A Bench-Stable Transfer Reagent facilitates the generation of Trifluoromethyl-sulfonimidamides.

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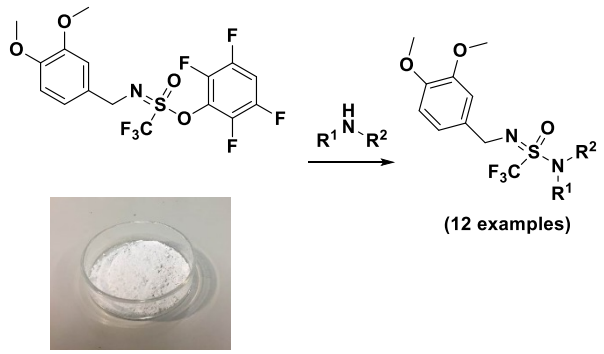


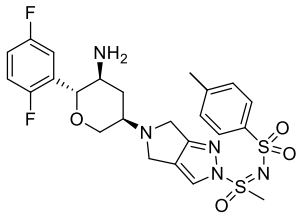
ABSTRACT; Sulfonimidamides are an emerging bioisosteric replacement in medicinal chemistry projects and therefore new chemistries are necessary to access this functionality. The general synthesis of CF_3-sulfonimidamides from an activated bench-stable transfer reagent is described. A diverse reaction scope is demonstrated, with a wide range of nucleophilic amines being tolerated in this transformation. The CF_3-sulfonimidamides obtained contain an additional diversity point, in the form a protected imine, that could be unmasked to allow late stage modification.

Sulfonimidamides (SIAs) are evolving to be a key functional group in the medicinal chemist's toolbox. They are a close structural analog of sulfonamides, one in which the S=O is replaced with an S=N, this minor structural variation affords a stereogenic sulfur and also offers the opportunity to further functionalize the system.

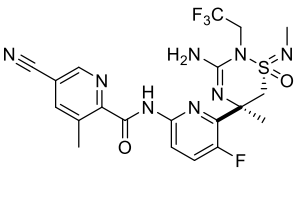
Since their discovery,[1,2] SIAs have proved their utility in multiple arenas, including applications in asymmetric metal catalysis.[3-9] The addition of the sp^2-hybridised nitrogen atom enables chemical modification for optimizing physiochemical and biological properties.[10] Tautomerism through proton transfer between imine and amide nitrogen of the SIA, potentially offers interesting properties in drug discovery as the imine nitrogen can act either as a hydrogen donor or acceptor.[11,12] The use of SIAs in drug discovery has become increasingly more popular, not only as a way of optimizing/tuning the drug properties of sulfonamides, but also for achieving novel chemical and intellectual property space.

Merck, Sharp and Dohme Corporation published on sulfonimidamide dihydropyrrolopyrazoles, exemplified by compound **1**, used for the treatment of type-2 diabetes (Figure 1).[13] More recently, SIA-containing inhibitors of β-secretase enzyme 1 (BACE1) such as **2** for the treatment of Alzheimer's disease were reported by Hoffmann-La Roche.[14] Similarly Sehgelmeble et al. recently published the utility of sulfonimidamides as bioisosteres of sulfonamides. They used γ-secretase inhibitors as model systems and supported the comparison with detailed in vitro and vivo data.[15]

Figure 1. Sulfonimidamides in medicinal chemistry



1
DPP-4 IC_{50} = 18 nM



2
BACE1 IC_{50} = 0.59 nM
(pure epimer)

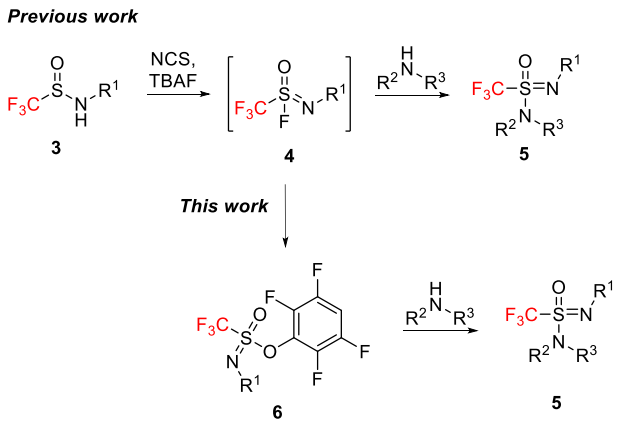
The growing interest in the SIA functional group in drug discovery has resulted in the development of novel synthetic methodologies.[16] A recent publication reported an electrophilic NH transfer to tertiary sulfinamides to afford unprotected SIAs.[17] Davies *et al*. reported a multi-component synthesis of SIAs using stable *N*-sulfinyltritylamine (TrNSO), organometallic reagents and amines.[18] They showed a broad scope of reactivity.

The incorporation of fluorine atoms has routinely been used in drug development to optimize compound properties such as pKa, metabolic stability and membrane permeability.[19] We hypothesized that the CF_3 group would impart desired properties to the SIA.

Previously in the group, we published a method for the synthesis of CF_3-SIAs **5** from sulfinamides **3** via oxidative chlorination and *in situ* fluorination, to afford the corresponding sulfonimidoyl fluoride **4** and subsequent reaction with various amines (Scheme 1).[20] This method had a good sulfinamide and amine scope, allowing access to a diverse range of trifluoromethyl SIAs in good yield. The main disadvantage was the need to pre-generate the sulfonimidoyl fluoride **4**, which was performed regularly due to concerns over its long-term stability. Herein, we report the synthesis of a bench-stable transfer reagent **6** that can be made on large scale in one step for the synthesis of CF_3-SIAs. Not only is this reagent more

reactive than the corresponding sulfonimidoyl fluoride **4**, it also appears to be less susceptible to sulfonamide byproduct formation.

Scheme 1: Preparation of CF_3-SIAs

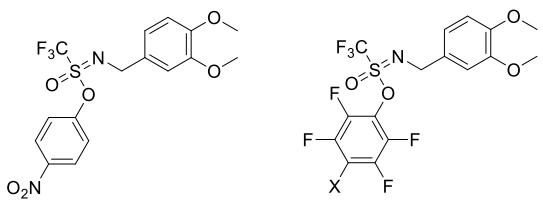


To expand the utility of the transfer reagent, in additional to the tetrafluorophenoxy leaving group we included a protected imine, which would allow late stage modification to the SIAs as recently described by Lücking et. al.[21]

A stable pentafluorophenol vinylsulfonate was synthesised by Caddick *et al*. as a replacement for sulfonyl chlorides in the preparation of sulfonamides.[22] We postulated that this strategy could be applied to the synthesis of SIAs. We chose dimethoxybenzyl (DMPM) as the imine protecting group as it is stable to various conditions, decreases the volatility of the sulfinamide intermediate and is easily removed at a later stage.

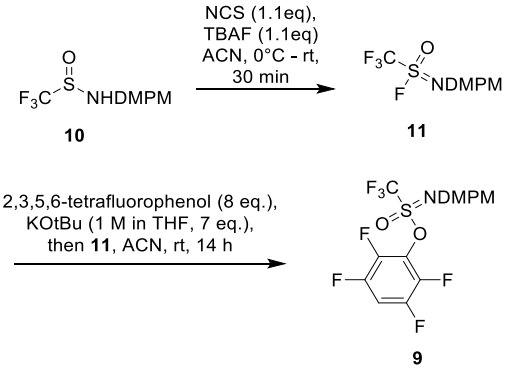
Different leaving groups on the sulfur were trialed including para-nitrophenol **7**, pentafluorophenol **8** and tetrafluorophenol **9** (Figure 2). Para-nitrophenol was a good nucleophile for reaction with sulfonimidoyl fluoride for formation of the transfer reagent but reactivity with simple amines resulted in slow conversion and some side products. Pentafluorophenol was less nucleophilic and was thus required in large excess, in order to form the activated reagent. Gratifyingly, we discovered that tetrafluorophenol offered a good compromise between the nucleophilicity required to form the reagent and the subsequent displacement by amines.

Figure 2 - Trifluoromethyl sulfonimidate compounds



Tetrafluorophenol sulfonimidate **9** was formed in two steps from sulfonamide **10** (Scheme 2). The first step involved formation of sulfonimidoyl fluoride as previously described through oxidative chlorination and subsequent in situ fluorination using N-chlorosuccinimide (NCS) and tetrabutyl ammonium fluoride (TBAF).[20] The sulfonimidoyl fluoride **11** was isolated in 89% yield was subjected to an excess of potassium tetrafluorophenoxide at room temperature to afford the desired transfer reagent **9** in yield of 68% on a 3 g scale. The reaction could be performed in one-pot, via the concentration of sulfonimidoyl fluorination and in situ reaction with phenoxide but the yield was reduced to a disappointing 42% due to the formation of the sulfonamide side product. The transfer reagent was isolated as a white solid, which in addition to being more stable than the corresponding sulfonimidoyl fluoride, is much easier to handle than an oil.

Scheme 2: Synthesis of Tetrafluorophenol sulfonimidate 9

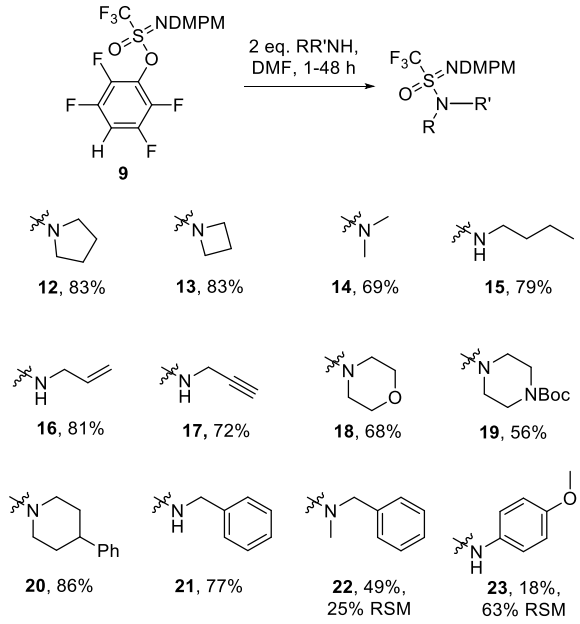


The formation of CF_3-SIAs through reaction of the activated tetrafluorophenol transfer reagent **9** and a diverse range of amines was very successful (Scheme 3). Simple secondary amine nucleophiles such as pyrrolidine and azetidine afforded **12** and **13** respectively in yields of 83% within one hour at room temperature. The reaction with dimethylamine required heating for good conversion of starting material but **14** was obtained in reasonable yield. Primary amines, such as butylamine, also reacted under mild conditions to give **15** in 79% yield. The reaction with 2 equivalents of electron deficient primary amines, allylamine and propargyl amine, led to **16** and **17** respectively in 81% and 72% yield. This is in contrast to the previously reported reaction with sulfonimidoyl fluoride **4** which required more forcing conditions with 8 equivalents of amine being needed for good conversion to the product.[20]

Six-membered cyclic amines were also successful at forming the corresponding SIAs in good to moderate yields. Sulfonimidamide **18** was formed under the same reaction conditions from morpholine, which was previously unsuccessful with trifluoromethyl sulfonimidoyl fluoride. Pleasingly, reaction with Boc-piperazine and phenyl piperidine afforded **19** and **20** respectively. The formation of **19** allows for further functionalization through selective deprotection of the Boc group in the presence of the DMPM group. Benzylamine sulfonimidamide **21** was obtained in 77% yield at room temperature. The bulkier secondary amine, *N*-methyl benzylamine, required heating to 50 °C for 49% conversion to

22 with some recovered starting material. Some conversion was observed with 2 equivalents of para-methoxy aniline to afford **23** in 18% yield with good recovery of starting material. The yield could be improved using more equivalents of the amine to force conversion of the starting material. In conclusion, we have demonstrated the improved reactivity of the transfer reagent, when compared to sulfonimidoyl fluoride, over a wide range of amines, including less nucleophilic amines such as anilines.

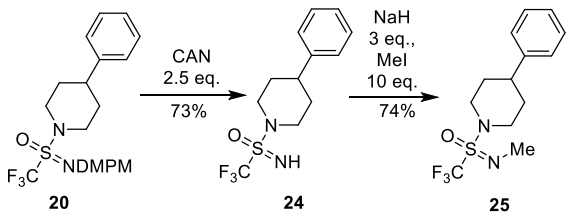
Scheme 3. Amine scope with transfer reagent



RSM = Recovered Starting Material

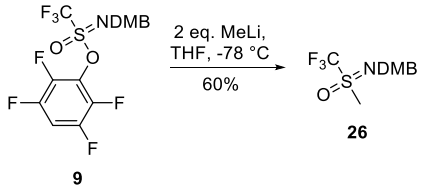
To demonstrate further utility of this transfer reagent for the synthesis of CF_3-SIAs, the dimethoxybenzyl protecting group was removed (Scheme 4). Phenylpiperidine SIA **20** was deprotected using cerium ammonium nitrate (CAN) to give **24** in good yield. This could be further functionalized through alkylation of the nitrogen with methyl iodide to give **25**. Therefore, demonstrating the potential for this reagent to be used in the synthesis of pharmaceutical compounds, where unmasking diversity points at the later stages of a synthetic sequence is desired, for optimal SAR generation and efficiency.

Scheme 4. Deprotection and alkylation.



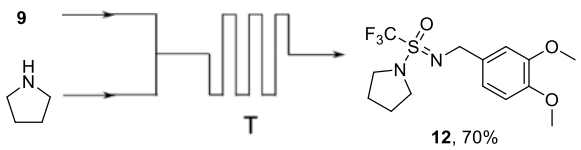
The formation of CF_3-sulfoximines was successful using CF_3-sulfonimidoyl fluoride so we were interested to test whether the transfer reagent was also reactive towards carbon nucleophiles. Synthesis of CF_3-sulfoximine **26** was achieved through reaction of the transfer reagent **9** with methyl lithium in 60% yield (Scheme 5). There was no observed sulfonamide formation unlike using sulfonimidoyl fluoride. Given the greater reactivity and stability under basic conditions compared to the sulfonimidoyl fluoride, the conditions could be optimised for reaction with other C-nucleophiles for the synthesis of structurally-diverse CF_3-sulfoximines.

Scheme 5. Synthesis of trifluoromethyl sulfoximine 26



The formation of CF_3-SIAs from transfer reagent **9** was also successful using flow chemistry in a two-flow chip reactor. Solutions of **9** and pyrrolidine were passed through separate tubes before being mixed in a reactor heated to 80 °C at a flow rate of 0.05 mL/min to afford **12** in 70% yield (Scheme 6). Interestingly, no sulfonamide formation was detected as is often observed in batch under basic conditions at temperatures above 60 °C. Therefore, despite the slightly lower yield, the efficient mixing properties of flow chemistry results in fewer byproducts.

Scheme 6. Flow reaction conditions to CF_3-SIAs



Reaction conditions: **9**, pyrrolidine (2 equiv.), ACN, 80 ºC, 0.05 mL/min.

The aim of this investigation was to develop a bench-stable transfer reagent that could be formed in large quantities, allowing simple handling and long-term storage without degradation. To assure these criteria had been met, we exposed both tetrafluorophenol sulfonimidate **9** and the corresponding sulfonimidoyl fluoride **11** to a range of conditions within a series of chemical stability tests (Supporting Information, Table 1 and 2). As expected sulfonimidoyl fluoride **11** demonstrated lower chemical stability, and was degraded to the corresponding sulfonamide when exposed to acidic conditions and basic conditions. Interestingly some degradation was also observed in MeOH and DMSO under neutral conditions. In contrast, transfer reagent **9** was stable to the same acidic and neutral pH conditions. Albeit, as seen during reaction optimisation, some conversion to the sulfonamide was observed under strongly basic conditions. Therefore, sulfonimidoyl fluoride **11** is not suitable for long term storage while transfer reagent **9** has demonstrated to have the properties required to be a practical and useful bench-stable solid that can be made on a large scale.

To conclude, we have developed a transfer reagent **9** for the synthesis of CF_3-SIAs which is bench-stable and reactive to a diverse range of amines. The products can be easily deprotected at a later stage to give either the free imine or a diversity point for further functionalization. In addition, the reagent is reactive towards methyl lithium so has the potential for synthesis of a wide range of CF_3-sulfoximines from C-nucleophiles. This method is also applicable to flow chemistry conditions, which facilitates efficient upscaling. Overall, this reagent will be highly useful in drug discovery programs for the bioisosteric replacement of sulfonamides or amides with CF_3-SIAs and/or CF_3-sulfoximines.

General Experimental The ^1H, ^{19}F and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance-400, -377 and -101 MHz spectrometer respectively. ^{19}F NMR were referenced to C_6F_6 (δ -164.90 ppm). Chemical shifts are given in ppm (δ). Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad. Melting points were measured with differential scanning calorimetry on a Mettler-Toledo-DCS823. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light or potassium permanganate stains. Column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). High resolution mass spectra were recorded on a QToF mass spectrometer configured with an electrospray ionization source, maintained at 140 °C, using nitrogen as the nebulizer gas, argon as collision gas and Lockmass device for mass calibration using Leucine-Enkephaline as standard substance. Spectra were acquired either in positive or in negative ionization mode, by scanning from 50 to 1200 Da in 0.1 s. In positive mode the capillary needle voltage was either 0.5 or 2.0 kV. In negative mode the capillary needle voltage was 2.0 kV. Cone voltage was 25 V in both ionization modes. N-Chlorosuccinimide (NCS) was recrystallized from warm acetic acid and then washed with acetic acid and heptane. All other reagents and solvents were used directly as received.

General Procedures. *Procedure A*; To a solution of transfer reagent **9** (1 equiv.) in DMF (0.1 M) was added amine (2 equiv.). The reaction was stirred at rt. After completion, the reaction mixture was concentrated *in vacuo* and then purified by flash chromatography to afford the product.

Procedure B; To a solution of transfer reagent **9** (1 equiv.) in DMF (0.1 M) was added amine (2 equiv.). The reaction was stirred at 50 °C. After completion, the reaction mixture was concentrated *in vacuo* and then purified by flash chromatography to afford the product.

Sulfonimidamides; *N*-(3,4-Dimethoxybenzyl)-1,1,1-trifluoro-methanesulfinamide (**10**). Prepared following a literature procedure.[23] To a 250 mL round bottom flask at 0 °C was added a solution of trifluorosulfonyl chloride (1.1 mL, 9.95 mmol) in CH_2Cl_2 (30 mL) and a solution of PPh_3 (2.6 g, 9.9 mmol), Et_3N (2.77 mL, 19.9 mmol) and 3,4-dimethoxybenzylamine (1.5 mL, 9.9 mmol) in CH_2Cl_2 (30 mL) using a syringe pump at the same rate over 1 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography eluting with 0-30% EtOAc in heptane to give **10** (1.4 g, 47%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94-6.54 (m, 3H), 4.67 - 4.53 (m, 1H), 4.51 - 4.39 (m, 1H), 4.32 - 4.18 (m, 1H), 3.88 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ ppm 149.4, 149.1, 129.0, 120.6, 128.7, 125.4, 122.1, 118.7, 111.3, 55.9, 46.3; HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calcd for $C_{10}H_{16}F_3N_2O_3S^+$, 301.0828; found, 301.0836.

N-(3,4-Dimethoxybenzyl)-1,1,1-trifluoromethanesulfonimidoyl fluoride (**11**); Prepared following a literature procedure.[20] To a solution of **10** (3.5 g, 12.2 mmol) and NCS (1.8 g, 13.4 mmol) in ACN (82 mL) at 0°C was added TBAF (1M in THF) (13.4 mL, 13.4 mmol). The reaction mixture was stirred for 30 min and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-5% EtOAc in heptane to give **11** (3.3 g, 88%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89-6.83 (m, 3H), 4.57 (d, *J*=9.0 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm 64.4 (dtd, *J*=33.8, 17.0, 17.0, 8.5 Hz, 1F) -73.1 (d, *J*=17.1 Hz, 3F); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ ppm 149.1, 148.7, 129.7, 129.6, 119.5, 117.9 (dd, *J*=320.7, 66.7 Hz, 1C), 111.1, 110.5, 55.9, 55.8, 47.4, 47.3, no ionization observed – in line with previous account.

4-Nitrophenyl N-(3,4-dimethoxybenzyl)trifluoromethanesulfonimidate (**7**); To a solution of 4-nitrophenol (196.4 mg, 1.4 mmol) in THF (2 mL) was added KOtBu (1 M in THF) (1.4 mL, 1.4 mmol) and the solution was stirred at rt for 30 mins. The reaction mixture was concentrated in vacuo to give the potassium salt. A solution of **11** (100 mg, 0.35 mmol) in ACN (2 mL, 0.786 g/mL, 38.3 mmol) was added to the potassium salt. The reaction mixture was stirred at rt for 1 hr. LCMS showed full conversion to the desired product. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography eluting with 0-20% EtOAc in heptane to give **7** (92 mg, yield 62%) as a yellow oil; ^1H NMR (400MHz, $CDCl_3$) δ ppm 8.19 (d, *J=9.2* Hz, 2H), 7.21 (d, *J=9.2* Hz, 2H), 6.74 (m, 3H), 4.46 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm -73.93 (s, 3F);); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ ppm 153.2, 149.1, 130.8, 125.4, 123.1, 120.6, 119.7, 117.5, 110.9, 110.8, 55.9, 55.8, 47.8; HRMS (ESI-TOF) m/z: [M-H]- calcd for $C_{16}H_{14}F_3N_2O_6S$-, 419.0530; found, 419.0527.

Perfluorophenyl N-(3,4-dimethoxybenzyl)-trifluoromethanesulfonimidate (**8**); To a solution of pentafluorophenol (194.9 mg, 1.06 mmol) in THF (4.5 mL) was added KOtBu (1M in THF) (1.1 mL, 1.06 mmol). The reaction mixture was stirred at rt for 30 mins. The reaction mixture was concentrated in vacuo to give the potassium salt. A solution of **11** (150 mg, 0.53 mmol) in ACN (3 mL) was added to the potassium salt and stirred at rt for 2 hrs. The reaction mixture was concentrated in vacuo. The crude product was purified by flash chromatography eluting with 0-15% EtOAc in heptane to give **8** as a white solid (50 mg, yield 20.3%). (Mpt = 73.0 °C); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.81 - 6.73 (m, 3H) 4.57 - 4.43 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm -73.37 (t, *J=6.0 Hz*, 3F), -151.30 - -151.11 (m, 2F), -155.33 (t, *J=21.6* Hz, 1F), -161.11 - -160.92 (m, 2F); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ ppm 149.1, 148.6, 135.8 - 143.5 (m), 130.4, 119.5, 118.6 (q, *J=321.4* Hz), 110.9, 110.4, 55.9, 55.7, 47.2; HRMS (ESI-TOF) m/z: [M-H]- calcd for $C_{16}H_{10}F_8NO_4S$-, 464.02083; found, 464.0213.

2,3,5,6-Tetrafluorophenyl *N*-(3,4-dimethoxybenzyl)trifluoro-methanesulfonimidate (**9**); To a solution of 2,3,5,6-tetrafluorophenol (13.3 g, 80.2 mmol) in THF (500 mL) was added KO^{t}Bu (1M in THF) (69.7 mL, 69.7 mmol). The reaction mixture was stirred at rt for 30 min. The reaction mixture was concentrated *in vacuo* to give the potassium salt. A solution of **11** (3 g, 9.9 mmol) in ACN (50 mL) was added to the potassium salt and the reaction mixture was stirred at rt for 14 h. The reaction mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-10% EtOAc in heptane to give **9** (3.0 g, 68%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.03 – 6.94 (m, 1H), 6.80 - 6.74 (m, 3H), 4.60 - 4.45 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.5 (s, 3F), -137.7 (d, *J*=15.1 Hz, 2F), -151.6 (d, *J*=37.7 Hz, 2F); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.0, 148.5, 145.9 (dtd, *J*=251.5, 11.1, 4.0 Hz, 1C), 141.1 (ddd, *J*=254.5, 15.2, 4.0 Hz, 1C), 130.4, 118.7 (q, *J*=322.2 Hz, 1C), 119.4, 111.0, 110.3, 104.4 (t, *J*=22.7 Hz, 1C), 55.9, 55.7, 47.1; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $C_{16}H_{11}F_7NO_4S$-, 446.0302; found, 446.0300.

1-(*N*-(3,4-Dimethoxybenzyl)-S-(trifluoromethyl)-sulfonimidoyl) pyrrolidine (**12**); Prepared following Procedure A using **9** (250 mg, 0.559 mmol) and pyrrolidine (0.1 mL, 1.12 mmol) and stirring at rt for

1 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **12** (163 mg, 83%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.97 - 6.92 (m, 1H), 6.83 - 6.80 (m, 1H), 4.43 - 4.24 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.58 - 3.28 (m, 4H), 1.93 (m, 4H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.5 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.0, 132.7, 121.1 (q, *J*=329.3 Hz, 1C), 119.2, 111.0, 110.7, 56.0, 55.8, 48.8, 45.5, 25.9; HRMS (ESI-TOF) *m/z*: calcd for $C_{14}H_{18}F_3N_2O_3S^-$ [M-H]$^-$ 351.0995, found 351.1006.

1-(*N*-(3,4-Dimethoxybenzyl)-*S*-(trifluoromethyl)sulfonimidoyl)-azetidine (**13**); Prepared following Procedure A using **9** (200 mg, 0.447 mmol) and azetidine (0.06 mL, 0.9 mmol) and stirring at rt for 1 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **13** (126 mg, 83%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.92 - 6.88 (m, 1H), 6.84 - 6.81 (m, 1H), 4.35 (d, *J*=8.1 Hz, 2H), 4.11 (m, 4H), 3.89 (s, 3H), 3.87 (s, 3H), 2.33 - 2.24 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.6 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.0, 132.8, 120.9 (q, *J*=329.3 Hz, 1C), 119.2, 111.0, 110.7, 56.0, 55.8, 52.1, 45.7, 15.0; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{13}H_{16}F_3N_2O_3S^-$, 337.0839; found, 337.0831.

N'-(3,4-Dimethoxybenzyl)-1,1,1-trifluoro-*N*,*N*-dimethylmethane-sulfonimidamide (**14**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and dimethylamine (2M in THF) (0.45 mL, 0.9 mmol) and stirring at 50 °C for 21 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **14** (100 mg, 69%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 - 6.92 (m, 1H), 6.91 - 6.86 (m, 1H), 6.86 - 6.76 (m, 1H), 4.40 - 4.17 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.01 – 2.98(s, 6H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.8 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.0, 132.5, 120.7 (q, *J*=327.2 Hz, 1C), 119.3, 111.0, 110.7, 56.0, 55.8, 45.2, 38.4; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{12}H_{16}F_3N_2O_3S^-$, 325.0839; found, 325.0837.

N-Butyl-*N*'-(3,4-dimethoxybenzyl)-1,1,1-trifluoromethane-sulfonimidamide (**15**); Prepared following Procedure A using **9** (250 mg, 0.56 mmol) and butylamine (110 µL, 1.12 mmol) and stirring at rt for 1 h. Column chromatography (25 g silica, 0-15% EtOAc in heptane) yielded **15** (157 mg, 79%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 - 6.78 (m, 3H), 4.52 - 4.41 (br s, 1H), 4.41 - 4.29 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.30 - 3.12 (m, 2H), 1.55-1.49 (m, 2H), 1.44 - 1.30 (m, 2H), 0.92 (t, *J*=7.5 Hz, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.2 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.1, 148.4, 131.3, 120.5 (q, *J*=328.3 Hz, 1C), 119.6, 111.1, 110.8, 56.0, 55.8, 46.4, 43.3, 33.0, 19.7, 13.5; HRMS (ESI-TOF) m/z: [M-H]- calcd for $C_{14}H_{20}F_3N_2O_3S^-$, 353.1152; found, 353.1146.

N-Allyl-*N*'-(3,4-dimethoxybenzyl)-1,1,1-trifluoromethane-sulfonimidamide (**16**); Prepared following Procedure A using **9** (250 mg, 0.559 mmol) and allylamine (0.08 mL, 1.2 mmol) and stirring at rt for 17 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **16** (154 mg, 81%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.82 (m, 3H), 5.92 - 5.82 (m, 1H), 5.27 (dd, *J*=17.1, 1.2 Hz, 1H), 5.15 (dd, *J*=10.4, 1.4 Hz, 1H), 4.71 (s, 1H), 4.34 (d, *J*=6.9 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 - 3.82 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.4 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 148.6, 134.4, 130.6, 120.4 (q, *J*=327.2 Hz, 1C), 119.7, 116.7, 111.2, 110.8, 56.0, 55.9, 46.8, 45.6; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{13}H_{16}F_3N_2O_3S^-$, 337.0839; found, 337.0838.

N'-(3,4-Dimethoxybenzyl)-1,1,1-trifluoro-*N*-(prop-2-yn-1-yl)-methane- sulfonimidamide (**17**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and propargyl amine (0.06 mL, 0.9 mmol) and stirring at 50 °C for 21 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **17** (109 mg, 72%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.81 (d, *J*=14.7 Hz, 3H), 5.03-4.95 (m, 1H), 4.36 (d, *J*=9.7 Hz, 2H), 4.12-3.92 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.28 (t, *J*=2.5 Hz, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.9 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.3, 148.9, 129.4, 120.1 (q, *J*=325.2 Hz, 1C), 120.1, 111.2, 111.0, 80.2, 71.9, 56.0, 55.9, 47.4, 32.1; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{13}H_{14}F_3N_2O_3S^-$, 335.0682; found, 335.0684.

4-(*N*-(3,4-Dimethoxybenzyl)-S-(trifluoromethyl)sulfonimidoyl)-morpholine (**18**); Prepared following Procedure B using **9** (200 mg, 0.447 mmol) and morpholine (0.08 mL, 0.9 mmol) and stirring at 50 °C for 27 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **18** (112 mg, 68%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J*=2.0 Hz, 1H), 6.91 - 6.87 (m, 1H), 6.84 - 6.80 (m, 1H), 4.33 (d, *J*=15.6 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.66 - 3.63 (m, 4H), 3.49 - 3.34 (m, 4H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.5 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.0, 148.2, 132.2, 120.4 (q, *J*=327.2 Hz, 1C), 119.4, 111.1, 110.8, 66.6, 56.0, 55.9, 46.9, 45.4; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{14}H_{18}F_3N_2O_4S^-$, 367.0944; found, 367.0919.

tert-Butyl-4-(*N*-(3,4-dimethoxybenzyl)-*S*-(trifluoromethyl)-sulfonimid-oyl)piperazine-1-carboxylate (**19**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and 1-(*tert*-butoxycarbonyl)piperazine (167 mg, 0.9 mmol) and stirring at 50 °C for 40 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **19** (101 mg, 48%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 - 6.91 (m, 1H), 6.90 - 6.87 (m, 1H), 6.84 - 6.81 (m, 1H), 4.40 - 4.26 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.28 - 3.51 (m, 8H), 1.46 (s, 9H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.8 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.2, 149.0, 148.1, 132.1, 120.3 (q, *J*=327.2 Hz, 1C), 119.3, 111.0, 110.8, 80.6, 55.9, 55.8, 46.7, 45.4, 28.3; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{19}H_{27}F_3N_3O_5S^-$, 466.1629; found, 466.1615.

1-(*N*-(3,4-Dimethoxybenzyl)-*S*-(trifluoromethyl)sulfonimidoyl)-4-phenylpiperidine (**20**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and 4-phenylpiperidine (144 mg, 0.9 mmol) and stirring at 50 °C for 4 h. Column chromatography (25 g silica, 0-15% EtOAc in heptane) yielded **20** (170 mg, 86%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.29 (m, 2H), 7.25 - 7.20 (m, 1H), 7.18 - 7.15 (m, 2H), 6.98 - 6.96 (m, 1H), 6.94 - 6.90 (m, 1H), 6.84 - 6.81 (m, 1H), 4.35 (d, *J*=15.8 Hz, 2H), 4.15 - 4.02 (m, 2H), 3.89 (s, 3H) 3.86 (s, 3H), 3.03 (br t, *J*=12.3 Hz, 2H), 2.63 (tt, *J*=12.2, 3.5 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.72 (qd, *J*=12.7, 4.3 Hz, 1H), 1.60 - 1.49 (m, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.9 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.0. 148.1, 144.6, 132.5, 128.6, 126.7, 126.6, 120.5 (q, *J*=326.2 Hz, 1C), 119.4, 111.1, 110.9, 55.9, 55.8, 47.7, 47.5, 45.4, 41.9, 33.2, 32.9; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{21}H_{24}F_3N_2O_3S^-$, 441.1465; found, 441.1439.

N-Benzyl-*N*'-(3,4-dimethoxybenzyl)-1,1,1-trifluoromethane-sulfonimidamide (**21**); Prepared following Procedure A using **9** (200 mg, 0.45 mmol) and benzylamine (0.1 mL, 0.9 mmol) and stirring at rt for 22 h. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **21** (133 mg, 77%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.24 (m, 5H), 6.87 - 6.77 (m, 3H), 4.42 - 4.25 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.2 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 148.6, 138.0, 130.4, 128.6, 127.6, 127.4, 120.5 (q, *J*=327.2 Hz, 1C), 119.8, 111.2, 110.9, 55.9, 55.8, 46.9, 46.8; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{17}H_{19}F_3N_2O_3S^-$, 387.0995; found, 387.0995.

N-Benzyl-*N*'-(3,4-dimethoxybenzyl)-1,1,1-trifluoro-*N*-methyl-methane-sulfonimidamide (**22**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and *N*-methylbenzylamine (0.12 mL, 0.9 mmol) and stirring at 50 °C for 48 h. Column chromatography (25 g silica, 0-15% EtOAc in heptane) yielded **22** (88 mg, 49%) and **9** (50 mg, 25%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 5H), 6.93 - 6.91 (m, 1H), 6.89 - 6.86 (m, 1H), 6.80 - 6.77 (m, 1H), 4.66 - 4.61 (m, 1H) 4.44 - 4.28 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 2.84 (d, *J*=1.1 Hz, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.2 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.0, 135.4, 132.4, 128.8, 128.1, 128.1, 120.8 (q, *J*=328.3 Hz, 1C), 119.3, 111.0, 110.7, 55.9, 55.8, 54.8, 45.4,

35.0; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{18}H_{20}F_3N_2O_3S^-$, 401.1152; found, 401.1147.

N'-(3,4-Dimethoxybenzyl)-1,1,1-trifluoro-*N*-(4-methoxyphenyl)-methanesulfonimidamide (**23**); Prepared following Procedure B using **9** (200 mg, 0.45 mmol) and *p*-anisidine (0.1 g, 0.9 mmol) and stirring at 50 °C for 6 days. Column chromatography (25 g silica, 0-20% EtOAc in heptane) yielded **23** (32 mg, 18%) and **9** (127 mg, 64%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 - 7.04 (m, 2H), 6.82 - 6.77 (m, 4H), 6.72 - 6.70 (m, 1H), 4.37 (d, *J*=4.4 Hz, 2H), 3.86 (s, 3H) 3.79 (s, 3H), 3.77 (s, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.1 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ ppm 156.2, 149.2, 132.87, 128.2, 124.8, 120.5, 120.3 (q, *J*=323.2 Hz, 1C), 114.6, 111.2, 111.0, 56.0, 55.9, 55.5, 48.4; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{17}H_{18}F_3N_2O_4S^-$, 403.0945; found, 403.0944.

4-Phenyl-1-(*S*-(trifluoromethyl)sulfonimidoyl)piperidine (**24**); To a solution of **20** (100 mg, 0.23 mmol) in ACN (2 mL) and water, distilled (1 mL) at 0 °C was added CAN (310 mg, 0.56 mmol). The reaction mixture was stirred for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-15% EtOAc in heptane to give **24** (48 mg, 73%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.27 - 7.18 (m, 3H), 4.29 - 4.16 (m, 2H), 3.15 – 2.98 (m, 3H), 2.73 - 2.64 (m, 1H), 1.99 – 1.92 (m, 2H), 1.85 - 1.73 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.4 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.5, 128.7, 126.7, 126.7, 121.0 (q, *J*=328.2 Hz, 1C), 48.0, 47.1, 41.9, 33.2, 33.1; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{12}H_{14}F_3N_2OS^-$, 291.0785; found, 291.0784.

1-(*N*-Methyl-*S*-(trifluoromethyl)sulfonimidoyl)-4-phenylpiperidine (**25**); To a solution of **24** (65 mg, 0.2 mmol) in THF (1.5 mL) was added NaH (60% dispersion in mineral oil) (26.7 mg, 0.67 mmol) at 0 °C. The reaction mixture was stirred for 30 min. MeI (0.14 mL, 2.2 mmol) was added and the solution was stirred at rt for 20 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water. The aqueous layer was back-extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-15% EtOAc in heptane to give **25** (34 mg, 74%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.25 - 7.19 (m, 3H), 4.14 – 4.04 (m, 2H), 3.13 – 3.04 (br t, *J*=12.3 Hz, 2H), 2.88 (s, 3H), 2.72 – 2.68 (m, 1H), 1.99 - 1.92 (m, 2H), 1.85 - 1.71 (m, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.6 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.6, 128.7, 126.7, 126.7, 120.5 (q, *J*=326.2 Hz, 1C), 47.6, 47.3, 42.0, 33.3, 33.1, 27.9; HRMS (ESI-TOF) *m/z*: [M+H]$^-$ calcd for $C_{13}H_{18}F_3N_2OS^-$, 307.1097; found 307.1095.

((3,4-Dimethoxybenzyl)imino)(methyl)(trifluoromethyl)-λ$_6$-sulfanone (**26**); To a solution of **9** (50 mg, 0.1 mmol) in THF (1 mL) at -78 °C was added methyl lithium (1.6 M in THF) (0.14 mL, 0.2 mmol). The reaction mixture was stirred for 15 min. The reaction mixture was washed with saturated ammonium chloride (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-20% EtOAc in heptane to **26** (20 mg, 60%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 - 6.81 (m, 3H), 4.45 - 4.38 (m, 1H), 4.24 - 4.17 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.09 (d, *J*=0.7 Hz, 3H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.71 (s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.0, 148.2, 132.1, 121.4 (q, *J*=341.4 Hz, 1C), 119.7, 111.1, 110.9, 56.0, 55.8, 46.7, 37.7; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{11}H_{13}F_3NO_3S^-$, 296.0573; found, 296.0556.

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Supporting Information Available:. (1) Chemical stability of **9** and **11**, (2) ^{1}H, ^{13}C{^{1}H}, ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org." For complete instructions on how to prepare this material for publication, check the Guidelines for Authors.

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