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2-Azidoethane-1-sulfonylfluoride (ASF), a Versatile *Bis*-clickable Reagent for SuFEx and CuAAC Click Reactions

Xu Zhang,[†] [a] Balakrishna Moku,[†] [a] Jing Leng,[a] K. P. Rakesh[a] and Hua-Li Qin *[a]

Abstract: A new reagent, 2-azidoethane-1-sulfonylfluoride (ASF), was synthesized from 2-chloroethane-1-sulfonyl fluoride in 50g-scale with 87% yield. This novel reagent possesses two selectively clickable functionalities to be used for both CuAAC and SuFEx click reactions. The application of this reagent ASF to the construction of a class of novel 1,2,3-triazole derived S(VI)-F analogues was achieved in a quick, efficient and atom-economical manner. Orthogonally clickable construction of a new class of dendrimers was also accomplished.

Introduction

Click chemistry has been widely applied as a powerful tool in a large variety of fields because of its unique features of operational simplicity, mild conditions, substrate scopes, bio-orthogonality, favorable kinetics, and high yields.[1] Among the available clickable reactions, the copper catalyzed azide−alkyne cycloaddition (CuAAC), had a profound influence on the evolution of click chemistry since the first reports by the groups of Sharpless and Meldal.[2] Sulfur(VI) Fluoride Exchange (SuFEx), a rapidly developing new family of click chemistry transformations, was introduced by professor Sharpless in 2014, encompassing those reactions that facilitate the modular synthesis of S^{VI}-X (where X can be NR^1R^2 or OR) connections from a parent S^{VI}-F containing compound under defined conditions.[3] Many attractive features such as strong electron withdrawing nature, stability against hydrolysis, resistance to reduction at sulfur, and crisp preference for two-electron processes over radical processes, have already made this “grabber” group applicable to many productive fields within a short period.[4] Dendrimers are a class of macromolecules with a well-defined globular structure possessing a large number of peripheral functional groups of numerous specific characteristics for a wide range of applications.[5] Typically, the synthesis of dendrimers requires a large excess of monomers, and/or the protection-deprotection procedures, or implements at least two orthogonal chemistries together with purification steps, all of which suffer from low atom efficiency.[6] Therefore, orthogonal click chemistries with high reaction enthalpy, high chemo-selectivity and atom-economy has been widely investigated for dendrimer synthesis. [7] However, the utilization of both SuFEx and CuAAC click chemistries for the orthogonal synthesis of dendrimers has rare been explored due to the very limited and available reagents suitable for both types of click reactions.

To date, several S^{VI}-F reagents have been developed as SuFEx clickable hubs (Figure 1). Arylfluorosulfates (Ar-O-SO_2-F) and iminosulfur oxydifluorides (R-N=SOF_2) are accessible through the reactions of two gases, sulfuryl fluoride (SO_2F_2)[3,8] and thionyl tetrafluoride (SOF_4),[9] with oxygen or nitrogen nucleophiles respectively under appropriate conditions to provide robust click connecters for further SuFEx manifestation (Figure 1a, 1b). 2-Heteroaryl ethenesulfonyl fluorides (Figure 1c), a class of selectively addressable *bis*-electrophiles for SuFEx transformations can be readily synthesized through manipulating another excellent SuFEx reagent, the ethenesulfonyl fluoride (ESF) using Heck-type couplings[10] or direct fluorosulfonylvinylation of aryl C-H bonds.[11]

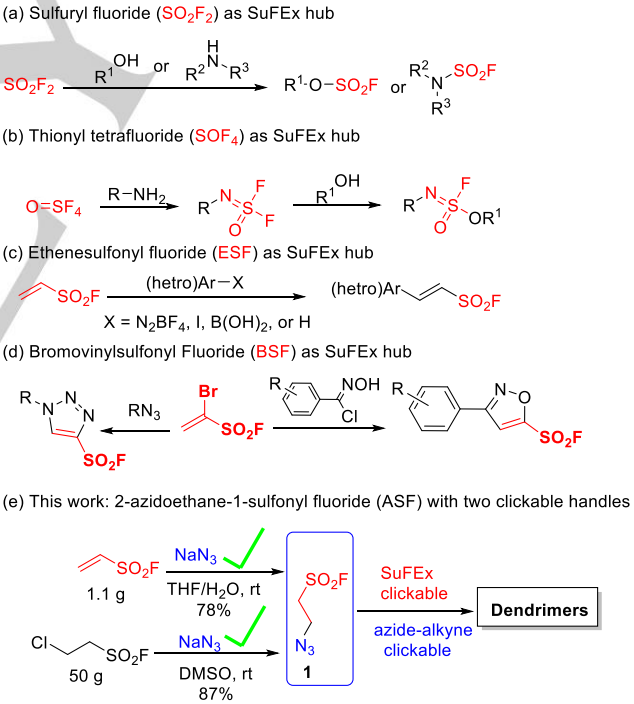

Figure 1 Evolution of Sulfur (VI) fluoride exchange (SuFEx) click chemistry.

Recently, the constructions of fluorosulfonyl isoxazoles and fluorosulfonyl 1,2,3-triazoles (Figure 1d) were accomplished by using 1-bromoethene-1-sulfonyl fluoride (1-Br-ESF).[12] It provided two classes of novel heterocycles-functionalized sulfur(VI)-F motifs for SuFEx click chemistry as robust tools. These approaches to preparation of diverse compound libraries bearing S^{VI}-F increased the chance of identifying lead compounds [13] and synthesizing new materials, especially dendrimers. Therefore, design and synthesis of S(VI)-F new reagents to enrich SuFEx cabinet for a quick access to S(VI)-F

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containing molecules are highly desirable. Herein, we report the development of 2-azidoethane-1-sulfonylfluoride (**ASF**) (Figure 1e) as a new portal to both azide-alkyne and SuFEx click reactions allowing quick, efficient and atom-economical synthesis of 1,2,3-triazole derived S(VI)-F libraries and as a versatile *bis*-clickable reagent for orthogonal synthesis of dendrimers.

Accordingly, after screening a variety of conditions, we achieved the synthesis of 2-azidoethane-1-sulfonylfluoride (**ASF**) (Figure 1e) bearing an S^{VI}-F motif and an azide functionality connected to two vicinal carbon atoms, from the readily accessible 2-chloroethane-1-sulfonyl fluoride [10] by substituting chloride with azide anion in a reasonable scale (50 g) with 87% yield. It is very interesting to note that unlike sulfonyl chloride which can be easily converted to sulfonylazide in the presence of NaN_3, [14] the sulfonyl fluoride remains untouched in the presence of NaN_3. Alternatively, we also accomplished **ASF** construction through Michael addition of hydrazoic acid (HN_3, *in situ* generated from NaN_3 and H_2O) to ESF in a small scale (1.1 g) with 78% yield minimizing the effect of high explosibility of HN_3.[15] It is worth noting that when Michael addition was carried out in the presence of a strong base, the azide group of ASF might undergo a *β*-elimination (or retro-Michael) process, to regenerate ESF, and some strong base may even cause a hydrolysis of the sulfonyl fluoride moiety to destroy ASF.[16] Therefore, the substitution reaction between 2-chloroethane-1-sulfonyl fluoride and NaN_3 in DMSO is the preferred method for ASF preparation.

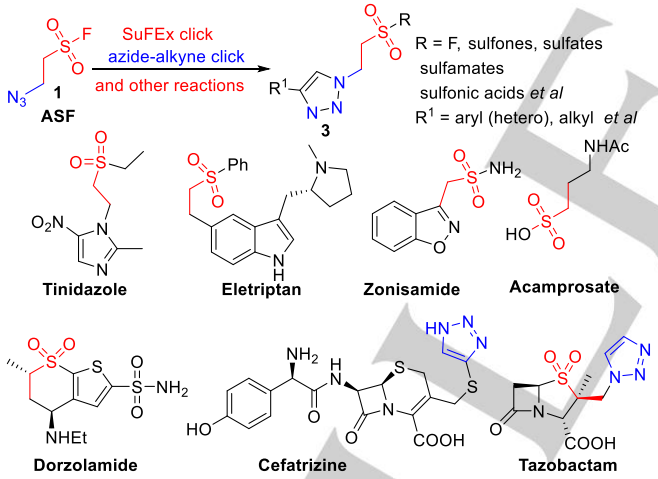


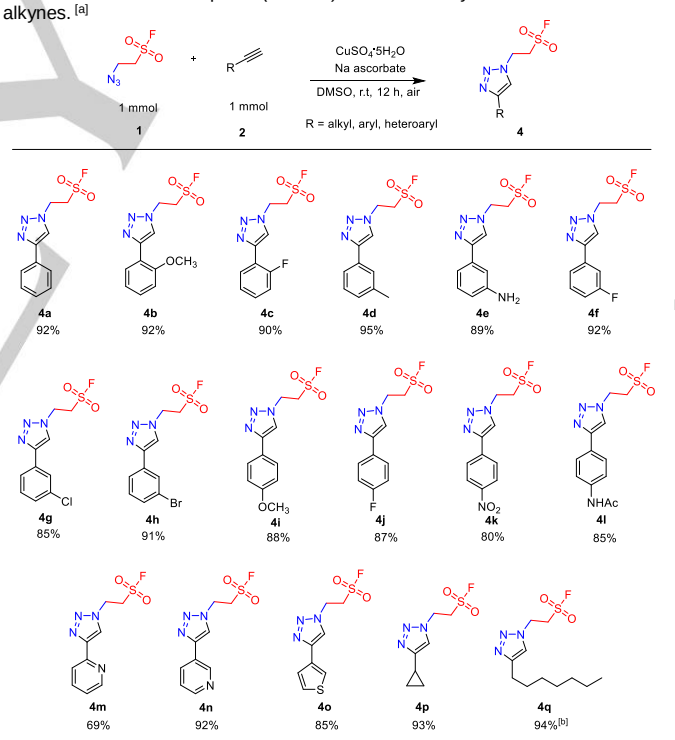
Figure 2 Representative drugs bearing ethylsulfonyl (VI) moieties or/and 1,2,3-triazoles.

The sulfonyl (S^{VI}) moieties have significant impact in the fields of pharmaceutical and medicinal chemistry, and there are more than 150 drugs bearing S^{VI} motif, which include some blockbuster drugs, such as Tindamax (Tinidazole), Relpax (Eletriptan), Zonegran (Zonisamide), Campral (Acamprosate) and Trusopt (Dorzolamide), possess ethylsulfonyl (S^{VI}) functionality (Figure 2).[17] On the other hand, 1,2,3-triazoles also play irreplaceably important roles in medicinal chemistry and drug discovery, and a few triazole-containing drugs have been approved, such as Cefatrizine and Tazobactam.[1,18] The unique structure of ASF **1** provides an azide functionality and a sulfonyl fluoride motif to be selectively clickable for furnishing both 1,2,3-triazoles and S^{VI} derivatives linked by two adjacent carbons (sulfamates, sulfonic acids, sulfones, sulfates *et al.*) though azide−alkyne click, SuFEx click and other reactions. Therefore, libraries of molecules (**3**) bearing both ethylsulfonyl (S^{VI}) and triazoles can be easily accessed for drug discovery using reliable and robust click reactions, in which Tazobactam (Figure 2) is a good example to show the value of this class of motifs.

Results and Discussion

Based on the potential significance of this designed 2-azidoethane-1-sulfonylfluoride (**ASF**) for medicinal chemistry and pharmaceutical industry, we started our initial investigation of application of this new clickable hub in copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) click chemistry to testify the robustness of this reagent for constructing a class of novel 1,4-disubsituted 1,2,3-triazoles bearing a sulfonyl fluoride functionality for further addressing.

Table 1: Substrates scope of (CuAAC) click chemistry of ASF with terminal alkynes. [a]



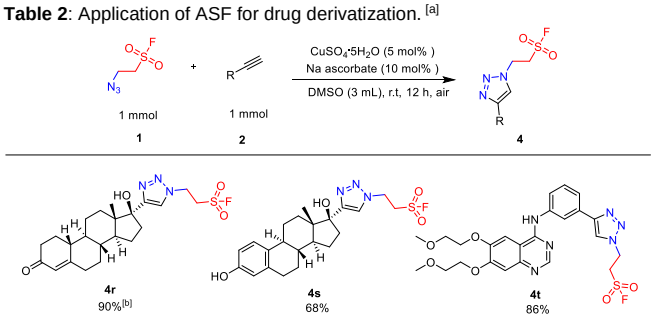
[a] Isolated yields, ASF (**1**, 1 mmol), terminal alkynes (**2**, 1 mmol), 5 mol% of $CuSO_4{\cdot}5H_2O$ and 10 mol% of Na ascorbate were added into DMSO (3 mL), the mixture was stirred at room temperature for 12 h; [b] 10 mol% of $CuSO_4{\cdot}5H_2O$ was used.

As illustrated in Table 1, examination of ASF (**1**) with various structurally and electronically diverse terminal alkynes **2** revealed that this click reaction is compatible with a broad scope of substrates. Not surprisingly, all of the 1,4-disubstituted 1,2,3-

triazoles were obtained in excellent yields regardless the electron-donating or electron-withdrawing groups, such as methyl, methoxyl, amine, halogen, nitro and amide moieties (Table 1, **4a-4l**). Heteroaryl and aliphatic alkynes were also transformed into their corresponding products in good to nearly quantitative yields (Table 1, **4m-4q**).

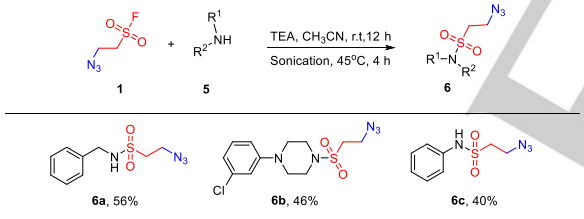
To further demonstrate the practicality of the new reagent ASF **1** in drug derivatization, steroidal drugs (**2r** and **2s)** and antineoplastic drug (**2t**) were chosen as the representative examples, and much to our delight, their corresponding modified products were smoothly furnished in good to excellent yields (Table 2, **4r-4t**).

Table 2: Application of ASF for drug derivatization. [a]



[a] Isolated yields, ASF (**1**, 1 mmol), terminal alkynes (**2**, 1 mmol), 5 mol% of $CuSO_4{\cdot}5H_2O$ and 10 mol% of Na ascorbate were added into DMSO (3 mL), the mixture was stirred at room temperature for 12 h; [b] 10 mol% of $CuSO_4{\cdot}5H_2O$ was used.

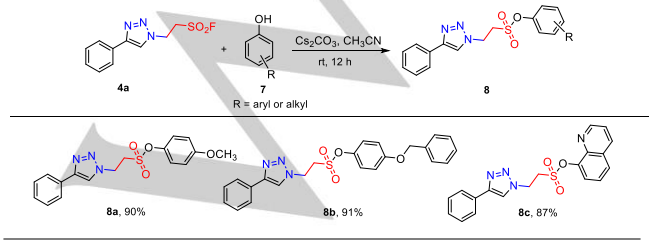
Table 3: SuFEx of ASF with amines for construction of sulfonyl amides.[a]



[a] 2-azidoethane-1-sulfonyl fluoride (**1**, 1 mmol) reacted with amine (**5**, 1.0 eq.) in the presence of triethylamine (1.1 eq.) in acetonitrile (1 M) at room temperature for 12 h, followed by sonication at 45 °C for 4 h. The yields were based on the amounts of isolated products.

In view of the potential application of ASF **1** in SuFEx click reactions, two representative aliphatic (primary and secondary) amines and an aromatic amine were selected to test the feasibility of our proposed SuFEx reaction. Gratifyingly, their corresponding amides were successfully generated in moderate

Table 4: Synthesis of triazolo sulfonates.[a]

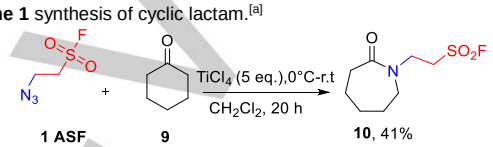


[a] Isolated yield, cesium carbonate (1 mmol) and phenol (**7**, 1 mmol) were added to a stirred solution of triazolo sulfonyl fluoride (**4a**, 1 mmol) in acetonitrile (2 mL) at room temperature and stirred for 12 h.

yields (Table 3, **6a-6c**) where 2-azido-*N*-phenylethane-1-sulfonamide **6c** was obtained in slightly lower yield than its counterparts attributing to the sluggish reactivity of aniline. In addition, **4a**, a representative of the new class of 1,4-disubstituted 1,2,3-triazoles **4** was smoothly converted to the corresponding sulfonates **8** (Table 4, **8a-8c**) in excellent yields upon reacting with phenols **7** *via* a SuFEx process.

As illustrated in Scheme 1, ASF (**1**) also exhibited good reactivity toward cyclohexanone **9** for generation of a unique seven-membered lactam **10** bearing ethyl sulfonyl fluoride moiety in moderate yield.

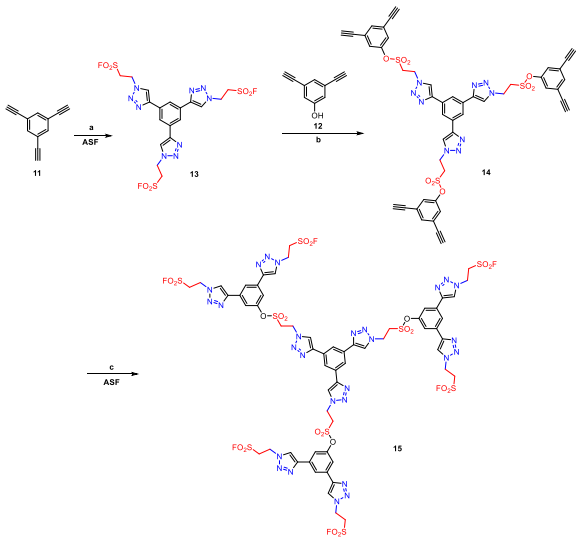
Scheme 1 synthesis of cyclic lactam.[a]



[a] Isolated yield, cyclohexanone (**9**, 1 mmol) and ASF (**1**, 1 mmol) were added to a stirred solution in dichloromethane (3 mL), then $TiCl_4$ was dropwise at 0℃ and recovered to room temperature for 20 h.

Utilization of *bis*-clickable reagent through orthogonal CuAAC and SuFEx click reactions for chemoselective assembly of dendrimers was investigated to demonstrate the versatility of this novel reagent. As shown in Scheme 2, dendrimers **15** was successfully synthesized from versatile *bis*-clickable reagent ASF in 54% overall isolated yield in a three-step sequence (Scheme 2) without requiring any protecting-deprotecting processes. This new class of dendrimers allow controlled molecular weight building, controlled branching and versatility in design and modification of the terminal end groups. Therefore, with this novel reagent (ASF), the highly efficient and orthogonal SuFEx and CuAAC click reactions have provided promising possibilities for the preparation of unique polymers.

Scheme 2 synthesis of dendrimers using SuFEx and CuAAC click reactions.



Reaction conditions: (**a**) 1,3,5-triethynylbenzene (**11,** 1 mmol), ASF (6 eq.), $CuSO_4.5H_2O$ (1 eq.), Na ascorbate (1 eq.), DMSO (0.3 M), room temperature, 12 h (90 %); (**b**) 3,5-diethynylphenol (**12**, 5 eq.), Cs_2CO_3 (5 eq.), CH_3CN (5 mL), H_2O (5 mol %), room temperature, 12 h (61 %); (**c**) ASF (12 eq.), $CuSO_4{\cdot}5H_2O$ (1 eq.), Na ascorbate (1 eq.), DMSO (3 mL), room temperature, 12 h (98 %).

Conclusions

We have developed a new reagent, 2-azidoethane-1-sulfonylfluoride (**ASF**), which possesses two selectively clickable functionalities for both sulfur(VI) fluoride exchange (SuFEx) and CuAAC click reactions. This new molecule has great potential for quick introducing sulfonyl fluoride into biological systems to develop new covalent enzyme inhibitors through versatile, reliable and robust click chemistry. The utilization of **ASF** for orthogonally clickable construction of a new class of dendrimers was accomplished. The possible future wide applications of **ASF** will significantly accelerate the preparation of diverse compound libraries bearing S^{VI}-F moieties to increase the chance of identifying new targeted covalent inhibitors.

Experimental Section

General procedure for compound 4.

2-azidoethane-1-sulfonyl fluoride (**1**, 1.0 mmol, 153.1 mg), acetylene (**2**, 1.0 mmol, 1.0 eq.), $CuSO_4{\cdot}5H_2O$ (5 mol%, 13 mg), Na ascorbate (10 mol%, 20 mg), DMSO (3.0 mL) were added in a reaction tube (10 mL) and stirred at room temperature for 12 h. Then the reaction mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The crude product was further purified by column chromatography on silica gel using petroleum ether / ethyl acetate (v / v) as eluent to get desired compound **4**.

General procedure for compound 6.

2-azidoethanesulfonyl fluoride (**1,** 1 mmol) was added to a solution of amine (**5**, 1 mmol) and triethylamine (1.1 mmol) in acetonitrile (1 mL) and stirred at room temperature for 12 h. Then the reaction mixture was sonicated at 45 ºC for 4 h. After completion of reaction, the mixture was concentrated to dryness and purified by column chromatography to obtain the corresponding azido sulfonamide **6**.

General procedure for compound 8.

Cesium carbonate (1 mmol) and phenol (**7**, 1 mmol) were added to a stirred solution of triazolo sulfonyl fluoride (**4a**, 1 mmol) in acetonitrile (2 mL) and stirred at room temperature for 12 h. After completion of reaction, the mixture was concentrated to dryness and purified by column chromatography to get the corresponding triazolo sulfonates **8**.

General procedure for compound 10.

Cyclohexanone (**9**, 1 mmol) and **ASF** (**1**, 1 mmol) were added to a stirred solution in dichloromethane (3 mL), then $TiCl_4$ was dropwise at 0℃ and recovered to room temperature for 20 h.

General procedure for dendrimers.

(**a**) 1,3,5-triethynylbenzene (**11**, 1 mmol), $CuSO_4{\cdot}5H_2O$ (1 eq.) and Na ascorbate (1 eq.) were added to a stirred solution of ASF (**1**, 6 eq.) in DMSO (3 mL) and stirred at room temperature for 12 h. After completion of reaction, the mixture was purified by recrystallization to get the corresponding compound **13**.

(**b**) **13** (1 mmol), 3,5-diethynylphenol (**12**, 5 eq.) and Cs_2CO_3 (5 eq.) were added to a stirred solution of H_2O (5 mol %) in CH_3CN (5 mL) and stirred at room temperature for 12 h. After completion of reaction, the mixture was concentrated to dryness and purified by column chromatography to obtain the corresponding compound **14**.

(**c**) **14** (1 mmol), $CuSO_4{\cdot}5H_2O$ (1 eq.) and Na ascorbate (1 eq.) were added to a stirred solution of ASF (**1**, 12 eq.) in DMSO (3 mL) and stirred at room temperature for 12 h. After completion of reaction, the mixture was purified by recrystallization to get the corresponding compound **15**.

Acknowledgments

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Keywords: Click chemistry • SuFEx • Azides • Dendrimers

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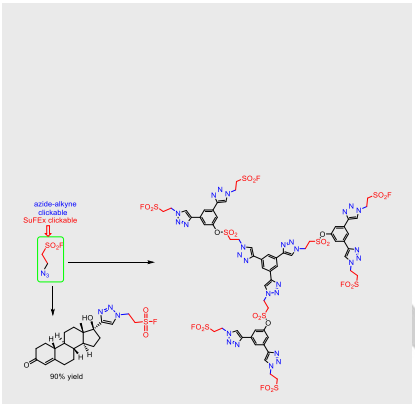
Entry for the Table of Contents

COMMUNICATION

A novel unique reagent, 2-azidoethane-1-sulfonylfluoride (ASF), which can be used for both azide-alkyne and SuFEx click reactions, was developed to provide a portal to unique 1,2,3-triazole derived S(VI)-F libraries for medicinal chemistry, chemical biology and drug discovery in a quick, efficient and atom-economical manner using a robust click chemistry strategy. A new class of dendrimers was developed using this reagent through orthogonal CuAAC and SuFEx click reactions.



SuFEx and **CuAAC**

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Title: 2-Azidoethane-1-sulfonylfluoride (ASF), a Versatile *Bis*-clickable Reagent for SuFEx and CuAAC Click Reactions