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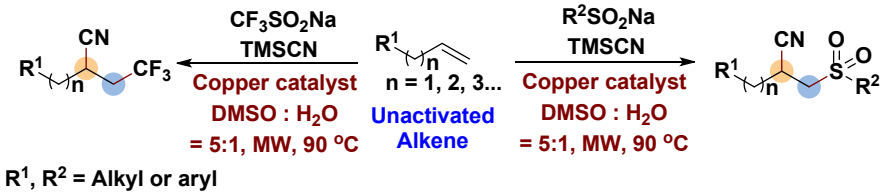
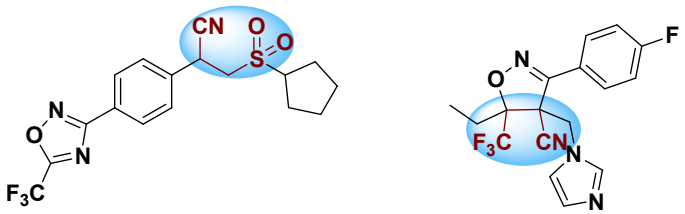



**ABSTRACT:** A novel and practical copper-catalyzed strategy for intermolecular cyanosulfonylation and cyanotrifluoromethylation of unactivated alkenes in water-containing solvents is described. The methodology developed provides an efficient and convenient access to a variety of *β*-sulfonyl nitriles and *β*-trifluoromethyl nitriles, which would have wide applications in chemical and pharmaceutical industries.

## Introduction

Difunctionalization of alkenes is an excellent step-economic strategy that incorporates two functional groups onto one carbon–carbon double bond, providing tremendous convenience for chemists to construct multifunctional and complicated skeletons in organic synthesis.[1,2] Among the methods developed, the atom transfer radical addition (ATRA) is a fascinating methodology for the difunctionalization of alkenes to form vicinal carbon–carbon or carbon–heteroatom bonds in a single step and has been broadened in recent decades.[3] Although significant progress on the three-component ATRA-type difunctionalization of alkenes has been made through the unremitting endeavours of chemists, there still existed a lot of challenges due to low conversion, selectivity and yield, as well as undesired by-products such as formation of oligomers.[4]

**Figure 1. Biologically active compounds containing *β*-sulfonyl nitrile and *β*-trifluoromethyl nitrile core structure**



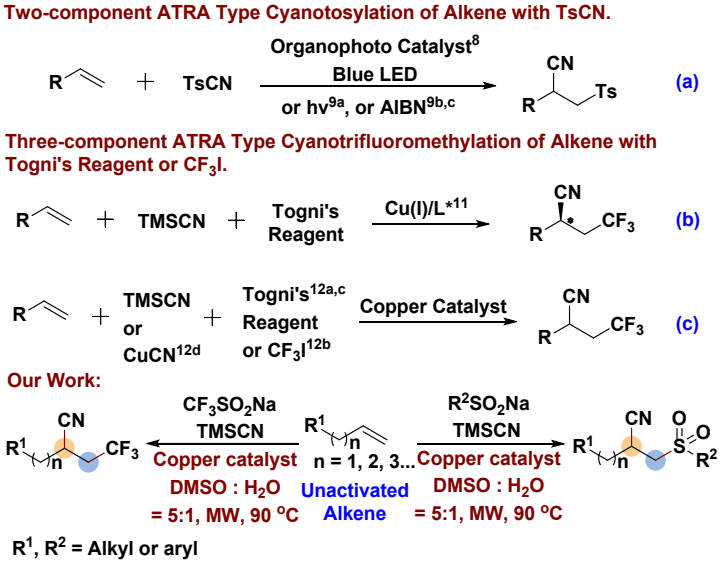

A B

*β*-Sulfonyl nitriles and *β*-trifluoromethyl nitriles comprise a substantial proportion in pharmaceuticals and agrochemicals due to their unique properties in modulating physicochemical, pharmacokinetic and pharmacodynamic profiles of drug molecules.[5] For example, compound **A** (Figure 1) containing *β*-sulfonyl nitrile moiety is extremely useful in the control of plant diseases caused by fungal plant pathogens,[6] while compound **B** containing *β*-trifluoromethyl nitrile moiety plays an important role in preventing microbial infection, particularly fungal infection.[7] Tremendous progress has been made toward the incorporation of cyano, sulfonyl or trifluoromethyl groups into aromatic compounds.[8] However, direct cyanosulfonylation and cyanotrifluoromethylation of alkenes, especially for synthesizing *β*-sulfonyl nitriles and *β*-trifluoromethyl nitriles using inexpensive and easily available sodium sulfinates such as sodium benzenesulfinate and sodium trifluoromethanesulfinate as radical precursors were seldom reported.

Recently, Chu group reported a catalytic, metal-free two-component sulfonylcyanation of alkenes by using tosyl cyanide (TsCN) under visible light organophotoredox catalysis.[9] Primitive work of the radical addition of alkenes with TsCN in the presence of UV-light irradiation or radical initiators were described by Fang and Barton group independently.[10] (Scheme 1. (**a**)) However, these reactions were restricted only to tosylcyanation, whereas other interesting and practical *β*-sulfonyl nitriles, especially alkyl substituted sulfonyl nitriles which were frequently appeared in pharmaceuticles[11], cannot be obtained through this method. Also, the reagent TsCN is a bit expensive. In 2016, Liu group reported a pioneering work on enantioselective copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes with TMSCN and Togni's reagent generating a variety of $CF_3$-containing alkylnitriles with excellent enantiomeric excess.[12] (Scheme 1. (**b**)) Similar works producing racemic $CF_3$-containing alkylnitriles were reported by Liang, Wang and Szabo et al.[13] (Scheme 1. (**c**)) Togni's reagent exhibited high reactivity in the cyanotrifluoromethylation of alkenes, but is relative expensive and requires multistep synthesis. Based on the reported cyanosulfonylation and cyanotrifluoromethylation reactions of alkenes, we tried to develop a new methodology that uses inexpensive and easily available reagents, employs green reaction system and widens substrate scope. Herein, we report a free-radical-promoted copper-catalyzed three-component ATRA-type difunctionalization of

alkenes, providing a broad substrate scope of *β*-sulfonyl and *β*-trifluoromethyl nitriles under mild, convenient and eco-friendly conditions. To the best of our knowledge, this is the first example of cyanosulfonylation and cyanotrifluoromethylation of alkenes performed in water-containing solvents.

**Scheme 1. Research background and summary of this work**

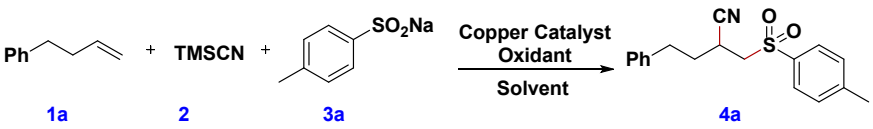



## Results and Discussion

Initially, 4-phenyl-1-butene (**1a**), TMSCN (**2**) and sodium *p*-tolylsulphinate (**3a**) were taken as representative reactants to optimize the intermolecular cyanosulfonylation reaction condition under copper-catalyzed system. As depicted in entry 1 of Table 1, only 9% of the desired cyanosulfonylation product **4a** was detected by using $CuSO_4 \cdot 5H_2O$ as catalyst, $Na_2S_2O_8$ as oxidant and DMSO as solvent. Further attempts in screening of a series of oxidants showed that no other oxidant was superior to $Na_2S_2O_8$ (Table S1, entry 1-7, ESI†). Obviously, the reaction could not occur in the absence of oxidant (Table 1, entry 2). We speculated that the low solubility of sodium sulfinate **3a** and inorganic oxidant in DMSO could possibly cause low yield of the reaction. Gratifyingly, a markedly increase of yield was observed by using water as an additive to the solution which possibly promotes the dissolution of sodium sulfinate **3a** and oxidant $Na_2S_2O_8$ (Table 1, entry 3 and 4). Further screening focusing on different amounts of water indicated that one-sixth of water in DMSO performed best by delivering the desired product **4a** in 74% yield (Table 1, entry 5-7). A slightly increase of yield to 84% was obtained by raising the temperature to 90 °C (Table 1, entry 8). Further varying species of copper catalysts showed that cupric nitrate trihydrate was the best catalyst among the tested,

with the isolated yield of 85% (Table 1, entry 9). The controlled experiment showed that the copper catalyst was essential in this intermolecular cyanosulfonylation reaction (Table 1, entry 10).

**Table 1. Screening of the reaction conditions**[a]




1a 2 3a 4a

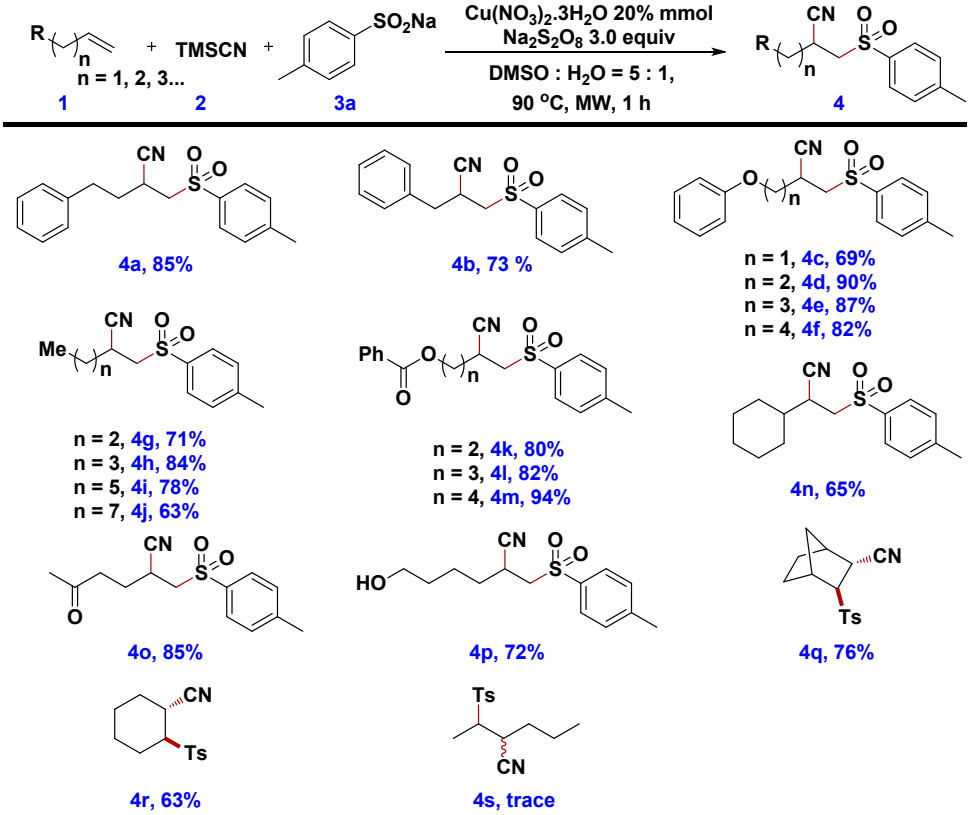
| Entry | Catalyst | Oxidant | Additive (equiv) | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | - | DMSO | 9 |
| 2 | $CuSO_4 \cdot 5H_2O$ | - | - | DMSO | NR |
| 3 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | $H_2O$ (5) | DMSO | 15 |
| 4 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | $H_2O$ (50) | DMSO | 35 |
| 5 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | - | DMSO:$H_2O$ (10:1) | 70 |
| 6 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | - | DMSO:$H_2O$ (5:1) | 74 |
| 7 | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | - | DMSO:$H_2O$ (1:1) | 35 |
| 8[c] | $CuSO_4 \cdot 5H_2O$ | $Na_2S_2O_8$ | - | DMSO:$H_2O$ (5:1) | 84 |
| **9**[c] | **$Cu(NO_3)_2 \cdot 3H_2O$** | **$Na_2S_2O_8$** | **-** | **DMSO:$H_2O$ (5:1)** | **89(85[d])** |
| 10[c] | - | $Na_2S_2O_8$ | - | DMSO:$H_2O$ (5:1) | NR |

[a] Reaction conditions: **1a** (0.4 mmol), **2** (1.5 euqiv, 0.6 mmol), **3a** (3.0 equiv, 1.2 mmol), catalyst (20% mmol, 0.08 mmol), oxidant (3.0 equiv, 1.2 mmol), additive, solvent, microwave, 80 °C, 1 h, air; [b] HPLC yield; [c] 90 °C; [d] Isolated yield based on **1a**.

Under the optimized reaction conditions, a wide range of inactivated alkenes bearing multiple functional groups were subjected to the intermolecular cyanosulfonylation reactions, as summarized in Table 2. Simple alkenes (Table 2, **1a** and **1b**) processed smoothly to transform into the desired products in good yields. Phenyl allyl ethers were found to be suitable candidates to provide the corresponding products **4c**-**4f** in good to excellent yields. Besides, some linear

olefins were well tolerated in this protocol (Table 2, **4g**-**4i**). Terminal olefins bearing a benzoate group exhibited a higher reactivity in this transformation (Table 2, **4k**-**4m**). In addition, vinylcyclohexane could give the desired product **4n** in 65% yield. It is noteworthy that terminal alkenes with a hydroxyl or carbonyl group could undergo cyanosulfonylation in satisfactory yields (Table 2, **4o** and **4p**). Furthermore, for the less reactive internal alkenes such as norbornene and cyclohexene, excellent regio-selectivity was observed to generate the desired product **4q** and **4r**. Unfortunately, when *trans*-2-hexene was used as a substrate, trace of the desired difunctionalization product 4**s** was detected.

**Table 2. Substrate scope for cyanosulfonylation reaction of various unactivated alkenes[ab]**

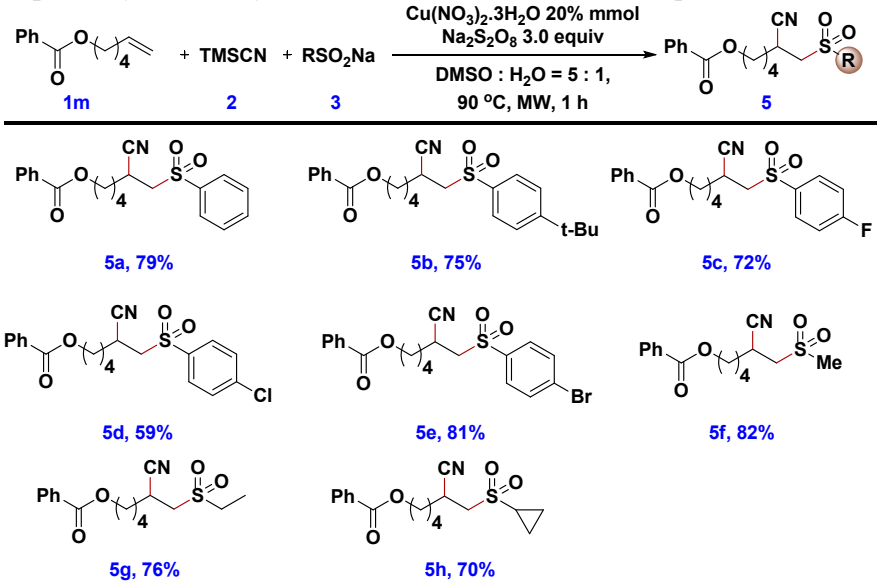



[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), **3a** (1.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol), $Na_2S_2O_8$ (1.2 mmol), DMSO : $H_2O$ = 5:1, microwave, 90 °C, 1 h, air; [b] Isolated yield based on **1**.

Significantly, the scope of this protocol could be extended to various aromatic sodium sulfinates and pharmaceutically relevant aliphatic sodium sulfinates (Table 3). For example, benzenesulfinate and tertiary butyl substituted benzenesulfinate could smoothly generate the corresponding products **5a** and **5b** in 79% and 75% yields.

With respect to electron-withdrawing substituents such as fluoro- (**5c**), chloro- (**5d**) and bromo- (**5e**) on the *para* position of the aromatic ring, the reactions gave the desired products in moderate to good yields. Strikingly, the developed cyanosulfonylation reaction could also be applied to alkyl substituted sodium sulfinates such as sodium methanesulfinate, sodium ethanesulfinate and sodium cyclopropanesulfinate by delivering the corresponding *β*-sulfonyl nitriles **5f-5h** in 70-82% yields, which are important in pharmaceuticals.

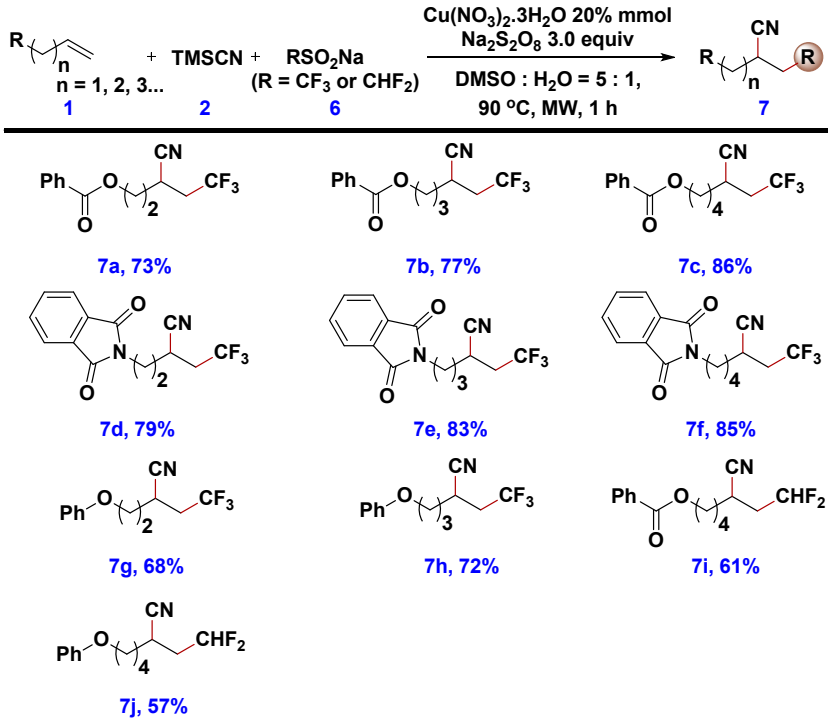
**Table 3. Substrate scope for cyanosulfonylation reaction of aromatic and aliphatic sodium sulfinates[ab]**




[a] Reaction conditions: **1m** (0.4 mmol), **2** (0.6 mmol), **3** (1.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol), $Na_2S_2O_8$ (1.2 mmol), DMSO : $H_2O$ = 5:1, microwave, 90 °C, 1 h, air; [b] Isolated yield based on **1m**.

Encouraged by the promising results, we continued our efforts toward exploring the reactivity of cyanotrifluoromethylation by using sodium trifluoromethanesulfinate as radical precursor. As shown in Table 4, terminal olefins bearing a benzoate group were proved to be highly efficient in this transformation (Table 4, **7a-7c**). Furthermore, the nitrogen-containing phthaloyl group was well tolerated delivering the corresponding products in good yields (Table 4, **7d-7f**). Phenyl allyl ethers were also compatible with this three-component cyanotrifluoromethylation system (Table 4, **7g** and **7h**). Gratifyingly, moderate yield of *β*-difluoromethyl nitriles were achieved under the same reaction conditions (Table 4, **7i** and **7j**), expending the use of this intermolecular cyanotrifluoromethylation protocol.

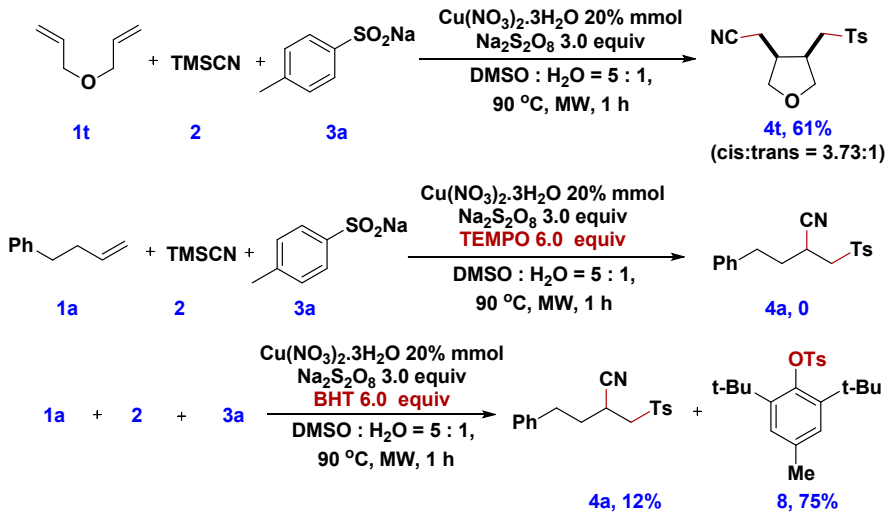
**Table 4. Substrate scope for cyanotrifluoromethylation reaction of sodium trifluoromethanesulfinate[ab]**



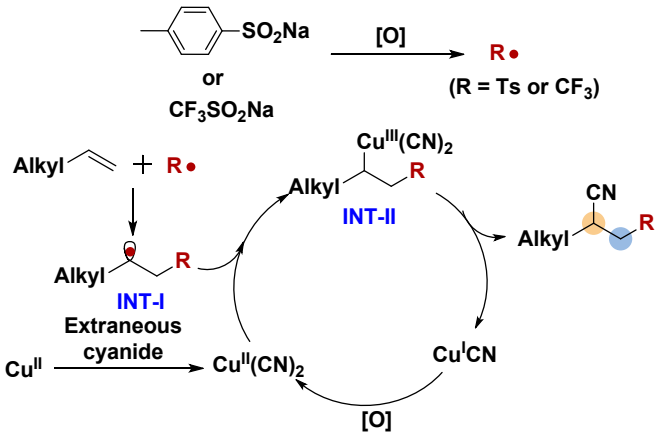

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), **6** (1.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol), $Na_2S_2O_8$ (1.2 mmol), DMSO : $H_2O$ = 5:1, microwave, 90 °C, 1 h, air; [b] Isolated yield based on **1**.

To gain some insight into the mechanism, several experiments were designed and performed (Scheme 2). First，reaction with the radical clock precursor **1t** provided the cyclized product **4t** in 71% yield (*cis*:*trans* = 3.73:1), which was a direct evidence for a radical mechanism. Then 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was attempted under the optimized conditions, the desired transformation was found to be completely quenched. Furthermore, when 2,6-di-tert-butyl-4-methylphenol (BHT) was added as a radical scavenger, the yield of desired product **4a** was sharply decreased to 12%, and meanwhile, the radical trapping product **8** was isolated in 75% yield. The above experimental results indicated that the reaction proceeded through a free-radical mechanism. According to the literature precedent and experimental evidence, a plausible mechanism was proposed as shown in Scheme 3. Initially, the radical of Ts or $CF_3$ was produced under the role of oxidant.[14] Addition of **●R** to alkene gave radical **INT-I**. The $Cu^{II}$ species was generated by rapid ligand exchange, which was subsequently combined with **INT-I** delivering a $Cu^{III}$ species (**INT-II**).[12, 13b] A reductive elimination of **INT-II** then occurred, generating the desired product and simultaneously releasing a $Cu^{I}$ species. The detailed mechanism is still not clear and needs further investigation.

**Scheme 2. Experimental probes on the reaction mechanism**




**Scheme 3. Proposed mechanism**




## Conclusions

In summary, we have developed a new intermolecular cyanosulfonylation and cyanotrifluoromethylation of unactivated alkenes in water-containing solvents based on the difunctionalization strategy. Good functional group compatibility and expanded substrate scope were exhibited in this context. In particular, less costly and easily available feedstock sodium benzenesulfinate and sodium trifluoromethanesulfinate were used as radical precursors in the protocol providing an efficient and convenient access to a variety of *β*-sulfonyl nitriles and *β*-trifluoromethyl nitriles, which had wide applications in chemical and pharmaceutical industries. Further investigation on detailed mechanistic study and synthetic applications are currently underway.

## Experimental Section

**General Information:** All commercially available reagents were used without further purification unless otherwise stated. All of the microwave-assisted reactions were performed in an initiator microwave system at the specified temperature which was monitored by external surface sensor using the standard mode of operation. The reactions were monitored by thin-layer chromatography (TLC analysis. Silica gel (200-300 mesh) was used for column chromatography. High-resolution MS (HRMS) was analyzed by a TOF analyzer. The ion source is electrospray ionization (ESI). $^{1}H$, $^{19}F$ NMR spectra were recorded at 400 MHz and $^{13}C$ NMR spectra was recorded on 600 MHz. Chemical shifts in $^{1}H$ NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of $CDCl_3$ (7.26 ppm). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of $^{13}C$ NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale.

**The procedure for the synthesis of sodium 4-(*tert*-butyl)benzenesulfinate (3b) [15]**

To a round-bottom flask added sodium sulfite (1.25 g, 10 mmol), sodium bicarbonate (0.84 g, 10 mmol) and 4-*tert*-butylbenzenesulfonyl chloride (2.33g, 10 mmol) and $H_2O$ (5.0 mL). After stirred at 80 °C for 4 h. Water was removed by rotary evaporator. Then the remaining solid was extracted and recrystallized by ethanol to get a white solid - the required compound **3b**. Other sodium sulfites are commercial available.

**General procedures of the cyanosulfonylation and cyanofluoroalkylation of alkenes.**

To a sealed microwave reaction vial were added olefins **1** (0.4 mmol), TMSCN (0.6 mmol, 59.5 mg), sodium *p*-tolylsulfinate (1.2 mmol, 213.7 mg), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol, 19.3 mg), $Na_2S_2O_8$ (1.2 mmol, 285.7 mg), DMSO (2.0 mL) and $H_2O$ (0.4 mL). Then the reaction mixture was stirred at 90 °C for 1 h in microwave reactor. After completion of the reaction, the resulting mixture was diluted with ethyl acetate (EA) and washed with water. The separated aqueous phase was washed with EA. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The crude mixture was purified by column chromatography on silica gel (petroleum: ethyl acetate = 10:1~3:1) to afford the desired product **4a-4t**.

To a sealed microwave reaction vial were added hex-5-en-1-yl benzoate (0.4 mmol, 81.6 mg), TMSCN (0.6 mmol, 59.5 mg), sodium sulfinate **3** (1.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol, 19.3 mg), $Na_2S_2O_8$ (1.2 mmol, 285.7 mg), DMSO (2.0 mL) and $H_2O$ (0.4 mL). Then the reaction mixture was stirred at 90 °C for 1 h in microwave reactor. After completion of the reaction, the resulting mixture was diluted with ethyl acetate (EA) and washed with water. The separated aqueous phase was washed with EA. The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated under vacuo. The crude mixture was purified by column chromatography on silica gel (petroleum: ethyl acetate = 8:1~2:1) to afford the desired product **5a-5h**.

To a sealed microwave reaction vial were added olefins **1** (0.4 mmol), TMSCN (0.6 mmol, 59.5 mg), $CF_3SO_2Na$ (1.2 mmol, 187.3 mg) or $CHF_2SO_2Na$ (1.2 mmol, 165.7 mg), $Cu(NO_3)_2 \cdot 3H_2O$ (0.08 mmol, 19.3 mg), $Na_2S_2O_8$ (1.2 mmol, 285.7 mg), DMSO (2.0 mL) and $H_2O$ (0.4 mL). Then the reaction mixture was stirred at 90 °C for 1 h in microwave reactor. After completion of the reaction, the resulting mixture was diluted with ethyl acetate (EA) and washed with water. The separated aqueous phase was washed with EA. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The crude mixture was purified by column chromatography on silica gel (petroleum: ethyl acetate = 10:1~4:1) to afford the desired product **7a-7j**.

***4-phenyl-2-(tosylmethyl)butanenitrile (4a)*** 106.5 mg, 85% yield; Pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 6.4 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 3.42 (dd, *J* = 14.4, 7.3 Hz, 1H), 3.21 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.07 – 3.01 (m, 1H), 2.93 – 2.87 (m, 1H), 2.78 – 2.70 (m, 1H), 2.46 (s, 3H), 2.18 – 1.99 (m, 2H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.7, 139.0, 135.0, 130.2, 128.8, 128.4, 128.2, 126.7, 118.8, 57.0, 33.6, 32.7, 25.9, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{20}NO_2S$: 314.1209, found: 314.1215.

***2-benzyl-3-tosylpropanenitrile (4b)***[9] 87.3 mg, 73% yield; Pale yellow solid, mp: 101.1 – 102.8 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 3H), 7.24 (d, *J* = 6.7 Hz, 2H), 3.40 – 3.32 (m, 2H), 3.26 – 3.23 (m, 1H), 3.12 – 3.02 (m, 2H), 2.47 (s, 3H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.8, 135.3, 134.8, 130.3, 129.2, 129.0, 128.2, 127.9, 118.7, 56.1, 37.6, 28.2, 21.7; MS (ESI) m/z 300.2 $[M + H]^+$.

***3-phenoxy-2-(tosylmethyl)propanenitrile (4c)*** 87.0 mg, 69% yield; Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.28 (dd, *J* = 13.9, 6.2 Hz, 2H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.23 (d, *J* = 4.0 Hz, 2H), 3.63 – 3.51 (m, 3H), 2.45 (s, 3H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 157.3, 145.9, 135.2, 130.3, 129.7, 128.2, 122.2, 117.2, 114.7, 66.0, 54.1, 27.3, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{18}NO_3S$: 316.1002, found: 316.0995.

***4-phenoxy-2-(tosylmethyl)butanenitrile (4d)*** 118.5 mg, 90% yield; White solid, mp: 89.5 – 91.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.29 (t, *J* = 7.8, 2H), 6.98 (t, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.12 (t, *J* = 5.4 Hz, 2H), 3.56 – 3.41 (m, 2H), 3.37 (dd, *J* = 13.0, 4.2 Hz, 1H), 2.46 (s, 3H), 2.33 (td,

*J* = 12.3, 5.5 Hz, 1H), 2.20 – 2.12 (m, 1H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.0, 145.8, 135.1, 130.2, 129.5, 128.3, 121.4, 118.6, 114.4, 63.9, 56.9, 31.6, 24.0, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{20}NO_3S$: 330.1158, found: 330.1149.

***5-phenoxy-2-(tosylmethyl)pentanenitrile (4e)*** 119.4 mg, 87% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 3.96 (t, *J* = 4.0 Hz, 2H), 3.50 – 3.44 (m, 1H), 3.26 – 3.23 (m, 2H), 2.43 (s, 3H), 2.02 – 1.85 (m, 4H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.0, 145.7, 135.1, 130.2, 129.4, 128.1, 120.9, 118.9, 114.3, 66.3, 57.1, 29.2, 26.3, 26.2, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{22}NO_3S$: 344.1315, found: 344.1308.

***6-phenoxy-2-(tosylmethyl)hexanenitrile (4f)*** 117.1 mg, 82% yield; Pale yellow solid, mp: 66.0 – 67.9 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.27 (t, *J* = 7.7, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 3.94 (t, *J* = 5.8 Hz, 2H), 3.45 (dd, *J* = 13.6, 7.9 Hz, 1H), 3.18 (dt, *J* = 13.1, 5.2 Hz, 2H), 2.45 (s, 3H), 1.89 – 1.64 (m, 6H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.7, 145.7, 135.3, 130.2, 129.4, 128.1, 120.6, 118.9, 114.3, 66.9, 57.1, 31.7, 28.3, 26.4, 23.4, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{24}NO_3S$: 358.1471, found: 358.1474.

***2-(tosylmethyl)hexanenitrile (4g)*** 71.3 mg, 71% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 3.43 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.21 (dd, *J* = 14.2, 5.2 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.46 (s, 3H), 1.79 – 1.64 (m, 2H), 1.62 – 1.41 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 145.7, 135.3, 130.2, 128.2, 119.1, 57.2, 34.0, 26.2, 21.7, 19.9, 13.2; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{17}NO_2SNa$: 274.0872, found: 274.0870.

***2-(tosylmethyl)hexanenitrile (4h)*** 89.1 mg, 84% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 3.44 (dd, *J* = 14.2, 7.9 Hz, 1H), 3.21 (dd, *J* = 14.2, 5.2 Hz, 1H), 3.17 – 3.10 (m, 1H), 2.47 (s, 3H), 1.83 – 1.66 (m, 2H), 1.52 – 1.25 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 145.7, 135.3, 130.2, 128.2, 119.1, 57.3, 31.8, 28.6, 26.4, 21.9, 21.7, 13.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{20}NO_2S$: 266.1209, found: 266.1211.

***2-(tosylmethyl)octanenitrile (4i)*** 91.4 mg, 78% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 3.44 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.20 (dd, *J* = 14.3, 4.8 Hz, 1H), 3.15 – 3.10 (m, 1H), 2.47 (s, 3H), 1.81 – 1.66 (m, 2H), 1.52 – 1.28 (m, 8H), 0.88 (t, *J* = 5.0 Hz, 3H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ

145.7, 135.4, 130.2, 128.2, 119.1, 57.3, 32.1, 31.3, 28.4, 26.5, 26.4, 22.4 21.7, 13.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{24}NO_2S$: 294.1522, found: 294.1524.

***2-(tosylmethyl)decanenitrile (4j)*** 80.9 mg, 63% yield; Colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.83 (d, $J$ = 7.5 Hz, 2H), 7.41 (d, $J$ = 7.5 Hz, 2H), 3.44 (dd, $J$ = 13.9, 7.9 Hz, 1H), 3.21 – 3.13 (m, 2H), 2.48 (s, 3H), 1.77 – 1.69 (m, 2H), 1.50 – 1.26 (m, 12H), 0.87 (t, $J$ = 6.0 Hz, 3H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 145.8, 135.4, 130.3, 128.2, 119.1, 57.3, 32.2, 31.7, 29.1, 29.0, 28.7, 26.6, 26.5, 22.6, 21.7, 14.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{28}NO_2S$: 322.1835, found: 322.1838.

***3-cyano-4-tosylbutyl benzoate (4k)*** 114.3 mg, 80% yield; White solid, mp: 127.5 – 128.0 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.01 (d, $J$ = 7.6 Hz, 2H), 7.79 (d, $J$ = 7.6 Hz, 2H), 7.59 (t, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.5 Hz, 2H), 7.34 (d, $J$ = 7.8 Hz, 2H), 4.55 – 4.42 (m, 2H), 3.51 (dd, $J$ = 12.4, 5.4 Hz, 1H), 3.40 – 3.32 (m, 2H), 2.42 (s, 3H), 2.38 – 2.33 (m, 1H), 2.26 – 2.17 (m, 1H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.1, 145.8, 135.0, 133.3, 130.2, 129.6, 129.4, 128.4, 128.1, 118.5, 61.1, 56.6, 31.0, 24.0, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_4S$: 358.1108, found: 358.1104.

***4-cyano-5-tosylpentyl benzoate (4l)*** 121.7 mg, 82% yield; White solid, mp: 75.8 – 77.6 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $J$ = 7.7 Hz, 2H), 7.80 (d, $J$ = 7.7 Hz, 2H), 7.57 (t, $J$ = 6.4 Hz, 1H), 7.45 (t, $J$ = 7.3 Hz, 2H), 7.37 (d, $J$ = 7.6 Hz, 2H), 4.33 (t, $J$ = 8.0 Hz, 2H), 3.47 (dd, $J$ = 15.6, 9.3 Hz, 1H), 3.24 (d, $J$ = 10.0 Hz, 2H), 2.44 (s, 3H), 2.03 – 1.87 (m, 4H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.4, 145.8, 135.2, 133.1, 130.3, 129.8, 129.5, 128.4, 128.2, 118.7, 63.5, 57.1, 29.1, 26.4, 26.0, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{22}NO_4S$: 372.1264, found: 372.1265.

***5-cyano-6-tosylhexyl benzoate (4m)*** 144.8 mg, 94% yield; Colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $J$ = 8.0 Hz, 2H), 7.81 (d, $J$ = 8.0 Hz, 2H), 7.56 (t, $J$ = 7.0 Hz, 1H), 7.44 (t, $J$ = 7.4 Hz, 2H), 7.38 (d, $J$ = 7.2 Hz, 2H), 4.31 (t, $J$ = 5.0 Hz, 2H), 3.47 – 3.42 (m, 1H), 3.24 – 3.16 (m, 2H), 2.45 (s, 3H), 1.90 – 1.61 (m, 6H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.5, 145.8, 135.3, 133.0, 130.2, 130.1, 129.5, 128.3, 128.2, 118.8, 64.0, 57.1, 31.7, 27.9, 26.4, 23.3, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{24}NO_4S$: 386.1421, found: 386.1436.

***2-cyclohexyl-3-tosylpropanenitrile (4n)***[9] 75.7 mg, 65% yield; White solid, mp: 107.2 – 109.0 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.83 (d, $J$ = 7.9 Hz, 2H), 7.41 (d, $J$ = 7.9 Hz, 2H), 3.41 (dd, $J$ = 14.4, 9.0 Hz, 1H), 3.22 (dd, $J$ = 14.4, 4.1 Hz, 1H), 3.07 – 3.05 (m, 1H), 2.48 (s, 3H), 1.78 – 1.63 (m, 6H), 1.26 – 1.19 (m, 5H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 145.7, 135.4, 130.2, 128.3, 118.2, 55.7, 39.6, 32.6, 31.1, 28.4, 25.7, 25.6, 25.5, 21.7; MS (ESI) m/z 292.2 $[M + H]^+$.

***5-oxo-2-(tosylmethyl)hexanenitrile (4o)***[9] 94.9 mg, 85% yield; White solid, mp: 94.4 – 95.7 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 3.43 (dd, *J* = 15.7, 9.4 Hz, 1H), 3.21 (dd, *J* = 9.4, 6.2 Hz, 2H), 2.75 – 2.60 (m, 2H), 2.45 (s, 3H), 2.15 (s, 3H), 2.13 – 2.06 (m, 1H), 1.90 – 1.81 (m, 1H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 206.0, 145.7, 135.1, 130.2, 128.2, 118.7, 57.1, 39.7, 29.9, 25.8, 25.6, 21.6; MS (ESI) m/z 280.2 $[M + H]^+$.

***6-hydroxy-2-(tosylmethyl)hexanenitrile (4p)*** 81.0 mg, 72% yield; White solid, mp: 43.7 – 45.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 3.61 (t, *J* = 4.0 Hz, 2H), 3.43 (dd, *J* = 14.0, 8.1 Hz, 1H), 3.21 (dd, *J* = 14.2, 5.1 Hz, 1H), 3.17 – 3.11 (m, 1H), 2.45 (s, 3H), 1.99 (s, 1H), 1.84 – 1.71 (m, 2H), 1.62 – 1.51 (m, 4H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.8, 135.2, 130.2, 128.1, 119.1, 61.9, 57.0, 31.7, 31.4, 26.3, 22.9, 21.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{20}NO_3S$: 282.1158, found: 282.1147.

***3-tosylbicyclo[2.2.1]heptane-2-carbonitrile (4q)*** 83.6 mg, 76% yield; White solid, mp: 129.2 – 130.8 °C; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 3.14 (ddd, *J* = 6.0, 3.9, 2.0 Hz, 1H), 3.09 (d, *J* = 6.0 Hz, 1H), 2.88 (d, *J* = 2.9 Hz, 1H), 2.69 (s. 1H), 2.47 (s, 3H), 1.98 (d, *J* = 10.7 Hz, 1H), 1.75 – 1.70 (m, 2H), 1.67 – 1.60 (m, 2H), 1.42 – 1.40 (m, 1H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.5, 134.5, 130.3, 128.4, 119.2, 70.3, 40.4, 38.8, 36.6, 33.9, 29.2, 23.9, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{18}NO_2S$: 276.1053, found: 276.1042.

***2-tosylcyclohexanecarbonitrile (4r)***[9] 66.3 mg, 63% yield; White solid, mp: 133.2 – 134.6 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H), 3.19 (td, *J* = 9.4, 4.2 Hz, 1H), 2.90 (td, *J* = 9.3, 4.0 Hz, 1H), 2.46 (s, 3H), 2.31 – 2.26 (m, 1H), 2.13 – 2.09 (m, 1H), 1.94 – 1.87 (m, 1H), 1.78 – 1.64 (m, 2H), 1.62 – 1.53 (m, 1H), 1.42 – 1.32 (m, 2H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.5, 134.0, 130.0, 129.1, 119.5, 62.6, 29.6, 27.8, 24.4, 23.3, 22.9, 21.7; MS (ESI) m/z 264.1 $[M + H]^+$.

***4-(tosylmethyl)tetrahydrofuran-3-yl)acetonitrile (4s)*** 68.1 mg, 61% yield; Colorless oil; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.04 (dd, *J* = 9.5, 6.9 Hz, 0.22H), 3.98 (t, *J* = 8.6 Hz, 0.81H), 3.94 (dd, *J* = 9.4, 6.6 Hz, 0.22H), 3.90 (dd, *J* = 9.4, 5.6 Hz, 0.81H), 3.77 (dd, *J* = 9.4, 2.9 Hz, 0.80H), 3.58 – 3.53 (m, 1H), 3.51 (dd, *J* = 9.5, 6.0 Hz, 0.20H), 3.28 (dd, *J* = 14.0, 5.1 Hz, 0.22H), 3.20 (dd, *J* = 14.1, 6.6 Hz, 0.82H), 3.12 (dd, *J* = 14.2, 7.2 Hz, 0.17H), 3.08 (dd, *J* = 14.1, 8.0 Hz, 0.85H), 2.85 – 2.79 (m, 0.81H), 2.69 – 2.66 (m, 0.81H), 2.51 (dd, *J* = 7.7, 6.5 Hz, 0.38H), 2.48 (dd, *J* = 16.7, 5.3 Hz, 0.86H), 2.42 (s, 3H), 2.34 (dd, *J* = 16.7, 9.4 Hz, 0.81H); $^{13}$C {$^1$H} NMR (150 MHz, $CDCl_3$) δ 145.3, 145.2, 135.7, 135.5, 130.0, 129.9, 127.7, 127.6, 118.3, 117.8, 72.6, 71.9, 71.6, 70.3, 58.7,

54.1, 40.9, 38.9, 38.1, 35.9, 21.4, 20.0, 16.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{18}NO_3S$: 280.1002, found: 280.1011.

***5-cyano-6-(phenylsulfonyl)hexyl benzoate (5a)*** 117.3 mg, 79% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.70 (t, *J* = 6.9 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 4.31 (t, *J* = 5.6 Hz, 2H), 3.47 (dd, *J* = 13.7, 7.2 Hz, 1H), 3.23 (dd, *J* = 20.5, 6.6 Hz, 2H), 1.92 – 1.61 (m, 6H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.4, 138.2, 134.6, 132.9, 130.0, 129.6, 129.5, 128.3, 128.1, 118.8, 64.0, 57.0, 31.7, 27.9, 26.3, 23.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{22}NO_4S$: 372.1264, found: 372.1257.

***6-((4-(tert-butyl)phenyl)sulfonyl)-5-cyanohexyl benzoate (5b)*** 128.1 mg, 75% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 4.32 (t, *J* = 5.7 Hz, 2H), 3.45 (dd, *J* = 15.1, 8.2 Hz, 1H), 3.25 – 3.17 (m, 2H), 1.95 – 1.59 (m, 6H), 1.35 (s, 9H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.5, 158.7, 135.3, 133.0, 130.1, 129.5, 128.4, 128.0, 126.7, 118.9, 64.1, 57.1, 35.3, 31.7, 31.0, 28.0, 26.4, 23.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{30}NO_4S$: 428.1890, found: 428.1875.

***5-cyano-6-((4-fluorophenyl)sulfonyl)hexyl benzoate (5c)*** 112.1 mg, 72% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.97 (dd, *J* = 8.2, 5.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.49 (dd, *J* = 14.0, 8.1 Hz, 1H), 3.23 – 3.16 (m, 2H), 1.92 – 1.59 (m, 6H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.4, 166.2 (d, *J* = 256.5 Hz), 134.3, 133.0, 131.2 (d, *J* = 9.7 Hz), 130.0, 129.4, 128.3, 118.7, 117.0 (d, *J* = 22.8 Hz), 64.0, 57.2, 31.7, 27.9, 26.4, 23.2; $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -101.45; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{21}FNO_4S$: 390.1170, found: 390.1163.

***6-((4-chlorophenyl)sulfonyl)-5-cyanohexyl benzoate (5d)*** 95.6 mg, 59% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 8.4 Hz, 3H), 7.44 (t, *J* = 7.6 Hz, 2H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.46 (dd, *J* = 14.0, 7.9 Hz, 1H), 3.26 – 3.17 (m, 2H), 1.93 – 1.77 (m, 4H), 1.75 – 1.59 (m, 2H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.5, 141.6, 136.8, 133.0, 130.1, 130.0, 129.7, 129.5, 128.4, 118.6, 64.0, 57.2, 31.7, 28.0, 26.4, 23.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{21}ClNO_4S$: 406.0874, found: 406.0864.

***6-((4-bromophenyl)sulfonyl)-5-cyanohexyl benzoate (5e)*** 145.5 mg, 81% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.73 (t, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 4.32 (t, *J* = 5.9 Hz, 2H), 3.47 (dd, *J* = 13.9, 7.9 Hz, 1H), 3.26 – 3.18 (m, 2H), 1.92 – 1.56 (m, 6H), 1.75

– 1.59 (m, 2H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.4, 137.2, 132.9, 132.6, 130.1, 130.0, 129.7, 129.5, 128.3, 118.7, 64.0, 57.0, 31.6, 27.9, 26.3, 23.2; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{21}BrNO_4S$: 450.0369, found: 450.0361.

***5-cyano-6-(methylsulfonyl)hexyl benzoate (5f)*** 101.4 mg, 82% yield; White solid, mp: 97.7 – 99.0 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 3.44 (dd, *J* = 14.1, 9.1 Hz, 1H), 3.29 – 3.22 (m, 1H), 3.14 (dd, *J* = 14.4, 3.4 Hz, 1H), 3.05 (s, 3H), 1.86 – 1.60 (m, 6H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.4, 132.9, 130.0, 129.4, 128.3, 119.4, 64.0, 55.6, 42.0, 31.5, 27.8, 26.3, 23.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{20}NO_4S$: 310.1108, found: 310.1111.

***5-cyano-6-(ethylsulfonyl)hexyl benzoate (5g)*** 98.2 mg, 76% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 6.7 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.39 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.32 – 3.23 (m, 1H), 3.14 (q, *J* = 7.9 Hz, 2H), 3.06 (d, *J* = 13.9 Hz, 1H), 1.85 – 1.65 (m, 6H), 1.42 (t, *J* = 7.2 Hz, 3H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.5, 132.9, 130.0, 129.4, 128.3, 119.4, 64.0, 52.9, 48.5, 31.6, 27.9, 26.1, 23.4, 6.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{22}NO_4S$: 324.1264, found: 324.1262.

***5-cyano-6-(cyclopropylsulfonyl)hexyl benzoate (5h)*** 93.8 mg, 70% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.46 (dd, *J* = 13.9, 8.8 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.14 (dd, *J* = 14.1, 4.6 Hz, 1H), 2.55 (qd, *J* = 7.5, 5.0 Hz, 1H), 1.89 – 1.58 (m, 6H), 1.38 – 1.35 (m, 1H), 1.24 – 1.08 (m, 3H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.5, 132.9, 130.0, 129.4, 128.3, 119.5, 64.0, 55.0, 31.7, 30.3, 27.9, 26.3, 23.4, 5.6, 5.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{22}NO_4S$: 336.1264, found: 336.1272.

***3-cyano-5,5,5-trifluoropentyl benzoate (7a)*** 79.2 mg, 73% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 4.58 (dt, *J* = 10.6, 5.3 Hz, 1H), 4.52 – 4.46 (m, 1H), 3.18 – 3.11 (m, 1H), 2.67 – 2.56 (m, 1H), 2.48 – 2.40 (m, 1H), 2.26 – 2.14 (m, 2H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.1, 133.4, 129.6, 129.4, 128.5, 124.9 (q, *J* = 277.3 Hz), 118.9, 61.1, 36.2 (q, *J* = 30.1 Hz), 31.2, 22.9 (d, *J* = 2.4 Hz); $^{19}$F {$^{1}$H} NMR (376 MHz, $CDCl_3$) δ -64.83 (t, *J* = 10.6 Hz, 3F); HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{12}F_3NO_2Na$: 294.0712, found: 294.0722.

***4-cyano-6,6,6-trifluorohexyl benzoate (7b)***[13a] 87.8 mg, 77% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 4.44 – 4.34 (m, 2H), 3.02 – 2.95 (m, 1H), 2.59 – 2.51 (m, 1H), 2.43 – 2.31 (m, 1H), 2.13 – 2.05 (m, 1H), 2.01 – 1.92 (m, 1H), 1.89 (t, *J* = 7.4 Hz, 2H); $^{13}$C {$^{1}$H} NMR

(150 MHz, $CDCl_3$) δ 166.4, 133.2, 129.8, 129.5, 128.4, 125.0 (q, *J* = 277.2 Hz), 119.2, 63.4, 36.4 (q, *J* = 30.0 Hz), 28.9, 26.1, 25.4 (d, *J* = 2.0 Hz); $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -64.71 (t, *J* = 10.7 Hz, 3F); MS (ESI) m/z 286.1 $[M + H]^+$.

***5-cyano-7,7,7-trifluoroheptyl benzoate (7c)*** 102.9 mg, 86% yield; Colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 4.58 (t, *J* = 5.8 Hz, 2H), 2.94 – 2.87 (m, 1H), 2.62 – 2.48 (m, 1H), 2.37 – 2.28 (m, 1H), 1.84 – 1.78 (m, 5H), 1.71 – 1.59 (m, 1H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 166.5, 133.0, 130.1, 129.5, 128.4, 125.0 (q, *J* = 277.3 Hz), 119.4, 64.1, 36.4 (q, *J* = 29.9 Hz), 31.6, 28.0, 25.6 (d, *J* = 2.0 Hz), 23.4; $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -65.01 (t, *J* = 10.8 Hz, 3F); HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{16}F_3NO_2Na$: 322.1025, found: 322.1024.

***2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4,4,4-trifluorobutanenitrile (7d)*** 93.6 mg, 79% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2H), 7.73 (dt, *J* = 5.3, 2.4 Hz, 2H), 3.89 (t, *J* = 6.7 Hz, 2H), 3.00 – 2.95 (m, 1H), 2.62 – 2.53 (m, 1H), 2.47 – 2.37 (m, 1H), 2.22 – 2.07 (m, 2H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 168.1, 134.3, 131.7, 125.8 (q, *J* = 277.4 Hz), 123.5, 118.9, 35.9 (q, *J* = 30.1 Hz), 34.8, 30.6, 23.4 (d, *J* = 2.2 Hz); $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -64.73 (t, *J* = 10.7 Hz, 3F); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{12}F_3N_2O_2$: 297.0845, found: 297.0841.

***5-(1,3-dioxoisoindolin-2-yl)-2-(2,2,2-trifluoroethyl)pentanenitrile (7e)***[13c] 103.0 mg, 83% yield; White solid, mp: 99.5 – 101.0 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 3.2 Hz, 2H), 7.74 (d, *J* = 2.5 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.04 – 2.97 (m, 1H), 2.59 – 2.46 (m, 1H), 2.35 – 2.26 (m, 1H), 2.05 – 1.85 (m, 2H), 1.81 – 1.64 (m, 2H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 168.3, 134.2, 131.9, 125.9 (q, *J* = 277.3 Hz), 123.4, 119.2, 36.6, 36.4 (q, *J* = 29.9 Hz), 29.3, 26.0, 25.1; $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -65.23 (t, *J* = 10.8 Hz, 3F); MS (ESI) m/z 311.1 $[M + H]^+$.

***6-(1,3-dioxoisoindolin-2-yl)-2-(2,2,2-trifluoroethyl)hexanenitrile (7f)*** 110.2 mg, 85% yield; White solid, mp: 86.7 – 87.5 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.8 Hz, 2H), 7.74 (d, *J* = 1.0 Hz, 2H), 3.70 (t, *J* = 6.8 Hz, 2H), 2.90 – 2.83 (m, 1H), 2.54 – 2.46 (m, 1H), 2.37 – 2.27 (m, 1H), 1.78 – 1.73 (m, 4H), 1.68 – 1.47 (m, 2H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 168.3, 134.0, 131.9, 125.9 (q, *J* = 277.3 Hz), 123.2, 119.4, 37.1, 36.2 (q, *J* = 29.8 Hz), 31.4, 27.7, 25.4 (d, *J* = 1.6 Hz), 23.8; $^{19}F$ {$^1H$} NMR (376 MHz, $CDCl_3$) δ -64.84 (t, *J* = 11.0 Hz, 3F); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{16}F_3N_2O_2$: 325.1158, found: 325.1170.

***4,4,4-trifluoro-2-(2-phenoxyethyl)butanenitrile (7g)*** 66.1 mg, 68% yield; Pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.6 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 4.18 (t, *J* = 5.5 Hz, 2H), 3.36 –

3.26 (m, 1H), 2.69 – 2.56 (m, 1H), 2.54 – 2.41 (m, 1H), 2.25 – 2.12 (m, 2H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.0, 129.6, 125.1 (q, *J* = 277.3 Hz), 121.5, 119.1, 114.5, 63.9, 36.3 (q, *J* = 30.0 Hz), 31.8, 22.8 (d, *J* = 1.6 Hz); $^{19}$F {$^{1}$H} NMR (376 MHz, $CDCl_3$) δ -64.85 (t, *J* = 10.9 Hz, 3F); HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{12}F_3NONa$: 266.0763, found: 266.0754.

5-***phenoxy-2-(2,2,2-trifluoroethyl)pentanenitrile (7h)*** 74.0 mg, 72% yield; Yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 6.9 Hz, 2H), 6.96 (t, *J* = 6.9 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 3.97 (t, *J* = 5.4 Hz, 2H), 2.99 – 2.97 (m, 1H), 2.54 (dq, *J* = 19.1, 9.7 Hz, 1H), 2.42 – 2.30 (m, 1H), 2.09 – 1.88 (m, 4H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.5, 129.5, 125.1 (q, *J* = 277.3 Hz), 121.0, 119.5, 114.3, 66.4, 36.4 (q, *J* = 29.9 Hz), 29.2, 26.5, 25.4 (d, *J* = 2.0 Hz); $^{19}$F {$^{1}$H} NMR (376 MHz, $CDCl_3$) δ -65.01 (t, *J* = 10.7 Hz, 3F); HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}F_3NONa$: 280.0920, found: 280.0930.

***5-cyano-7,7-difluoroheptyl benzoate (7i)*** 68.6 mg, 61% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 6.01 (t, *J* = 55.6 Hz, 1H), 4.34 (t, *J* = 6.2 Hz, 2H), 2.80 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.30 – 2.02 (m, 2H), 1.84 – 1.58 (m, 6H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 166.5, 133.0, 130.1, 129.5 128.4, 120.1, 114.7 (t, *J* = 240.4 Hz), 64.1, 36.4 (t, *J* = 22.6 Hz), 31.8, 28.1, 25.6 (t, *J* = 6.0 Hz), 23.6; $^{19}$F {$^{1}$H} NMR (376 MHz, $CDCl_3$) δ -116.50 (dt, *J* = 55.9, 14.6 Hz, 1F), -117.15 (ddd, *J* = 56.6, 22.1, 15.6 Hz, 1F); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{18}F_2NO_2$: 282.1300, found: 282.1304.

***2-(2,2-difluoroethyl)-6-phenoxyhexanenitrile (7j)*** 57.7 mg, 57% yield; Colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.01 (t, *J* = 55.4 Hz, 1H), 3.98 (t, *J* = 5.6 Hz, 2H), 2.85 – 2.77 (m, 1H), 2.21 – 2.03 (m, 2H), 1.84 – 1.66 (m, 6H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 158.8, 129.5, 120.8, 120.3, 114.8 (t, *J* = 238.5 Hz), 114.4, 67.1, 36.5 (t, *J* = 22.6 Hz), 31.9, 28.5, 25.6 (t, *J* = 4.5 Hz), 23.8; $^{19}$F {$^{1}$H} NMR (376 MHz, $CDCl_3$) δ -116.50 (dt, *J* = 56.1, 14.6 Hz, 1F), -117.15 (ddd, *J* = 56.7, 22.3, 15.5 Hz, 1F); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{18}F_2NO$: 254.1351, found: 254.1352.

***2,6-di-tert-butyl-4-methylphenyl 4-methylbenzenesulfonate (8)***[16] 336.7 mg, 75% yield; White solid, mp: 106.4 – 107.9 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.62 (s, 2H), 2.34 (s, 3H), 1.79 (s, 3H), 1.08 (s, 18H); $^{13}$C {$^{1}$H} NMR (150 MHz, $CDCl_3$) δ 183.6, 151.1, 145.2, 135.6, 130.6, 130.2, 128.7, 65.7, 35.1, 28.9, 21.5, 18.5; MS (ESI) m/z 375.1 $[M + H]^+$.

## Associated Content

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX

Segmental experiment data, $^{1}H$, $^{13}C$ and $^{19}F$ NMR data for all compounds. (PDF)

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## Notes

The authors declare no competing financial interest.

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