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Catalyst-Free and Metal-Free Electrophilic Bromoamidation of Unactivated Olefins Using the *N*-Bromosuccinimide/Sulfonamide Protocol

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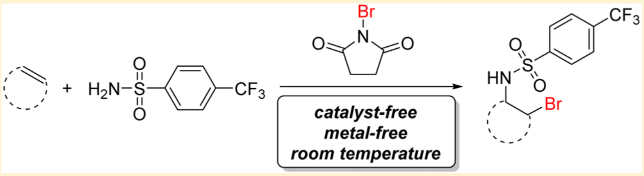
Supporting Information

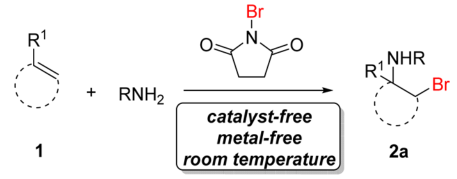
ABSTRACT: An efficient, catalyst-free, and metal-free bromoamidation of unactivated olefins has been developed. 4-(Trifluoromethyl)benzenesulfonamide and *N*-bromosuccinimide were used as the nitrogen and halogen sources, respectively. The methodology is applicable to both cyclic and aliphatic olefins.



Haloamidation of unactivated olefins is an important halogenation process. In this type of reaction, both carbon−halogen and carbon−nitrogen bonds are introduced in a chemical operation. On the basis of the widely accepted mechanism, it is believed that the reaction involves the formation of a halonium intermediate followed by S_N2 attack of the nitrogen nucleophile to form the corresponding *trans*-vicinal haloamide adduct. Because of its usefulness, this type of reaction has been widely applied in various areas. The vicinal haloamide compounds are valuable synthetic intermediates for the construction of complex organic molecules.[1] Furthermore, biologically active molecules containing vicinal haloamide functionalities exist in nature frequently.[2]

Unlike activated olefins, unactivated olefins are much less reactive toward haloamidation. Over the decades, numerous transition-metal-catalyzed strategies for haloamidation of unactivated olefins have been documented.[3] In many cases, highly reactive and electrophilic *N*,*N*-dihalosulfonamides (RSO_2NX_2, X = Cl, Br) were employed as the nitrogen and halogen sources. It was noted that removal of the catalysts/promoters would significantly diminish the reactivity and/or regioselectivity in the reaction systems.[4] Other catalytic systems utilizing a combination of $TsNH_2$/NBS for bromoamidation of electron-deficient olefins have been described as well.[5] In view of these developments, a catalyst-free haloamidation process with good regioselectivity would be greatly desired in organic synthesis. To the best of our knowledge, haloamidation of unactivated olefins using a simple halogen source such as *N*-bromosuccinimide (NBS) but without the use of any catalyst is highly lacking in the literature. An example was reported with a TsNHMe/NBS combination, and the reaction was conducted at an elevated temperature of 45 °C.[6] However, subsequent manipulation of the haloamide product is not trivial when the N−Me moiety is not the desired substituent in the target molecule. Herein, we are pleased to report a mild, efficient, and catalyst-free electrophilic bromoamidation of olefins using RSO_2NH_2/NBS with good regioselectivity and stereospecificity (Scheme 1). This is also a metal-free process, making it suitable for the pharmaceutical industry.[7]

Scheme 1. Catalyst-Free and Metal-Free Bromoamidation



Recently, we have reported several electrophilic multicomponent bromofunctionalizations of alkenes using cyclic ethers or nitriles as the solvents and nucleophilic partners.[8] It was observed that the acidity of the secondary nucleophilic partners (e.g., carboxylic acids, phenols, and sulfonamides) is important for the efficiency of the reactions. Unexpectedly, when the nucleophilic solvent was replaced with a relatively nonpolar solvent such as methylene chloride, *a direct haloamidation took place efficiently without the need of any external NBS activator*. Initially, a reaction was performed using styrene (**1a**) as the olefinic substrate and NBS. Benzamide and trifluoromethanesulfonamide were first examined, but no desired product was observed (Table 1, entries 1 and 2). To our delight, a moderate yield of the desired product **2a** was obtained when 3-nosylamide or 4-nosylamide was used (entries 5 and 6). An improved yield (82%) was obtained with 4-(trifluoromethyl)benzenesulfonamide (entry 7). The reaction was also found to be readily scalable (entry 8). Other halogen sources, including *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), were also examined, and NBS remained superior (entries 9 and 10). The reaction yield was further improved when 2 equiv of NBS was used (entry 13). We also investigated the effect of the catalyst on this reaction.

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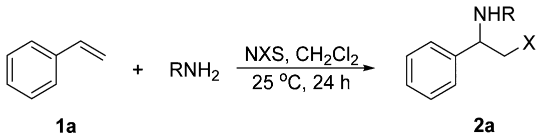
Table 1. Reaction Optimization[a]



entry	R	halogen source	X	yield (%)[b]
1	PhCO	NBS	Br	–
2	CF_3SO_2	NBS	Br	–
3	4-Ts	NBS	Br	62
4	$PhSO_2$	NBS	Br	69
5	3-Ns	NBS	Br	67
6	4-Ns	NBS	Br	68
7	4-$CF_3C_6H_4SO_2$	NBS	Br	82
8[c]	4-$CF_3C_6H_4SO_2$	NBS	Br	75
9	4-$CF_3C_6H_4SO_2$	NCS	Cl	–
10	4-$CF_3C_6H_4SO_2$	NIS	I	58
11[d]	4-$CF_3C_6H_4SO_2$	NBS	Br	68
12[e]	4-$CF_3C_6H_4SO_2$	NBS	Br	20
13[f]	4-$CF_3C_6H_4SO_2$	NBS	Br	93

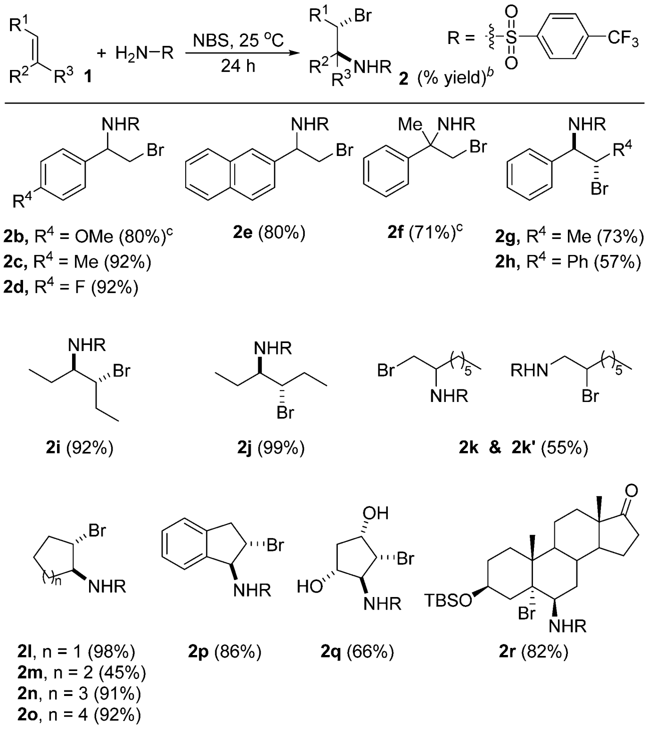
[a] Reactions were carried out with styrene (**1a**) (0.22 mmol), RNH_2 (0.26 mmol), and NXS (0.26 mmol) in CH_2Cl_2 (3.0 mL) in the absence of light. [b] Isolated yields. [c] The reaction was conducted on a 2.0 mmol scale. [d] $FeCl_2$ (0.027 mmol) was added. [e] $SPPh_3$ (0.027 mmol) was added. [f] NBS (0.37 mmol) was used.

Surprisingly, Lewis acidic iron(II) chloride resulted in a decrease in the yield (entry 11) while Lewis basic triphenylphosphine sulfide had a detrimental effect on the conversion (entry 12).

Next, we expanded the scope by examining a range of aliphatic to cyclic olefinic substrates, as shown in Table 2. Good yields were obtained when styrenes with electron-rich and electron-deficient substituents were subjected to the reaction conditions (**2b**−**d**). Only Markovnikov products were obtained with the amide substituted at the benzylic position when benzylic olefins were used as the substrates (**2b**−**g**). For aliphatic non-benzylic olefins *cis*-3-hexene (**1i**) and *trans*-3-hexene (**1j**), the corresponding products **2i** and **2j** were obtained in excellent yields. A 1:1 product mixture of **2k** and **2k′** was obtained with an alkyl-substituted terminal olefin. For the case of various ring systems, generally good to excellent yields of the bromoamide adducts were obtained (**2l**−**p**). Interestingly, **2q** containing a *trans*-1,2-bromoamide with the Br *syn* to the hydroxyl groups was obtained in 66% yield. The stereoselectivity could be attributed to the directing effect of the bromination by the hydroxyl groups.[9] The structures of **2l** and **2q** were confirmed by an X-ray crystallographic study. These mild reaction conditions were also suitable for the bromoamidation of highly functionalized cholesterol derivative **1r**, which contains *O*-silyl and ketone groups, to furnish **2r** in 82% yield.[10]

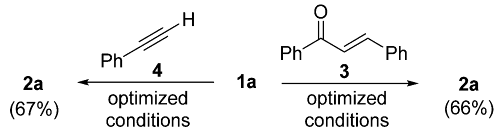
We were also interested in studying whether the reaction is selective toward unactivated alkenes. A competition experiment was conducted using a 1:1 mixture of styrene (**1a**) and chalcone (**3**) under the optimized conditions (Scheme 2). Product **2a** was obtained in 66% yield, and the relatively electron-deficient olefinic system **3** was recovered quantitatively. Notably, the other competition reaction between **1a** and phenylacetylene (**4**) gave bromoamide **2a** in 67% yield together with total recovery of **4**, suggesting that this catalyst-free bromoamidation is highly chemoselective.

Table 2. Bromoamidation of Aliphatic Olefins[a]



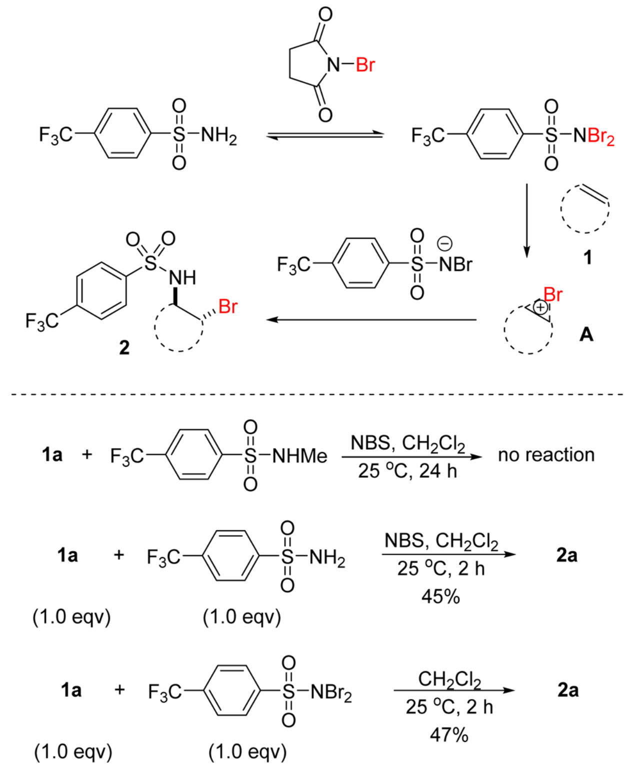
[a] Reactions were carried out with olefin **1** (0.22 mmol), 4-$CF_3C_6H_4SO_2NH_2$ (0.26 mmol), and NBS (0.26 mmol) in CH_2Cl_2 (3.0 mL) in the absence of light. [b] Isolated yields. [c] 0.37 mmol of NBS was used.

Scheme 2. Competition Experiments



To obtain a better understanding on the reaction, particularly the sole origin of the reactivity, a series of experiments were performed. First, an ^1H NMR study of a mixture of 4-$CF_3C_6H_4SO_2NH_2$ and NBS in $CDCl_3$ was performed. Two new sets of signals were observed that could be assigned to 4-$CF_3C_6H_4SO_2NHBr$ and 4-$CF_3C_6H_4SO_2NBr_2$.[11] The signals of 4-$CF_3C_6H_4SO_2NBr_2$ disappeared upon the addition of styrene, whereas the signal intensities for 4-$CF_3C_6H_4SO_2NHBr$ exhibited no significant change. We also attempted to mix 4-$CF_3C_6H_4SO_2NH_2$ and 4-$CF_3C_6H_4SO_2NBr_2$ in $CDCl_3$, and some 4-$CF_3C_6H_4SO_2NHBr$ was generated, as indicated by the ^1H NMR signals.[11,12] This result suggests that the Br in 4-$CF_3C_6H_4SO_2NBr_2$ was readily exchangeable with 4-$CF_3C_6H_4SO_2NH_2$ to give 4-$CF_3C_6H_4SO_2NHBr$. However, we cannot rule out the possibility that 4-$CF_3C_6H_4SO_2NHBr$ might also be the active species, since attempts to prepare pure 4-$CF_3C_6H_4SO_2NHBr$ were unsuccessful. Nevertheless, a combination of 4-$CF_3C_6H_4SO_2NHMe$/NBS was used as a mimic of the monobromide $CF_3C_6H_4SO_2NHBr$ in the same reaction under the optimized conditions with styrene as the substrate. A significant amount of 4-$CF_3C_6H_4SO_2NMeBr$ was detected, but no bromoamidation of styrene was observed after 24 h (Scheme 3), which suggests that 4-$CF_3C_6H_4SO_2NHBr$ might not be a good brominating agent. On the basis of these

Scheme 3. Plausible Reaction Mechanism

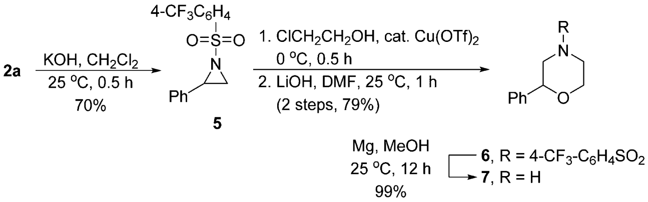


observations, it appears that the in situ-generated 4-$CF_3C_6H_4SO_2NBr_2$ might be the active brominating source.[13]

A plausible reaction mechanism is depicted in Scheme 3. We speculate that the highly electrophilic brominating species 4-$CF_3C_6H_4SO_2NBr_2$ could be generated in situ through Br exchange between NBS and 4-$CF_3C_6H_4SO_2NH_2$. Indeed, it was found that the bromoamidation proceeded effectively when 4-$CF_3C_6H_4SO_2NBr_2$ was used. The olefinic substrate **1** could then be brominated to give bromonium intermediate **A**. Subsequent nucleophilic attack on **A** by 4-$CF_3C_6H_4SO_2NBr^-$ in a Markovnikov fashion could give the desired product **2**.

We attempted to synthesize morpholine **6** by initial conversion of **2a** into aziridine **5** followed by ring opening with 2-chloroethanol and cyclization.[14] Subsequent deprotection of **6** with Mg in MeOH gave morpholine **7** in 99% yield (Scheme 4).

Scheme 4. Synthesis of 7



In summary, we have developed a catalyst-free bromoamidation reaction using 4-(trifluoromethyl)benzenesulfonamide as the nucleophilic partner and NBS as the halogen source. Mechanistic studies suggest that 4-$CF_3C_6H_4SO_2NBr_2$ was generated in situ and might be the active halogenating species. Further mechanistic study is underway.

EXPERIMENTAL SECTION

General Information. Commercially available reagents and solvents were used without further treatment. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl under N_2 prior to use. CH_2Cl_2 was freshly distilled from CaH_2. Thin-layer chromatography (TLC) was performed using precoated silica gel foils, and compounds were visualized with a spray of 5% (w/v) dodecamolybdophosphoric acid in ethanol and subsequent heating. Chromatographic purification was performed on silica gel (0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded on either a spectrometer operating at 300 MHz for protons and 75 MHz for carbon nuclei or a spectrometer operating at 500 MHz for protons and 125 MHz for carbon nuclei. Data for ^1H NMR spectra are reported as follows: chemical shift (δ) in parts per million (multiplicity, coupling constant (Hz), integration). Data for ^1H NMR spectra are referenced to the center line of $CDCl_3$ (δ 7.26) as the internal standard. Data for ^{13}C NMR spectra are referenced to the center line of $CDCl_3$ (δ 77.0). High-resolution mass spectra were obtained on a mass spectrometer in ESI or EI mode using a TOF mass analyzer. Optical rotations were recorded by the use of a polarimeter and are reported as follows: $[\alpha]_D^T$ (*c* in g per 100 mL, solvent).

Preparation of 1r Using a Literature Procedure.[15] To a solution of *trans*-dehydroandrosterone (577 mg, 2 mmol, 1.0 equiv) and imidazole (163 mg, 2.4 mmol, 1.2 equiv) was added *tert*-butyldimethylsilyl chloride (317 mg, 2.1 mmol, 1.1 equiv) at 25 °C. The reaction solution was stirred at 25 °C for 12 h and then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc 12:1 as the eluent) to yield **1r**.

*(3S,10R,13S)-3-((tert-Butyldimethylsilyl)oxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17H-cyclopenta-[a]phenanthren-17-one (**1r**).* 692 mg, 86%; white solid, mp 151.1–153.0 °C; IR (KBr) 2949, 2929, 2891, 2859, 1747, 1470, 1379, 1253, 1092, 1007, 888, 870, 837, 774, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, J = 5.1 Hz, 1H), 3.53–3.43 (m, 1H), 2.50–2.41 (m, 1H), 2.31–2.02 (m, 5H), 1.98–1.90 (m, 1H), 1.89–1.78 (m, 2H), 1.75–1.45 (m, 8H), 1.32–1.23 (m, 2H), 1.02 (s, 3H), 0.88 (s, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 141.8, 120.4, 72.4, 51.8, 50.3, 47.5, 42.8, 37.3, 36.7, 35.8, 32.0, 31.5, 31.4, 30.8, 25.9, 21.9, 20.3, 19.4, 18.2, 13.5, −4.6; HRMS (ESI) calcd for $C_{25}H_{42}NaO_2Si$ m/z $[M + Na]^+$ 425.2846, found 425.2862; R_f = 0.44 (hexane/EtOAc = 3:1).

Preparation of *N*,*N*-Dibromo-4-(trifluoromethyl)benzenesulfonamide Using a Modified Literature Procedure.[11] To a suspension of 4-(trifluoromethyl)benzenesulfonamide (5 g, 22.2 mmol) in water (25 mL) in a 100 mL two-neck flask was added KOH (3.6 g, 64.2 mmol) at 25 °C. The resultant solution was stirred vigorously, and bromine (10 g, 62.6 mmol) was added dropwise. The resulting precipitate was filtered, washed with water, and dried under vacuum to give *N*,*N*-dibromo-4-(trifluoromethyl)benzenesulfonamide.

N,N-Dibromo-4-(trifluoromethyl)benzenesulfonamide. 8.3 g, 98%; yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.8, 126.2.

Preparation of *N*-Methyl-4-(trifluoromethyl)benzenesulfonamide Using a Modified Literature Procedure.[16] To a solution of 4-(trifluoromethyl)benzenesulfonyl chloride (248 mg, 1.0 mmol, 1.0 equiv) and NaOH (48.7 mg, 1.2 mmol, 1.2 equiv) in anhydrous dichloromethane (1 mL) was added methylamine (0.18 mL, 4.0 mmol, 4.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 5 h at 25 °C. Upon completion, the reaction mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 9:1 → 3:1 as the eluent) to yield *N*-methyl-4-(trifluoromethyl)benzenesulfonamide.

N-Methyl-4-(trifluoromethyl)benzenesulfonamide. 186 mg, 78%; white solid, mp 81.3−83.0 °C; IR (KBr) 3295, 1420, 1328, 1172, 1131, 1108, 1061, 1014, 836, 718, 597, 428 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 4.72 (d, J = 4.2 Hz, 1H), 2.70 (d, J = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.7, 126.3, 126.3, 29.3; HRMS (ESI) calcd for $C_8H_8F_3NNaO_2S$ m/z $[M + Na]^+$ 262.0120, found 262.0128; R_f = 0.21 (hexane/EtOAc = 3:1).

Representative Procedure for the Catalyst-Free Bromoamidation of Olefins. To a solution of 4-trifluoromethylbenzenesulfonamide (40.0 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) in the absence of light was added styrene (**1a**) (30.6 μL, 0.27 mmol, 1.5 equiv) and *N*-bromosuccinimide (47.2 mg, 0.27 mmol, 1.5 equiv) at 25 °C. Upon completion, 0.26 g of silica gel was added, and the mixture was concentrated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc 9:1 → 7:1 as the eluent) to yield **2a**.

*N-(2-Bromo-1-phenylethyl)benzenesulfonamide (**2a**; R = PhSO$_2$, X = Br).* 52 mg, 69%; pale-yellow solid, mp 84.6−86.6 °C; IR (KBr) 3297, 1457, 1421, 1325, 1165, 1091, 938, 835, 752, 719, 701, 685, 604, 521 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.24−7.22 (m, 3H), 7.11−7.09 (m, 2H), 5.20 (d, J = 6.5 Hz, 1H), 4.61 (q, J = 6.0 Hz, 1H), 3.60 (d, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 137.5, 132.7, 128.9 (2C), 128.6 (2C), 128.3, 127.1 (2C), 126.7 (2C), 58.2, 36.5; HRMS (ESI) calcd for $C_{14}H_{14}NNaO_2S^{81}Br$ m/z $[M + Na]^+$ 363.9800, found 363.9808; R_f = 0.28 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-phenylethyl)-4-methylbenzenesulfonamide (**2a**; R = Ts, X = Br).*[4] 48 mg, 62%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 2H), 7.25−7.19 (m, 5H), 7.13−7.10 (m, 2H), 5.21 (d, J = 6.0 Hz, 1H), 4.58 (q, J = 6.0 Hz, 1H), 3.59 (dd, J = 1.5, 6.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 137.6, 136.9, 129.6 (2C), 128.7 (2C), 128.4, 127.2 (2C), 126.7 (2C), 58.0, 36.8, 21.5; HRMS (ESI) calcd for $C_{15}H_{16}{}^{79}BrNNaO_2S$ m/z $[M + Na]^+$ 375.9977, found 375.9981; R_f = 0.29 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-phenylethyl)-4-nitrobenzenesulfonamide (**2a**; R = 4-Ns, X = Br).* 57 mg, 68%; yellow solid, mp 144.1−146.1 °C; IR (KBr) 3250, 1607, 1531, 1454, 1347, 1313, 1165, 1092, 938, 853, 736, 704, 682, 637, 522, 465 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 1.5, 8.8 Hz, 2H), 7.82 (dd, J = 2.0, 9.0 Hz, 2H), 7.25−7.19 (m, 2H), 7.08 (d, J = 8.5 Hz, 2H), 5.39 (d, J = 6.5 Hz, 1H), 4.73 (q, J = 6.0 Hz, 1H), 3.67−3.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 145.8, 136.8, 128.8 (2C), 128.8, 128.4 (2C), 126.7 (2C), 124.0 (2C), 58.6, 36.3; HRMS (ESI) calcd for $C_{14}H_{12}{}^{79}BrN_2O_4S$ m/z $[M - H]^-$ 382.9707, found 382.9704; R_f = 0.26 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-phenylethyl)-3-nitrobenzenesulfonamide (**2a**; R = 3-Ns, X = Br).* 57 mg, 67%; white solid, mp 150.6−152.2 °C; IR (KBr) 3305, 3082, 1604, 1523, 1425, 1353, 1165, 1019, 945, 880, 734, 673, 605, 526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.28 (dd, J = 1.5, 8.3 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.19−7.16 (m, 3H), 7.07 (dd, J = 1.5, 7.3 Hz, 2H), 5.45 (broad s, 1H), 4.75 (q, J = 6.0 Hz, 1H), 3.68−3.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 142.3, 136.6, 132.5, 130.1, 128.8 (2C), 128.7, 126.9, 126.8 (2C), 122.6, 58.7, 36.2; HRMS (ESI) calcd for $C_{14}H_{13}{}^{79}BrN_2NaO_4S$ m/z $[M + Na]^+$ 406.9672, found 406.9669; R_f = 0.21 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-phenylethyl)-4-(trifluoromethyl)benzenesulfonamide (**2a**; R = 4-CF$_3$C$_6$H$_4$SO$_2$, X = Br).* 73 mg, 82%; white solid, mp 114.1−116.1 °C; IR (KBr) 3249, 2961, 1457, 1423, 1407, 1324, 1168, 1132, 1061, 842, 713, 614, 530, 428 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.24−7.16 (m, 3H), 7.06 (dd, J = 0.9, 7.7 Hz, 2H), 5.37 (d, J = 6.6 Hz, 1H), 4.68 (q, J = 6.3 Hz, 1H), 3.67−3.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 136.9, 134.3 (q, J = 32.7 Hz), 128.7 (2C), 128.6, 127.6 (4C), 126.7 (2C), 125.9 (q, J = 3.7 Hz), 58.5, 36.3; HRMS (ESI) calcd for $C_{15}H_{12}{}^{79}BrF_3NO_2S$ m/z $[M - H]^-$ 405.9730, found 405.9730; R_f = 0.35 (hexane/EtOAc = 3:1).

*N-(2-Iodo-1-phenylethyl)-4-(trifluoromethyl)benzenesulfonamide (**2a**; R = 4-CF$_3$C$_6$H$_4$SO$_2$, X = I).* 58 mg, 58%; yellow solid, mp 138.3−139.6 °C; IR (KBr) 3261, 1458, 1407, 1326, 1166, 1123, 1060, 928, 844, 709, 609, 431 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.26−7.17 (m, 3H), 7.03 (d, J = 7.3 Hz, 2H), 5.33 (d, J = 6.8 Hz, 1H), 4.51 (q, J = 6.8 Hz, 1H), 3.48−3.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 134.2 (q, J = 32.7 Hz), 128.7 (2C), 128.5, 127.6 (4C), 126.4 (2C), 125.9 (q, J = 3.8 Hz), 58.9, 10.3; HRMS (ESI) calcd for $C_{15}H_{13}F_3INNaO_2S$ m/z $[M + Na]^+$ 477.956, found 477.9569; R_f = 0.35 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-(4-methoxyphenyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**2b**).* 77 mg, 80%; white solid, mp 141.7−143.2 °C; IR (KBr) 3246, 2959, 2844, 1613, 1515, 1454, 1322, 1257, 1167, 1128, 1059, 831, 711, 614, 427 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 5.31 (d, J = 5.5 Hz, 1H), 4.61 (q, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.61−3.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 143.6, 134.2 (q, J = 32.7 Hz), 128.8, 128.0 (4C), 127.7 (2C), 125.9 (q, J = 3.8 Hz), 114.0 (2C), 58.0, 55.2, 36.5; HRMS (ESI) calcd for $C_{16}H_{15}{}^{79}BrF_3NNaO_3S$ m/z $[M + Na]^+$ 459.9800, found 459.9795; R_f = 0.25 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-(p-tolyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**2c**).* 85 mg, 92%; white solid, mp 171.5−173.1 °C; IR (KBr) 3245, 1607, 1515, 1455, 1424, 1405, 1342, 1174, 1080, 938, 843, 816, 725, 710, 606, 554, 515, 434 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 10.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 5.38 (d, J = 6.5 Hz, 1H), 4.65−4.61 (m, 1H), 3.63−3.54 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.6, 134.2 (q, J = 32.7 Hz), 133.9, 129.3 (2C), 127.7 (4C), 126.7 (2C), 125.8 (q, J = 3.8 Hz), 58.3, 36.5, 20.9; HRMS (ESI) calcd for $C_{16}H_{15}{}^{79}BrF_3NNaO_2S$ m/z $[M + Na]^+$ 443.9851, found 443.9858; R_f = 0.38 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-(4-fluorophenyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**2d**).* 86 mg, 92%; white solid, mp 148.1−150.0 °C; IR (KBr) 3247, 2959, 2915, 1606, 1512, 1454, 1407, 1324, 1171, 1060, 1016, 935, 834, 712, 613, 426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.07 (dd, J = 13.5, 3.5 Hz, 2H), 6.92−6.89 (m, 2H), 5.32 (d, J = 6.0 Hz, 1H), 4.66 (q, J = 6.0 Hz, 1H), 3.61−3.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.5, 134.5 (q, J = 32.7 Hz), 132.9 (d, J = 2.5 Hz), 128.6, 128.5 (2C), 127.6 (4C), 126.0 (q, J = 3.8 Hz), 115.7 (d, J = 21.4 Hz, 2C), 57.7, 36.3; HRMS (ESI) calcd for $C_{15}H_{11}{}^{79}BrF_4NO_2S$ m/z $[M - H]^-$ 423.9635, found 423.9638; R_f = 0.32 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-(naphthalene-2-yl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**2e**).* 80 mg, 80%; yellow solid, mp 123.1−124.8 °C; IR (KBr) 3256, 3060, 2959, 1605, 1454, 1404, 1337, 1166, 1061, 937, 940, 750, 712, 677, 612, 475, 429 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.73 (m, 2H), 7.66−7.61 (m, 2H), 7.51−7.46 (m, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.13 (dd, J = 1.5, 6.9 Hz, 1H), 5.84 (d, J = 6.9 Hz, 1H), 4.86 (q, J = 6.3 Hz, 1H), 3.69−3.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.4, 134.7, 134.1 (q, J = 33.2 Hz), 134.0, 132.9, 132.7, 128.7, 127.7, 127.6 (2C), 126.7 (2C), 126.6, 125.7 (q, J = 3.8 Hz), 123.6, 58.8, 35.9; HRMS (ESI) calcd for $C_{19}H_{14}{}^{79}BrF_3NO_2S$ m/z $[M - H]^-$ 455.9886, found 455.9882; R_f = 0.36 (hexane/EtOAc = 3:1).

*N-(1-Bromo-2-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (**2f**).* 66 mg, 71%; white solid, mp 155.6−158.6 °C; IR (KBr) 3262, 1448, 1421, 1381, 1323, 1166, 1139, 1063, 989, 844, 712, 608, 554, 430 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.25−7.21 (m, 3H), 7.19−7.18 (m, 2H), 5.41 (broad s, 1H), 3.95 (d, J = 11.0 Hz, 1H), 3.68 (d, J = 11.0 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 139.5, 133.9 (q, J = 3.3 Hz), 128.4 (4C), 128.1, 127.5 (2C), 126.4 (2C), 125.8 (q, J = 3.8 Hz), 60.8, 43.4, 25.7; HRMS (ESI) calcd for $C_{16}H_{15}{}^{79}BrF_3NNaO_2S$ m/z $[M + Na]^+$ 443.9851, found 443.9853; R_f = 0.41 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1-phenylpropyl)-4-(trifluoromethyl)benzenesulfonamide (**2g**).* 68 mg, 73%; white solid, mp 136.4−138.4 °C; IR (KBr) 3281, 2919, 1495, 1405, 1336, 1172, 1061, 913, 841, 712, 611, 429 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5

Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 7.25 Hz, 1H), 7.12−7.09 (m, 2H), 7.01 (d, J = 7.5 Hz, 2H), 5.92 (d, J = 9.0 Hz, 1H), 4.58 (q, J = 4.5 Hz, 1H), 4.48−4.43 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.1, 134.0 (q, J = 32.7 Hz), 128.3, 128.1 (4C), 127.8 (2C), 127.5 (2C), 125.7 (q, J = 3.8 Hz), 62.6, 53.3, 22.2; HRMS (ESI) calcd for $C_{16}H_{15}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 443.9851, found 443.9848; R_f = 0.37 (hexane/EtOAc = 3:1).

*N-(2-Bromo-1,2-diphenylethyl)-4-(trifluoromethyl)-benzenesulfonamide (**2h**).* 61 mg, 57%; yellow solid, mp 168.2−169.8 °C; IR (KBr) 3280, 1456, 1419, 1326, 1166, 1130, 1063, 839, 699, 610, 534, 430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.28−7.22 (m, 3H), 7.17−7.04 (m, 5H), 6.67 (d, J = 7.5 Hz, 2H), 5.21−5.17 (m, 2H), 4.91−4.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.7, 135.9, 129.0, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.5, 127.4, 125.6 (q, J = 3.8 Hz), 63.3, 57.3; HRMS (ESI) calcd for $C_{21}H_{17}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 506.0008, found 506.0007; R_f = 0.35 (hexane/EtOAc = 3:1).

*N-(3R,4R)-(4-Bromohexan-3-yl)-4-(trifluoromethyl)-benzenesulfonamide (**2i**).* 78 mg, 92%; white solid, mp 85.2−87.2 °C; IR (KBr) 3276, 2974, 1462, 1420, 1323, 1182, 1063, 1001, 906, 843, 711, 609, 430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 4.76 (d, J = 9.6 Hz, 1H), 4.02−3.97 (m, 1H), 3.35−3.31 (m, 1H), 1.82−1.45 (m, 4H), 0.98 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 134.3 (q, J = 32.7 Hz), 127.3 (4C), 126.2 (q, J = 3.8 Hz), 62.1, 59.3, 29.3, 27.8, 12.5, 10.4; HRMS (ESI) calcd for $C_{13}H_{17}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 410.0008, found 410.0014; R_f = 0.47 (hexane/EtOAc = 3:1).

*N-(3R,4S)-(4-Bromohexan-3-yl)-4-(trifluoromethyl)-benzenesulfonamide (**2j**).* 84 mg, 99%; white solid, mp 81.3−82.9 °C; IR (KBr) 3291, 2971, 1462, 1418, 1320, 1173, 1062, 1012, 844, 712, 617, 541, 429 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 4.90 (d, J = 10.0 Hz, 1H), 3.90−3.86 (m, 1H), 3.23 (tt, J = 3.0, 9.9 Hz, 1H), 1.79−1.75 (m, 2H), 1.61−1.47 (m, 3H), 0.98 (t, J = 7.0 Hz, 3H), 0.78 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 134.4 (q, J = 33.2 Hz), 127.4 (4C), 126.2 (q, J = 3.7 Hz), 64.9, 59.5, 29.1, 23.1, 12.7, 10.2; HRMS (ESI) calcd for $C_{13}H_{17}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 410.0008, found 410.0005; R_f = 0.54 (hexane/EtOAc = 3:1).

*N-(1-Bromooctan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (**2k**) and N-(2-Bromooctyl)-4-(trifluoromethyl)benzenesulfonamide (**2k′**).* 50 mg, 55% (**2k**:**2k′** = 1:1); yellow solid, mp 60.9−62.0 °C; IR (KBr) 3300, 2931, 2857, 1407, 1324, 1171, 1133, 1109, 1063, 842, 712, 603, 430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (1) **2k** δ 8.03−8.00 (m, 2H), 7.81−7.79 (m, 2H), 5.12 (t, J = 6.2 Hz, 1H), 4.02−3.97 (m, 1H), 3.47−3.37 (m, 2H), 1.77 (q, J = 7.5 Hz, 2H), 1.30−1.25 (m, 4H), 1.21−1.14 (m, 4H), 0.89−0.82 (m, 3H); (2) **2k′** δ 8.03−8.00 (m, 2H), 7.81−7.79 (m, 2H), 4.93 (d, J = 8.7 Hz, 1H), 3.47−3.37 (m, 2H), 3.25−3.19 (m, 1H), 1.57−1.44 (m, 3H), 1.30−1.25 (m, 4H), 1.21−1.14 (m, 3H), 0.89−0.82 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 143.6, 134.6 (q, J = 34.0 Hz), 134.5 (q, J = 34.0 Hz), 127.5 (8C), 126.4 (q, J = 3.8 Hz), 126.3 (q, J = 3.8 Hz), 55.3, 53.7, 49.6, 38.1, 36.0, 33.6, 31.5, 28.6, 28.5, 27.2, 25.3, 22.5, 22.4, 14.0, 13.9; HRMS (ESI) calcd for $C_{15}H_{21}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 438.0326, found 438.0333; R_f = 0.52 (hexane/EtOAc = 3:1).

*N-(2-Bromocyclopentyl)-4-(trifluoromethyl)benzenesulfonamide (**2l**).* 80 mg, 98%; white solid, mp 123.8−125.6 °C; IR (KBr) 3270, 2974, 1450, 1406, 1322, 1170, 1139, 1061, 922, 839, 712, 602, 558, 493, 430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 5.19 (d, J = 6.3 Hz, 1H), 4.05 (q, J = 6.0 Hz, 1H), 3.72 (quintet, J = 6.0 Hz, 1H), 2.30−2.17 (m, 2H), 2.01−1.92 (m, 1H), 1.87−1.67 (m, 2H), 1.50−1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 134.6 (q, J = 33.2 Hz), 127.8 (4C), 126.4 (q, J = 3.8 Hz), 63.2, 53.5, 34.0, 30.9, 21.3; HRMS (ESI) calcd for $C_{12}H_{13}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 393.9695, found 393.9707; R_f = 0.35 (hexane/EtOAc = 3:1).

*N-(2-Bromocyclohexyl)-4-(trifluoromethyl)benzenesulfonamide (**2m**).* 38 mg, 45%; white solid, mp 137.1−138.8 °C; IR (KBr) 3270, 2937, 1451, 1405, 1329, 1166, 1090, 1060, 841, 715, 624, 551, 432 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 4.87 (d, J = 5.5 Hz, 1H), 3.79 (td, J = 4.0, 10.5 Hz, 1H), 3.22−3.20 (m, 1H), 2.36−2.30 (m, 2H), 1.80 (qd, J = 3.5, 11.5 Hz, 1H), 1.72−1.68 (m, 2H), 1.56 (m, 1H), 1.37−1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 134.4 (q, J = 34.0 Hz), 127.9 (4C), 126.1 (q, J = 3.8 Hz), 59.4, 54.8, 36.4, 34.0, 25.7, 23.8; HRMS (ESI) calcd for $C_{13}H_{15}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 407.9851, found 407.9863; R_f = 0.33 (hexane/EtOAc = 3:1).

*N-(2-Bromocycloheptyl)-4-(trifluoromethyl)benzenesulfonamide (**2n**).* 80 mg, 91%; white solid, mp 108.5−110.0 °C; IR (KBr) 3249, 2926, 2860, 1455, 1404, 1324, 1161, 1142, 1061, 940, 863, 841, 714, 657, 630, 599, 426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 4.94 (d, J = 6.5 Hz, 1H), 3.99 (td, J = 3.5, 7.5 Hz, 1H), 3.52−3.50 (m, 1H), 2.17−2.05 (m, 2H), 1.67−1.61 (m, 5H), 1.54−1.49 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 134.4 (q, J = 32.7 Hz), 127.9 (4C), 126.1 (q, J = 3.8 Hz), 62.9, 58.3, 35.0, 32.2, 27.2, 24.0, 22.9; HRMS (ESI) calcd for $C_{14}H_{17}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 422.0008, found 422.0016; R_f = 0.34 (hexane/EtOAc = 3:1).

*N-(2-Bromocyclooctyl)-4-(trifluoromethyl)benzenesulfonamide (**2o**).* 84 mg, 92%; white solid, mp 110.1−112.1 °C; IR (KBr) 3251, 2930, 2870, 1445, 1404, 1322, 1166, 1060, 842, 811, 713, 668, 640, 599, 426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 4.85 (d, J = 5.0 Hz, 1H), 4.05−4.01 (m, 1H), 3.56−3.51 (m, 1H), 2.29−2.23 (m, 1H), 2.15−2.10 (m, 1H), 2.06−1.99 (m, 1H), 1.82−1.63 (m, 5H), 1.56−1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 134.4 (q, J = 32.7 Hz), 128.0 (4C), 126.0 (q, J = 3.8 Hz), 61.5, 59.1, 32.4, 32.4, 25.6, 25.4, 25.4, 25.0; HRMS (ESI) calcd for $C_{15}H_{19}{}^{79}BrF_3NNaO_2S$ m/z [M + Na]$^+$ 436.0164, found 436.0169; R_f = 0.38 (hexane/EtOAc = 3:1).

*N-(2-Bromo-2,3-dihydro-1H-inden-1-yl)-4-(trifluoromethyl)-benzenesulfonamide (**2p**).*[5f] 79 mg, 86%; white solid, mp 160.4−162.1 °C; IR (KBr) 3271, 2960, 1467, 1338, 1163, 1067, 934, 840, 736, 715, 615, 547, 430 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.32−7.29 (m, 1H), 7.24−7.18 (m, 3H), 5.01−4.98 (m, 1H), 4.93 (d, J = 8.5 Hz, 1H), 4.25 (q, J = 6.5 Hz, 1H), 3.55 (dd, J = 7.0, 16.5 Hz, 1H), 3.21 (dd, J = 6.5, 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 139.9, 139.0, 134.6 (q, J = 32.5 Hz), 129.4, 127.9 (4C), 127.9, 126.3 (q, J = 3.8 Hz), 124.7, 124.3, 67.3, 31.2, 40.9; HRMS (ESI) calcd for $C_{16}H_{12}{}^{79}BrF_3NO_2S$ m/z [M − H]$^-$ 417.9730, found 417.9729; R_f = 0.43 (hexane/EtOAc = 3:1).

*N-((3S,5R)-2-Bromo-3,5-dihydroxycyclopentyl)-4-(trifluoromethyl)benzenesulfonamide (**2q**).* 59 mg, 66%; white solid, mp 116.7−117.9 °C; $[\alpha]_D^{25}$ −9.8 (c 1.0, MeOH); IR (KBr) 3358, 2978, 2924, 1718, 1599, 1456, 1396, 1298, 1231, 1150, 1113, 965, 843, 812, 694, 598, 534 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 8.10 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 3.98−3.96 (m, 1H), 3.91−3.83 (m, 3H), 2.36−2.30 (m, 1H), 1.77−1.73 (m, 1H); ^{13}C NMR (125 MHz, MeOD) δ 147.2, 134.8 (q, J = 32.7 Hz), 129.1 (4C), 127.1 (q, J = 3.8 Hz), 75.5, 71.0, 69.3, 58.2, 40.5; HRMS (ESI) calcd for $C_{12}H_{13}{}^{79}BrF_3NNaO_4S$ m/z [M + Na]$^+$ 425.9593, found 425.9596; R_f = 0.34 ($CHCl_3$/MeOH = 8:1).

*N-((3S,10R,13S)-5-Bromo-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-6-yl)-4-(trifluoromethyl)benzenesulfonamide (**2r**).* 127 mg, 82%; white solid, mp 150.1−152.1 °C; $[\alpha]_D^{25}$ −4.5 (c 1.0, $CHCl_3$); IR (KBr) 2952, 2859, 1741, 1472, 1444, 1406, 1324, 1254, 1171, 1139, 1096, 867, 836, 777, 713, 606, 429 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 5.92 (d, J = 9.6 Hz, 1H), 4.31−4.29 (m, 1H), 3.75−3.73 (m, 1H), 2.41−2.32 (dd, J = 7.8, 19.1 Hz, 1H), 2.27−2.19 (m, 2H), 2.05−2.03 (m, 1H), 1.99−1.89 (m, 1H), 1.76−1.71 (m, 3H), 1.64−1.53 (m, 6H), 1.31−1.22 (m, 8H), 0.86 (s, 9H), 0.78 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 134.7 (q, J = 34.0 Hz), 127.8 (4C), 126.4, 86.7, 69.1, 60.3, 58.2, 50.0, 47.7, 47.3, 43.3, 41.1, 36.0, 35.5, 31.1, 31.0, 30.6, 30.1, 25.7 (3C), 21.2, 20.3, 18.4, 18.0, 14.1, 13.7, −4.8, −4.8; HRMS (ESI) calcd for $C_{32}H_{47}{}^{79}BrF_3NNaO_4SSi$ m/z [M + Na]$^+$ 728.2023, found 728.2036; R_f = 0.27 (hexane/EtOAc = 3:1).

*Synthesis of 2-Phenylmorpholine (**7**).*[14,17] The formation of aziridine **5** was effected by treatment of bromoamide **2a** (820 mg, 2.01 mmol, 1 equiv) in CH_2Cl_2 (35 mL) with KOH (451 mg, 8.04 mmol, 4 equiv). The resulting mixture was stirred for 0.5 h at 25 °C. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel, eluting with hexane/EtOAc 6:1, to yield 2-phenyl-1-(4-(trifluoromethyl)phenylsulfonyl)aziridine (**5**).

The synthesis of morpholine **6** was effected by adding anhydrous copper(II) triflate (101 mg, 0.28 mmol, 0.2 equiv) to a solution of **5** (456 mg, 1.39 mmol, 1 equiv) in 2-chloroethanol (0.94 mL, 13.9 mmol, 10 equiv) at 0 °C under a nitrogen atmosphere and stirring for 0.5 h. The reaction mixture was then diluted with anhydrous DMF (13.9 mL), and $LiOH{\cdot}H_2O$ (175 mg, 4.18 mmol, 3 equiv) was added. After 1 h of stirring at 25 °C, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel, eluting with hexane/EtOAc 6:1, to yield 2-phenyl-4-(4-(trifluoromethyl)phenylsulfonyl)morpholine (**6**).

Deprotection of the sulfonyl group was effected by adding **6** (37 mg, 0.1 mmol, 1 equiv) to a suspension of Mg (24 mg, 1.0 mmol, 10 equiv) in MeOH (1 mL) under N_2. The resulting suspension was stirred vigorously for 12 h at 25 °C. The reaction mixture was then quenched with aqueous HCl (10%, 5 mL) and diluted with CH_2Cl_2 (2.5 mL). The aqueous phase was washed with CH_2Cl_2 (5 mL). The resulting mixture was adjusted to pH 9 by the addition of Na_2CO_3 and saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated to yield 2-phenylmorpholine (7).

2-Phenyl-1-(4-(trifluoromethyl)phenylsulfonyl)aziridine (***5***). 456 mg, 70%; white solid, mp 115.8−117.4 °C; IR (KBr) 1408, 1326, 1167, 1062, 914, 847, 803, 753, 699, 617, 568, 429 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.33−7.31 (m, 3H), 7.24−7.22 (m, 2H), 3.88 (dd, J = 4.5, 14.0 Hz, 1H), 3.07 (d, J = 7.0 Hz, 1H), 2.47 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 135.3 (q, J = 32.7 Hz), 134.4, 128.7 (4C), 128.6, 128.4 (2C), 126.5 (2C), 126.3 (q, J = 3.8 Hz), 41.6, 36.4; HRMS (ESI) calcd for $C_{15}H_{13}F_3NO_2S$ m/z $[M + H]^+$ 328.0614, found 328.0615; R_f = 0.47 (hexane/EtOAc = 3:1).

2-Phenyl-4-(4-(trifluoromethyl)phenylsulfonyl)morpholine (***6***). 408 mg, 79%; white solid, mp 135.0−137.0 °C; IR (KBr) 1453, 1407, 1356, 1324, 1170, 1130, 1062, 969, 743, 706, 594, 551, 429 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.36−7.30 (m, 5H), 4.61 (dd, J = 21.0, 2.5 Hz, 1H), 4.10 (dd, J = 3.5, 24.0 Hz, 1H), 3.87 (td, J = 2.6, 23.3 Hz, 1H), 3.81 (d, J = 11.6, 1H), 3.69 (d, J = 11.0, 1H), 2.56 (td, J = 3.4, 23.1 Hz, 1H), 2.29 (t, J = 10.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.3, 134.7 (q, J = 32.8 Hz), 128.5 (4C), 128.4, 128.2 (2C), 126.3 (q, J = 3.5 Hz), 125.9 (2C), 66.1, 51.8, 45.3; HRMS (ESI) calcd for $C_{17}H_{16}F_3NNaO_3S$ m/z $[M + Na]^+$ 394.0695, found 394.0698; R_f = 0.38 (hexane/EtOAc = 3:1).

2-Phenylmorpholine (***7***).[8i] 16 mg, 99%; colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.49 (dd, J = 2.5, 20.2 Hz, 1H), 4.04 (d, J = 11.0 Hz, 1H), 3.78 (td, J = 3.0, 22.5 Hz, 1H), 3.07 (d, J = 12.0 Hz, 1H), 3.01 (td, J = 2.5, 24.0 Hz, 1H), 2.90 (d, J = 12.0 Hz, 1H), 2.80 (t, J = 10.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 128.4, 127.8, 126.0, 79.1, 68.1, 52.8, 45.4; MS (ESI) $[M + H]^+$ 164.1; R_f = 0.18 (EtOAc/MeOH/NH_4OH = 9:1:0.1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

CIF files of **2a**, **2b**, **2g**, **2l**, **2q**, and **5** and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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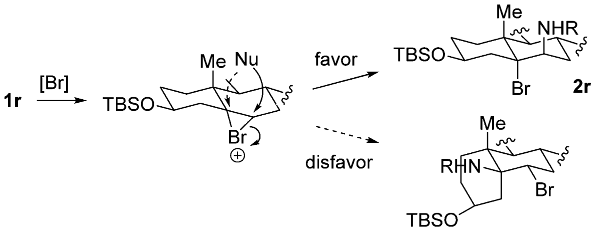
hindered α-face, followed by antiperiplanar attack by the sulfonamide to yield the more favorable **2r**.



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