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SuFExable Isocyanides for Ugi Reaction: Facile Synthesis of Sulfonyl Fluoro Peptides

Shuheng Xu¹, and Sunliang Cui^{1,*}

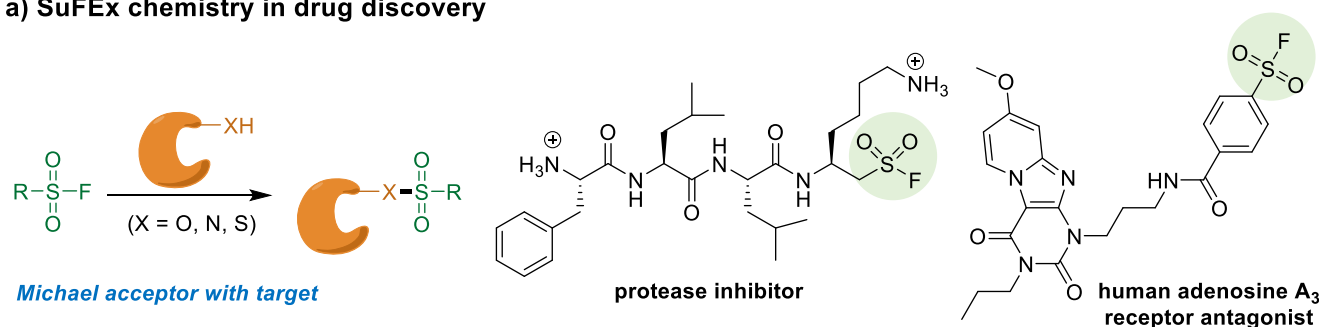
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Abstract: The sulfur(VI) fluoride exchange (SuFEx) reaction has become a good click chemistry transformation and acted as a powerful tool in medicinal chemistry and materials science. Therefore, the investigation of versatile SuFExable synthon and SuFEx compatible reactions is highly desirable. Herein, the sulfonyl fluoro isocyanides were first developed as a new type of SuFExable synthon, and used as flexible building blocks in the Ugi four-component reaction (U-4CR). Hence, the preparation methods of differential SuFExable isocyanides were set up, including both aryl and alkyl sulfonyl fluoro isocyanides. Meanwhile, the sulfonyl fluoro tolerable Ugi reaction was established and the substrate scope was investigated, and various sulfonyl fluoro α -amino amides and peptides could be reached in a one-step synthesis. Therefore, this protocol opens a new vision for SuFExable building block and click chemistry, and also provides a distinct approach to sulfonyl fluoro peptides.

The sulfur(VI) fluorides exhibit unique physical and chemical properties, and their distinctive reactivities were discovered in early times¹⁻⁵. Recently, the sulfur(VI) fluoride exchange (SuFEx) reaction has been revived by Sharpless as another good click chemistry transformation⁶. In typical, the reaction between S-F moiety and silyl-protected phenol has become a powerful and enabling connective technology for a wealth of applications (Fig. 1)⁷⁻¹². For example, the sulfonyl fluoride group was revealed as an alternative Michael acceptor in covalent drug discovery with distinctive pharmacological properties

(Fig. 1a), and there are many reports concerning the sulfonyl fluoro structured protease inhibitor, human adenosine A₃ receptor antagonist and lysine-targeting covalent inhibitor¹³⁻²¹. Besides, it also serve as a type of polysulfate unit which could constitute a practical approach to polysulfates and polysulfonates material with high molecular weight, narrow polydiversity and excellent functional group tolerance (Fig. 1b)²²⁻²⁴.

a) SuFEx chemistry in drug discovery



b) SuFEx chemistry in materials science

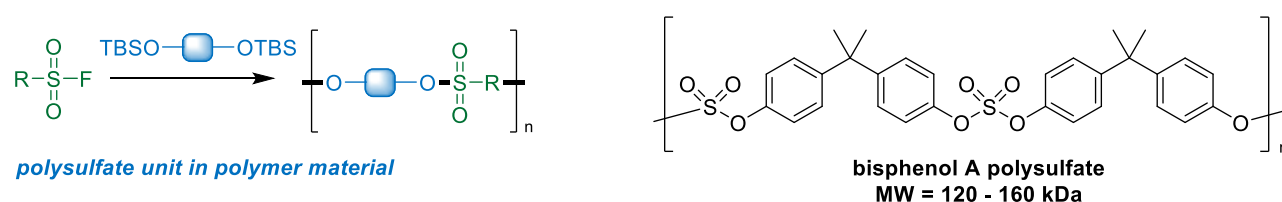


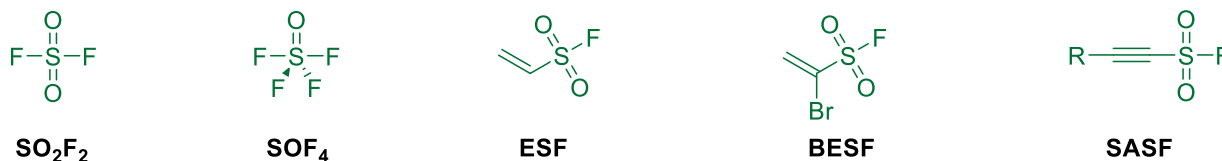
Fig. 1 Sulfonyl fluoro chemistry. **a** SuFEx chemistry in drug discovery. **b** SuFEx chemistry in materials science.

Accordingly, the investigation of SuFExable building blocks and SuFEx compatible reactions received much attention (Fig. 2a). The classical SuFExable synthon is sulfonyl fluoride (SO₂F₂)^{7-12, 25-28}. In recent time, Sharpless and coworkers disclosed that SOF₄ was another SuFEx connector²⁹⁻³⁰. They revealed that ethylenesulfonyl fluoride (ESF) was a selectively addressable bis-electrophilic SuFExable building block³¹⁻³³, and its bromo derivative (BESF) was also found as a SuFExable reagent³⁴⁻³⁵. More recently, Moses reported that the 2-substituted alkynyl-1-sulfonyl fluoride (SASF) could serve as flexible and SuFExable synthon in diversity oriented click reaction³⁶. Therefore, the development of versatile

SuFExable building blocks remains continuous interesting and importance.

Ugi reaction is a well-known multicomponent reaction which rapidly assembles aldehydes, amines, carboxylic acids and isocyanides to form α -amino amides as peptide units³⁷. It has been widely used in organic synthesis, drug discovery and materials science³⁸⁻³⁹. Recently, the asymmetric version of Ugi reaction has also been established⁴⁰⁻⁴⁴. Respecting to the mechanism, the isocyanides serve as essential and bifunctional C1 synthon in this process.⁴⁵⁻⁴⁶ Moreover, the functional group tethered isocyanides such as α -boryl isocyanides were used in Ugi reaction to furnish boropeptides⁴⁷. This indicated that an additional functionality in isocyanides and Ugi reaction could significantly expand the chemical space of products. Recently, Sharpless and Kelly reported that the fluorosulfated tyrosine could be used as building block in solid-phase synthesis toward sulfotyrosine-containing peptides, which would bestow the peptides with distinctive sulfonyl fluoro functionalities⁴⁸. In continuation of our interests in multicomponent reaction and drug discovery⁴⁹⁻⁵³, we hypothesized that the sulfonyl fluoro group and isocyanide moiety could be merged in a molecule to render a versatile sulfonyl fluoro-containing synthon, which might enable the combination of SuFEx click reaction and Ugi reaction to achieve SuFExable peptides directly. Herein, we describe the development of sulfonyl fluoro isocyanides which were used as flexible building blocks in Ugi reaction for facile synthesis of sulfonyl fluoro peptides and peptide units (Fig. 2b).

a) reported SuFExable building block



b) this work

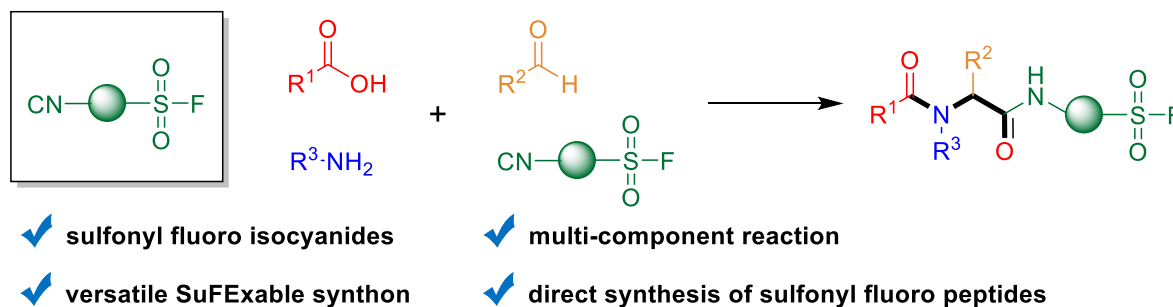


Fig. 2 SuFExable building blocks. a. Reported SuFExable synthon. b. Sulfonyl fluoro isocyanides as a new SuFExable building block.

Results

Reaction optimization.

At the beginning, the preparation of SuFExable isocyanides were explored. After various exploration and optimization, four types of preparation methods toward differential SuFExable isocyanides were established with practicability and scalability (Fig. 3, for details, see Supporting Information). For example, Taurine is a readily available feedstock and could convert to fluorated salt **A** upon a four-step transformation, and **A** could convert to the 2-isocyanoethane-1-sulfonyl fluoride with another two-step synthesis. Interestingly, the amino acids could transform to the chiral sulfonyl fluorated amino salt **B** with a eight-step synthesis, and **B** could transform to the chiral SuFExable isocyanides smoothly. On the other hand, phenylalkyl amines like benzylamine and 2-phenylethyl amine could convert to sulfonyl fluorated formylamide **C** and then reached the corresponding SuFExable aryl isocyanides through another one-step synthesis. Meanwhile, 4-isocyanobenzenesulfonyl fluoride could be easily prepared

from the commercial 4-nitrobenzenesulfonyl chloride in a four-step synthetic route. Notably, all these preparation procedures of SuFExable isocyanides are practical and reproducible.

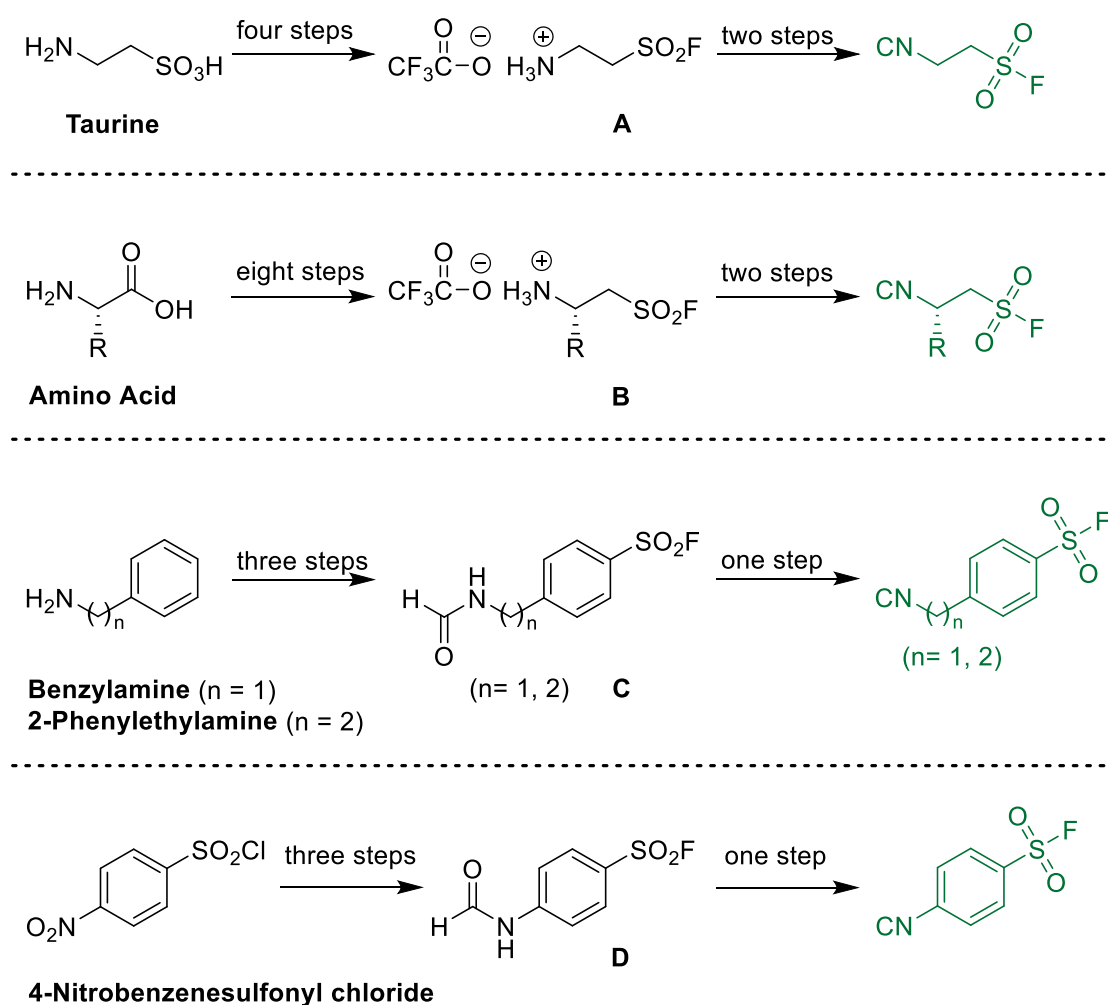


Fig. 3 Practical preparation of SuFExable Isocyanides.

When the sulfonyl fluoro isocyanides were obtained, the SuFExable Ugi reaction was then explored. Benzoic acid **1a**, benzaldehyde **2a**, amine **3a** and 2-isocyanoethane-1-sulfonyl fluoride **4a** were used as model substrates to investigate the reaction condition. Initially, **2a** and **3a** were mixed in methanol and kept for 2 hours to deliver imine intermediate, then **1a** and **4a** were added and kept for 1 h (entry 1). To our delight, a sulfonyl fluoro α -amino amide **5a** was truly formed, albeit in a low yield (13% isolated yield). The next survey of solvents showed that DCM, THF, dioxane, CH_3CN and toluene, were inferior to decrease the yields (entries 2-6). Gratifyingly, the use of trifluoroethanol (TFE) and

hexafluoroisopropanol (HFIP) as solvent could significantly improve the yield to 45% and 68%, respectively (entry 7-8). We assumed that the weak acidity, polarity and non-nucleophilicity of HFIP could promote the imine intermediate formation and avoid side reaction, thus facilitating the Ugi reaction. Interestingly, adding these four reagents to HFIP simultaneously and kept the reaction at RT for 3 h, the yield of **5a** could be further improved (entry 9). However, the addition of 4 Å MS would decrease the yield (entry 10). Besides, when the amount of **2a**, **3a** and **4a** was slightly elevated, **5a** could be obtained in 85% yield (entry 11).

Table 1. Reaction Optimization^a.

Entry	Solvent	Yield ^[b]	
1	MeOH	13	
2	DCM	10	
3	THF	<5	
4	Dioxane	–	
5	MeCN	<5	
6	Toluene	<5	
7	TFE	45	
8	HFIP	68	
9 ^c	HFIP	82	
10 ^d	HFIP	70	
11 ^e	HFIP	85	

^aReaction conditions: **2a** (0.12 mmol) and **3a** (0.12 mmol) were added to solvent (1 mL) and kept at RT for 2 h, then **1a** (0.1 mmol) and **4a** (0.12 mmol) were added and kept for another 1 h.

^bYield refers to isolated product.

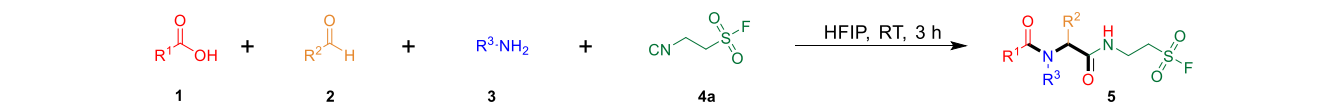
^cFour reagents were added simultaneously and kept for 3 h.

^d4Å MS (15 mg) was added.

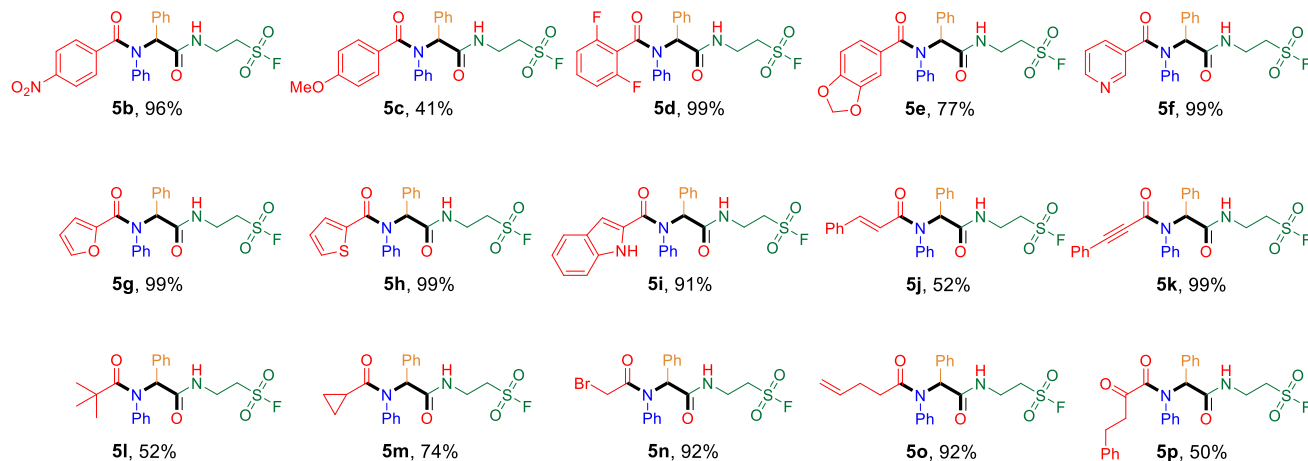
^e**1a** (0.1 mmol), **2a** (0.15 mmol), **3a** (0.15 mmol) and **4a** (0.15 mmol) were added simultaneously and kept for 3 h.

Reaction scope study. With the optimized reaction condition in hand, we next tested the scope of this SuFExable Ugi reaction. As shown in Fig. 4, various substituted benzoic acids could well engage in this process to deliver the products, and the electron-withdrawing substitution could give higher yields than those electron-donating substitution (**5b-5e**). The heteroaryl carboxylic acids like nicotinic acid, furan-2-carboxylic acid, thiophene-2-carboxylic acid, and indole-2-carboxylic acid, could participate in this SuFExable Ugi reaction to give the sulfonyl fluoro α -amino amides in excellent yields (**5f-5i**). Besides, the unsaturated carboxylic acids like cinnamic acid and 3-phenylpropionic acid were also tolerable (**5j-5k**). The aliphatic carboxylic acids with the functionalities like cyclopropane, bromo, alkene and ketone, were compatible in this process (**5l-5p**). Besides, these functionalities could offer ample opportunities for further functionalization. Respecting to aldehydes, a series of substituted benzaldehydes with the substitution of fluoro, chloro, bromo, methoxy, cyano, nitro, could undergo the Ugi reaction smoothly to give the products in good to excellent yields (**5q-5u**), and the electron-deficient benzaldehydes could give higher yields than those electron-rich benzaldehydes. The naphthyl aldehyde and heterocyclic aldehydes including pyridine-3-aldehyde, thiophene-2-aldehyde, N-tosyl pyrrole-2-aldehyde, N-Boc indole-2-aldehyde, could well engage in this multicomponent reaction process to deliver sulfonyl fluoro

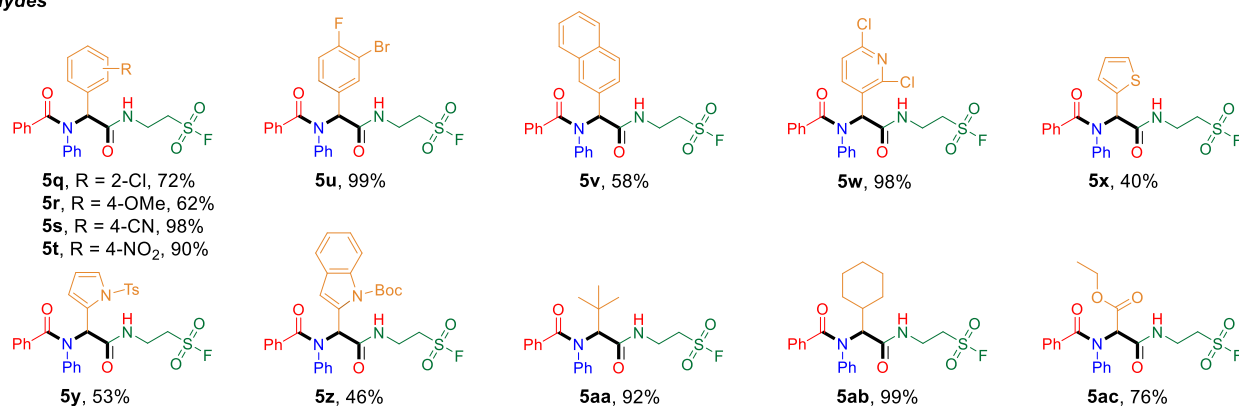
α -amino amides in moderate to excellent yields (**5v-5z**). Furthermore, the structure of **5y** was confirmed by X-ray analysis⁵⁴. The aliphatic carboxaldehydes were also subject to this Ugi reaction. For instance, the pivalic aldehyde and cyclohexanal were applicable in this process to give the products in almost quantitative yields (**5aa-5ab**). Moreover, the ethyl oxoacetate could also proceed well to furnish the product (**5ac**). On the other hand, a series of amines were explored. For example, various anilines with differential substitutions like methoxy, chloro, bromo, trifluoromethyl, and nitro, could well tolerate and the electron-rich substitution could facilitate the reaction to give excellent yields (**5ad-5ah**). The naphthyl amine could also engage in this process to give the product **5ai** with a *d.r.* value of 3.7:1. In addition, a variety of alkyl amines with diverse functionalities like alkene, alkyne, sulfone, protected alcohol, trifluoromethyl and cyclopropane, could undergo this multicomponent reaction smoothly to deliver the sulfonyl fluoro α -amino amides in moderate to excellent yields (**5aj-5ao**). When the chiral (*S*)-1-phenylethan-1-amine was used, the product **5ap** could be formed in 84% yield with a *d.r.* value of 1.3:1. Furthermore, the amino acids like methyl glycine, and methyl *L*-Aspartic acid were also applicable to deliver the products in excellent yields (**5aq-5ar**).



• Carboxylic Acids



• Aldehydes



• Amines

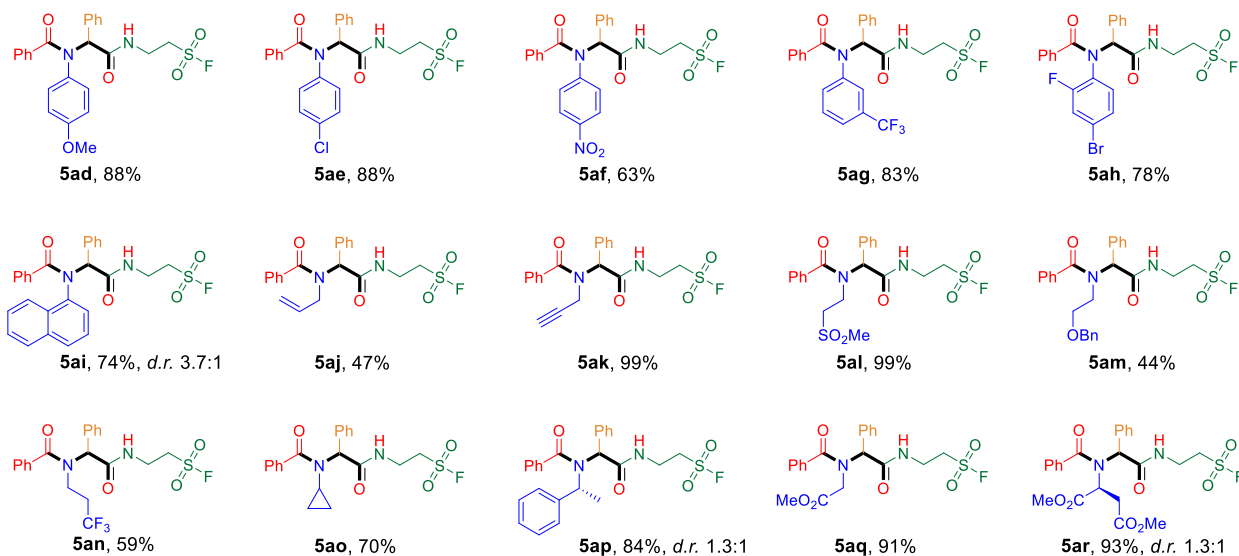


Fig. 4. Scope of Ugi Reaction for Synthesis of Sulfonyl Fluoro α -Amino Amides. Reaction condition:

1 (0.1 mmol), **2** (0.15 mmol), **3** (0.15 mmol) and **4a** (0.15 mmol) were added to HFIP (1 mL) and kept at

RT for 3 h. Yield refers to isolated products, and *d.r.* value was determined by ¹H NMR.

At this stage, we turned our attention to this SuFExable Ugi reaction using the *N*-protected amino acids as carboxylic acid component for synthesis of sulfonyl fluoro peptides. As shown in Fig. 5, the *N*-tosyl glycine could assemble with aldehyde, amine and differential SuFExable isocyanides to deliver the sulfonyl fluoro peptides in excellent yields (**6a-6d**). Meanwhile, the *N*-Cbz *L*-alanine could engage in this process to deliver the structural divergent peptides efficiently with excellent yields (**6e-6h**), and the chiral SuFExable isocyanides were found well applicable to furnish the protease inhibitor analogues tethering with sulfonyl fluoro moiety. Meanwhile, the *N*-Cbz *L*-leucine and *N*-Boc *L*-proline could also undergo the Ugi reaction smoothly (**6i-6j**). Considering the wealth of sulfonyl fluoro peptides in medicinal chemistry^{19, 20, 55}, this protocol provides a direct approach to these molecules with high efficiency, structural diversity and molecular complexity.

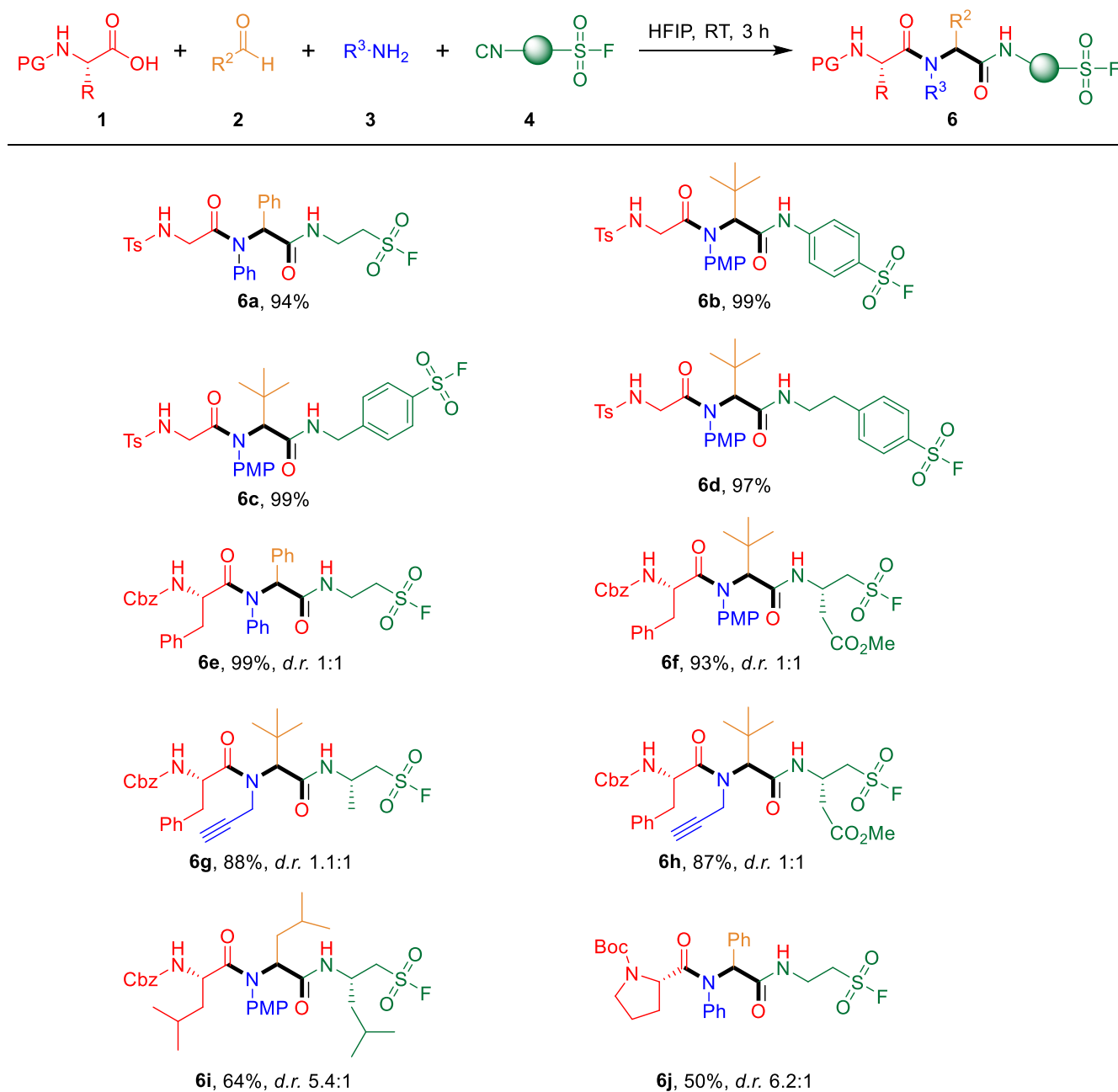


Fig. 5. Synthesis of Sulfonyl Fluoro Peptides. Reaction condition: **1** (0.1 mmol), **2** (0.15 mmol), **3** (0.15 mmol) and **4** (0.15 mmol) were added to HFIP (1 mL) and kept at RT for 3 h. Yield refers to isolated products, and *d.r.* value was determined by ^{19}F NMR. PMP = *para*-methoxyphenyl.

Synthetic applications and mechanism study. To showcase the utility of this protocol, the synthetic application was conducted. Those complex molecules such as drugs are amenable to the transformation

upon this SuFExable Ugi reaction. For example, the approved drugs like Indometacin and Tranilcypromine could be derived to **7** and **8** upon this method, and **7** could be prepared in gram-scale (Fig. 6a). Meanwhile, the Ugi reaction-derived compound **9** was discovered as a heat shock transcription factor 1 inhibitor to induce apoptosis in multiple myeloma cells⁵⁶, and this protocol could deliver the sulfonyl fluoro derivative **10** in one-step which could significantly facilitate the covalent drug discovery (Fig. 6b). Furthermore, the peptide **6** which was tethered with an alkyne moiety and a sulfonyl fluoro moiety, could enable a Huisgen click reaction and a SuFEx click reaction for selective entry to **11** and **12** (Fig. 6c). This would offer ample opportunity for small molecule biological probes development.

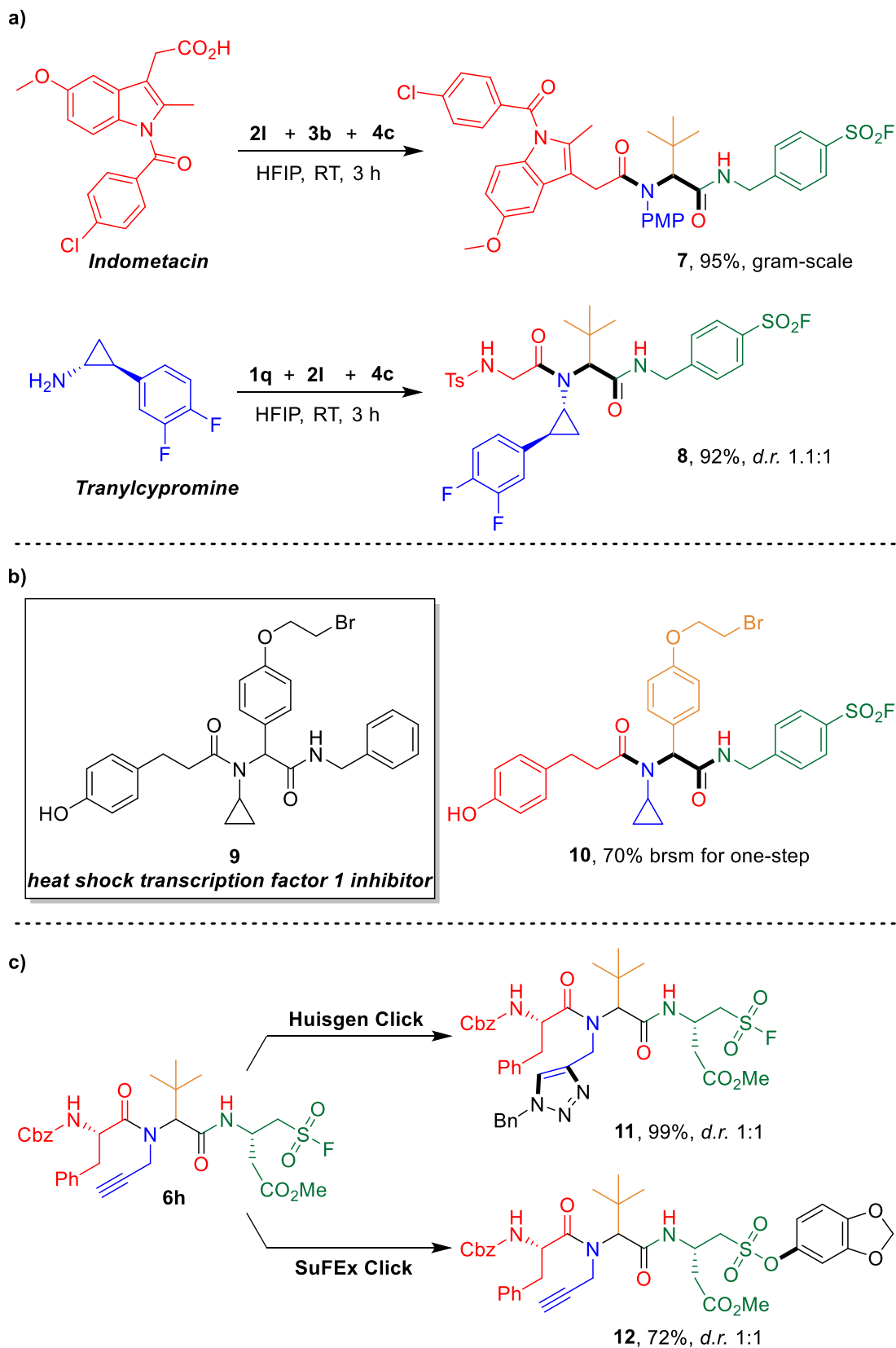


Fig. 6. Synthetic applications. **a.** Synthesis of drug derivatives and gram-scale reaction. **b.** Synthesis of a heat shock transcription factor 1 inhibitor derivative. **c.** Click reaction with sulfonyl fluoro peptide **6**.

Discussion

In summary, the sulfonyl isocyanides were developed as a new type of SuFExable synthon, which were used as flexible building block in the Ugi four-component reaction. Therefore, various sulfonyl fluoro α -amino amides and peptides could be achieved in a direct and efficient manner. This protocol opens a new vision for the discovery of SuFExable building blocks and SuFEx click chemistry, and would be useful in drug discovery and materials science.

Methods

General procedure for the synthesis of 5. A 5 ml vial was charged with acid **1** (0.1 mmol), aldehyde **2** (0.15 mmol), amine **3** (0.15 mmol) and isocyanide **4a** (0.15 mmol), HFIP (1.0 mL) was added as solvent. The solution was stirred at room temperature for 3 hours. Afterwards, the solvent was evaporated under vacuum, and the residues were purified by flash column chromatography on silica gel using ethyl acetate / petroleum ether (v / v, 1:2 to 1:1) as eluent to give **5**.

General procedure for the synthesis of 6. A 5 ml vial was charged with acid **1** (0.1 mmol), aldehyde **2** (0.15 mmol), amine **3** (0.15 mmol) and isocyanide **4** (0.15 mmol), HFIP (1.0 mL) was added as solvent. The solution was stirred at room temperature for 3 hours. Afterwards, the solvent was evaporated under vacuum, and the residues were purified by flash column chromatography on silica gel using ethyl acetate / petroleum ether (v / v, 1:3 to 1:1) as eluent to give **6**.

Data availability

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center (CCDC) under the deposition numbers CCDC: 2046088 (**5y**). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study, including experimental procedures and compound characterization,

are available within the paper and its Supplementary Information files, or from the corresponding authors on request.

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Author contributions

S. Xu performed experiments. S. Cui conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

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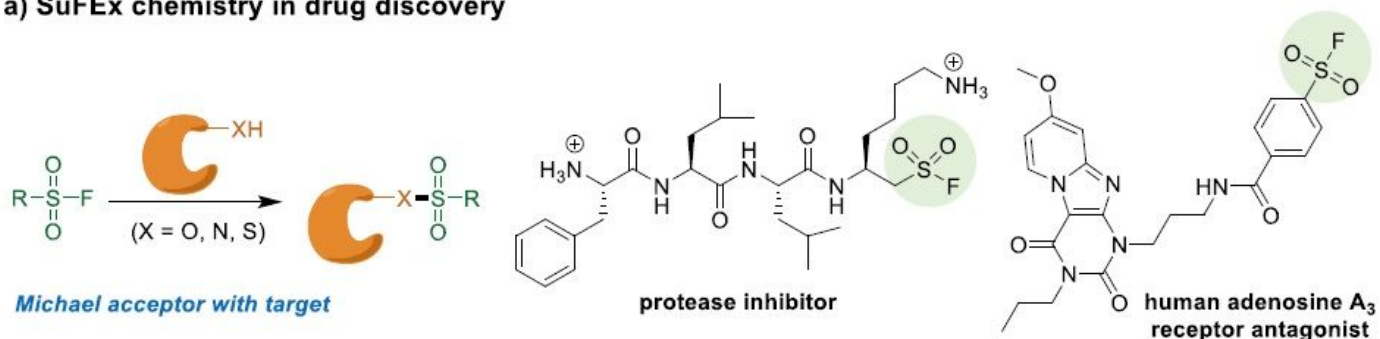
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Figures

a) SuFEx chemistry in drug discovery



b) SuFEx chemistry in materials science

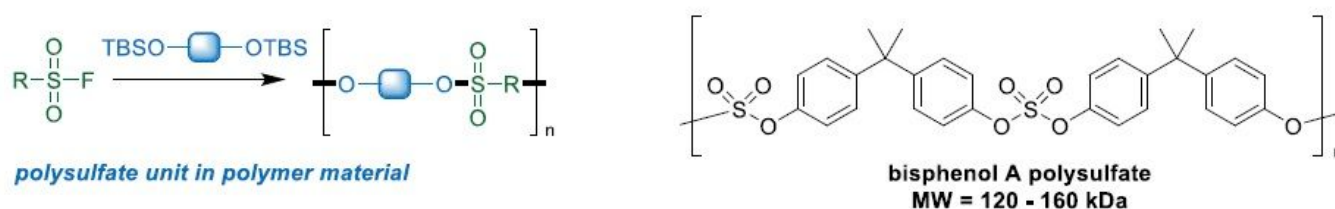
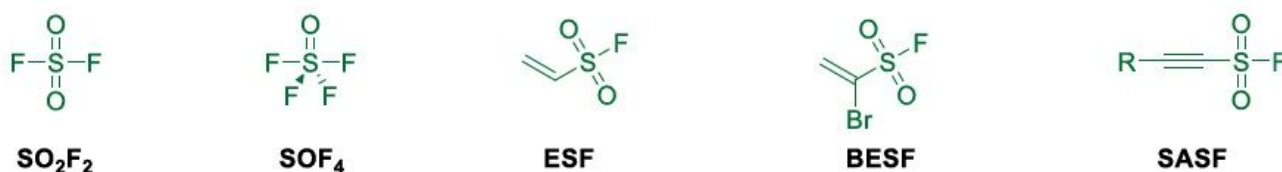


Figure 1

Sulfonyl fluoro chemistry. a SuFEx chemistry in drug discovery. b SuFEx chemistry in materials science.

a) reported SuFExable building block



b) this work

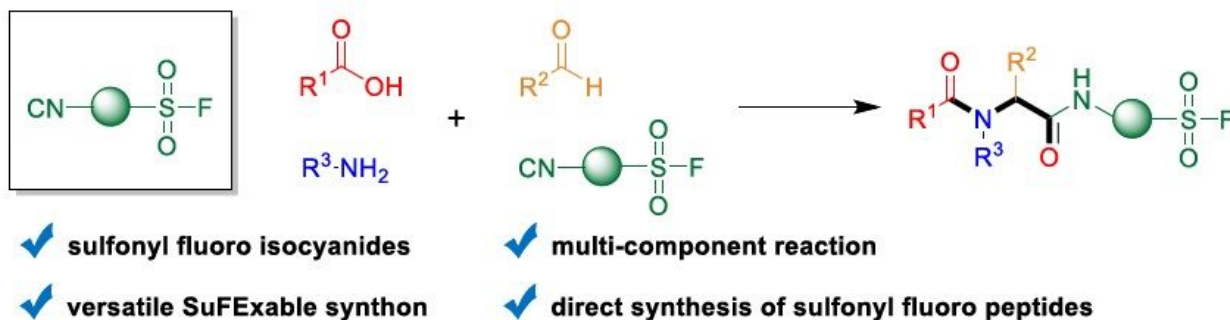


Figure 2

SuFExable building blocks. a. Reported SuFExable synthon. b. Sulfonyl fluoro isocyanides as a new SuFExable building block.

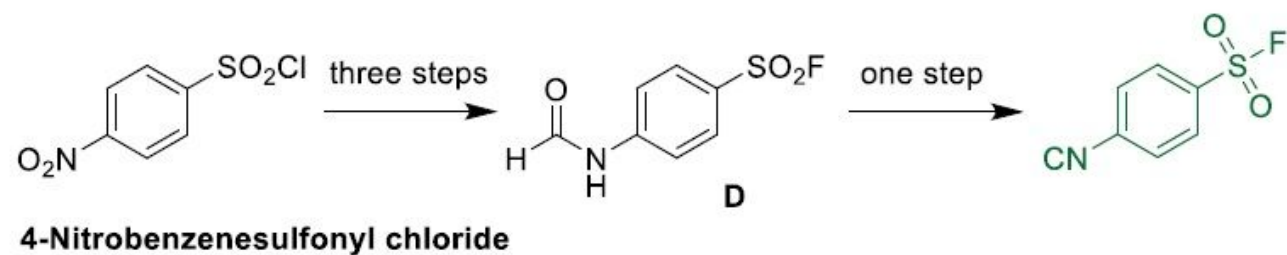
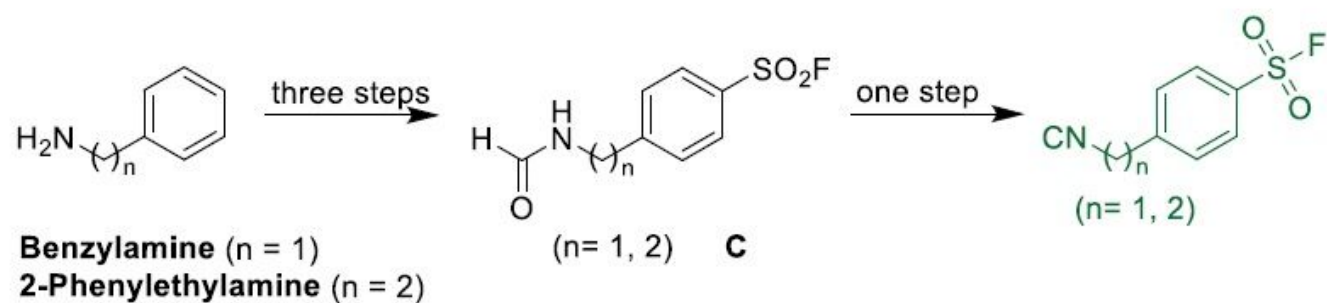
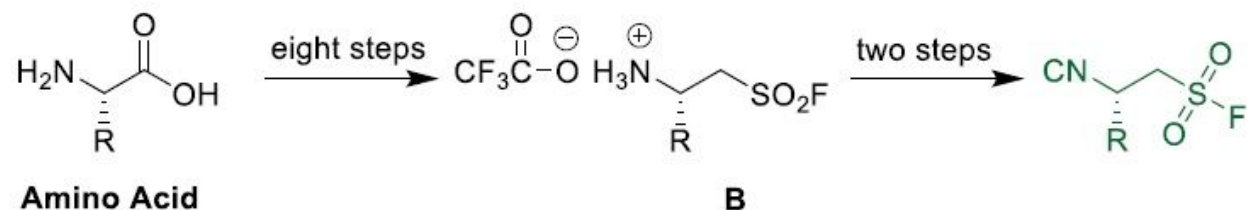
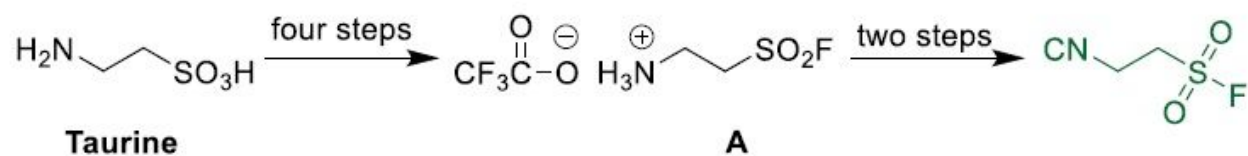


Figure 3

Practical preparation of SuFExable Isocyanides.

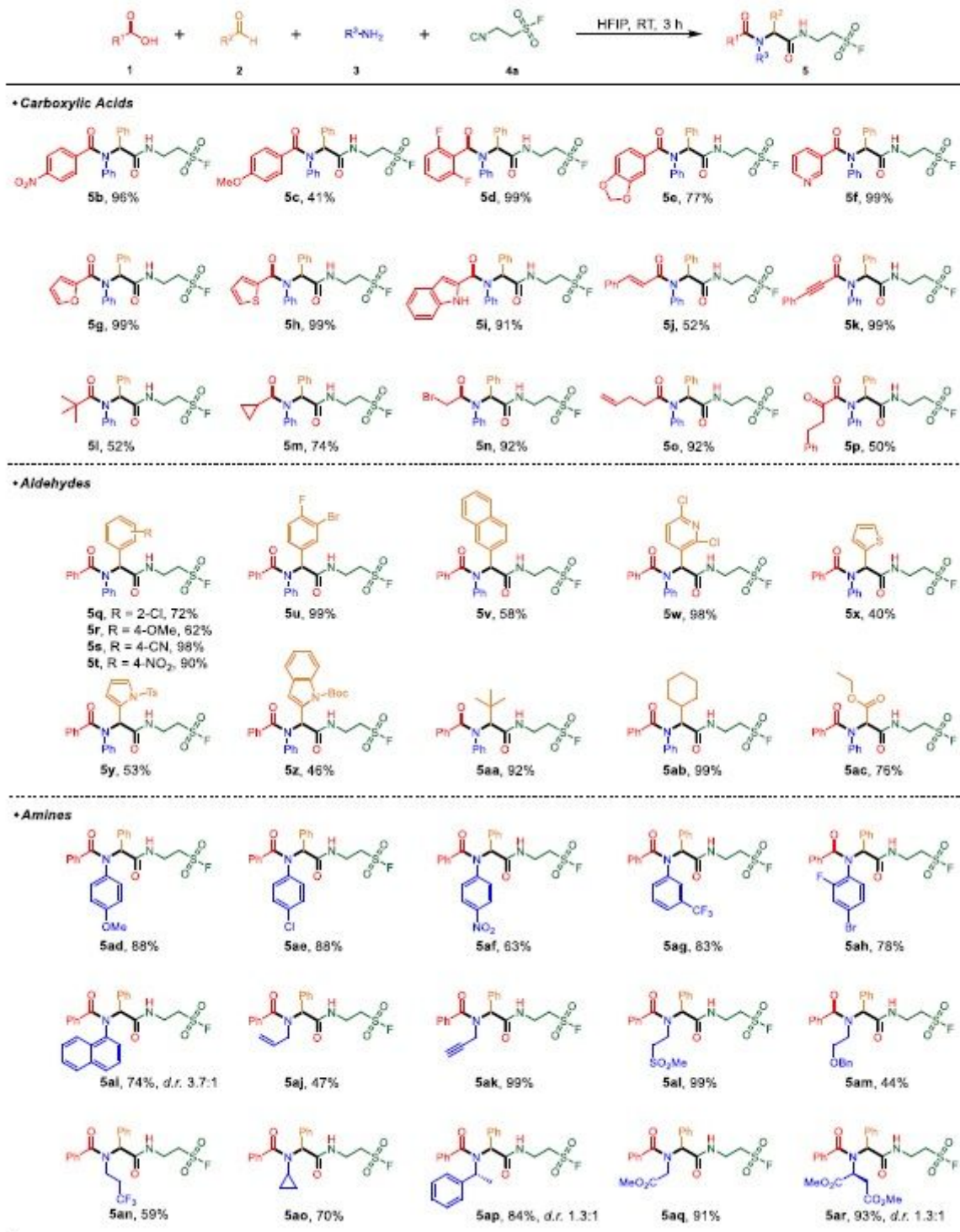


Figure 4

Scope of Ugi Reaction for Synthesis of Sulfonyl Fluoro α -Amino Amides. Reaction condition: 1 (0.1 mmol), 2 (0.15 mmol), 3 (0.15 mmol) and 4a (0.15 mmol) were added to HFIP (1 mL) and kept at RT for 3 h. Yield refers to isolated products, and d.r. value was determined by ¹H NMR.

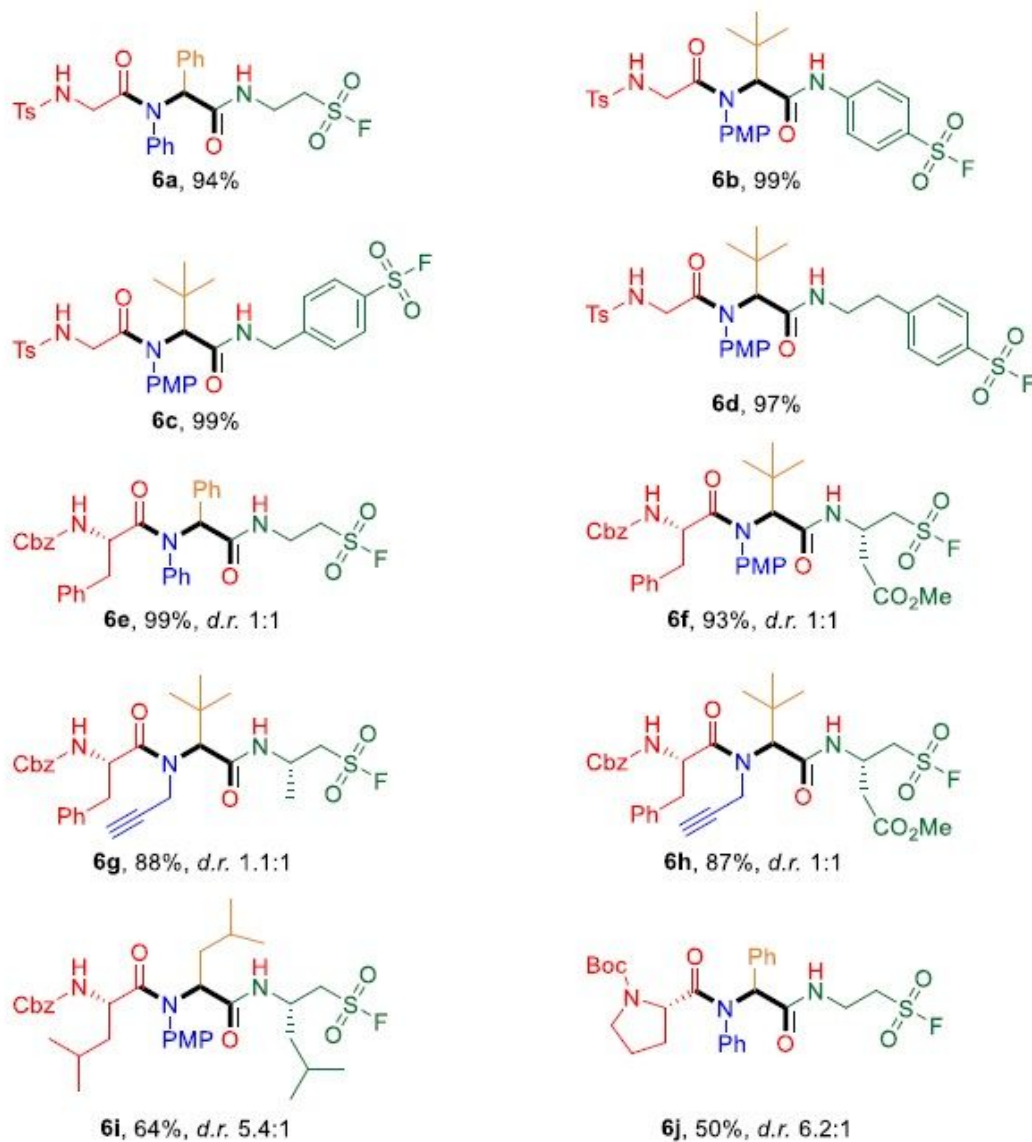
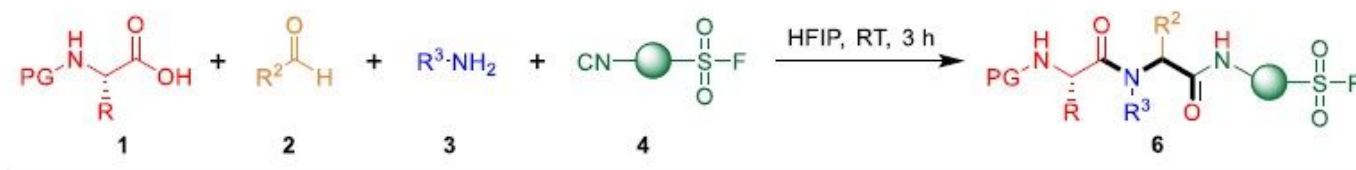


Figure 5

Synthesis of Sulfonamide Peptides. Reaction condition: 1 (0.1 mmol), 2 (0.15 mmol), 3 (0.15 mmol) and 4 (0.15 mmol) were added to HFIP (1 mL) and kept at RT for 3 h. Yield refers to isolated products, and d.r. value was determined by ^{19}F NMR. PMP = para-methoxyphenyl.

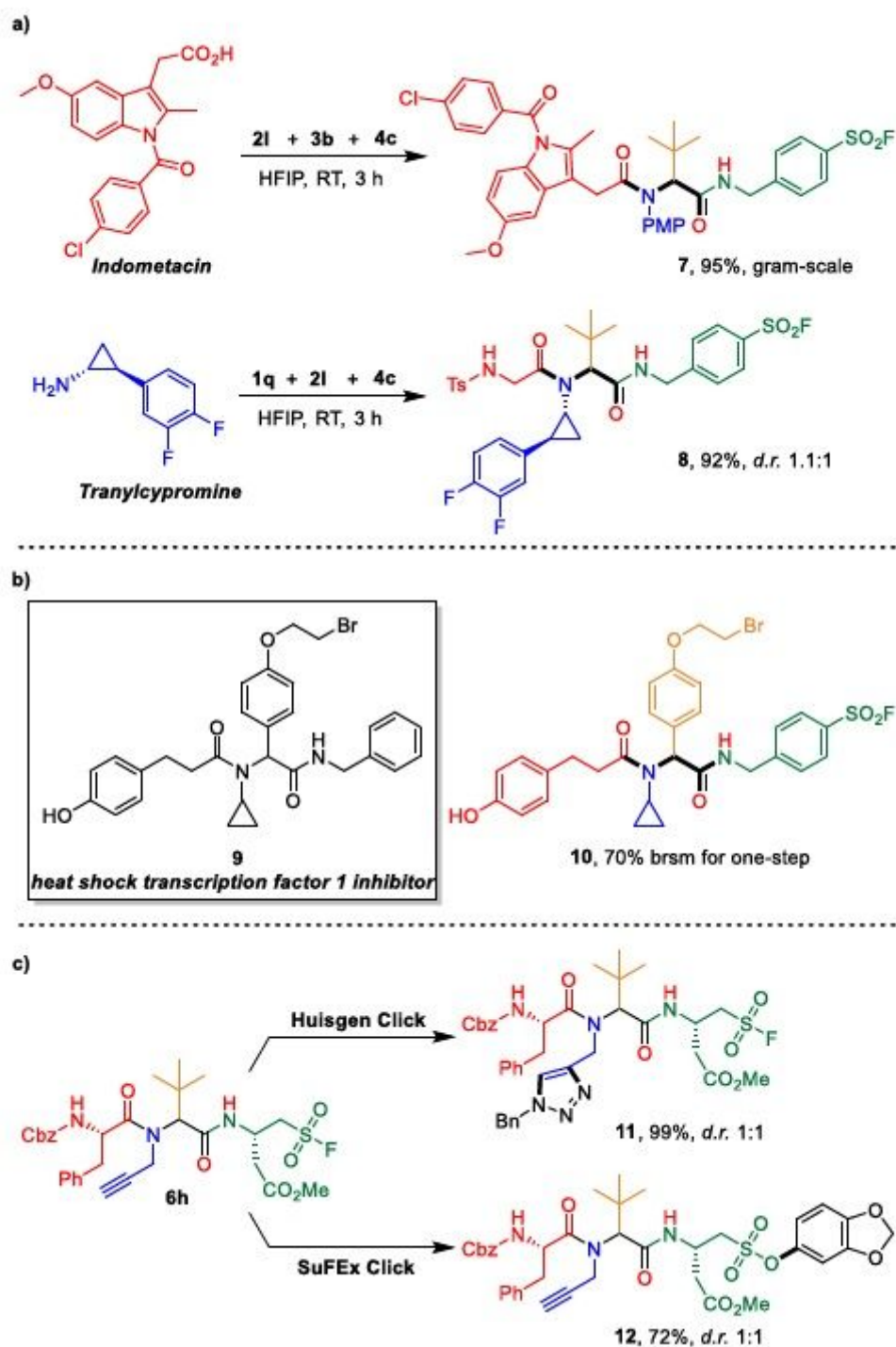


Figure 6

Synthetic applications. a. Synthesis of drug derivatives and gram-scale reaction. b. Synthesis of a heat shock transcription factor 1 inhibitor derivative. c. Click reaction with sulfonyl fluoro peptide 6.

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