Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Jereb and K. Gosak, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C4OB02633K.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C4OB02633K

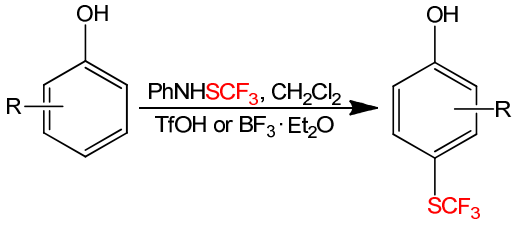
Acid-promoted direct electrophilic trifluoromethylthiolation of phenols

Marjan Jereb* and Kaja Gosak

Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, Večna pot 113, 1000 Ljubljana, Slovenia
Tel.: (++386) 1 479 8577 Fax: (++386) 1 241 9144, E-mail: marjan.jereb@fkkt.uni-lj.si

† Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of all products.

Graphical abstract



Textual abstract

Highly selective and effective, acid-promoted, electrophilic trifluoromethylthiolation of phenols is described.

The electrophilic aromatic ring trifluoromethylthiolation of variously substituted phenols was accomplished by $PhNHSCF_3$ (*N*-trifluoromethylsulfanyl)aniline **1** in the presence of $BF_3{\cdot}Et_2O$ **2** or triflic acid as promoters. The functionalization was exclusively *para*-selective; the phenols bearing unsubstituted both the *ortho*- and *para* positions in all cases solely gave the *para*-substituted SCF_3-products, while the *para*-substituted phenols gave the *ortho*-substituted SCF_3-products. 3,4-Dialkyl substituted phenols yielded the corresponding products according to the Mills-Nixon effect, and estrone and estradiol furnished biologically interesting SCF_3-analogues. The highly reactive catechol and pyrogallol gave the expected products smoothly in the presence of $BF_3{\cdot}Et_2O$, whereas less reactive phenols required triflic acid. 2-allylphenol gave the expected *p*-SCF_3 analogue, which underwent addition/cyclization sequence and furnished a new di-trifluoromethylthio substituted 2,3-dihydrobenzofurane derivative. Some additional transformations of 4-(trifluoromethylthio)phenol with NBS, NIS, HNO_3, HNO_3/H_2SO_4 and 4-bromobenzyl bromide were performed giving bromo-, iodo-, nitro- and benzyl substituted products. The latter derivative underwent Suzuki-Miyaura coupling with phenylboronic acid.

Introduction

The introduction of a fluorine atom or a fluorine-containing substituent into an organic molecule often favorably modulates the compounds' properties, thus making new functional and advanced materials.[1,2,3,4,5,6] The fluorinated organic molecules frequently possess enhanced stability, binding affinity and biological activity in comparison with their non-fluorinated precursors.[7,8] The trifluoromethyl group shares an exceedingly important part in the biologically relevant molecules, and number of the newly introduced trifluoromethylated substances in the pharmaceutical and medicinal chemistries has been growing considerably.[9,10,11] Consequently, there has been a strong interest in the direct introduction of CF_3- group

View Article Online
DOI: 10.1039/C4OB02633K

into organic molecules regardless of the approach via radical, nucleophilic or electrophilic mode, thus making trifluoromethylation a current topic of great interest.[12,13,14,15,16,17,18,19]

An interesting variety of CF_3- group is trifluoromethylthiol group SCF_3-, which considerably contributes to the enhanced lipophilicity, and is an indispensable moiety in the agrochemistry and in medicinal chemistry;[20] however its introduction received considerably less attention than CF_3- group. The 2'-SCF_3 substituted uridine derivative was found to be a powerful label for probing structure and function of RNA by ^{19}F NMR spectroscopy.[21]

Recently, significant progress in the introduction of SCF_3 moiety has been achieved.[22] The introduction of the SCF_3- group could be direct with CF_3SCl[23] or $(CF_3)_2S$,[24] (extremely noxious and hazardous gases that are not suitable for non-specialized laboratories) or indirect *i.e.* by interconversion of functional groups[25]. Nucleophilic and radical sources of SCF_3 group are often copper-[26] or silver-based[27] metallic reagents, $[NH_4][SCF_3]$;[28] furthermore, trifluoromethylthiolation can also be realized with a combination of two different sources of sulfur functionality and CF_3 group.[29] In particular, the popularity of electrophilic trifluoromethylthiolation has grown remarkably in the recent years; the new period began with the work of Billard, Langlois and coworkers.[30] They prepared $PhNHSCF_3$ and its derivatives: an easy handling electrophilic SCF_3-transfer agent into alkenes and alkynes,[31] indoles,[32] tryptamines,[33] organometallic species,[34] amines,[35] and allyl silanes.[36] In addition, terminal alkynes were trifluoromethylthiolated in the presence of a catalytic amount of base.[37] Internal alkynes reacted with $PhNHSCF_3$ yielding the corresponding 3-((trifluoromethyl)thio derivatives of indoles,[38] benzofuranes, benzothiophenes[39] and 1*H*-isochromen-1-ones.[40] Similarly, 4-((trifluoromethyl)thio)-*2H*-benzo[e][1,2]thiazine 1,1-dioxides were efficiently prepared in the presence of $BiCl_3$ in dichloroethane.[41] An interesting trifluoromethanesulfonyl hypervalent iodonium ylide able to deliver the trifluoromethylthiol group was developed recently.[42] *N*-(trifluoromethylthio)succinimide was utilized in Pd-catalyzed trifluoromethylthiolation of arenes,[43] while an *in-situ* formed reagent from $AgSCF_3$ and NCS was employed in functionalization of alkynes.[44] A new, thioperoxide[45,46] type of electrophilic trifluoromethylthiolating reagent was able to react with β-ketoesters, boronic acids,[47] alkynes and aliphatic carboxylic acids,[48] giving the corresponding SCF_3-substituted products. This thioperoxide reagent in combination with TMSOTf was also found to be a powerful activating agent of different thioglycosides;[49] additionally, the thioperoxide reagent was used in enantioselective catalytic trifluoromethylthiolations[50] as well as *N*-trifluoromethylthiophthalimide[51] and an $AgSCF_3$/trichloroisocyanuric acid system.[52] The latter system was also utilized in the synthesis of 3-((trifluoromethyl)thio)-4*H*-chromen-4-

View Article Online
DOI: 10.1039/C4OB02633K

ones.[53] Electrophilic trifluoromethylthiolation of various carbonyl compounds[54] and aromatics[55] was accomplished by a new *N*-((trifluoromethyl)thio)benzenesulfonamide type of reagent. *N*-trifluoromethylthiosaccharin was developed recently and utilized in the trifluoromethylation of alcohols, amines, thiols, electron-rich aromatics, aldehydes, ketones, acyclic β-ketoesters and alkynes.[56]

$PhNHSCF_3$ (*N*-trifluoromethylsulfanyl)aniline **1** is a simple and easy-handling electrophilic reagent for the direct introduction of the SCF_3- group into organic molecules. Its electrophilic power usually requires activation with appropriate promoters of the Lewis or Brønsted type. Its reactivity is mostly unexplored, and we decided to test it on phenols, since there are many biologically relevant phenols *i.e.* steroids of estrone type, epinephrine, thymol and others. We report on a direct and remarkably highly regioselective trifluoromethylthiolation of phenols with $PhNHSCF_3$ in combination with boron trifluoride etherate complex and triflic acid.

Results and disscussion

Initially, the reaction conditions were examined on phenol **3a** as a model substrate; the results are summarized in Table 1. Initially **3a** was reacted with **1** without activator, and remained unreacted (Table 1, entry 1). $BF_3{\cdot}Et_2O$ and *p*-$TsOH{\cdot}H_2O$ were found to be rather unpromising promoters for this reaction (entries 2–5).

Table 1 Optimization of the reaction conditions[a]

3a **4a**

Entry	Activator	Amount (equiv.)	Conversion (%)[b]
1	/	/	0
2	$BF_3{\cdot}Et_2O$	2.5	0
3		5	0
4	p-$TsOH{\cdot}H_2O$	2.5	0
5		5	0
6	CH_3SO_3H	1.5	0
7		2	30
8	TfOH	1.2	91
9		1.3	100 (77)[c]

[a] Conditions: **3a** (1 mmol), **1** (1.2–1.3 mmol), activator, DCM (10 mL), 14 h, rt. [b] Conversion determined by ^1H NMR. [c] Isolated yield.

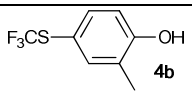
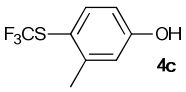
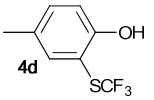
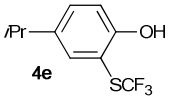
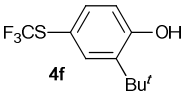
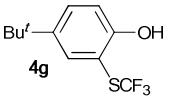
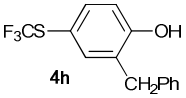
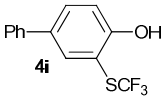
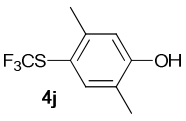
We decided to examine the role of considerably stronger activators, i.e. CH_3SO_3H (MSA) and triflic acid (TfOH). MSA was found somewhat better activator (entries 6 and 7), while TfOH was the promoter of choice (entries 8 and 9). In all cases, 4-trifluoromethylthiophenol **4a** was obtained, and no *ortho* substitution was noted. Results of the functionalization of different phenols are presented in Table 2. 2-methylphenol **3b** and 3-methylphenol **3c** both yielded 4-

View Article Online
DOI: 10.1039/C4OB02633K

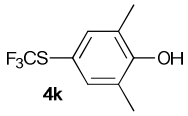
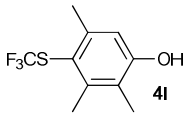
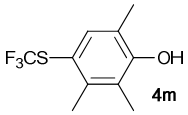
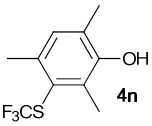
SCF_3-substituted products **4b** and **4c** exclusively (Table 2, entries 1 and 2). 4-methylphenol **3d** and 4-*i*-propylphenol **3e** yielded the corresponding 2-SCF_3-substituted products **4d** and **4e** as the sole products. In the cases of 2-*t*-butylphenol **3f** and 4-*t*-butylphenol **3g**, *ipso* substitution could have been observed; however, 4-SCF_3- **4f** and 2-SCF_3-substituted product **4g** were formed as the sole products (entries 5 and 6). Similarly, 2-benzylphenol **3h** yielded 4-SCF_3-substituted product **4h**, while no *ipso* substitution was observed. 4-phenylphenol **3i** was regioselectively transformed into its 2-SCF_3-substituted product **4i**. Reactions of 2,5-dimethylphenol **3j** and 2,6-dimethylphenol **3k** cleanly furnished their 4-SCF_3-substituted derivatives **4j** and **4k** (entries 9 and 10). 2,3,5-trimethylphenol **3l** and 2,3,6-trimethylphenol **3m** gave their 4-SCF_3-substituted derivatives **4l** and **4m** as the sole products (entries 11 and 12).

Table 2 Acid-promoted trifluoromethylthiolation of phenols[a]

3 **4**

Entry	Reactant	Product	Yield (%)[b]
1	*o*-cresol **3b**	 **4b**	81
2	*m*-cresol **3c**	 **4c**	79
3	*p*-cresol **3d**	 **4d**	80
4	4-*i*-propylphenol **3e**	 **4e**	82
5	2-*t*-butylphenol **3f**	 **4f**	64
6	4-*t*-butylphenol **3g**	 **4g**	87
7	2-benzylphenol **3h**	 **4h**	86
8	4-phenylphenol **3i**	 **4i**	48
9	2,5-dimethylphenol **3j**	 **4j**	90

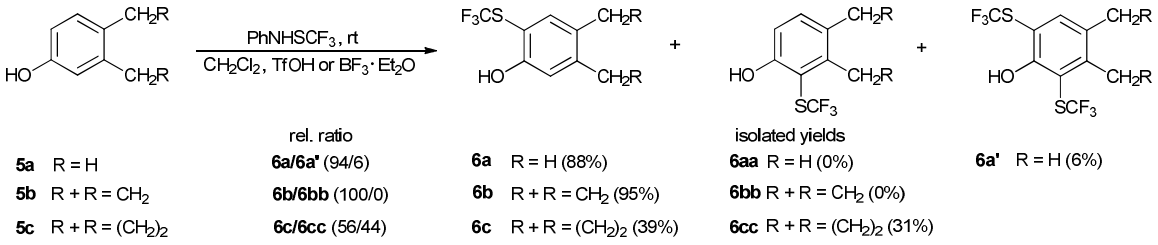
View Article Online
DOI: 10.1039/C4OB02633K

10	2,6-dimethylphenol **3k**	 **4k**	91
11	2,3,5-trimethylphenol **3l**	 **4l**	84
12	2,3,6-trimethylphenol **3m**	 **4m**	93
13	2,4,6-trimethylphenol **3n**	 **4n**	83

[a] Conditions: **3** (1 mmol), **1** (1.2–1.3 mmol), TfOH (1.2–5 mmol), DCM (10 mL), 14 h, rt. [b] Isolated yield.

2,4,6-trimethylphenol **3n** was an interesting substrate, because all potentially reacting positions were substituted. None of the possible *ipso* adducts was observed, but 2,4,6-trimethyl-3-trifluoromethylthiophenol **4n** was isolated as a sole product (entry 13).

Next, we examined the reactivity of 3,4-dimethylphenol **5a**, 5-indanol **5b** and 5,6,7,8-tetrahydro-2-naphthol **5c** (Scheme 1).

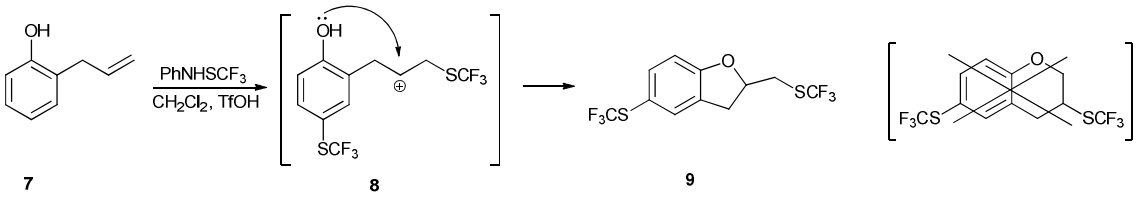


Scheme 1 The effect of structure of 3,4-dialkyl substituted phenols on trifluoromethylthiolation.

Such compounds possess unequally reactive *ortho* positions; the phenomenon is known as the Mills-Nixon effect.[57] **5a** furnished the expected **6a** as the major product, while no **6aa** was detected. Instead, double functionalization took place, yielding **6a'** as a minor product. The relative distribution ratio **6a**/**6a'** was 94/6. **5b** yielded only one expected product **6b**; whereas no **6bb** was detected. **5c** reacted in accordance with the anticipated reactivity giving **6c** and **6cc** in a relative ratio of 56/44. Regioselectivity of trifluoromethylthiolation of 3,4-dimethylphenol and 5-indanol is similar to the bromination reaction,[58] while bromination of 5,6,7,8-tetrahydro-2-naphthol was more selective (78/22) than trifluoromethylthiolation. Nitration of 3,4-dimethylphenol (57/43) and 5-indanol (58/42) with $NaNO_2/H_2O_2/H_2SO_4$ was less regioselective than trifluoromethylthiolation, while nitration was more selective in the case of 5,6,7,8-tetrahydro-2-naphthol (63/37).[59]

View Article Online
DOI: 10.1039/C4OB02633K

It is known that $PhNHSCF_3$ reacts with alkenes,[31] and we examined the reactivity of 2-allylphenol **7** due to the two diverse potential reacting sites (Scheme 2).



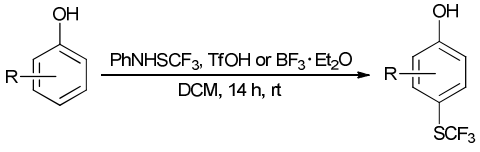
7 **8** **9**

Scheme 2 Double functionalization of 2-allylphenol with $PhNHSCF_3$.

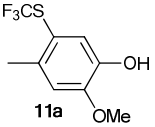
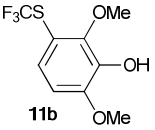
We established that **7** reacted with **1** in the presence of TfOH as phenol and as alkene, thus proposing a secondary carbocationic intermediate **8**. Reaction proceeded in dichloromethane in the absence of a good nucleophile, and phenolic oxygen atom took part in an intramolecular cyclization thus producing a five-membered product **9** as a novel type of trifluoromethylthiolated product. It appears that the stability of **8** was of crucial importance for the reaction selectivity. The other possible six-membered isomeric product originating from the reversed addition of $PhNHSCF_3$ to the double bond that would have generated a primary carbocation, was not observed. The structure of **9** was confirmed with NMR spectroscopy, and the key experiment was DEPT 135. The carbon atom attached to the $–SCF_3$ group appeared as a quartet in the same phase with the second aliphatic signal, whereas the third aliphatic signal was in an opposite phase. This was a clear indication that $–SCF_3$ group was attached to the CH_2-, and not to the CH- group.

The reactivity of highly reactive bicyclic- and alkoxy- and hydroxyphenols with $PhNHSCF_3$ is summarized in Table 3.

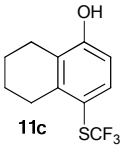
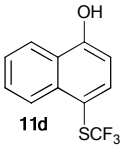
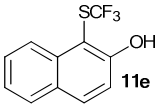
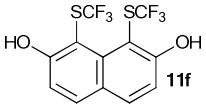
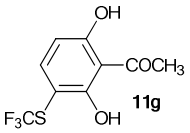
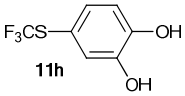
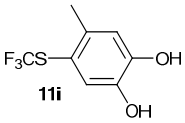
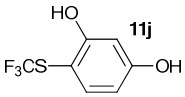
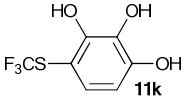
Table 3 Reactivity of the highly electron-rich phenols with $PhNHSCF_3$[a]



10 **11**

Entry	Reactant	Product	Yield (%)[b]
1	2-methoxy-4-methylphenol **10a**	 **11a**	97
2	2,6-dimethoxyphenol **10b**	 **11b**	84

View Article Online
DOI: 10.1039/C4OB02633K

3	5,6,7,8-tetrahydronaphth-1-ol **10c**	 **11c**	93
4	1-naphthol **10d**	 **11d**	95
5	2-naphthol **10e**	 **11e**	82
6	2,7-dihidroxynaphthalene **10f**	 **11f**	86
7	2',6'-dihydroxyacetophenone **10g**	 **11g**	79
8	catechol **10h**	 **11h**	70
9	4-methylcatechol **10i**	 **11i**	88
10	resorcinol **10j**	 **11j**	80
11	pyrogallol **10k**	 **11k**	60

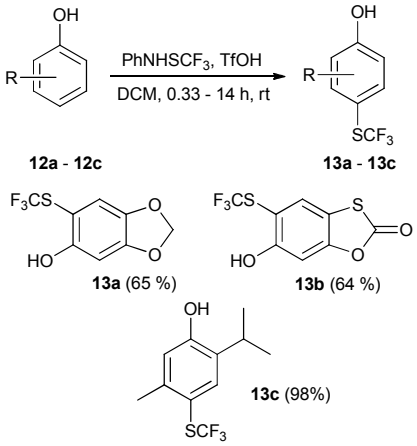
[a] Conditions: **10** (1 mmol), **1** (1.2–1.3 mmol), TfOH (1.3–4 mmol) or **2** (2–3 mmol), DCM (10 mL), 14 h, rt. [b] Isolated yield.

2-methoxy-4-methylphenol **10a** produced 6-SCF_3 analogue **11a** as a sole product, while 2,6-dimethoxyphenol **10b** selectively yielded its 3-SCF_3 derivative **11b** (Table 3, entries 1 and 2). 5,6,7,8,-tetrahydro-1-naphthol **10c** was regioselectively transformed into its 4-SCF_3 analogue **11c** in good yield. Transformation of 1-naphthol **10d** and 2-naphthol **10e** was completely selective in both cases. The former led to its 4-SCF_3 derivative **11d**, whereas the latter to its 1-SCF_3 analogue **11e** (entries 4 and 5). Additionally, 2,7-dihydroxynaphthalene **10f** was tested due to the possibility of double functionalization. Indeed, 1,8-diSCF_3 derivative **11f** was isolated as a single product in good yield. 2',6'-dihydroxyacetophenone **10g** was smoothly converted into its 3-SCF_3 derivative **11g** (entry 7). In continuation, some naturally occurring phenols were successfully transformed into their trifluoromethylthio analogues. Catechol **10h** selectively produced its 4-SCF_3 derivative **11h**, and 4-methylcatechol **10i** yielded its 5-SCF_3 derivative **11i** exclusively (entries 8 and 9). Functionalization of resorcinol **10j** smoothly

View Article Online
DOI: 10.1039/C4OB02633K

afforded its 4-SCF_3 analogue **11j** in a good yield. Highly oxidation-prone pyrogallol **10k** was also efficiently transformed into its 3-SCF_3 derivative **11k** (entry 11). It could be concluded that the reaction system $PhNHSCF_3$/activator is compatible with highly electron-rich phenols and the introduction of -SCF_3 groups took place efficiently without noticeable portion of oxidation.

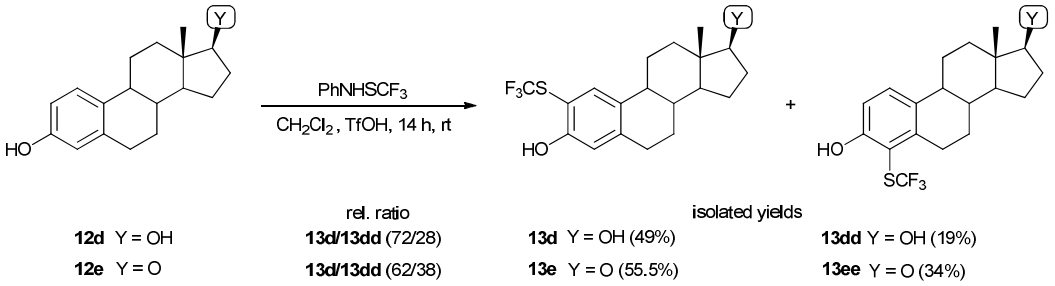
In addition, we tested some of the biologically relevant molecules possessing the phenolic functionality (Scheme 3). 3,4-(methylenedioxy)phenol **12a** as highly reactive substance afforded the corresponding 6-SCF_3 derivative **13a** as a sole product. The reaction was completed in 20 minutes, and the product **13a** was obtained in good yield. 6-hydroxy-1,3-benzoxathiol-2-one **12b** was successfully converted into its 5-SCF_3 derivative **13b** in spite of an acid-sensitive oxathiolone functional group. This is a good demonstration that the acidic reaction system is also compatible with the sensitive functionalities. Thymol **12c** was effectively transformed into its 4-SCF_3 derivative **13c** in high yield. Estrone **12d** and estradiol **12e** are important steroid hormones bearing the phenolic functionality. Both were regioselectively transformed into the corresponding *o*-SCF_3 analogues **13d**, **13dd**, **13e** and **13ee** (Scheme 4).



Scheme 3 Reactivity of some biologically active phenols with $PhNHSCF_3$.

Regioselectivity of functionalization of estrone is similar to the nitration reaction; however, the selectivity was higher in the case of nitration.[59]

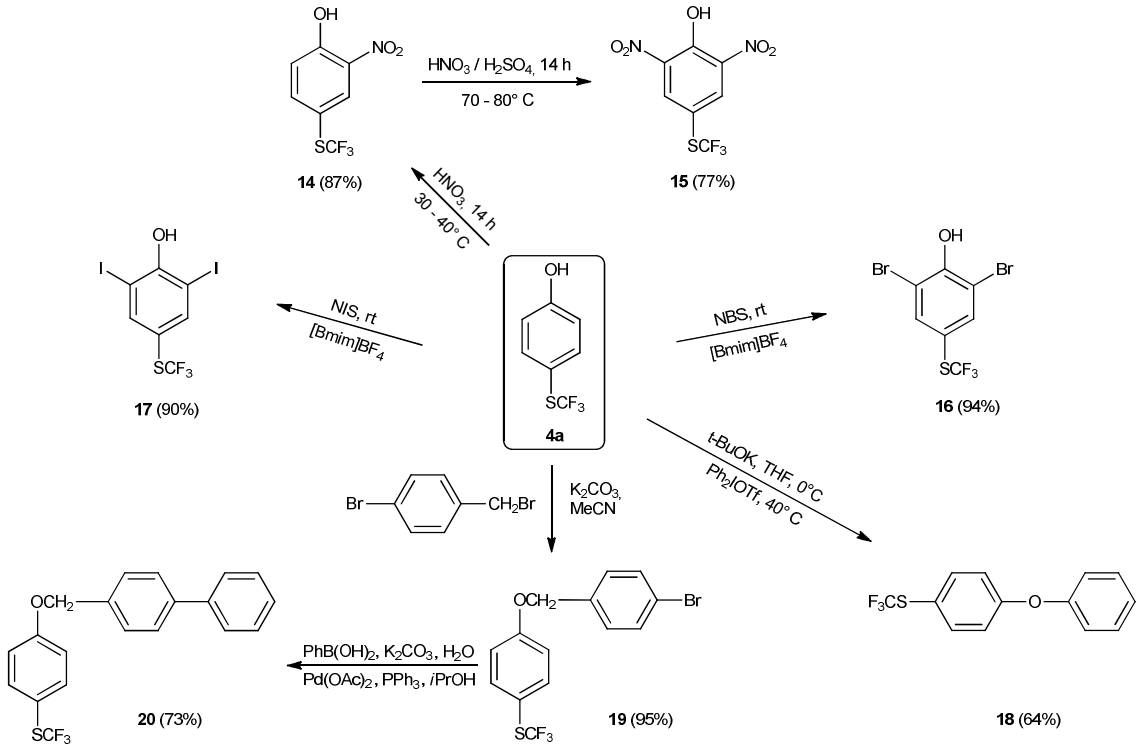
View Article Online
DOI: 10.1039/C4OB02633K



Scheme 4 Electrophilic trifluoromethylthiolation of estrogenic hormones with $PhNHSCF_3$.

In addition, some further functionalizations of 4-(trifluoromethylthio)phenol **4a** were studied (Scheme 5). The strong electron-withdrawing nature of the trifluoromethylthio group significantly influences the reactivity of such compounds. **4a** was nitrated with 65% HNO_3 under solvent-free reaction conditions in 14 hours at 30–40°C, selectively yielding mono-nitrated product **14**, and no over-nitration took place. The reason for the perfect selectivity is that dinitration required considerably more rigorous reaction conditions to occur: 70–80° C and the presence of concentrated sulfuric acid. Dinitrophenol derivative **15** was isolated in a 78% yield. The introduction of halogens is highly significant because of the possibility of additional reactions, particularly various cross-couplings. Bromination of **4a** with NBS in 1-methyl-3-butylimidazolium tetrafluoroborate $[Bmim]BF_4$ in the presence of small amount of water[60] afforded dibromo analogue **16** in 94% yield. Iodination was performed using the same reaction medium, producing diiodo derivative **17**. Preparation of diphenyl ether derivative **18** was accomplished using *t*-BuOK and diphenyliodonium triflate[61] in THF.

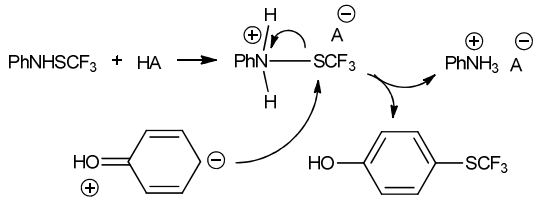
View Article Online
DOI: 10.1039/C4OB02633K



Scheme 5 Reactivity of 4-(trifluoromethylthio)phenol **4a** with different reagents

Finally, **4a** was converted into its 4-bromobenzyl ether **19**, which reacted with phenyl boronic acid in the presence of $Pd(OAc)_2$ and PPh_3 yielding a cross-coupled derivative **20** in a good yield.

A detailed reaction mechanism is not known; however, the most likely reaction pathway is an electrophilic one. The reaction selectivity *para*- and *ortho*- is one of the strong arguments in favor of the electrophilic pathway. Reagent $PhNHSCF_3$ **1** is principally an amine and relatively a weak electrophilic reagent. The strong Brønsted acid TfOH seemingly protonated **1**, thus forming a corresponding salt with considerably more pronounced polarization between nitrogen and sulfur atom. The strong electron deficiency of nitrogen atom presumably tends to attract the electron density; thus making a weaker bond C–S and stronger sulfur electrophile able to react with phenols (Scheme 6).



Scheme 6 A plausible reaction mechanism

View Article Online
DOI: 10.1039/C4OB02633K

Trifluoromethylthiolation of *m*-cresol in the presence of a free radical TEMPO[62,63] took place the same as without TEMPO. This is another indication that radical pathway is not very likely to be a chief reaction course.

Conclusions

In summary, we have developed a new, highly regioselelective and efficient method for the trifluoromethylthiolation of phenols. The reaction pathway is most likely to be an electrophilic substitution. The method is suitable for non-specialized laboratories because the transformation was accomplished with $PhNHSCF_3$ and without extremely noxious CF_3SCl and $(CF_3)_2S$. An additional advantage was operational simplicity; specifically, reactions were performed with non-dried dichloromethane in an air atmosphere at room temperature. The reaction selectivity was remarkably high; when both *para*- and *ortho*- sites were unsubstituted, only *para*- functionalization took place. When the *para*- position was already substituted, the functionalization of the *ortho*- site took place, and no *ipso*-substitution was noted. The reaction conditions were also demonstrated to be compatible with the acid sensitive *i.e*. thioxolone moiety.

Experimental Section

General information

All transformations were carried out in untreated dichloromethane under an air atmosphere with stirring at room temperature. Starting phenols and other chemicals were obtained from commercial sources; $PhNHSCF_3$ **1** was prepared using the literature procedure.[30] Crude products were purified by column chromatography on silica gel (63–200 μm, 70–230 mesh ASTM; Fluka). TLC was performed on Merck-60-F_{254} plates using mixtures of hexane and diethyl ether. The melting points were determined in open-capillaries on Büchi 535 apparatus and are uncorrected. All products were characterized with ^1H, ^{13}C and ^{19}F NMR spectra, IR, HRMS and/or elemental analysis, and also with the melting points when solid. The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300 DPX and Bruker Avance III 500 instruments, while ^{19}F NMR spectra were only recorded on the latter instrument. Chemical shifts are reported in δ (ppm) values relative to δ = 7.26 ppm in $CDCl_3$ and δ = 2.05 ppm in acetone-d_6 for ^1H NMR, and to the central line of $CDCl_3$ (δ = 77.00 ppm) and to the central line of acetone-d_6 (δ = 30.83 ppm) for ^{13}C NMR. ^{19}F NMR spectra are referenced to $CFCl_3$ (δ = 0.00 ppm).

Representative procedure of acid-promoted trifluoromethylthiolaton of phenols

View Article Online
DOI: 10.1039/C4OB02633K

To a solution of phenol (1 mmol or 0.5 mmol in the case of steroids) in dichloromethane (10 mL), $PhNHSCF_3$ (1.2–1.3 equiv.) was added and the corresponding amount of triflic acid (1.2–5 equiv.) or $BF_3{\cdot}Et_2O$ (2–3 equiv.). The resulting mixture was stirred at room temperature up to 16 h. In most cases, the starting phenol was fully consumed, as determined by TLC. The reaction mixture was diluted with 10 ml of dichloromethane, washed with 10% solution of $NaHCO_3$, water and dried over anhydrous Na_2SO_4. Crude reaction mixture was subjected to column chromatography after removal of solvent. In numerous cases, it was only 'filtration' over silica gel, because of excellent reaction selectivity.

Reactivity of 4a with different reagents

a) Reaction with HNO_3

To 4-(trifluoromethylthio)phenol **4a** (0.4 mmol, 77 mg) HNO_3 (65%, 1.6 mmol, 156 mg) was added and the resulting reaction mixture was stirred at 30–40°C overnight. TLC revealed the full consumption of **4a**. The reaction mixture was cooled to room temperature, and product was extracted three times with 5 mL of dichloromethane, two times with water, and dried over anhydrous Na_2SO_4. Pure product **14** (84 mg, 87%) was obtained as a yellow solid after column chromatography (hexane/diethyl ether).

b) Reaction with HNO_3/H_2SO_4

HNO_3 (65%, 1.6 mmol, 156 mg) was added to **4a** (0.4 mmol, 77 mg) and the resulting reaction mixture was stirred at 30–40 °C overnight. TLC revealed the full consumption of **4a**. HNO_3 (65%, 1.6 mmol, 156 mg) and concentrated H_2SO_4 (98%, 0.8 mmol, 80 mg) were added and reaction mixture was stirred at 70–80 °C overnight. TLC showed disappearance of mononitro product. The reaction mixture was cooled to room temperature, and the product was extracted three times with 5 mL of dichloromethane and brine. The organic phase was dried over anhydrous Na_2SO_4, and solvent evaporated. After column chromatography (hexane/diethyl ether) pure product **15** (88 mg, 77%) was obtained as a yellow solid.

c) Reaction with NBS in $[Bmim]BF_4$

Reaction was performed according to the reported procedure.[60] **4a** (0.3 mmol, 58 mg) reacted with *N*-bromosuccinimide (0.72 mmol, 128 mg) in 20 minutes. Crude reaction mixture was chromatographed (hexane/diethyl ether), and yellowish solid product **16** (98 mg, 94%) was obtained.

d) Reaction[60] with NIS in $[Bmim]BF_4$

The same reaction procedure and amounts as in the case of NBS. From **4a** (0.3 mmol, 58 mg) after column chromatography **17** (120 mg, 90%) was obtained as a grey solid.

e) Reaction with Ph_2IOTf/*t*-BuOK

View Article Online
DOI: 10.1039/C4OB02633K

Transformation was performed according to the literature.[61] A solution of **4a** (0.4 mmol, 77 mg) in dry THF (1 mL) under argon atmosphere was cooled to 0 °C and *t*-BuOK (0.5 mmol, 56 mg) was added, and the mixture was stirred for 15 minutes at 0 °C. The reaction mixture was warmed to 40 °C, diphenyliodonium triflate (0.6 mmol, 258 mg) was added and the mixture stirred for three hours at 40 °C. The crude product was chromatographed (hexane/diethyl ether), and a colorless oily product **18** (69 mg, 64%) was obtained.

f) Reaction with 4-bromobenzyl bromide/K_2CO_3

A mixture of **4a** (0.4 mmol, 77 mg), 4-bromobenzyl bromide (0.4 mmol, 100 mg) and K_2CO_3 (0.48 mmol, 66 mg) was stirred one hour at 80 °C in acetonitrile. TLC showed consumption of the starting phenol **4a**. A reaction mixture was cooled to room temperature, and the solvent was removed under vacuum. The product was extracted three times with 5 mL of dichloromethane, with water and dried over anhydrous Na_2SO_4. A solvent was removed and the product chromatographed (hexane/diethyl ether), thus giving bright yellow product **19** (137 mg, 95%).

g) Suzuki-Miyaura coupling

Phenylboronic acid (0.275 mmol, 33 mg) was added to a solution of **18** (0.25 mmol, 90 mg) in isopropanol (5 mL) and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.022 mmol, 5 mg), triphenylphosphine (0.095 mmol, 25 mg), a degassed solution of K_2CO_3 (1.5 mL, 2M) and deionized water (1 mL) were added consecutively. The resulting mixture was stirred for 1 hour at reflux temperature, and TLC showed consumption of **18**. The mixture was cooled, concentrated under vacuum, diluted with dichloromethane (10 mL) and water (10 mL). After separation of phases, the aqueous phase was additionally extracted three times with 5 mL of dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and solvent removed. The crude product was chromatographed (hexane/diethyl ether), thus yielding white solid **20** (66 mg, 73%).

Spectroscopic and analytic data

4-(Trifluoromethylthio)phenol **4a**.[56] Colorless solid; mp 52.9–53.5 °C; (1 mmol **3a**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.23 (br s, 1H), 6.84–6.90 (m, 2H), 7.51–7.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 115.2 (q, J = 2.0 Hz), 116.5, 129.5 (q, J = 308.1 Hz), 138.6, 158.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3221, 1670, 1584, 1493, 1436, 1364, 1346, 1226, 1083, 826, 754, 650 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_4F_3OS$ $(M-H)^-$ 192.9935, found 192.9945.

2-Methyl-4-(trifluoromethylthio)phenol **4b**. Yellow, viscous liquid; (1 mmol **3b**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H), 5.07 (br s, 1H), 6.79 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.3, 1.8 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6, 114.7 (q, J = 1.7 Hz), 115.9, 125.3, 129.6 (q, J = 308.1 Hz), 136.0, 139.4, 156.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3409,

View Article Online
DOI: 10.1039/C4OB02633K

1588, 1495, 1401, 1261, 1087, 891, 814, 755 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_6F_3OS$ $(M-H)^-$ 207.0097, found 207.0095.

3-Methyl-4-(trifluoromethylthio)phenol **4c**. Orange, viscous liquid; (1 mmol **3c**, 1.3 mmol $PhNHSCF_3$, 1.2 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 2.49 (s, 3H), 5.13 (br s, 1H), 6.70 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 114.1, 114.8 (q, *J* = 1.5 Hz), 117.8, 129.8 (q, *J* = 308.6 Hz), 140.3, 146.4, 158.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.0 (s, SCF_3); IR: 3348, 1594, 1575, 1480, 1453, 1294, 1240, 1098, 1046, 947, 857, 812, 754, 731 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_6F_3OS$ $(M-H)^-$ 207.0097, found 207.0095.

4-Methyl-2-(trifluoromethylthio)phenol **4d**. Light yellow solid; mp 42.5–43.1 °C; (1 mmol **3d**, 1.3 mmol $PhNHSCF_3$, 2 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.14 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2, 107.7 (q, *J* = 1.2 Hz), 115.9, 128.7 (q, *J* = 310.5 Hz), 130.9, 135.1, 138.0, 155.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.4 (s, SCF_3); IR: 3417, 1489, 1136, 1097, 1055, 825 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_6F_3OS$ $(M-H)^-$ 207.0097, found 207.0094.

4-Isopropyl-2-(trifluoromethylthio)phenol **4e**. White solid; mp 36.8–37.4 °C; (1 mmol **3e**, 1.3 mmol $PhNHSCF_3$, 2.0 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.9 Hz, 6H), 2.87 (septet, *J* = 6.9 Hz, 1H), 6.15 (br s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 33.1, 107.7 (q, *J* = 1.2 Hz), 115.9, 128.8 (q, *J* = 310.5 Hz), 132.5, 135.6, 142.0, 156.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.4 (s, SCF_3); IR: 3429, 3410, 1487, 1467, 1456, 1283, 1183, 1103, 832, 728 cm^{-1}; ESI-HRMS m/z calcd for $C_{10}H_{10}F_3OS$ $(M-H)^-$ 235.0410, found 235.0409.

2-*tert*-butyl-4-(trifluoromethylthio)phenol **4f**. Yellow, viscous liquid; (1 mmol **3f**, 1.3 mmol $PhNHSCF_3$, 1.2 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 9H), 5.15 (br s, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.53 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.3, 34.7, 114.8 (d, *J* = 1.8 Hz), 117.5, 129.7 (q, *J* = 308.1 Hz), 135.7, 136.0, 137.6, 156.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3408, 2962, 1587, 1494, 1260, 1113, 1097, 1080, 815, 755 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{12}F_3OS$ $(M-H)^-$ 249.0566, found 249.0566.

4-*tert*-butyl-2-(trifluoromethylthio)phenol **4g**. Yellow, viscous liquid; (1 mmol **3g**, 1.3 mmol $PhNHSCF_3$, 2 mmol TfOH) ; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 9H), 6.14 (br s, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.4, Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.3, 34.2, 107.5 (q, *J* = 1.1 Hz), 115.6, 128.8 (q, *J* = 310.5 Hz), 131.6, 134.7, 144.5, 155.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.4 (s, SCF_3); IR: 3507, 1490, 1365, 1103, 822, 755 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{12}F_3OS$ $(M-H)^-$ 249.0561, found 249.0566.

2-Benzyl-4-(trifluoromethylthio)phenol **4h**. Yellow, viscous liquid; (1 mmol **3h**, 1.3 mmol $PhNHSCF_3$, 1.5 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 2H), 5.12 (br s, 1H), 6.77–6.81 (m, 1H), 7.18–7.26 (m, 3H), 7.28–7.33 (m, 2H), 7.39–7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.2, 115.1 (q, *J* = 1.9 Hz), 116.8, 126.7, 128.5, 128.6, 128.8, 129.6 (q, *J* = 308.1 Hz), 136.6, 138.8, 139.4, 156.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3523, 1587, 1494, 1453, 1411, 1091, 823, 729, 697 cm^{-1}; ESI-HRMS m/z calcd for $C_{14}H_{10}F_3OS$ $(M-H)-$ 283.0410, found 283.0410.

View Article Online
DOI: 10.1039/C4OB02633K

3-(Trifluoromethylthio)biphenyl-4-ol **4i**. White solid; mp 101.6–101.9 °C; (1 mmol **3i**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (br s, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.32–7.40 (m, 1H), 7.40–7.49 (m, 2H), 7.50–7.58 (m, 2H), 7.68 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.7 (q, *J* = 1.2 Hz), 116.6, 126.7, 127.4, 128.7 (q, *J* = 310.7 Hz), 128.9, 133.0, 134.9, 136.5, 139.2, 157.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.2 (s, SCF_3); IR: 3408, 1602, 1473, 1334, 1194, 1155, 1132, 1100, 1055, 895, 860, 763, 738, 700 cm^{-1}; ESI-HRMS m/z calcd for $C_{13}H_8F_3OS$ $(M-H)^-$ 269.0253, found 269.0253.

2,5-Dimethyl-4-(trifluoromethylthio)phenol **4j**. Yellow, viscous liquid; (1 mmol **3j**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.45 (s, 3H), 4.91 (br s, 1H), 6.73 (s, 1H), 7.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 20.8, 114.3 (q, *J* = 1.6 Hz), 117.3, 122.6, 129.9 (q, *J* = 308.7 Hz), 141.1, 143.6, 156.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.0 (s, SCF_3); IR: 3602, 3412, 2866, 1395, 1377, 1256, 1222, 1094, 1017, 892, 852, 754, 625 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_8F_3OS$ $(M-H)^-$ 221.0253, found 221.0255.

2,6-Dimethyl-4-(trifluoromethylthio)phenol **4k**. Yellow solid; mp 40.4–42.7 °C; (1 mmol **3k**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 6H), 4.91 (br s, 1H), 7.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.7, 113.9 (q, *J* = 1.8 Hz), 124.3, 129.7 (q, *J* = 308.0 Hz), 137.0, 154.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3613, 3449, 1586, 1473, 1330, 1153, 1093, 876, 754, 730 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_8F_3OS$ $(M-H)^-$ 221.0253, found 221.0253.

2,3,5-Trimethyl-4-(trifluoromethylthio)phenol **4l**. White solid; mp 82.1–82.4 °C; (1 mmol **3l**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.50 (s, 3H), 2.55 (s, 3H), 5.02 (br s, 1H), 6.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 19.1, 22.3, 115.0 (q, *J* = 1.2 Hz), 115.1, 121.7, 130.1 (q, *J* = 309.5 Hz), 144.0, 145.8, 155.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.5 (s, SCF_3); IR: 3321, 1690, 1575, 1446, 1298, 1097, 1076, 858, 846, 753 cm^{-1}; ESI-HRMS m/z calcd for $C_{10}H_{10}F_3OS$ $(M-H)^-$ 235.0410, found 235.0411.

2,3,6-Trimethyl-4-(trifluoromethylthio)phenol **4m**. Yellow solid; mp 51.6–54.2 °C (1 mmol **3m**, 1.3 mmol $PhNHSCF_3$, 1.2 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.23 (s, 3H), 2.48 (s, 3H), 4.89 (br s, 1H), 7.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 15.5, 18.2, 114.2 (q, *J* = 1.5 Hz), 121.1, 123.4, 129.9 (q, *J* = 308.6 Hz), 138.0, 142.0, 154.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.3 (s, SCF_3); IR: 3477, 1465, 1400, 1213, 1184, 1144, 1100, 1020, 909, 754 cm^{-1}; ESI-HRMS m/z calcd for $C_{10}H_{10}F_3OS$ $(M-H)^-$ 235.0410, found 235.0412.

2,4,6-Trimethyl-3-(trifluoromethylthio)phenol **4n**. Light yellow solid; mp 75.5–76.4 °C; (1 mmol **3n**, 1.3 mmol $PhNHSCF_3$, 5 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 4.62 (br s, 1H), 6.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 16.1, 21.6, 121.3 (q, *J* = 1.4 Hz), 126.9, 130.1, 130.1 (q, *J* = 309.4 Hz), 130.2, 137.0, 150.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ -42.8 (s, SCF_3); IR: 3365, 1470, 1378, 1299, 1151, 1096, 998, 871, 801, 753 cm^{-1}; ESI-HRMS m/z calcd for $C_{10}H_{10}F_3OS$ $(M-H)^-$ 235.0410, found 235.0408.

4,5-Dimethyl-2-(trifluoromethylthio)phenol **6a**. White solid; mp 65.6–65.8 °C (1 mmol **5a**, 1.3 mmol $PhNHSCF_3$, 1.2 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.26 (s, 3H), 6.06 (s, 1H), 6.88 (s, 1H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.6, 20.1, 104.5 (q, *J* = 1.2 Hz), 117.0, 128.8 (q, *J* = 310.6 Hz), 129.9, 138.2, 144.0, 156.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.8 (s, SCF_3); IR: 3398, 3372, 1480, 1313, 1210, 1145, 1101, 1022, 871 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_8F_3OS$ $(M-H)-$ 221.0253, found 221.0250.

View Article Online
DOI: 10.1039/C4OB02633K

3,4-Dimethyl-2,6-bis(trifluoromethylthio)phenol **6a'**. White solid; mp 48.5–48.9 °C; (1 mmol **5a**, 1.3 mmol $PhNHSCF_3$, 1.2 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.53 (s, 3H), 6.86 (s, 1H), 7.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 20.1, 107.0 (q, J = 1.7 Hz), 110.9 (q, J = 1.3 Hz), 128.9 (q, J = 311.3 Hz), 129.1 (q, J = 310.1 Hz), 130.6, 142.7, 149.1, 158.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -42.6 (s, SCF_3); -43.2 (s, SCF_3); IR: 3455, 1440, 1391, 1271, 1092, 904, 755, 671 cm^{-1}; Anal Calcd for $C_{10}H_8F_6OS_2$: C, 37.27; H, 2.50. Found: C, 37.41; H, 2.48.

6-(Trifluoromethylthio)-2,3-dihydro-1*H*-inden-5-ol **6b**. White solid; mp 73.7–74.5 °C; (1 mmol **5b**, 1.3 mmol $PhNHSCF_3$, 3 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.09 (quintet, J = 7.4 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 6.19 (br s, 1H), 6.94 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 31.7, 33.3, 105.1 (q, J = 1.2 Hz), 111.8, 128.8 (q, J = 310.7 Hz), 133.0, 137.3, 152.0, 156.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.9 (s, SCF_3); IR: 3418, 3401, 1471, 1440, 1430, 1330, 1129, 1103, 897, 879 cm^{-1}; ESI-HRMS m/z calcd for $C_{10}H_8F_3OS$ $(M-H)^-$ 233.0248, found 233.0253.

3-(Trifluoromethylthio)-5,6,7,8-tetrahydronaphthalen-2-ol **6c**. White solid; mp 52.8–53.0 °C; (1 mmol **5c**, 1.3 mmol $PhNHSCF_3$, 3 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.74–1.81 (m, 4H), 2.67–2.73 (m, 2H), 2.73–2.79 (m, 2H), 6.03 (br s, 1H), 6.78 (s, 1H), 7.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 22.9, 28.3, 29.6, 105.0 (q, J = 1.1 Hz), 115.8, 128.8 (q, J = 310.5 Hz), 130.6, 138.2, 144.4, 155.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.7 (s, SCF_3); IR: 3411, 2941, 2857, 1612, 1564, 1476, 1210, 1129, 1099, 1031, 863, 754 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{10}F_3OS$ $(M-H)^-$ 247.0410, found 247.0411.

1-(Trifluoromethylthio)-5,6,7,8-tetrahydronaphthalen-2-ol **6cc**. White solid; mp 49.3–49.5 °C; (1 mmol **5c**, 1.3 mmol $PhNHSCF_3$, 3 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.72–1.85 (m, 4H), 2.69–2.74 (m, 2H), 2.92–2.97 (m, 2H), 6.39 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 22.9, 28.8, 29.1, 107.8, 113.1, 128.9 (q, J = 311.7 Hz), 130.6, 134.9, 143.2, 156.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ -42.2 (s, SCF_3); IR: 3422, 2938, 1592, 1579, 1471, 1430, 1303, 1204, 1146, 1128, 1094, 832, 818, 752, 734 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{10}F_3OS$ $(M-H)^-$ 247.0410, found 247.0410.

5-(Trifluoromethylthio)-2-((trifluoromethylthio)methyl)-2,3-dihydrobenzofuran **9**. Yellow, viscous liquid; (1 mmol **7**, 2.5 mmol $PhNHSCF_3$, 4 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 3.08 (dd, J = 16.1, 6.6 Hz, 1H), 3.16 (dd, J = 14.0, 6.3 Hz, 1H), 3.28 (dd, J = 14.0, 6.3 Hz, 1H), 3.46 (dd, J = 16.1, 9.2 Hz, 1H), 5.05–5.13 (m, 1H), 6.82 (d, J = 8.1 Hz, 1H), 7.42–7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.2, 81.6, 110.7, 115.2 (d, J = 1.9 Hz), 127.4, 129.6 (q, J = 308.2 Hz), 130.7 (q, J = 306.4 Hz), 133.6, 137.9, 161.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ -41.4 (s, SCF_3); -44.5 (s, SCF_3); IR: 1604, 1589, 1474, 1237, 1092, 974, 819, 755 cm^{-1}; Anal Calcd for $C_{11}H_8F_6OS_2$: C, 39.52; H: 2.41. Found: C, 39.30; H, 2.34.

2-Methoxy-4-methyl-5-(trifluoromethylthio)phenol **11a**. Light yellow solid; mp 51.9–52.1 °C; (1 mmol **10a**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.91 (s, 3H), 5.49 (br s, 1H), 6.79 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 55.9, 112.6, 114.4 (q, J = 1.5 Hz), 123.6, 129.8 (q, J = 308.8 Hz), 136.7, 143.8, 148.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.7 (s, SCF_3); IR: 3343, 1580, 1266, 1135, 1100, 1043, 872, 850, 817, 753 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_8F_3O_2S$ $(M-H)^-$ 237.0203, found 237.0200.

2,6-Dimethoxy-3-(trifluoromethylthio)phenol **11b**. Brown solid; mp 44.7–46.5 °C; (1 mmol **10b**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.97 (s, 3H), 5.66 (br s, 1H), 6.69 (d,

View Article Online
DOI: 10.1039/C4OB02633K

J = 8.7 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.3, 61.2, 106.7, 109.5 (d, *J* = 1.8 Hz), 129.0, 129.4 (q, *J* = 308.7 Hz), 139.2, 148.9, 150.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.6 (s, SCF_3); IR: 3523, 3371, 1594, 1489, 1469, 1439, 1294, 1219, 1083, 892, 796 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_8F_3O_3S$ $(M-H)^-$ 253.0152, found 253.0151.

4-(Trifluoromethylthio)-5,6,7,8-tetrahydronaphthalen-1-ol **11c**. Grey solid; mp 65.2–67.5 °C; (1 mmol **10c**, 1.3 mmol $PhNHSCF_3$, 3 mmol $BF_3{\cdot}Et_2O$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76–1.86 (m, 4H), 2.61–2.67 (m, 2H), 2.93–2.99 (m, 2H), 5.04 (br s, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 22.5, 23.2, 28.9, 112.8, 114.7 (q, *J* = 1.5 Hz), 125.3, 129.8 (q, *J* = 308.7 Hz), 137.1, 144.7, 156.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.8 (s, SCF_3); IR: 3590, 3461, 1573, 1456, 1440, 1416, 1073, 1029, 819, 805, 750 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{10}F_3OS$ $(M-H)^-$ 247.0410, found 247.0411.

4-(Trifluoromethylthio)naphthalen-1-ol **11d**. Gray solid; mp 64.8–67.2 °C; (1 mmol **10d**, 1.3 mmol $PhNHSCF_3$, 3 mmol $BF_3{\cdot}Et_2O$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, *J* = 7.9 Hz, 1H), 7.54–7.61 (m, 1H), 7.64–7.71 (m, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 8.23 – 8.29 (dd, *J* = 8.3, 0.5 Hz, 1H), 8.47– 8.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.6, 112.5 (q, *J* = 1.5 Hz), 122.3, 125.1, 125.9, 126.0, 128.2, 129.6 (q, *J* = 309.5 Hz), 136.7, 138.7, 155.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.8 (s, SCF_3); IR: 3346, 1591, 1569, 1510, 1348, 1158, 1092, 1047, 830, 763, 753 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_6F_3OS$ $(M-H)^-$ 243.0097, found 243.0096.

1-(Trifluoromethylthio)naphthalen-2-ol **11e**. Light yellow solid; mp 91.8–92.2 °C (lit.[56] 88.8–90.7 °C); (1 mmol **10e**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (br s, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.39–7.47 (m, 1H), 7.58–7.67 (m, 1H), 7.77–7.85 (m, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 8.30–8.36 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 100.8 (q, *J* = 0.6 Hz), 117.1, 124.3, 124.4, 128.4, 128.5, 128.8 (q, *J* = 312.8 Hz), 129.4, 134.9, 135.8, 158.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -42.3 (s, SCF_3); IR: 3415, 1618, 1591, 1569, 1462, 1384, 1196, 1146, 1125, 1101, 1029, 867, 772, 655 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_6F_3OS$ $(M-H)^-$ 243.0097, found 243.0097.

1,8-bis(trifluoromethylthio)naphthalene-2,7-diol **11f**. Light orange solid; mp 90.3–91.4 °C; (1 mmol **10f**, 2.4 $PhNHSCF_3$, 4.0 mmol TfOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 7.71 (s, 2H), 7.87 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 99.9, 115.0, 125.9, 128.5 (q, *J* = 312.8 Hz), 136.5, 137.2, 161.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.5 (s, SCF_3); IR: 3411, 1607, 1514, 1430, 1355, 1155, 1084, 841, 752 cm^{-1}; ESI-HRMS m/z calcd for $C_{12}H_5F_6O_2S_2$ $(M-H)^-$ 358.9641, found 358.9650.

1-(2,6-Dihydroxy-3-(trifluoromethylthio)phenyl)ethanone **11g**. Yellow solid; mp 114.7–117.5 °C; (1 mmol **10g**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (s, 3H), 6.60 (d, *J* = 8.8 Hz, 1H), 7.58 (br s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 13.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.5, 98.2 (q, *J* = 1.5 Hz), 110.0, 111.9, 128.4 (q, *J* = 311.7 Hz), 144.1, 160.7, 168.1, 204.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.4 (s, SCF_3); IR: 3343, 1622, 1581, 1472, 1440, 1373, 1245, 1235, 1158, 1120, 1097, 1042, 963, 903, 819, 656 cm^{-1}; ESI-HRMS m/z calcd for $C_9H_6F_3O_3S$ $(M-H)^-$ 250.9995, found 250.9994.

4-(Trifluoromethylthio)benzene-1,2-diol **11h**. White solid; mp 67.8–69.0 °C; (1 mmol **10h**, 1.3 mmol $PhNHSCF_3$, 2.0 mmol $BF_3{\cdot}Et_2O$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.60 (br s, 1H), 5.78 (br s, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 115.1 (q, *J* = 2.0 Hz), 116.0, 123.3, 129.5 (q, *J* = 308.2 Hz), 130.5, 143.6, 146.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.3 (s,

View Article Online
DOI: 10.1039/C4OB02633K

SCF_3); IR: 3533, 3486, 3349, 1593, 1507, 1276, 1245, 1124, 1100, 811, 782 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_4F_3O_2S$ $(M-H)^-$ 208.9890, found 208.9889.

4-Methyl-5-(trifluoromethylthio)benzene-1,2-diol **11i**. White solid; mp 71.1–71.5 °C; (1 mmol **10i**, 1.3 mmol $PhNHSCF_3$, 2.0 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 1H), 5.25 (br s, 1H), 5.61 (br s, 1H), 6.84 (s, 1H), 7.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 113.9 (q, J = 1.6 Hz), 117.5, 124.8, 129.8 (q, J = 308.8 Hz), 138.1, 141.3, 146.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.9 (s, SCF_3); IR: 3284, 1593, 1508, 1447, 1272, 1094, 875, 866, 816 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_6F_3O_2S$ $(M-H)^-$ 223.0046, found 223.0045.

4-(Trifluoromethylthio)benzene-1,3-diol **11j**. White solid; mp 48.5–49.7 °C; (1 mmol **10j**, 1.3 mmol $PhNHSCF_3$, 3.0 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.16 (br s, 1H), 6.30 (br s, 1H), 6.47 (dd, J = 8.5, 2.7 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 99.6 (q, J = 1.1 Hz), 102.9, 109.6, 128.6 (q, J = 310.9 Hz), 139.4, 159.4, 160.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.5 (s, SCF_3); IR: 3645, 3492, 3338, 1592, 1473, 1324, 1134, 1094, 1057, 968, 843, 809 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_4F_3O_2S$ $(M-H)^-$ 208.9890, found 208.9889.

4-(Trifluoromethylthio)benzene-1,2,3-triol **11k**. Brown solid; mp 82.0–84.9 °C; (1 mmol **10k**, 1.3 mmol $PhNHSCF_3$, 2.0 mmol $BF_3{\cdot}Et_2O$); ^1H NMR (300 MHz, $CDCl_3$/acetone): δ 6.47 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/acetone): δ 99.2 (q, J = 1.7 Hz), 108.4, 128.9 (q, J = 310.2 Hz), 129.4, 131.9, 147.0, 148.5; ^{19}F NMR (470 MHz, $CDCl_3$/acetone): δ -44.3 (s, SCF_3); IR: 3507, 3484, 3397, 3218, 1601, 1503, 1460, 1291, 1267, 1090, 1007, 888, 800, 754, 657 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_4F_3O_3S$ $(M-H)^-$ 224.9839, found 224.9838.

6-(Trifluoromethylthio)benzo[d][1,3]dioxol-5-ol **13a**. Light yellow solid; mp 82.2–82.7 °C; (1 mmol **12a**, 1.3 mmol $PhNHSCF_3$, 1.3 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 5.99 (s, 2H), 6.18 (br s, 1H), 6.59 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.7, 102.0, 115.0, 128.6 (q, J = 311.5 Hz), 142.0, 152.7, 154.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.5 (s, SCF_3); IR: 3433, 1614, 1496, 1470, 1160, 1099, 1030, 930, 871, 830, 754, 713 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_4F_3O_3S$ $(M-H)^-$ 236.9839, found 236.9840.

6-Hydroxy-5-(trifluoromethylthio)benzo[d][1,3]oxathiol-2-one **13b**. Light yellow solid; mp 128.9–131.7 °C; (1 mmol **12b**, 1.3 mmol $PhNHSCF_3$, 4.0 mmol TfOH); ^1H NMR (500 MHz, Acetone-d_6): δ 7.12 (s, 1H), 7.96 (s, 1H), 9.93 (br s, 1H); ^{13}C NMR (125 MHz, Acetone): δ 102.4, 108.6 (q, J = 1.5 Hz), 115.7, 131.5 (q, J = 308.4 Hz), 134.3, 153.7, 161.7, 170.6; ^{19}F NMR (470 MHz, Acetone-d_6): δ -43.0 (s, SCF_3); IR: 3416, 1732, 1603, 1454, 1428, 1327, 1145, 1090, 1032, 1013, 881, 865 cm^{-1}; ESI-HRMS m/z calcd for $C_8H_2F_3O_3S_2$ $(M-H)^-$ 266.9403, found 266.9404.

2-Isopropyl-5-methyl-4-(trifluoromethylthio)phenol **13c**. Colorless, viscous liquid; (1.0 mmol **12c**, 1.3 mmol $PhNHSCF_3$, 2.0 mmol TfOH); ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, J = 6.9 Hz, 6H), 2.44 (s, 3H), 3.14 (septet, J = 6.9 Hz, 1H), 4.95 (br s, 1H), 6.70 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 22.4, 26.8, 114.7 (q, J = 1.7 Hz), 117.7, 129.9 (q, J = 308.7 Hz), 133.4, 137.1, 143.1, 155.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.0 (s, SCF_3); IR: 3422, 1397, 1256, 1152, 1095, 1070, 736 cm^{-1}; ESI-HRMS m/z calcd for $C_{11}H_{12}F_3OS$ $(M-H)^-$ 249.0566, found 249.0567.

(13*S*)-13-Methyl-2-(trifluoromethylthio)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthrene-3,17-diol **13d**. White solid; mp 96.1–98.9 °C; (0.5 mmol **12d**; 0.65 mmol $PhNHSCF_3$, 0.65 mmol TfOH); ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (s, 3H), 1.10–1.60 (m, 8H), 1.63–1.77 (m, 1H), 1.83–2.02 (m, 2H), 2.06–2.22

View Article Online
DOI: 10.1039/C4OB02633K

(m, 2H), 2.24–2.35 (m, 1H), 2.81–2.91 (m, 2H), 3.74 (t, J = 8.4 Hz, 1H), 6.04 (br s, 1H), 6.79 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.0, 23.1, 26.2, 26.8, 29.6, 30.5, 36.5, 38.4, 43.2, 43.6, 49.9, 81.8, 105.1 (q, J = 0.9 Hz), 115.8, 128.8 (q, J = 310.6 Hz), 134.1, 135.0, 144.2, 155.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.7 (s, SCF_3); IR: 3318, 2921, 2867, 1560, 1447, 1102, 1055, 1011, 797 cm^{-1}; ESI-HRMS m/z calcd for $C_{19}H_{22}F_3O_2S$ $(M-H)^-$ 371.1298, found 371.1303.

(13*S*)-13-Methyl-4-(trifluoromethylthio)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthrene-3,17-diol **13dd**. White solid; mp 84.8–87.5 °C; (0.5 mmol **12d**; 0.65 mmol $PhNHSCF_3$, 0.65 mmol TfOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (s, 3H), 1.14–1.22 (m, 1H), 1.23–1.43 (m, 5H), 1.43–1.55 (m, 2H), 1.67–1.76 (m, 1H), 1.92–2.00 (m, 2H), 2.08–2.22 (m, 2H), 2.25–2.33 (m, 1H), 2.84–2.95 (m, 1H), 3.14–3.22 (m, 1H), 3.74 (t, J = 8.5 Hz, 1H), 6.43 (br s, 1H), 6.91 (d, J = 8.6 Hz 1H), 7.40 (d, J = 8.6 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.0, 23.0, 26.4, 27.0, 29.2, 30.6, 36.6, 38.0, 43.2, 44.1, 49.9, 81.8, 108.0, 113.0, 128.9 (q, J = 311.8 Hz), 131.1, 134.0, 143.2, 156.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ -42.0 (s, SCF_3); IR: 3645, 3455, 2938, 2857, 1572, 1352, 1156, 1114, 1098, 1009, 821, 802, 755 cm^{-1}; ESI-HRMS m/z calcd for $C_{19}H_{22}F_3O_2S$ $(M-H)^-$ 371.1298, found 371.1307.

(13*S*)-3-Hydroxy-13-methyl-2-(trifluoromethylthio)-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17(14*H*)-one **13e**. White solid; mp 160.4–160.9 °C; (0.5 mmol **12e**, 0.65 mmol $PhNHSCF_3$, 0.65 mmol TfOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.34–1.74 (m, 6H), 1.90–2.30 (m, 5H), 2.34–2.43 (m, 1H), 2.45–2.58 (m, 1H), 2.85– 2.97 (m, 2H), 6.09 (br s, 1H), 6.81 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 21.5, 25.8, 26.2, 29.5, 31.4, 35.8, 37.9, 43.6, 47.9, 50.4, 105.4 (q, J = 1.2 Hz), 115.9, 128.8 (q, J = 310.6 Hz), 133.5, 135.0, 143.9, 155.8, 220.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.7 (s, SCF_3); IR: 3323, 1723, 1601, 1502, 1410, 1103, 895, 877, 674 cm^{-1}; ESI-HRMS m/z calcd for $C_{19}H_{20}F_3O_2S$ $(M-H)^-$ 369.1142, found 369.1141.

(13*S*)-3-Hydroxy-13-methyl-4-(trifluoromethylthio)-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17(14*H*)-one **13ee**. White solid; mp 171.7–172.7 °C; (0.5 mmol **12e**, 0.65 mmol $PhNHSCF_3$, 0.65 mmol TfOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.37–1.58 (m, 5H), 1.59–1.70 (m, 1H), 1.93–2.00 (m, 1H), 2.02–2.11 (m, 2H), 2.11–2.20 (m, 1H), 2.21–2.29 (m, 1H), 2.34–2.42 (m, 1H), 2.48–2.66 (m, 1H), 2.89–3.00 (m, 1H), 3.21–3.28 (m, 1H), 6.44 (br s, 1H), 6.92 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 21.5, 26.0, 26.3, 29.0, 31.5, 35.8, 37.5, 44.1, 47.9, 50.3, 108.0, 113.2, 128.9 (q, J = 311.8 Hz), 131.1, 133.4, 143.0, 156.7, 220.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -41.9 (s, SCF_3); IR: 3396, 1732, 1471, 1154, 1118, 1092, 824, 754 cm^{-1}; ESI-HRMS m/z calcd for $C_{19}H_{20}F_3O_2S$ $(M-H)^-$ 369.1142, found 369.1143.

2-Nitro-4-(trifluoromethylthio)phenol **14**. Yellow solid; mp 51.6–52.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.8 Hz, 1H), 7.84 (dd, J = 8.8, 2.2 Hz, 1H), 8.45 (d, J = 2.2 Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.7 (q, J = 2.3 Hz), 121.5, 129.1 (q, J = 308.8 Hz), 133.6, 133.7, 144.8, 156.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.7 (s, SCF_3); IR: 3256, 1614, 1519, 1474, 1413, 1316, 1243, 1150, 1108, 1088, 1072, 848, 672 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_3F_3NO_3S$ $(M-H)^-$ 237.9791, found 237.9792.

2,6-Dinitro-4-(trifluoromethylthio)phenol **15**. Yellow solid; decomp., 170 °C; ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.38 (s, 2H); ^{13}C NMR (125 MHz, Acetone-d_6): δ 106.8, 131.3 (q, J = 308.0 Hz), 140.1, 143.5, 158.4; ^{19}F

View Article Online
DOI: 10.1039/C4OB02633K

NMR (470 MHz, Acetone-d_6): δ -44.0 (s, SCF_3); IR: 3438, 3091, 1624, 1527, 1338, 1252, 1136, 1090, 913, 776, 724, 683 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_2F_3N_2O_5S$ $(M-H)^-$ 282.9642, found 282.9643.

2,6-Dibromo-4-(trifluoromethylthio)phenol **16**. Yellow solid; mp 51.3–53.4 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.23 (br s, 1H), 7.77 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.2, 117.2 (q, J = 2.2 Hz), 129.1 (q, J = 308.9 Hz), 139.7, 152.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.8 (s, SCF_3); IR: 3459, 1452, 1383, 1325, 1159, 1094, 877, 735, 709 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_2Br_2F_3OS$ $(M-H)^-$ 348.8151, found 348.8152.

2,6-Diiodo-4-(trifluoromethylthio)phenol **17**. Gray solid; mp 86.0–87.6 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.05 (br s, 1H), 7.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.2, 118.3 (q, J = 2.0 Hz), 129.1 (q, J = 308.9 Hz), 146.7, 156.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ -43.8 (s, SCF_3); IR: 3439, 1440, 1375, 1302, 1105, 895, 753, 699 cm^{-1}; ESI-HRMS m/z calcd for $C_7H_2F_3I_2OS$ $(M-H)^-$ 444.7873, found 444.7883.

(4-Phenoxyphenyl)(trifluoromethyl)sulfane **18**. Colorless, viscous liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 6.96–7.03 (m, 2H), 7.04–7.10 (m, 2H), 7.16–7.23 (m, 1H), 7.35–7.44 (m, 2H), 7.56–7.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 117.2 (q, J = 1.9 Hz), 118.6, 120.1, 124.6, 129.5 (q, J = 308.2 Hz), 130.0, 138.3, 155.5, 160.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.1 (s, SCF_3); IR: 1581, 1485, 1240, 1110, 1081, 869, 834, 754, 692 cm^{-1}; Anal Calcd for $C_{13}H_9F_3OS$: C, 57.77; H, 3.36. Found: C, 57.73; H, 3.09.

(4-(4-Bromobenzyloxy)phenyl)(trifluoromethyl)sulfane **19**. Light yellow solid; mp 54.8–55.5 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 5.04 (s, 2H), 6.96 – 7.00 (m, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.56 – 7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 69.4, 115.4 (q, J = 1.9 Hz), 115.8, 122.2, 129.1, 129.6 (q, J = 308.2 Hz), 131.8, 135.2, 138.3, 160.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.3 (s, SCF_3); IR: 1590, 1494, 1453, 1411, 1377, 1251, 1107, 1088, 1042, 1012, 831, 809, 799, cm^{-1}; ESI-HRMS m/z calcd for $C_{14}H_9BrF_3OS$ $(M-H)^-$ 360.9515, found 360.9522.

(4-(Biphenyl-4-ylmethoxy)phenyl)(trifluoromethyl)sulfane **20**. White solid; mp 107.0–108.4 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 5.14 (s, 2H), 7.01–7.07 (m, 2H), 7.33–7.41 (m, 1H), 7.42–7.54 (m, 4H), 7.57–7. 67 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 69.9, 115.2 (q, J = 1.9 Hz), 115.8, 127.1, 127.5, 128.0, 128.8, 129.6 (q, J = 308.2 Hz), 135.1, 138.3, 140.6, 141.3, 161.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -44.3 (s, SCF_3); IR: 1589, 1491, 1380, 1247, 1106, 1083, 1028, 1005, 826, 763, 700 cm^{-1}; ESI-HRMS m/z calcd for $C_{20}H_{14}F_3OS$ $(M-H)^-$ 359.0723, found 359.0720.

Acknowledgement

Mrs. T. Stipanovič and Prof. B. Stanovnik for the elemental combustion analyses, Dr. D. Urankar and Prof. J. Košmrlj for HRMS, and Ministry of Higher Education, Science and Technology (P1-0134) for financial support are gratefully acknowledged.

References

View Article Online
DOI: 10.1039/C4OB02633K

1 W. K. Hagmann, *J. Med. Chem*. 2008, **51**, 4359–4369.
2 K. Müller, C. Faeh and F. Diederich, *Science* 2007, **317**, 1881–1886.
3 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2006.
4 J. Scheirs, Ed. *Modern Fluoropolymers: High Performance Polymers for diverse Applications* John Wiley & Sons, Chichester, 2000.
5 W. Grot, *Fluorinated Ionomers,* Elsevier, Oxford, 2011.
6 J. A. Gladysz, D. P. Curran and I. T. Horváth, *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, 2004.
7 A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15–25.
8 K. L. Kirk, *J. Fluorine Chem*. 2006, **127**, 1013–1029.
9 D. O'Hagan, *J. Fluorine Chem*. 2010, **131**, 1071–1081.
10 J.-P. Bégué and D. Bonnet-Delpon, *J. Fluorine Chem.* 2006, **127**, 992–1012
11 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.* 2008, **37**, 320–330.
12 (a) Z. Jin, G. B. Hammond and B. Xu, *Aldrichimica Acta* 2012, **45**, 67–83; (b) H. Egami and M. Sodeoka, *Angew. Chem. Int. Ed.* 2014, **53**, 8294–8308.
13 J.-A. Ma and D. Cahard, *Chem. Rev.* 2008, **108**, PR1–PR43.
14 N. Shibata, A. Matsnev and D. Cahard, *Beilstein J. Org. Chem*. 2010, **6**, 65.
15 O. A. Tomashenko and V. V. Grushin, V. V. *Chem. Rev.* 2011, **111**, 4475–4521.
16 A. Studer, *Angew. Chem. Int. Ed.* 2012, **51**, 8950–8958.
17 (a) P. Chen and G. Liu, *Synthesis* 2013, **45**, 2919–2939; (b) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors and F. R. Leroux, *Beilstein J. Org. Chem*. 2013, **9**, 2476–2536.
18 X.-F.; H. Neumann and M. Beller, *Chem. Asian J.* 2012, **7**, 1744–1754.
19 L. Chu and F.-L. Qing, *Acc. Chem. Res.* 2014, **47**, 1513–1522.
20 G. Landelle, A. Panossian and F. R. Leroux, *Curr. Top. Med. Chem.* 2014, **14**, 941–951.
21 K. Fauster, C. Kreutz and R. Micura, *Angew. Chem. Int. Ed.* 2012, **51**, 13080–13084.
22 (a) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.* 2014, 2415–2428; (b) A. Tlili and T. Billard *Angew. Chem. Int. Ed.* 2013, **52**, 6818–6819.
23 S. Munavalli, D. K. Rohrbaugh, D. I. Rossman and H. D. Durst, *J. Fluorine Chem.* 1999, **98**, 3–9.
24 L. Dieu, I. Popov and O. Daugulis, *J. Am. Chem. Soc.* 2012, **134**, 18237–18240.
25 V. N. Boiko, *Beilstein J. Org. Chem.* 2010, **6**, 880–921.
26 (a) D. J. Adams, A. Goddard, J. H. Clark and D. J. Macquarrie, *Chem. Commun.* 2000, 987–988; (b) M. Hu, J. Rong, W. Miao, C. Ni, Y. Han and J. Hu, *Org. Lett.* 2014, **16**, 2030–2033; (c) M. Rueping, N. Tolstoluzhsky and P. Nikolaienko, *Chem. Eur. J.* 2013, **19**, 14043–14046; (d) G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.* 2014, **5**, 1312–1316; (e) Q. Lefebvre, E. Fava, P. Nikolaienko and M. Rueping, *Chem. Commun.* 2014, **50**, 6617–6619; (f) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan and Z. Weng, *Tetrahedron* 2013, **69**, 6046–6050; (g) P. Zhu, X. He, X. Chen, Y. You, Y. Yuan and Z. Weng, *Tetrahedron* 2014, **70**, 672–677; (h) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem. Int. Ed.* 2013, **52**, 1548–1552; (i) Z. Wang, Q. Tu and Z. Weng, *J. Organomet. Chem*. 2014, **751**, 830–834; (j) B. Bayarmagnai, C. Matheis, E. Risto and L. J. Goossen, *Adv. Synth. Catal.* 2014, **356**, 2343–2348.
27 (a) Q. Xiao, J. Sheng, Q. Ding and J. Wu, *Eur. J. Org. Chem.* 2014, 217–221; (b) F. Yin and X.-S. Wang, *Org. Lett.* 2014, **16**, 1128–1131; (c) X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang and J. Wang, *Eur. J. Org. Chem.* 2014, 3093–3096; (d) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem. Int. Ed.* 2011, **50**, 7312–7314; (e) D. J. Adams and J. H. Clark, *J. Org. Chem.* 2000, **65**, 1456–1460; (f) C. Chen, X.-H. Xu, B. Yang and F.-L. Qing, *Org. Lett.* 2014, **16**, 3372–3375.
28 (a) C.-P, Zhang and D. A. Vicic, *J. Am. Chem. Soc.* 2012, **134**, 183–185; (b) C.-P. Zhang and D. A. Vicic, *Chem. Asian J.* 2012, **7**, 1756–1758.
29 See, for example: (a) C. Pooput, M. Medebielle and W. R. Dolbier, Jr., *Org. Lett.* 2004, **6**, 301–303; (b) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem. Int. Ed.* 2007, **46**, 754–757; (c) N. Santschi and A. Togni, *J. Org. Chem.* 2011, **76**, 4189–4193; (d) S. Capone, I. Kieltsch, O. Flögel, G. Lelais, A. Togni and D. Seebach, *Helv. Chim. Acta* 2008, **91**, 2035–2056; (e) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem. Int. Ed.* 2012, **51**, 2492–2495; (f) C. Chen, L. Chu and F.-L. Qing, *J. Am. Chem. Soc.* 2012, **134**, 12454–12457; (g) L. Zhai, Y. Li, J. Yin, K. Jin, R. Zhang, X. Fu and C. Duan, *Tetrahedron* 2013, **69**, 10262–10266; (h) V. N. Movchun, A. A. Kolomeitsev and Y. L. Yagupolskii, *J. Fluorine Chem.* 1995, **70**, 255–257; (i) T. Billard, S. Large and B. R. Langlois, *Tetrahedron Lett.* 1997, **38**, 65–68; (j) Y. Huang, X. He, X. Lin, M. Rong and Z. Weng, *Org. Lett.* 2014, **16**, 3284–3287.
30 A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *J. Org. Chem.* 2008, **73**, 9362–9365.
31 A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *Angew. Chem. Int. Ed.* 2009, **48**, 8551–8555.
32 A. Ferry, T. Billard, E. Bacqué and B. R. Langlois, *J. Fluorine Chem.* 2012, **134**, 160–163.

View Article Online
DOI: 10.1039/C4OB02633K

33 Y. Yang, X. Jiang and F.-L. Qing, *J. Org. Chem.* 2012, **77**, 7538–7547.
34 F. Baert, J. Colomb and T. Billard, *Angew. Chem. Int. Ed.* 2012, **51**, 10382–10385.
35 S. Alazet, K. Ollivier and T. Billard, *Beilstein J. Org. Chem.* 2013, **9**, 2354–2357.
36 J. Liu, L. Chu and F.-L. Qing, *Org. Lett.* 2013, **15**, 894–897.
37 S. Alazet, L. Zimmer and T. Billard, *Angew. Chem. Int. Ed.* 2013, **52**, 10814–10817.
38 J. Sheng, S. Li and J. Wu, *Chem. Commun.* 2014, **50**, 578–580.
39 J. Sheng, C. Fan and J. Wu, *Chem. Commun.* 2014, **50**, 5494–5496.
40 Y. Li, G. Li and Q. Ding, *Eur. J. Org. Chem.* 2014, 5017–5022.
41 Q. Xiao, J. Sheng, Z. Chen and J. Wu, *Chem. Commun.* 2013, **49**, 8647–8649.
42 Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.* 2013, **135**, 8782–8785.
43 C. Xu and Q. Shen, *Org. Lett.* 2014, **16**, 2046–2049.
44 S.-Q. Zhu, X.-H. Xu and F.-L. Qing, *Eur. J. Org. Chem.* 2014, 4453–4456.
45 X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem. Int. Ed.* 2013, **52**, 3457–3460.
46 E. V. Vinogradova, P. Müller and S. L. Buchwald, *Angew. Chem. Int. Ed.* 2014, **53**, 3125–3128.
47 X. Shao, T. Liu, L. Lu and Q. Shen, *Org. Lett.* 2014, **16**, 4738–4741.
48 F. Hu, X. Shao, D. Zhu, L. Lu and Q. Shen, *Angew. Chem. Int. Ed.* 2014, **53**, 6105–6109.
49 H. He and X. Zhu, *Org. Lett.* 2014, **16**, 3102–3105.
50 (a) X. Wang, T. Yang, X. Cheng and Q. Shen, *Angew. Chem. Int. Ed.* 2013, **52**, 12860–12864; (b) Q.-H. Deng, C. Rettenmeier, H. Wadepohl and L. H. Gade, *Chem. Eur. J.* 2014, **20**, 93–97.
51 (a) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei and M. Rueping, *Angew. Chem. Int. Ed.* 2013, **52**, 12856–12859; (b) M. Rueping, X. Liu, T. Bootwicha, R. Pluta and C. Merkens, *Chem. Commun.* 2014, **50**, 2508–2511.
52 X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu and B. Tan, *Org. Lett.* 2014, **16**, 2192–2195.
53 H. Xiang and C. Yang, *Org. Lett.* 2014, **16**, 5686–5689.
54 S. Alazet, L. Zimmer and T. Billard, *Chem. Eur. J.* 2014, **20**, 8589–8593.
55 S. Alazet and T. Billard, *Synlett* 2015, **26**, 76–78.
56 C. Xu, B. Ma and Q. Shen, *Angew. Chem. Int. Ed.* 2014, **53**, 9316–9320.
57 W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 1930, 2510–2524.
58 J. L. G. Nilsson, H. Selander, H. Sievertsson, I. Skånberg and K.-G. Svensson, *Acta Chem. Scand.,* 1971, **25**, 94–100.
59 M. Jereb, *Curr. Org. Chem*. 2013, **17**, 1694–1700.
60 R.-Y. Tang, P. Zhong and Q.-L. Lin, *J. Fluorine Chem.* 2007, **128**, 636–640.
61 N. Jalalian, T. B. Petersen and B. Olofsson, *Chem. Eur. J.* 2012, **18**, 14140–14149.
62 W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.* 2013, **52**, 13086–13090.
63 E. Pair, N. Monteiro, D. Bouyssi and O. Baudoin, *Angew. Chem. Int. Ed.* 2013, **52**, 5346–5349.