# Organocatalytic Silicon-Free SuFEx reactions for modular synthesis of sulfonates and sulfonamides

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**Abstract:** Sulfur(VI) fluoride exchange (SuFEx) click chemistry provides a powerful tool for rapid construction of modular connections. Here, we report a novel catalytic silicon-free SuFEx reaction with sulfonyl fluorides. Under the catalysis of 10 mol% N-heterocyclic carbene (NHC), a range of phenols and alcohols react with different sulfonyl fluorides to afford sulfonate esters in 49-99% yields. In addition, Under the relay catalysis of 10 mol% N-heterocyclic carbene and 10 mol% 1-hydroxybenzotriazole (HOBt), a variety of primary and secondary amines react with different sulfonyl fluorides to produce sulfonamides in 58%-99% yields. More than 140 sulfonylated products, including 17 natural product derivatives have been prepared through this method. Mechanism study showed that NHCs might act as a carbon-centered Brønsted base to catalyse the SuFEx click reactions via the formation of hydrogen bonding with phenols or alcohols.

Sulfonats and sulfonamides are key structural motifs that exist widely in numerous pharmaceuticals, biologically active molecules and advanced functional materials[1-3]. Owing to their unique physicochemical properties, a variety of sulfonate- and sulfonamide-containing drugs have been developed and used widely for antibacterial, anti-tumoral, anti-inflammatory and other treatments[4-6]. Accordingly, tremendous eff-

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orts have been devoted to the development of new methods for the construction of these valuable sulfonyl-containing compounds[7-11]. To date, the esterification reaction of sulfonyl chlorides with alcohols and the amination reaction of sulfonyl chlorides with amines provide the most straightforward and general method for the synthesis of sulfonates and sulfonamides, respectively. However, these traditional methods encounter some issues[12], such as the inherent instability and high moisture sensitivity of sulfonyl chlorides, the competing chlorination reaction, and the facile reduction of $S^{VI}$ to $S^{IV}$. Therefore, the development of novel and robust protocol for the construction of these sulfonated compounds is highly significant. Different to sulfonyl chlorides, sulfonyl fluorides exhibit remarkable thermodynamic and redox stability. Based on these unique properties of $S^{VI}$-F bond, Sharpless and coworkers developed sulfur(VI)-fluoride exchange click chemistry[13-15] in 2014. This new generation click chemistry provides powerful technology for rapid assembly of functional molecules through $S^{VI}$-F exchange with different nucleophiles, which has been employed widely in organic synthesis[16-21], chemical biology[22-25], drug discovery[26-28] and polymer chemistry[29-31]. SuFEx click reactions of sulfonyl fluorides provide an attractive alternative approach for the synthesis of sulfonates and sulfonamides. However, the reduced reactivity of sulfonyl fluorides is a great challenge for the reaction. Although base-catalysed SuFEx reactions of sulfonyl fluorides and silyl ethers have been well established[13,17,18,29-31], the silicon-free reaction of sulfonyl fluorides is still a challenge for the research. Very recently, Moses[32] and coworkers introduced a very interesting accelerated SuFEx click reaction. They found that under the catalysis of 1-20 mol%

Barton's base, various aryl and alkyl alcohols react with different SuFExable hubs efficiently to afford a range of products. However, authors found that stoichiometric amount of silicon additive hexamethyldisilazane was required for the reaction, which was assumed to react with alcohol and led to the *in situ* generation of the reactive silyl ether intermediates. On the other hand, compared to the extensively studied SuFEx click reactions of sulfonyl fluorides and silyl ethers, the analogous click reactions of amines are underdeveloped. In 2018, Ball, am Ende and coworkers reported[33] an $Ca(NTf_2)_2$ mediated SuFEx reaction of sulfonyl fluorides and amines for the synthesis of sulfonamides. However, the reaction was not catalytic and stoichiometric amount of $Ca(NTf_2)_2$ was required in order to get good reaction yields. Very recently, Li and coworkers[34] documented an interesting HOBt-catalysed SuFEx reaction of sulfonyl fluorides with amines, which offers a novel methodology for facile access to sterically hindered sulfonamides. However, the authors revealed that excess of silicon additive TMDS and organic base were required for the reaction. Despite significant progress made in this research field, general catalytic silicon- and base-free methods for SuFEx click reactions of sulfonyl fluorides are still unavailable.

As an important type of organocatalyst, N-heterocyclic carbenes (NHCs) have been used widely in organic synthesis[35-37]. Based on the strong Lewis basicity of NHCs, a broad variety of transformations, including benzoin reaction[38-39], Stetter reaction[40-41], homoenolate transformations[42-45], redox reactions[46-47], photo-reactions[48-50] and other reactions[51-54] have been intensively studied. In sharp contrast, reactions based on the Brønsted basic properties of NHCs are far less examined. To date, only several very

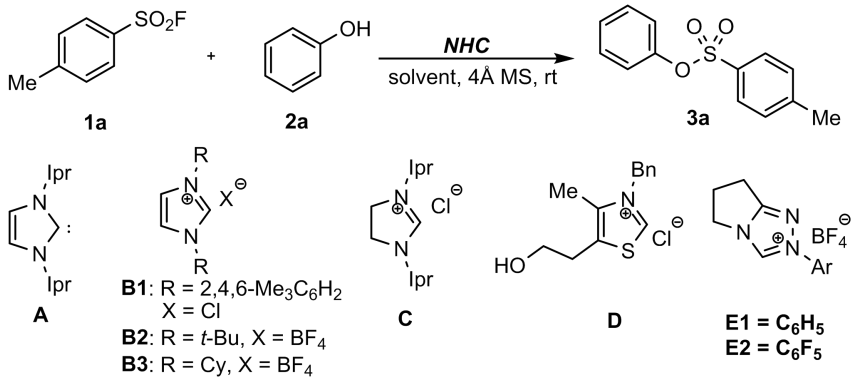
limited reactions, such as NHC-catalysed transesterifications[55-56] and Michael additions[57-60] had been reported. In these reactions, NHCs acted as strong Brønsted base to activate proton-containing nucleophiles through the formation of hydrogen bonding. We reasoned that NHCs could also be employed as Brønsted base to catalyse the SuFEx click reactions of sulfonyl fluorides with alcohols and amines to construct sulfonates and sulfonamides. Herein, we would like to report this result (Fig. **1c**).

**Results**

**Optimization studies.** As shown in Table 1, our study commenced by selecting commercially available sulfonyl fluoride **1a** and phenol **2a** as the model substrates for optimization of the reaction conditions. To our delight, in the presence of 4Å molecular sieves and 10 mol% of a stable NHC, **A** ((1,3-bis(2,6-dissopropylphenyl)-imidazole-2-ylidene, IPr), the reaction proceeded smoothly in acetonitrile at ambient temperature to afford the desired sulfonic ester **3a** in 97% yield (Table 1, entry 1). Encouraged by this success, several other common NHCs were then evaluated. NHCs generated from imidazolium **B1**, **B2**, **B3** and imidazolinium **C** catalysed the reaction efficiently to give **3a** in excellent yield (Table 1, entries 2-5). Thiazolium **D** derived NHC showed moderate catalytic reactivity for the reaction (Table 1, entry 6). NHC derived from triazolium **E1** catalysed the reaction in 94% yield, whereas perfluorophenyl substituted triazolium **E2** catalysed the reaction in very low yield owing to the lower basicity (Table 1, entries 7 and 8). A brief screening of the reaction media showed that toluene, dichloromethane and THF are all suitable for the reaction, giving the desired product in excellent yields, whereas dichloroethane and

1,4-dioxane showed low efficiency (Table 1, entries 9-13). Reduction of NHC loading to 5 mol% led to slightly decreased reaction yield (Table 1, entry 14). However, further reducing the catalyst loading to 2 mol% resulted in dramatic decrease of reaction efficiency (Table 1, entry 15). The excellent yield of **3a** was maintained when the loading of sulfonyl fluoride **1a** was reduced to 1.2 equiv. (Table 1, entry 16).

**Table 1 Optimization of reaction conditions** [a]



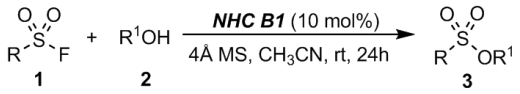

| Entry | Catalyst | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **A** | $CH_3CN$ | 24 | 97 |
| 2 | **B1** | $CH_3CN$ | 24 | 99 |
| 3 | **B2** | $CH_3CN$ | 24 | 96 |
| 4 | **B3** | $CH_3CN$ | 24 | 98 |
| 5 | **C** | $CH_3CN$ | 24 | 96 |
| 6 | **D** | $CH_3CN$ | 24 | 43 |
| 7 | **E1** | $CH_3CN$ | 24 | 94 |
| 8 | **E2** | $CH_3CN$ | 48 | 12 |
| 9 | **B1** | toluene | 24 | 99 |
| 10 | **B1** | DCM | 24 | 92 |
| 11 | **B1** | THF | 24 | 85 |
| 12 | **B1** | DCE | 24 | 52 |
| 13 | **B1** | 1,4-dioxane | 24 | 64 |
| 14[c] | **B1** | $CH_3CN$ | 24 | 90 |
| 15[d] | **B1** | $CH_3CN$ | 24 | 37 |
| 16[e] | **B1** | $CH_3CN$ | 24 | 99 |

[a] **1a** (0.30 mmol), **2a** (0.20 mmol), NHC **A** (10 mol%) or NHC precursor (11 mol%), DBU (10 mol%), 4Å MS (200 mg), $CH_3CN$ (1.0 mL), room temperature. [b] Isolated yield. [c] **B1** (5.5 mol%), DBU (5 mol%). [d] **1a** (0.60 mmol), **2a** (0.40 mmol), **B1** (2.2 mol%), DBU (2 mol%), 4Å MS (400 mg), $CH_3CN$ (1.0 mL). [e] **1a** (0.24 mmol), **2a** (0.20 mmol), NHC **B1** (11 mol%), DBU (10 mol%), 4Å MS (200 mg), $CH_3CN$ (1.0 mL), room temperature.

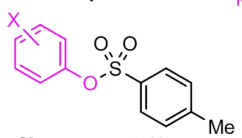
**Scope of NHC-catalysed SuFEx reaction with phenols and alkyl alcohols.** Having the optimal reaction conditions realized, we then evaluated the substrate scope and the results are summarized in **Table 2**. A variety of phenols underwent the SuFEx reaction with sulfonyl fluoride **1a** smoothly to afford the corresponding sulfonate esters in high yields. The electronic properties and varied positions of the substituents on the aromatic ring of phenols had no obvious effect on the reaction yield (**3b**-**3z**). Many useful functional groups, such as halogen atoms (**3b-3d**, **3o-3q**, **3t**), nitrile (**3e**), aldehyde (**3f**), ketone (**3g**) and ester group (**3h**) were well tolerated. Pinacol boronic ester group substituted phenol coupled with sulfonyl fluoride **1a** to produce **3n** in 76% yield. Sterically hindered phenol **2y** performed the reaction to give the desired product **3y** in 95% yield. Both naphthols and tetrahydronaphthol were proved to be competent reactants for the click reaction, affording the corresponding products in high yield (**3aa**-**3ac**). Pyridinol underwent the reaction to produce **3ad** in 95% yield. When 4-aminophenol was used for the reaction, the phenol hydroxy group selectively reacted with sulfonyl fluoride to give **3ae** in 83% yield. Differently, hydroquinone showed no chemoselectivity for the reaction, and the corresponding disulfonylated

product **3af** were formed in 96% yield. The scope of sulfonyl fluorides was also examined. Both electron-withdrawing and -donating substituents substituted aryl sulfonyl fluorides reacted with phenol efficiently to furnish the corresponding sulfonates in high yields (**3ag-3ar**). The bulky aryl sulfonyl fluoride and heteroaryl derived sulfonyl fluorides reacted very well, giving the desired products efficiently (**3as-3ay**). Alkyl sulfonyl fluorides were proved to be good reactants for this SuFEx reaction, providing products **3az-3bb** in high yields. The more challenging SuFEx click reaction of alcohols[32] and sulfonyl fluorides were also tested under the optimal reaction conditions. However, the reaction was sluggish and the product **3bc** was only obtained in 21% yield (Table S2, entry 1, see Supporting Information). Pleasingly, switching the solvent from acetonitrile to dichloromethane and reversing the molar ratio of reactants, the yield of **3bc** was improved to 84% (Table S2, entry 7). Under this modified reaction conditions, various alcohols underwent the click reaction to afford the corresponding sulfonates in high yields (**3bd-3bn**). Notably, different natural phenols and alcohols, such as estrone, (+)-δ-tocopherol, deoxyarbutin, D-tyrosine and so on, underwent the reaction to afford the corresponding sulfonylated derivatives in high yields (**3bo-3ca**). This NHC-catalysed SuFEx click reaction can also be performed on a gram scale, and D-tyrosine derived sulfonate **3br** was obtained in 1.29 g and 96% yield.

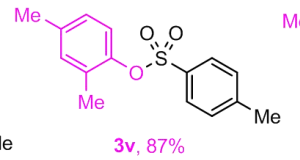
**Table 2 Substrates scope for the synthesis of sulfonates**



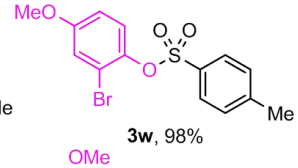

***Different phenols***[a]



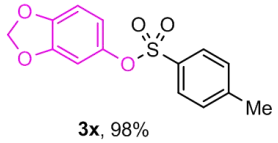
**3b**, X = *p*-F, 98%
**3c**, X = *p*-Cl, 99%
**3d**, X = *p*-Br, 99%
**3e**, X = *p*-CN, 90%
**3f**, X = *p*-CHO, 87%
**3g**, X = *p*-CO$^n$Bu, 99%
**3h**, X = *p*-$CO_2$Me, 92%
**3i**, X = *p*-Et, 90%
**3j**, X = *p*-$^i$Pr, 98%
**3k**, X = *p*-Ph, 95%
**3l**, X = *p*-OMe, 99%
**3m**, X = *p*-SMe, 98%
**3n**, X = *p*-BPin, 76%
**3o**, X = *o*-Cl, 90%
**3p**, X = *o*-Br, 99%
**3q**, X = *o*-I, 99%
**3r**, X = *o*-Ph, 96%
**3s**, X = *o*-OMe, 99%
**3t**, X = *m*-Br, 83%
**3u**, X = *m*-OMe, 89%



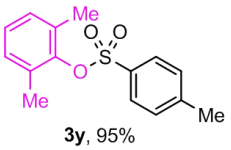
**3v**, 87%



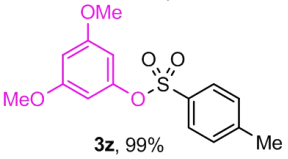
**3w**, 98%



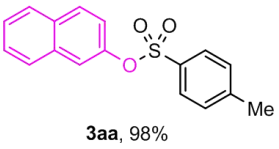
**3x**, 98%



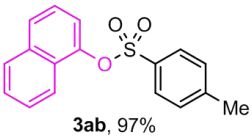
**3y**, 95%



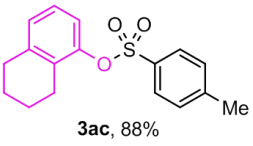
**3z**, 99%



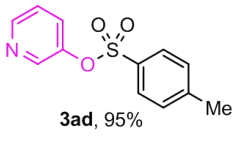
**3aa**, 98%



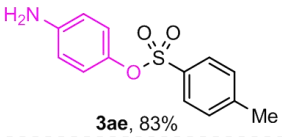
**3ab**, 97%



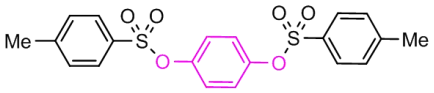
**3ac**, 88%



**3ad**, 95%

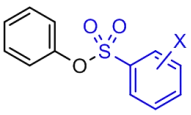


**3ae**, 83%

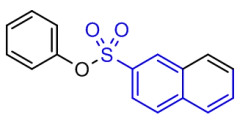


**3af**, 96%

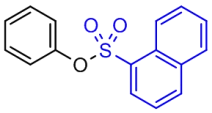
***Different sulfonyl fluorides***[a]



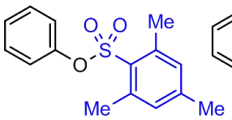
**3ag**, X = H, 93%
**3ah**, X = *p*-F, 99%
**3ai**, X = *p*-Cl, 99%
**3aj**, X = *p*-Br, 99%
**3ak**, X = *p*-$NO_2$, 99%
**3al**, X = *p*-$CF_3$, 94%
**3am**, X = *p*-COMe, 87%
**3an**, X = *p*-OMe, 99%
**3ao**, X = *o*-Me, 90%
**3ap**, X = *m*-Me, 86%
**3aq**, X = *m*-Cl, 96%
**3ar**, X = *m*-Br, 95%



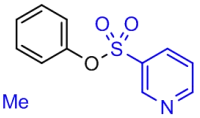
**3as**, 87%



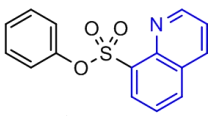
**3at**, 87%



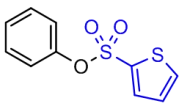
**3au**, 86%



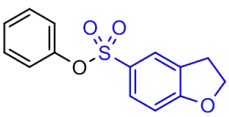
**3av**, 97%



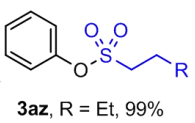
**3aw**, 92%



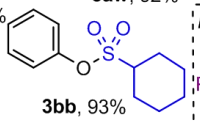
**3ax**, 73%



**3ay**, 87%

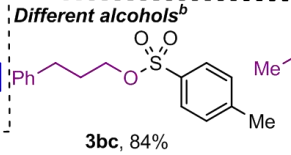


**3az**, R = Et, 99%
**3ba**, R = Ph, 86%

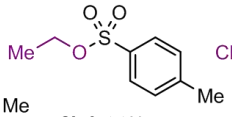


**3bb**, 93%

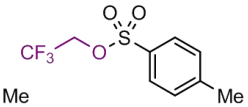
***Different alcohols***[b]



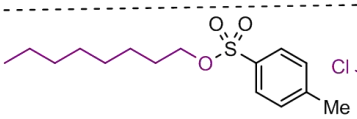
**3bc**, 84%



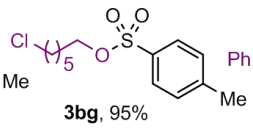
**3bd**, 91%



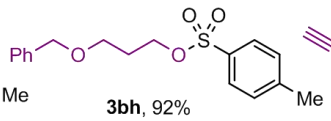
**3be**, 92%



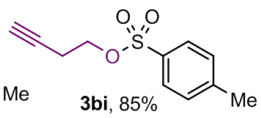
**3bf**, 93%



**3bg**, 95%



**3bh**, 92%



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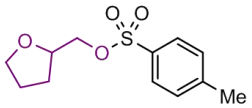

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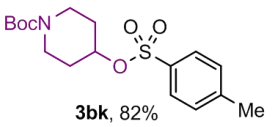
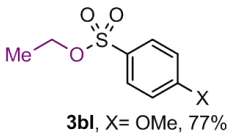
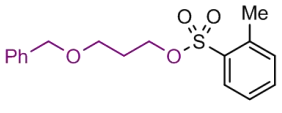


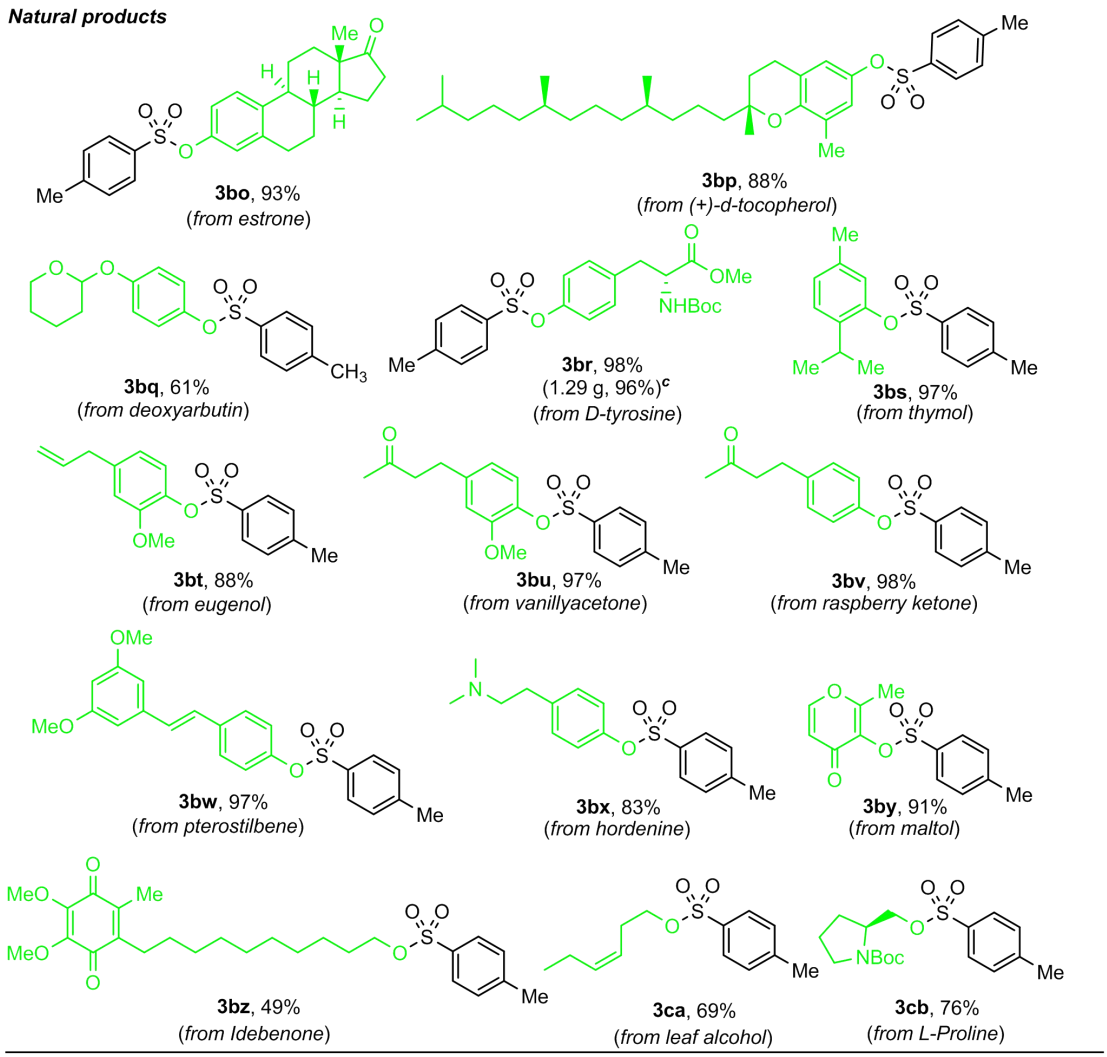
**3bk**, 82%



**3bl**, X= OMe, 77%
**3bm**, X = Br, 71%



**3bn**, 69%



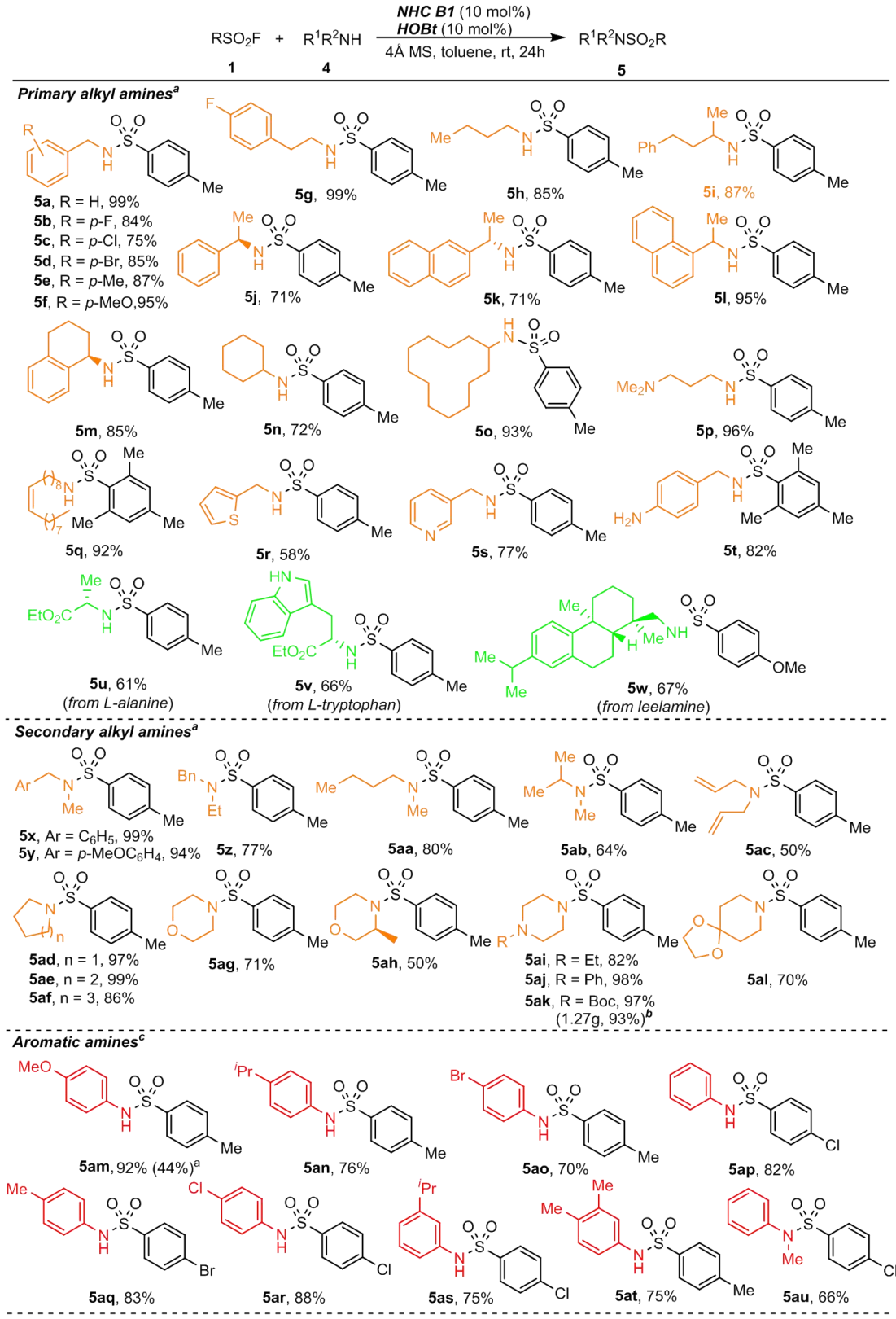

[a] **1** (0.24 mmol), **2** (0.20 mmol), NHC **B1** (11 mol%), DBU (10 mol%), 4 Å MS (200 mg), $CH_3CN$ (1.0 mL), room temperature, 24h, isolated yield. [b] **1** (0.20 mmol), **2** (0.40 mmol), NHC **B1** (11 mol%), DBU (10 mol%), 4 Å MS (200 mg), $CH_2Cl_2$ (0.50 mL), room temperature, 24h, isolated yield. [c] **1a** (3.6 mmol), methyl(tert-butoxycarbonyl)-D-tyrosinate (3.0 mmol), NHC **B** (5.5 mol%), DBU (5 mol%), 4 Å MS (3.0 g), $CH_3CN$ (8 mL), room temperature, 36h.

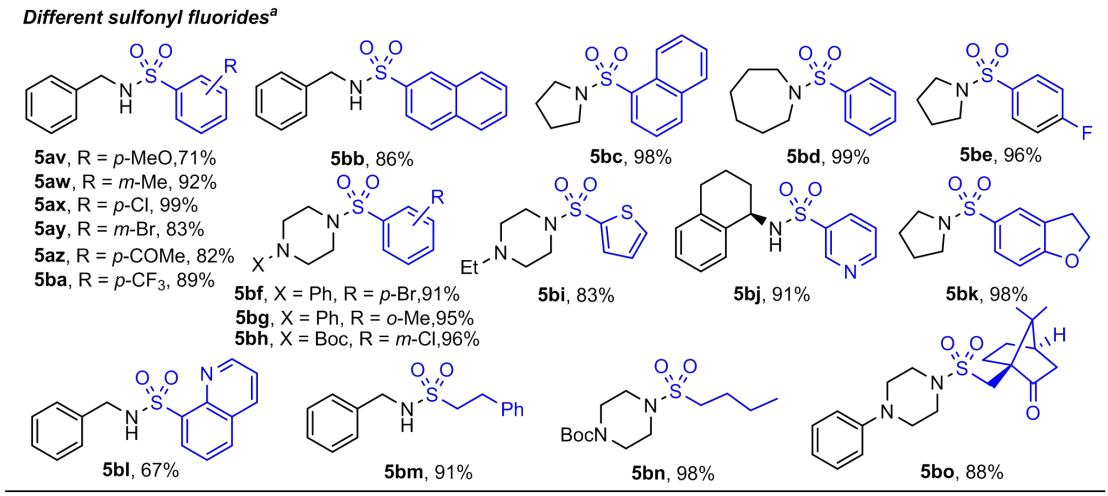
**Scope of NHC-catalysed SuFEx reaction with amines.** We next studied the SuFEx click reaction of sulfonyl fluorides and amines for the synthesis of sulfonamides. Under the standard reaction conditions, sulfonamide **5a** was formed in very low yield (Table S3, entry 1, see Supporting Information). But fortunately, with the addition of

10 mol% HOBt as cocatalyst, the reaction yield of **5a** was dramatically improved to 92% (Table S3, entry 10). Further evaluation of the reaction media showed that quantitative yield was obtained when the reaction was conducted in toluene (Table S3, entry 28). Under this improved reaction conditions, a range of primary and secondary aliphatic amines were efficiently transformed into the corresponding sulfonamides in good to excellent yields (Table 3). Common functional groups, including halogen atoms (**5b-5d**), amine (**5p**), olefins (**5q** and **5ac**) and heterocycles (**5r** and **5s**) can be incorporated into the amine substrates. Interestingly, diamine substrate **4t** selectively underwent monosulfonation with sulfonyl fluoride to afford sulfonamide **5t** in 82% yield. Substrates derived from natural amino acids, such as **4u** and **4v**, performed the SuFEx click reaction smoothly to afford the corresponding products in good yields. The natural leelamine **4w** was proved to be a successful candidate for the reaction, giving sulfonamide **5w** in 67% yield. Cyclic amines, such as pyrrolidine, piperidines, hexamethyleneimine, morpholines, and piperazines underwent the reaction to furnish the corresponding products in good to quantitative yields (**5ad-5al**). In addition, acid-sensitive groups such as Boc and ketal were well tolerated for the reaction (**5ak** and **5al**). Increasing the amount of catalysts to 20 mol%, the less nucleophilic aromatic amines can also couple with sulfonyl fluorides to produce the desired sulfonamides in good to high yields (**5am-5au**). On the other hand, a range of aryl, heteroaryl and alkyl sulfonyl fluorides were proved to be very good electrophiles for the click reaction, delivering the desired products in moderate to excellent yields (**5av-5bo**). Notably, the reaction can be conducted on a gram scale and an excellent

yield can be maintained (**5ak**).

## Table 3 Scope of amines

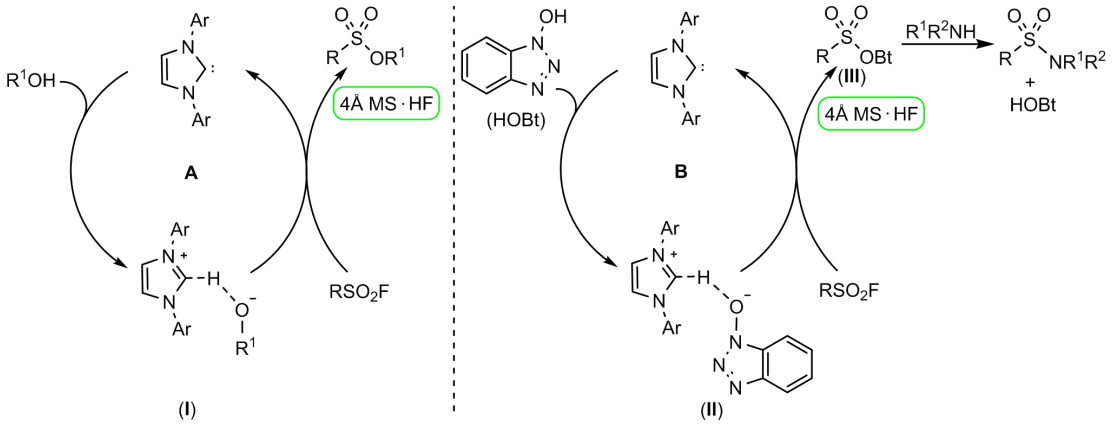





[a] **1** (0.30 mmol), **4** (0.20 mmol), NHC **B1** (11 mol%), DBU (10 mol%), HOBt (10 mol%), 4 Å MS (200 mg), toluene (1.0 mL), room temperature, 24h, isolated yield. [b] **1a** (6.0 mmol), N-Boc-piperazine (4.0 mmol), NHC **B1** (2.2 mol%), DBU (2 mol%), HOBt (2 mol%), 4 Å MS (4.0 g), toluene (10 mL), room temperature, 48h. [c] **1** (0.30 mmol), **4** (0.20 mmol), NHC **B1** (22 mol%), DBU (20 mol%), HOBt (20 mol%), 4 Å MS (200 mg), toluene (1.0 mL), room temperature, 24h, isolated yield.

**Mechanistic studies.** Based on the previous studies of the Brønsted basicity of NHCs[58-61] and the NMR experimental results (see Supporting Information), a plausible mechanism for the reaction was proposed and depicted in Scheme 1. NHC acts as a carbon-centered Brønsted base to attack the acidic proton of phenols or alcohols through hydrogen bonding to form an oxy anion/azolium ion complex Ⅰ, which might trigger the following SuFEx click reaction with sulfonyl fluoride to produce sulfonate product with releasing of free carbene. For NHC-catalysed synthesis of sulfonamide, NHC firstly interacts with HOBt to form intermediate Ⅱ, which reacts with sulfonyl fluoride to form sulfonate Ⅲ. The active sulfonated Ⅲ

subsequently undergoes ester-aminolysis reaction[35] with an amine to produce the sulfonamide product with releasing of HOBt.




**Scheme 1 Proposed Mechanism**

## Conclusion

In summary, NHC-catalysed SuFEx click reactions of sulfonyl fluorides have been demonstrated. The silicon and base-free conditions, broad substrate scope, generally high yields and easy scalability provide a novel organocatalytic protocol for the synthesis of sulfonates and sulfonamides. Further applications of NHCs in other SuFEx click reactions are ongoing in our laboratory.

## Methods

**General procedure for the synthesis of sulfonic ester 3.**

To a suspension of imidazolium **B1** (0.022 mmol, 7.5 mg, 11 mol%) and 4Å MS (200 mg) in anhydrous $CH_3CN$ (1.0 mL) was added DBU (0.02 mmol, 3.0 mg, 10 mol%) under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 0.5 h. Sulfonyl fluoride **1** (0.24 mmol, 1.2 equiv) and phenol **2** (0.20 mmol, 1.0 equiv) were added subsequently and the solution was stirred at ambient temperature until full consumption of the starting phenol indicated by TLC. The reaction mixture was then diluted with ethyl acetate, filtered through a short pad of

silica gel and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the pure product.

## Data availability

Experimental procedures, mechanism studies and characterization of the compounds are available in the Supplementary Information. All other data are available from the corresponding authors upon reasonable request.

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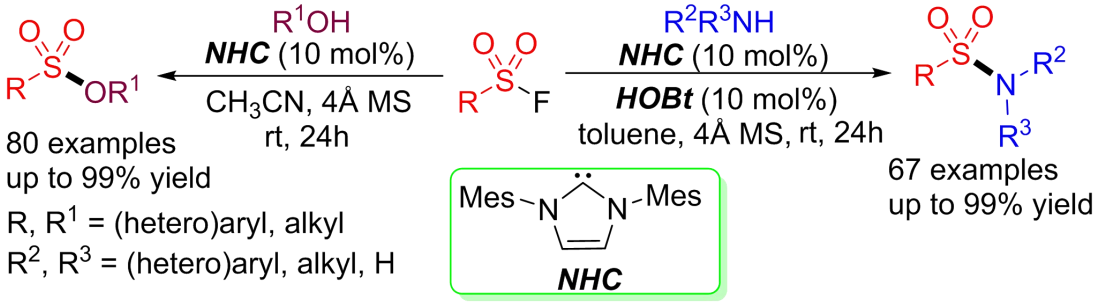
## Author contributions

M.L., J.L., Y.X. and Z.C.conducted and analysed the experiments. G.D., B.D. and L.H. designed and directed the project and G.D. and L.H. wrote the manuscript.

## Competing interests

The authors declare no competing interests.

## Graphical abstract




- silicon and base free
- broad substrate scope
- high reaction yield
- mild conditions
- gram-scale synthesis
- 17 natural products