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Radical-mediated vicinal addition of alkoxysulfonyl/fluorosulfonyl and trifluoromethyl groups to aryl alkyl alkynes†

Xinrui Dong, ‡[a] Wenhua Jiang, ‡[a] Dexiang Hua, [a] Xiaohui Wang, [a] Liang Xu *[b] and Xiaoxing Wu *[a]

The addition of sulfonyl radicals to alkenes and alkynes is a valuable method for constructing useful highly functionalized sulfonyl compounds. The underexplored alkoxy- and fluorosulfonyl radicals are easily accessed by CF_3 radical addition to readily available allylsulfonic acid derivatives and then β-fragmentation. These substituted sulfonyl radicals add to aryl alkyl alkynes to give vinyl radicals that are trapped by trifluoromethyl transfer to provide tetra-substituted alkenes bearing the privileged alkoxy- or fluorosulfonyl group on one carbon and a trifluoromethyl group on the other. This process exhibits broad functional group compatibility and allows for the late-stage functionalization of drug molecules, demonstrating its potential in drug discovery and chemical biology.

Introduction

Sulfonic acid derivatives are valuable pharmaceutical compounds, biochemical probes, novel materials, and synthetic intermediates (Scheme 1a).[1] Moreover, sulfur(VI)-fluoride exchange (SuFEx) has recently gained intense interest as one of the most powerful reactions in click chemistry.[2] This stems from the incredible stability and unique reactivity of the fluorosulfonyl (SO_2F) motif and provides an additional need for the development of efficient fluorosulfonylation methods. Sulfonate esters[3] and sulfonyl fluorides[4] are usually obtained from the corresponding sulfonyl chlorides. However, these sulfonyl chloride precursors are generally prepared under harsh conditions with highly corrosive reagents or by the oxidative chlorination of organosulfur compounds.[5] Consequently, these methods are not compatible with sensitive functional groups and often suffer from tedious purification procedures or limited sources of the organosulfur starting materials. Recent methods for introduction of a sulfonate moiety focus on arylsulfonates,[6] while the diversity-oriented synthesis of alkenylsulfonate esters by Wittig reactions is limited by the strongly basic conditions employed.[1d,7] Alkenylsulfonyl fluorides are of special interest due to the electrophilic character of both the sulfur center and the β-carbon, representing a unique warhead for covalent binders.[1j] To access alkenylsulfonyl fluorides, the groups of Sharpless, Arvidsson, Qin, Yu, Huestis, Willis, and others reported transition-metal catalyzed cross-coupling reactions with ethenesulfonyl fluoride (ESF),[8] 1-bromoethenesulfonyl fluoride (BESF),[9] or 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO)/*N*-fluorobenzenesulfonimide (NFSI).[10] These reactions work well, but don't provide access to tetra-substituted alkenyl sulfonyl fluorides that should also be valuable for SuFEx click chemistry.

Recently, sulfonyl radical-mediated processes have been developed that provide direct methods to construct valuable carbon–SO_2 bonds.[11] In this context, alkoxysulfonyl radicals ($ROSO_2^{\bullet}$)[12] were found to add to alkenes in hot benzene.[13] Later, other groups reported the cyclization of alkoxysulfonyl radicals tethered to alkenes and alkynes.[14,15] Unfortunately, these methods either suffer from narrow substrate scope or restriction to intramolecular processes, limiting their applicability in the context of late-stage functionalization of complex molecules. The use of the fluorosulfonyl radical ($FSO_2^{\bullet}$) in organic synthesis has rarely been reported, presumably due to its instability and limited synthetic access.[16] In 2021, the Liao group disclosed a radical fluorosulfonylation of alkenes using sulfuryl chlorofluoride (FSO_2Cl) as the fluorosulfonyl radical source.[17] Thus, the discovery of new SO_2-containing reagents and the development of efficient synthetic methods to access alkoxy- or fluorosulfonyl compounds are of great significance. Allylsulfonyl compounds have been recognized as facile and practical precursors for generating such radical species through an addition–fragmentation process (Scheme 1b).[18] However, only aryl, alkyl, and amide groups have been used as

[a]*State Key Laboratory of Natural Medicines, Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 211198, China. E-mail: wu_xiaoxing@cpu.edu.cn*

[b]*School of Chemistry and Chemical Engineering, Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi 832003, China. E-mail: xuliang4423@shzu.edu.cn*

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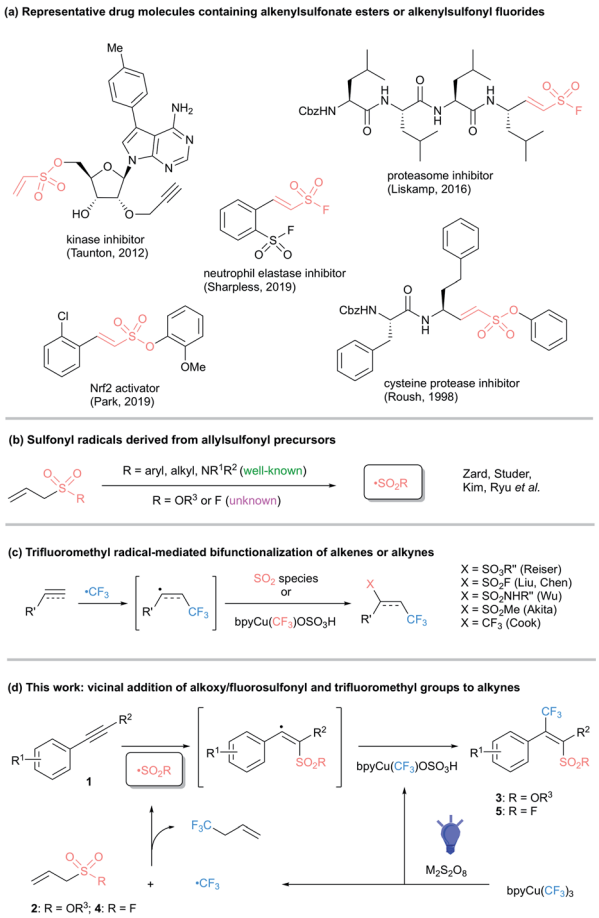
‡ These authors contributed equally to this work.



Scheme 1 Alkenyl SO_3R- or SO_2F-containing drug molecules and sulfonyl radical-involved reactions.

substituents on the allylsulfonyl reagents. The generation of alkoxy- or fluorosulfonyl radicals by this process has not been reported. This prompted us to explore the use of alkyl allylsulfonates and allylsulfonyl fluorides to form useful carbon–SO_2 bonds by radical processes.

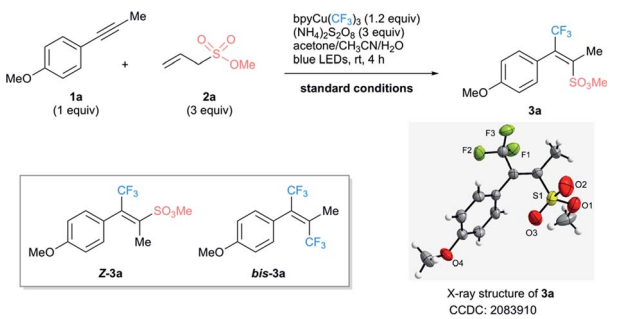
Trifluoromethyl compounds have been prepared by direct trifluoromethylation with the CF_3 radical.[19] Thus, a few groups have independently reported the addition of the CF_3 radical to alkenes or alkynes followed by trapping to form sulfonic acid derivatives (Scheme 1c).[20] In our continuing efforts to discover new trifluoromethylation methods,[21] we envisioned that the addition of an alkoxysulfonyl or fluorosulfonyl radical to an alkyne or alkene followed by trapping with a trifluoromethyl moiety would provide an alternative route to vicinal alkoxy- or fluorosulfonyltrifluoromethylation (Scheme 1d). This would give **3** and **5** with the opposite regiochemistry to the reactions shown in Scheme 1c, opening up access to new scaffolds for drug discovery and chemical biology. To realize this conception, we sought to use readily-prepared allylsulfonyl reagents as the sulfonyl radical sources, in combination with commercially-available bpyCu$(CF_3)_3$.[22] This was inspired by the recent work described by Cook, in which photo-induced bistrifluoromethylation of terminal alkynes was efficiently realized in the presence of bpyCu$(CF_3)_3$ and persulfate (Scheme 1c).[23] As shown in Scheme 1d, the CF_3 radical could react preferentially with the unhindered double bond of alkyl allylsulfonate **2** or allylsulfonyl fluoride **4**, rather than the triple bond in alkyne **1** that would initiate the bistrifluoromethylation reported by Cook. Subsequent β-fragmentation would lead to $RSO_2^{\bullet}$ and volatile 4,4,4-trifluoro-1-butene.[24] The addition of $RSO_2^{\bullet}$ across the triple bond of **1** followed by carbon–CF_3 bond formation with bpyCu$(CF_3)OSO_3H$ would produce trifluoromethylalkenylsulfonate esters **3** and trifluoromethylalkenylsulfonyl fluorides **5**, respectively. These tetrasubstituted alkenes are challenging to access through known cross-coupling methods.[8–10]

Results and discussion

Reaction condition optimization

The optimized reaction conditions are outlined in Table 1 (see ESI† for details). Treatment of alkyne **1a**[25] with methyl allylsulfonate **2a** (3 equiv.), bpyCu$(CF_3)_3$ (1.2 equiv.), and $(NH_4)_2S_2O_8$ (3 equiv.) under blue LED irradiation ($\lambda_{max} = 460$ nm) affords 77% (^{19}F NMR yield) of the desired CF_3-containing alkenylsulfonate **3a** (Table 1, entry 1). The yield is lower with sodium or potassium persulfate, and only 4% of **3a** is obtained in the absence of $(NH_4)_2S_2O_8$ (Table 1, entries 2–4). The yield is slightly lower in the absence of water (Table 1, entry 5). The reaction does not proceed in the dark and the yield is 13% lower under irradiation with 365 nm light (Table 1, entries 6 and 7). Under most conditions, an approximately 10 : 1 mixture of **3a** and the isomer ***Z*-3a** is obtained (see ESI† for details). The methyl protons of **3a** absorb at δ 2.44 in the ^{1}H NMR spectra, whereas those of the minor isomer ***Z*-3a** absorb at δ 2.01 due to shielding

Table 1 Selected conditions for optimization of reaction parameters[a]



Entry	Reaction conditions	Yield of **3a**/***Z*-3a**[b]
1	Standard conditions	77% (73%)[c]/6%
2	$Na_2S_2O_8$ instead of $(NH_4)_2S_2O_8$	52%/5%
3	$K_2S_2O_8$ instead of $(NH_4)_2S_2O_8$	46%/4%
4	Without $(NH_4)_2S_2O_8$	4%/0%
5	Without H_2O	64%/8%
6	365 nm instead of blue LEDs	64%/5%
7	Performed in dark	0%/0%
8	2 equiv. of **2a** used instead	66%/7%

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), bpyCu$(CF_3)_3$ (0.24 mmol), $(NH_4)_2S_2O_8$ (0.6 mmol) under blue LED irradiation for 4 h at room temperature. [b] Yields were determined by ^{19}F NMR spectroscopy with trifluoromethoxybenzene as an internal standard. [c] Isolated yield.

by the aryl group. The selectivity likely arises from the greater steric bulk of the methoxysulfonyl moiety as compared to the methyl group. To our delight, bistrifluoromethylated product **bis-3a** was produced in no more than 15% ^{19}F NMR yield under the standard conditions. This allowed a good isolated yield (73%) of desired product **3a**, whose structure was unambiguously determined by single-crystal X-ray diffraction.

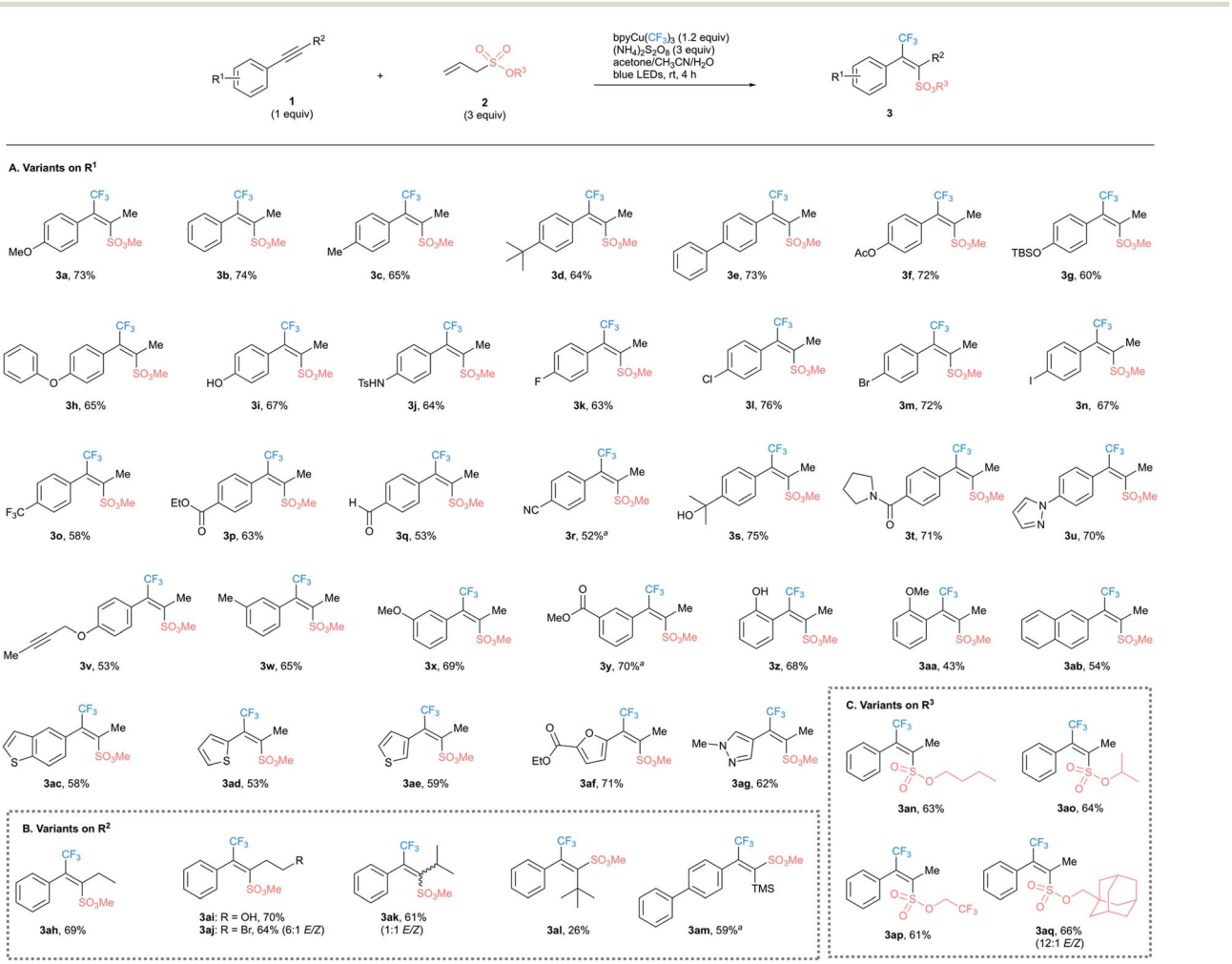
The use of only 2 equiv. of **2a** leads to a decreased yield (66%) of **3a** and the formation of more **bis-3a** (26%) as expected (Table 1, entry 8).

Substrate scope

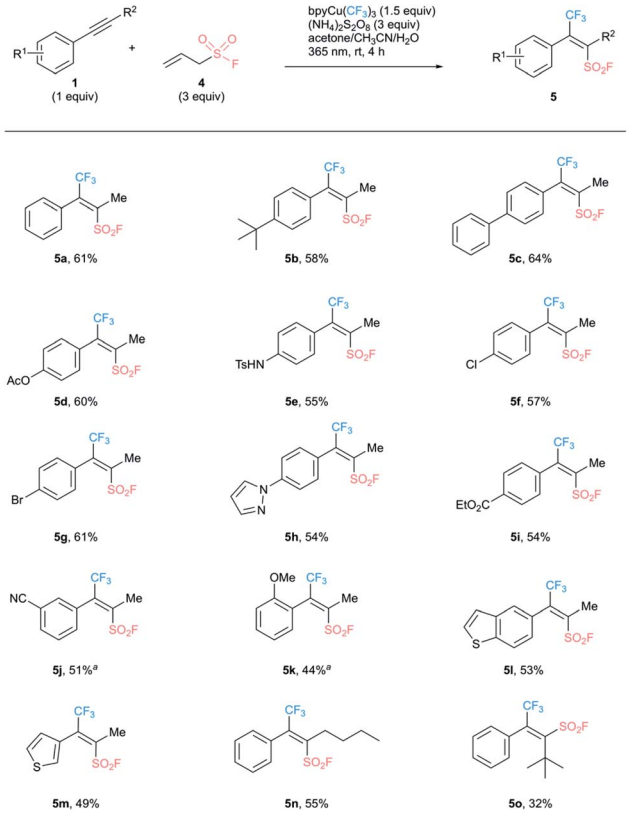
With the optimized protocol in hand, we explored the generality of this transformation on a range of alkynes with several alkyl allylsulfonates (Scheme 2). Various functional groups, such as halides, ethers, aldehydes, esters, amides, sulfonamides, nitriles, and hydroxyl groups are well tolerated, giving products **3a–3aq** in moderate to good yields. *Meta*-substitution on the aryl ring has little effect on the reaction efficiency (**3w–3y**). With *ortho*-substitution on the aryl ring, the yield of **3z** is higher than that of **3aa**, presumably because a hydroxy group is smaller than a methoxy group. As exemplified by **3v**, aryl alkyl alkynes are much more reactive than bisalkyl alkynes. We have established that a variety of heteroarenes, such as pyrazole, (benzo)thiophenes, and furans, are suitable substrates for this transformation as shown in **3ac–3ag**. The stereochemistry of the major products was assigned by analogy to that of **3a** and by the chemical shift of the methyl group at δ 2.51–2.41.

This reaction is compatible with primary, secondary, and tertiary alkyl groups and trimethylsilyl group as the R^2 substituent on the alkyne (**3ah–3am**). Intriguingly, the configuration in products shifts from *anti*- to *syn*-addition with the increased bulkiness of the R^2 group. For instance, a nearly 1 : 1 *E*/*Z* mixture is obtained for **3ak** with an isopropyl group, while exclusively *syn*-addition occurs to give **3al** with a *tert*-butyl group and **3am** with a TMS substituent. The structures of **3al** and **3am** were determined by single-crystal X-ray analysis (see ESI† for details). These results indicate that the methoxysulfonyl group is larger than a methyl group, smaller than a *tert*-butyl or TMS group, and about the same size as an isopropyl group. Other alkyl allylsulfonates smoothly undergo this transformation to afford **3an–3aq** in good yields.

Considering the high value of SO_2F-containing compounds in SuFEx click chemistry, we next examined the reaction of



Scheme 2 Substrate scope for alkoxysulfonyltrilfuoromethylation of alkynes. Unless otherwise noted, all the reactions were run on a 0.2 mmol scale under standard conditions. [a] 1.5 equiv. of bpyCu(CF$_3$)$_3$ was used for 8 h.



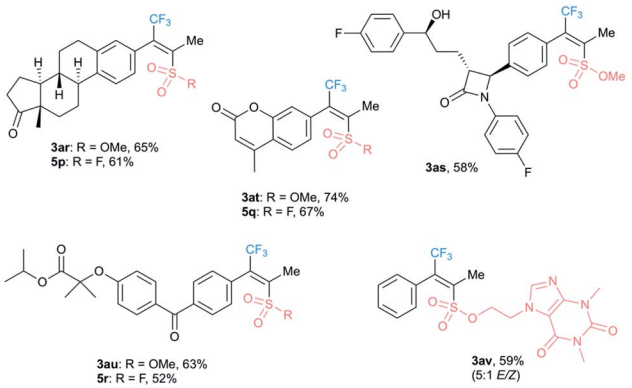
Scheme 3 Substrate scope for fluorosulfonyltrifluoromethylation of alkynes. Unless otherwise noted, all the reactions were run on a 0.2 mmol scale under standard conditions. [a] 4.0 equiv. of **4** was used for 8 h.

alkynes **1** with allylsulfonyl fluoride **4** (Scheme 3). To our delight, a variety of alkynes undergo this transformation smoothly to afford the desired products **5a–5o** using 365 nm irradiation. In contrast to the reaction with methyl allylsulfonate **2** to give **3**, which worked slightly better with blue LED than 365 nm irradiation, the yields of **5** are 10–20% lower with blue LED irradiation. The optimal wavelength appears to be a balance between its efficiency in generating trifluoromethyl radicals and photo-induced side reactions.

A variety of electron-donating or electron-withdrawing aryl substituents and heteroarenes (**5h**, **5l**, and **5m**) are compatible with these reaction conditions. *Anti*-addition occurs predominately for alkynes with primary alkyl R^2 substituents (**5a–5n**), and *syn*-addition to give **5o** occurs exclusively with the bulky *tert*-butyl group. The structure of **5o** was established by single-crystal X-ray analysis (see ESI† for details). In comparison to the alkoxysulfonyl trifluoromethylation discussed above, slightly increased amounts of undesired *Z*-isomers and bistrifluoromethylated products were detected. This might arise from the subtle differences in size, stability, and reactivity between fluorosulfonyl and alkoxysulfonyl radicals.[12a,16b,c]

Synthetic application

To demonstrate the potential of this transformation, we applied this methodology to the late-stage functionalization of both drug-derived alkynes and allylsulfonates. As shown in Scheme 4, alkynes derived from estrone (**3ar** and **5p**), ezetimibe (**3as**), 4-methylumbelliferone (**3at** and **5q**), and fenofibrate (**3au** and **5r**) react smoothly to afford the expected products in moderate to good yields. In addition, the etofylline-derived allylsulfonate (**3av**) undergo alkoxysulfonyl trifluoromethylation as well.

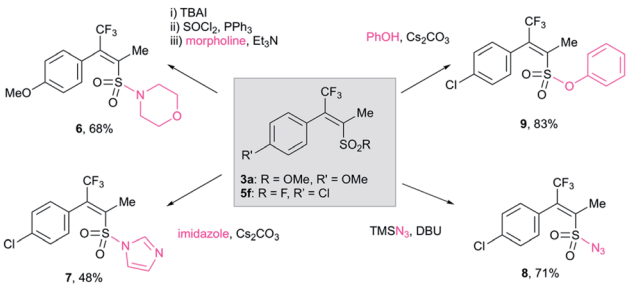


Scheme 4 Late-stage functionalization of complex drug molecules.

To further demonstrate the synthetic utility of the products, sulfonate ester **3a** was efficiently converted to sulfonamide **6** in 68% yield (Scheme 5). Nucleophilic substitution on sulfonyl fluoride **5f** was achieved by reaction with imidazole to afford sulfonamide **7** in 48% yield, with $TMSN_3$ to afford sulfonyl azide **8** in 71% yield, and with phenol to afford sulfonate ester **9** in 83% yield. This suggests that this method is applicable to construct molecular complexity and diversity, which is beneficial for drug discovery and chemical biology.

Computational studies

We then performed DFT calculations to provide insights on the reaction mechanism and selectivity of this process (Fig. 1, see ESI† for details). On the basis of Cook's work[22c,23] and our TEMPO-trapping studies (see ESI† for details), the alkyne **1b**, methyl allylsulfonate **2a**, and the initial products upon light irradiation, the CF_3 radical and $bpyCu(CF_3)OSO_3H$, were chosen as the starting point. The energy of **TS1**, the transition state for the addition of the CF_3 radical to methyl allylsulfonate **2a** to give **INT1**, was calculated to be 9.2 kcal mol^{-1}. This is 0.8 kcal mol^{-1} lower than the energy of **TSA**, the transition state for the



Scheme 5 Derivatization on alkenyl sulfonate esters or alkenyl sulfonyl fluorides.

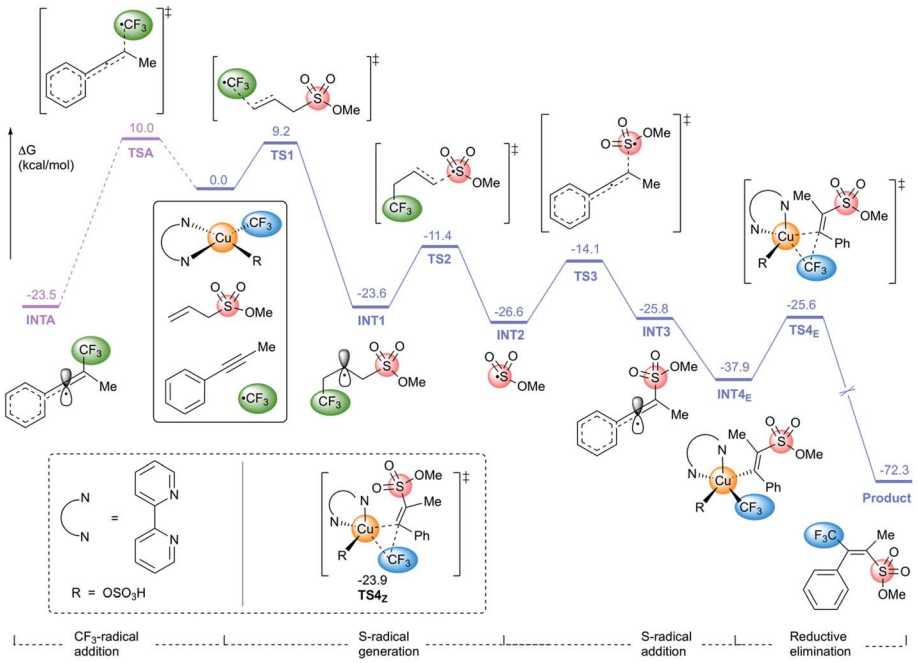


Fig. 1 Computational energy profiles in alkoxysulfonyl trifluoromethylation of alkynes.

addition of the CF_3 radical to the alkyne to give **INTA**. The newly-formed intermediates **INT1** and **INTA** are more stable than the corresponding transition states **TS1** and **TSA** by >30 kcal mol^{-1}, rendering the radical addition processes irreversible. The steps from **INT1** to final product **3** proceed readily because the activation barriers in the subsequent transition states are all less than 13 kcal mol^{-1}. The calculated energy for **TS1** that is 0.8 kcal mol^{-1} lower than that of **TSA** is consistent with the observed preferential formation of methoxysulfonyltrifluoromethylation to form **3**/***Z*-3** rather than bistrifluoromethylation to form **bis-3**. Moreover, the transition state $\mathbf{TS4_E}$ leading to the formation of *anti*-addition product **3** is 1.7 kcal mol^{-1} more stable than transition state $\mathbf{TS4_Z}$ leading to *syn*-addition product ***Z*-3**, in good agreement with the approximately 10 : 1 ratio of *E*- and *Z*-isomers observed.

Conclusion

In conclusion, a method for alkoxy- and fluorosulfonyltrifluoromethylation of alkynes has been developed. This process uses readily-prepared alkyl allylsulfonates or allylsulfonyl fluoride as sulfonyl radical donors and good selectivity is achieved. Numerous functional groups and heteroarenes are tolerated, allowing access to a broad range of tetra-substituted alkenes that are valuable for drug discovery, chemical biology and other fields. In addition, this methodology further expands the application of allylsulfonyl reagents in radical coupling reactions.

Data availability

The datasets (experimental procedures, characterization, copies of NMR spectra for all new compounds, mechanistic studies, and computational studies) supporting this article have been uploaded as part of the ESI.† Crystallographic data for **3a**, **3al**, **3am**, and **5o** has been deposited at the CCDC under 2083910–2083913 and can be obtained from https://www.ccdc.cam.ac.uk/structures.

Author contributions

X. D., W. J., D. H., and X. W. planned, conducted, and analysed the experiments. L. X. conducted the computational studies. Prof. X. W. conceived this concept, directed the project, and prepared this manuscript. All authors contributed to discussions and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) A. Haddow and W. C. J. Ross, *Nature*, 1956, **177**, 995–996; (*b*) S. O. Ciurea and B. S. Andersson, *Biol. Blood Marrow Transplant.*, 2009, **15**, 523–536; (*c*) J. W. Choi, S. J. Shin, H. J. Kim, J.-H. Park, H. J. Kim, E. H. Lee, A. N. Pae, Y. S. Bahn and K. D. Park, *ACS Med. Chem. Lett.*, 2019, **10**, 1061–1067; (*d*) W. R. Roush, S. L. Gwaltney II, J. Cheng,

K. A. Scheidt, J. H. McKerrow and E. Hansell, *J. Am. Chem. Soc.*, 1998, **120**, 10994–10995; (*e*) S. M. Pauff and S. C. Miller, *Org. Lett.*, 2011, **13**, 6196–6199; (*f*) K. A. Pardeshi, G. Ravikumar and H. Chakrapani, *Org. Lett.*, 2018, **20**, 4–7; (*g*) C.-B. Kim, H. Jo, B.-K. Ahn, C. K. Kim and K. Park, *J. Org. Chem.*, 2009, **74**, 9566–9569; (*h*) Q. Zheng, J. L. Woehl, S. Kitamura, D. Santos-Martins, C. J. Smedley, G. Li, S. Forli, J. E. Moses, D. W. Wolan and K. B. Sharpless, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, **116**, 18808–18814; (*i*) N. N. Gushwa, S. Kang, J. Chen and J. Taunton, *J. Am. Chem. Soc.*, 2012, **134**, 20214–20217; (*j*) A. J. Brouwer, N. H. Álvarez, A. Ciaffoni, H. van de Langemheen and R. M. J. Liskamp, *Bioorg. Med. Chem.*, 2016, **24**, 3429–3435; (*k*) J. Dong, K. B. Sharpless, L. Kwisnek, J. S. Oakdale and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2014, **53**, 9466–9470.

2 (*a*) J. Dong, L. Krasnova, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2014, **53**, 9430–9448; (*b*) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong and J. E. Moses, *Chem. Soc. Rev.*, 2019, **48**, 4731–4758; (*c*) L. Xu and J. Dong, *Chin. J. Chem.*, 2020, **38**, 414–419; (*d*) Z. Liu, J. Li, S. Li, G. Li, K. B. Sharpless and P. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 2919–2925; (*e*) D. E. Mortenson, G. J. Brighty, L. Plate, G. Bare, W. Chen, S. Li, H. Wang, B. F. Cravatt, S. Forli, E. T. Powers, K. B. Sharpless, I. A. Wilson and J. W. Kelly, *J. Am. Chem. Soc.*, 2018, **140**, 200–210; (*f*) Q. Li, Q. Chen, P. C. Klauser, M. Li, F. Zheng, N. Wang, X. Li, Q. Zhang, X. Fu, Q. Wang, Y. Xu and L. Wang, *Cell*, 2020, **182**, 85–97; (*g*) Q. Zhao, X. Ouyang, X. Wan, K. S. Gajiwala, J. C. Kath, L. H. Jones, A. L. Burlingame and J. Taunton, *J. Am. Chem. Soc.*, 2017, **139**, 680–685; (*h*) G. J. Brighty, R. C. Botham, S. Li, L. Nelson, D. E. Mortenson, G. Li, C. Morisseau, H. Wang, B. D. Hammock, K. B. Sharpless and J. W. Kelly, *Nat. Chem.*, 2020, **12**, 906–913; (*i*) P. Martín-Gago and C. A. Olsen, *Angew. Chem., Int. Ed.*, 2019, **58**, 957–966; (*j*) S. Kitamura, Q. Zheng, J. L. Woehl, A. Solania, E. Chen, N. Dillon, M. V. Hull, M. Kotaniguchi, J. R. Cappiello, S. Kitamura, V. Nizet, K. B. Sharpless and D. W. Wolan, *J. Am. Chem. Soc.*, 2020, **142**, 10899–10904; (*k*) B. Gao, L. Zhang, Q. Zheng, F. Zhou, L. M. Klivansky, J. Lu, Y. Liu, J. Dong, P. Wu and K. B. Sharpless, *Nat. Chem.*, 2017, **9**, 1083–1088.

3 M. Gagné-Boulet, C. Bouzriba, A. C. C. Alvarez and S. Fortin, *Eur. J. Med. Chem.*, 2021, **213**, 113136–113151.

4 A. Talko and M. Barbasiewicz, *ACS Sustainable Chem. Eng.*, 2018, **6**, 6693–6701.

5 (*a*) L. Zhang, C. Guo, X. Zheng, R. Zhu, X. Yang and C. Tang, *Chin. J. Synth. Chem.*, 2009, **17**, 133–139; (*b*) S. Madabhushi, R. Jillella, V. Sriramoju and R. Singh, *Green Chem.*, 2014, **16**, 3125–3131; (*c*) G. K. S. Prakash, T. Mathew, C. Panja and G. A. Olah, *J. Org. Chem.*, 2007, **72**, 5847–5850.

6 (*a*) S. P. Blum, D. Schollmeyer, M. Turks and S. R. Waldvogel, *Chem.–Eur. J.*, 2020, **26**, 8358–8362; (*b*) X. Hong, Q. Tan, B. Liu and B. Xu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3961–3965.

7 C. Gennari, B. Salom, D. Potenza and A. Williams, *Angew. Chem., Int. Ed.*, 1994, **33**, 2067–2069.

8 (*a*) H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2016, **55**, 14155–14158; (*b*) G.-F. Zha, Q. Zheng, J. Leng, P. Wu, H.-L. Qin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2017, **56**, 4849–4852; (*c*) P. K. Chinthakindi, K. B. Govender, A. S. Kumar, H. G. Kruger, T. Govender, T. Naicker and P. I. Arvidsson, *Org. Lett.*, 2017, **19**, 480–483; (*d*) C. Li, S.-M. Wang and H.-L. Qin, *Org. Lett.*, 2018, **20**, 4699–4703; (*e*) X.-Y. Chen, Y. Wu, J. Zhou, P. Wang and J.-Q. Yu, *Org. Lett.*, 2019, **21**, 1426–1429; (*f*) G. Ncube and M. P. Huestis, *Organometallics*, 2019, **38**, 76–80.

9 J. Leng, N. S. Alharbi and H.-L. Qin, *Eur. J. Org. Chem.*, 2019, 6101–6105.

10 T. S.-B. Lou, S. W. Bagley and M. C. Willis, *Angew. Chem., Int. Ed.*, 2019, **58**, 18859–18863.

11 (*a*) S. M. Hell, C. F. Meyer, G. Laudadio, A. Misale, M. C. Willis, T. Noël, A. A. Trabanco and V. Gouverneur, *J. Am. Chem. Soc.*, 2020, **142**, 720–725; (*b*) S. Yang, X. Wu, S. Wu and C. Zhu, *Org. Lett.*, 2019, **21**, 4837–4841; (*c*) Y. Ning, Q. Ji, P. Liao, E. A. Anderson and X. Bi, *Angew. Chem., Int. Ed.*, 2017, **56**, 13805–13808; (*d*) A. García-Domínguez, S. Müller and C. Nevado, *Angew. Chem., Int. Ed.*, 2017, **56**, 9949–9952; (*e*) X.-J. Tang and W. R. Dolbier Jr, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246–4249; (*f*) Q. Lu, J. Zhang, G. Zhao, Y. Qi, H. Wang and A. Lei, *J. Am. Chem. Soc.*, 2013, **135**, 11481–11484; (*g*) K. Liu and A. Studer, *J. Am. Chem. Soc.*, 2021, **143**, 4903–4909.

12 (*a*) C. Chatgilialoglu, D. Griller and S. Rossini, *J. Org. Chem.*, 1989, **54**, 2734–2737; (*b*) J. J. Douglas, H. Albright, M. J. Sevrin, K. P. Cole and C. R. J. Stephenson, *Angew. Chem., Int. Ed.*, 2015, **54**, 14898–14902; (*c*) M. Bossart, R. Fässler, J. Schoenberger and A. Studer, *Eur. J. Org. Chem.*, 2002, 2742–2757.

13 M. S. Heller, D. P. Lorah and C. G. Cox, *J. Chem. Eng. Data*, 1983, **28**, 134–137.

14 E. Bonfand, W. B. Motherwell, A. M. K. Pennell, M. K. Uddin and F. Ujjainwalla, *Heterocycles*, 1997, **46**, 523–534.

15 L. Cala, O. García-Pedrero, R. Rubio-Presa, F. J. Fañanás and F. Rodríguez, *Chem. Commun.*, 2020, **56**, 13425–13428.

16 (*a*) X. Zeng, H. Beckers and H. Willner, *J. Am. Chem. Soc.*, 2013, **135**, 2096–2099; (*b*) C. A. McDowell, F. G. Herring and J. C. Tait, *J. Chem. Phys.*, 1975, **63**, 3278–3283; (*c*) Y. R. Sekhar, H. Bill and D. Lovy, *Chem. Phys. Lett.*, 1987, **136**, 57–61.

17 X. Nie, T. Xu, J. Song, A. Devaraj, B. Zhang, Y. Chen and S. Liao, *Angew. Chem., Int. Ed.*, 2021, **60**, 3956–3960.

18 (*a*) B. Quiclet-Sire and S. Z. Zard, *J. Am. Chem. Soc.*, 1996, **118**, 1209–1210; (*b*) S. Kim and C. J. Lim, *Angew. Chem., Int. Ed.*, 2002, **41**, 3265–3267; (*c*) S. Kim, S. Kim, N. Otsuka and I. Ryu, *Angew. Chem., Int. Ed.*, 2005, **44**, 6183–6186; (*d*) Y. Xia and A. Studer, *Angew. Chem., Int. Ed.*, 2019, **58**, 9836–9840; (*e*) C. Moutrille and S. Z. Zard, *Chem. Commun.*, 2004, 1848–1849; (*f*) Y. Xia, L. Wang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12940–12944; (*g*) L. Wang, Y. Xia, K. Bergander and A. Studer, *Org. Lett.*, 2018, **20**, 5817–5820.

19 (*a*) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598–6608; (*b*) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*,

2014, **53**, 8294–8308; (*c*) P. Gao, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem.–Eur. J.*, 2015, **21**, 7648–7661; (*d*) S. Barata-Vallejo and A. Postigo, *Chem.–Eur. J.*, 2020, **26**, 11065–11084.

20 (*a*) Y. Li, Y. Xiang, Z. Li and J. Wu, *Org. Chem. Front.*, 2016, **3**, 1493–1497; (*b*) T. Rawner, M. Knorn, E. Lutsker, A. Hossain and O. Reiser, *J. Org. Chem.*, 2016, **81**, 7139–7147; (*c*) Y. Liu, H. Wu, Y. Guo, J.-C. Xiao, Q.-Y. Chen and C. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15432–15435; (*d*) S. Tanaka, Y. Nakayama, Y. Konishi, T. Koike and M. Akita, *Org. Lett.*, 2020, **22**, 2801–2805.

21 (*a*) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li and X. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6962–6966; (*b*) J. Lei, X. Liu, S. Zhang, S. Jiang, M. Huang, X. Wu and Q. Zhu, *Chem.–Eur. J.*, 2015, **21**, 6700–6703; (*c*) J. Lei, X. Wu and Q. Zhu, *Org. Lett.*, 2015, **17**, 2322–2325.

22 (*a*) X. Tan, Z. Liu, H. Shen, P. Zhang, Z. Zhang and C. Li, *J. Am. Chem. Soc.*, 2017, **139**, 12430–12433; (*b*) M. Paeth, W. Carson, J.-H. Luo, D. Tierney, Z. Cao, M.-J. Cheng and W. Liu, *Chem.–Eur. J.*, 2018, **24**, 11559–11563; (*c*) S. Guo, D. I. AbuSalim and S. P. Cook, *J. Am. Chem. Soc.*, 2018, **140**, 12378–12382; (*d*) H. Shen, Z. Liu, P. Zhang, X. Tan, Z. Zhang and C. Li, *J. Am. Chem. Soc.*, 2017, **139**, 9843–9846; (*e*) G. Choi, G. S. Lee, B. Park, D. Kim and S. H. Hong, *Angew. Chem., Int. Ed.*, 2021, **60**, 5467–5474; (*f*) A. M. Romine, N. Nebra, A. I. Konovalov, E. Martin, J. Benet-Buchholz and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2015, **54**, 2745–2749.

23 S. Guo, D. I. AbuSalim and S. P. Cook, *Angew. Chem., Int. Ed.*, 2019, **58**, 11704–11708.

24 The boiling point of 4,4,4-trifluoro-1-butene is 10 °C: R. N. Haszeldine, K. Leedham and B. R. Steele, *J. Chem. Soc.*, 1954, 2040–2042.

25 Reaction with a terminal alkyne under the standard conditions formed an approximately 1 : 1 mixture of the desired *E*-product and the bistrifluoromethylated one, indicating that the alkyl substituent on alkyne **1** is necessary to reduce the reactivity of the alkyne so that the trifluoromethyl radical adds mainly to the allylsulfonate **2** to generate the alkoxysulfonyl radical rather than directly to the alkyne (see ESI† for details).