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The stability and reactivity of tri-, di-, and monofluoromethyl/methoxy/methylthio groups on arenes under acidic and basic conditions†

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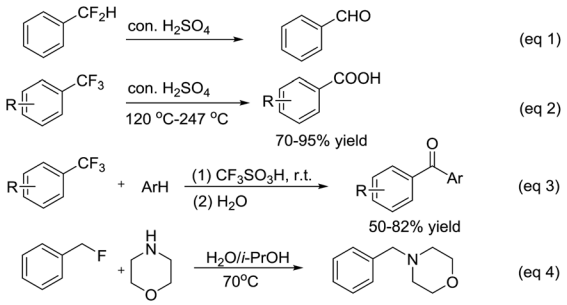
Little attention has been paid to the stability and reactivity of the C–F bond under different conditions. In this study, the stability and reactivity of tri-, di-, and monofluoromethyl/methoxy/methylthio moiety groups on arenes under acidic or basic conditions are carefully investigated.

Introduction

Over the past few decades, fluorine-containing organic molecules have been widely used in the fields of agrochemicals, pharmaceuticals and functional materials, mainly due to the fact that the introduction of a fluorinated moiety often leads to dramatic changes in physical, chemical and biological properties.[1,2] Among various fluorinated moieties, tri-, di- and monofluoromethyl/methoxy/methylthio moieties have attracted much attention, and numerous efforts have been made for the introduction of these fluorinated moieties onto aromatic rings.[1a] It is commonly believed that the C–F bond is one of the most inert bonds in organic chemistry, and strenuous efforts have been made for C–F activation to accomplish various purposes.[3] Moreover, due to the demand of agriculture and ecology, methods of defluorination and hydro-defluorination have also been intensively exploited.[4] However, to the best of our knowledge, there has been little focus on the investigation of the stability and reactivity of these fluorinated moieties on arenes under different conditions.[5] It was previously found that di- and trifluoromethyl benzene could be hydrolysed to benzaldehyde or benzylic acid by concentrated sulfuric acid, respectively (Scheme 1, eqn (1) and (2)).[6] Recently, Hu and co-workers disclosed that trifluoromethanesulfonic acid could mediate C–F bond activation for the inter- and intramolecular arylation of trifluoromethylated arenes (Scheme 1, eqn (3)).[7a] Paquin also demonstrated that morpholine could substitute the fluorine atom of benzylic fluorides (Scheme 1, eqn (4)).[8]



Scheme 1 Previously reported reactions of fluoromethyl-benzene under acidic conditions.

In the process to prepare some fluoro-containing target compounds in medicinal or agricultural chemistry, the fluorinated moieties need to remain unchanged in the steps under different conditions, especially under acidic or basic conditions. Therefore, it is a meaningful work to investigate the stability and reactivity of fluorinated moieties under different conditions, which may provide some useful guidelines for synthetic and medicinal chemistry. Herein, we wish to disclose the stability and reactivity of tri-, di- and monofluoromethyl/methoxy/methylthio groups on arenes under acidic or basic conditions.

At the onset of our investigation, the fluorinated arenes with 4-methoxy or 4-nitro groups were synthesized for comparison of the electronic effect on the stability of the fluorinated arenes. Then we found that most of these nitro-containing substrates were very easily decomposed under basic conditions (this phenomenon was also reported by a lot of literature studies previously),[9] and this instability of the nitro group under basic conditions would disturb the results. So we

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replaced the NO_2 group with the $PhSO_2$ group as an electron-withdrawing substituent due to its better stability. For the reaction conditions, triflic acid was employed as the first acidic condition. If the substrates showed low stability under such a condition, TFA or CH_3COOH would be used to decrease the acidity. Similarly, potassium bis(trimethylsilyl)amide (KHMDS) was used as the first basic condition and KO^{t}Bu, NaOMe, or morpholine was employed as a weaker base subsequently.

Results and discussion

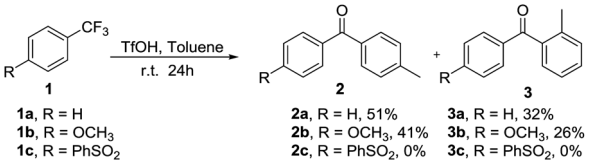
CF_3 group

The trifluoromethyl moiety is the most extensively studied group among all the fluoroalkyl-containing compounds,[10] and trifluoromethylated arenes were examined firstly in a TfOH/toluene system (Scheme 2). As expected, benzotrifluoride (**1a**) and 4-methoxy-benzotrifluoride (**1b**) converted to the corresponding benzophenone derivatives **2a**, **3a** and **2b**, **3b** in good yields (51% + 32%, 41% + 26%), respectively, which is fully consistent with our previous report.[7] 4-Phenylsulfonylbenzotrifluoride (**1c**) was very stable under these conditions, probably the formation of the benzoyl cation was blocked by the strong electron-withdrawing phenylsulfonyl group in the aromatic ring.[7,11] In addition, we also found that the trifluoromethylated arenes (**1a** and **1b**) are very stable in CF_3COOH (TFA) even at elevated temperatures (see Table S1† for details).

The stability of compounds **1a**, **1b** and **1c** in the KHMDS/THF system was investigated. The results showed that compounds **1a** and **1b** were 100% recovered, indicating their high stability under this strong alkaline condition. For compound **1c**, the CF_3 remain unchanged on arenes, while a portion of the substrate suffered from the cleavage of the phenylsulfonyl group (see Table S1† for details).[12]

OCF_3 group

Next, the stability of trifluoromethoxybenzene derivatives **4a**, **4b** and **4c** was evaluated under the same conditions. The results showed that all the three compounds remained unchanged in the presence of triflic acid or KHMDS (Fig. 1), indicating the very high stability of the trifluoromethoxy group on the arene under both severe acidic and alkaline conditions. These results also indicated that the OCF_3-containing arenes may extend more applications in materials chemistry fields under severe conditions.[13]



Scheme 2 Reactions of the trifluoromethyl group on arenes.

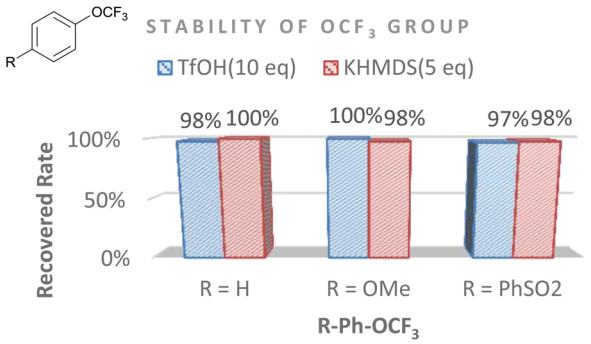
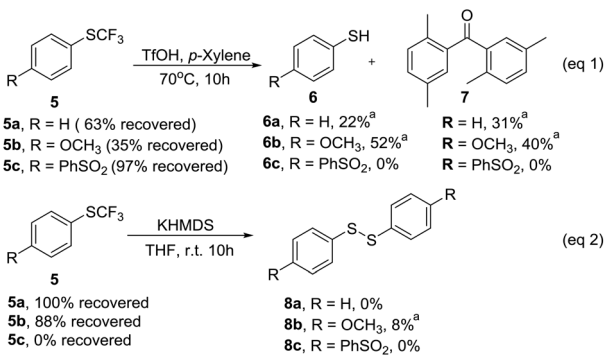


Fig. 1 The stability of the trifluoromethoxy group on arenes.

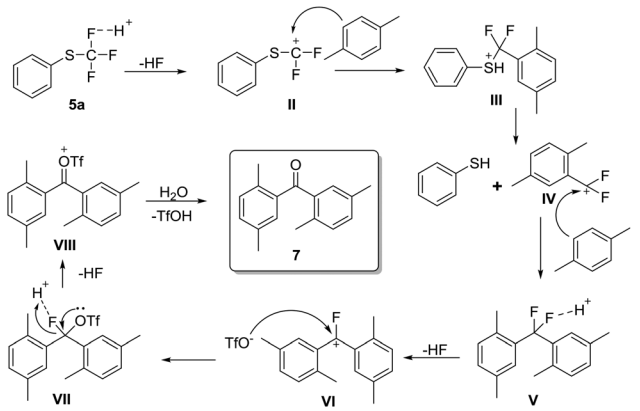
SCF_3 group

Compounds (**5a**, **5b** and **5c**) containing SCF_3 moieties demonstrated diverse stability (Scheme 3) under acidic conditions. The 4-phenylsulfonyl substrate **5c** was very stable even under a heated TfOH/toluene system with 97% recovery, while the 4-methoxy substrate **5b** converted to the corresponding 4-OMe-thiophenol in 52% yield, accompanied by the formation of compound **7** in 40% yield, indicating the formation of the difluorobenzylic cation. Compound **5a** also underwent a similar reaction with relatively low yields (22% of thiophenol, 31% of compound **7**). The above results showed that the electron donating moiety was unfavorable for the stability of the trifluoromethylthio moiety on arenes under strong acidic conditions.

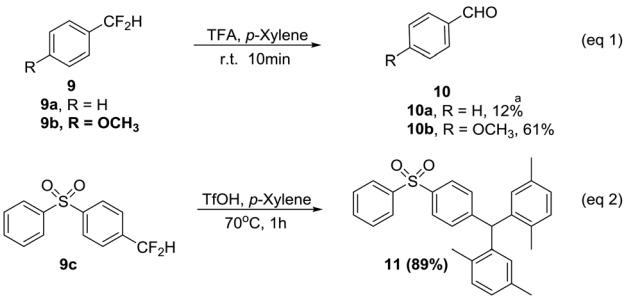
In addition, the plausible mechanism is proposed in Scheme 3.[7] In the presence of triflic acid, one C–F bond of compound **5** was cleaved *via* the strong interaction of CF···H$^+$ to release one molecule of HF and generate difluorophenylthio carbocation species **II**, which was then captured by the solvent *p*-xylene to give carbocation **III**. Subsequent cleavage of the C–S bond of **III** formed cation **IV** with the release of one molar thiophenol. The cation **IV** continued to react with *p*-xylene to form **V**, followed by second acid-mediated C–F bond cleavage to achieve the monofluorophenylthio cation **VI**. Then, it was captured by a triflate anion and experienced a third C–F



Scheme 3 Reactions of the trifluoromethylthio group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.



Scheme 4 Plausible mechanism for the reaction of the SCF_3 group and TfOH.



Scheme 5 Reactions of the difluoromethyl group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.

cleavage to give intermediate **VIII**, which was quenched with water to give compound **7** (Scheme 4).

Compounds **5a**, **5b** and **5c** also demonstrated different stabilities in the KHMDS/THF system (Scheme 3, eqn (2)). Substrate **5a** was very stable with 100% recovery. For substrate **5b**, 8% yield of 1,2-bis(4-methoxyphenyl)disulfane (**8b**) was detected by GC-MS, indicating the formation of *p*-OMe-thiophenol, which experienced oxidation to produce a phenyl disulfide compound. Compound **5c** remained unchanged in the NaOMe system, while it was completely deteriorated into an unidentified complex in the presence of KHMDS or KO^{t}Bu, indicating that electron-withdrawing substitution would reduce the stability under basic conditions (see Table S3† for details). We also tried every way but failed to synthesize 4-(phenylsulfonyl)benzenethiol and compound **8c**, which might explain why this reaction turned into complete chaos.

Based on the above observation, it could be speculated that the SCF_3 group exhibited less stability than the OCF_3 group under both acidic and basic conditions. The plausible reason could be that the electronegativity of sulfur is smaller than oxygen, which makes sulfur more polarizable, so the C–S bond is more vulnerable than the O–C bond. Clearly, the presence of an electron-withdrawing group (phenylsulfonyl) at the benzene ring prevented the formation of an intermediate carbocation, and thus increased the stability of the C–F bond under strong acidic conditions, while the electron-donating OMe group acted oppositely. Similarly, the *p*-OMe group on the phenyl ring also promoted the cleavage of CF_3 and SCF_3 on the arene under severe basic conditions, while the phenylsulfonyl group demonstrated poor stability under such conditions.

CF_2H group

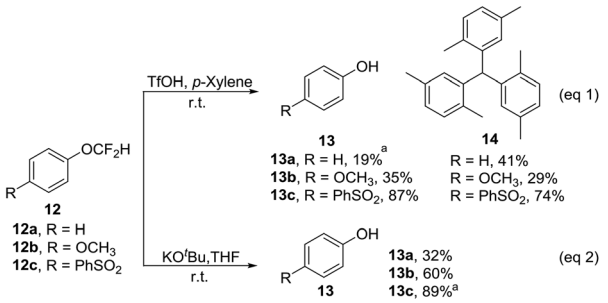
Compounds containing the CF_2 group (**9a**, **9b** and **9c**) manifested diverse stability under different acidic conditions. Compounds **9a** and **9b** deteriorated chaotically to unidentified products in the TfOH/toluene system, while they converted to the corresponding benzaldehydes (**10a** and **10b**) in the TFA/*p*-xylene system with 12% and 61% yields, which was fully consistent with the reference.[6,11,14] To our surprise, when substrate **9c** was stirred with TfOH in *p*-xylene, *p*-xylene-containing compound **11** was achieved in excellent yield (89%) instead of benzaldehyde. The possible mechanism was as follows, the C–F bond was broken *via* CF$\cdots$H$^+$ interaction and the newly formed carbocation reacted with *p*-xylene to furnish compound **11** (Scheme 5).

In the presence of KHMDS, substrates **9a** and **9b** remained stable while compound **9c** rapidly decomposed to a messy and unidentified mixture, also indicating the instability of the phenylsulfonyl group under these conditions (see Table S4† for details).

OCF_2H group

The C–O bonds of three difluoromethoxy substrates **12a**, **12b** and **12c** were broken to give the corresponding phenols (**13a**, **13b**, **13c**) in moderate to good yields (19% to 87%).[15] Simultaneously, the formation of tri(2,5-dimethyl-phenyl)-methane (**14**) in moderate yields (29%–74%) was also observed, which indicated the formation of a carbocation during this process. In addition, all the three substrates were very stable in the TFA/toluene system even at elevated temperatures (see Table S5†).

In the presence of KHDMS, the three substrates **12a**, **12b** and **12c** were decomposed to an unidentified mixture. With KO^{t}Bu, they were decomposed to the corresponding phenols **13a–13c** in moderate to good yields (32%–89%). Further investigation into the NaOMe/THF system revealed that three substrates demonstrated decreased stability in the order of **12a** > **12b** > **12c** (in 93%, 76%, 43%, respectively, see Table S5†). It has been known that efficient difluoromethylations of phenols with difluorocarbene reagents are generally achieved in the presence of water and a base (such as KOH).[16] We speculated that the decomposition of dufluoromethyl ether (**12a–c**) may be attributed to the existence of a strong base (KO^{t}Bu) in non-aqueous solution. The strong base deprotonates the proton of the CF_2H group, and the resulting $ArOCF_2^-$ undergoes decompositions such as α-elimination reactions, eventually giving ArO^- as a major product (Scheme 6).



Scheme 6 Reactions of the difluoromethoxy group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.

SCF_2H group

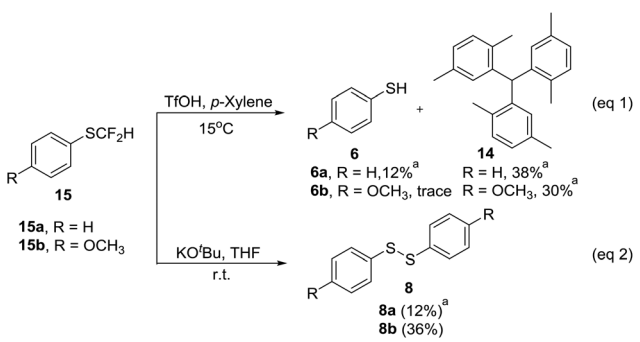
For difluoromethylthio-containing compounds, the 4-phenyl sulfonyl derivative **15c** was too unstable to be obtained after arduous efforts. In the TfOH/*p*-xylene solution, both compounds **15a** and **15b** deteriorated to the corresponding thiophenols accompanied by a moderate yield of compound **14**, indicating the breakdown of the C–S bond and the formation of the difluoro carbocation. While in the TFA/toluene system, the two compounds were very stable even under heated conditions with more than 90% recovery (see Table S6† for details).

Compounds **15a** and **15b** were completely deteriorated to an unidentified complex when treated with KHDMS/THF. In the presence of KO^{t}Bu, the two compounds converted to the corresponding phenyl disulfides **8a** and **8b** in low yields (12% and 36%, respectively, Scheme 7, eqn (2)), indicating the formation of thiophenol.

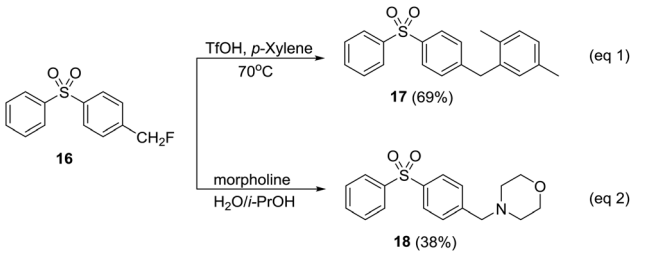
CH_2F group

Fluoromethyl benzene and 1-(fluoromethyl)-4-methoxybenzene were too difficult to be obtained due to their volatility and instability. Therefore, only 1-(fluoromethyl)-4-(phenylsulfonyl)-benzene (**16**) was prepared to perform the following experiments.

As shown in Scheme 8, in the presence of TfOH, the C–F bond of **16** was activated and compound **17** was obtained in



Scheme 7 Reactions of the difluoromethylthio group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.



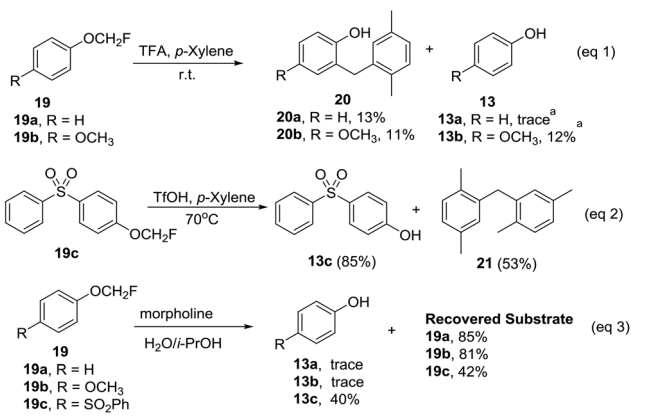
Scheme 8 Reactions of the monofluoromethyl group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.

69% yield (Scheme 8, eqn (1)), which confirmed the production of the 4-(phenylsulfonyl)benzyl cation and the following electronic addition reaction with *p*-xylene, while TFA was not capable of activating the C–F bond even under heated conditions (see Table S7†).

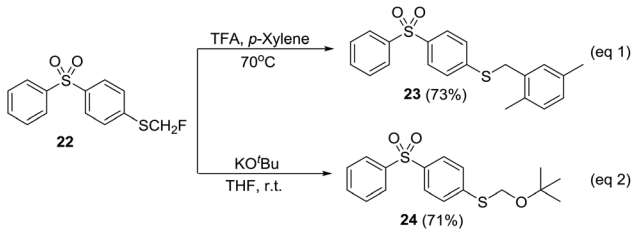
Compound **16** deteriorated and turned into unidentified products in the presence of KHDMS or KO^{t}Bu, while it remained stable in the NaOMe/THF system (see Table S7† for detail). It reacted with morpholine to obtain compound **18** in 38% yield in the H_2O/i-PrOH system, which was fully consistent with Paquin's report (Scheme 8, eqn (2)).[8,17]

OCH_2F group

Monofluoromethoxy compounds **19a** and **19b** deteriorated completely when treated with TfOH, while interestingly, they were converted to the corresponding diphenyl methylene derivatives **20a** and **20b** in TFA/*p*-xylene with 13% and 11% yields, respectively, (Scheme 9, eqn (1)) accompanied by a little of the corresponding phenols **13a** and **13b**. The above result revealed that compounds **20a** and **20b** probably experienced the following mechanism, the C–F bonds of two substrates were disrupted by TFA to obtain phenoxy-methylene cations, followed by the rearrangement of the cation to give the *ortho*-hydroxy benzyl cation, which reacted with *p*-xylene to furnish compound **20** finally.[18]



Scheme 9 Reactions of the monofluoromethoxy group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.



Scheme 10 Reactions of the monofluoromethylthio group on arenes. Yields are of the isolated products. (a) The yield was determined by GC-MS.

Different from compounds **19a** and **19b**, in the presence of TfOH, the phensulfonyl derivative **19c** decomposed to phenol **13c** in 85% yield, accompanied by 53% yield of bis(2,5-dimethylphenyl)methane (**21**) (Scheme 9, eqn (2)).

Furthermore, the three compounds were extremely stable in the presence of KHMDS and KO^{t}Bu even under heated conditions (see Table S8†), while in the morpholine/H_2O/i-PrOH solution, they displayed different stabilities. 85% and 81% of substrates **19a** and **19b** recovered with trace amounts of **13a** and **13b** were detected, in comparison with 42% recovery of **19c** and 40% of **13c**. This result indicated that the electron-withdrawing group was more favorable to activate the OCH_2F moiety on the arene (Scheme 9, eqn (3)).[17]

SCH_2F group

Similar to monofluoromethyl derivatives, only one monofluoromethylthio arene substrate **22** was prepared due to the instability of other derivatives at ambient temperature or silica gel. Interestingly, when it was treated with TfOH/*p*-xylene, an electrophilic addition product **23** was produced in 73% yield (Scheme 10, eqn (1)), indicating the formation of the phenylthiomethylene cation.

Compound **22** was unstable in the presence of KHDMS/THF with the formation of an unidentified complex, while to our surprise, when treated with KO^{t}Bu, a nucleophilic substitution reaction occurred and compound **24** was produced in 71% yield (Scheme 9, eqn (2)); this is the first report on the nucleophilic substitution reaction of the SCH_2F moiety. Our result also confirmed the good stability of the phenylthiomethylene cation.

Conclusions

Overall, we have carefully evaluated the stability and reactivity of tri-, di- and monofluoromethyl/methoxy/methylthio moieties on arenes under acidic and basic conditions, and the general results are summarized in Table 1.

Among all the substrates containing tri-, di- and monofluoromethyl, methoxy and methylthio groups, the trifluoromethyl and trifluoromethoxy groups on arenes definitely exhibit the highest stability under both acidic and alkaline conditions. The monofluoromethyl and monofluoromethylthio derivatives are difficult to prepare and they demonstrated the lowest stability under different conditions, which also seriously restricts their wide application in different chemistry fields.

The C–F bond is the strongest bond that carbon can form. This awareness, to a certain extent, overgeneralized the whole idea about the stability and reactivity of the C–F bond. According to a previous report, the strength of the C–F bond is slightly affected by the number of fluorine on the carbon atom. Due to the strongest electronegativity of the fluorine atom, the increasing number of the fluorine atom in the $CH_{3-n}F_n$ group leads to more occupation of the p-orbital of the hybrid orbital of the carbon atom, which makes the ratio of the s-orbital of the C–H bond increased and thus the bond becomes stronger, also indicating the stronger acidity of the C–H bond.[2] Therefore, replacement of hydrogen with fluorine can stabilize the whole fluoro-containing group against severe conditions, which was consistent with the results in our study. Overall, as we can summarize from all the above results, these fluorine-containing moieties demonstrated a rough stability sequence of OCF_3 > SCF_3, CF_3 > OCF_2H > CF_2H, SCF_2H > OCH_2F, CH_2F, SCH_2F; while under basic conditions, the sequence is OCF_3 > SCF_3 > CF_3, CF_2H > OCF_2H, SCF_2H, OCH_2F, CH_2F.

Experiment section

Unless otherwise noted, solvents and reagents were purchased from commercial sources and used as received. DMF was dried over CaH_2 and purified by distillation before being used. THF was freshly distilled from Na before use. And all experimental manipulations were carried out on the bench. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz NMR spectrometer. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of the residual solvent peak: $CHCl_3$ in $CDCl_3$: δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. For the isolated compounds, ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Data for ^{1}H, ^{13}C and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad). Coupling constants are reported in hertz (Hz). HRMS data were obtained using ESI.

Preparation of substrates

CF_3-containing substrates (**1a**, **1b**), OCF_3-containing substrates (**4a**, **4b**), SCF_3-containing substrates (**5a**), OCF_2H-containing substrates (**11a**) and SCF_2H containing substrates (**14a**) were either purchased commercially or used directly from lab resources.

CF_3-containing substrates

1-(Phenylsulfonyl)-4-(trifluoromethyl)benzene (1c).[19] A mixture of 1-iodo-4-(trifluoromethyl)benzene (2.71 g, 10.0 mmol), sodium benzenesulfinate (1.96 g, 12.0 mmol), copper iodide (190 mg, 1 mmol), L-proline sodium salt (274 mg, 2.0 mmol)

Table 1 General results of substrates under acidic or basic conditions

Structure	TfOH, 70 °C	TfOH, r.t.	TFA, 70 °C	TFA, r.t.	CH_3COOH, r.t.,	KHMDS/THF, r.t.	KO^{t}BU/THF, r.t.	MeONa/THF, r.t.	Morpholine, 70 °C
Ph-CF_3									
p-MeOPhCF_3	—	M	H	—	—	M	H	—	H
p-PhSO_2PhCF_3	H	H	—	—	—	L	H	—	H
PhOCF_3	H	H	—	—	—	H	—	—	H
p-MeO-PhOCF_3	H	H	—	—	—	H	—	—	H
p-PhSO_2-PhOCF_3	H	H	—	—	—	H	—	—	H
PhSCF_3	M	H	—	—	—	H	—	—	H
p-MeO-PhSCF_3	M	H	—	—	—	M	M	H	H
p-PhSO_2-PhSCF_3	H	H	—	—	—	H	—	—	H
PhCF_2H	—	L	H	—	—	H	—	—	H
p-MeO-PhCF_2H	—	L	L	L	H	H	—	—	H
p-PhSO_2-PhCF_2H	L	M	H	H	—	L	H	—	H
PhOCF_2H	L	M	H	—	—	L	L	H	H
p-MeO-PhOCF_2H	L	M	H	—	—	L	L	M	H
p-PhSO_2-PhOCF_2H	L	L	H	—	—	L	L	M	H
PhSCF_2H	—	L	H	H	—	L	L	M	H
p-MeO-PhSCF_2H	—	L	H	H	—	L	L	H	H
p-PhSO_2-PhSCF_2H	Unstable in silica gel								
PhCH_2F	Not obtained								
p-MeO-PhCH_2F	Unstable in silica gel								
p-PhSO_2-PhCH_2F	L	L	H	H	—	—	L	H	L
Ph-OCH_2F	—	—	L	L	H	H	—	—	M
p-MeO-PhOCH_2F	—	—	L	L	H	H	—	—	M
p-PhSO_2-PhOCH_2F	L	L	H	H	—	H	—	—	M
Ph-SCH_2F	Not obtained								
p-MeO-PhSCH_2F	—	L	L	L	H	—	L	H	M
p-PhSO_2-PhSCH_2F	Unstable in silica gel								

All substrates are *p*-substituted. H represents high stability (recovered rate ≥90%). M represents medium stability (recovered rate ≥20%). L represents low stability (recovered rate <20%).

and DMSO (15 mL) in a sealed tube was heated to 80 °C under argon. After cooling to room temperature, H_2O was added to the mixture and the mixture was extracted with ethyl acetate three times. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the resulting residual was purified by silica gel column chromatography with ethyl acetate and *n*-hexane to give products. White solid, 2.31 g, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 6.8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.2 (s, 3F).[19]

OCF_3-containing substrates

1-(Phenylsulfonyl)-4-(trifluoromethoxy)benzene (4c). Compound **4c** was prepared according to the method of **1c**, with 1-iodo-4-(trifluoromethoxy)benzene as the starting material. Light yellow solid, 3.87 g, 78% yield, mp 56.5–58.4 °C; ^{1}H NM1R (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 141.2, 140.1, 133.6, 120.0, 129.6, 127.8, 121.2, 120.2 (q, $^1J_{C-F}$ = 259.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.7 (s, 3F). HRMS (ESI): calcd for $C_{13}H_9F_3O_3S$ $(M + H)^+$ m/z 303.0297, found: 303.0301.

SCF_3-containing substrates

(4-Methoxyphenyl)(trifluoromethyl)sulfane (5b). In a glove-box, KF (102 mg, 1.75 mmol) was added to an oven-dried Schlenk tube equipped with a stir bar. Then the Schlenk tube was sealed with a septum and brought to the bench with the additon of anhydrous DMF (10 mL) and 1,2-bis(4-methoxyphenyl)disulfane (1.95 g, 7.0 mmol) subsequently. Then, trimethyl(trifluoromethyl)silane (1.99 g, 14.0 mmol) was syringed into the tube slowly and the mixture was stirred at room temperature for 3 h. Water was added to stop the reaction and the resulting mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $NaSO_4$. After the removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography. Colorless oil, 771 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −44.1 (s, 3F).[20]

(4-(Phenylsulfonyl)phenyl)(trifluoromethyl)sulfane (5c). Compound **5c** was prepared according to the method of **1c**, with (4-iodophenyl)(trifluoromethyl)sulfane as the starting material. White solid, 2.07 g, 65% yield, mp 68.3–70.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (t, J = 8.0 Hz, 4H), 7.76 (d, J = 8.4 Hz, 2H), 7.61 (t, J = 6.8 Hz, 1H), 7.54 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 140.8, 136.2, 133.9, 130.9, 129.7, 129.2 (q, $^1J_{C-F}$ = 307 Hz), 128.7, 128.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −41.5 (s, 3F). HRMS (ESI): calcd for $C_{13}H_{10}F_3O_2S_2$ $(M + H)^+$ m/z 319.0069, found: 319.0069.

CF_2H-containing substrates

Difluoromethylbenzene (9a). At room temperature, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate)(27 g, 84.7 mmol) and sodium persulfate (2.5 g, 10.6 mmol) were added under an argon atmosphere to a 100.0 mL Schlenk tube equipped with a stir bar. H_2O (20 mL) and CH_3CN (20 mL) were added and stirred for 5 min. Then toluene (1.9 g, 21.2 mmol) and $AgNO_3$ (719.0 mg, 4.2 mmol) were added under an argon atmosphere. The mixture was heated to 80 °C and stirred for 8 hours. After the reaction was completed, the reaction mixture was extracted with Et_2O and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography with pure n-hexane to give the product. Colorless liquid, 1.07 g, yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.52–7.39 (m, 4H), 6.65 (t, J = 56.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −110.6 (d, J = 56.4 Hz, 2F).[21]

1-(Difluoromethyl)-4-methoxybenzene (9b). In a glovebox, CuI (0.95 g, 5 mmol) and CsF (2.27 g, 15 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. Then the Schlenk tube was sealed with a septum and brought to the bench. After addition of anhydrous NMP (10.0 mL) and 1-iodo-4-methoxybenzene (1.2 g, 5 mmol), (difluoromethyl)trimethylsilane (3.1 g, 25 mmol) was added into the tube slowly while stirring. The mixture was stirred at 120 °C for 24 h. The mixture was cooled to room temperature and diluted with diethyl ether. The mixture was extracted with Et_2O and H_2O, and the organic layer was dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography with hexane/ethyl acetate as the eluent to give the product. Colorless oil, 612 mg, yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.45 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.61 (t, J = 56.0 Hz, 1H), 3.84 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −108.2 (d, J = 56.4 Hz, 2F).[22]

1-(Difluoromethyl)-4-(phenylsulfonyl)benzene (9c). At room temperature, benzenesulfonamide (1.57 g, 10.0 mmol), iodobenzene (4.08 g, 20.0 mmol) and triflic anhydride (2.82 g, 10 mmol) were mixed with $Cl_2CHCHCl_2$ (15 mL)and heated to 120 °C for 12 hours under a nitrogen atmosphere. The mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography with hexane/ethyl acetate as the eluent to give the product 1-iodo-4-(phenylsulfonyl)benzene as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 7.92 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H).[23] In a glovebox, CuCl (594.0 mg, 6.0 mmol) and KO^{t}Bu (1.3 g, 12.0 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. Then, the Schlenk tube was sealed with a septum and brought to the bench. After addition of DMF (5.0 mL), (difluoromethyl) trimethylsilane (1.49 g, 12.0 mmol), 1,10-phenanthroline (1.08 g, 6.0 mmol) and 1-iodo-4-(phenylsulfonyl)benzene (1.24 g, 5.0 mmol) were added subsequently to the mixture under an argon atmosphere. The reaction mixture was stirred at room temperature for 4 hours and then treated with diethyl ether and H_2O. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography with hexane/ethyl acetate to give the final product.[24] White solid, 643 mg, 48% yield, mp 89.4–91.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 8.04 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 6.67 (t, J = 56.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 141.1, 139.1, 133.7, 129.6, 128.3, 128.0, 126.8 (t, $^2J_{C-F}$ = 6.0 Hz), 113.5 (t, $^1J_{C-F}$ = 239.0 Hz).^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −112.8 (d, J = 56.4 Hz, 2F). HRMS (ESI): calcd for $C_{13}H_{11}F_2O_2S$ $(M + H)^+$ m/z 269.0442, found: 269.0444.

OCF_2H-containing substrates

1-(Difluoromethoxy)-4-methoxybenzene (12b). In a three-necked bottle, KOH (5.09 g, 91 mmol) was added to a mixture of 4-methoxyphenol (1.24 g, 10 mmol) in H_2O/dioxane (20 mL, 10 mL). Then dichlorofluoromethane was bubbled into the bottle and the mixture was stirred at 80 °C. After the reaction completed, the mixture was cooled to room temperature and treated with Et_2O and H_2O. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography with hexane/ethyl acetate to provide the target compound. Colorless liquid, 748 mg, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.07 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H), 6.42 (t, J = 74.4 Hz, 1H), 3.79 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −80.47 (d, J = 37.6 Hz, 2F).[25]

1-(Difluoromethoxy)-4-(phenylsulfonyl)benzene (12c). Compound **11c** was prepared according to the method of **11b**, with 4-(phenylsulfonyl)phenol as the starting material. White solid, 2.01 g, 71% yield, mp 46.5–48.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.95 (t, J = 9.6 Hz, 4H), 7.58 (t, J = 6.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.57 (t, J = 72.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 141.6, 138.4, 133.5, 130.1, 129.5, 127.7, 119.7, 115.3 (t, $^1J_{C-F}$ = 261.0 Hz).^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −87.30 (d, J = 37.6 Hz, 2F). HRMS (ESI): calcd for $C_{13}H_{11}F_2O_3S$ $(M + H)^+$ m/z 285.0391, found: 285.0397.

SCF_2H-containing substrates

(Difluoromethyl)(4-methoxyphenyl)sulfane (15b). Compound **14b** was prepared according to the method of **11b**, with

4-methoxybenzenethiol as the starting material. Light yellow liquid, 779 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.52 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.63 (t, J = 57.6 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −92.29 (d, J = 52.6 Hz, 2F).

CH_2F-containing substrates

1-(Fluoromethyl)-4-(phenylsulfonyl)benzene (16).[26] At room temperature, 1-methyl-4-(phenylsulfonyl)benzene (2.3 g, 10 mmol) was added into a Schlenk tube equipped with a stir bar. Then Selectfluor (5.3 g, 15 mmol), $Na_2S_2O_8$ (3.6 g, 15 mmol) and MeCN/H_2O (10 mL, 10 mL) were added sequentially. The mixture was stirred at 80 °C in the sealed tube for 12 hours. After cooling down, the resulting mixture was extracted with CH_2Cl_2/H_2O and the organic layer was dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography with hexane/ethyl acetate to give the final product. White solid, 1.02 g, 40% yield, mp 106.7–111.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.99–7.44 (m, 4H), 7.58 (t, J = 6.8 Hz, 1H), 7.53–7.48(m, 4H), 5.43 (d, J = 47.2 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 141.9, 141.5, 133.4, 129.5, 128.2, 127.8, 127.3 (d, $^2J_{C–F}$ = 7.0 Hz), 83.3 (d, $^1J_{C–F}$ = 169.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −214.81 (t, J = 47.0 Hz, 1F). HRMS (ESI): calcd for $C_{13}H_{12}FO_2S$ $(M + H)^+$ m/z 251.0537, found: 251.0540.

OCH_2F-containing substrates

(Fluoromethoxy)benzene (19a). At room temperature, phenol (9.4 g, 0.1 mol), DMF (40 mL) and NaH (60 wt%, 4.4 g, 0.11 mol) were added sequentially in a pressure tube. After stirring for 15 minutes, chlorofluoromethane was then bubbled into the mixture for about 30 minutes. The tube was sealed and stirred at 80 °C for 3–6 hours. The mixture was cooled down and extracted with Et_2O/H_2O, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by distillation. Colorless liquid, 2.5 g, 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.34 (t, J = 8.4 Hz, 2H), 7.12–7.08 (m, 3H), 5.70 (d, J = 54.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −148.49 (t, J = 56.4 Hz, 1F).[27]

1-(Fluoromethoxy)-4-methoxybenzene (19b). Compound **19b** was prepared according to the method of **19a**, with 4-methoxyphenol as the starting material. Colorless liquid, 951 mg, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.03 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 5.64 (d, J = 55.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −147.36 (t, J = 56.4 Hz, 1F).[27]

1-(Fluoromethoxy)-4-(phenylsulfonyl)benzene (19c). Compound **19c** was prepared according to the method of **19a**, with 4-(phenylsulfonyl)phenol as the starting material. White solid, 1.5 g, 55% yield, mp 67.1–70.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.93 (d, J = 7.6 Hz, 4H), 7.56 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 5.74 (d, J = 53.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 141.6, 140.4, 133.5, 129.5, 129.1 (d, $^2J_{C–F}$ = 3.0 Hz), 128.5, 127.8, 86.6 (d, $^1J_{C–F}$ = 217.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −151.12 (t, J = 52.6 Hz, 1F). HRMS (ESI): calcd for $C_{13}H_{12}FO_3S$ $(M + H)^+$ m/z 267.0486, found: 267.0492.

SCH_2F-containing substrates

(Fluoromethyl)(4-(phenylsulfonyl)phenyl)sulfane (22). In a three-necked bottle, 4-aminobenzenethiol (6.25 g, 50.0 mmol) was mixed with 30 mL water and the solution was cooled to 0 °C. Then concentrated HCl (45.0 mL) and concentrated H_2SO_4 (19.0 mL) were added into the bottle slowly. After the mixture was stirred for 10 min at 0 °C, sodium nitrite was added in 4 portions and the mixture was stirred for another 1 h. Afterwards, urea (0.3 g, 5.0 mmol) and a solution of potassium iodide (16.6 mg, 100.0 mmol) in 80.0 mL of water were added in portions, and the resulting mixture was stirred for 5 hours at 0 °C. The disappearance of the starting material was checked by thin layer chromatography. The mixture was then extracted with EtOAc and the organic layer was washed with $Na_2S_2O_3$ solution, and evaporated under reduced pressure. The crude product was washed with ethanol and filtered to afford 1,2-bis(4-iodophenyl)disulfane as a yellow solid.[28]

To a round-bottom flask capped with a rubber septum were added anhydrous THF (30.0 mL) and 1,2-bis-(4-iodophenyl)disulfane (4.7 g, 10 mmol) under argon. The flask was immersed in an ice/water bath and sodium borohydride (1.51 g, 40 mmol) was added in portion to the mixture. The color of the mixture turned to red-brown immediately and the mixture became homogeneous. After 8 h, the reaction was quenched with cold water and acidified with diluted hydrochloride acid. The precipitated product was filtered, washed with water, and dried to give 4-iodobenzenethiol as a light yellow solid.[29]

(Fluoromethyl)(4-iodophenyl)sulfane was achieved through the same method as for **19a**. And the resulting mixture was directly used for the next step by the same method as for **1c** to obtain (fluoromethyl)(4-(phenylsulfonyl)phenyl)sulfane (**22**). White solid, 465 mg, 33% yield, mp 97.2–98.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.92 (d, J = 8.4 Hz, 4H), 7.56 (t, J = 6.8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 5.73 (d, J = 53.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 142.0, 136.4, 133.3, 130.1, 129.4, 127.6, 116.9, 99.8 (d, $^1J_{C–F}$ = 221.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −151.08 (t, J = 52.6 Hz, 1F). HRMS (ESI): calcd for $C_{13}H_{12}FO_2S_2$ $(M + H)^+$ m/z 283.0257, found: 283.0258.

Typical procedure for the reactions of substrates and acid

At room temperature, the acid (2.0 mmol) and the solvent (toluene or *p*-xylene, 3.0 mL) were added into a sealed Schlenk tube equipped with a stir bar. Then the substrate (0.2 mmol) was added while stirring. The resulting mixture was stirred at room temperature for 10 hours and would be heated to 70 °C for another 10 hours if the substrate stayed stable at ambient temperature. The reaction was monitored by ^{19}F NMR spectroscopy using $PhSO_2CF_3$ as an internal standard.

Typical procedure for the reactions of substrates and base

At room temperature, the base (1.0 mmol) and the solvent (anhydrous THF or DMF, 3.0 mL) were added into an over-dried

Schlenk tube equipped with a stir bar. Then the substrate (0.2 mmol) was added while stirring. The resulting mixture was stirred at room temperature for 10 hours and heated to 50 °C for another 10 hours if the substrate stayed stable at ambient temperature. The reaction was monitored by ^{19}F NMR spectroscopy using 1-fluoronaphthalene as an internal standard.

Phenyl(*p*-tolyl)methanone (2a). White solid; isolated yield: 51%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.76 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 143.3, 138.0, 134.9, 132.2, 130.3, 129.9, 129.0, 128.2, 21.7.

(4-Methoxyphenyl)(*p*-tolyl)methanone (2b). White solid; isolated yield: 41%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.81 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 163.1, 142.6, 135.5, 132.4, 130.5, 130.0, 128.9, 113.5, 55.5, 21.6.

Phenyl(*o*-tolyl)methanone (3a). Colorless oil; isolated yield: 32%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.80 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.39 (td, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H), 7.30 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 138.6, 137.8, 136.8, 133.1, 131.0, 130.3, 130.1, 128.5, 128.4, 125.2, 20.0.

(4-Methoxyphenyl)(*o*-tolyl)methanone (3b). Colorless oil; isolated yield: 26%.^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.79 (d, J = 9.2 Hz, 2H), 7.37 (td, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H), 7.29–7.22 (m, 3H), 6.93 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 163.7, 139.2, 136.2, 132.5, 130.8, 130.6, 129.8, 127.9, 125.2, 113.7, 55.5, 19.8.

4-Methoxybenzenethiol (6b). Yellow solid; GC-MS yield: 52%. ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 7.25 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H).

Bis(2,5-dimethylphenyl)methanone (7). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.22–7.14 (m, 4H), 7.10 (s, 2H), 2.49 (s, 6H), 2.44 (s, 6H).

1,2-Bis(4-methoxyphenyl)disulfane (8b). White solid; isolated yield: 36%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.80 (s, 6H).

4-Methoxybenzaldehyde (10b). Colorless liquid; isolated yield: 61%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 9.89 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 7.2 Hz, 2H), 3.90 (s, 3H).

2,2′-((4-(Phenylsulfonyl)phenyl)methylene)bis(1,4-dimethylbenzene) (11). White solid; isolated yield: 89%, mp 151.1–159.1 °C. ^1H NMR (500 MHz, $CDCl_3$/TMS): δ 7.93 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 7.5 Hz, 2H), 6.43 (s, 2H), 5.65 (s, 1H), 2.18 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 142.0, 140.6, 139.5, 135.5, 133.4, 133.2, 130.8, 130.6, 129.9, 129.4, 127.8, 127.8, 127.6, 50.3, 21.3, 19.3. HRMS (ESI): calcd for $C_{13}H_{10}F_3O_2S_2$ $(2M + Na)^+$ m/z 903.3512, found: 903.3512.

4-Methoxyphenol (13b). White crystal; isolated yield: 35%. ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 8.92 (s, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 3.69 (s, 3H).

4-(Phenylsulfonyl)phenol (13c). White solid; isolated yield: 87%. ^1H NMR (500 MHz, DMSO-d_6/TMS): δ 10.64 (s, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H).

Tris(2,5-dimethylphenyl)methane (14). White solid, mp 182.3–185.5 °C. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.03 (d, J = 7.6 Hz, 3H), 6.94 (d, J = 7.6 Hz, 3H), 6.50 (s, 3H), 5.59 (s, 1H), 2.20 (s, 9H), 2.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 135.1, 133.6, 130.2, 129.9, 127.0, 47.3, 21.4, 19.1. HRMS (ESI): calcd for $C_{25}H_{29}$ $(M + H)^+$ m/z 329.2264, found: 329.2265.

1,4-Dimethyl-2-(4-(phenylsulfonyl)benzyl)benzene (17). White solid; isolated yield: 69%, mp 92.4–95.3 °C. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.93 (d, J = 6.0 Hz, 2H), 7.83 (d, J = 6.4 Hz, 2H), 7.55 (t, J = 6.0 Hz, 1H), 7.49 (t, J = 6.4 Hz, 2H), 7.24 (d, J = 6.8 Hz, 2H), 7.05 (d, J = 6.4 Hz, 1H), 6.98 (d, J = 6.0 Hz, 1H), 6.88 (s, 1H), 3.97 (s, 2H), 2.28 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 142.0, 139.3, 137.2, 135.8, 133.5, 133.2, 130.9, 130.6, 129.6, 129.3, 127.9, 127.8, 127.7, 39.4, 21.0, 19.3. HRMS (ESI): calcd for $C_{21}H_{20}O_2S$ $(2M + Na)^+$ m/z 695.2260, found: 695.2267.

4-(4-(Phenylsulfonyl)benzyl)morpholine (18). Yellow solid; isolated yield: 38%, mp 125.3–130.1 °C. ^1H NMR (500 MHz, $CDCl_3$/TMS): δ 7.95 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.52–7.47 (m, 4H), 3.68 (t, J = 4.5 Hz, 4H), 3.51 (s, 2H), 2.41 (t, J = 4.0 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 141.8, 140.5, 133.3, 129.8, 129.4, 127.9, 127.8, 67.1, 62.8, 53.7. HRMS (ESI): calcd for $C_{17}H_{20}NO_3S$ $(M + H)^+$ m/z 318.1158, found: 318.1173.

2-(2,5-Dimethylbenzyl)phenol (20a). White solid; isolated yield: 13%. ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 9.35 (s, 1H), 7.04–6.98 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.84–6.80 (m, 2H), 6.74 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 6.67 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz,1H), 3.79 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.9, 138.6, 134.4, 132.9, 130.1, 129.7, 129.5, 126.9, 126.5, 126.4, 118.8, 114.8, 32.3, 20.7, 18.7.

2-(2,5-Dimethylbenzyl)-4-methoxyphenol (20b). White solid; isolated yield: 11%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.08 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.88 (s, 1H), 6.75 (d, J = 8.8 Hz, 1H), 6.68 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 3.90 (s, 2H), 3.71 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 147.9, 137.2, 135.9, 133.8, 130.5, 130.0, 127.7, 127.5, 116.6, 116.3, 112.1, 55.8, 34.1, 21.1, 19.3.

Bis(2,5-dimethylphenyl)methane (21). White solid, isolated yield: 53%. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.09 (d, J = 7.6 Hz, 2H), 6.97 (d, J = 7.6 Hz, 2H), 6.72 (s, 2H), 3.85 (s, 2H), 2.25 (s, 6H), 2.24 (s, 6H).

(2,5-Dimethylbenzyl)(4-(phenylsulfonyl)phenyl)sulfane (23). White solid; isolated yield: 73%, mp 129.2–133.0 °C. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.93 (d, J = 6.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.08–7.06 (m, 2H), 7.00 (d, J = 8.0 Hz, 1H), 4.13 (s, 2H), 2.34 (s, 3H), 2.26 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ 145.7, 142.0, 138.2, 136.0, 133.8, 133.2, 133.1, 130.7, 130.5, 129.4, 128.9, 128.1, 127.7, 127.6, 35.7, 21.0, 18.8. HRMS (ESI): calcd for $C_{21}H_{20}O_2S_2$ $(2M + Na)^+$ m/z 759.1702, found: 759.1705.

(*tert*-Butoxymethyl)(4-(phenylsulfonyl)phenyl)sulfane (24). White solid; isolated yield: 71%, mp 65.6–70.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 7.92 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.57–7.52 (m, 3H), 7.49 (t, J = 6.5 Hz, 2H), 4.95 (s, 2H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 145.3, 141.9, 138.4, 133.2, 129.4, 128.1, 128.0, 127.6, 76.2, 66.7, 27.9. HRMS (ESI): calcd for $C_{17}H_{20}O_3S_2$ $(2M + Na)^+$ m/z 695.1600, found: 695.1617.

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