Copper-Catalyzed Regioselective Aminothiolation of Alkenes with *N*-Fluorobenzenesulfonimide and Thiols through Three-Component Radical Coupling

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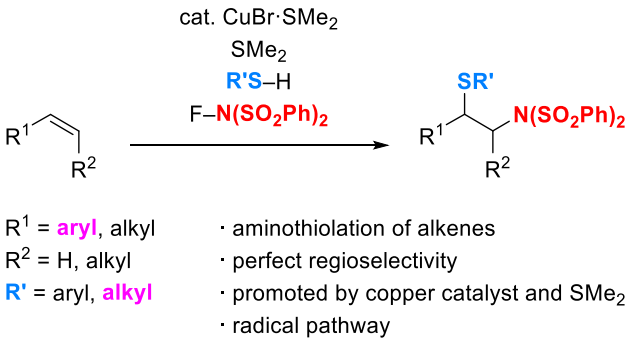


Abstract: Copper-catalyzed regioselective aminothiolation of terminal and internal alkenes with *N*-fluorobenzenesulfonimide and thiols has been developed. The three-component reaction is promoted by the addition of dimethyl sulfide. In addition to aromatic alkenes, aliphatic alkenes are subjected to the reaction, affording various aminothiolation adducts as single regioisomers. The reaction of internal alkenes proceeds with a high diastereoselectivity. The radical process is proposed by preliminary mechanistic studies, involving radical trap and radical clock experiments.

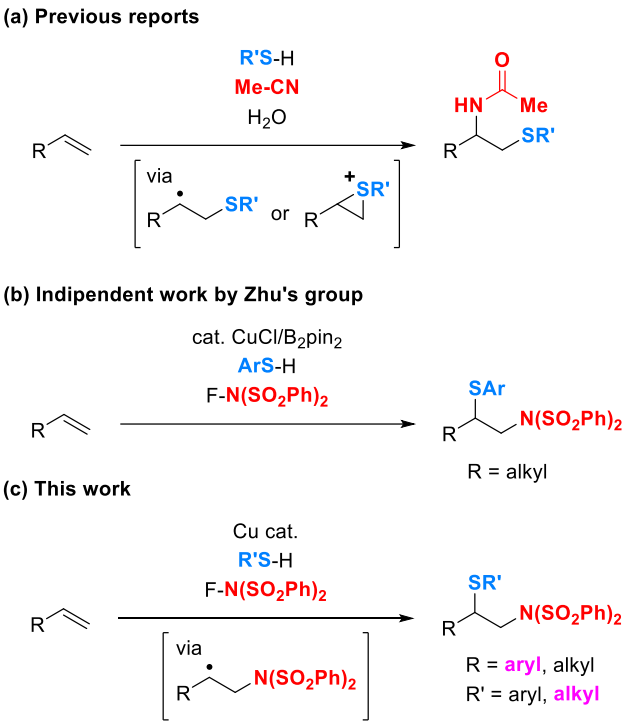
Introduction

Sulfur-containing alkaloids are one of the most important motifs in organic chemistry, most of which show significant bioactive properties.[1] Aminothiolation of alkenes represents the direct synthetic method of 2-aminoalkyl sulfides, in which two different functionalities can be installed simultaneously. This transformation has been realized by the reaction of alkenes with thiols in acetonitrile under oxidative reaction conditions (Scheme 1a).[2] The reaction proceeds with a high regioselectivity through the formation of a sulfur-centered radical or a thiiranium intermediate followed by Ritter-type reaction with the nitrile. Recently, the similar aminothiolation with nitrogen nucleophiles has also been reported.[3,4] Although these reactions provided the corresponding adducts bearing an amino group at the α-position and a sulfenyl group at the β-position, respectively, aminothiolation with the reverse regioselectivity has yet to be well documented. We reasoned that the reaction initiated by the addition of a nitrogen-centered radical to an alkene can provide the aminothiolation adduct with a reverse regioselectivity.

In order to design the desired reaction, we selected *N*-fluorobenzenesulfonimide (NFSI) as a nitrogen-centered radical precursor.[5] It should be noted that a sulfonimide moiety can readily be transformed after the reaction.[6] Thereby, NFSI can be considered as a formal amination reagent. Recently, vicinal difunctionalization of alkenes with NFSI has been well developed by several research groups,[7a–k] as well as our group.[7l] During the course of our studies, we also focused on the development of highly efficient catalytic carbon–sulfur bond formation reactions.[8] Recently, the related aminothiolation was independently reported by Zhu's group (Scheme 1b),[9] where the reaction of aliphatic terminal alkenes gave the corresponding products in good yields, but the reaction of internal alkenes gave poor results. Furthermore, in a sharp contrast to our work, styrene could not be applied in the reaction. We herein report unprecedented copper-catalyzed aminothiolation of alkenes with NFSI and thiols in an opposite regioselective manner (Scheme 1c). The addition of a copper catalyst and dimethyl sulfide efficiently promoted the three-component reaction, giving the adducts substituted by an amino group at the β-

position and a sulfenyl group at the α-position, respectively. Notably, aromatic alkenes as well as aliphatic alkenes smoothly underwent the desired aminothiolation.

Scheme 1. Aminothiolation of Alkenes

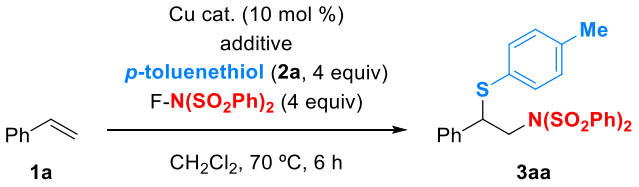


Results and Discussion

First, we commenced optimizing the reaction of styrene (**1a**) with *p*-toluenethiol (**2a**) and NFSI (Table 1). When CuBr was used as the catalyst, the desired aminothiolation proceeds with a perfect regioselectivity to give the target product **3aa** in 18% yield as a sole product (entry 1). The structure of **3aa** was unambiguously confirmed by X-ray diffraction analysis.[10] To our delight, the addition of dimethyl sulfide was found to be effective (entry 2). The product yield was improved when the loading amount of dimethyl sulfide was increased (entry 3). However, the reaction with diphenyl sulfide gave an inferior result (entry 4). Moreover, commercially available CuBr•SMe_2 complex also gave a comparable result (entry 5). After the further optimization of reaction conditions (entries 6 and 7), **3aa** was obtained in 89% isolated yield when CuBr•SMe_2 catalyst was used with 1.5 equiv of dimethyl

sulfide (entry 7).[11] It is of note that even in the absence of copper catalyst, the same product **3aa** was obtained in 41% yield (entry 8). On the other hand, the reaction without the copper catalyst and dimethyl sulfide provided **3aa** in a low yield (entry 9).

Table 1. Aminothiolation of Styrene (**1a**) with *N*-Fluorobenzenesulfonimide and *p*-Toluenethiol (**2a**)[a]



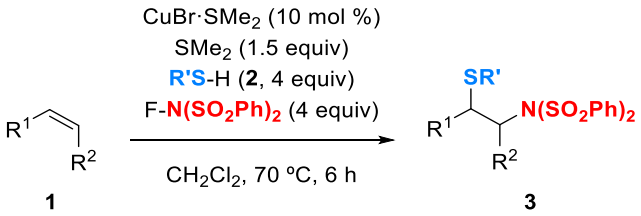
entry	Cu cat.	additive (equiv)	yield (%)[b]
1	CuBr	none	18
2	CuBr	SMe_2 (0.1)	75
3	CuBr	SMe_2 (1)	84
4	CuBr	SPh_2 (1)	66
5	CuBr•SMe_2	none	72
6	CuBr•SMe_2	SMe_2 (1)	93
7	CuBr•SMe_2	SMe_2 (1.5)	99 (89)
8[c]	none	SMe_2 (1.5)	41
9[c]	none	none	13

[a]Reactions were carried out with **1a** (0.2 mmol), **2a** (0.8 mmol), *N*-fluorobenzenesulfonimide (0.8 mmol), Cu cat. (0.02 mmol), and additive in CH_2Cl_2 (0.5 mL) at 70 °C for 6 h. [b]Determined by ^{1}H NMR. An isolated yield is given in parentheses. [c]Conducted with new apparatuses to exclude the contamination of any trace amount of copper salts.

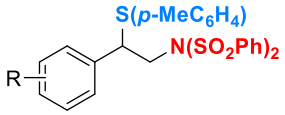
We next investigated the substrate scope in regioselective aminothiolation of alkenes **1** with thiols **2** and NFSI (Scheme 2). The reaction of styrenes bearing electron-rich and -deficient functional groups gave the corresponding products **3ba**–**3ha** in good yields. In addition, bromo and chloro functionalities were tolerated under the reaction conditions. The reaction of aliphatic alkenes **1j**–**1l** also provided the

desired adducts **3ja**–**3la** in good yields although the reaction of allylbenzene without a copper catalyst resulted in a low yield. Moreover, when cyclooctene was used, the diastereoselective aminothiolation proceeded to afford the single diastereomer **3ma** in 63% yield. The *anti*-configuration of **3ma** was determined by NOESY analysis.[12] The reaction of unsymmetrical internal alkenes such as indene and *β*-methylstyrene only gave the products in modest yields.[13] With respect to scope of thiols **2**, various arenethiols were applicable to the present aminothiolation. Regardless of the electronic and steric properties of thiols employed, the corresponding products **3ab**–**3ae** were obtained in good yields. The reactions with alkanethiols also gave the corresponding products **3af** and **3ag** in moderate yields.

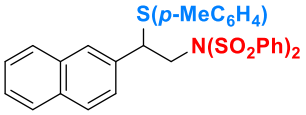
Scheme 2. Substrate Scope[a]



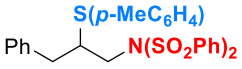
Scope of Alkenes



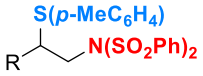
R = *p*-Me (**3ba**): 59%
m-OMe (**3ca**): 88%
p-CF_3 (**3da**): 68%
m-CF_3 (**3ea**): 76%
p-Cl (**3fa**): 80%
p-Br (**3ga**): 71%
o-Cl (**3ha**): 67%



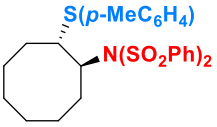
3ia
57%



3ja
93%
13% (w/o Cu cat.[b])

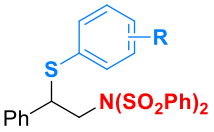


R = $^{n}C_8H_{17}$ (**3ka**): 97%
^{t}Bu (**3la**): 83%



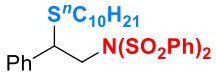
3ma
63%
(single diasteromer)

Scope of Thiols



R = H (**3ab**): 78%
p-OMe (**3ac**): 96%
p-Cl (**3ad**): 66%
o-Me (**3ae**): 62%

3af
54%



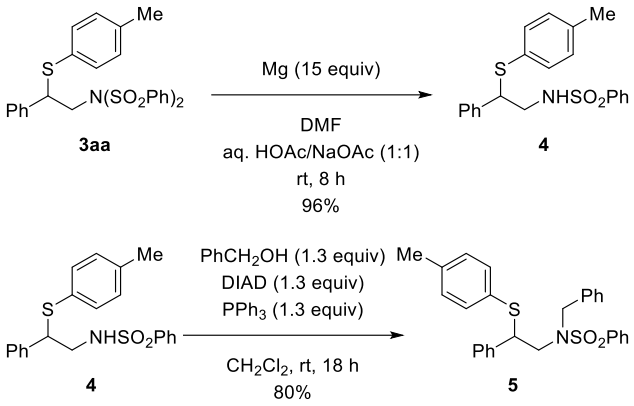
3ag
49%

[a]Reactions were carried out with **1** (0.2 mmol), **2** (0.8 mmol), *N*-fluorobenzenesulfonimide (0.8 mmol), CuBr•SMe_2 (0.02 mmol), and SMe_2 (0.3 mmol) in CH_2Cl_2 (0.5 mL) at 70 °C for 6 h. [b]Reactions were carried out with **1** (0.2 mmol), **2** (0.8 mmol), *N*-fluorobenzenesulfonimide (0.8 mmol), and SMe_2 (0.3 mmol) in CH_2Cl_2 (0.5 mL) at 70 °C for 6 h.

The present aminothiolation can be scalable in practical synthesis. The desired product **3aa** (710 mg) was obtained in 68% yield by simply performing the reaction on 10-fold scale (2 mmol). Furthermore, a sulfonyl moiety in **3aa** was readily removed by magnesium metal (Scheme 3).[14] The obtained sulfonamide **4** is known to be further transformed to a variety of potentially bioactive sulfur-containing

alkaloids. For example, treatment of **4** with benzyl alcohol in the presence of DIAD (diisopropyl azodicarboxylate) and triphenylphosphine afforded *N*-benzylated product **5**.[15]

Scheme 3. Transformation of Aminothiolation Adduct

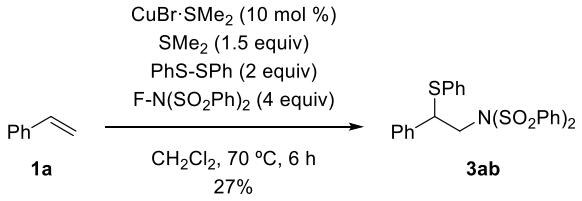


To gain mechanistic insights into the present aminothiolation, we investigated some control experiments (Scheme 4). Since the amination reagent NFSI is also known as an oxidant, thiols **2** might be oxidized to disulfides in the reaction. We then investigated the reaction with diphenyl disulfide instead of **2a**. As a result, the reaction only gave **3aa** in 27% yield (Scheme 4a), indicating that thiols might act as thiolating reagents in the reaction.[16] We next performed the radical trap experiments to confirm our hypothesis that the present aminothiolation proceeds through a radical process. The addition of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), completely suppressed the copper-catalyzed reaction (Scheme 4b). Since the reaction of **1a** proceeded even without a copper catalyst, the same investigation was performed under the copper-free conditions. As a result, the reactions did not proceed at all regardless of the presence or absence of dimethyl sulfide. These results imply that some radical species might be involved in any of these reactions, but the corresponding adduct of TEMPO could not be detected. We then investigated the radical clock experiments using *α*-cyclopropylstyrene (**1n**). As a result, the ring-opened adduct **3na** was obtained in 83% yield as a single product (Scheme 4c).[17] In addition, copper-free reactions also provided **3na** regardless of the presence

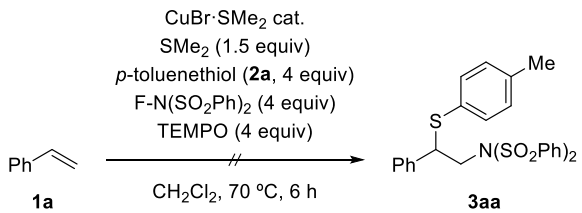
or absence of dimethyl sulfide. These results strongly suggest the formation of a benzyl radical as the intermediate.

Scheme 4. Mechanistic Studies

(a) Reaction with disulfide

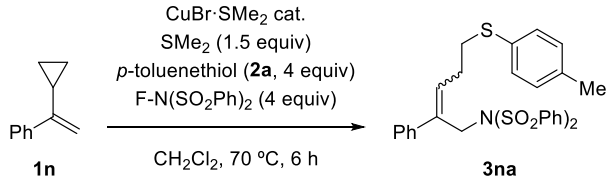


(b) Reactions in the presence of radical scavenger



entry	$CuBr{\cdot}SMe_2$ (mol %)	yield (%)
1	10	0
2	0	0

(c) Radical clock experiments

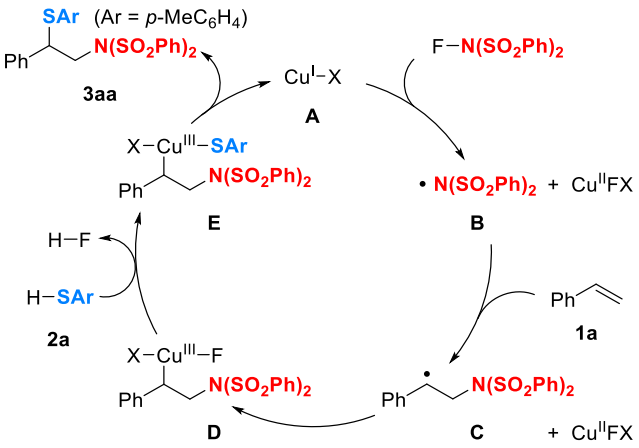


entry	$CuBr{\cdot}SMe_2$ (mol %)	yield (%)
1	10	83
2	0	29

Based on our obtained results and previous reports,[5,7] we proposed that the reaction proceeds as shown in Scheme 5. First, nitrogen-centered radical **B** is generated from single-electron transfer from copper(I) species **A** to NFSI. The detailed reaction mechanism of this step was revealed by DFT calculations.[18] The formed imidyl radical **B** adds at the less-hindered terminal position of **1a** to afford

the more stable benzyl radical intermediate **C**. After recombination of **C** with copper(II) gives benzylcopper(III) species **D**, ligand exchange with **2a** followed by reductive elimination provides **3aa** and regenerates the initial copper(I) species **A**. As an alternative pathway, the formation of a benzyl cation is also conceivable. Namely, single-electron transfer from benzyl radical **C** to copper(II) affords the corresponding benzyl cation, which reacts with thiol **2a** to give **3aa**.[19] The role of dimethyl sulfide and the reaction pathway without the copper catalyst are discussed in the Supporting Information.

Scheme 5. A Proposed Reaction Pathway with Copper Catalyst



Conclusions

In summary, we have developed copper-catalyzed regioselective aminothiolation of alkenes with NFSI and thiols. The three-component reaction proceeded with a perfect regioselectivity to afford the adducts as sole products with an unprecedented reverse regioselectivity. The addition of a copper catalyst and dimethyl sulfide promoted the reaction efficiently. Various alkenes, including terminal aromatic and aliphatic alkenes and internal alkenes, can be transformed to the corresponding aminothiolation adducts in good yields. Some control experiments revealed that the reaction proceeds through a radical pathway. Currently, additional mechanistic studies and further application of the newly developed aminothiolation is under investigation in our group.

Experimental Section

General. Glassware was dried in an oven (150 °C) and heated under reduced pressure before use. Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^1H and at 77.16 ppm for $^{13}C\{^1H\}$, respectively. The $^{19}F\{^1H\}$ NMR spectra were measured by using CCl_3F (δ = 0.00 ppm) as an external standard. The NMR yields were determined by ^1H NMR spectra with dibromomethane as an internal standard. HRMS analyses were obtained by using an ESI-TOF mass spectrometer and a double focusing magnetic sector fast atom bombardment (FAB) mass spectrometer.

Chemicals. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Alkene **1m** was prepared according to the literature[20] and showed the identical spectra reported.

A Typical Procedure for Copper-Catalyzed Regioselective Aminothiolation of Alkenes with *N*-Fluorobenzenesulfonimide and Thiols: Synthesis of *N*-[2-phenyl-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (**3aa**) is representative. Copper(I) bromide-dimethyl sulfide complex (4.1 mg, 0.02 mmol), *N*-fluorobenzenesulfonimide (252 mg, 0.8 mmol), and *p*-toluenethiol (99.4 mg, 0.8 mmol) were placed in a 10-mL glass pressure vial. Dichloromethane (0.5 mL) was then added at room temperature. After the resulting solution was stirred for 5 min, dimethyl sulfide (18.6 mg, 0.3 mmol) and styrene (20.8 mg, 0.2 mmol) were added to the mixture. The vial was flushed with argon and sealed with a PTFE screw cap. The mixture was stirred at 70 °C for 6 h. After the mixture was cooled to room temperature, the volatiles were evaporated. The resulting residue was purified by silica gel column chromatography (hexane/dichloromethane = 1:2) to provide **3aa** as white solid (93.4 mg, 0.178 mmol, 89%).

Characterization of Compounds.

***N*-[2-Phenyl-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3aa):** M.p. 156 °C. FT-IR (KBr, cm^{-1}): 1447 (m), 1371 (s), 1169 (s). ^1H NMR (300 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.55 (dd, J = 15.3, 4.2 Hz, 1H), 4.64 (dd, J = 15.3, 10.8 Hz, 1H), 4.81 (dd, J = 10.8, 4.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2 H), 7.27–7.46 (m, 15H), 7.50–7.56 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rt): δ 21.4, 51.8,

52.9, 128.3, 128.78, 128.81, 129.1, 129.4, 130.1, 130.4, 133.7, 134.4, 138.1, 138.4, 138.5. Anal. Calcd for $C_{27}H_{25}NO_4S_3$: C, 61.93; H, 4.81; N, 2.67%. Found: C, 61.83; H, 4.95; N, 2.65%.

***N*-(Phenylsulfonyl)-*N*-[2-(*p*-tolyl)-2-(*p*-tolylthio)ethyl]benzenesulfonamide (3ba):** The product **3ba** was obtained as white solid (63.4 mg, 0.118 mmol, 59%). M.p. 181 °C. IR (KBr): 1449 (m), 1369 (s), 1169 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.42 (s, 3H), 2.44 (s, 3H), 3.53 (dd, J = 15.3 Hz, 3.9 Hz, 1H), 4.61 (dd, J = 15.3, 10.8 Hz, 1H), 4.80 (dd, J = 10.8, 3.9 Hz, 1H), 7.15–7.22 (m, 4H), 7.29–7.37 (m, 10H), 7.46 (d, J = 8.1 Hz, 2H), 7.50–7.56 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, rt): δ 11.1, 21.4, 51.9, 52.5, 128.7, 128.8, 129.3, 129.7, 130.1, 130.6, 133.7, 134.3, 134.9, 138.1, 138.3, 138.6. HRMS (ESI+): Calcd for $C_{28}H_{27}NNaO_4S_3$: 560.1000. Found: 560.1005 $[M+Na]^+$.

***N*-[2-(*m*-Methoxyphenyl)-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ca):** The product **3ca** was obtained as white solid (97.5 mg, 0.176 mmol, 88%). M.p. 136 °C. IR (KBr): 1449 (m), 1369 (s), 1165 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.55 (dd, J = 15.3, 3.9 Hz, 1H), 3.77 (s, 3H), 4.62 (dd, J = 15.6, 10.8 Hz, 1H), 4.78 (dd, J = 10.8, 3.9 Hz, 1H), 6.89–6.92 (m, 2H), 7.02 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.28–7.47 (m, 11H), 7.50–7.56 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 21.4, 51.9, 52.9, 55.4, 114.1, 114.8, 121.5, 128.73, 128.75, 130.0, 130.1, 130.3, 133.7, 134.4, 138.4, 138.5, 139.5, 160.0. Anal. Calcd for $C_{28}H_{27}NO_5S_3$: C, 60.74; H, 4.92; N, 2.53%. Found: C, 60.40; H, 4.80; N, 2.49%.

***N*-(Phenylsulfonyl)-*N*-[2-(*p*-tolylthio)-2-{*p*-(trifluoromethyl)phenyl}ethyl]benzenesulfonamide (3da):** The product **3da** was obtained as white solid (80.8 mg, 0.137 mmol, 68%). M.p. 189 °C. IR (KBr): 1449 (m), 1373 (s), 1169 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.61 (dd, J = 15.6, 4.0 Hz, 1H), 4.62 (dd, J = 15.6, 10.8 Hz, 1H), 4.85 (dd, J = 10.8, 4.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.30–7.34 (m, 4H), 7.39–7.44 (m, 6H), 7.49–7.60 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt): δ 21.4, 51.8, 52.5, 124.2 (q, $^1J_{C–F}$ = 271 Hz), 125.9 (q, $^3J_{C–F}$ = 3.8 Hz), 128.6, 128.8, 129.5, 129.8, 130.2, 130.5 (q, $^2J_{C–F}$ = 32.2 Hz), 134.0, 134.5, 138.4, 138.9, 142.3; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, rt) δ –62.4. Anal. Calcd for $C_{28}H_{24}F_3NO_4S_3$: C, 56.84; H, 4.09; N, 2.37%. Found: C, 56.81; H, 3.85; N, 2.32%.

***N*-(Phenylsulfonyl)-*N*-[2-(*p*-tolylthio)-2-{*m*-(trifluoromethyl)phenyl}ethyl]benzenesulfonamide (3ea):** The product **3ea** was obtained as white solid (90.4 mg, 0.153 mmol, 76%). M.p. 149 °C. IR (KBr): 1447 (m), 1373 (s), 1169 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 2.43 (s, 3H), 3.67 (dd, J = 15.6, 4.4 Hz, 1H), 4.60 (dd, J = 15.6, 8.1 Hz, 1H), 4.81 (dd, J = 8.1, 4.4 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.31–7.48 (m, 11H), 7.54–7.61 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt): δ 21.4, 51.7, 52.5, 124.0 (q, $^{1}J_{C–F}$ = 271 Hz), 125.1 (q, $^{3}J_{C–F}$ = 3.8 Hz), 126.3 (q, $^{3}J_{C–F}$ = 3.6 Hz), 128.6, 128.9, 129.4 (2C), 130.2, 131.1 (q, $^{2}J_{C–F}$ = 32.6 Hz), 132.5, 133.9, 134.5, 138.5, 138.9, 139.1; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, rt) δ –62.5. Anal. Calcd for $C_{28}H_{24}F_3NO_4S_3$: C, 56.84; H, 4.09; N, 2.37%. Found: C, 56.82; H, 3.84; N, 2.31%.

***N*-[2-(*p*-Chlorophenyl)-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3fa)**: The product **3fa** was obtained as white solid (89.3 mg, 0.160 mmol, 80%). M.p. 161 °C. IR (KBr): 1449 (m), 1381 (s), 1167 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.54 (dd, J = 15.3, 4.2 Hz, 1H), 4.54 (dd, J = 15.3, 10.8 Hz, 1H), 4.77 (dd, J = 10.8, 4.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.28–7.44 (m, 14H), 7.53–7.59 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 21.4, 52.06, 52.13, 128.7, 128.8, 129.2, 129.8, 130.1, 130.7, 133.9, 134.2, 134.4, 136.6, 138.4, 138.7. Anal. Calcd for $C_{27}H_{24}ClNO_4S_3$: C, 58.11; H, 4.33; N, 2.51%. Found: C, 57.95; H, 4.06; N, 2.42%.

***N*-[2-(*p*-Bromophenyl)-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ga):** The product **3ga** was obtained as white solid (85.3 mg, 0.142 mmol, 71%). M.p. 179 °C. IR (KBr): 1449 (m), 1369 (s), 1167 (s). ^{1}H NMR (600 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.55 (dd, J = 15.6, 4.8 Hz, 1H), 4.54 (dd, J = 15.6, 10.8 Hz, 1H), 4.76 (dd, J = 10.8, 4.8 Hz, 1H), 7.20–7.25 (m, 4H), 7.34–7.36 (m, 4H), 7.41–7.44 (m, 8H), 7.55–7.58 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt): δ 21.4, 52.0, 52.2, 122.3, 128.6, 128.8, 129.8, 130.1, 131.0, 132.1, 133.8, 134.4, 137.1, 138.4, 138.6. Anal. Calcd for $C_{27}H_{24}BrNO_4S_3$: C, 53.82; H, 4.01; N, 2.32%. Found: C, 53.55; H, 3.82; N, 2.46%.

***N*-[2-(*o*-Chlorophenyl)-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ha):** The product **3ha** was obtained as white solid (150.5 mg, 0.270 mmol, 67%). M.p. 159 °C. IR (KBr): 1447 (m), 1373 (s), 1169 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.41 (s, 3H), 3.72 (dd, J = 15.6, 4.8 Hz, 1H),

4.61 (dd, J = 15.6, 10.2 Hz, 1H), 5.39 (brs, 1H), 7.18–7.27 (m, 4H), 7.31–7.42 (m, 8H), 7.50–7.57 (m, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt): δ 21.4, 48.6, 51.1, 127.3, 128.6, 128.9, 129.3, 129.9, 129.99, 130.02, 130.3, 133.8, 134.2, 134.9, 135.8, 138.5, 138.8. Anal. Calcd for $C_{27}H_{24}ClNO_4S_3$: C, 58.11; H, 4.33; N, 2.51%. Found: C, 57.93; H, 4.15; N, 2.43%.

***N*-[2-(2-Naphthyl)-2-(*p*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ia):** The product **3ia** was obtained as white solid (65.2 mg, 0.114 mmol, 57%). M.p. 144 °C. IR (KBr): 1449 (m), 1373 (s), 1169 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 2.44 (s, 3H), 3.62 (dd, J = 15.6, 4.0 Hz, 1H), 4.73 (dd, J = 15.6, 10.8 Hz, 1H), 4.99 (d, J = 10.8, 4.0 Hz, 1H), 7.02 (t, J = 7.6 Hz, 4H), 7.21–7.26 (m, 5H), 7.38 (t, J = 7.6 Hz, 2H), 7.48–7.62 (m, 6H), 7.72–7.74 (m, 2H), 7.88 (d, J = 8.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt): δ 21.4, 52.1, 53.2, 126.2, 126.45, 126.52, 127.8, 128.3, 128.5, 128.6, 128.9, 129.1, 130.1, 130.2, 133.3, 133.55, 133.62, 134.4, 135.3, 138.4, 138.5. HRMS (ESI+): Calcd for $C_{31}H_{27}NNaO_4S_3$: 596.1000. Found: 596.1003 $[M+Na]^+$.

***N*-[3-Phenyl-2-(*p*-tolylthio)propyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ja):** The product **3ja** was obtained as white solid (100.0 mg, 0.186 mmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.35 (s, 3H), 2.68 (dd, J = 14.4, 9.0 Hz, 1H), 3.01 (dd, J = 14.4, 5.1 Hz, 1H), 3.71–3.95 (m, 3H), 7.03–7.13 (m, 4H), 7.24–7.32 (m, 5H), 7.44–7.49 (m, 4H), 7.60–7.65 (m, 2H), 7.84–7.88 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt): δ 21.3, 38.4, 49.9, 52.2, 126.7, 128.5, 128.7, 129.1, 129.3, 129.9, 130.0, 133.1, 134.0, 137.8, 138.6, 139.1. Compound **3ja** was consistent with the literature data.[9]

***N*-(Phenylsulfonyl)-*N*-[2-(*p*-tolylthio)decyl]benzenesulfonamide (3ka):** The product **3ka** was obtained as white solid (108.2 mg, 0.193 mmol, 97%). M.p. 75 °C. IR (KBr): 1449 (m), 1381 (s), 1171 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 0.89–0.92 (m, 3H), 1.15–1.31 (m, 12H), 1.60–1.66 (m, 2H), 2.37 (s, 3H), 3.39–3.46 (m, 1H), 3.76 (dd, J = 15.2, 4.8 Hz, 1H), 3.87 (dd, J = 15.2, 10.4 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.47–7.51 (m, 4H), 7.61–7.65 (m, 2H), 7.88 (dd, J = 8.8, 1.6 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt): δ 14.3, 21.3, 22.8, 27.1, 29.4, 29.5, 29.6, 30.9, 32.0, 47.8, 53.2, 128.5, 129.1, 129.9, 130.2, 132.8, 134.0, 137.6, 139.5. Anal. Calcd for $C_{29}H_{37}NO_4S_3$: C, 62.22; H, 6.66; N, 2.50%. Found: C, 62.45; H, 6.86; N, 2.46%.

***N*-[3,3-Dimethyl-2-(*p*-tolylthio)butyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3la):** The product **3la** was obtained as white solid (83.5 mg, 0.166 mmol, 83%). M.p. 122 °C. IR (KBr): 1449 (m), 1371 (s), 1169 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 1.03 (s, 9H), 2.28 (s, 3H), 3.54 (dd, J = 11.1, 3.0 Hz, 1H), 3.78 (dd, J = 15.9, 3.0 Hz, 1H), 4.11 (dd, J = 15.9, 11.1 Hz, 1H), 6.96 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.42–7.47 (m, 4H), 7.54–7.60 (m, 2H), 8.14–8.17 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 21.1, 27.8, 36.7, 50.3, 62.2, 128.8, 129.3, 129.6, 130.7, 133.9, 134.3, 136.1, 139.2. Anal. Calcd for $C_{25}H_{29}NO_4S_3$: C, 59.62; H, 5.80; N, 2.78%. Found: C, 59.46; H, 5.74; N, 2.77%.

***trans*-*N*-(Phenylsulfonyl)-*N*-[2-(*p*-tolylthio)cyclooctyl]benzenesulfonamide (3ma):** The product **3ma** was obtained as white solid (66.8 mg, 0.126 mmol, 63%). M.p. 136 °C. IR (KBr): 1447 (m), 1371 (s), 1167 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 0.87–0.90 (m, 2H), 1.27–1.32 (m, 4H), 1.49–1.68 (m, 3H), 1.93–2.00 (m, 3H), 2.33 (s, 3H), 4.21–4.26 (m, 1H), 4.36–4.40 (m, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.18–7.21 (m, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.55–7.59 (m, 3H), 7.65–7.69 (m, 1H), 8.06–8.09 (m, 2H), 8.24–8.27 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt): δ 21.2, 22.6, 25.0, 25.9, 26.4, 29.2, 35.3, 51.1, 67.1, 128.6, 128.7, 129.22, 129.25, 129.9, 131.3, 131.9, 133.5, 134.3, 136.6, 138.8, 142.0. Anal. Calcd for $C_{27}H_{31}NO_4S_3$: C, 61.22; H, 5.90; N, 2.64%. Found: C, 61.13; H, 5.89; N, 2.62%.

***N*-[2-Phenyl-2-(phenylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ab):** The product **3ab** was obtained as white solid (79.5 mg, 0.156 mmol, 78%). M.p. 127 °C. IR (KBr): 1449 (m), 1373 (s), 1169 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 3.58 (dd, J = 15.6, 4.4 Hz, 1H), 4.64 (dd, J = 15.6, 10.8 Hz, 1H), 4.87 (dd, J = 10.8, 4.4 Hz, 1H), 7.29–7.33 (m, 5H), 7.36–7.44 (m, 11H), 7.51–7.60 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 51.9, 52.5, 128.1, 128.4, 128.7, 128.8, 129.0, 129.31, 129.34, 133.68, 133.72, 134.0, 137.9, 138.4. HRMS (ESI+): Calcd for $C_{26}H_{23}NNaO_4S_3$: 532.0687. Found: 532.0667 $[M+Na]^+$.

***N*-[2-{(*p*-Methoxyphenyl)thio}-2-phenylethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ac):** The product **3ac** was obtained as white solid (103.5 mg, 0.192 mmol, 96%). M.p. 121 °C. IR (KBr): 1449 (s), 1375 (m), 1169 (s). ^{1}H NMR (600 MHz, $CDCl_3$, rt): δ 3.56 (dd, J = 15.6, 4.2 Hz, 1H), 3.87 (s, 3H), 4.66 (dd, J = 15.6, 10.8 Hz, 1H), 4.76 (dd, J = 10.8, 4.2 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.30–7.43 (m,

13H), 7.49–7.54 (m, 4H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt): δ 51.7, 53.3, 55.6, 114.8, 124.3, 128.3, 128.73, 128.75, 129.0, 129.4, 133.7, 136.7, 138.0, 138.4, 160.2. HRMS (ESI+): Calcd for $C_{27}H_{25}NNaO_5S_3$: 562.0793. Found: 562.0783 $[M+Na]^+$.

***N*-[2-{(*p*-Chlorophenyl)thio}-2-phenylethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ad)**: The product **3ad** was obtained as white solid (71.6 mg, 0.132 mmol, 66%). M.p. 185 °C. IR (KBr): 1447 (m), 1371 (s), 1167 (s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 3.53 (dd, J = 15.6, 4.4 Hz, 1H), 4.60 (dd, J = 15.6, 10.4 Hz, 1H), 4.82 (dd, J = 10.4, 4.4 Hz, 1H), 7.33–7.46 (m, 17H), 7.55 (t, J = 7.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt): δ 51.8, 52.9, 128.5, 128.7, 128.9, 129.1, 129.4, 129.5, 132.5, 133.9, 134.5, 135.2, 137.6, 138.5. Anal. Calcd for $C_{26}H_{22}ClNO_4S_3$: C, 57.40; H, 4.08; N, 2.57%. Found: C, 57.44; H, 4.29; N, 2.43%.

***N*-[2-Phenyl-2-(*o*-tolylthio)ethyl]-*N*-(phenylsulfonyl)benzenesulfonamide (3ae):** The product **3ae** was obtained as white solid (64.8 mg, 0.124 mmol, 62%). M.p. 142 °C. IR (KBr): 1449 (m), 1375 (s), 1171 (s). ^{1}H NMR (600 MHz, $CDCl_3$, rt): δ 2.52 (s, 3H), 3.52 (dd, J = 15.0, 3.6 Hz, 1H), 4.70 (dd, J = 15.0, 11.4 Hz, 1H), 4.82 (dd, J = 11.4, 3.6 Hz, 1H), 7.25–7.35 (m, 11H), 7.39–7.41 (m, 3H), 7.47 (dd, J = 7.8, 1.8 Hz, 2H), 7.51–7.53 (m, 2H), 7.60 (d, J = 7.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt): δ 21.0, 51.7 (2C), 126.8, 128.4, 128.6, 128.7, 128.8, 129.1, 129.4, 130.9, 133.1, 133.7, 135.1, 138.0, 138.4, 141.9. Anal. Calcd for $C_{27}H_{25}NO_4S_3$: C, 61.93; H, 4.81; N, 2.67%. Found: C, 61.99; H, 4.85; N, 2.37%.

***N*-(2-Benzylthio-2-phenylethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (3af):** The product **3af** was obtained as a colorless liquid (56.6 mg, 0.108 mmol, 54%). IR (KBr): 1449 (m), 1377 (s), 1169 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 3.51 (d, J = 13.5 Hz, 1H), 3.64 (d, J = 13.5 Hz, 1H), 3.83–3.94 (m, 1H), 4.27–4.38 (m, 2H), 7.23–7.35 (m, 10H), 7.40–7.46 (m, 4H), 7.57–7.63 (m, 2H), 7.72 (dd, J = 8.4, 1.2 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, rt): δ 36.2, 49.1, 52.7, 127.3, 128.0, 128.6, 128.7, 128.9, 129.0 (2C), 129.1, 133.9, 137.9, 139.0, 139.2. HRMS (ESI+): Calcd for $C_{27}H_{25}NNaO_4S_3$: 546.0843. Found: 546.0844 $[M+Na]^+$.

***N*-(2-Decylthio-2-phenylethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (3ag):** The product **3ag** was obtained as a colorless liquid (55.8 mg, 0.0972 mmol, 49%). IR (KBr): 1449 (m), 1377 (s), 1169

(s). ^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 0.88 (t, J = 6.8 Hz, 3H), 1.23–1.30 (m, 14H), 1.44–1.51 (m, 2H), 2.29–2.41 (m, 2H), 3.87 (q, J = 10.0 Hz, 1H), 4.33–4.40 (m, 2H), 7.31 (s, 5H), 7.46 (t, J = 7.6 Hz, 4H), 7.61 (t, J = 7.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 14.2, 22.8, 28.9, 29.3, 29.4, 29.5, 29.6, 29.7, 32.0 (2C), 49.4, 52.8, 127.9, 128.7, 128.8, 128.9, 129.0, 133.9, 139.2, 139.5. Anal. Calcd for $C_{30}H_{39}NO_4S_3$: C, 62.79; H, 6.85; N, 2.44%. Found: C, 62.92; H, 7.01; N, 2.43%.

***N*-[2-Phenyl-5-(*p*-tolylthio)pent-2-en-1-yl]-*N*-(phenylsulfonyl)benzenesulfonamide (3na):** A 5:1 mixture of (*Z*/*E*)-isomers **3na** was obtained as a brown liquid (94.0 mg, 0.167 mmol, 83%). IR (KBr): 1449 (m), 1377 (s), 1169 (s). Anal. Calcd for $C_{30}H_{29}NO_4S_3$: C, 63.92; H, 5.19; N, 2.48%. Found: C, 64.27; H, 5.20; N, 2.54%.

(*Z*)-**3na**: ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.32 (s, 3H), 2.50 (dd, J = 15.9, 7.8 Hz, 2H), 3.73 (dd, J = 10.2, 6.0 Hz, 2H), 3.91 (s, 2H), 5.75 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.28–7.36 (m, 4H), 7.40–7.43 (m, 3H), 7.47–7.54 (m, 4H), 7.58–7.66 (m, 2H), 8.01–8.04 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 21.23, 29.7, 35.0, 48.4, 126.4, 126.7, 127.63, 128.3, 128.52, 129.24, 129.8, 131.4, 132.5, 134.0, 137.0, 138.3, 139.9, 141.1.

(*E*)-**3na**: ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.22 (dd, J = 16.5, 7.8 Hz, 2H), 2.29 (s, 3H), 3.47–3.53 (m, 2H), 3.73 (s, 2H), 5.31 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.28–7.36 (m, 4H), 7.40–7.43 (m, 3H), 7.47–7.54 (m, 4H), 7.58–7.66 (m, 2H), 7.86–7.88 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt): δ 21.17, 29.9, 43.9, 48.6, 125.1, 127.55, 128.1, 128.49, 128.6, 129.15, 129.7, 131.7, 132.1, 133.9, 136.8, 138.9, 139.5, 140.0.

Desulfonylation of 3aa:[14] **Synthesis of *N*-[2-Phenyl-2-(*p*-tolylthio)ethyl]benzenesulfonamide (4)** [CAS: 881601-66-7]**:** Under an atmosphere of argon, compound **3aa** (471 mg, 0.9 mmol) was placed in a 50-mL Schlenk tube. DMF (15 mL) and HOAc/NaOAc (1:1) buffer solution (8 M, 7.2 mL) were added. Magnesium turning (328 mg, 13.5 mmol) was added to the mixtures in portions. After being stirred at room temperature for 8 h, the reaction mixture was poured to water (40 mL) and extracted with diethyl ether (30 mL × 3). The combined organic layers were dried over sodium sulfate and

evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (chloroform) to provide **4** as yellow solid (331.6 mg, 0.865 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 2.32 (s, 3H), 3.35–3.39 (m, 2H), 4.04 (t, J = 7.2 Hz, 1H), 4.74–4.80 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.07–7.11 (m, 4H), 7.25–7.29 (m, 3H), 7.49 (t, J = 8.0 Hz, 2H), 7.58–7.61 (m, 1H), 7.75 (dd, J = 8.0, 1.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt): δ 21.2, 47.0, 52.8, 127.0, 127.9, 128.0, 128.8, 129.1, 129.2, 129.8, 132.7, 133.4, 138.1, 138.3, 139.8.

Benzylation of 4:[15] **Synthesis of *N*-Benzyl-*N*-[2-Phenyl-2-(*p*-tolylthio)ethyl]benzenesulfonamide (5):** Under an atmosphere of argon, benzyl alcohol (56.2 mg, 0.52 mmol) was dissolved in dichloromethane (3 mL) in a 20-mL Schlenk tube. Compound **4** (153.4 mg, 0.4 mmol) and triphenylphosphine (136.4 mg, 0.52 mmol) were added to the solution. Diisopropyl azodicarboxylate (1.9 M toluene solution, 274 μL, 0.52 mmol) was added to the mixtures at 0 ℃. After being stirred at room temperature for 18 h, the reaction mixture was poured to saturated aqueous sodium hydrogen carbonate solution (5 mL) and extracted with dichloromethane (5 mL × 3). The combined organic layers were dried over sodium sulfate and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 8:1) to provide **5** as a red liquid (152.0 mg, 0.321 mmol, 80%).

IR (neat): 1447 (m), 1341 (s), 1159 (s). ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ 2.35 (s, 3H), 3.49 (dd, J = 14.7, 9.9 Hz, 1H), 3.60 (dd, J = 14.7, 5.4 Hz, 1H), 3.84 (d, J = 15.0 Hz, 1H), 4.27 (d, J = 15.0 Hz, 1H), 4.34 (dd, J = 9.9, 5.4 Hz, 1H), 6.92 (d, J = 7.5 Hz, 2H), 7.05–7.10 (m, 4H), 7.16–7.25 (m, 8H), 7.42 (t, J = 7.5 Hz, 2H), 7.54–7.61 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, rt): δ 21.3, 52.17, 52.23, 52.8, 127.4, 127.80, 127.83, 128.2, 128.4, 128.6, 128.7, 129.1, 129.8, 130.5, 132.6, 132.9, 135.6, 137.7, 139.0, 139.7. HRMS (FAB+): Calcd for $C_{28}H_{28}NO_2S_2$: 474.1561. Found: 474.1547 $[M+H]^+$.

Associated Content

Supporting Information Available.

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

More detailed results of copper-catalyzed reactions and ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra for products (PDF)

X-ray crystallographic data (CIF)

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Notes.

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