JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b03191 • Publication Date (Web): 06 Feb 2018

ACS Publications

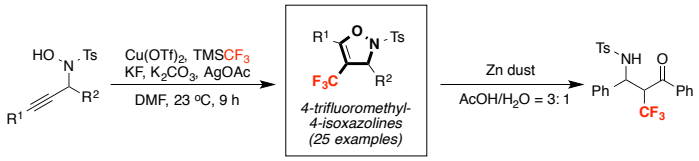
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Copper-Mediated Domino Cyclization/Trifluoromethylation of Propargylic *N*-Hydroxylamines: Synthesis of 4-Trifluoromethyl-4-isoxazolines

Quande Wang and Gavin Chit Tsui*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR

Supporting Information Placeholder



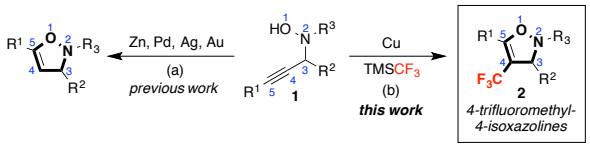
ABSTRACT: A $Cu(OTf)_2$-mediated synthesis of novel trifluoromethylated 4-isoxazolines is described. In one step from readily available propargylic *N*-hydroxylamines, a domino *5-endo-dig* cyclization followed by trifluoromethylation takes place to construct the 4-isoxazoline core with concomitant installation of the CF_3 group at the C-4 position. Such compounds could also be useful precursors for the preparation of α-trifluoromethyl β-amino ketones.

4-Isoxazolines (2,3-dihydroisoxazoles) represent a class of heterocycles that are versatile building blocks for organic synthesis, [1a-b] which are also known for their biological activities.[1c-d] In particular, the *trifluoromethylated* isoxazolines have attracted significant attentions in recent years as potential pharmaceuticals and agrochemicals.[2, 3] Ample examples exist for the synthesis of 2-isoxazolines containing the trifluoromethyl units. In stark contrast, the synthesis of trifluoromethylated 4-isoxazolines has been rarely described, and therefore hampering the biomedical applications of this class of compounds. Only few methods are available for the preparation of 4-isoxazolines bearing a CF_3 group at the C-5 position using building-block approaches.[5] To the best of our knowledge, the synthesis of *4-trifluoromethyl-4-isoxazolines* has not been reported.

The most common approaches for obtaining 4-isoxazolines are the intermolecular 1,3-dipolar cycloaddition of nitrones and alkynes, and the intramolecular cyclization of propargylic *N*-hydroxylamines.[1a] The cyclization method has emerged as a more useful alternative due to predictable regioselectivities. Indeed, a variety of transition metal-catalyzed cyclization of propargylic *N*-hydroxylamines **1**, including Zn,[6a] Pd,[6b] Ag[6c] and Au,[6d-f] have been reported for the synthesis of 2,3,5-trisubstituted 4-isoxazolines (Scheme 1a). In the context of our interest in developing domino methods for the synthesis of trifluoromethylated heterocycles,[7] herein we report a novel strategy for synthesizing 4-trifluoromethyl-4-isoxazolines **2** *via* copper-mediated cyclization/trifluoromethylation of propargylic *N*-hydroxylamines **1** (Scheme 1b).

From the outset, we envisioned that an oxidative trifluoromethylation step can be incorporated into the intramolecular cyclization of propargylic *N*-hydroxylamines using copper, based on our studies of the synthesis of trifluoromethylated pyrazoles.[7a] Such convenient domino approach for synthesizing C-4 functionalized 4-isoxazolines has not been explored in other metal-catalyzed cyclization processes,[6] and in fact, copper-mediated cyclization of propargylic *N*-hydroxylamines has no precedents. We began the optimization studies by subjecting the tosyl (Ts)-protected propargylic *N*-hydroxylamines **1a** to the previously found cyclization/trifluoromethylation conditions using $Cu(OTf)_2$, KF and $TMSCF_3$ in air (Table 1, entry 1). The desired product **2a** was not obtained and instead, side product **2a'** from background cyclization was formed exclusively.

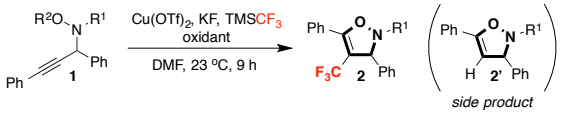
Scheme 1. Synthesis of 4-isoxazolines via metal-mediated cyclization of propargylic *N*-hydroxylamines.



On the other hand, running the reaction under argon without added oxidant gave 17% yield of **2a** (entry 2). A strong impact on reaction yield was revealed during the screening of various oxidants (see Supporting Information for full details). Besides 1,4-benzoquinone (BQ) (13%, entry 3), commonly used oxidants such as DDQ, $PhI(OAc)_2$, $K_2S_2O_8$, benzoyl peroxide (BPO) and *N*-fluorobenzenesulfonimide (NFSI) did not afford any desired product. Silver salts such as Ag_2CO_3 (27%, entry 4) and AgOTf (51%, entry 5) were more effective oxidants, and the highest yield was obtained with AgOAc (63%, entry 6). Lowering the amount of $Cu(OTf)_2$ decreased the yield sharply (entry 7), but lowering the amount of AgOAc in a more diluted reaction did not affect the yield (entry 8). We found that decreasing the amount of the relatively expensive KF led to a decrease in yield (entry 9), however, this could be circumvented by using a combination of KF (5.0 equiv) and inexpensive K_2CO_3 (5.0 equiv) to return to the same level of yield (69%,

62% isolated) and improve the reaction reproducibility (entry 10). The *N*-protecting group of the substrate significantly influenced the reaction, while *N*-Ts substrate **1a** clearly showed suitability for the reaction, the *N*-Ph **3** and commonly used *N*-Bn **4**[6a, c-d] substrates gave no product (entry 11-12). It is worth noting that apart from an isolated example,[6e] the cyclization of propargylic *N*-hydroxylamines containing an electron-withdrawing *N*-sulfonyl protecting group is rare. Furthermore, replacing the -OH group of **1a** with -OMe **5** immediately shut down the reactivity (entry 13). Other reaction parameters including copper source, base, solvent and temperature were screened and showed no further improvement. Also, changing the CF_3 sources to the fluoroform-derived [$CuCF_3$][9a-c] or electrophilic Togni's reagent[9d] did not afford the product.

Table 1. Optimization studies[a]

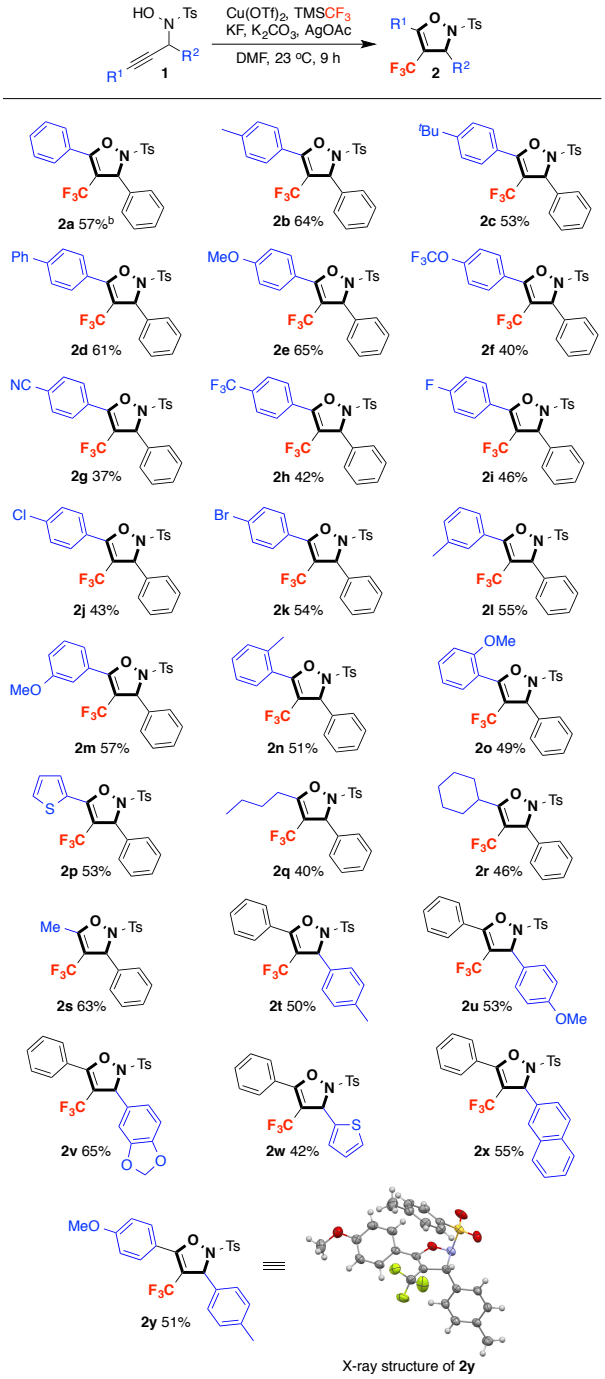


entry	R^1, R^2	oxidant (equiv)	yield of **2** (%)[b]
1[d]	Ts, H **1a**	air	0
2	Ts, H **1a**	none	17
3	Ts, H **1a**	BQ (2.0)	13
4	Ts, H **1a**	Ag_2CO_3 (2.0)	27
5	Ts, H **1a**	AgOTf (2.0)	51
6	Ts, H **1a**	AgOAc (2.0)	63
7[e]	Ts, H **1a**	AgOAc (2.0)	26
8[f]	Ts, H **1a**	AgOAc (1.0)	67
9[f,g]	Ts, H **1a**	AgOAc (1.0)	42
10[f,h]	**Ts, H 1a**	**AgOAc (1.0)**	**69, 62**[c]
11[f,h]	Ph, H **3**	AgOAc (1.0)	0
12[f,h]	Bn, H **4**	AgOAc (1.0)	0
13[f,h]	Ts, Me **5**	AgOAc (1.0)	0

[a]General conditions: **1** (0.1 mmol), $Cu(OTf)_2$ (1.0 equiv), KF (10 equiv), $TMSCF_3$ (5.0 equiv), DMF (0.2 M), under argon. [b]Determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. [c]Isolated yield. [d]Reaction was open to air. [e]0.5 equiv of $Cu(OTf)_2$. [f]Concentration = 0.1 M. [g]5.0 equiv of KF. [h]5.0 equiv of KF + 5.0 equiv of K_2CO_3.

Under the optimized conditions, twenty-five novel 4-trifluoromethyl-4-isoxazolines **2** were successfully synthesized from propargylic *N*-hydroxylamines **1** in one step (Table 2). This modular approach allows easy variation of substituent groups at the C-5 (R^1) and C-3 (R^2) positions of the isoxazoline core by using substrates **1** bearing suitable acetylenic R^1 and propargylic R^2 groups. For R^1, aromatic (**2a-o**), heteroaromatic (**2p**) and alkyl (**2q-s**) substituents were tolerated. Electron-rich aryl groups were generally higher yielding (**2a-e** *vs* **2f-i**). Sensitive halogen groups (**2j-k**), which were known to undergo aromatic trifluoromethylation with $TMSCF_3$ and copper,[10] remained intact. Substituents were also tolerated at the *meta*- and *ortho*-positions of the benzene ring (**2l-o**). For R^2, a variety of substituted aromatic and heteroaromatic groups were demonstrated (**2t-x**). In fact, both R^1 and R^2 groups could be changed at will, as exemplified by compound **2y**. Its structure and the CF_3 group at the C-4 position were unambiguously confirmed by X-ray crystallography.[11]

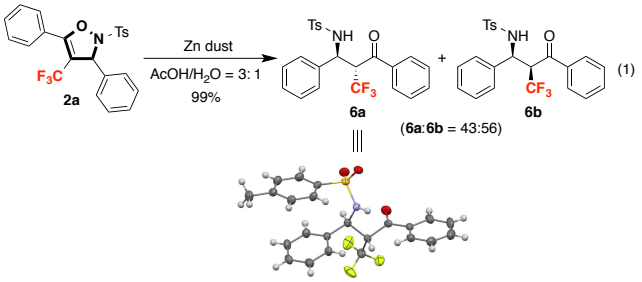
Table 2. Scope of 4-trifluoromethyl-4-isoxazolines 2.[a]



[a]General conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (1.0 equiv), $TMSCF_3$ (5.0 equiv), KF (5.0 equiv), K_2CO_3 (5.0 equiv), AgOAc (1.0 equiv), DMF (0.1 M), under argon. Isolated yields. [b]2.0 mmol scale.

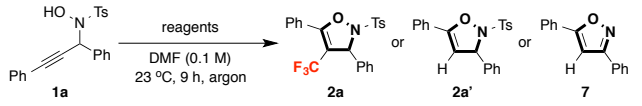
The application of the 4-isoxazoline product was demonstrated in the reductive ring opening of **2a** (eq 1). By following a literature procedure[12] using Zn dust, **2a** was converted into the α-trifluoromethyl β-amino ketones **6** as a diastereomeric mixture in 99% yield. The two diastereomers **6a** and **6b** can be

separated by column chromatography and the structure of **6a** was confirmed by X-ray crystallography.[11]



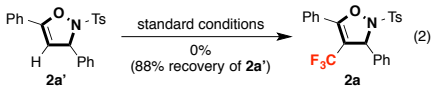
Control experiments were conducted to gain insights into the reaction mechanism (Table 3). Reaction without AgOAc provided a mixture of products including the desired product **2a**, a similar amount of isoxazoline **2a'** and a small amount of isoxazole **7** (entry 1). In contrast, reaction without $Cu(OTf)_2$ gave no desired product and mainly isoxazole **7** (entry 2), highlighting the importance of copper in the trifluoromethylation process. When reaction was run without added base (KF and K_2CO_3), only **2a'** was obtained in a high yield (entry 3). On the other hand, using bases without added metals, cyclization of **1a** proceeded to provide mainly isoxazole **7** (entry 4), similar observations have been reported using TBAF.[13] In fact, the cyclization of **1a** could be promoted by AgOAc alone providing **2a'** in 86% yield (entry 5), comparable to the literature report.[6c] This was not the case for copper, reaction of **1a** with $Cu(OTf)_2$ alone did not lead to significant cyclization (65% S.M. recovery). These results suggested that **1a** was very prone to cyclization to either **2a'** (promoted by Ag) or **7** (promoted by bases), and yet remarkably under the optimized conditions, the trifluoromethylated product **2a** predominated. Additionally, we proved that **2a'** was not a suitable intermediate towards **2a** under the standard conditions (eq 2).

Table 3. Control experiments[a]



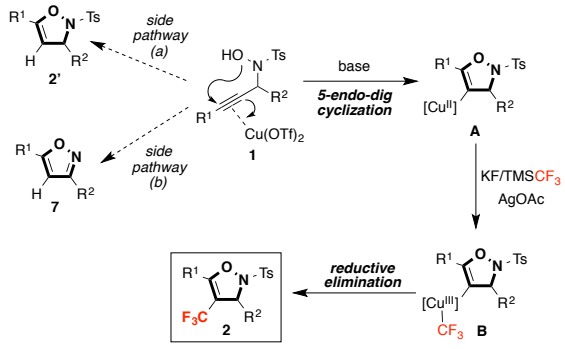
entry	variation from standard conditions	yield of **2a**/**2a'**/**7** (%)[b]
1	without AgOAc	38/35/10
2	without $Cu(OTf)_2$	0/nd[c]/70
3	without KF and K_2CO_3	0/94/nd[c]
4	without $Cu(OTf)_2$ and AgOAc	0/nd[c]/88
5	with AgOAc only	-/86/10

[a]Reagent equivalents: $Cu(OTf)_2$ (1.0 equiv), $TMSCF_3$ (5.0 equiv), KF (5.0 equiv), K_2CO_3 (5.0 equiv), AgOAc (1.0 equiv). [b]Isolated yield. [c]Not determined.



Based on these findings and known literature reports, we proposed the following plausible reaction mechanism for the formation of 4-trifluoromethyl-4-isoxazolines **2** from propargylic *N*-hydroxylamines **1** (Scheme 2). The alkyne moiety of **1** is activated by $Cu(OTf)_2$ acting as a Lewis acid.[14a-b] In the presence of base (KF or K_2CO_3), the *5-endo-dig* cyclization initiated by the nucleophilic attack of the oxygen atom onto the triple bond furnishes the 4-cuprated isoxazoline **A**.[6, 13] The hydroxy group and its acidity (enhanced by electron-withdrawing *N*-tosyl group) is important for the cyclization (*cf.* Table 1, entries 10-13). The Cu(II) spcies **A** is invoked here although the exact oxidation state is unclear as $Cu(OTf)_2$ is known to undergo disproportionation to Cu(I) and Cu(III).[15] **A** can be intercepted with CF_3^- (generated *in situ* from KF and $TMSCF_3$), in the presence of AgOAc as an oxidant,[14c] to afford the highly reactive trifluoromethylated Cu(III) species **B**.[16] Final reductive elimination constructs the key C-CF_3 bond of product **2**. Partial yield loss (*cf.* Table 2) was due to the propensity of *N*-hydroxylamines **1** to form protonated isoxazoline **2'** (side pathway a), *via* Ag-mediated cyclization[6c] or proto-demetallation of **A**, or to form isoxazole **7** *via* base-promoted cyclization/elimination[13] (side pathway b). Nevertheless, under the newly developed conditions, cyclization/trifluoromethylation pathway proceeds affording 4-trifluoromethyl-4-isoxazolines **2**.

Scheme 2. Proposed mechanism.



In conclusion, we have developed a $Cu(OTf)_2$-mediated synthesis of novel 4-trifluoromethyl-4-isoxazolines with good functional group tolerability. These compounds, which would be difficult to access by conventional methods, may find applications in drug discovery considering the promising biological activities of trifluoromethylated isoxazolines. Further exploration of efficient domino strategies for the synthesis of trifluoromethylated heterocycles is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Experimental. Unless otherwise noted, reactions were carried out under argon in a glass tube with magnetic stirring. Analytical thin layer chromatography (TLC) was performed with EM Science silica gel 60 F254 aluminum plates. Visualization was done under a UV lamp (254 nm). Organic solutions were concentrated by rotary evaporation at 23-35 °C. Purification of products were generally done by flash column chromatography with Grace Materials Technologies 230-400 mesh silica gel. tention factors (R_f) are given for such TLC analyses. $TMSCF_3$ (98%) and potassium fluoride (98.5%, anhydrous) were purchased from J&K Scientific. Potassium carbonate was purchased from Farco Chemical Suppliers. Copper (II) triflate (98%) and silver acetate (99%) were purchased from Acros. DMF was dried over Solvent Purification System. Terminal alkynes including phenyl acetylene, ethynyltrimethylsilane, 1-hexyne, 1-ethynyl-2-methylbenzene and ethynylcyclohexane, substituted benzaldehydes, substituted iodobenzenes, 4-toluenesulfonyl chloride, hydroxylamine hydrochlo-

ride, *p*-toluenesulfonic acid and other chemicals for the substrate preparation were purchased from Dieckmann Chemical Industry, Acros, J&K Scientific and Aldrich. Compound **1a**[13], **3**[17], **4**[18], and **7**[13] were known compound and prepared according to literature procedures. Melting points were determined on STUART melting point apparatus SMP40. Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra, carbon nuclear magnetic resonance spectra (^{13}C NMR) and fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded at 23 °C on a Bruker 400 spectrometer in $CDCl_3$ or Acetone-d_6 (400 MHz for ^{1}H and 100 MHz for ^{13}C and 376 MHz for ^{19}F) and Bruker 500 spectrometer in $CDCl_3$ or Acetone-d_6 (500 MHz for ^{1}H and 125 MHz for ^{13}C and 470 MHz for ^{19}F). Chemical shifts for protons were reported as parts per million in δ scale using solvent residual peak ($CHCl_3$: 7.26 ppm and Acetone-d_6: 2.05 ppm). Chemical shifts of ^{13}C NMR spectra were reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) and Acetone-d_6 (29.84 ppm) on the δ scale. Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constant (*J*, Hz). High resolution mass spectra (HRMS) were obtained on a Thermo Scientific Q Exactive Focus Orbitrap Mass Spectrometer.

General procedures (A) for the synthesis of propargylic *N*-hydroxylamines 1[13]: *p*-Toluenesulfonic acid (0.05 equiv.) was added to a mixture of *α,β*-alkynic alcohol[19a-c] (1.0 equiv.) and *N*-protected hydroxylamine[20] (1.1 equiv.) in dichloromethane at 23 °C and stirred at this temperature. The completion of the reactions was confirmed by TLC, and the mixture was concentrated in vacuo and purified by column chromatography on silica gel to afford propargylic *N*-hydroxylamines **1**.

General procedures (B) for the synthesis of 4-trifluoromethyl-4-isoxazolines 2 (*cf.* Table 2): In a glove box, to a glass tube equipped with a stir bar was charged $Cu(OTf)_2$ (1.0 equiv.), KF (5.0 equiv.), K_2CO_3 (5.0 equiv.), AgOAc (1.0 equiv.) and propargylic *N*-hydroxylamines (1.0 equiv.). The tube was sealed with a septum and brought out. A solution of $TMSCF_3$ (5.0 equiv.) in DMF was added to the glass tube in one portion at 23 °C. The reaction mixture was then stirred at 23 °C under argon for 9 hours, diluted with water and extracted with diethyl ether for two times. The combined organic layers were evaporated to dryness and the crude residue was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent to afford the 4-trifluoromethyl-4-isoxazolines **2**.

Sythesis of α-trifluoromethyl β-amino ketones 6a and 6b (*cf.* eq 1): To a mixture of activated zinc dust (65.5 mg, 10 mmol, 5.0 equiv.) in AcOH/H_2O (0.23 mL/0.072 mL) was added a solution of **2a** (89.0 mg, 0.2 mmol, 1.0 equiv.) in DCM (1 mL). After stirring for 5 mins, another portion of zinc dust (65.5 mg, 10 mmol, 5.0 equiv.) was added to the reaction mixture, then stirred at 23 °C for 15 h. The reaction mixture was diluted with DCM and washed with sat. aqeous $NaHCO_3$ solution. The combined organic layers were washed with brine and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate = 6: 1) to afford *α*-trifluoromethyl *β*-amino ketones **6a** (38.2 mg, 43% yield) and **6b** (50.1 mg, 56% yield).

Characterization Data. *N-hydroxy-4-methyl-N-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)benzenesulfonamide (**1b**).* Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Off-white solid (2.0 mmol scale, 342 mg, 44% yield), R_f = 0.30 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.29 (br s, 0.41H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.41 - 7.34 (m, 5H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 2H), 5.97 (s, 1H), 2.31 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.4, 139.3, 138.1, 133.7, 132.3, 130.7, 130.1, 129.6, 129.3, 129.1, 129.0, 120.3, 88.8, 82.7, 58.0, 21.5, 21.4 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_3SNa$ $[M+Na]^+$: 414.1134; found: 414.1131.

*N-(3-(4-(tert-butyl)phenyl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**1c**).* Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 15: 1). White solid (1.0 mmol scale, 300 mg, 69% yield), R_f = 0.33 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.64 - 7.62 (m, 2H), 7.39 - 7.33 (m, 3H), 7.26 - 7.21 (m, 4H), 7.02 - 7.00 (m, 2H), 5.99 (s, 1H), 2.20 (s, 3H), 1.30 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 145.1, 136.2, 131.7, 131.5, 130.0, 129.5, 128.6 (3), 125.1, 119.1, 89.3, 80.6, 57.4, 34.9, 31.3, 21.6 ppm; HRMS *m/z* (ESI) calcd. for $C_{26}H_{27}NO_3SNa$ $[M+Na]^+$: 456.1604; found: 456.1604.

*N-(3-([1,1'-biphenyl]-4-yl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**1d**).* Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.0 mmol scale, 186 mg, 41% yield), R_f = 0.26 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.31 (br s, 0.15H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.68 - 7.61 (m, 6H), 7.49 - 7.46 (m, 2H), 7.43 - 7.34 (m, 6H), 7.18 - 7.16 (m, 2H), 6.01 (s, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.6, 141.7, 140.8, 138.0, 133.7, 132.9, 130.7, 130.2, 129.8, 129.4, 129.2, 129.1, 128.6, 127.7, 127.4, 122.2, 88.5, 84.2, 58.0, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{28}H_{23}NO_3SNa$ $[M+Na]^+$: 476.1291; found: 476.1291.

*N-hydroxy-N-(3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-yl)-4-methylbenzenesulfonamide (**1e**).* Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 7: 1). Off-white solid (1.0 mmol scale, 210 mg, 52% yield), R_f = 0.25 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.26 (br s, 0.45H), 7.93 - 7.91 (m, 2H), 7.62 - 7.61 (m, 2H), 7.41 - 7.32 (m, 5H), 7.03 - 7.00 (m, 2H), 6.88 - 6.85 (m, 2H), 5.95 (s, 1H), 3.81 (s, 3H), 2.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 160.7, 145.4, 138.2, 133.9, 133.7, 130.7, 130.1, 129.4, 129.1, 129.0, 115.2, 114.6, 88.7, 81.9, 58.0, 55.7, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_4SNa$ $[M+Na]^+$: 430.1084; found: 430.1081.

*N-hydroxy-4-methyl-N-(1-phenyl-3-(4-(trifluoromethoxy)-phenyl)prop-2-yn-1-yl)benzenesulfonamide (**1f**).* Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 20: 1). White solid (1.3 mmol scale, 164 mg, 27% yield), R_f = 0.35 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.34 (br s, 0.36H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.42 - 7.34 (m, 5H), 7.30 - 7.28 (m, 2H), 7.23 - 7.20 (m, 2H), 5.99 (s, 1H), 2.26 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 149.5 (d, J_{CF} = 2.0 Hz), 145.5, 137.7, 134.2, 133.6, 130.7, 130.1, 129.3, 129.2, 129.1, 122.5, 121.8, 121.3 (q, J_{CF} = 254.5 Hz), 87.1, 84.7, 57.9, 21.4 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{18}F_3NO_4SNa$ $[M+Na]^+$: 484.0801; found: 484.0801.

*N-(3-(4-cyanophenyl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**1g**).* Prepared according to the

general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.3 mmol scale, 241 mg, 47% yield), R_f = 0.14 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.42 (br s, 0.31H), 7.94 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.62 - 7.60 (m, 2H), 7.43 - 7.34 (m, 5H), 7.25 (d, J = 8.3 Hz, 2H), 6.02 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.7, 137.4, 133.5, 133.1, 132.8, 130.8, 130.2, 129.32, 129.26, 129.2, 127.9, 118.9, 112.5, 88.0, 87.1, 57.9, 21.4 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{18}N_2O_3SNa$ $[M+Na]^+$: 425.0930; found: 425.0930.

N-hydroxy-4-methyl-N-(1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)benzenesulfonamide ***(1h)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (0.88 mmol scale, 181 mg, 39% yield), R_f = 0.32 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.41 (br s, 0.54H), 7.95 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.63 - 7.61 (m, 2H), 7.43 - 7.35 (m, 5H), 7.29 (d, J = 8.0 Hz, 2H), 6.02 (s, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.6, 137.6, 133.6, 133.0, 130.8, 130.3 (q, J_{CF} = 32.2 Hz), 130.2, 129.4, 129.3, 129.2, 127.4, 126.0 (q, J_{CF} = 3.7 Hz), 125.0 (q, J_{CF} = 269.8 Hz), 87.2, 86.5, 57.9, 21.4 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{18}F_3NO_3SNa$ $[M+Na]^+$: 468.0852; found: 468.0853.

N-(3-(4-fluorophenyl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide ***(1i)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.0 mmol scale, 216 mg, 55% yield), R_f = 0.30 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (400 MHz, Acetone-d_6): δ 9.35 (br s, 0.45H), 7.93 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.42 - 7.33 (m, 5H), 7.15 - 7.07 (m, 4H), 5.97 (s, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, Acetone-d_6): δ 163.5 (d, J_{CF} = 246.1 Hz), 145.5, 137.9, 134.6 (d, J_{CF} = 8.5 Hz), 133.7, 130.7, 130.1, 129.3, 129.2, 129.1, 119.6 (d, J_{CF} = 3.5 Hz), 116.1 (d, J_{CF} = 22.1 Hz), 87.5, 83.3, 57.9, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{22}H_{18}FNO_3SNa$ $[M+Na]^+$: 418.0884; found: 418.0883.

N-(3-(4-chlorophenyl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide ***(1j)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 15: 1). Yellow solid (1.0 mmol scale, 200 mg, 49% yield), R_f = 0.38 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.34 (br s, 0.58H), 7.93 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.41 - 7.35 (m, 7H), 7.08 (d, J = 8.2 Hz, 2H), 5.98 (s, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.5, 137.8, 134.7, 133.9, 133.7, 130.7, 130.2, 129.34, 129.25, 129.2, 129.1, 122.0, 87.4, 84.8, 57.9, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{22}H_{18}ClNO_3SNa$ $[M+Na]^+$: 434.0588; found: 434.0589.

N-(3-(4-bromophenyl)-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide ***(1k)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 15: 1). White solid (1.0 mmol scale, 150 mg, 33% yield), R_f = 0.30 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.36 (br s, 0.52H), 7.93 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.41 - 7.34 (m, 5H), 7.02 (d, J = 8.1 Hz, 2H), 5.97 (s, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.5, 137.7, 134.1, 133.7, 132.2, 130.7, 130.2, 129.3, 129.2, 129.1, 123.0, 122.4, 87.5, 84.9, 58.0, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{22}H_{18}BrNO_3SNa$ $[M+Na]^+$: 480.0064; found: 480.0061.

N-hydroxy-4-methyl-N-(1-phenyl-3-(m-tolyl)prop-2-yn-1-yl)benzenesulfonamide ***(1l)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Off-white solid (1.0 mmol scale, 212 mg, 54% yield), R_f = 0.32 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.28 (br s, 0.64H), 7.94 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.41 - 7.33 (m, 5H), 7.20 - 7.14 (m, 2H), 6.89 - 6.87 (m, 2H), 5.97 (s, 1H), 2.30 (s, 6H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.4, 138.6, 138.1, 133.7, 132.8, 130.7, 130.1, 130.0, 129.5, 129.3, 129.1, 129.0, 128.9, 123.1, 88.9, 83.1, 57.9, 21.5, 21.2 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_3SNa$ $[M+Na]^+$: 414.1134; found: 414.1132.

N-hydroxy-N-(3-(3-methoxyphenyl)-1-phenylprop-2-yn-1-yl)-4-methylbenzenesulfonamide ***(1m)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.0 mmol scale, 100 mg, 25% yield), R_f = 0.16 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (400 MHz, Acetone-d_6): δ 9.38 (br s, 0.75H), 7.93 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 7.41 - 7.33 (m, 5H), 7.24 - 7.20 (m, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.66 - 6.61 (m, 2H), 5.97 (s, 1H), 3.79 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, Acetone-d_6): δ 160.2, 145.6, 138.0, 133.6, 130.7, 130.1 (2), 129.3, 129.2, 129.1, 124.8, 124.3, 117.6, 115.2, 88.6, 83.2, 57.9, 55.7, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_4SNa$ $[M+Na]^+$: 430.1084; found: 430.1081.

N-hydroxy-4-methyl-N-(1-phenyl-3-(o-tolyl)prop-2-yn-1-yl)benzenesulfonamide ***(1n)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (0.79 mmol scale, 161 mg, 52% yield), R_f = 0.29 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.32 (br s, 0.38H), 7.91 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.41 - 7.33 (m, 3H), 7.28 (d, J = 7.9 Hz, 2H), 7.23 - 7.17 (m, 2H), 7.14 - 7.11 (m, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.02 (s, 1H), 2.21 (s, 3H), 2.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.6, 140.9, 138.2, 133.6, 132.7, 130.6, 130.1, 130.0, 129.4, 129.20, 129.16, 129.0, 126.2, 123.2, 87.6, 87.4, 58.1, 21.4, 20.7 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_3SNa$ $[M+Na]^+$: 414.1134; found: 414.1134.

N-hydroxy-N-(3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-yl)-4-methylbenzenesulfonamide ***(1o)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 6: 1). White solid (1.26 mmol scale, 315 mg, 61% yield), R_f = 0.2 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.20 (br s, 0.37H), 7.93 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.41 - 7.28 (m, 6H), 6.97 (d, J = 8.4 Hz, 1H), 6.88 - 6.81 (m, 2H), 5.99 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 161.3, 145.4, 138.1, 134.1, 133.7, 130.8, 130.7, 130.0, 129.6, 129.0, 128.9, 120.8, 112.5, 111.7, 87.1, 85.6, 58.2, 56.0, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_4SNa$ $[M+Na]^+$: 430.1084; found: 430.1083.

N-hydroxy-4-methyl-N-(1-phenyl-3-(thiophen-2-yl)prop-2-yn-1-yl)benzenesulfonamide ***(1p)***. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Yellow solid (1.1 mmol scale, 163 mg, 37% yield), R_f = 0.29 (hexane: ethyl

acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.32 (br s, 0.49H), 7.92 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H), 7.44 - 7.35 (m, 6H), 7.00 - 6.97 (m, 2H), 6.00 (s, 1H), 2.33 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 137.8, 133.4, 130.6, 130.2, 129.3, 129.2, 129.1, 128.5, 127.7, 122.9, 87.3, 81.8, 58.12, 58.10, 21.6 ppm; HRMS *m/z* (ESI) calcd. for $C_{20}H_{17}NO_3S_2Na$ $[M+Na]^+$: 406.0542; found: 406.0542.

*N-hydroxy-4-methyl-N-(1-phenylhept-2-yn-1-yl)benzenesulfonamide (**1q**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.43 mmol scale, 200 mg, 23% yield), R_f = 0.36 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.03 (br s, 0.57H), 7.89 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.36 - 7.29 (m, 3H), 5.72 (s, 1H), 2.48 (s, 3H), 1.88 - 1.78 (m, 2H), 1.27 - 1.20 (m, 4H), 0.84 (t, J = 7.1 Hz, 14.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.1, 138.5, 134.0, 130.8, 129.9, 129.3, 129.0, 128.8, 89.5, 73.8, 57.6, 31.1, 22.6, 21.6, 18.8, 13.8 ppm; HRMS *m/z* (ESI) calcd. for $C_{20}H_{23}NO_3SNa$ $[M+Na]^+$: 380.1291; found: 380.1291.

*N-(3-cyclohexyl-1-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**1r**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 20: 1). White solid (1.4 mmol scale, 160 mg, 30% yield), R_f = 0.25 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.04 (br s, 0.44H), 7.89 (d, J = 8.2 Hz, 2H), 7.56 - 7.54 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.37 - 7.31 (m, 3H), 5.73 (s, 1H), 2.48 (s, 3H), 2.02 - 1.99 (m, 1H), 1.59 - 1.52 (m, 3H), 1.49 - 1.44 (m, 2H), 1.24 - 1.19 (m, 3H), 1.13 - 1.06 (m, 2H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.2, 138.7, 134.1, 130.7, 130.0, 129.3, 129.0, 128.8, 93.4, 73.7, 57.5, 32.89, 32.86, 26.5, 25.4, 21.6 ppm; HRMS *m/z* (ESI) calcd. for $C_{22}H_{25}NO_3SNa$ $[M+Na]^+$: 406.1447; found: 406.1444.

*N-hydroxy-4-methyl-N-(1-phenylbut-2-yn-1-yl)benzenesulfonamide (**1s**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 8: 1). White solid (2.0 mmol scale, 323 mg, 51% yield), R_f = 0.27 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.05 (br s, 0.54H), 7.89 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.36 - 7.29 (m, 3H), 5.69 (s, 1H), 2.48 (s, 3H), 1.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.2, 138.3, 133.8, 130.8, 129.8, 129.3, 128.9, 128.8, 85.0, 72.9, 57.6, 21.5, 3.28 ppm; HRMS *m/z* (ESI) calcd. for $C_{17}H_{17}NO_3SNa$ $[M+Na]^+$: 338.0821; found: 338.0819.

*N-hydroxy-4-methyl-N-(3-phenyl-1-(p-tolyl)prop-2-yn-1-yl)benzenesulfonamide (**1t**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 15: 1). White solid (2.0 mmol scale, 460 mg, 59% yield), R_f = 0.32 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.25 (br s, 0.32H), 7.93 - 7.91 (m, 2H), 7.50 - 7.48 (m, 2H), 7.37 - 7.29 (m, 5H), 7.20 (d, J = 7.5 Hz, 2H), 7.08 - 7.06 (m, 2H), 5.93 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.5, 138.7, 135.1, 133.7, 132.3, 130.7, 130.1, 129.7, 129.3, 129.2, 129.0, 123.4, 88.5, 83.7, 57.7, 21.5, 21.1 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_3SNa$ $[M+Na]^+$: 414.1134; found: 414.1135.

*N-hydroxy-N-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-4-methylbenzenesulfonamide (**1u**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 6: 1). White solid (2.0 mmol scale, 542 mg, 67% yield), R_f = 0.21 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.24 (br s, 0.43H), 7.92 (d, J = 8.3 Hz, 2H), 7.54 - 7.51 (m, 2H), 7.36 - 7.28 (m, 5H), 7.08 - 7.06 (m, 2H), 6.95 - 6.93 (m, 2H), 5.92 (s, 1H), 3.80 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 160.7, 145.4, 133.7, 132.3, 130.7 (2), 130.1, 129.9, 129.2, 129.0, 123.4, 114.4, 88.4, 83.8, 57.5, 55.6, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_4SNa$ $[M+Na]^+$: 430.1084; found: 430.1084.

*N-(1-(benzo[d][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-yl)-N-hydroxy-4-methylbenzenesulfonamide (**1v**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Yellow solid (2.0 mmol scale, 373 mg, 44% yield), R_f = 0.18 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.31 (br s, 0.28H), 7.91 (d, J = 8.0 Hz, 2H), 7.36 - 7.28 (m, 5H), 7.11 - 7.07 (m, 4H), 6.85 (d, J = 8.0 Hz, 1H), 6.01 (s, 2H), 5.89 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 148.6, 148.5, 145.5, 133.6, 132.3, 131.8, 130.6, 130.1, 129.2, 129.0, 123.2, 123.1, 109.6, 108.6, 102.3, 88.5, 83.6, 57.7, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{19}NO_5SNa$ $[M+Na]^+$: 444.0876; found: 444.0874.

*N-hydroxy-4-methyl-N-(3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)benzenesulfonamide (**1w**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Pale yellow solid (1.0 mmol scale, 150 mg, 39% yield), R_f = 0.26 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.54 (br s, 0.64H), 7.91 (d, J = 8.3 Hz, 2H), 7.45 - 7.44 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.34 - 7.29 (m, 3H), 7.27 - 7.25 (m, 1H), 7.08 - 6.99 (m, 2H), 7.00 - 6.99 (m, 1H), 6.22 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.6, 141.5, 133.4, 132.3, 130.7, 130.1, 129.4, 129.0, 128.0, 127.31, 127.29, 123.0, 87.7, 83.4, 54.1, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{20}H_{17}NO_3S_2Na$ $[M+Na]^+$: 406.0542; found: 406.0540.

*N-hydroxy-4-methyl-N-(1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1x**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). White solid (1.0 mmol scale, 314 mg, 73% yield), R_f = 0.29 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.14 (s, 1H), 7.97 - 7.92 (m, 5H), 7.74 - 7.72 (m, 1H), 7.55 - 7.53 (m, 2H), 7.38 - 7.33 (m, 5H), 7.14 - 7.12 (m, 2H), 6.16 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 145.5, 135.4, 134.1, 134.0, 133.6, 132.4, 130.7, 130.1, 129.3, 129.0 (2), 128.9, 128.5, 128.4, 127.3, 127.2, 127.1, 123.3, 88.9, 83.4, 58.2, 21.5 ppm; HRMS *m/z* (ESI) calcd. for $C_{26}H_{21}NO_3SNa$ $[M+Na]^+$: 450.1134; found: 450.1132.

*N-hydroxy-N-(3-(4-methoxyphenyl)-1-(p-tolyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**1y**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 10: 1). Off-white solid (2.3 mmol scale, 600 mg, 62% yield), R_f = 0.23 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.22 (br s, 0.39H), 7.91 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.02 -6.99 (m, 2H), 6.87 - 6.84 (m, 2H), 5.90 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 160.7, 145.4, 138.6, 135.3, 133.83, 133.80, 130.7, 130.1, 129.7, 129.3, 115.3, 114.6, 88.5, 82.1, 57.8, 55.7, 21.5, 21.1

ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{23}NO_4SNa$ $[M+Na]^+$: 444.1240; found: 444.1236.

*N-(1,3-diphenylprop-2-yn-1-yl)-N-methoxy-4-methylbenzenesulfonamide (**5**)*. Prepared according to the general procedure (A) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). White solid (1.0 mmol scale, 100 mg, 26% yield), R_f = 0.39 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.3 Hz, 2H), 7.67 - 7.65 (m, 2H), 7.40 - 7.33 (m, 3H), 7.28 - 7.20 (m, 5H), 7.03 - 7.01 (m, 2H), 5.89 (s, 1H), 3.47 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 136.3, 132.5, 131.8, 130.0, 129.3, 129.0, 128.7, 128.6, 128.5, 128.0, 122.3, 88.5, 82.0, 66.4, 57.5, 21.6 ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{21}NO_3SNa$ $[M+Na]^+$: 414.1134; found: 414.1134.

*3,5-diphenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2a**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). White solid (0.2 mmol scale, 55.4 mg, 62% yield; 2 mmol scale, 505.7 mg, 57%), R_f = 0.37 (hexane: ethyl acetate = 4: 1). Mp: 86 - 88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.9 Hz, 2H), 7.53 - 7.50 (m, 3H), 7.45 - 7.38 (m, 7H), 7.33 (d, J = 7.9 Hz, 2H), 6.13 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (q, J_{CF} = 4.3 Hz), 146.4, 137.7, 131.9, 130.6, 130.2, 129.5, 129.4, 129.2, 128.8, 128.7, 127.5, 124.7, 121.9 (q, J_{CF} = 266.1 Hz), 101.6 (q, J_{CF} = 36.5 Hz), 69.7, 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{18}F_3NO_3SNa$ $[M+Na]^+$: 468.0852; found: 468.0852.

*3-phenyl-5-(p-tolyl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2b**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). White solid (0.2 mmol scale, 58.6 mg, 64% yield), R_f = 0.34 (hexane: ethyl acetate = 4: 1). Mp: 133 - 134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.9 Hz, 2H), 7.42 - 7.34 (m, 7H), 7.29 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 6.08 (s, 1H), 2.38 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (q, J_{CF} = 4.2 Hz), 146.3, 142.6, 137.7, 130.5, 130.2, 129.44, 129.40, 129.3, 129.2, 128.7 (q, J_{CF} = 1.9 Hz), 127.4, 122.0 (q, J_{CF} = 265.9 Hz), 121.7, 100.7 (q, J_{CF} = 36.6 Hz), 69.7 (d, J_{CF} = 1.3 Hz), 21.8, 21.7 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 482.1008; found: 482.1005.

*5-(4-(tert-butyl)phenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2c**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). White solid (0.2 mmol scale, 53.1 mg, 53% yield), R_f = 0.60 (hexane: ethyl acetate = 4: 1). Mp: 136 - 137 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 2H), 7.49 - 7.38 (m, 9H), 7.34 (d, J = 8.0 Hz, 2H), 6.13 (s, 1H), 2.42 (s, 3H), 1.35 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (q, J_{CF} = 4.2 Hz), 155.6, 146.3, 137.8, 130.6, 130.1, 129.4, 129.3, 129.1, 128.6 (d, J_{CF} = 1.9 Hz), 127.5, 125.7, 122.1 (q, J_{CF} = 265.9 Hz), 121.7, 100.7 (q, J_{CF} = 36.6 Hz), 69.7 (d, J_{CF} = 1.2 Hz), 35.2, 31.2, 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{27}H_{26}F_3NO_3SNa$ $[M+Na]^+$: 524.1478; found: 524.1475.

*5-([1,1'-biphenyl]-4-yl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2d**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 60: 1). White solid (0.2 mmol scale, 63.0 mg, 61% yield), R_f = 0.49 (hexane: ethyl acetate = 4: 1). Mp: 140 - 141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.9 Hz, 2H), 7.69 - 7.61 (m, 6H), 7.51 - 7.41 (m, 8H), 7.35 (d, J = 7.9 Hz, 2H), 6.16 (s, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9 (q, J_{CF} = 4.3 Hz), 146.4, 144.7, 139.6, 137.6, 130.3, 130.2, 129.41, 129.38, 129.24, 129.23, 129.20, 129.1, 128.4, 127.4, 127.3, 123.2, 121.9 (q, J_{CF} = 266.1 Hz), 101.3 (q, J_{CF} = 36.6 Hz), 69.8 (d, J_{CF} = 2.0 Hz), 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -54.9 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{29}H_{22}F_3NO_3SNa$ $[M+Na]^+$: 544.1165; found: 544.1164.

*5-(4-methoxyphenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2e**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 20: 1). White solid (0.2 mmol scale, 61.7 mg, 65% yield), R_f = 0.37 (hexane: ethyl acetate = 4: 1). Mp: 120 - 121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 7.9 Hz, 2H), 7.49 - 7.30 (m, 9H), 6.93 (d, J = 8.5 Hz, 2H), 6.08 (s, 1H), 3.86 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 157.2 (d, J_{CF} = 4.0 Hz), 146.3, 137.8, 130.54, 130.46, 130.1, 129.4, 129.3, 129.1, 127.4, 122.1 (q, J_{CF} = 265.8 Hz), 116.7, 114.1, 99.6 (q, J_{CF} = 36.5 Hz), 69.8, 55.5, 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -54.9 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_4SNa$ $[M+Na]^+$: 498.0957; found: 498.0956.

*3-phenyl-2-tosyl-5-(4-(trifluoromethoxy)phenyl)-4-(trifluoromethyl)-4-isoxazoline (**2f**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). White solid (0.2 mmol scale, 42.3 mg, 40% yield), R_f = 0.57 (hexane: ethyl acetate = 4: 1). Mp: 106 - 108 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 - 7.91 (m, 2H), 7.58 - 7.55 (m, 2H), 7.43 - 7.38 (m, 5H), 7.34 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.16 (s, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8 (q, J_{CF} = 4.2 Hz), 151.6 (d, J_{CF} = 1.9 Hz), 146.5, 137.4, 130.7 (d, J_{CF} = 1.9 Hz), 130.6, 130.2, 129.49, 129.46, 129.3, 127.4, 123.1, 121.7 (q, J_{CF} = 266.2 Hz), 120.7, 120.4 (q, J_{CF} = 257.3 Hz), 102.5 (q, J_{CF} = 36.6 Hz), 69.6 (d, J_{CF} = 1.3 Hz), 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.2 (s, 3F), -57.7 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{17}F_6NO_4SNa$ $[M+Na]^+$: 552.0675; found: 552.0675.

*4-(3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline-5-yl)benzonitrile (**2g**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 3). White solid (0.2 mmol scale, 35.0 mg, 37% yield), R_f = 0.36 (hexane: ethyl acetate = 4: 1). Mp: 168 - 169 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.44 - 7.38 (m, 5H), 7.34 (d, J = 8.0 Hz, 2H), 6.19 (s, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0 (q, J_{CF} = 4.2 Hz), 146.7, 137.0, 132.4, 130.5, 130.3, 129.6, 129.44, 129.40, 129.3, 128.9, 127.4, 121.4 (q, J_{CF} = 266.6 Hz), 117.8, 115.6, 104.4 (q, J_{CF} = 36.9 Hz), 69.5, 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.2 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{17}F_3N_2O_3SNa$ $[M+Na]^+$: 493.0804; found: 493.0807.

*3-phenyl-2-tosyl-4-(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-4-isoxazoline (**2h**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). White solid (0.2 mmol scale, 42.7 mg, 42% yield), R_f = 0.59 (hexane: ethyl acetate = 4: 1). Mp: 119 - 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.63 (d, J

= 8.1 Hz, 2H), 7.44 - 7.39 (m, 5H), 7.35 (d, J = 8.0 Hz, 2H), 6.19 (s, 1H), 2.44 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7 (q, J_{CF} = 4.2 Hz), 146.6, 137.2, 133.6 (q, J_{CF} = 32.8 Hz), 130.5, 130.3, 129.56, 129.49, 129.29, 129.27, 128.2, 127.4, 125.7 (q, J_{CF} = 3.9 Hz), 123.6 (q, J_{CF} = 271.1 Hz), 121.6 (q, J_{CF} = 266.4 Hz), 103.6 (q, J_{CF} = 36.6 Hz), 69.6, 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.3 (s, 3F), -63.2 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{17}F_6NO_3SNa$ $[M+Na]^+$: 536.0726; found: 536.0727.

*5-(4-fluorophenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2i**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 70: 1). White solid (0.2 mmol scale, 42.1 mg, 46% yield), R_f = 0.5 (hexane: ethyl acetate = 4: 1). Mp: 114 - 116 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.0 Hz, 2H), 7.54 - 7.51 (m, 2H), 7.44 - 7.38 (m, 5H), 7.33 (d, J = 8.1 Hz, 2H), 7.14 - 7.10 (m, 2H), 6.14 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 163.7, 156.3 (q, J_{CF} = 4.4 Hz), 146.5, 137.5, 131.1 (dd, J_{CF} = 8.8 Hz, 1.9 Hz), 130.5, 130.2, 129.4, 129.2, 127.4, 121.8 (q, J_{CF} = 265.9 Hz), 120.8 (d, J_{CF} = 3.3 Hz), 116.1(d, J_{CF} = 22.0 Hz), 101.7 (q, J_{CF} = 36.6 Hz), 69.6 (d, J_{CF} = 1.3 Hz), 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.2 (s, 3F), -106.3 (m, 1F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{17}F_4NO_3SNa$ $[M+Na]^+$: 486.0758; found: 486.0758.

*5-(4-chlorophenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2j**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). White solid (0.2 mmol scale, 41.6 mg, 43% yield), R_f = 0.61 (hexane: ethyl acetate = 4: 1). Mp: 117 - 118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 - 7.90 (m, 2H), 7.46 - 7.37 (m, 9H), 7.33 (d, J = 8.1 Hz, 2H), 6.14 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1 (q, J_{CF} = 4.2 Hz), 146.5, 138.3, 137.4, 130.5, 130.2, 130.1 (d, J_{CF} = 1.8 Hz), 129.5, 129.4, 129.2, 129.1, 127.4, 123.0, 121.8 (q, J_{CF} = 266.1 Hz), 102.2 (q, J_{CF} = 36.6 Hz), 69.7 (d, J_{CF} = 1.5 Hz), 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{17}ClF_3NO_3SNa$ $[M+Na]^+$: 502.0462; found: 502.0462.

*5-(4-bromophenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2k**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 50: 1). White solid (0.2 mmol scale, 57.0 mg, 54% yield), R_f = 0.53 (hexane: ethyl acetate = 4: 1). Mp: 116 - 117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2H), 7.59 - 7.57 (m, 2H), 7.43 - 7.36 (m, 7H), 7.33 (d, J = 8.1 Hz, 2H), 6.14 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2 (q, J_{CF} = 4.2 Hz), 146.5, 137.4, 132.1, 130.5, 130.21, 130.18, 129.44, 129.41, 129.2, 127.4, 126.7, 123.5, 121.7 (q, J_{CF} = 266.3 Hz), 102.2 (q, J_{CF} = 36.7 Hz), 69.7 (d, J_{CF} = 1.4 Hz), 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{17}BrF_3NO_3SNa$ $[M+Na]^+$: 547.9938; found: 547.9937.

*3-phenyl-5-(m-tolyl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2l**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). Light yellow solid (0.2 mmol scale, 50.9 mg, 55% yield), R_f = 0.50 (hexane: ethyl acetate = 4: 1). Mp: 104 - 105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 2H), 7.42 - 7.37 (m, 5H), 7.34 - 7.27 (m, 6H), 6.12 (s, 1H), 2.42 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5 (q, J_{CF} = 4.2 Hz), 146.3, 138.5, 137.7, 132.7, 130.5, 130.2, 129.5, 129.34, 129.30 (d, J_{CF} = 1.8 Hz), 129.2, 128.5, 127.5, 126.0 (q, J_{CF} = 2.0 Hz), 124.5, 121.9 (q, J_{CF} = 266.1 Hz), 101.4 (q, J_{CF} = 36.5 Hz), 69.7 (d, J_{CF} = 2.0 Hz), 21.8, 21.5 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 482.1008; found: 482.1007.

*5-(3-methoxyphenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2m**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). White solid (0.2 mmol scale, 54.1 mg, 57% yield), R_f = 0.36 (hexane: ethyl acetate = 4: 1). Mp: 124 - 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.3 Hz, 2H), 7.45 - 7.37 (m, 5H), 7.35 - 7.32 (m, 3H), 7.09 (d, J = 7.7 Hz, 1H), 7.05 - 7.03 (m, 1H), 7.00 - 6.99 (m, 1H), 6.13 (s, 1H), 3.83 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 157.1 (q, J_{CF} = 4.2 Hz), 146.4, 137.6, 130.5, 130.2, 129.8, 129.5, 129.4, 129.2, 127.4, 125.7, 121.9 (q, J_{CF} = 266.1 Hz), 121.2 (q, J_{CF} = 2.1 Hz), 117.8, 114.1 (d, J_{CF} = 2.1 Hz), 101.7 (q, J_{CF} = 36.6 Hz), 69.7 (d, J_{CF} = 1.4 Hz), 55.5, 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_4SNa$ $[M+Na]^+$: 498.0957; found: 498.0957.

*3-phenyl-5-(o-tolyl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2n**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 50: 1). White solid (0.2 mmol scale, 46.6 mg, 51% yield), R_f = 0.55 (hexane: ethyl acetate = 4: 1). Mp: 108 - 110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.47 - 7.36 (m, 6H), 7.25 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 15.1 Hz, 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.29 (s, 1H), 2.49 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9 (q, J_{CF} = 4.1 Hz), 146.2, 138.2, 137.9, 131.2, 131.1, 130.5, 130.1 (2), 129.9, 129.3, 129.1, 127.6, 125.7, 124.5, 121.5 (q, J_{CF} = 266.4 Hz), 104.5 (q, J_{CF} = 35.7 Hz), 68.6, 21.9, 19.7 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -57.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 482.1008; found: 482.1008.

*5-(2-methoxyphenyl)-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2o**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 3). White solid (0.2 mmol scale, 46.5 mg, 49% yield), R_f = 0.34 (hexane: ethyl acetate = 4: 1). Mp: 132 - 134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 7.0 Hz, 2H), 7.46 - 7.38 (m, 6H), 7.09 (d, J = 7.2 Hz, 1H), 6.99 - 6.92 (m, 2H), 6.19 (s, 1H), 3.82 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 154.7 (q, J_{CF} = 4.1 Hz), 146.1, 137.8, 133.0, 131.0, 130.8, 130.1, 129.8, 129.3, 129.0, 127.9, 121.6 (q, J_{CF} = 265.8 Hz), 120.3, 114.0, 111.3, 103.4 (q, J_{CF} = 35.9 Hz), 69.3, 55.6, 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -58.8 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_4SNa$ $[M+Na]^+$: 498.0957; found: 498.0958.

*3-phenyl-5-(thiophen-2-yl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2p**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). White solid (0.2 mmol scale, 48.2 mg, 53% yield), R_f = 0.44 (hexane: ethyl acetate = 4: 1). Mp: 116 - 117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 3.9 Hz, 1H), 7.44 - 7.37 (m, 5H), 7.30 (d, J = 8.10 Hz, 2H), 7.12 (t, J = 8.8 Hz, 4.3 Hz, 1H), 6.08 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.5 (q, J_{CF} = 4.4 Hz), 146.4, 137.4, 131.9 (q,

J_{CF} = 2.7 Hz), 131.1, 130.2, 130.0, 129.39, 129.37, 129.2, 128.0, 127.4, 124.9, 121.9 (q, J_{CF} = 266.1 Hz), 99.9 (q, J_{CF} = 37.0 Hz), 69.9 (d, J_{CF} = 1.8 Hz), 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.6 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{21}H_{16}F_3NO_3S_2Na$ $[M+Na]^+$: 474.0416; found: 474.0414.

5-butyl-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2q)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 80: 1). Light yellow solid (0.2 mmol scale, 34.0 mg, 40% yield), R_f = 0.56 (hexane: ethyl acetate = 4: 1). Mp: 82 - 83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.41 - 7.33 (m, 7H), 5.92 (s, 1H), 2.47 (s, 3H), 2.33 - 2.21 (m, 2H), 1.54 - 1.43 (m, 2H), 1.38 - 1.30 (m, 2H), 0.92 (t, J = 14.6 Hz, 7.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8 (q, J_{CF} = 4.2 Hz), 146.3, 137.9, 130.4, 130.0, 129.6, 129.2, 129.0, 127.4, 122.1 (q, J_{CF} = 265.8 Hz), 101.5 (q, J_{CF} = 35.8 Hz), 68.7, 28.8, 25.0, 22.4, 21.9, 13.7 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -56.9 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{21}H_{22}F_3NO_3SNa$ $[M+Na]^+$: 448.1165; found: 448.1163.

5-cyclohexyl-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2r)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 50: 1). White solid (0.2 mmol scale, 41.5 mg, 46% yield), R_f = 0.66 (hexane: ethyl acetate = 4: 1). Mp: 106 - 107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 8.3 Hz, 2H), 7.39 - 7.32 (m, 7H), 5.98 (s, 1H), 2.59 - 2.54 (m, 1H), 2.47 (s, 3H), 1.82 - 1.77 (m, 3H), 1.71 - 1.69 (m, 1H), 1.55 - 1.43 (m, 3H), 1.32 - 1.18 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2 (q, J_{CF} = 3.9 Hz), 146.1, 138.2, 130.8, 130.0, 129.8, 129.2, 129.0, 127.4, 122.3 (q, J_{CF} = 265.8 Hz), 100.0 (q, J_{CF} = 35.8 Hz), 68.2, 35.6, 30.4, 29.4, 26.0, 25.8, 25.4, 21.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -56.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{24}F_3NO_3SNa$ $[M+Na]^+$: 474.1321; found: 474.1322.

5-methyl-3-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2s)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 50: 1). White solid (0.2 mmol scale, 48.4 mg, 63% yield), R_f = 0.47 (hexane: ethyl acetate = 4: 1). Mp: 104 - 106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.40 - 7.33 (m, 7H), 5.85 (s, 1H), 2.47 (s, 3H), 1.91 - 1.90 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1 (q, J_{CF} = 3.9 Hz), 146.4, 137.6, 130.1, 130.0, 129.4, 129.2, 129.0, 127.4, 121.9 (q, J_{CF} = 265.6 Hz), 102.0 (q, J_{CF} = 36.1 Hz), 68.9, 21.9, 10.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -57.5 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{18}H_{16}F_3NO_3SNa$ $[M+Na]^+$: 406.0695; found: 406.0694.

5-phenyl-3-(p-tolyl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2t)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 70: 1). White solid (0.2 mmol scale, 45.7 mg, 50% yield), R_f = 0.54 (hexane: ethyl acetate = 4: 1). Mp: 116 - 118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 8.0 Hz, 2H), 7.52 - 7.51 (m, 3H), 7.45 - 7.42 (m, 2H), 7.34 - 7.32 (m, 4H), 7.26 - 7.22 (m, 2H), 6.11 (s, 1H), 2.41 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1 (q, J_{CF} = 4.2 Hz), 146.3, 139.3, 134.6, 131.9, 130.4, 130.1, 129.9, 129.4, 128.8, 128.6, 127.4, 124.6, 121.9 (q, J_{CF} = 266.0 Hz), 101.5 (q, J_{CF} = 36.5 Hz), 69.5, 21.8, 21.4 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 482.1008; found: 482.1008.

3-(4-methoxyphenyl)-5-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2u)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 40: 1). Light yellow solid (0.2 mmol scale, 50.3 mg, 53% yield), R_f = 0.36 (hexane: ethyl acetate = 4: 1). Mp: 108 - 110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.0 Hz, 2H), 7.51 - 7.49 (m, 3H), 7.44 - 7.41 (m, 2H), 7.36 - 7.31 (m, 4H), 6.94 (d, J = 8.4 Hz, 2H), 6.10 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 157.1 (q, J_{CF} = 4.3 Hz), 146.3, 131.9, 130.6, 130.1, 129.7, 129.4, 128.8, 128.77 (d, J_{CF} = 1.9 Hz), 128.7, 124.7, 121.9 (q, J_{CF} = 266.1 Hz), 114.5, 101.6 (q, J_{CF} = 36.5 Hz), 69.3 (d, J_{CF} = 1.3 Hz), 55.4, 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{20}F_3NO_4SNa$ $[M+Na]^+$: 498.0957; found: 498.0957.

3-(benzo[d][1,3]dioxol-5-yl)-5-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2v)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 20: 1). Off-white solid (0.2 mmol scale, 63.6 mg, 65% yield), R_f = 0.38 (hexane: ethyl acetate = 4: 1). Mp: 110 - 111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.3 Hz, 2H), 7.52 - 7.49 (m, 3H), 7.44 - 7.41 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.93 - 6.90 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.05 (s, 1H), 5.98 (s, 2H), 2.41 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (q, J_{CF} = 4.2 Hz), 148.6, 148.4, 146.4, 131.9, 131.4, 130.5, 130.1, 129.4, 128.8 (d, J_{CF} = 1.9 Hz), 128.7, 124.6, 121.8 (q, J_{CF} = 266.0 Hz), 121.4, 108.7, 107.7, 101.5, 101.4 (q, J_{CF} = 36.5 Hz), 69.6 (d, J_{CF} = 1.9 Hz), 21.8 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -55.1 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{24}H_{18}F_3NO_5SNa$ $[M+Na]^+$: 512.0750; found: 512.0750.

5-phenyl-3-(thiophen-2-yl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2w)***. Prepared according *to* the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 60: 1). Yellow solid (0.2 mmol scale, 37.5 mg, 42% yield), R_f = 0.49 (hexane: ethyl acetate = 4: 1). Mp: 132 - 133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.1 Hz, 2H), 7.53 - 7.50 (m, 3H), 7.45 - 7.42 (m, 2H), 7.38 (d, J = 5.1 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 3.5 Hz, 1H), 7.03 (t, J = 8.7 Hz, 4.2 Hz, 1H), 6.45 (s, 1H), 2.41 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9 (q, J_{CF} = 4.1 Hz), 146.5, 141.1, 132.1, 130.5, 130.2, 129.4, 128.8 (d, J_{CF} = 1.9 Hz), 128.7 (2), 127.4, 126.8, 124.5, 121.8 (q, J_{CF} = 266.2 Hz), 101.4 (q, J_{CF} = 37.0 Hz), 65.0 (d, J_{CF} = 1.8 Hz), 21.8 ppm; ^{19} F NMR (470 MHz, $CDCl_3$): δ -55.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{21}H_{16}F_3NO_3S_2Na$ $[M+Na]^+$: 474.0416; found: 474.0416.

3-(naphthalen-2-yl)-5-phenyl-2-tosyl-4-(trifluoromethyl)-4-isoxazoline ***(2x)***. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 50: 1). White solid (0.2 mmol scale, 54.6 mg, 55% yield), R_f = 0.44 (hexane: ethyl acetate = 4: 1). Mp: 122 - 123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 - 7.96 (m, 2H), 7.92 - 7.87 (m, 4H), 7.57 - 751 (m, 6H), 7.47 - 7.44 (m, 2H), 7.34 (d, J = 2.0 Hz, 2H), 6.33 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (q, J_{CF} = 4.2 Hz), 146.4, 134.9, 133.7, 133.3, 132.0, 130.5, 130.2, 129.5, 129.4, 128.8 (d, J_{CF} = 1.8 Hz), 128.7, 128.5, 127.9, 126.89, 126.87, 126.7, 124.62, 124.63, 121.9 (q, J_{CF} = 266.2 Hz), 101.6 (q, J_{CF} = 36.6 Hz), 69.9 (d, J_{CF} = 1.8 Hz), 21.8 ppm; ^{19} F NMR (470 MHz, $CDCl_3$): δ -55.0 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{27}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 518.1008; found: 518.1005.

*5-(4-methoxyphenyl)-3-(p-tolyl)-2-tosyl-4-(trifluoromethyl)-4-isoxazoline (**2y**)*. Prepared according to the general procedure (B) and purified by flash column chromatography (hexane: ethyl acetate = 20: 1). White solid (0.2 mmol scale, 49.8 mg, 51% yield), R_f = 0.39 (hexane: ethyl acetate = 4: 1). Mp: 130 - 131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.33 - 7.30 (m, 4H), 7.21 (d, J = 7.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.07 (s, 1H), 3.85 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 157.0 (q, J_{CF} = 4.2 Hz), 146.2, 139.2, 134.8, 130.51, 130.50, 130.1, 129.8, 129.3, 127.3, 122.1 (q, J_{CF} = 265.8 Hz), 116.8, 114.1, 99.7 (q, J_{CF} = 36.5 Hz), 69.6 (d, J_{CF} = 2.0 Hz), 55.5, 21.8, 21.3 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ -54.9 (s, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{25}H_{22}F_3NO_4SNa$ $[M+Na]^+$: 512.1114; found: 512.1111. X-ray crystallography data for **2y** (recrystallized from CH_2Cl_2/hexanes) were acquired to confirm its structure (CCDC 1587879).

*3,5-diphenyl-2-tosyl-4-isoxazoline (**2a'**, cf. Table 3, entry 3)*. Prepared according to the general procedure (B) without KF and K_2CO_3. White solid (0.2 mmole scale, 71.2 mg, 94% yield), R_f = 0.30 (hexane: ethyl acetate = 4: 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.1 Hz, 2H), 7.45 - 7.43 (m, 4H), 7.39 - 7.31 (m, 6H), 7.21 (d, J = 8.1 Hz, 2H), 5.96 (d, J = 2.9 Hz, 1H), 5.21 (d, J = 2.9 Hz, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 145.5, 139.6, 130.8, 129.84, 129.75, 129.4, 128.9, 128.6, 127.3, 126.9, 125.7, 96.3, 69.9, 21.8 ppm; HRMS *m/z* (ESI) calcd. for $C_{22}H_{19}NO_3SNa$ $[M+Na]^+$: 400.0978; found: 400.0990.

*N-(trans-2-benzoyl-3,3,3-trifluoro-1-phenylpropyl)-4-methylbenzenesulfonamide (**6a**)*. White solid (38.2 mg, 43% yield), R_f = 0.21 (hexane: ethyl acetate = 4: 1). Mp: 182 - 184 °C. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.03 - 8.01 (m, 2H), 7.71 - 7.68 (m, 1H), 7.56 - 7.53 (m, 2H), 7.38 - 7.34 (m, 4H), 7.16 - 7.13 (m, 3H), 7.04 (d, J = 8.0 Hz, 1H), 5.25 (d, J = 9.7 Hz, 1H), 5.16 - 5.10 (m, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 193.6 (q, J_{CF} = 2.0 Hz), 143.4, 139.3, 138.4, 138.0, 135.0, 129.8, 129.7, 129.6. 129.0, 128.6, 128.5, 127.6, 124.6 (q, J_{CF} = 279.5 Hz), 58.2 (d, J_{CF} = 2.3 Hz), 54.2 (q, J_{CF} = 23.7 Hz), 21.3 ppm; ^{19}F NMR (470 MHz, Acetone-d_6): δ -62.7 (d, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 470.1008; found: 470.1021. X-ray crystallography data for **6a** (recrystallized from CH_2Cl_2/hexanes) were acquired to confirm its structure (CCDC 1810882).

*N-(cis-2-benzoyl-3,3,3-trifluoro-1-phenylpropyl)-4-methylbenzenesulfonamide (**6b**)*. White solid (50.1 mg, 56% yield), R_f = 0.11 (hexane: ethyl acetate = 4: 1). Mp: 185 - 187 °C. ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.72 - 7.70 (m, 2H), 7.55 - 7.52 (m, 1H), 7.43 - 7.36 (m, 4H), 7.16 - 7.14 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.93 - 6.91 (m, 3H), 5.21 - 5.13 (m, 2H), 2.25 (s, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 193.3 (q, J_{CF} = 2.1 Hz), 143.3, 139.5, 137.8, 137.4, 134.8, 129.8, 129.6, 129.1, 128.9, 128.7, 128.5, 127.6, 125.1 (q, J_{CF} = 280.2 Hz), 57.5, 54.6 (q, J_{CF} = 23.9 Hz), 21.2 ppm; ^{19}F NMR (470 MHz, Acetone-d_6): δ -62.3 (d, 3F) ppm; HRMS *m/z* (ESI) calcd. for $C_{23}H_{20}F_3NO_3SNa$ $[M+Na]^+$: 470.1008; found: 470.1026.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallograpy data for **2y** and **6a**.

^{1}H and ^{13}C NMR spectra for all new compounds.

AUTHOR INFORMATION

Corresponding Author

*Email: gctsui@cuhk.edu.hk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Research Grants Council of Hong Kong (CUHK 24301217) and the Chinese University of Hong Kong (the Faculty Strategic Fund for Research from the Faculty of Science and the Direct Grant for Research 4053199).

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