A Broad-Spectrum, Catalytic Amidation of Sulfonyl Fluorides and Fluorosulfates

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Abstract: A broad-spectrum, catalytic method has been developed for the synthesis of sulfonamides and sulfamates. With the activation by the combination of a catalytic amount of 1-hydroxybenzotriazole (HOBt) and silicon additives, amidations of sulfonyl fluorides and fluorosulfates proceeded smoothly and excellent yields were generally obtained (87%–99%). Noticeably, this protocol is particularly efficient for sterically hindered substrates. Catalyst loading is generally low and only 0.02 mol% of catalyst is required for the multidecagram-scale synthesis of an amantadine derivative. In addition, the potential of this method in medicinal chemistry has been demonstrated by the synthesis of the marketed drug Fedratinib via a key intermediate sulfonyl fluoride **13**. Since a large number of amines are commercially available, this route provides a facile entry to access Fedratinib analogues for biological screening.

Introduction

Sulfonamide has been marked as one of privileged structural motifs in pharmaceutical and agrochemical industries.[1] Many commercial therapeutic agents and herbicides contain a sulfonamide functional group (Figure 1). Although a number of modern methods have been developed such as oxidative N–S bond formation,[2] metal-catalyzed cross coupling,[3] N–functionalization of primary sulfonamides,[4] C–H amination,[5] and other miscellaneous methods,[6] traditional amidation of sulfonyl chlorides with amines remained one of the most general methods to prepare sulfonamides in terms of cost and availability of raw materials. However, sulfonyl chloride chemistry faces inevitable challenges due to the electrophilic and oxidative nature of sulfonyl chlorides. Indeed, reactions of sulfonyl chlorides with amines are compromised by multiple undesired pathways such as non-selective sulfonylation, hydrolysis, reduction of S(VI), and chlorination.[7]

Sulfonyl fluorides[8,9f] have been regarded as an attractive surrogate for sulfonyl chlorides due to their superior stability and tunable reactivity. To emphasize such unique reactivity involving S(VI)–F bonds, Sharpless recently coined the term "sulfur(VI) fluoride exchange (SuFEx) chemistry".[9] Meanwhile, sulfonyl fluorides, fluorosulfates,[9c,f] and other compounds[10] with S(VI)−F bonds, have gained increasing attention on drug

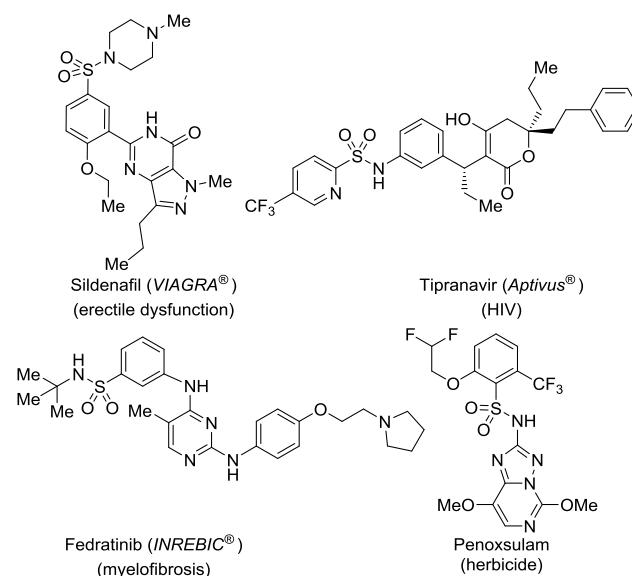discovery,[11] chemical biology,[12] and material science.[9e,13]

Figure 1. Representative sulfonamide molecules.

In the context of synthetic chemistry, highly efficient protocols developed by Gembus[14] and Sharpless[9e,f] have been exceptionally successful in connecting O–nucleophiles with S(VI) fluorides such as sulfonyl fluorides and fluorosulfates (Scheme 1b). However, the SuFEx reactivities of sulfonyl fluorides and fluorosulfates with N–nucleophiles have not been fully unlocked. Viable N–nucleophiles are limited to "deprotonated" amides and heterocycles such as imidazoles.[15] Sulfonamidations with simple aliphatic and aromatic amines have met with limited success until recently.[16] Most reactions with reasonable yields involved the use of activated substrates. Very recently, am Ende and Ball developed an elegant system for the activation of sulfur(VI) fluorides. With 1.1 equiv of $Ca(NTf_2)_2$, a group of sulfonamides were prepared from sulfonyl fluorides in good to excellent yields (Scheme 1c).[17] Strikingly, this protocol was also effective for the activation of less active fluorosulfates and sulfamoyl fluorides. However, the authors mentioned that a stoichiometric amount of calcium activator was required for reaction completion. It is highly desirable to develop a broad-spectrum, catalytic method for this synthetically useful transformation. In addition, sterically hindered substrates, which have been rarely investigated by existing methods, deserve special attention since bulky sulfonamides have shown promising properties in medicinal chemistry (e.g. Fedratinib and Penoxsulam). Herein, we present that a two-component catalytic system (cat. 1-hydroxybenzotriazole (HOBt) with a silicon additive) provides a

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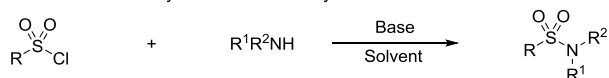   lile26@mail.sysu.edu.cn
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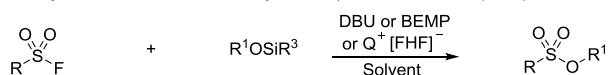[‡]   These authors contributed equally.

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        the document.

general solution to the amidation of sulfonyl fluorides and fluorosulfates (Scheme 1d).
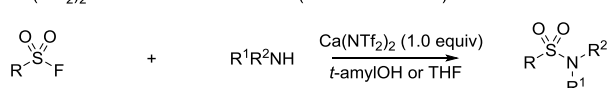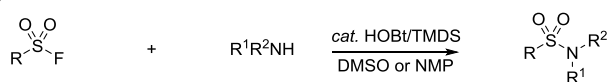

Scheme 1. Common amidation methods of sulfur(VI) halides.

Results and Discussion

This study started with our original efforts towards building a ligand library of *ortho*-phosphinoarenesulfonamides.[18] Attempts on the preparation of *ortho*-phosphinoarenesulfonyl chlorides failed since the sulfonyl chloride group was incompatible with phosphines. Then, we turned our attention to the more stable *ortho*-phosphinoarenesulfonyl fluorides as precursors to sulfonamides. To ensure that the amidation protocol would be applicable for a broad range of substrates, we chose the reaction of 2-(diphenylphosphanyl)-5-methylbenzenesulfonyl fluoride (**1a**) with bulky *tert*-butylamine (**2a**) as a model reaction. Unfortunately, only a small amount of the desired product **3a** (up to 2%) was obtained with literature methods (Table S1). We then decided to develop a more effective catalytic system to solve this challenge.

We focused on the development of new nucleophilic catalysts since fluoride ions were able to deactivate most Lewis acid catalysts. Mechanistically, an S_N2 or addition-elimination pathway will be more favorable than S_N1 pathway due to strong electric static interactions[19] between S(VI) and F. We speculated that the diminished reactivity for **1a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 4-dimethylamino-pyridine (DMAP) was attributed to the bulkiness of both substrates and intermediates. A highly congested transition state inhibited the reaction for sterically encumbered substrates. We proposed that a less sterically hindered catalyst may catalyze the targeted transformation.

O– and S–based nucleophiles have been widely used as stoichiometric activators in peptide chemistry[20] but have been less recognized as catalysts. We first investigated a series of O– and S–nucleophiles with a broad pK_a range in a stoichiometric amount. Gratifyingly, the reactions promoted by HOBt[21] and its analogues gave the superior performance (Table 1, entries 7–9). The product **3a** was obtained in 87% yield when the condition was set by utilizing HOBt (1.0 equiv) as an activator and anhydrous dimethyl sulfoxide (DMSO) as solvent (Table 1, entry 9). Only a trace amount of product was observed when the reactions were run with other activating

reagents such as electron-deficient phenols, thiophenols, and hydroxy imides (Table 1, entries 1–6). Interestingly, Oxyma,[22] an alternative of HOBt in peptide coupling, failed to promote the amidation (Table 1, entry 10).
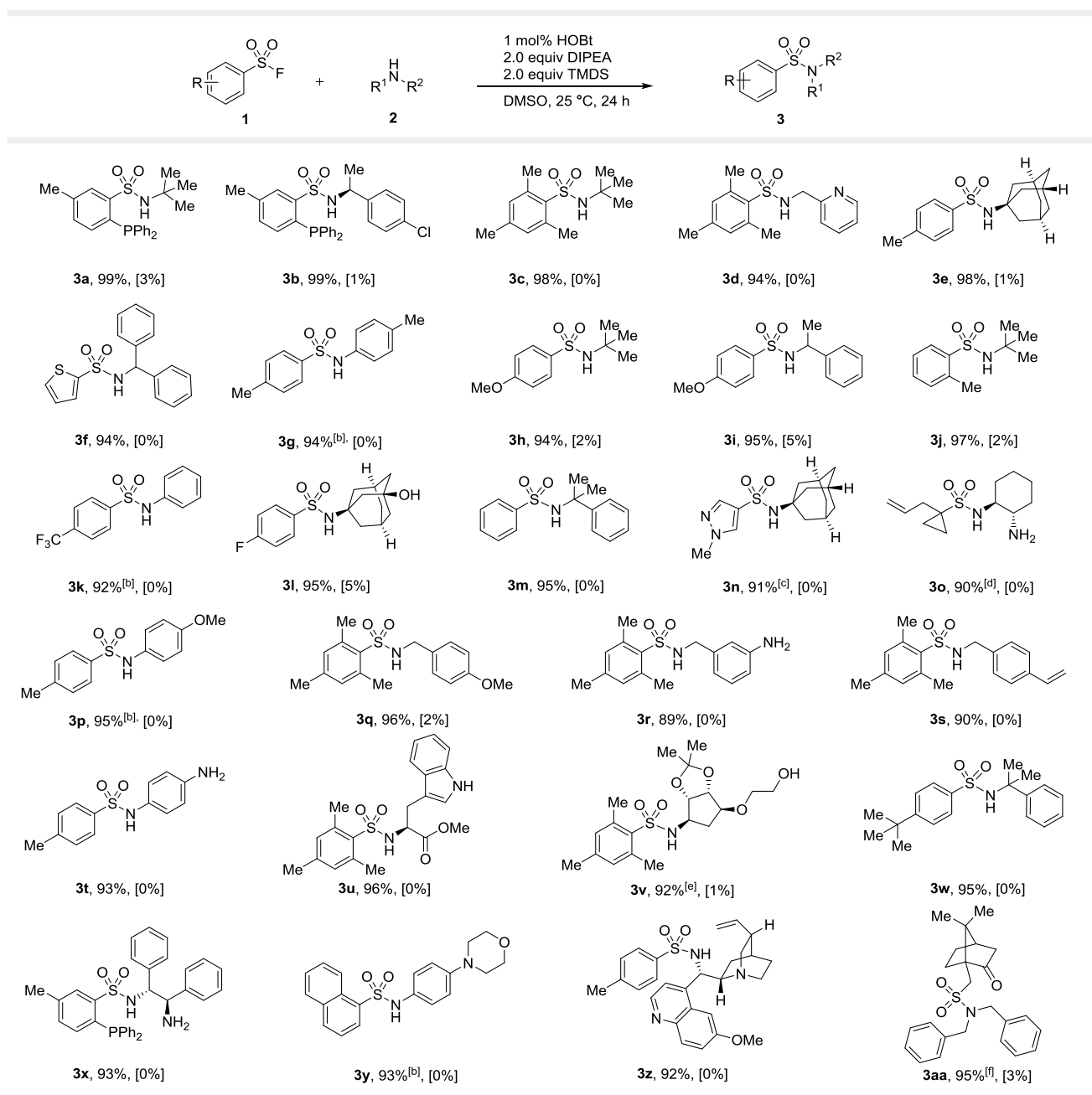
Table 1. Optimization of the reaction conditions.[a]

Entry	Catalyst or Activator	Additive	Base	Yield[%][b]
1	4-Bromophenol	none	t-BuNH₂	0
2	4-Nitrophenol	none	t-BuNH₂	4
3	Pentafluorophenol	none	t-BuNH₂	7
4	Thiophenol	none	t-BuNH₂	0
5	4-Nitrobenzenethiol	none	t-BuNH₂	0
6	HOSu	none	t-BuNH₂	0
7	HOAt	none	t-BuNH₂	65
8	HOCt	none	t-BuNH₂	75
9	HOBt	none	t-BuNH₂	87
10	Oxyma	none	t-BuNH₂	7
11	1 mol% HOBt	none	DIPEA	3[c]
12	1 mol% HOBt	Et₃SiH	DIPEA	14[c]
13	1 mol% HOBt	Ti(OEt)₄	DIPEA	37[c]
14	1 mol% HOBt	PMHS	DIPEA	80[c]
15	1 mol% HOBt	(EtO)₂MeSiH	DIPEA	91[c]
16	1 mol% HOBt	TMDS	DIPEA	100[c]

[a] Reactions were run with sulfonyl fluoride **1a** (0.20 mmol), t-BuNH₂ **2a** (0.60 mmol), and activator (0.20 mmol) in anhydrous DMSO (0.25 mL) at 40 °C for 24 h. The full names of all abbreviations can be found in the supporting information. [b] The yield of **3a** was determined by ^{31}P NMR. [c] Reactions were run with sulfonyl fluoride **1a** (0.24 mmol), t-BuNH₂ **2a** (0.20 mmol), HOBt (1 mol%), DIPEA (0.40 mmol), and TMDS (0.40 mmol) in anhydrous DMSO (0.25 mL) at 25 °C for 24 h.

Initial efforts with a catalytic amount of HOBt were unsuccessful (Table 1, entry 11). However, the addition of external fluoride scavengers[23] enabled the catalyst turnover and significantly accelerated the reaction. Among the additives we tested, 1,1,3,3-tetramethyldisiloxane (TMDS) gave the optimal results (Table 1, entry 16). With only 1 mol% catalyst loading, **3a** was obtained in 100% yield at 25 °C. Noticeably, more electrophilic chlorine-containing silicon reagents (Table S3, entries 2, 5–6, 8, 15, 19) yielded no expected products.

With the optimal conditions in hand, the substrate scope was explored with sulfonyl fluorides and amines (Table 2). We intentionally selected either bulky or less nucleophilic amines as substrates since the background reactions of these less active substrates were neglectable (no more than 5%). Sulfonamides with diverse structures were obtained in excellent yields under our catalytic conditions. Strikingly, even in the cases that both reaction partners are sterically hindered and/or
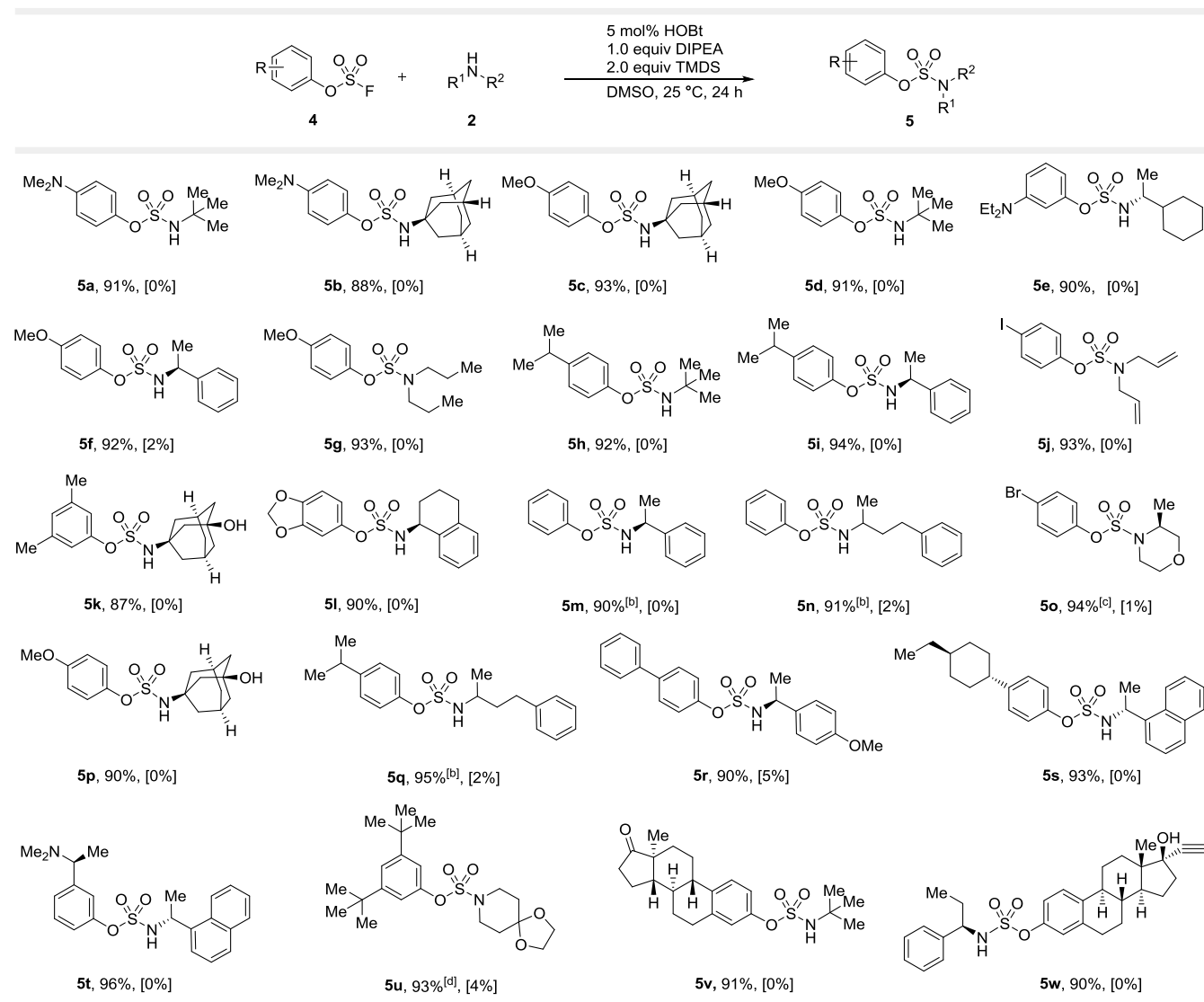
Table 2. Scope of amidation reactions of sulfonyl fluorides.[a]

3a, 99%, [3%] 3b, 99%, [1%] 3c, 98%, [0%] 3d, 94%, [0%] 3e, 98%, [1%]

3f, 94%, [0%] 3g, 94%[b], [0%] 3h, 94%, [2%] 3i, 95%, [5%] 3j, 97%, [2%]

3k, 92%[b], [0%] 3l, 95%, [5%] 3m, 95%, [0%] 3n, 91%[c], [0%] 3o, 90%[d], [0%]

3p, 95%[b], [0%] 3q, 96%, [2%] 3r, 89%, [0%] 3s, 90%, [0%]

3t, 93%, [0%] 3u, 96%, [0%] 3v, 92%[e], [1%] 3w, 95%, [0%]

3x, 93%, [0%] 3y, 93%[b], [0%] 3z, 92%, [0%] 3aa, 95%[f], [3%]

[a] Reactions were run with sulfonyl fluoride 1 (1.20 mmol), amine 2 (1.00 mmol), HOBt (1 mol%), DIPEA (2.00 mmol), and TMDS (2.00 mmol) in anhydrous DMSO (1.25 mL) at 25 °C for 24 h. All yields were isolated yields. Yields in parentheses were for the control experiments in the absence of HOBt and TMDS and determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Reactions were run with sulfonyl fluoride 1 (1.0 equiv) and amine 2 (2.0 equiv). [c] Reaction was run at 60 °C. [d] Reaction was run with sulfonyl fluoride 1 (2.0 equiv) and HOBt (5 mol%) at 60 °C. [e] Reaction was run with sulfonyl fluoride 1 (1.5 equiv). [f] Reaction was run for 48 h.

oxidation-sensitive, the desired products **3a–3b, 3x** were obtained in nearly quantitative yields. In addition, the current method well discriminated amino groups with different reactivity and hence retained the second amino group for later functionalization (Table 2, **3o, 3r, 3t, 3x**). Substrates with a hydroxyl group were also well tolerated (Table 2, **3l, 3v**), which were somewhat problematic in sulfonyl chloride chemistry. Furthermore, the scope of amines was not restricted to alkyl amines. Less nucleophilic aromatic amines were also exemplified as viable substrates (Table 2, **3g, 3k, 3t, 3p, 3y**).

Next, we extended our methodology to more challenging fluorosulfates. Fluorosulfate is one of the essential building blocks in SuFEx chemistry. Although fluorosulfates react efficiently with phenols and their corresponding silyl ether, their reactions with amines are quite slow and complicated by multiple side reactions. Sulfamates are susceptible to a nucleophilic attack by water or amines. Side products such as phenolates, sulfamic acids, and sulfamides form under weakly basic and even neutral conditions. With a couple of modifications of our standard conditions, a broad range of structurally diverse fluorosulfates and amines were

Table 3. Scope of amidation reactions of fluorosulfates.[a]

The reaction scheme shows fluorosulfate **4** plus amine **2** with conditions: 5 mol% HOBt, 1.0 equiv DIPEA, 2.0 equiv TMDS, DMSO, 25 °C, 24 h, giving product **5**.

Product scope:

5a, 91%, [0%]   **5b**, 88%, [0%]   **5c**, 93%, [0%]   **5d**, 91%, [0%]   **5e**, 90%, [0%]

5f, 92%, [2%]   **5g**, 93%, [0%]   **5h**, 92%, [0%]   **5i**, 94%, [0%]   **5j**, 93%, [0%]

5k, 87%, [0%]   **5l**, 90%, [0%]   **5m**, 90%[b], [0%]   **5n**, 91%[b], [2%]   **5o**, 94%[c], [1%]

5p, 90%, [0%]   **5q**, 95%[b], [2%]   **5r**, 90%, [5%]   **5s**, 93%, [0%]

5t, 96%, [0%]   **5u**, 93%[d], [4%]   **5v**, 91%, [0%]   **5w**, 90%, [0%]

[a] Reactions were run with fluorosulfates 4 (2.00 mmol), amine 2 (1.00 mmol), HOBt (5 mol%), DIPEA (1.00 mmol), and TMDS (2.00 mmol) in anhydrous DMSO (1.25 mL) at 25 °C for 24 h. All yields were isolated yields. Yields in parentheses were for the control experiments in the absence of HOBt and TMDS and determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Reactions were run in NMP. [c] Reaction was run with fluorosulfates 4 (1.0 equiv) and amine 2 (2.0 equiv) for 48 h. [d] Reaction was run with (TMS)2O in NMP at 50 °C.

transformed into the desired sulfamate products smoothly (Table 3). Most of amine substrates were branched and even sterically hindered, and all of sulfamate products were generally obtained in excellent yields. Strikingly, even the reactions with *tert*-butyl amine and amantadine furnished the corresponding sulfamates **5a–5d, 5h, 5k, 5p,** and **5v** in satisfactory yields.

Furthermore, we applied our methodology to synthesize the orphan drug of myelofibrosis, Fedratinib,[24] which was approved by US–FDA very recently. The original route for Fedratinib went through an early-stage amidation of sulfonyl chloride with **2a**, followed by two nucleophilic aromatic substitutions. Instead of a sulfonyl chloride, our new route started with readily available 3-nitrobenzenesulfonyl fluoride **8**, followed by reduction and sequential nucleophilic aromatic substitutions to generate the key intermediate **13**. To complete the synthesis of Fedratinib **14**, a late-stage amidation of bench-stable sulfonyl fluoride **13** was conducted

and the desired product **14** (1.22 g, 93% yield) was obtained under our protocols. The route via sulfonyl fluoride enables the late-stage functionalization and diversification of Fedratinib at the sulfonamide terminal and hence provides a facile entry to access Fedratinib analogues for further biological screening.

To demonstrate the potential of our catalytic system in process chemistry, a multidecagram-scale reaction was conducted with **1i** and **2d** with a 0.02 mol% catalyst loading (Scheme 3). 32.8 g of sulfonamide **15** was isolated in 90% yield with the use of only 3.4 mg of HOBt catalyst, and no chromatography was needed for purification. In contrast, **1i** significantly decomposed under the condition without HOBt and TMDS.

To understand the roles of HOBt and TMDS, we performed a series of experiments for the discovered catalytic system (Scheme 4). We prepared the proposed key intermediate *N*-hydroxybenzotriazole sulfonate[25] **16**.
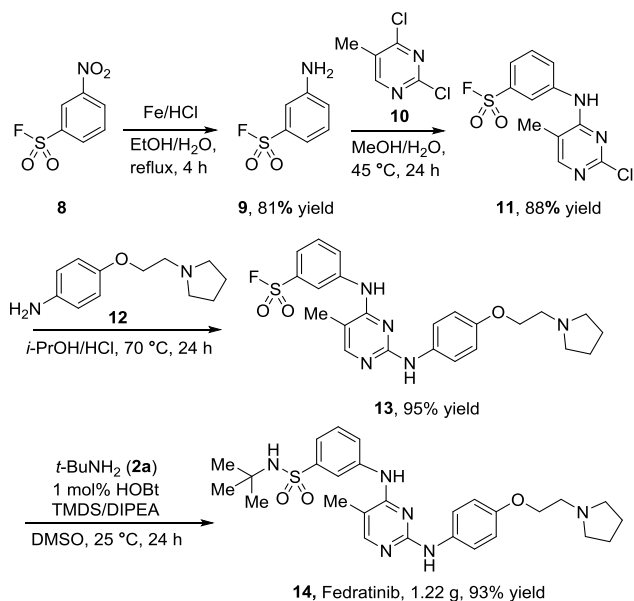
Scheme 2. Synthesis of Fedratinib via a sulfonyl fluoride intermediate.

Although **16** was unstable in DMSO, we were able to carry out the mechanistic experiments in *N*-methyl-2-pyrrolidinone (NMP) instead. Experiments (Scheme 4, eq a) indicated that TMDS promoted the formation of **16**. Without a silicon additive, only a trace amount of **16** formed at elevated temperature. On the other hand, the consumption of **16** with amines (Scheme 4, eq b)
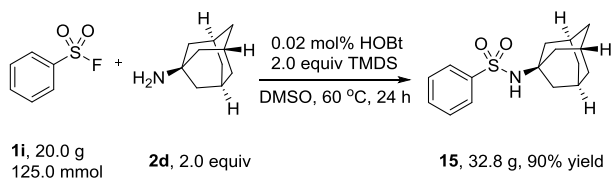
**Scheme 3.** Multidecagram-scale derivatization of antiviral drug amantadine.

was faster than its formation. It suggested that the step of the activation of S(VI)–F bond to form **16** was the rate-determining
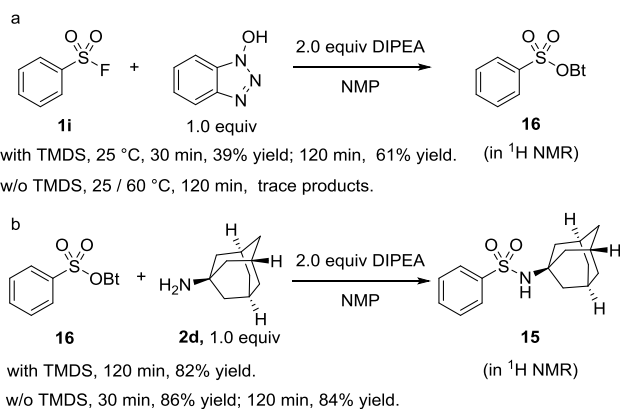
Scheme 4. Mechanistic experiments.

step for the overall process. Another finding was that TMDS did not promote the formation of sulfonamide **15**.

The proposed reaction pathway was also verified with our preliminary computational studies (Scheme 5). It starts with a nucleophilic attack of ⁻OBt anion to the electrophilic S(VI) center. The subsequent fluoride departure drives the formation of **INT-2**, which is 3.3 kcal/mol higher than the starting complex **INT-1**. This is consistent with the experimental results (Scheme 4, eq a) that *N*-hydroxybenzotriazole sulfonate **16** was not detected without the addition of TMDS. Although the exact roles of silicon additives are not completely clear, our experimental results indicate that it can abstract the generated fluoride ions and promote the formation of key intermediate **16**. Compared to the first step of activation (**INT-1** to **TS-1**: 20.6 kcal/mol), the second step of amidation went through a slightly lower transition state (**INT-2** to **TS-2**: 20.1 kcal/mol). This result also supported our mechanistic experiments that the generation of intermediate **16** is slower than the amidation (Scheme 4).
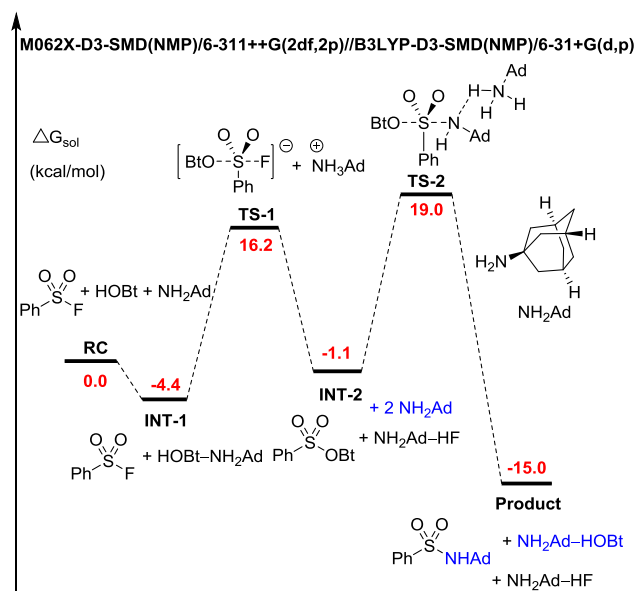
Scheme 5. Calculated reaction pathways.

Conclusion

In summary, we have developed a broad-spectrum, catalytic method for the synthesis of sulfonamides and sulfamates from sulfonyl fluorides and fluorosulfates. With this methodology, we are able to access a set of sterically hindered sulfonamides and sulfamates with excellent yields including the marketed drug Fedratinib. The experimental and mechanistic results have revealed that HOBt is an outstanding nucleophilic catalyst to activate S(VI)–F bond. Further elucidation of detailed mechanisms and applications of this catalytic system to other transformations are currently under our investigation.

Acknowledgements

Conflict of interest

Sun Yat-sen University has filed two patent applications.

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Entry for the Table of Contents

R = Ar, Alkyl, and ArO
1.0–125.0 mmol

HOBt (0.02–5 mol%)
TMDS (2.0 equiv)
DMSO or NMP
rt–60 °C

>50 examples,
87–99% isolated yields

✔ sterically hindered substrates ✔ late-stage drug functionaliztion and diversification
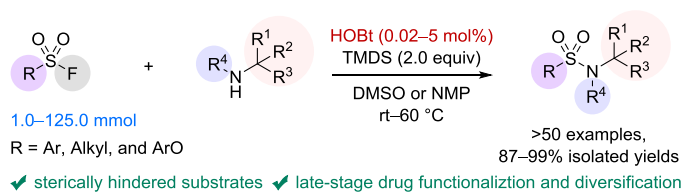
1-Hydroxybenzotriazole (HOBt) was identified as an efficient nucleophilic catalyst to activate sulfonyl fluorides and fluorosulfates. A broad-spectrum, catalytic amidation has been developed to prepare various sulfonamides and sulfamates including sterically hindered ones. In addition, the potentials of this methodology in medicinal and process chemistry have been demonstrated by the multidecagram-scale synthesis of an amantadine derivative and the synthesis of the marketed drug Fedratinib for myelofibrosis.