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Novel N(SCF₃)(CF₃)-amines: synthesis, scalability and stability†

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We disclosed herein a straightforward strategy for the synthesis of unprecedented *N*-((trifluoromethyl)thio), *N*-(trifluoromethyl) amines using a combination of isothiocyanates with a fluoride source and an electrophilic trifluoromethylthiolation reagent. More interestingly, the scalability of the methodology has been demonstrated and the stability of the new motif has been studied.

Organofluorine chemistry is by far one of the most active fields of research in modern organic chemistry. The unique properties induced by the fluorine atom or fluorinated motifs including high lipophilicity, increased solubility and metabolic stability have witnessed the efforts for extensive development during the last few years.¹ Nowadays, fluorinated molecules are extensively used in agrochemicals² as well as for pharmaceutical³ applications. In this span of time, several efficient procedures for the incorporation of trifluoromethyl and trifluoromethyl chalcogens have been reported in the literature through reagent and/or catalyst design as well as methodology developments.⁴

Nitrogen is also a predominant atom in life science technologies;⁵ therefore the association of amines with fluorine-based motifs such as trifluoromethyl groups has been the quest of several research groups. For example, *N*-trifluoromethyl azoles have demonstrated excellent *in vitro* aqueous stability which might improve metabolic stability and membrane permeability compared to their *N*-methyl counterparts.⁶

In this context, several direct methodologies have been developed to access *N*-CF₃ amines making use of electrophilic trifluoromethylation reagents, namely Umemoto⁷ and Togni⁸ reagents or radical trifluoromethyl sources (Scheme 1A).^{9,10} However, these strategies offer limited scope especially with regard to the amine starting material. A breakthrough was disclosed by the Schoenebeck group in 2017. In their study, the authors demonstrated that a wide range of trifluoromethylamines could be accessed *via in situ* generation of thiocarbonyl fluoride using bench stable (Me₄N)SCF₃ (Scheme 1A).¹¹ Afterwards, several groups designed new strategies to access the key thiocarbonyl

fluoride intermediate.^{12–15} Finally, the group of Xu recently reported an elegant oxidative approach for the synthesis of trifluoromethyl amine reagents which have been used for the transfer of the *N*-CF₃ moiety.¹⁶

Another way to access trifluoromethylamines relies on the use of isothiocyanates. Indeed, in 1965, Shepard¹⁷ initially reported that nucleophilic amines could be formed from isothiocyanates using mercury fluoride. Inspired by this precedent, the group of Schoenebeck¹⁸ elegantly demonstrated that silver fluoride could efficiently replace the mercury-based reagent offering a practical and general way to synthesize *N*-trifluoromethyl carbamoyl fluoride (Scheme 1B). This procedure has been also adapted by the groups of Toste and Wilson¹⁹ for the synthesis of *N*-trifluoromethyl amides (Scheme 1B).

N,N-bis(trifluoromethyl) amines represent another valuable motif due to their enhanced lipophilicity and stability in comparison to aliphatic and aromatic *N*-trifluoromethylamines.^{20,21} Despite these interesting properties, access to *N*-(CF₃)₂ amines remains very scarce with most promising synthesis employing a combination of *N,N*-bis(trifluoromethyl)trifluoromethanesulphonamide and a metal-based reagent (Scheme 1C).²²

Therefore, there is a clear need for developing new motifs that could be easily and robustly accessible while modulating the properties around the nitrogen atom such as the lipophilicity (Scheme 1D).²³ In this context, we report herein an unprecedented, mild and efficient protocol for accessing novel *N*-((trifluoromethyl)thio)-*N*-(trifluoromethylamines) starting with isothiocyanates and electrophilic trifluoromethylthiolation reagents (Scheme 1E).

From a reaction design standpoint, inspired by the work of Schoenebeck, we envisioned that a trifluoromethylamino nucleophile intermediate could be first *in situ* generated by the reaction of isothiocyanate with silver fluoride before subsequently reacting with an electrophilic trifluoromethylthiolating source to furnish the desired compounds.

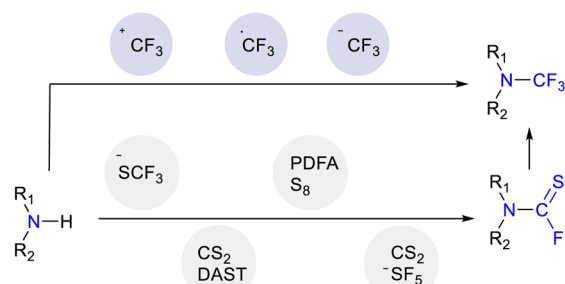
We initiated our study by using benzyl isothiocyanate **1a** as a model substrate in the presence of three equivalents of silver

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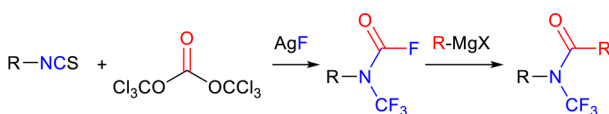
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† Electronic supplementary information (ESI) available. CCDC 2211357. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2sc06542h>

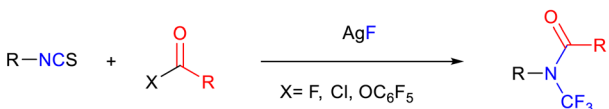
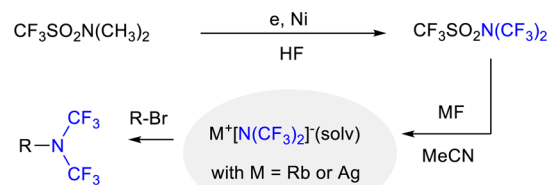


A. Strategies for the synthesis of N-CF₃ alkyl aminesB. Strategies for the synthesis of N-CF₃ amides

Schoenebeck, 2019

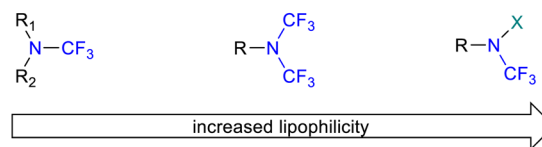
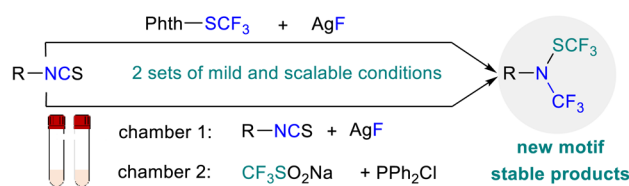


Toste & Wilson, 2021

C. Electrochemical synthesis of N-(CF₃)₂ alkyl amines

D. Need for invention: More lipophilic N-fluorinated amines

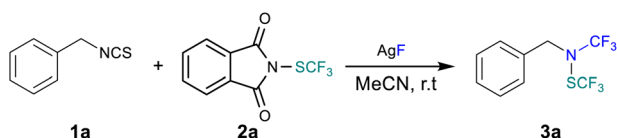
Which X could increase the lipophilicity of N-fluorinated amines?

E. This work: Novel N-(SCF₃)(CF₃)

Scheme 1 (A–E) State of the art for the synthesis of trifluoromethylated amines and the need for accessing new motifs.

fluoride (Table 1). We found that the formed nucleophilic amine was able to react with the electrophilic Munavalli's²⁴ *N*-trifluoromethylthiophthalimide **2a** in MeCN at room temperature delivering the desired product **3a** in 50% yield (Table 1, entry 1). This encouraging result decided us to further investigate parameters that could enhance the reaction outcome. We first studied the impact of the solvent on the formation of the desired product.

Table 1 Optimization of the reaction



Entry ^a	Deviation from standard conditions	Yield ^b (%)
1	None	50
2	THF or dioxane instead of MeCN	0
3	DCM instead of MeCN	0
4	PhMe instead of MeCN	5
5	DMSO instead of MeCN	30
6	DMF instead of MeCN	40
7	50 °C instead of rt	35
8	2b (Shen's reagent) instead of 2a	30
9	With 1 equiv. of CsF	75
10	With 1 equiv. of KF	40

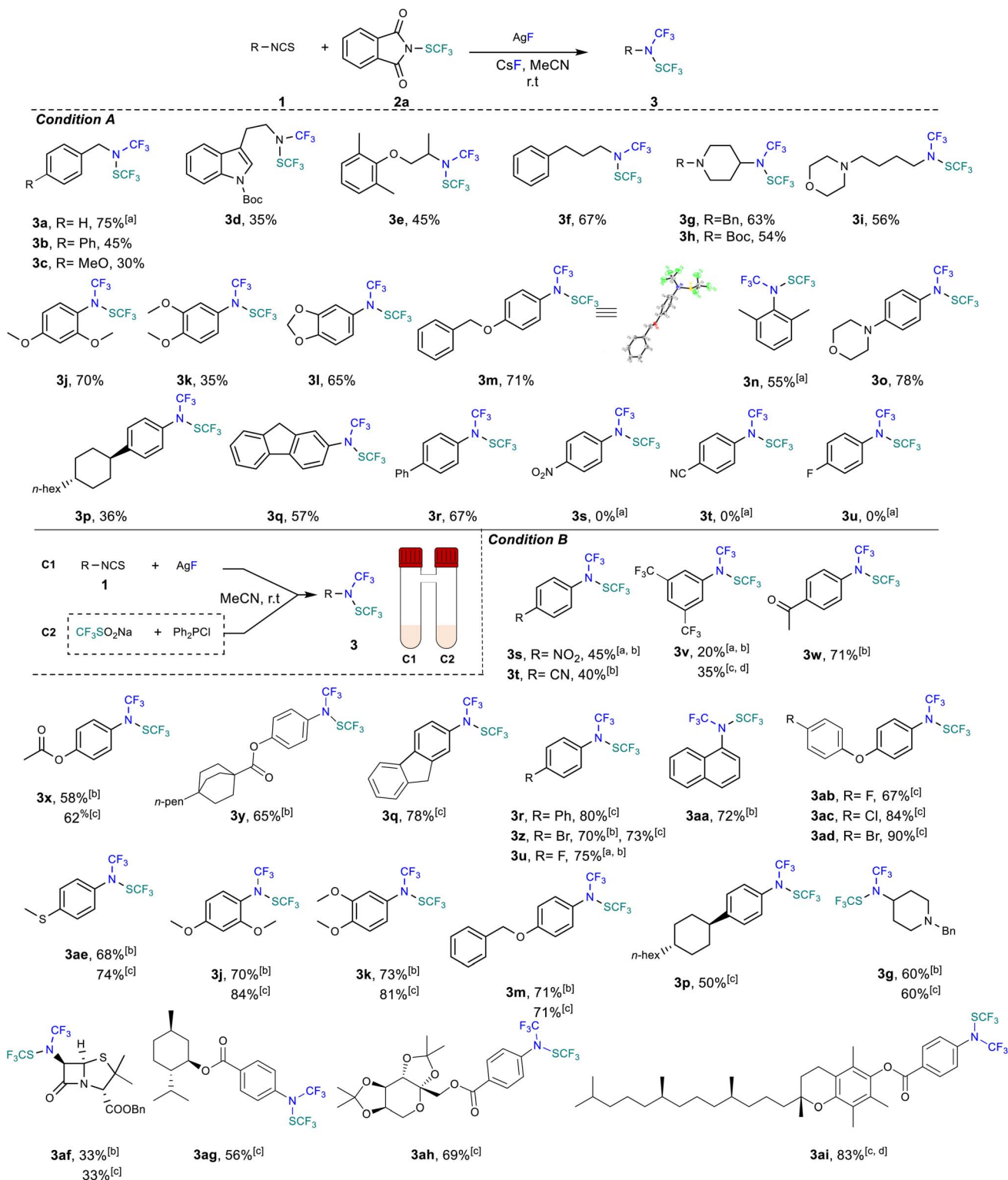
^a Reactions were performed with **1a** (0.2 mmol, 1 equiv.), **2a** (0.2 mmol, 1 equiv.), AgF (0.6 mmol, 3 equiv.) and solvent (1 mL) for 16 hours.

^b Determined by ¹⁹F NMR spectroscopy with PhCF₃ as an internal standard. Shen's reagent **2b** (*N*-trifluoromethylthiosaccharin).

THF and 1,4-dioxane as well as DCM were not suitable for the formation of **3a** (Table 1, entries 2 & 3). Lower yields were obtained when using DMSO and DMF, 30% and 40% respectively (Table 1, entries 2 and 3). In addition, increasing the temperature was found to be detrimental since only 35% of **3a** was obtained at 50 °C (Table 1, entry 7). Then, the impact of the trifluoromethylthiolating reagent was investigated. Surprisingly, the attempt in switching to the more electrophilic Shen's reagent (*N*-trifluoromethylthiosaccharin)²⁵ resulted in lower efficiency with compound **3a** only obtained in 30% yield (Table 1, entry 8). To our delight, adding one equivalent of cesium fluoride allowed for the formation of the desired product in 75% yield (Table 1, entry 9). Finally, potassium fluoride did not improve the overall efficiency of the process (Table 1, entry 10).

With the best set of conditions in hand, we evaluated the effectiveness of the protocol for different isothiocyanate starting materials. Initial tests were devoted to subjecting benzylic isothiocyanate to our reaction conditions. The desired compounds were obtained from low to very good yields (Scheme 2, products **3a–c**). Afterwards, aliphatic isothiocyanates were exposed to the reaction conditions and proved compatible with yields up to 67% (Scheme 2, products **3d–3i**). Noteworthy, the melatonin precursor derivative (Scheme 2, compound **3d**) was derivatized in a synthetically useful isolated yield of 35%. Several protected tertiary amines were also found to be effective under the reaction conditions (Scheme 2, products **3g–3i**). Next, aromatic isothiocyanates were evaluated. Electron rich aryl starting materials were tolerated using our protocol and the desired products were obtained with yields up to 78% (Scheme 2, products **3j–3q**). It should be mentioned that





Scheme 2 Substrate scope. Condition A: reactions were performed with **1** (0.2 mmol, 1 equiv.), **2a** (0.2 mmol, 1 equiv.), AgF (0.6 mmol, 3 equiv.) and CsF (0.2 mmol, 1 equiv.) in MeCN (1 mL) Yields of isolated compounds. Yields of isolated compounds for 16 hours. ^a Yield determined by ¹⁹F NMR spectroscopy with PhCF₃ as an internal standard. ^b Condition B: reactions were performed with chamber 1 (**C1**): **1** (0.2 mmol, 1 equiv.) and AgF (0.8 mmol, 4 equiv.) in MeCN (1 mL); chamber 2 (**C2**): CF₃SO₂Na (0.6 mmol, 3 equiv.) and Ph₂PCl (0.6 mmol, 3 equiv.) in MeCN (1 mL) for 16 hours, yields of isolated compounds. ^c Reactions were performed with chamber 1 (**C1**): **1** (0.2 mmol, 1 equiv.) and AgF (0.8 mmol, 4 equiv.) in MeCN (1 mL); chamber 2 (**C2**): CF₃SO₂Na (0.6 mmol, 3 equiv.) and Ph₂PCl (1.2 mmol, 6 equiv.) in MeCN (1 mL) for 16 hours, yields of isolated compounds. ^d 1.5 mL of ether and 0.5 mL of ACN as a solvent mixture in tube **C1**.

ortho, *meta* or *para* substituted isothiocyanates are suitable partners.

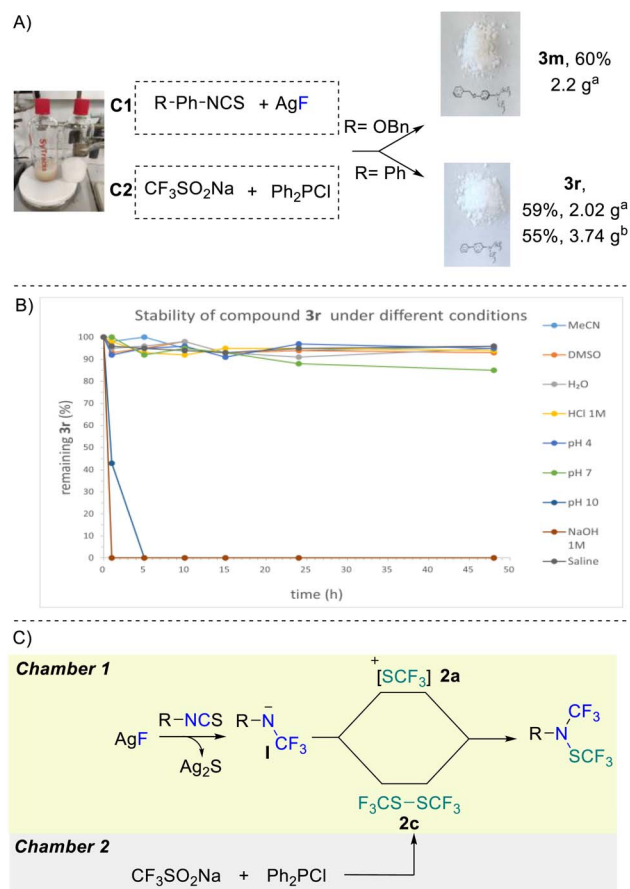
The *para* substituted phenylisothiocyanate with a phenyl ring furnishes the desired product in 67% yield (Scheme 2, **3r**). Interestingly, the structure of **3m** was unambiguously confirmed by X-ray crystallographic analysis.²⁶ Afterwards, we evaluated the influence of electron withdrawing substituents on the starting aryl isothiocyanate derivatives. Unfortunately, the presence of strong electron withdrawing groups including NO₂, CN or fluorine was detrimental to the reaction and no product formation was observed (Scheme 2, products **3s–3u**) probably due to a decrease of the nucleophilicity of the resulting trifluoromethyl amine anion intermediate. Knowing that Shen's reagent would be too electrophilic (*vide supra*) and based on the relative trifluoromethylthio cation-donating scale,²⁷ we identified the trifluoromethylthio dimer ((SCF₃)₂) as the most promising reagent to employ. In addition, the *in situ* generation of such a reactive species has been well documented in the literature.⁴⁴ Indeed, the Langlois reagent can react with phosphine derivatives to yield nucleophilic SCF₃ (ref. 28) which can easily be oxidized to the desired dimer. Disappointingly, our initial *in situ* test turned out to be ineffective. Being aware of the incompatibility issues that could arise from mixing together of all the reaction components, we decided to use a two-chamber reactor. In chamber 2, formation of the –SCF₃ anion was achieved by reacting chloro diphenylphosphine with the Langlois reagent.

This unstable anion readily collapses to afford the trifluoromethylthio dimer ((SCF₃)₂) (see ESI for details†). The formation of nucleophilic trifluoromethylamine through fluorinative desulfurization with AgF also yield the Ag₂S by-product that could potentially oxidize AgSCF₃ to afford the trifluoromethylthio dimer ((SCF₃)₂). Our hypothesis turned out to be effective when isothiocyanate was mixed with silver fluoride in the first chamber while Langlois's reagent reacted with PPh₂Cl in the second chamber. Under these conditions, electron poor arenes including NO₂, CN, CF₃, acetyl, and ester could be transformed into the desired products with isolated yields up to 80% (Scheme 2, products **3s–3r**). Halogen substituted arenes including bromo and fluoro derivatives were also obtained in excellent yields of 70% and 75%, respectively (Scheme 2, products **3z**, **3u**). Naphthalene derivative **3aa** was obtained in 72% yield. Finally, we decided to assess this protocol for electron donating arene derivatives as well as for aliphatic compounds to offer a complementary approach to the original one (condition A) using commercially available reagents. It turns out that these new conditions are also effective with electron donating aryl isocyanate derivatives and the desired products are formed with very good yields up to 90% (Scheme 2, products **3ab**, **3j–m**). Herein also diarylether derivatives substituted with halogens, including fluoro, chloro and bromo were tolerated and the desired products were obtained in an excellent yield up to 90% (Scheme 2, products **3ab**, **3ac** & **3ad**). Moreover, aliphatic product **3g** was also obtained in good yield (60%) while the penicillin core structure was derivatized in a synthetically useful yield of 33% (Scheme 2, product **3af**). Finally, the robustness of our strategy was further demonstrated starting with other complex structures. Indeed, using DL-menthol derivatives allowed us to obtain the desired product **3ag** in good isolated

yield of 56%. Also, using the diacetonefructose derivatives allows the formation of the compound **3ah** in very good yield. Finally, vitamin E derivative **3ai** was obtained with an excellent yield of 83% when the reaction was performed in a mixture of ether/MeCN to increase the solubility of the starting **1a**.

The robustness of the second protocol was further demonstrated by performing a large-scale experiment. Starting with 10 mmol of isothiocyanate and using a 300 mL two-chamber reactor allowed both desired products **3m** and **3r** to be synthesized in very good yields of 60% and 59%, respectively (Scheme 3A).

Unsurprisingly, product **3r** turned out to be completely stable in CH₃CN and DMSO as well as in water for more than 48 hours (Scheme 3B). This compound also demonstrated high stability under acidic conditions (HCl 1 M and pH 4) and in pH = 7 buffer with more than 90% recovery. Rapid degradation was observed under basic conditions (pH 10 and NaOH (1 M)). Interestingly, very high stability under saline conditions was also observed.



Scheme 3 (A) Scale-up experiments: ^a reactions were performed with chamber 1 (C1): **1** (10 mmol, 1 equiv.) and AgF (40 mmol, 4 equiv.) in MeCN (50 mL); chamber 2 (C2): CF₃SO₂Na (30 mmol, 3 equiv.) and Ph₂PCL (60 mmol, 6 equiv.) in MeCN (50 mL) for 24 hours. ^b Reactions were performed with chamber 1 (C1): **1** (20 mmol, 1 equiv.) and AgF (80 mmol, 4 equiv.) in MeCN (100 mL); chamber 2 (C2): CF₃SO₂Na (60 mmol, 3 equiv.) and Ph₂PCL (120 mmol, 6 equiv.) in MeCN (100 mL) for 24 hours yields of isolated compounds. (B) Stability of compound **3r** in various media. (C) Proposed mechanism.



From a mechanistic standpoint, condition A proceeds *via* the generation of trifluoromethyl amine anion **I** that subsequently reacts with the electrophilic trifluoromethylthiolating reagent **2a** yielding the desired product (Scheme 3C). On the other hand, for condition B, the key to success is the generation of the electrophilic CF₃SSCF₃ dimer **2c**. Dimer **2c** finally reacts with nucleophilic amine **I** intermediate to deliver the desired product (Scheme 3C).

Conclusions

In summary, we reported the discovery of two efficient and complementary protocols for the synthesis of unprecedented *N*-((trifluoromethyl)thio), *N*-(trifluoromethyl) amines. While one uses a shelf-stable electrophilic trifluoromethylthiolation reagent, the other employs a two-chamber reactor for the *in situ* generation of an electrophilic trifluoromethylthiolating reagent. The desired products have been obtained in moderate to excellent yields. The scalability of the reaction was demonstrated through the preparation of more than 3.7 grams of the desired compounds. Importantly, N(SCF₃)CF₃ shows high aqueous stability. We assume that this discovery will pave the way to future developments in this exciting field of research.

Data availability

Experimental data have been provided in the ESI.†

Author contributions

Y. Y. and A. T. conceived the project. J. C. V. and A. T. supervised the work and wrote the manuscript. N. S. M. performed the X-ray analysis. All the co-authors contributed to the editing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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