ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Leng and H. Qin, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC00986D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC00986D

Journal Name

COMMUNICATION

1-Bromoethene-1-Sulfonyl Fluoride (1-Br-ESF), a New SuFEx Clickable Reagent, and the Application for Regioselective Construction of 5-Sulfonylfluoro Isoxazoles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jing Leng,[a] Hua-Li Qin * [a]

A new fluorosulfonylation reagent 1-bromoethene-1-sulfonyl fluoride was developed (1-Br-ESF). This unique reagent possesses three addressable handles (vinyl, bromide, and sulfonyl fluoride) and has great potentiality to functionalize as a *tris*-electrophile and as a sulfur(VI) fluoride exchange (SuFEx) clickable material to enrich SuFEx tool cabinet. The application of this reagent for regioselective synthesis of 5-sulfonylfluoro isoxazoles has been realized through a [3+2] cycloaddition with *N*-hydroxybenzimidoyl chloride. This practical protocol provides a general and direct route to functionalized isoxazoles possessing sulfonyl fluoride moieties.

Sulfur(VI) fluoride exchange (SuFEx) is an emerging and widely prevailing tool in click chemistry which enable the synthesis of S^{VI} covalently linked modules due to the special properties of S^{VI}-F compounds appearing in the nucleophilic substitutions. [1] Recently, many S^{VI} hub reagents have been developed and widely used in the SuFEx field (Figure 1). Sulfuryl fluoride (SO_2F_2), [2] when reacted with oxygen or nitrogen nucleophiles under appropriate condition provides fluorosulfates (or fluorosulfonates) or fluorosulfonamides, which can functionalize as robust click connecters for further nucleophilic substitutions; ethenesulfonyl fluoride (ESF), [3] another excellent S^{VI}-F construction reagent, is a selectively addressable *bis*-electrophile for SuFEx click chemistry; thionyl tetrafluoride (SOF_4), [4] provides two SuFExable sites through a tetrahedral imino sulfur (VI) link by the reaction of primary amino groups. Therefore, design and synthesis of new highly connectable S^{VI}-F reagent to enrich SuFEx click chemistry tool cabinet for further expanding the applications of click chemistry in the fields of material science, drug discovery, chemical biology and fine chemical industry is of great significance and rather desirable. [5] Herein, we report the development of 1-bromoethene-1-sulfonyl fluoride (1-Br-ESF) [6] as another SuFEx clickable reagent and its utilization for regioselective construction of 5-sulfonylfluoro isoxazoles.

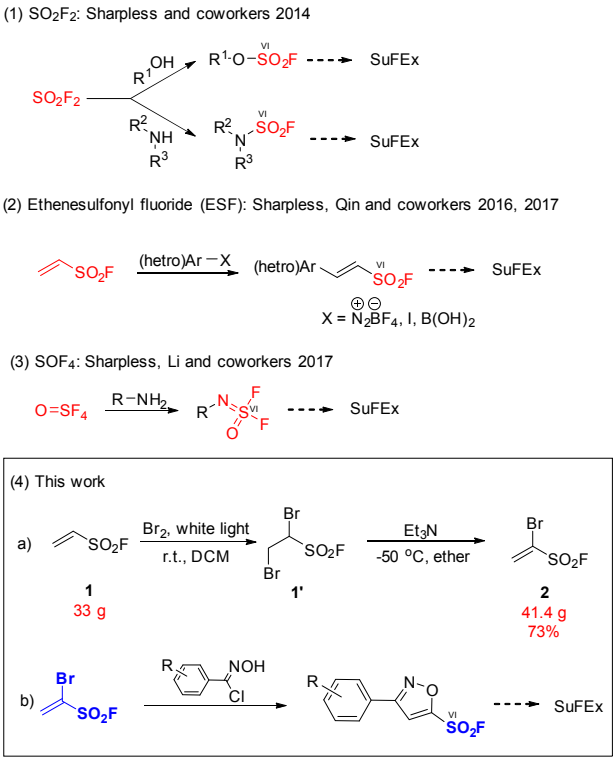


Figure 1 Developments in Sulfur(VI) fluoride exchange (SuFEx) click chemistry.

1-Bromoethene-1-sulfonyl fluoride (1-Br-ESF) **2**, with a bromide moiety connected directly to the vinyl group adjacent to sulfonyl fluoride, is readily accessible from ethenesulfonyl fluoride (ESF) **1** in 40-gram scale (Figure 1, 4a). As the unique structure of ethenesulfonyl fluoride (ESF) **1** provides a vinyl and a sulfonyl fluoride to act as excellent selectively addressable *bis*-electrophile, the specifically designed 1-

[a] *State Key Laboratory of Silicate Materials for Architectures; and School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, 205 Luoshi Road, Wuhan, Hubei Province, 430070, P. R. China; qinhuali@whut.edu.cn.*
** Corresponding author: Hua-Li Qin*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8CC00986D

bromoethene-1-sulfonyl fluoride (1-Br-ESF) **2** with one more active site can be regarded as a *tris*-electrophile. In addition, with two electron-withdrawing groups attached to one terminal of the ethylene, the olefin of 1-Br-ESF **2** will be an even stronger Michael acceptor than that of ethenesulfonyl fluoride (ESF), a described "the most perfect Michael acceptor ever found".[1, 7] In this paper, we describe an application of 1-bromoethene-1-sulfonyl fluoride (1-Br-ESF) **2** for regioselective construction of 5-sulfonylfluoro isoxazoles *via* a 1,3-dipolar cycloaddition process (Figure 1, 4b).

Isoxazoles, a family of important five-membered aromatic heterocycles, have emerged as significantly valuable heterocyclic moieties presented in pharmaceuticals and materials, and also been widely used as versatile building blocks in natural product synthesis, material science, medicinal chemistry.[8] Parecoxib, a COX-2 selective inhibitor; sulfamethoxazole, an antibiotic; oxacillin, a penicillinase-resistant β-lactam; isocarboxazid, a non-selective, irreversible monoamine oxidase inhibitor (MAOI) are all life-saving drugs containing isoxazole structure (Figure 2). Recent advances in the synthesis of isoxazole are mainly divided into following five aspects: [3+2] cycloaddition of alkenes / alkynes with nitrile oxides;[9] cycloisomerization reactions;[10] condensation reactions;[11] functionalization of isoxazoles[12] and other methods.[13] However, most of these procedures suffer from some drawbacks more or less, such as transition-metal catalysts, harsh reaction conditions or tedious multistep process. The sulfonyl fluorides are also a class of potential covalent pharmacophores to provide permanent inhibition of target proteins, which will be valuable starting points for the discovery of covalent drugs, in addition, there are already 152 approved S^{VI}-containing drugs in the market.[3b, 14] In addition, sulfonyl fluorides biological probes (Figure 2) have also captured widely attention worldwidely.[15] The typical approach for the introducing of sulfonyl fluoride group is by Cl-F exchange from their corresponding sulfonyl chloride using KF/18-crown-6 in water.[16] Recently, several protocols were successfully developed by employing the DABSO as a "SO_2" source followed by electrophilic fluorination with fluorinated reagent for the sulfonyl fluoride compounds.[17, 18] Limitations of such strategies include harsh acidic treatment of arenes to access sulfonyl chloride precursors by electrophilic aromatic sulfonation,[20] expensive starting material, and the requirement of metal catalysts. Viewing on the significance of both isoxazoles and sulfonyl fluoride as structurally ubiquitous motif in many important areas, we envision the development of a straightforward approach for simultaneously introducing isoxazole and sulfonyl fluoride groups will be particularly useful in medicinal chemistry and pharmaceutical industry.

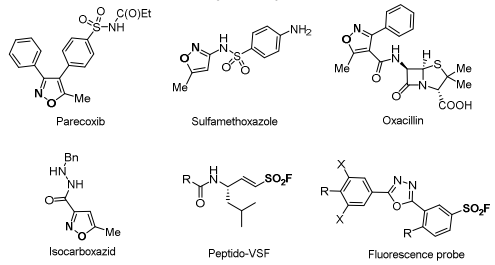
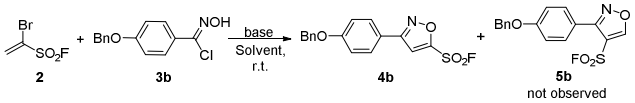


Figure 2 Representative isoxazoles and sulfonyl fluorides.

We initially began our exploration by using 4-(benzyloxy)-*N*-hydroxybenzimidoyl chloride **3b**, a general nitrile oxide precursor, and 1-bromoethene-1-sulfonyl fluoride **2** to testify the feasibility of formation of 3-(4-(benzyloxy)phenyl)isoxazole-5-sulfonyl fluoride **4b** and **5b**. To our delight, the [3+2] cycloaddition occurred at room temperature using Et_3N as the base in toluene, providing the desired isoxazole **4b** in 16% yield selectively (entry 1). The usage of other common solvents such as MeOH (entry 2), DMF (entry 4) did not improve the yield of this transformation, while the use of *t*-BuOH provided the desired product from isolatable level to moderate yield (entry 3, 6). The relatively weaker organic base tripropylamine performed the annulation smoothly (entry 6), while the inorganic bases (entry 9-12) were found unsuitable for this transformation. The examination of the effect of the amount of 1-Br-ESF **2** to this annulative process revealed that the use of 4.0 equivalents afforded the highest yield of the cyclization product (entry 13-15). Our experiments indicated that 1-Br-ESF **2** was sensitive to base conditions to decompose to very reactive species or undergo further polymerization. Therefore, the use of excess amount of 1-Br-ESF **2** is necessary to complete the consumption of the other starting materials, the *N*-hydroxybenzimidoyl chlorides **3**. However, it is interesting to observe, that the use of more than 4.0 equivalents of 1-Br-ESF decreased the yield of the [3+2] cycloaddition. The yield was increased to 80% when starting material **2** was dissolved in *t*-BuOH and added to the reaction mixture dropwise instead of in one single portion (entry 17), which was identified as the optimized condition.

Table 1. Selected optimization results.[a]



Entry	Base	**2** : **3b**	Solvent	Yield [b] (%)
1	Et_3N	1 : 1.5	Toluene	16
2	Et_3N	1 : 1.5	MeOH	0
3	Et_3N	1 : 1.5	*t*-BuOH	20
4	Et_3N	1 : 1.5	DMF	2
5	DIPEA	1 : 1.5	*t*-BuOH	14
6	Tripropylamine	1 : 1.5	*t*-BuOH	39
7	TMEDA	1 : 1.5	*t*-BuOH	20
8	DBU	1 : 1.5	*t*-BuOH	12
9	$NaHCO_3$	1 : 1.5	*t*-BuOH	<1
10	NaOAc	1 : 1.5	*t*-BuOH	9
11	K_3PO_4	1 : 1.5	*t*-BuOH	5
12	LiOAc	1 : 1.5	*t*-BuOH	6
13[c]	Tripropylamine	3 : 1	*t*-BuOH	37
14[d]	Tripropylamine	4 : 1	*t*-BuOH	47
15[e]	Tripropylamine	5 : 1	*t*-BuOH	32
16[f]	Tripropylamine	4 : 1	*t*-BuOH	57
17[f, g]	Tripropylamine	4 : 1	*t*-BuOH	80

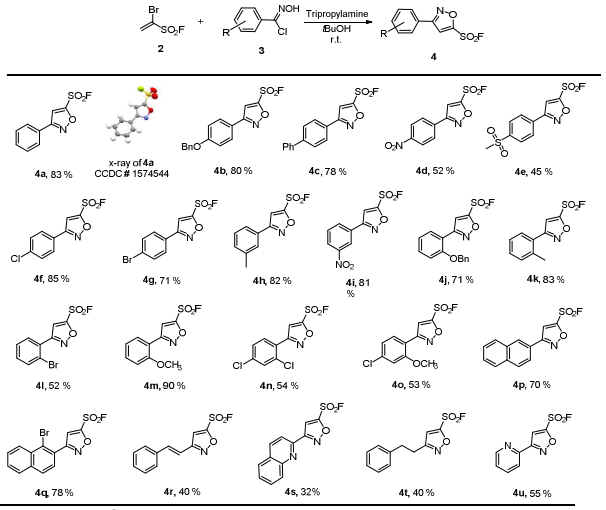
Conditions: [a] A mixture of **3b** (1.5 equiv., 0.15 mmol, 39 mg), **2** (1.0 equiv., 0.1 mmol, 18.9 mg), base (5 equiv., 0.5 mmol), and solvent (2 mL) was reacted at room temperature for 2 h.; [b] The yield was determined by HPLC using **4b** as the external standard. [$t_{\mathbf{4b}}$ = 9.416 min, λ_{max} = 240.5 nm, methanol / water = 80 : 20 (v / v)]; [c] the ratio of **2** to **3b** was 3 : 1; [d] the ratio of **2** to **3b** was 4 : 1; [e] the ratio of **2** to **3b** was 5 : 1; [f] the ratio of **2** to **3b** was 4 : 1, tripropylamine (2.5 equiv., 0.25 mmol); [g] **2** was

View Article Online
DOI: 10.1039/C8CC00986D

dissolved in another 2 mL *t*-BuOH and added to the reaction mixture dropwise.

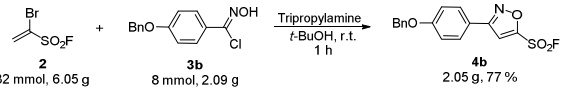
With the optimized reaction condition in hand, we then investigated the scope of *N*-hydroxybenzimidoyl chlorides for this cycloaddition reaction (Table 2). A series of different substituted *N*-hydroxybenzimidoyl chlorides **3** were reacted with 1-Br-ESF **2**, affording the desired products **4** in an acceptable to excellent yield within 1-2 h. The substrates with an electron-donating group (benzyloxy, **4b**; phenyl, **4c**; methyl, **4h**; methoxy, **4m**) on the phenyl ring were transformed into their corresponding isoxazoles in better yields than those with electron-withdrawing groups (**4d**, **4e** and **4g**). Substrates with functional groups of nitro (**4d**), mesyl (**4e**), halogen (**4f**, **4l**) were all compatible using this developed protocol. Interestingly, the sterically hindered *N*-hydroxybenzimidoyl chloride also proceeded efficiently, providing the corresponding products in satisfactory yields (**4j**, **4k** and **4m**). Polycyclic substrates (**3p**, **3q**) were also able to form their corresponding isoxazoles (**4p**, **4q**) in acceptable yields of 70% and 78% respectively. The product containing a vinyl group (**4r**) was also successfully obtained from its parent starting material cinnamyl aldehyde in a moderate yield of 40%. Alkyl and heteroaromatic starting materials could also transform into their corresponding products (**4t**, **4s** and **4u**) with acceptable yields.

Table 2. Scope of *N*-hydroxybenzimidoyl chlorides for the cycloaddition reaction.[a]



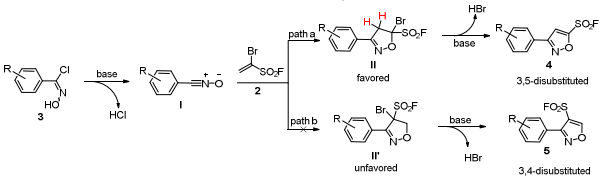
Conditions: [a] A mixture of **1** (1.0 equiv., 1.0 mmol), tripropylamine (2.5 equiv., 2.5 mmol, 358 mg), and *t*-BuOH (5 mL) was stirred in a tube, **2** (4 equiv., 4 mmol, 756 mg) was dissolved in another 5 mL *t*-BuOH and added to the reaction mixture dropwise.

To evaluate the practicality of this regioselective 1,3-dipolar cycloaddition, a gram-scale reaction was carried out. We were pleased to find that the efficiency of [3+2] cycloaddition was not decreased, the reaction of 2.09 grams of *N*-hydroxybenzimidoyl chloride **3b** (8 mmol) and 6.05 grams of 1-Br-ESF **2** (32 mmol) under the previous optimal conditions, smoothly provided 2.05 g of the desired 5-sulfonylfluoro isoxazole **4b** in one hour (Scheme 1).



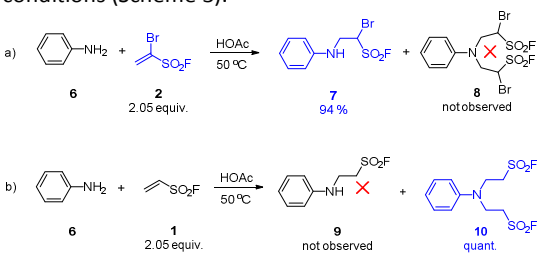
Scheme 1. Multigram scale synthesis of **4b**.

A plausible mechanism for the 1,3-dipolar cycloaddition reaction was proposed (Scheme 2). Firstly, the nitrile oxides **I** was generated from **3** with the assistance of base, which, subsequently, annulated with 1-Br-ESF **2** to generate intermediate isoxazoline **II** (path a), due to the steric hindrance, another possible cycloaddition intermediate **II'** (path b) was excluded**.** Finally, the exclusively regioselective product 3,5 -disubstituted isoxazole **4** was obtained through releasing of HBr under the effect of another equivalent of base.



Scheme 2. A plausible mechanism for the formation of isoxazole **4**.

It is interesting to find that the performance of 1-bromoethene-1-sulfonyl fluoride (1-Br-ESF) and ethenesulfonyl fluoride (ESF) vary significantly when react with aniline as Michael acceptors. The reaction of aniline **6** with excess (2.05 eq) of 1-Br-ESF **2** gave only mono-adducted product **7** in quantitative yield without the formation of any *bis*-adducted product **8** while in the reaction of aniline **6** and ethenesulfonyl fluoride (ESF) the opposite result was obtained under identical conditions (Scheme 3). [5a, 5b]

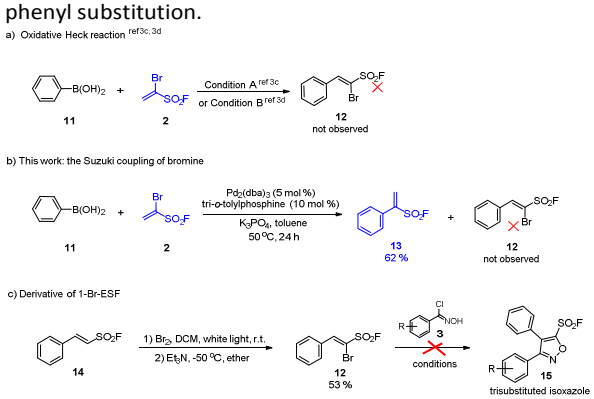


Scheme 3. A reactivity comparison between (1-Br-ESF) and ESF in Michael addition.

Another significant property of 1-Br-ESF appeared in the coupling reaction. It is interesting to find that the oxidative Heck coupling between 1-Br-ESF and arylbronoic acid didn't occur by employing the conditions used for coupling of ESF with arylbronoic acid (Scheme 4, a, b). It is worthy noting that the Suzuki coupling product **13** can be generated under a specific reaction condition using Pd catalyst to provide the first example of 1-aryl ethenesulfonyl fluoride of its kind with proceeding the competitive Heck type of oxidative coupling to form compound **12**. This new class of 1-aryl ethenesulfonyl fluorides **13** have great potentiality to be applied in polymer synthesis and chemical biology. [21] Interestingly, the oxidative heck-coupling product **12** was accessible through a cascade

View Article Online
DOI: 10.1039/C8CC00986D

process of the addition of Br_2 to (*E*)-2-phenylethene-1-sulfonyl fluoride **14** and the subsequent elimination with the promotion of base (Scheme 4, c), however, the treatment of 2-phenyl-1-bromoethene-1-sulfonyl fluoride **12** with *N*-hydroxybenzimidoyl chlorides **3** did not generate the desired trisubstituted isoxazole **15** due to steric hindrance effect of the phenyl substitution.



Scheme 4. Further derivatization of 1-Br-ESF.

In conclusion, we have developed a new fluorosulfonylation reagent 1-bromoethene-1-sulfonyl fluoride (1-Br-ESF), which possess enormous potential in the field of SuFEx click chemistry. Meanwhile, a method for the 1,3-dipolar cycloaddition between diverse *N*-hydroxybenzimidoyl chlorides and 1-Br-ESF was developed for the synthesis of a series of 5-sulfonyl fluoride substituted isoxazoles. Further applications of 1-Br-ESF in SuFEx click chemistry and their utilizations for discovery of new drug candidates and functional materials are ongoing in our laboratory.

We are grateful to the National Natural Science Foundation of China (Grant No. 21772150) and Wuhan University of Technology for their continuous encouragement towards the research and financial support.

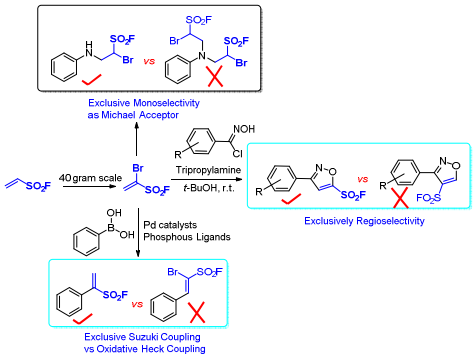
Conflicts of interest

There are no conflicts to declare.

Notes and references

1 J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2014, **53**, 9430.
2 J. S. Oakdale, L. Kwisnek, V. V. Fokin, *Macromolecules* 2016, **49**, 4473.
3 a) H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2016, **55**, 14155. b) G.-F. Zha, Q. Zheng, J. Leng, P. Wu, H.-L. Qin, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2017, **56**, 4849. c) P. K. Chinthakindi, K. B. Govender, A. S. Kumar, H. G. Kruger, T. Govender, T Naicker, P. I. Arvidsson, *Org. Lett.* 2017, **19**, 480. d) G.-F. Zha, G. A. L. Bare, J. Leng, Z.-P. Shang, Z. Luo, H.-L. Qin, *Adv. Synth. Catal.* 2017, **359**, 3237. e) Q. Zheng, J. Dong, K. B. Sharpless, *J. Org. Chem.* 2016, **81**, 11360.
4 S. Li, P. Wu, J. E. Moses, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2017, **56**, 2903.
5 a) B. Gao, L. Zhang, Q. Zheng, F. Zhou, L. M. Klivansky, J. Lu, Y. Liu, J. Dong, P. Wu, K. B. Sharpless, *Nat. Chem.* 2017, **9**, 1083. b) H. Wang, F. Zhou, G. Ren, Q. Zheng, H. Chen, B. Gao, L. Klivansky, Y. Liu, B. Wu, Q. Xu, J. Lu, K. B. Sharpless, P. Wu, *Angew. Chem. Int. Ed.* 2017, **56**, 11203. c) A. J. Brouwer, N. Herrero Álvarez, A. Ciaffoni, H. van de Langemheen, R. M. J. Liskamp, *Bioorg. Med. Chem.* 2016, **24**, 3429.
6 a) A. Champseix, J. Chanet, A. Etienne, A. Leberre, J. C. Masson, C. Napierala, R. Vessiere, *Bull. Soc. Chim. Fr.* 1985, 463. b) J. Chanet-Ray, R. Vessière, A. Zéroual, *Heterocycles,* 1987, **26**, 101.
7 Q. Chen, P. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* 2016, **55**, 12664.
8 a) J. B. Carr, H. G. Durham, D. K. Hass, *J. Med. Chem.* 1977, **20**, 934. b) R. Nesi, S. Chimichi, P. Sarti-Fantoni, P. Tedeschi, D. Giomi, *J. Chem. Soc. Perkin Trans,* 1985, 1871. c) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* 2005, **127**, 210. d) M. A. F. A. Manan, D. B. Cordes, A. M. Z. Slawin, M. Bühl, V. W. Y. Liao, H. C. Chua, M. Chebib, D. O'Hagan, *Chem. Eur. J.* 2017, **23**, 10848. e) A. Rietz, H. Li, K. M. Quist, J. J. Cherry, C. L. Lorson, B. G. Burnett, N. L. Kern, A. N. Calder, M. Fritsche, H. Lusic, P. J. Boaler, S. Choi, X. Xing, M. A. Glicksman, G. D. Cuny, E. J. Androphy, K, J. Hodgetts, *J. Med. Chem.* 2017, **60**, 4594. (f) F. Hu, M. Szostak, *Adv. Synth. Catal.* 2015, **357**, 2583.
9 a) A. Quilico, G. Stagno d'Alcontres, P. Grünanger, *Nature* 1950, **166**, 226. b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2002, **41**, 2596. c) C. Spiteri, S. K., J. E. Moses, *Org. Lett.* 2010, **12**, 3368.
10 a) J. P. Waldo, R. C. Larock, *Org. Lett.* 2005, **7**, 5203. b) T. Okitsu, K. Sato, T. M. Potewar, A. Wada, *J. Org. Chem.* 2011, **76**, 3438. c) C. Y. Wu, T. Horibe, C. B. Jacobsen, F. D. Toste, *Nature* 2015, **517**, 449. d) W. J. Wolf, M. S. Winston, F. D. Toste, *Nat. Chem.* 2014, **6**, 159.
11 a) R. Harigae, K. Moriyama, H. Togo, *J. Org. Chem.* 2014, **79**, 2049. b) H. Kawai, Y. Sugita, E. Tokunaga, N. Shibata, *Eur. J. Org. Chem.* 2012, 1295. c) A. Salomone, A. Scilimati, P. Vitale, *Synthesis* 2015, **47**, 807.
12 a) X. C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J. Q. Yu, *J. Am. Chem. Soc.* 2013, **135**, 10326. b) K. M. Engle, T. S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.* 2012, **45**, 788.
13 J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira, *Angew. Chem. Int. Ed.* 2011, **50**, 5379.
14 A. J. Brouwer, N. H. Álvarez, A. Ciaffoni, H. Langemheen, R. M. J. Liskamp, *Bioorg. Med. Chem.* 2016, **24**, 3429.
15 a) N. P. Grimster, S. Connelly, A. Baranczak, J. Dong, L. B. Krasnova, K. B. Sharpless, E. T. Powers, I. A. Wilson, J. W. Kelly, *J. Am. Chem. Soc.* 2013, **135**, 5656. b) Q. Zhao, X. Ouyang, X. Wan, K. S. Gajiwala, J. C. Kath, L. H. Jones, A. L. Burlingame, J. Taunton, *J. Am. Chem. Soc.* 2017, **139**, 680.
16 T. A. Bianchi, L. A. Cate, *J. Org. Chem.,* 1977, **42**, 2031.
17 A. T. Davies, J. M. Curto, S. W. Bagley, M. C. Willis, *Chem. Sci.*, 2017, **8**, 1233.
18 A. L. Tribby, I. Rodríguez, S. Shariffudin, N. D. Ball, *J. Org. Chem.* 2017, **82**, 2294.
19 A. S. Deeming, C. J. Russell, M. C. Willis, *Angew. Chem. Int. Ed.* 2016, **55**, 747.
20 E. E. Gilbert, *Synthesis* 1969, **1969**, 3.
21 S. Pan, S.-Y. Jang, S. S. Liew, J. Fu, D. Wang, J.-S. Lee, S. Q. Yao, *Angew. Chem. Int. Ed.* 2018**, 57**, 579.

View Article Online
DOI: 10.1039/C8CC00986D



A unique SuFEx clickable *tris*-electrophile, 1-Br-ESF, was developed and applied for the synthesis of 5-sulfonylfluoro isoxazoles with exclusive regioselectivity