Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides

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S *Supporting Information*

ABSTRACT: A method using calcium triflimide $[Ca(NTf_2)_2]$ as a Lewis acid to activate sulfonyl fluorides toward nucleophilic addition with amines is described. The reaction converts a wide array of sterically and electronically diverse sulfonyl fluorides and amines into the corresponding sulfonamides in good yield.

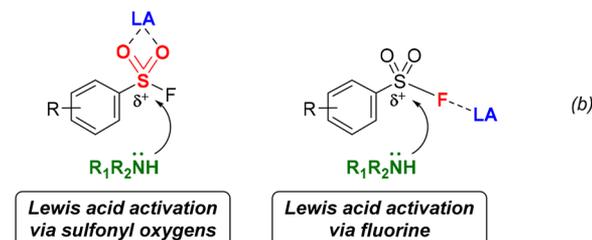- $Ca(NTf_2)_2$ activation of SF
- no strong base
- >20 examples
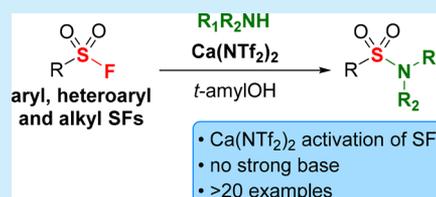
The sulfonamide structural class is prevalent within the pharmaceutical and agrochemical industries. In 2016, sulfonamides represented 15% of the top 100 most prescribed drugs, with therapeutic applications against cardiovascular, infectious, and neurological diseases.[1] In the agrochemical industry, the sulfonamide motif appears in a variety of pesticides, including asulam, orzalin, fomesafen, halosafen, and sulfentrazone.[2] To date, the most common methods to synthesize sulfonamides require the oxidation of sulfides or nucleophilic addition to sulfonyl chlorides. However, these approaches have several limitations. Sulfide oxidation employs the use of strong oxidants that are incompatible with many functional groups, precluding late-stage functionalization,[3] and the high reactivity of sulfonyl chlorides can result in poor selectivity in the presence of competing nucleophiles, detrimental reduction of S(VI) to S(IV), as well as instability during storage.[3c] Therefore, developing alternative methods to generate a diverse array of sulfonamides that employ more stable reactants would benefit pharmaceutical and agrochemical syntheses (Figure 1). In addition, highlighting the value of the sulfonyl fluoride (SF) as a useful and stable functional group provides support for the development and storage of a more diverse collection of these reagents.

In recent years, sulfonyl fluorides have gained renewed interest as alternatives to sulfonyl chlorides due to their inherent stability and chemoselective reactivity at sulfur.[4] The sulfur−fluorine (S−F) bond in SO_2F_2 is approximately 40 kcal mol^{-1} stronger than the sulfur−chlorine (S−Cl) bond in SO_2Cl_2.[5] An analogous comparison to aryl sulfonyl halides suggests that this added bond strength leads to thermodynamic stability and resistance to both reduction[6] and hydrolysis.[7] For the sulfonyl fluorides, a fortuitous balance between hydrolytic stability and reactivity has enabled their wide application as reactive electrophiles in chemical biology to modify specific amino acids in proteins.[7c,d,8]

Current methods of making sulfonamides from sulfonyl fluorides
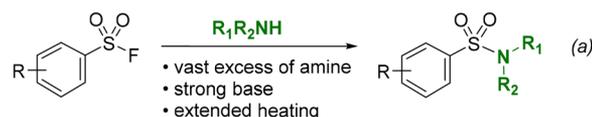
Our proposed modes of sulfonyl fluoride activation
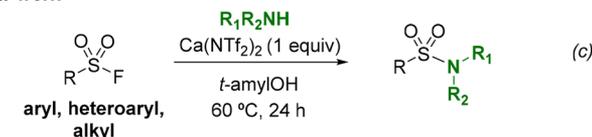

Our work

Figure 1. (a) Current methods toward converting sulfonyl fluorides to sulfonamides,[10] (b) proposed modes of Lewis acid activation sulfonyl fluoride for nucleophilic addition of amines, and (c) our method using $Ca(NTf_2)_2$ in *tert*-amyl alcohol.

Similarly, sulfonyl fluorides have gained importance as alternative precursors to generate sulfonamides.[4,9] However, the increased stability of sulfonyl fluorides comes with the duality of reduced reactivity. Existing methods for synthesizing sulfonamides from sulfonyl fluorides typically involve using a

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strong base/nucleophile, a vast excess of the amine component, and/or extended periods of heating (Figure 1a).[10] Additionally, sulfonamide formation is highly dependent on the electronic nature of the sulfonyl fluoride and the amine.[7c] Herein, we report a mild, calcium triflimide [Ca(NTf$_2$)$_2$] mediated activation of sulfonyl fluorides toward sulfonamide formation in *tert*-amyl alcohol (*t*-amylOH, Figure 1b,c). This method was demonstrated on a wide variety of aromatic, heteroaromatic, and alkyl sulfonamides and, to our knowledge, is the first example of a *single set* of reaction conditions to convert a myriad of sulfonyl fluorides and amines to sulfonamides.

The supposition that Lewis acid (LA) catalysis may facilitate nucleophilic displacement of fluoride under mild conditions guided our initial approach to this project.[11,12] This could potentially occur via formation of Lewis acid/base adducts either with the sulfonyl oxygens or the fluorine atom (Figure 1b).[8a,13,14] In turn, these adducts would increase the susceptibility of the sulfur atom toward nucleophilic addition. A screen of Lewis acids and solvents with benzenesulfonyl fluoride and aniline identified a promising lead: barium triflimide [Ba(NTf$_2$)$_2$] in *t*-amylOH, (Table 1, entry 2). Upon

Table 1. Lewis Acid Optimization[a]
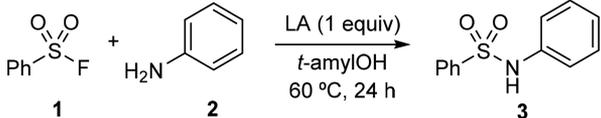
| entry	Lewis acid	yield (%)
1	Ca(NTf$_2$)$_2$	88
2	Ba(NTf$_2$)$_2$	80
3	Mg(NTf$_2$)$_2$	38
4	LiNTf$_2$	9
5	AgNTf$_2$	N/R[b]
6	KNTf$_2$	<2
7	CaF$_2$	N/R[b]
8	Ca(OTf)$_2$	4
9	La(OTf)$_3$·xH$_2$O	30
10	LiCl	2
11	HNTf$_2$	3
12	none	N/R[b]

[a]Reaction conditions: PhSO$_2$F (1 equiv), aniline (2 equiv), Lewis acid (1 equiv), *t*-amylOH (0.32 M), 60 °C, 24 h. [b]N/R denotes no reaction.

a thorough analysis of additional triflimide salts, divalent second group salts such as Ba(NTf$_2$)$_2$ and Ca(NTf$_2$)$_2$ emerged as superior Lewis acids, affording the sulfonamide product in higher yields than the monovalent cationic triflimides (Table 1, entries 1−3 and entries 4−6, respectively). Solubility of the Lewis acids showed a marked effect on the extent of reaction. In general, the triflimide salts were more soluble in the reaction than Lewis acids with other counteranions (Table 1, entries 7−10). Using the conjugate acid of the triflimide anion, HNTf$_2$, in lieu of a Lewis acid resulted in a marginal 3% isolated yield of compound **3** (Table 1, entry 11). We also note that calcium fluoride, a potential byproduct of the reaction, does not affect sulfonamide formation (Table 1, entry 7). Attempts to reduce the molar equivalents of Lewis acid and/or amine resulted in incomplete consumption of the benzenesulfonyl fluoride.

Calcium triflimide was selected for further examination of solvent effects due to its improved organic solubility and reduced cost vs barium triflimide. The reaction could be run in water, although a reduction in yield was observed, and the solubility of the starting materials was generally poor (Table 2, entry 2). Alcoholic solvents afforded the desired
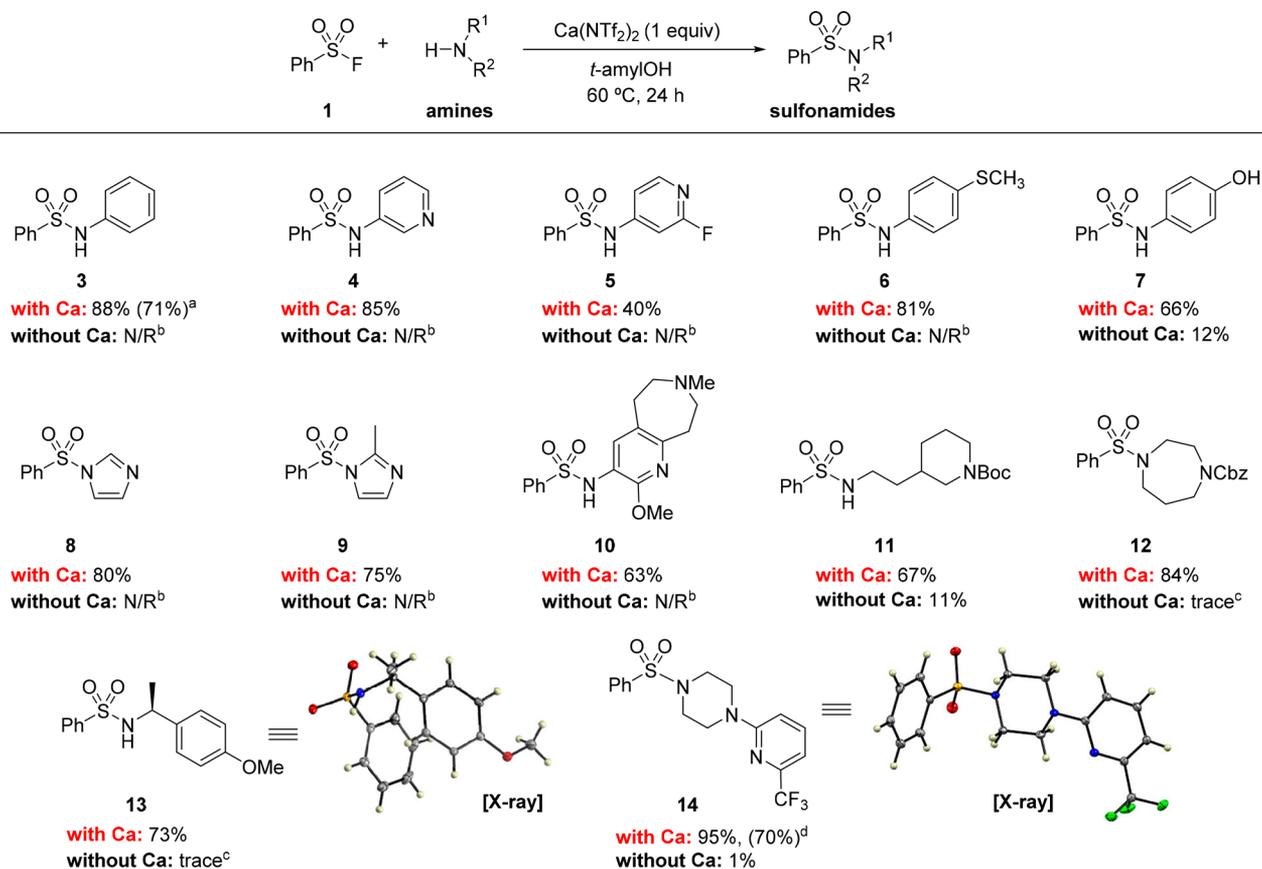
Table 2. Solvent Optimization[a]
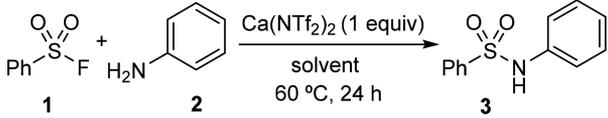
entry	solvent	yield (%)
1	*t*-amylOH	88
2	H$_2$O	63
3	MeOH	40
4	*i*-PrOH	71
5	*t*-BuOH	87
6	MeCN	42
7	DMF	13
8	toluene	51
9	HFIP	9[b]

[a]Reaction conditions: PhSO$_2$F (1 equiv), aniline (2 equiv), Ca(NTf$_2$)$_2$ (1 equiv), solvent (0.20 M), 60 °C, 24 h. Isolated yields are averages of two independent trials. [b]Ca(NTf$_2$)$_2$ showed minimal solubility in HFIP. Isolated yield is reported for one trial.

sulfonamide as well, with sterically congested alcohols providing higher conversion to sulfonamide (Table 2, entries 3−5). Switching to polar aprotic solvents such as MeCN and DMF (Table 2, entries 6 and 7), the conversion dropped significantly, while a nonpolar solvent such as toluene produced moderate yields of the sulfonamide (Table 2, entry 8). Reports in the literature suggest using hexafluoroisopropanol (HFIP) as a solvent or NBu$_4$PF$_6$ as an additive could improve the activation of Ca(NTf$_2$)$_2$.[12a,15] However, Ca(NTf$_2$)$_2$ showed minimal solubility in HFIP, and only 9% sulfonamide product **3** was isolated (Table 2, entry 9). Additionally, the NBu$_4$PF$_6$/Ca(NTf$_2$)$_2$ combination also resulted in considerably decreased yields of **3** (see the Supporting Information (SI)). Overall, *t*-amylOH and *t*-BuOH provided the highest yields with *t*-amylOH emerging as the solvent of choice due to convenience of use and environmental factors.[16]

With favorable conditions in hand, we next focused our attention on exploring the versatility of the method using sterically and electronically diverse aromatic and aliphatic amines as nucleophiles (Scheme 1). When aromatic and heteroaromatic amines were reacted with benzenesulfonyl fluoride, in the presence of Ca(NTf$_2$)$_2$, sulfonamide formation was achieved in good to excellent yield. It is noteworthy that in the absence of Lewis acid these reactions proceeded with little to no sulfonamide formation, highlighting the crucial role Ca(NTf$_2$)$_2$ plays in activating the sulfonyl fluorides toward nucleophilic addition. We generally used two molar equivalents of the amine component for these reactions but were pleased to show that when only 1 equiv of aniline was used in combination with triethylamine sulfonamide **3** was isolated in 71% yield (Scheme 1).[17]

Interestingly, 4-aminophenol reacts with sulfonyl fluoride **1** to form the sulfonamide **7** as the major product. This preference for sulfonamide formation is opposite to the

Scheme 1. Substrate Scope Reacting Aryl, Heteroaryl, and Aliphatic Amines with PhSO$_2$F*

3
with Ca: 88% (71%)[a]
without Ca: N/R[b]

4
with Ca: 85%
without Ca: N/R[b]

5
with Ca: 40%
without Ca: N/R[b]

6
with Ca: 81%
without Ca: N/R[b]

7
with Ca: 66%
without Ca: 12%

8
with Ca: 80%
without Ca: N/R[b]

9
with Ca: 75%
without Ca: N/R[b]

10
with Ca: 63%
without Ca: N/R[b]

11
with Ca: 67%
without Ca: 11%

12
with Ca: 84%
without Ca: trace[c]

13 [X-ray]
with Ca: 73%
without Ca: trace[c]

14 [X-ray]
with Ca: 95%, (70%)[d]
without Ca: 1%

*Reaction conditions: PhSO$_2$F (1 equiv), amine (2 equiv), Ca(NTf$_2$)$_2$ (1 equiv), *t*-amylOH (0.20 M), 60 °C, 24 h. Isolated yields for Ca(NTf$_2$)$_2$ reactions are averages of two independent trials. Reactions without Ca were conducted as a single reaction. Mass balance is unreacted starting material. [a]PhSO$_2$F (1 equiv), aniline (1 equiv), Ca(NTf$_2$)$_2$ (1 equiv), Et$_3$N (1 equiv), *t*-amylOH (0.20 M), 60 °C, 24 h. [b]N/R denotes no reaction. [c]Trace product was detected by LC/MS; however, it could not be isolated. [d]Yield of sulfonamide **14** on 6.2 mmol scale.

observed reactivity in the presence of Cs$_2$CO$_3$, which instead provides the corresponding sulfonic ester.[18] Analogues of compound **10** with variations on the arylsulfonyl were valuable leads in a drug discovery project within Pfizer.[19] Under our reaction conditions, we obtained compound **10** in 63% yield from benzenesulfonyl fluoride, highlighting the value of our chemistry on a pharmaceutically relevant template. Additionally, both primary and secondary aliphatic amines reacted with sulfonyl fluoride **1** to generate their corresponding sulfonamides (**11**–**14**) in good yield, with the synthesis of compound **14** exemplified on gram scale. Initial attempts to react phenylsulfonyl fluoride with weakly nucleophilic anilines containing electron withdrawing groups at the 4-position (e.g., −SCF$_3$ and −CF$_3$), using our general procedure, did not result in detectable sulfonamide product.
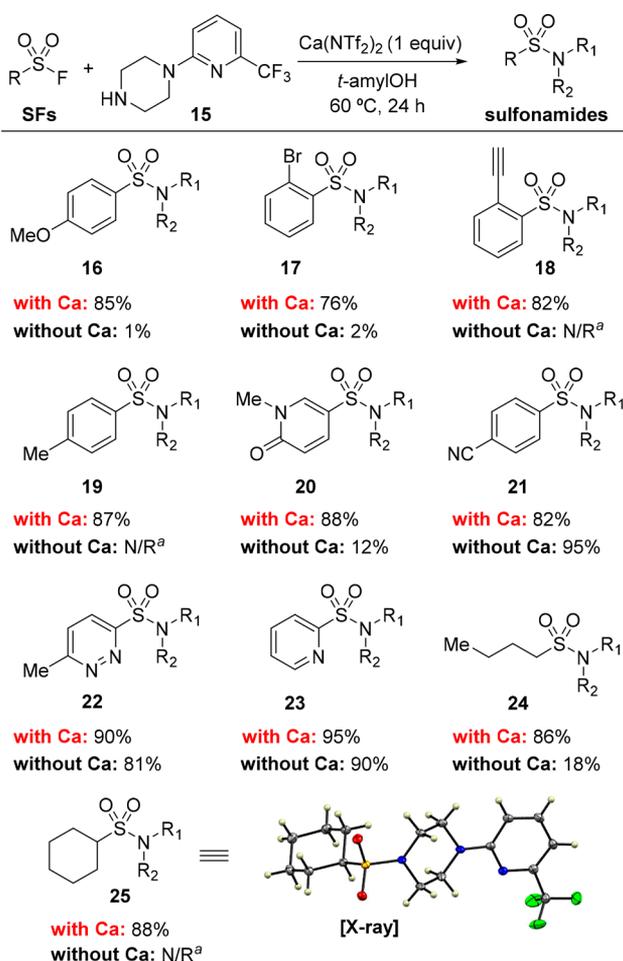
We selected 1-(5-(trifluoromethyl)-2-pyridinyl)piperazine (**15**) as the nucleophilic amine to assess the versatility of the method with various sulfonyl fluorides. Toward this end, we successfully synthesized an array of sulfonamides using aryl- and heteroarylsulfonyl fluorides (Scheme 2). Additionally, alkylsulfonyl fluorides provided the desired sulfonamides (**24** and **25**) under identical reaction conditions. Interestingly, while Ca(NTf$_2$)$_2$ was required for reactivity of electron-rich arylsulfonyl fluorides, reactions of electron-deficient sulfonyl fluorides with amine **15** proceeded in the absence of any Lewis acid (see **21**–**23**, Scheme 2). This is presumably due to

the increased electrophilicity of the sulfonyl fluoride resulting from the electron-withdrawing groups in the aryl ring.[7c]

We next wanted to explore a less nucleophilic amine in combination with the electron-deficient sulfonyl fluorides to determine if Ca(NTf$_2$)$_2$ would be required in those cases. Accordingly, 4-cyanobenzenesulfonyl fluoride was reacted with aniline in the presence and absence of Ca(NTf$_2$)$_2$ in *t*-amyl alcohol at 60 °C and analyzed by LC/MS (see the SI). In the absence of Ca(NTf$_2$)$_2$ no sulfonamide formation was detected after 24 h. However, in the presence of Ca(NTf$_2$)$_2$, the reaction was nearly complete after 1 h, affording sulfonamide **26** in 85% yield (Scheme 3 and SI). We observed similar reactivity with the heteroarylsulfonyl fluorides, as demonstrated in the synthesis of sulfonamides **27** and **28** (Scheme 3). Although Ca(NTf$_2$)$_2$ is not required for reaction between an electron-deficient sulfonyl fluoride and a highly nucleophilic amine, for all other combinations of sulfonyl fluorides and amines that we explored, Ca(NTf$_2$)$_2$ activation to generate sulfonamides in high yield has been demonstrated to be essential.

We wanted to show the complementarity of this method and the stability of the sulfonyl fluoride toward traditional sulfonamide synthesis from sulfonyl chlorides. Therefore, we subjected piperazine **29** to a sequential Boc deprotection, sulfonamidation with benzenesulfonyl chloride. The reactivity of the sulfonyl fluoride was then unveiled for reaction with 3-aminopyridine via the action of Ca(NTf$_2$)$_2$ to afford

Scheme 2. Substrate Scope Reacting Aryl- and Alkylsulfonyl Fluorides with Amine 15*

*Reaction conditions: RSO₂F (1 equiv), 1-(5-trifluoromethyl)-2-pyrdinyl piperazine, **18** (2 equiv), Ca(NTf₂)₂ (1 equiv), *t*-amylOH (0.20 M), 60 °C, 24 h. Isolated yields for Ca(NTf₂)₂ reactions are averages of two independent trials. Reactions without Ca where conducted as a single reaction. ᵃN/R denotes no reaction.

Scheme 3. Comparing the Reactivity of Electron-Deficient Sulfonyl Fluorides with Amines 2 and 15*
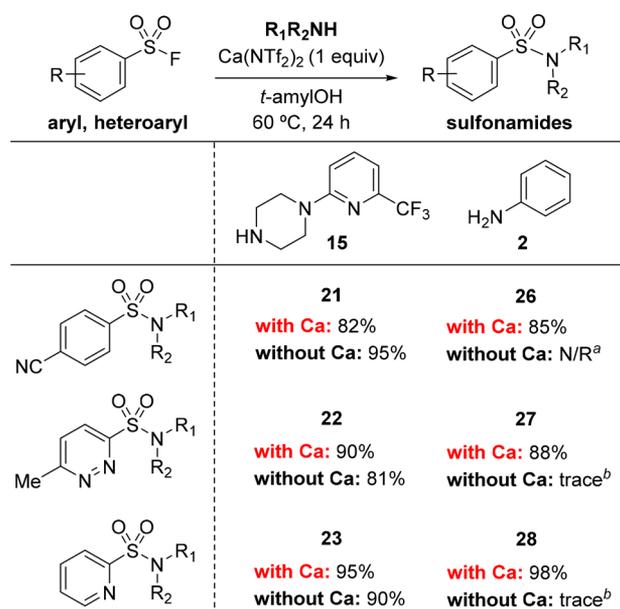
*Reaction conditions: RSO₂F (1 equiv), amine, **15** or **2** (2 equiv), Ca(NTf₂)₂ (1 equiv), *t*-amylOH (0.20 M), 60 °C, 24 h. Isolated yields for Ca(NTf₂)₂ reactions are averages of independent trials. Reactions without Ca weere conducted as a single reaction. ᵃN/R denotes no reaction. ᵇTrace product was detected by LC/MS; however, it could not be isolated.

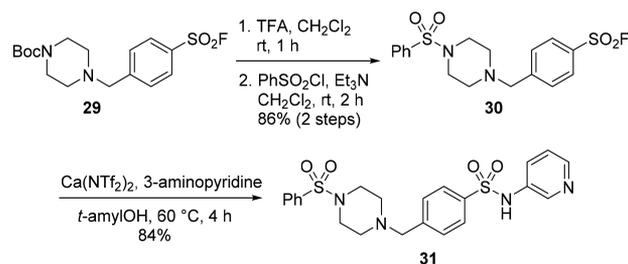## Scheme 4. Sulfonyl Fluoride as a Latent Electrophile

compound **31** in high yield (Scheme 4). Notably, sulfonyl fluoride **30** withstood the Boc-deprotection under acidic conditions, and the first sulfonamidation in the presence of triethylamine proceeded without detectable self-condensation. The synthesis of compound **31** demonstrates how synthetic strategies can exploit the robust nature of sulfonyl fluorides and then unlock the latent reactivity using calcium triflimide.

In conclusion, we have developed a method that employs calcium triflimide activation of aryl- and alkylsulfonyl fluorides to synthesize sulfonamides. This method can be used to couple a wide array of sterically and electronically diverse sulfonyl fluorides and amines to produce sulfonamides in good to excellent yields. Preliminary results suggest that divalent cations and the triflimide anion are essential for efficient conversion, with future studies focusing on developing a better understanding of the reaction mechanism. With the contribution of this new method, we envision that the sulfonyl fluorides will emerge as the preferred sulfonyl halide for a myriad of sulfonylation reactions.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01520.

Experimental methods and NMR spectra (PDF)

Accession Codes

CCDC 1842164−1842166 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.

(2) Devendar, P.; Yang, G.-F. *Top. Curr. Chem.* **2017**, *375*, 1.

(3) (a) Wright, S. W.; Hallstrom, K. N. *J. Org. Chem.* **2006**, *71*, 1080. (b) Bahrami, K.; Khodaei, M. M.; Abbasi, J. *Tetrahedron* **2012**, *68*, 5095. (c) Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P. *Drug Discovery Today* **2015**, *20*, 11.

(4) (a) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430 and references cited therein. (b) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Konovets, A. I.; Sadkova, I. V.; Tolmachev, A. *ACS Comb. Sci.* **2014**, *16*, 192.

(5) (a) Kiang, T.; Zare, R. N. *J. Chem. Soc., Chem. Commun.* **1980**, *24*, 1228. (b) Wray, K. L.; Feldman, E. V. *J. Chem. Phys.* **1971**, *54*, 3445.

(6) (a) Bertrand, M. P. *Org. Prep. Proced. Int.* **1994**, *26*, 257. (b) Chatgilialoglu, C. Sulfonyl Radicals. In *Sulphones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; John Wiley & Sons, Ltd: Chichester, 1988; pp 1089−1113.

(7) (a) Baker, B. R.; Lourens, G. J. *J. Med. Chem.* **1967**, *10*, 1113. (b) Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc., Perkin Trans. 2* **1972**, *4*, 468. (c) Mukherjee, H.; Debreczeni, J.; Breed, J.; Tentarelli, S.; Aquila, B.; Dowling, J. E.; Whitty, A.; Grimster, N. P. *Org. Biomol. Chem.* **2017**, *15*, 9685. (d) Huang, J. L.; Nagy, A.; Ivleva, V. B.; Blackstock, D.; Arnold, F.; Cai, C. X. *Anal. Chem.* **2018**, *90*, 4293. (e) Kice, J. L.; Lunney, E. A. *J. Org. Chem.* **1975**, *40*, 2125.

(8) (a) Narayanan, A.; Jones, L. H. *Chem. Sci.* **2015**, *6*, 2650 and references therein. (b) Zhao, Q.; Ouyang, X.; Wan, X.; Gajiwala, K. S.; Kath, J. C.; Jones, L. H.; Burlingame, A. L.; Taunton, J. *J. Am. Chem. Soc.* **2017**, *139*, 680.

(9) (a) Zelli, R.; Tommasone, S.; Dumy, P.; Marra, A.; Dondoni, A. *Eur. J. Org. Chem.* **2016**, *2016*, 5102. (b) Toulgoat, F.; Langlois, B. R.; Médebielle, M.; Sanchez, J.-Y. *J. Org. Chem.* **2008**, *73*, 5613.

(10) (a) Empfield, J. R.; Mayhugh, D.; Ohnmacht, C. J.; Frank, C. A.; Grant, T.; Li, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 775.

(b) Bebernitz, G. R.; Aicher, T. D.; Stanton, J. L.; Gao, J.; Shetty, S. S.; Knorr, D. C.; Strohschein, R. J.; Tan, J.; Brand, L. J.; Liu, C.; Wang, W. H.; Vinluan, C. C.; Kaplan, E. L.; Dragland, C. J.; DelGrande, D.; Islam, A.; Lozito, R. J.; Liu, X.; Maniara, W. M.; Mann, W. R. *J. Med. Chem.* **2000**, *43*, 2248. (c) Berg, S.; Bergh, M.; Hellberg, S.; Högdin, K.; Lo-Alfredsson, Y.; Söderman, P.; von Berg, S.; Weigelt, T.; Ormö, M.; Xue, Y.; Tucker, J.; Neelissen, J.; Jerning, E.; Nilsson, Y.; Bhat, R. *J. Med. Chem.* **2012**, *55*, 9107. (d) Harris, P. A.; Cheung, M.; Hunter, R. N.; Brown, M. L.; Veal, J. M.; Nolte, R. T.; Wang, L.; Liu, W.; Crosby, R. M.; Johnson, J. H.; Epperly, A. H.; Kumar, R.; Luttrell, D. K.; Stafford, J. A. *J. Med. Chem.* **2005**, *48*, 1610.

(11) For an example of base-catalyzed activation of sulfonyl fluorides, see: Gembus, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, *2008*, 1463.

(12) For representation of Lewis acid complexation with sulfonyl compounds, see: (a) Qi, C.; Hasenmaile, F.; Gandon, V.; Lebœuf, D. *ACS Catal.* **2018**, *8*, 1734. (b) Peyronneau, M.; Roques, N.; Mazieres, S.; Le Roux, C. *Synlett* **2003**, *5*, 0631.

(13) Begouin, J.-M.; Niggemann, M. *Chem. - Eur. J.* **2013**, *19*, 8030.

(14) There is also potential for interaction of the Lewis acid with the amine nucleophile. For an example of $Ca(NTf_2)_2$ participating in coordination of sulfonyl oxygens and NH bonds with the assistance of an alcoholic solvent, see: Lebœuf, D.; Gandon, V. *Synthesis* **2017**, *49*, 1500.

(15) Lebœuf, D.; Gandon, V. *Synthesis* **2017**, *49*, 1500 and references cited therein.

(16) Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950.

(17) Additional stoichiometry/base combinations were explored; see the Supporting Information for selected examples.

(18) Tribby, A. L.; Rodríguez, I.; Shariffudin, S.; Ball, N. D. *J. Org. Chem.* **2017**, *82*, 2294.

(19) Chappie, T. A.; Henderson, J. L.; Young, J. M.; Wager, T. T.; Kormos, B. L.; Patel, N. C.; Sciabola, S.; Tuttle, J. B.; Verhoest, P. R.; Tucker, J. W. (Pfizer, Inc., USA). Preparation of 6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine compounds as selective dopamine D3 ligands. PCT Int. Appl. WO 2017122116A1 20170720, 2017.