Hz), 128.2, 124.9, 123.6, 51.6, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.56 (s); FT-IR (thin film, neat) 3703, 3691, 2921, 2881, 2837, 1556, 1459, 1415, 1373, 1343, 1287, 1246, 1223, 1132, 1086, 1014, 922, 878, 843, 813, 799, 776, 730, 699, 665 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{27}F_3NOS$ 398.1765, found 398.1759.

*2,6-Di-tert-butyl-4-{thiophen-2-yl[(trifluoromethyl)thio]methyl}-phenol (**3t**).* Compound **3t** was purified by flash column chromatography on silica gel using an EtOAc/hexane (1/49) mixture as the eluent: pale yellow oil; 76% yield (45.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 5.3 Hz, 1H), 7.22 (s, 2H), 7.02 (d, J = 3.3 Hz, 1H), 6.94−6.91 (m, 1H), 5.83 (s, 1H), 5.24 (s, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.9, 144.3, 136.4, 130.2 (q, J_{C-F} = 310.0 Hz), 129.7, 126.8, 126.8, 126.1, 124.8, 49.7, 34.6, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.85 (s); FT-IR (thin film, neat) 3625, 2965, 2868, 1638, 1427, 1398, 1342, 1330, 1317, 1242, 1140, 1107, 852, 842, 769, 749, 699, 656, 601 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{25}F_3NaOS_2$ 425.1197, found 425.1216.

*2-(tert-Butyl)-6-methyl-4-{phenyl[(trifluoromethyl)thio]methyl}-phenol (**3u**).* Compound **3u** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 81% yield (43 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.3 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 5.61 (s, 1H), 4.77 (s, 1H), 2.19 (s, 3H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.5, 140.1, 136.1, 130.2, 130.2 (q, J_{C-F} = 308.7 Hz), 128.8, 128.3, 128.2, 127.9, 125.3, 123.5, 53.7, 34.8, 29.8, 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.70 (s); FT-IR (thin film, neat) 3564, 3537, 2922, 2888, 2837, 1581, 1462, 1436, 1416, 1375, 1346, 1307, 1280, 1263, 1237, 1205, 1183, 1130, 1091, 1018, 897, 875, 819, 785, 744, 688, 647, 615 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{19}H_{20}F_3OS$ 353.1187, found 353.1181.

*2,6-Diisopropyl-4-{phenyl[(trifluoromethyl)thio]methyl}phenol (**3v**).* Compound **3v** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 71% yield (39.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.32−7.27 (m, 1H), 7.08 (s, 2H), 5.69 (s, 1H), 4.83 (s, 1H), 3.14 (hept, J = 6.8 Hz, 2H), 1.26 (d, J = 6.9 Hz, 12H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.8, 140.0, 134.1, 130.8, 130.2 (q, J_{C-F} = 308.7 Hz), 128.8, 128.4, 128.3, 127.9, 123.7, 54.0, 53.9, 27.5, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.63 (s); FT-IR (thin film, neat) 3625, 2960, 2935, 2868, 1623, 1501, 1461, 1407, 1357, 1259, 1189, 1148, 1100, 856, 752, 700, 656, 605 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{20}H_{22}F_3OS$ 367.1343, found 367.1331.

*2,6-Dimethyl-4-{phenyl[(trifluoromethyl)thio]methyl}phenol (**3w**).* Compound **3w** was purified by flash column chromatography on silica gel using hexane as the eluent: colorless oil; 65% yield (30.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.30−7.26 (m, 1H), 6.99 (s, 2H), 5.59 (s, 1H), 4.65 (s, 1H), 2.22 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.0, 140.0, 130.8, 130.2 (q, J_{C-F} = 308.7 Hz), 128.8, 128.5, 128.2, 127.9, 123.5, 53.3, 16.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.74 (s); FT-IR (thin film, neat) 3447, 2917, 1627, 1489, 1400, 1259, 1187, 1145, 1102, 857, 753, 704, 649, 596 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{16}H_{14}F_3OS$ 311.0717, found 311.0707.

*2,6-Di-tert-butyl-4-{2,2-dimethyl-1-[(trifluoromethyl)thio]-propyl}phenol (**3x**).* Compound **3x** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 77% yield (43.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 5.16 (s, 1H), 4.04 (s, 1H), 1.46 (s, 18H), 1.02 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.1, 135.1, 131.4 (q, J_{C-F} = 306.2 Hz),

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130.7, 125.7, 62.1, 36.1, 34.5, 30.6, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −39.92 (s); FT-IR (thin film, neat) 3598, 2922, 2837, 1455, 1418, 1379, 1348, 1301, 1219, 1133, 1092, 1012, 920, 860, 796, 755, 636 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{32}F_3OS$ 377.2126, found 377.2127.

*2,6-Di-tert-butyl-4-{2-methyl-1-[(trifluoromethyl)thio]propyl}-phenol (**3y**).* Compound **3y** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 80% yield (43.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 5.17 (s, 1H), 4.09 (d, J = 6.9 Hz, 1H), 2.16 (dq, J = 13.5, 6.7 Hz, 1H), 1.45 (s, 18H), 1.04 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.2, 135.7, 131.2 (q, J_{C-F} = 307.4 Hz), 130.6, 124.8, 57.7, 34.5, 34.3, 30.5, 20.6, 20.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −39.67 (s); FT-IR (thin film, neat) 3601, 2922, 2837, 1450, 1418, 1373, 1347, 1302, 1220, 1131, 1088, 1013, 317, 876, 801, 785, 760, 744, 726, 660, 633, 612 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{30}F_3OS$ 363.1969, found 363.1972.

*4-{Bis[(trifluoromethyl)thio]methyl}-2,6-di-tert-butylphenol (**4**).* Compound **4** was purified by flash column chromatography on silica gel using hexane as the eluent: pale yellow oil; 62% yield (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 2H), 5.74 (s, 1H), 5.38 (s, 1H), 1.44 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.9, 136.9, 129.1 (q, J_{C-F} = 310.0 Hz), 126.6, 124.2, 50.8, 34.6, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.05 (s); FT-IR (thin film, neat) 3595, 2923, 2884, 2843, 1416, 1349, 1305, 1232, 1078, 876, 743, 716, 614 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{23}F_6OS_2$ 421.1095, found 421.1105.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01752.

Tables of the optimization of reaction conditions and mechanistic studies, copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all new compounds, crystal data of compound **3h**, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2018273 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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■ DEDICATION

Dedicated to Professor Srinivasan Chandrasekaran on the occasion of his 75th birthday.

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