Sulfonyl Fluorides Hot Paper

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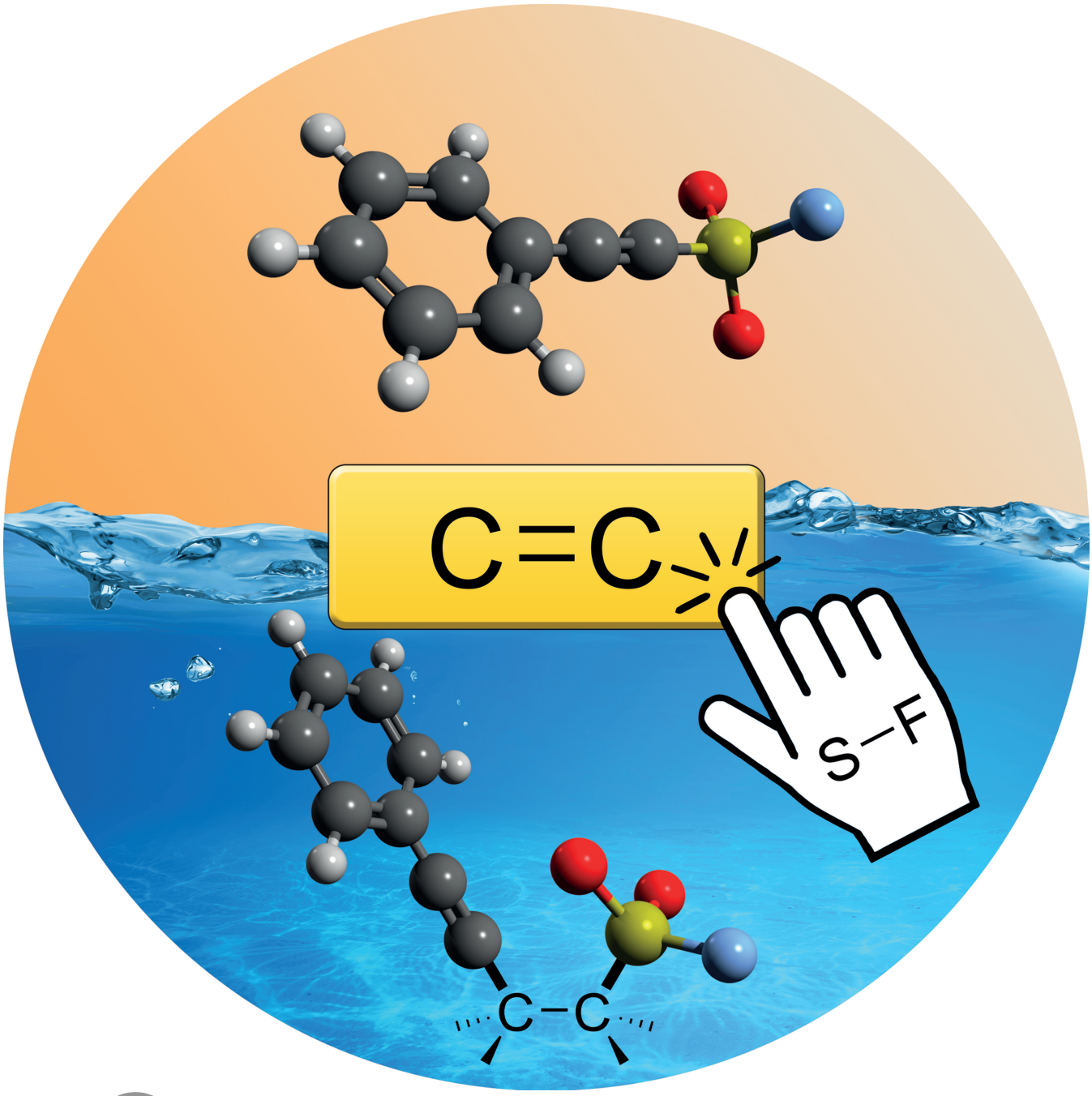
Radical 1-Fluorosulfonyl-2-alkynylation of Unactivated Alkenes

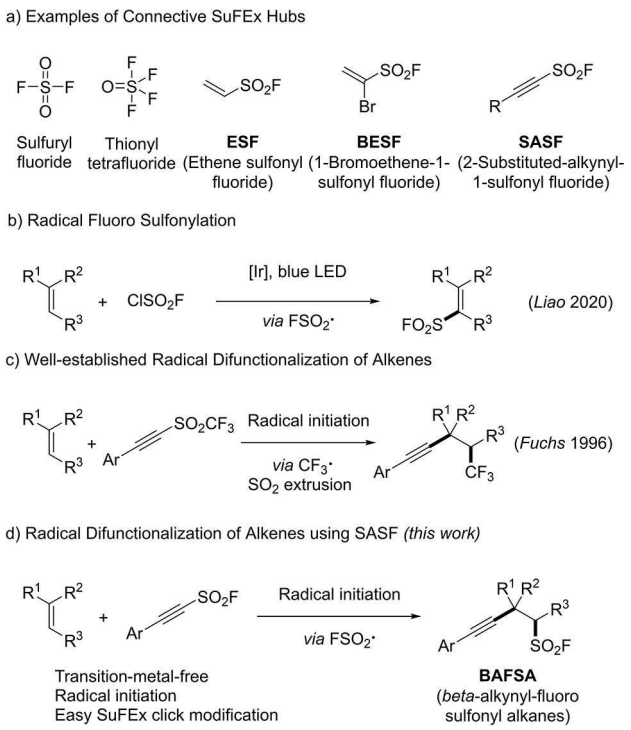
*Nils Lennart Frye, Constantin G. Daniliuc, and Armido Studer**



Abstract: *Sulfonyl fluorides have found widespread use in chemical biology and drug discovery. The development of synthetic methods for the introduction of the sulfonyl fluoride moiety is therefore of importance. Herein, a transition-metal-free radical 1,2-difunctionalization of unactivated alkenes via FSO_2-radical addition with subsequent vicinal alkynylation to access β-alkynyl-fluorosulfonylalkanes is presented. Alkynyl sulfonyl fluorides are introduced as highly valuable bifunctional radical trapping reagents that also serve as FSO_2-radical precursors. The β-alkynyl-fluorosulfonylalkanes obtained in these transformations can be readily diversified by using SuFEx click chemistry to obtain sulfonates and sulfonamides.*

Sulfonyl fluorides are important structural motifs in chemical biology and drug discovery.[1,2] Their use as precursors for click chemistry via sulfur(VI) fluoride exchange (SuFEx) has been highlighted by Sharpless in 2014[3] and they have received increasing attention since.[4,5] Sulfonyl fluorides differ from other typical electrophilic "warheads" as they show an excellent balance between biocompatibility, due to rather slow hydrolysis under aqueous conditions, and protein reactivity.[2,6] Along these lines, sulfonyl fluorides have been successfully applied to modify nucleophilic amino acid residues.[2,7] The unique reactivity of sulfonyl fluorides relies on the stabilization of the fluoride nucleofuge with for example H^+ or R_3Si^+.[3] In recent years, the development of methods for the synthesis of alkenyl sulfonyl fluorides,[8,9] alkynyl sulfonyl fluorides[10] and aryl sulfonyl fluorides[11] has therefore gained increasing interest. Advances in synthetic methodology are highlighted in recent reviews.[4a,12] Moreover, sulfonyl fluorides have also found use in polymer science.[13,14] These works aimed for the identification of new modular connective hubs such as sulfuryl fluoride, thionyl tetrafluoride, ethene sulfonyl fluoride (ESF), 1-bromoethene-1-sulfonyl fluoride (BESF) and 2-substituted-alkynyl-1-sulfonyl fluorides (SASF) (see Scheme 1a).[5]

In general, sulfonyl fluorides can be prepared by fluoride-chloride-exchange from the corresponding sulfonyl chlorides that are obtained from thiols, halides or sultones.[3] Other methods for the preparation of sulfonyl fluorides use conjugate additions[14,15] or cycloadditions[16] on sulfonyl fluoride containing Michael acceptors. Considering radical chemistry, Liu et al. developed a method for the trifluoromethylfluorosulfonylation of unactivated alkenes that uses a super stoichiometric amount of Ag salt as a CF_3-radical and a SO_2-precursor along with NFSI.[17] Furthermore, Liu, Chen, Weng and others expanded this approach of generating the sulfonyl fluoride moiety to other Ag and Zn mediated as well as photoredox-catalyzed difunctionalizations.[18] Recently, Liao et al. introduced a procedure for addition of C-centered radicals to ESF applying photoredox catalysis to access aliphatic sulfonyl fluorides.[19] Liao et al. demonstrated the generation of FSO_2-radicals via reduction of SO_2FCl with a photoredox catalyst and subsequent radical addition. Oxidation and deprotonation eventually afford alkenyl sulfonyl fluorides (Scheme 1b).[20] More recently, that strategy was also successfully used for the difunctionalization of alkynes to prepare β-chloro alkenyl sulfonyl fluorides.[8] In addition, electrochemistry by using air as the terminal oxidant was applied to access aliphatic β-keto sulfonyl fluorides with SO_2FCl as the FSO_2-radical precursor.[21]



Scheme 1. Radical functionalization of alkenes to access sulfonyl fluorides.

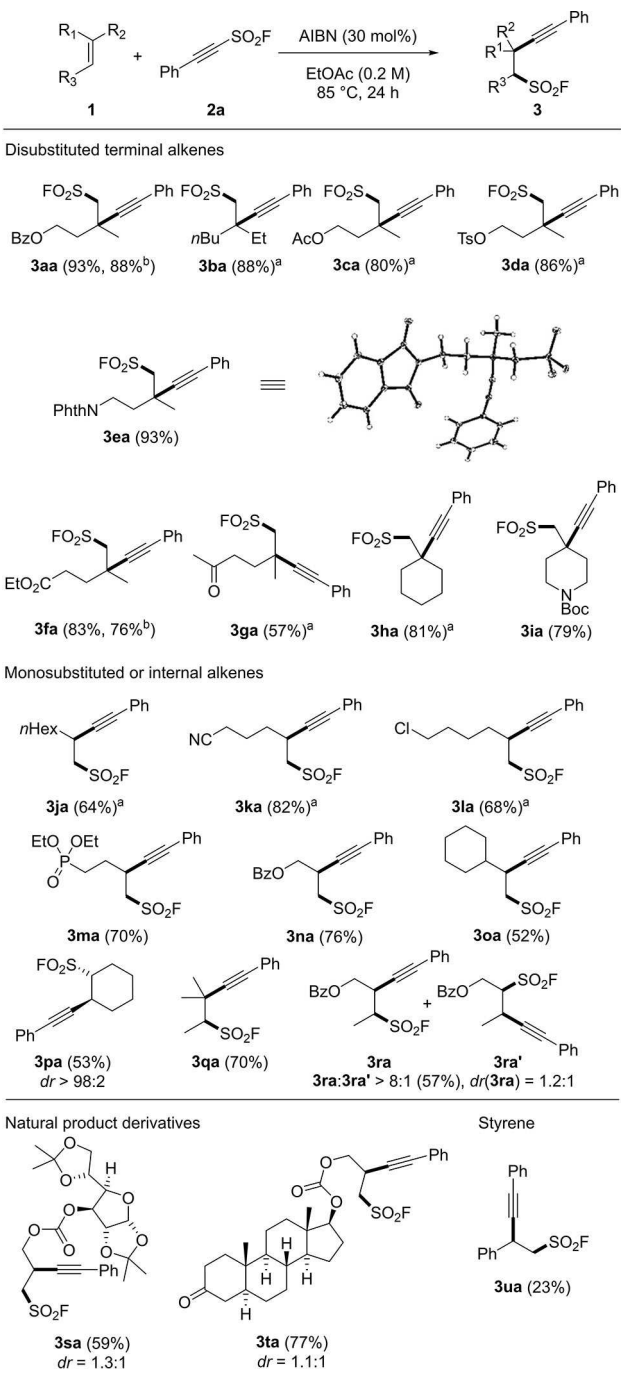
However, methods for the preparation of aliphatic sulfonyl fluorides although they show potential in chemical biology[22] and medicinal chemistry[23] are underdeveloped. Along these lines, Moses et al. introduced SASFs as connective hubs for click-cycloaddition reactions.[10] The SASF motif is reminiscent to the alkynyl triflones that were introduced 25 years ago by Fuchs as bifunctional reagents for radical 1-trifluoromethylation-2-alkynylation of alkenes (Scheme 1c).[24] In the meantime, such alkynyl triflones have been successfully used by us[25] and others[26] in various other radical transformations. We envisioned that SASFs might show similar bifunctional radical reactivity as the alkynyl triflones and may therefore serve as C-radical traps and at the same time as FSO_2-radical precursors. In contrast to the CF_3SO_2-radical, the FSO_2-radical would not release SO_2[20] and hence the SASF mediated alkene difunctionalization will show high atom economy. These radical 1,2-difunction-

[*] N. L. Frye, Dr. C. G. Daniliuc, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstraße 40, 48149, Münster (Germany)
E-mail: studer@uni-muenster.de

alizations would offer direct access to various β-alkynyl-fluorosulfonylalkanes (BAFSAs) from a broad feedstock of unactivated alkenes (Scheme 1d). Our procedure would not only install an alkyne moiety, which itself is a useful functionality,[27] but additionally provide aliphatic sulfonyl fluorides, which are known to be easily diversified by SuFEx click chemistry.

With this in mind, we tested the reaction of 3-methylbut-3-en-1-yl benzoate (**1a**, 1.0 equiv) with 2-phenylethyne-1-sulfonyl fluoride (**2a**, 1 equiv) with AIBN (30 mol%) as radical initiator at 85 °C in EtOAc (0.2 M). To our delight, the targeted BAFSA **3aa** bearing a quaternary center was formed in 52% yield, as analyzed by NMR-spectroscopy of the crude product. Upon increasing the amount of **2a** to 2 equivalents, **3aa** was formed near quantitatively (97% by NMR) and could be isolated in excellent 93% yield. Other radical initiators (BPO or DLP) and other solvents (hexane, CH_2Cl_2, MeCN, toluene and even water) can be used to obtain BAFSA **3aa** in similar yields (see the Supporting Information). **3aa** and all other BAFSAs prepared in this study were formed as racemates. In the absence of a radical initiator, reaction did not proceed.

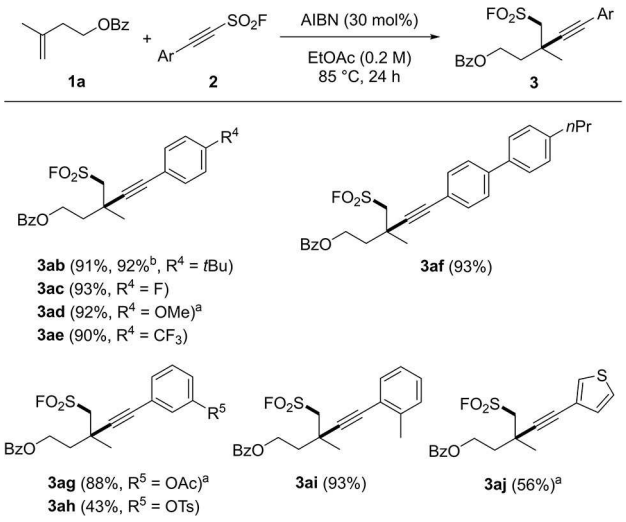
With the optimized conditions in hand, we next tested the reaction scope using various mono-, di- and trisubstituted alkenes as FSO_2-radical acceptors keeping SASF **2a** as the bifunctional reagent (Scheme 2). 2-Ethylhex-1-ene reacted with **2a** to give **3ba** in good yield (88%). The fluorosulfonyl alkynylation reaction features a good functional group tolerance, as benzoyl (**3aa**), acetyl (**3ca**) and tosyl protected alcohols (**3da**) were well tolerated (80–93%). The phthalimide-protected primary amine **3ea**, the ester **3fa** and the ketone **3ga** bearing the sulfonyl fluoride functionality were obtained in moderate to excellent yields (57–93%). The structure of **3ea** was confirmed by X-ray analysis.[28] Moreover, exocyclic alkenes are eligible substrates as documented by the preparation of the cyclohexyl derivative **3ha** and the *N*-Boc-protected piperidine **3ia** (79–81%). 1-Octene, as an example of an unfunctionalized monosubstituted alkene, was also successfully converted (see **3ja**), albeit in slightly lower yield (64%). In addition, cyano (**3ka**), chloro (**3la**) and diethyl phosphonate (**3ma**) functionalized monosubstituted alkenes were well tolerated (68–82%). Benzoyl-protected allylic alcohol and the sterically more demanding vinylcyclohexane were transformed to BAFSAs **3na** and **3oa** in moderate to good yields (52–76%). Pleasingly, internal alkenes such as cyclohexene and 2-methylbut-2-ene also engaged in the radical 1,2-difunctionalization and the secondary alkyl sulfonyl fluorides **3pa** ($dr > 98:2$) and **3qa** were isolated in moderate to good yields (53–70%). Applying our protocol to an unsymmetrical internal disubstituted alkene, the two regioisomers **3ra** and **3ra′** could be obtained in 57% combined yield. Surprisingly, a rather good regioselectivity was achieved (**3ra**:**3ra′** > 8:1), likely for steric reasons. However, the diastereoselectivity of the major isomer **3ra** was low ($dr = 1.0:1.2$). The method was also applied to the synthesis of natural product derived compounds like the protected carbohydrate **3sa** and the steroid derivative **3ta** (59–77%). Using styrene as radical acceptor, the product **3ua** was formed in low yield (23%).



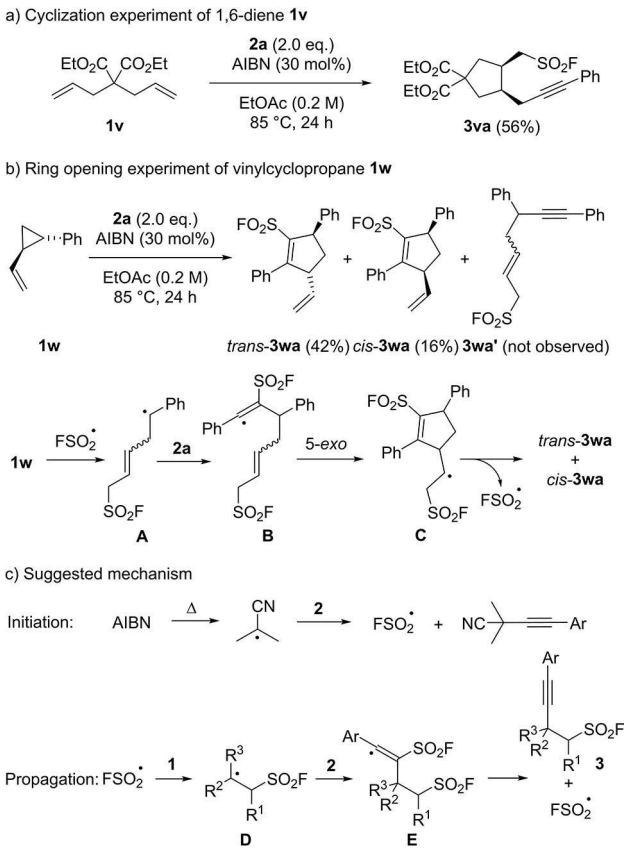
Scheme 2. Alkene scope. Reactions were conducted using alkene **1** (0.2 mmol), SASF **2a** (2.0 equiv), AIBN (30 mol%) in EtOAc (0.2 M) at 85 °C for 24 h. [a] Reactions were conducted on a 0.1 mmol scale. [b] Water (0.2 M) as solvent.

This is probably due to the relatively high stabilization of the intermediate benzylic radical, which is not efficiently trapped by the SASF **2a**.

Next, reaction scope with respect to the bifunctional sulfonyl fluoride reagent was investigated with alkene **1a** as the FSO_2-radical acceptor (Scheme 3). Variation on the aromatic ring of the SASF **2** with various electron donating and withdrawing *para*-substituents like *t*Bu, F, OMe and CF_3



Scheme 3. Alkyne scope. Reactions were conducted using alkene **1a** (0.2 mmol), SASF **2** (2.0 equiv), AIBN (30 mol%) in EtOAc (0.2 M) at 85 °C for 24 h. [a] Reactions were conducted on a 0.1 mmol scale. [b] Water (0.2 M) as solvent.



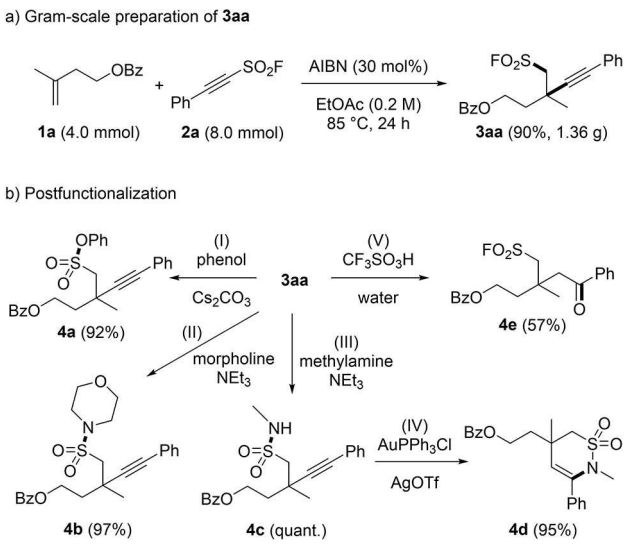
Scheme 4. Mechanistic experiments and proposed mechanism.

was tolerated and the BAFSAs **3ab**–**3ae** were obtained in excellent yields (90–93%). A BAFSA bearing a biaryl substituent (see **3af**) could be accessed (93%). Furthermore, SASFs bearing a *meta*-substituent like OAc and OTs, or an *ortho*-methyl group on the aryl moiety gave the sulfonyl fluorides **3ag**–**3ai** (43–93%). A heteroaryl substituent is also tolerated, as documented by the preparation of the thiophene-based BAFSA **3aj** (56%). Unfortunately, alkyl- and silyl-substituted SASFs showed no reaction under the optimized conditions (see Supporting Information). We assume that the addition of a tertiary C-radical onto such non-activated alkynes is too slow. Moreover, applying alkenyl sulfonyl fluorides, like 2-phenylethene-1-sulfonyl fluoride, under our optimized conditions did not result in β-alkenylated sulfonyl fluorides (see Supporting Information). Since the application of benign solvents is of increasing interest, we also tested the reaction in water. Pleasingly, targeted **3aa**, **3fa** (Scheme 2) and **3ab** (Scheme 3) were obtained in comparable yields (88%, 76% and 92%).

To investigate the mechanism of the fluorosulfonyl alkynylation reaction, radical probe experiments were conducted (Scheme 4a). With the 1,6 diene **1v** as the acceptor, the expected 5-*exo* product **3va** could be obtained in 56% yield with high *cis*-diastereoselectivity,[29] supporting the presence of radical intermediates. Moreover, a ring-opening experiment with vinyl cyclopropane **1w** was performed (Scheme 4b). Instead of the expected **3wa**′, we observed the ring opening products *trans*-**3wa** and *cis*-**3wa**. Thus, FSO_2-radical addition and ring opening leads to the benzylic radical **A** that is trapped by **2a** to give the vinyl radical **B** which further reacts via 5-*exo*-cyclization to **C**. β-Fragmentation of the FSO_2-radical finally leads to the products **3wa**, reminiscent to thiyl radical catalyzed ring openings reported by Feldmann et al.[30] Based on these experiments the following mechanism can be suggested for the alkene 1,2-difunctionalization with reagents of type **2** (Scheme 4c). Initiation with AIBN proceeds via addition of the AIBN-derived cyanopropyl radical to the alkyne and subsequent FSO_2-radical fragmentation. The FSO_2-radical then adds to the alkene **1** to give the adduct radical **D** that is trapped by the reagent **2** to generate the vinyl radical **E**. β-Fragmentation of the FSO_2-radical finally leads to the product **3** thereby propagating the chain.

To document the practicality of the novel transformation, **3aa** was successfully prepared in a gram-scale experiment without compromising the yield (90%, Scheme 5a). Finally, we addressed the reactivity of the BAFSA **3aa** to show the synthetic value of our products (Scheme 5b). Diversification of **3aa** with SuFEx click chemistry proceeded in excellent yields with phenol, morpholine and methylamine to provide the sulfonate **4a** and the sulfonamides **4b**,**c**. Since N-heterocycles are important substructures for pharmaceuticals,[31] we also demonstrated that secondary sulfonamides can be readily cyclized using Au catalysis to give α,β-unsaturated δ-sultams. For example, with **4c** the dioxodihydrothiazine **4d** was obtained in excellent yield. Furthermore, hydration of the alkyne functionality of **3aa** gave the ketone **4e** in 57% yield and the valuable sulfonyl fluoride moiety remained untouched.

In summary, we introduced an efficient and high-yielding radical alkene 1,2-difunctionalization for the preparation of BAFSAs. The process works in the absence of any transition-metal catalyst using classical AIBN initiation. The novel method which shows broad functional group tolerance



Scheme 5. Gram-scale synthesis of **3aa** and follow-up chemistry. I) Phenol (1.1 equiv), Cs_2CO_3 (2.0 equiv), MeCN (0.2 M), r.t., 16 h. II) Morpholine (2.0 equiv), NEt_3 (2.0 equiv), MeCN (0.2 M), 85 °C, 18 h. III) Methylamine (2.0 equiv), NEt_3 (2.0 equiv), MeCN (0.2 M), 85 °C, 18 h. IV) $AuPPh_3Cl$ (5.0 mol%), AgOTf (7.5 mol%), toluene (0.1 M), 85 °C, 18 h. V) Trifluorosulfonic acid (1.0 equiv), water (20 equiv), hexafluorisopropanol (0.1 M), 60 °C, 18 h.

offers an easy access to various aliphatic sulfonyl fluorides bearing a β-alkynyl substituent. Notably, the process allows formation of quaternary centers. The products can be further diversified by using established SuFEx click chemistry to access sulfonates and sulfonamides. Subsequent cyclization of secondary sulfonamides leads to sultams and the alkyne moiety can be hydrolyzed to give δ-keto sulfonyl fluorides. Our method further expands the portfolio of the emerging chemistry of the highly interesting fluorosulfonyl radical.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Alkynylation · Difunctionalization · Radical · SuFEx Chemistry · Sulfonyl Fluoride

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