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Synthesis of Benzofused Five-Ring Sultams via Rh-Catalyzed C−H Olefination Directed by an *N*-Ac-Substituted Sulfonamide Group

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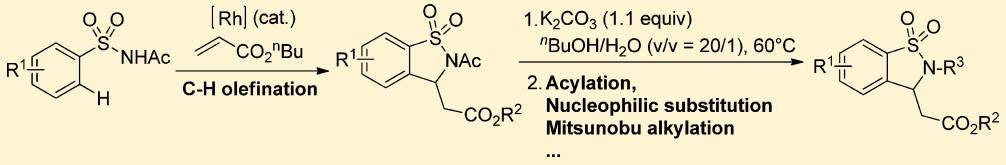
Supporting Information



ABSTRACT: A Rh-catalyzed *N*-Ac-sulfonamide group directed C−H olefination−cyclization to afford benzofused five-ring sultam is described with high yield and a wide range of substrate scope. The *N*-acetyl group is a key for this transformation implying that N−H acidity is the major influence. The acetyl group is removed under mild conditions in excellent yield to provide *NH*-free sultam that can be transformed into various benzofused five-ring sultam analogues via acylation, nucleophilic substitution, and Mitsunobu alkylation.

INTRODUCTION

In the process of drug research, a satisfactory protocol to look for lead compounds was identified to be basic and essential. Furthermore, to build up diverse drug-like compound libraries rapidly, an effective synthetic method of privileged-structures combined with advanced high-throughput screening will facilitate drug discovery. A benzofused five-ring sultam was found in many biologically active compounds such as selective CRTh2 antagonists, human leukocyte elastase inhibitors, active saccharin, and 5-HT2 receptor antagonists[1] (Figure 1); therefore, it acts as an important privileged structure in drug discovery. Synthetic methods of benzofused five-ring sultam were reported only in a few articles until recently. In 2008, Hanson and co-workers reported a cascade reaction to synthesize the benzofused five-ring sultam in a parallel approach from 2-bromobenzenesulfonamide via a Heck reaction (Scheme 1, eq 1).[2]

In previous study, we first reported a Rh-catalyzed *ortho* C−H olefination of arenas directed by a sulfonic acid group to afford olefinated products, and then the corresponding benzofused five-ring sultam was prepared smoothly via a multistep approach from this 2-olefinated benzenesulfonic acid (Scheme 1, eq 2).[3] This method was limited by a difficult preparation of sulfonamide via sulfonyl chloride imtermediate. In order to improve synthetic efficiency, we assumed that the synthesis of benzofused five-ring sultam could be achieved by a sulfonamide group's direction via an *ortho* C−H olefination in one pot. Herein, we describe an effective Rh-catalyzed *ortho* C−H olefination[4] directed by an *N*-Ac-sulfonamide group[5] to afford benzofused five-ring sultams directly with good yields and a range of substrate scopes.[6,7]

RESULTS AND DISCUSSION

Initially, 2-*N*-Ac-substituted 2-methylbenzenesulfonamide was selected as a model substrate for exploiting this Rh-catalyzed C−H activation in DMF at 100 °C. Fortunately, 79% yield of the desired product was gained as expected when $Cu(OAc)_2$ was used as an oxidant (Table 1, entry 1). Investigation of solvents proved that toluene was ideal that the isolated yield reached 90% in comparison to DMF, 1,4-dioxane, and xylene (Table 1, entries 1−4). This Rh-catalyzed reaction showed great dependence on oxidants obviously. The use of AgOAc led to a slightly lower yield (Table 1, entry 5), and no desired sultam was detected by LC−MS analysis when O_2 or BQ were used as oxidants (Table 1, entries 6 and 7). Catalyst screening showed that only $[RhCp^*Cl_2]_2$ gave a satisfactory result, and $[Rh(OAc)_2]_2$, $[Rh(CO)Cl]_2$m and $Rh(NH_4)_3Cl_6$ were not effective (Table 1, entries 8−10).

Under optimal conditions, we investigated the replacement (R^1) of the 2-*N*-Ac-substituted group considering acidic influence on the N−H bond for C−H activation and further cyclization (Table 1). A lower yield (31%) was obtained when R^1 was hydrogen substituted (entry 14), implying that the N−H acidity was important. Further, *N*-methylated or *N*-phenylated derivatives resulted in no desired product at all. These observations indicated that the acidity of N−H (entries 15 and 16) contributed significantly. To further understand this process, acetyl (entry 3), methyloxycarbonyl (entry 12), trifluoroacetyl (entry 13), and Boc group (entry 11) were introduced. The yields were 90%, 52%, 0%, and 0%, respectively.

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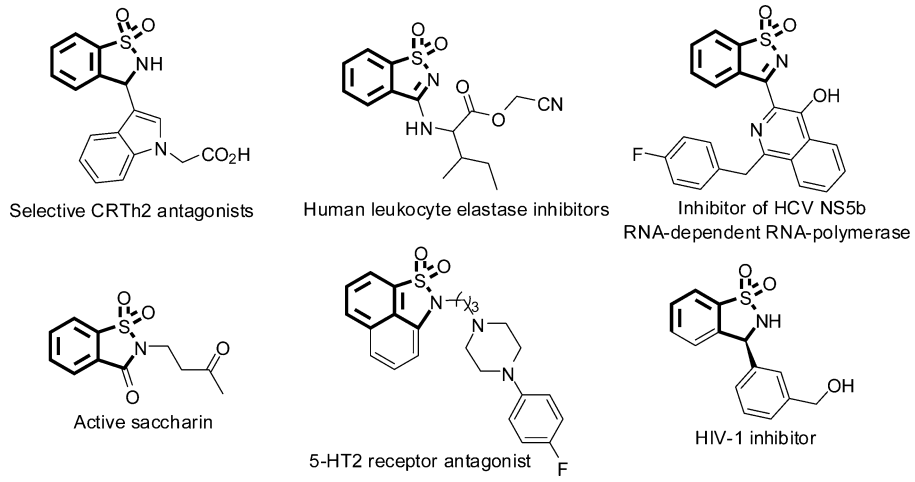
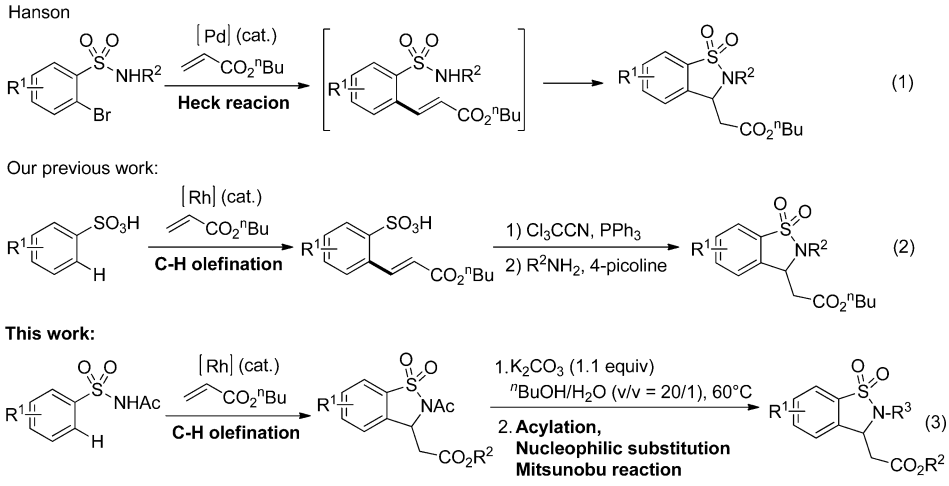


Figure 1. Active benzofused five-ring sultam analogues.

Scheme 1. Synthetic Methods of Benzofused Five-Ring Sultams



The scope of benzene substitution (R^2) is outlined in Table 2. All tested substituents were tolerant in these transformations; i.e., all electron-rich or electron-poor substitutions on both *ortho* and *meta* positions gave good yields (compounds **1**−**10**). It should be noted that, regardless of the electron-rich or electron-poor substitution introduced, *para*-substituted benzenesulfonamide also resulted in a 2-olefinated benzofused five-ring sultam in excellent yield when the amount of butyl acrylate was slightly improved to 2.5 equiv, such as compounds **11** and **12**. To our delight, multisubstituted substrates were able to offer the desired benzofused five-ring sultams (**4**−**10**) via this C−H activation by *N*-Ac-sulfonamide direction. Some electron-withdrawing functional groups such as NO_2 and CN were investigated, but no desired olefination−Michael addition occurred.

Under the optimal conditions, we continuously investigated various *α*,*β*-unsaturated carbonyl reagents (R^3). Acrylic acid esters were proved to be ideal substrates (Table 3), whereby all esters used, including benzyl (**13**), tetrahydrofurfuryl (**14**), tert-butyl (**15**), and methyl (**16**) esters, were conveniently tolerated in these transformations. The use of ethyl vinyl ketone (**17**) in this reaction gave a moderate yield because a noncyclic olefinated side product (**17′**) was observed in 46% yield. Lastly, acrylamides derivatives (**18**−**21**) worked well in this method. All of the above results illustrated that this new *N*-Ac-sulfonamide-directed C−H activation was very effective in synthesizing benzofused five-ring sultams with high substituent scopes.

As expected, the *N*-Ac group was easily removed under 1.1 equiv of K_2CO_3 in a solvent mixture of *n*-butyl alcohol and water (v/v = 20:1) at 60 °C for 5 h that provided **22** (Scheme 2). Compound **22** was further used for acylation, nucleophilic substitution, and Mitsunobu alkylation (Table 4). *N*-Methyl (**23**), *N*-benzyl (**24**), and *N*-allyl (**25**) products were gained by nucleophilic substitution, respectively, with 80%, 86%, and 85% yields in DMF at room temperature when 1.5 equiv of methyl iodide, benzyl bromide, and allyl bromide were used. When 4-fluorobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, and methanesulfonyl chloride were employed for acylation, products of acylation (**26**, **27**, and **28**) were prepared with 83%, 77%, and 84% yields. *N*-Ethyl (**30**) or *N*-butyl product (**31**)

Scheme 2. Removal of *N*-Ac Group

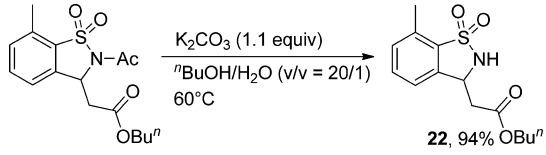


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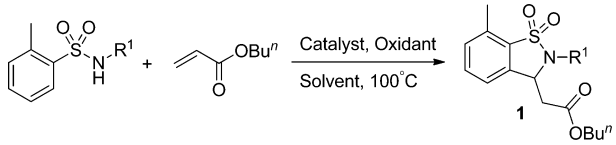
Table 1. Rh-Catalyzed C−H Olefination of *N*-Ac-Substituted Benzenesulfonamide Analogues with Butyl Acrylate To Afford Benzofused Five-Ring Sultam[a]



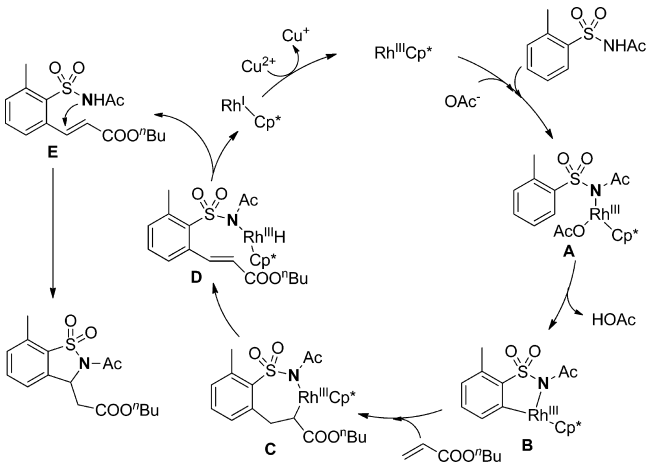
entry	R	[Rh]	oxidant	solvent	yield[b] (%)
1	Ac	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DMF	79
2	Ac	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	1,4-dioxane	71
3	**Ac**	$\mathbf{[RhCp^*Cl_2]_2}$	$\mathbf{Cu(OAc)_2}$	**toluene**	**90**
4	Ac	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	xylene	88
5	Ac	$[RhCp^*Cl_2]_2$	AgOAc	toluene	80
6	Ac	$[RhCp^*Cl_2]_2$	O_2	toluene	0
7	Ac	$[RhCp^*Cl_2]_2$	BQ	toluene	0
8	Ac	$[Rh(CO)Cl]_2$	$Cu(OAc)_2$	toluene	5
9	Ac	$[Rh(OAc)_2]_2$	$Cu(OAc)_2$	toluene	0
10	Ac	$Rh(NH_4)_3Cl_6$	$Cu(OAc)_2$	toluene	0
11	Boc	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	0
12	methoxycarbonyl	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	52
13	trifluoroacetyl	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	0
14	H	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	31
15	CH_3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	0
16	Ph	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	0

[a]Reaction conditions: N-substituted 2-methylbenzenesulfonamide (0.5 mmol), butyl acrylate (2.0 equiv), Rh catalyst (2.5 mol %), oxidant (2.0 equiv), solvent (2.0 mL), 100 °C. [b]Isolated yield.

was obtained with excellent yields via Mitsunobu reaction in the presence of DEAD, PPh_3, and corresponding alcohol. Interestingly, ethoxycarbonation occurred to afford compound **29** with an excellent yield without alcohol. Compound **22** could also transform to *N*-olefinated product (**32**) in 98% yield via Michael addition with ethyl propiolate.

A proposed mechanism was described in Scheme 3. Introducing an *N*-Ac group increased the acidity of N−H bond, which promoted the formation of intermediate **A** assisted by OAc^-. Then *ortho* deprotonation generated intermediate **B**. Subsequent coordination with alkene followed by 1,2-migratory insertion occurred to give intermediate **C**. *β*-H elimination of intermediate **C** gave the intermediate **D**, which underwent reductive elimination to provided olefinated product **E** and Rh(I). Finally, Michael addition resulted in the desired sultam under the current neutral conditions and 100 °C temperature,[8] and Rh(I) was oxidized to form Rh(III) via Cu(II) for the next catalytic cycle.

Scheme 3. Proposed Mechanism of Benzofused Five-Ring Sultam Formation



CONCLUSION

In summary, a new and efficient synthesis of benzofused five-ring sultam was described in this paper. Broad substrate scopes and good yields made this method more effective to synthesize sultam analogues. This tandem process of *ortho* C−H olefination/intramolecular Michael addition was very smooth, which allowed introduction of various substituents of benzofused five-ring sultams. Obviously, the acetyl group was the key for this transformation, implying that N−H acidity played a major influence. The acetyl group was removed easily under mild conditions to generate an *N*-free sultam. *N*-Free sultam derivations were performed via acylation, nucleophilic substitution, and Mitsunobu alkylation. Impressively, a diverse library of benzofused five-ring sultam analogues could be built rapidly by this new method, which would benefit from pharmacological activity screening in sultam drug discovery.

EXPERIMENTAL SECTION

General Procedure for Rh-Catalyzed Olefination of *N*-Ac-Substituted Benzenesulfonamide and Butyl Acrylate. A 10 mL sealed tube equipped with a magnetic stir bar was charged with $[RhCp^*Cl_2]_2$ (7.7 mg, 2.5 mol %), $Cu(OAc)_2$ (181 mg, 1.0 mmol), *N*-Ac-substituted 2-methylbenzenesulfonamide (107 mg, 0.5 mmol), and 2.0 mL of toluene. The mixture was stirred, and then butyl acrylate (1 mmol) was added. The reaction tube was capped and stirred at 100 °C. The reaction was monitored by LC−MS. When the starting material was consumed completely, solvent was removed under vacuum. The reaction mixture was diluted with ethyl acetate and then washed with 2 N HCl aqueous solution (2 × 20 mL). Subsequently, the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (20 mL) and then dried over anhydrous sodium sulfate. The organic solvent was

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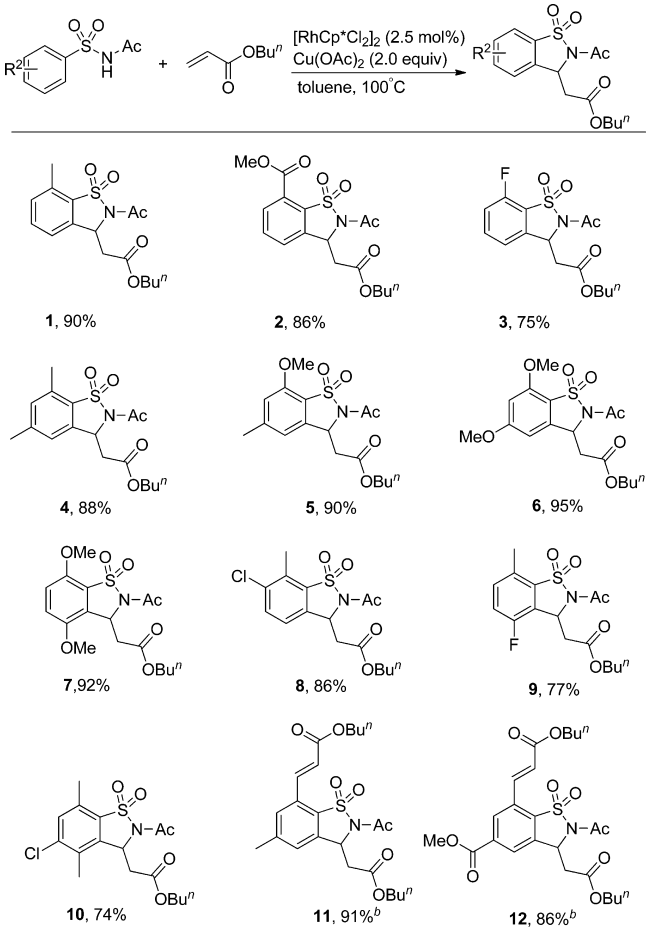
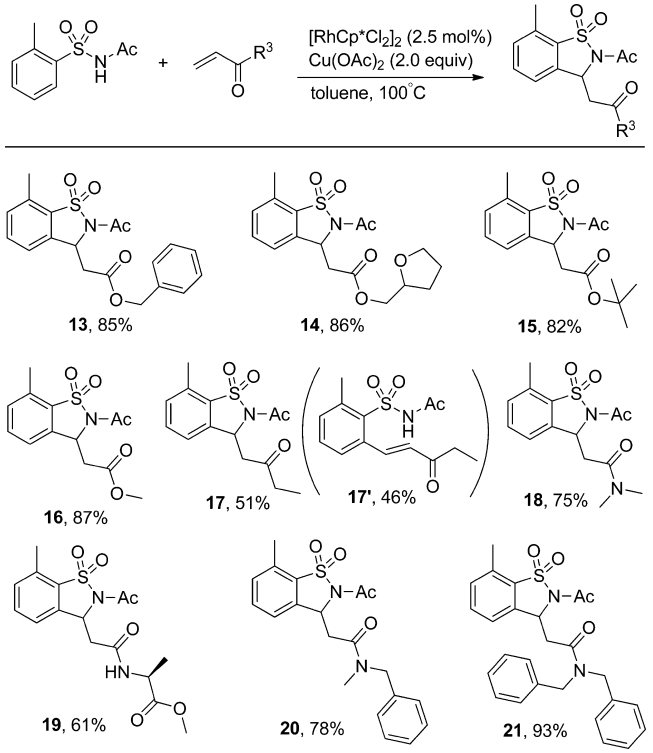
Table 2. Benzene Ring's Scope (R^2) for Synthesis of Benzofused Five-Ring Sultams[a]



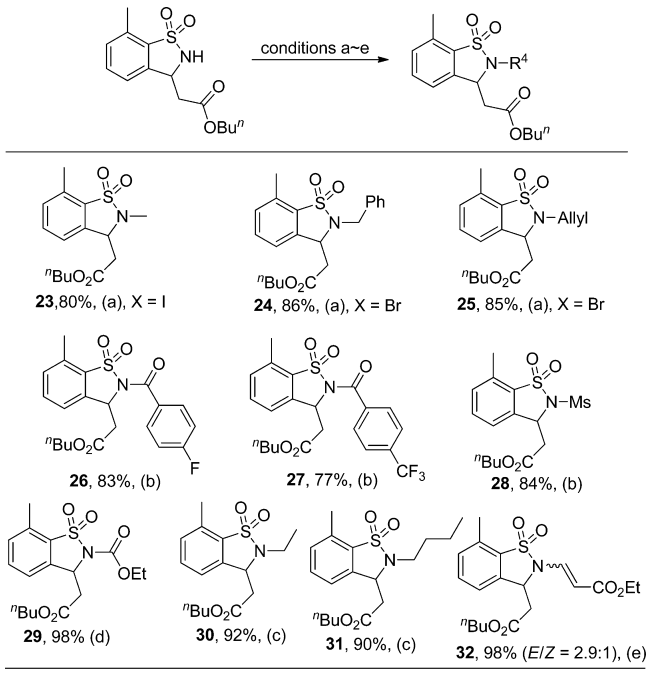
[a]Reaction conditions: *N*-Ac-benzenesulfonamide derivatives (0.5 mmol), butyl acrylate (2.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (2.0 equiv), toluene (2.0 mL), 100 °C. [b]2.5 equiv of butyl acrylate was used. Isolated yield.

Table 3. α,β-Unsaturated Carbonyl Reagent Scope (R^3) for Synthesis of Benzofused Five-Ring Sultams[a]



[a]Reaction conditions: *N*-Ac-2-methylbenzenesulfonamide (0.5 mmol), α,β-unsaturated carbonyl reagents (2.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (2.0 equiv), toluene (2.0 mL), 100 °C. Isolated yield.

Table 4. Diversity Investigation of Compound 22[a]



[a]Conditions (a) K_2CO_3, R-X, DMF, rt; (b) Et_3N, RCO(Cl) or MsCl, dichloromethane, rt; (c) DEAD, PPh_3, ROH, THF, rt; (d) DEAD, PPh_3, THF, rt; (e) *N*-methylmorpholine, ethyl propiolate, dichloromethane, rt.

removed on a rotary evaporator in vacuo. The residue was purified by preparative TLC on silica gel (EtOAc/petroleum ether = 1:5, R_f = 0.3) to afford **1** 153 mg (90% yield) as a white powder.

*Compound **1** (153 mg, 90% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.7 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 5.68 (dd, J = 7.7 Hz, 3.2 Hz, 1H), 4.08 (t, J = 6.7 Hz, 2H), 3.15 (dd, J = 15.9 Hz, 3.3 Hz, 1H), 2.92 (dd, J = 15.9 Hz, 7.8 Hz, 1H), 2.66 (s, 3H), 2.62 (s, 3H), 1.58−1.51 (m, 2H), 1.33−1.24 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 167.7, 135.4, 135.0, 134.3, 132.3, 131.6, 122.2, 65.1, 55.1, 39.4, 30.6, 23.8, 19.2, 17.1, 13.8. HRMS (ESI): m/z (M + Na^+) calcd for $C_{16}H_{21}O_5NNaS$ 362.1033, found 362.1024.

Compounds **2**−**21** were synthesized according to the synthesis of compound **1**.

*Compound **2** (165 mg, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (m, 1H), 7.81 (dt, J = 15.3 Hz, 7.5 Hz, 2H), 5.73 (dd, J = 7.9 Hz, 3.1 Hz, 1H), 4.08 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 3.18 (dd, J = 16.1 Hz, 3.2 Hz, 1H), 2.94 (dd, J = 16.1 Hz, 7.9 Hz, 1H), 2.64 (s, 3H), 1.58−1.51 (m, 2H), 1.34−1.23 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 167.9, 163.1, 137.5, 134.2 (2 × C), 132.2, 129.7, 126.9, 65.2, 54.2, 53.3, 39.3, 30.5, 23.8, 19.1, 13.8. HRMS (ESI): m/z (M + H^+) calcd for $C_{17}H_{22}O_7NS$ 384.1111, found 384.1105.

*Compound **3** (129 mg, 75% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (td, J = 8.1 Hz, 5.5 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.29−7.24 (m, 1H), 5.74 (dd, J = 8.0 Hz, 3.0 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.18 (dd, J = 16.2 Hz, 3.2 Hz, 1H), 2.95 (dd, J = 16.2 Hz, 8.1 Hz, 1H), 2.61 (s, 3H), 1.59−1.52 (m, 2H), 1.34−1.25 (m, 2H), 0.90 (t, J = 7.4

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Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6, 167.3, 156.6 (d, J = 259.1 Hz) 138.0, 136.8 (d, J = 7.4 Hz), 122.1 (d, J = 17.9 Hz), 120.8 (d, J = 3.9 Hz), 116.9 (d, J = 17.7 Hz), 65.3, 55.6, 39.1, 30.6, 23.8, 19.2, 13.8. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{15}H_{19}O_5FNS$ 344.0968, found 344.0971.

Compound **4** *(155 mg, 88% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 2.2 Hz, 2H), 5.62 (dd, J = 7.7 Hz, 3.3 Hz, 1H), 4.09 (td, J = 6.7 Hz, 1.7 Hz, 2H), 3.13 (dd, J = 15.9 Hz, 3.4 Hz, 1H), 2.91 (dd, J = 15.9 Hz, 7.7 Hz, 1H), 2.61 (s, 6H), 2.41 (s, 3H), 1.59−1.52 (m, 2H), 1.34−1.25 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.7, 145.5, 135.7, 134.7, 132.6, 129.6, 122.4, 65.1, 55.0, 39.5, 30.6, 23.7, 21.9, 19.2, 17.0, 13.8. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{17}H_{24}O_5NS$ 354.1370, found 354.1366.

Compound **5** *(166 mg, 90% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.78 (s, 1H), 5.61 (dd, J = 7.8 Hz, 3.3 Hz, 1H), 4.10 (td, J = 6.6 Hz, 1.8 Hz, 2H), 3.99 (s, 3H), 3.12 (dd, J = 15.9 Hz, 3.4 Hz, 1H), 2.89 (dd, J = 15.9 Hz, 7.8 Hz, 1H), 2.59 (s, 3H), 2.44 (s, 3H), 1.60−1.50 (m, 2H), 1.36−1.26 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.8, 155.4, 148.1, 137.5, 118.9, 116.6, 112.4, 65.1, 56.4, 55.0, 39.4, 30.6, 23.7, 22.6, 19.2, 13.8. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{17}H_{24}O_6NS$ 370.1319, found 370.1315.

Compound **6** *(183 mg, 95% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (d, J = 1.3 Hz, 1H), 6.47 (d, J = 1.7 Hz, 1H), 5.60 (dd, J = 8.1 Hz, 3.3 Hz, 1H), 4.10 (t, J = 6.7 Hz, 2H), 3.96 (s, 3H), 3.85 (s, 3H), 3.15 (dd, J = 16.1 Hz, 3.3 Hz, 1H), 2.85 (dd, J = 16.1 Hz, 8.2 Hz, 1H), 2.58 (s, 3H), 1.61−1.54 (m, 2H), 1.36−1.23 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 167.5, 166.4, 156.6, 139.2, 114.0, 99.7, 99.5, 65.0, 56.4, 56.0, 54.9, 39.3, 30.5, 23.5, 19.0, 13.6. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{17}H_{24}O_7NS$ 386.1268, found 386.1263.

Compound **7** *(177 mg, 92% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.55 (t, J = 4.2 Hz, 1H), 3.94 (t, J = 6.7 Hz, 2H), 3.91 (s, 2H), 3.85 (s, 2H), 3.22 (dd, J = 14.8 Hz, 4.8 Hz, 1H), 3.07 (dd, J = 14.8 Hz, 3.7 Hz, 1H), 2.56 (s, 3H), 1.48−1.38 (m, 2H), 1.24−1.15 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 167.6, 148.7, 148.3, 124.4, 122.6, 116.7, 112.5, 64.7, 56.6, 56.3, 54.0, 36.2, 30.4, 23.5, 19.0, 13.7. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{17}H_{23}NNaO_7S$ 408.1093, found 408.1093.

Compound **8** *(160 mg, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 5.63 (dd, J = 7.9 Hz, 3.2 Hz, 1H), 4.08 (t, J = 6.7 Hz, 2H), 3.14 (dd, J = 16.1 Hz, 3.3 Hz, 1H), 2.91 (dd, J = 16.1 Hz, 7.9 Hz, 1H), 2.67 (s, 3H), 2.61 (s, 3H), 1.58−1.51 (m, 3H), 1.33−1.24 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 167.4, 136.5, 134.9, 134.0, 133.9, 132.9, 123.3, 65.2, 54.4, 39.0, 30.5, 23.7, 19.1, 14.7, 13.7. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{16}H_{20}ClNNaO_5S$ 396.0648, found 396.0649.

Compound **9** *(137 mg, 77% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, J = 8.3 Hz, 4.3 Hz, 1H), 7.19 (t, J = 8.7 Hz, 1H), 5.58 (d, J = 4.0 Hz, 1H), 5.14−5.10 (m, 1H), 4.16 (t, J = 6.7 Hz, 2H), 3.12 (dd, J = 17.0 Hz, 2.5 Hz, 1H), 2.74 (dd, J = 17.0 Hz, 10.6 Hz, 1H), 2.60 (s, 3H), 1.67−1.60 (m, 2H), 1.43−1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9, 167.6, 155.9 (d, J = 250.2 Hz), 134.1 (d, J = 3.9 Hz), 133.6 (d, J = 6.5 Hz), 130.7 (d, J = 4.4 Hz), 122.5 (d, J = 19.1 Hz), 120.7 (d, J = 19.7 Hz), 65.1, 53.0, 36.9, 30.4, 23.6, 19.1, 16.4, 13.8. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{16}H_{20}FNNaO_5S$, 380.0944, found 380.0934.

Compound **10** *(143 mg, 74% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 5.72−5.70 (m, 1H), 4.04 (td, J = 6.7 Hz, 1.8 Hz, 2H), 3.08 (dd, J = 15.3 Hz, 3.5 Hz, 1H), 2.80 (dd, J = 15.3 Hz, 5.2 Hz, 1H), 2.60 (s, 6H), 2.40 (s, 3H), 1.58−1.48 (m, 2H), 1.33−1.24 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 167.5, 141.0, 135.1, 133.4, 132.5, 131.4, 130.0, 65.3, 55.2, 38.8, 30.5, 23.7, 19.2, 16.5, 15.5, 13.8. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{17}H_{22}ClNNaO_5S$ 410.0805, found 410.0804.

Compound **11** *(212 mg, 91% yield).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 15.9 Hz, 1H), 7.56 (s, 1H), 7.35 (s, 1H), 6.63 (d, J = 15.9 Hz, 1H), 5.66 (dd, J = 7.7 Hz, 3.2 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.15 (dd, J = 16.0 Hz, 3.3 Hz, 1H), 2.94 (dd, J = 16.0 Hz, 7.8 Hz, 1H), 2.61 (s, 3H), 2.48 (s, 3H), 1.75−1.68 (m, 2H), 1.60−1.50 (m, 2H), 1.48−1.40 (m, 2H), 1.33−1.26 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 167.5, 165.7, 145.7, 136.4, 135.8, 131.1, 129.8, 128.9, 126.2, 124.7, 65.2, 65.1, 54.9, 39.3, 30.8, 30.6, 23.8, 22.0, 19.3, 19.2, 13.9, 13.8. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{23}H_{32}O_7NS$ 466.1894, found 466.1890.

Compound **12** *(219 mg, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 15.9 Hz, 1H), 7.26 (s, 1H), 6.74 (d, J = 15.9 Hz, 1H), 5.73 (d, J = 4.4 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.08 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 3.17 (dd, J = 15.9 Hz, 2.8 Hz, 1H), 3.03 (dd, J = 16.1 Hz, 7.5 Hz, 1H), 2.63 (s, 3H), 1.75−1.68 (m, 2H), 1.56−1.51 (m, 2H), 1.48−1.40 (m, 2H), 1.32−1.25 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.4, 167.3, 165.4, 164.7, 136.6, 136.0, 135.5, 134.7, 131.9, 129.0, 126.6, 126.0, 65.4, 65.3, 55.1, 53.3, 38.9, 30.8, 30.6, 23.9, 19.3, 19.2, 13.9, 13.8. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{24}H_{32}O_9NS$ 510.1792, found 510.1789.

Compound **13** *(159 mg, 85% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (t, J = 7.7 Hz, 1H), 7.36−7.30 (m, 3H), 7.28−7.22 (m, 4H), 5.68 (dd, J = 7.6 Hz, 3.4 Hz, 1H), 5.14−5.07 (m, 2H), 3.19 (dd, J = 15.8 Hz, 3.5 Hz, 1H), 2.98 (dd, J = 15.8 Hz, 7.7 Hz, 1H), 2.63 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.5, 167.7, 135.4, 135.2, 135.0, 134.3, 132.2, 131.7, 128.7 (2 × C), 128.6 (2 × C), 128.5, 122.1, 67.1, 55.1, 39.4, 23.7, 17.1. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{19}H_{20}O_5NS$ 374.1057, found 374.1053.

Compound **14** *(158 mg, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 5.69 (dd, J = 7.7 Hz, 3.3 Hz, 1H), 4.18−4.15 (m, 1H), 4.11−4.00 (m, 2H), 3.88−3.73 (m, 2H), 3.20 (dt, J = 16.0 Hz, 3.4 Hz, 1H), 2.99−2.91 (m, 1H), 2.66 (s, 3H), 2.62 (s, 3H), 2.00−1.84 (m, 3H), 1.59−1.51 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 167.7, 135.3, 135.0, 134.4, 132.2, 131.7, 122.3, 76.3, 68.5, 67.2, 55.0, 39.4, 28.1, 25.8, 23.8, 17.1. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{17}H_{22}O_6NS$ 368.1162, found 368.1160.

Compound **15** *(139 mg, 82% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, J = 7.7 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 5.66 (dd, J = 8.2 Hz, 3.2 Hz, 1H), 3.12 (dd, J = 15.9 Hz, 3.3 Hz, 1H), 2.77 (dd, J = 15.9 Hz, 8.2 Hz, 1H), 2.66 (s, 3H), 2.62 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.1, 167.6, 135.7, 135.0, 134.2, 132.2, 131.5, 122.3, 81.9, 55.2, 40.5, 28.1 (3 × C), 23.8, 17.0. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{16}H_{21}O_5NNaS$ 362.1033, found 362.1027.

Compound **16** *(129 mg, 87% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 5.68 (dd, J = 7.7 Hz, 3.5 Hz, 1H), 3.68 (s, 3H), 3.15 (dd, J = 16.0 Hz, 3.5 Hz, 1H), 2.92 (dd, J = 16.0 Hz, 7.7 Hz, 1H), 2.66 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 167.7, 135.3, 135.1, 134.3, 132.3, 131.7, 122.1, 55.0, 52.2, 39.2, 23.8, 17.1. HRMS (ESI): m/z (M + Na$^+$) calcd for $C_{13}H_{15}O_5NNaS$ 320.0563, found 320.0558.

Compound **17** *(75 mg, 51% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, J = 7.7 Hz, 1H), 7.35−7.31 (m, 2H), 5.78 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 3.33 (dd, J = 17.6 Hz, 2.7 Hz, 1H), 2.87 (dd, J = 17.6 Hz, 8.7 Hz, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 2.53−2.43 (m, 1H), 2.40−2.30 (m, 1H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.0, 167.5, 136.4, 134.9, 134.4, 132.0, 131.5, 122.7, 54.3, 47.4, 36.6, 23.8, 17.1, 7.7. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{14}H_{18}O_4NS$ 296.0951, found 296.0948.

Compound **18** *(116 mg, 75% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 5.87 (dd, J = 9.5 Hz, 2.3 Hz, 1H), 3.24 (dd, J = 16.0 Hz, 2.4 Hz, 1H), 2.97 (s, 3H), 2.91 (s, 3H), 2.70−2.63 (m, 4H), 2.61 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.1, 167.4, 136.6, 134.6, 134.3, 132.0, 131.4, 123.6, 55.5, 39.0, 37.3, 35.6, 23.9, 17.1. HRMS (ESI): m/z (M + H$^+$) calcd for $C_{14}H_{19}O_4N_2S$ 311.1060, found 311.1056.

Compound **19** *(112 mg, 61% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 6.28−6.07 (m, 1H), 5.70 (td, J = 8.6 Hz, 2.9 Hz, 1H),

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4.63−4.56 (m, 1H), 3.80−3.71 (m, 3H), 3.19−3.11 (m, 1H), 2.77−2.59 (m, 6H), 1.39 (dd, J = 7.2 Hz, 1.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) 173.3, 168.3, 167.9, 135.6, 134.9, 134.4, 132.8, 131.6, 122.8, 55.7, 52.7, 48.3, 41.5, 23.8, 18.5, 17.1. HRMS (ESI): m/z (M + H^+) calcd for $C_{16}H_{21}O_6N_2S$ 369.1115, found 369.1114.

Compound ***20*** *(151 mg, 78% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.59 (m, 1H), 7.57−7.47 (m, 1H), 7.35−7.20 (m, 5H), 7.06−7.01 (m, 1H), 5.97−5.90 (m, 1H), 4.71−4.37 (m, 2H), 3.37−3.29 (m, 1H), 2.99−2.58 (m, 10H), ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.1, 166.6, 137.2, 136.7, 129.0, 128.7, 128.3(2 × C), 128.2, 128.1, 127.7 (2 × C), 127.4, 126.5, 53.5, 51.1, 40.0, 34.9, 34.1, 29.8. HRMS (ESI): m/z (M + H^+) calcd for $C_{20}H_{23}O_4N_2S$ 387.1373, found 387.1370.

Compound ***21****(215 mg, 93% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.34−7.24 (m, 7H), 7.21 (d, J = 6.6 Hz, 2H), 7.00 (d, J = 6.3 Hz, 2H), 5.98 (dd, J = 9.2 Hz, 2.2 Hz, 1H), 4.62 (s, 2H), 4.34 (s, 2H), 3.38 (dd, J = 15.9 Hz, 2.6 Hz, 1H), 2.80 (dd, J = 15.9 Hz, 9.4 Hz, 1H), 2.63 (s, 3H), 2.57 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$): δ 169.8, 167.4, 137.0, 136.5, 135.8, 134.8, 134.2, 132.1, 131.5, 129.1 (2 × C), 128.8 (2 × C), 128.5 (2 × C), 127.9, 127.7, 126.5 (2 × C), 123.4, 55.6, 50.0, 48.4, 38.8, 23.9, 17.1. HRMS (ESI): m/z (M + H^+) calcd for $C_{26}H_{27}O_4N_2S$ 463.1686, found 463.1682.

Synthesis of Compound 22. K_2CO_3 (1.1 equiv, 46 mg) was added to a solution of compound **1** (0.3 mmol, 80 mg) in 5 mL of ^{n}BuOH/H_2O (v/v = 20/1), and the reaction mixture was heated to 60 °C and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with column chromatography on silica gel to afford 63 mg of white solid (94% yield).

Compound ***22*** *(63 mg, 94% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 5.44 (s, 1H), 5.04 (d, J = 9.9 Hz, 1H), 4.16 (t, J = 6.7 Hz, 3H), 2.96 (dd, J = 16.9 Hz, 3.4 Hz, 1H), 2.77 (dd, J = 16.9 Hz, 10.0 Hz, 1H), 2.65 (s, 3H), 1.66−1.59 (m, 2H), 1.42−1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.0, 138.4, 134.9, 134.2, 133.4, 131.3, 121.2, 65.5, 53.2, 40.6, 30.7, 19.2, 17.1, 13.8. HRMS (ESI): m/z (M + H^+) calcd for $C_{14}H_{20}O_4NS$, 298.1108, found 298.1105.

Synthesis of Compounds 23−25. General synthetic procedure of compound **23−25**: K_2CO_3 (2.0 equiv, 27.6 mg) and R-X (1.5 equiv) were added to a solution of compound **22** (0.1 mmol, 30 mg) in 1 mL of DMF, and the reaction mixture was stirred at room temperature and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with column chromatography on silica gel (EtOAc/petroleum ether) to afford a colorless oil.

Compound ***23*** *(25 mg, 80% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 4.73 (t, J = 5.9 Hz, 1H), 4.14 (t, J = 6.7 Hz, 2H), 2.96−2.90 (m, 4H), 2.80 (dd, J = 16.3 Hz, 6.0 Hz, 1H), 2.66 (s, 3H), 1.60 (dt, J = 14.6, 6.8 Hz, 2H), 1.33 (dq, J = 14.7 Hz, 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 137.6, 134.6, 133.0 (2 × C), 131.1, 121.3, 65.3, 59.4, 39.3, 30.6, 29.5, 19.2, 17.1, 13.8. HRMS (ESI): m/z (M + Na^+) calcd for $C_{15}H_{21}NNaO_4S$ 334.1089, found 334.1088.

Compound ***24*** *(33 mg, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.9 Hz, 3H), 7.34−7.27 (m, 4H), 7.15 (d, J = 7.7 Hz, 1H), 4.78 (t, J = 5.9 Hz, 1H), 4.63 (d, 15.7 Hz, 1H), 4.51 (d, 15.7 Hz, 1H), 4.04−3.93 (m, 2H), 2.85 (dd, J = 16.1 Hz, 5.2 Hz, 1H), 2.73−2.64 (m, 4H), 1.52−1.45 (m, 2H), 1.24−1.21 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 137.6, 135.6, 134.4, 133.2, 132.9, 131.0, 128.8 (2 × C), 128.6 (2 × C), 128.1, 121.4, 65.1, 56.7, 46.5, 39.3, 30.5, 19.1, 17.1, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{21}H_{25}NNaO_4S$ 410.1402, found 410.1397.

Compound ***25*** *(29 mg, 85% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 5.97−5.87 (m, 1H), 5.39 (d, J = 13.6 Hz, 1H), 5.29 (d, J = 13.6 Hz, 1H), 4.89 (t, J = 6.0 Hz, 1H), 4.13−4.07 (m, 3H), 3.91 (dd, J = 15.8 Hz, 7.7 Hz, 1H), 2.95 (dd, J = 16.2 Hz, 5.6 Hz, 1H), 2.79−2.74 (m, 1H), 2.65 (s, 3H), 1.61−1.54 (m, 2H), 1.30 (dt, J = 14.9 Hz, 7.5 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 137.9, 134.4, 133.5, 133.0, 132.7, 131.0, 121.4, 120.0, 65.2, 56.7, 46.5, 39.8, 30.6, 19.2, 17.0, 13.8. HRMS (ESI): m/z (M + Na^+) calcd for $C_{17}H_{23}NNaO_4S$ 360.1245, found 360.1253.

Synthesis of Compounds 26−28. General synthetic procedure of compound **26−28**: Et_3N (3.0 equiv, 41 mg) and RCO(Cl) or MsCl (1.5 equiv) was added to a solution of compound **22** (0.1 mmol, 30 mg) in 1 mL of DCM, and the reaction mixture was stirred at room temperature and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with column chromatography on silica gel (EtOAc/petroleum ether) to afford a colorless oil.

Compound ***26*** *(35 mg, 83% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.5 Hz, 5.3 Hz, 2H), 7.57 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 8.6 Hz, 2H), 6.14 (t, J = 5.7 Hz, 1H), 4.08 (t, J = 6.7 Hz, 2H), 3.05 (d, J = 5.8 Hz, 2H), 2.56 (s, 3H), 1.55−1.48 (m, 2H), 1.28−1.22 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 167.5, 165.6 (d, J = 252.3 Hz), 135.3, 134.9, 134.2, 132.7, 131.6, 131.4 (d, J = 9.1 Hz), 130.8 (d, J = 3.2 Hz, 2 × C), 122.1, 115.8 (d, J = 22 Hz, 2 × C), 65.3, 54.9, 40.1, 30.5, 19.1, 16.9, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{21}H_{22}FNNaO_5S$ 442.1100, found 442.1093.

Compound ***27*** *(36 mg, 77% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.59 (t, J = 7.7 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 6.12 (t, J = 5.7 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.08 (d, J = 5.7 Hz, 2H), 2.55 (s, 3H), 1.54−1.50 (m, 2H), 1.28−1.23 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 169.4, 167.4, 137.8, 135.2, 135.0, 134.3, 134.0, 132.5, 131.7, 129.1 (2 × C), 125.6 (q, J = 3.6 Hz), 125.1 (2 × C), 122.1, 65.3, 55.0, 39.9, 30.5, 19.1, 16.9, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{22}H_{22}F_3NNaO_5S$ 492.1068, found 492.1073.

Compound ***28*** *(32 mg, 84% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.7 Hz, 2H), 5.49 (dd, J = 8.7 Hz, 3.3 Hz, 1H), 4.13 (t, J = 6.7 Hz, 2H), 3.40 (dd, J = 16.7 Hz, 3.4 Hz, 1H), 3.27 (s, 3H), 2.98 (dd, J = 16.7 Hz, 8.7 Hz, 1H), 2.66 (s, 3H), 1.62−1.55 (m, 2H), 1.33 (dd, J = 15.0 Hz, 7.5 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 135.5, 135.1, 134.3, 132.8, 132.0, 122.3, 65.4, 57.9, 42.4, 40.4, 30.6, 19.2, 17.1, 13.8. HRMS (ESI): m/z (M + Na^+) calcd for $C_{15}H_{21}NNaO_6S_2$ 398.0708, found 398.0710.

Synthesis of Compound 29. DEAD (2.0 equiv, 31 μL) and PPh_3 (2.0 equiv, 52 mg) were added to a solution of compound **22** (0.1 mmol, 30 mg) in 1 mL of THF, and the reaction mixture was stirred at room temperature and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL of water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with column chromatography on silica gel (EtOAc/petroleum ether) to afford a colorless oil.

Compound ***29*** *(36 mg, 98% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.7 Hz, 1H), 7.34 (dd, J = 7.6 Hz, 2.9 Hz, 2H), 5.53 (dd, J = 7.7 Hz, 3.2 Hz, 1H), 4.52−4.40 (m, 2H), 4.10 (tt, J = 6.1 Hz, 3.2 Hz, 2H), 3.20 (dd, J = 16.0 Hz, 3.3 Hz, 1H), 2.97 (dd, J = 16.0 Hz, 7.7 Hz, 1H), 2.67 (s, 3H), 1.60−1.53 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.32 (dd, J = 16.5 Hz, 7.5 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 150.8, 134.9, 134.8, 133.9, 132.5, 131.6,

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121.8, 65.1, 64.0, 55.4, 39.6, 30.5, 19.1, 17.0, 14.3, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{17}H_{23}NNaO_6S$ 392.1144, found 392.1140.

Synthesis of Compounds 30 and 31. General synthetic procedure of compound **30** and **31**: DEAD (2.0 equiv, 31 μL), PPh_3 (2.0 equiv, 52 mg), and ROH (2.0 equiv) was added to a solution of compound **22** (0.1 mmol, 30 mg) in 1 mL of THF, and the reaction mixture was stirred at room temperature and monitored by LC−-MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL of water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and purified with column chromatography on silica gel (EtOAc/petroleum ether) to afford a colorless oil.

*Compound **30** (30 mg, 92% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 4.91 (t, J = 6.0 Hz, 1H), 4.13 (t, J = 6.7 Hz, 2H), 3.52−3.38 (m, 2H), 2.97−2.91 (m, 1H), 2.77 (dd, J = 16.2 Hz, 6.4 Hz, 1H), 2.64 (s, 3H), 1.62−1.55 (m, 2H), 1.36−1.32 (m, 5H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.7, 134.2, 133.4, 132.7, 130.9, 121.2, 65.1, 56.5, 39.7, 38.3, 30.5, 19.0, 16.8, 13.6, 13.6. HRMS (ESI): m/z (M + Na^+) calcd for $C_{16}H_{23}NNaO_4S$ 348.1245, found 348.1249.

*Compound **31** (32 mg, 90% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 4.88 (t, J = 6.0 Hz, 1H), 4.13 (t, J = 6.7 Hz, 2H), 3.35−3.31 (m, 2H), 2.95 (dd, J = 16.2 Hz, 5.5 Hz, 1H), 2.75 (dd, J = 16.2 Hz, 6.6 Hz, 1H), 2.64 (s, 3H), 1.76−1.69 (m, 2H), 1.62−1.55 (m, 2H), 1.42 (td, J = 14.2 Hz, 7.1 Hz, 2H), 1.32 (dt, J = 12.2 Hz, 6.2 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 137.8, 134.3, 133.4, 132.8, 131.1, 121.3, 65.2, 57.2, 43.4, 39.7, 30.6, 30.3, 20.2, 19.1, 17.0, 13.8, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{18}H_{27}NNaO_4S$ 376.1558, found 376.1555.

Synthesis Compound 32. *N*-Methyl morpholine (1.5 equiv, 16 μL) and ethyl propiolate (1.5 equiv, 15 μL) were added to a solution of compound **22** (0.1 mmol, 30 mg) in 1 mL of DCM, and the reaction mixture was stirred at room temperature and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, and the residue was diluted with 10 mL of ethyl acetate, washed with 10 mL water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with column chromatography on silica gel (EtOAc/petroleum ether = 1:5) to afford 29.1 mg of colorless (*E*)-**32** and 10 mg of colorless (*Z*)-**32**.

*Compound (E)-**32** (29 mg, 73% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 14.1 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.36−7.32 (m, 2H), 5.37 (d, J = 14.1 Hz, 1H), 5.28 (dd, J = 9.1 Hz, 3.0 Hz, 1H), 4.23 (qd, J = 7.2 Hz, 3.0 Hz, 2H), 4.17 (t, J = 6.7 Hz, 2H), 3.18 (dd, J = 16.6 Hz, 3.1 Hz, 1H), 2.72 (dd, J = 16.6 Hz, 9.2 Hz, 1H), 2.67 (s, 3H), 1.65−1.58 (m, 2H), 1.38−1.26 (m, 5H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.6, 136.2, 135.5, 134.8, 134.0, 131.8, 131.7, 122.0, 99.3, 65.5, 60.5, 55.1, 38.3, 30.6, 19.1, 17.2, 14.5, 13.7. HRMS (ESI): m/z (M + Na^+) calcd for $C_{19}H_{25}NNaO_6S$ 418.1300, found 418.1298.

*Compound (Z)-**32** (10 mg, 25% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 10.6 Hz, 1H), 6.35 (dd, J = 8.5 Hz, 2.7 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.06 (t, J = 6.7 Hz, 2H), 3.15 (dd, J = 16.3 Hz, 2.9 Hz, 1H), 2.70 (dd, J = 16.8 Hz, 8.9 Hz, 1H), 2.66 (s, 2H), 1.53 (dq, J = 13.7 Hz, 6.7 Hz, 2H), 1.31−1.26 (m, 5H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 165.3, 137.4, 134.4, 133.8, 131.2, 131.1, 130.7, 122.4, 99.7, 64.9, 60.5, 57.6, 38.3, 30.6, 19.1, 17.2, 14.4, 13.8. HRMS (ESI): m/z (M + Na^+) calcd for $C_{19}H_{25}NNaO_6S$ 418.1300, found 418.1303.

Synthesis of *N*-(*o*-Tolylsulfonyl)acetamide (1a). $ZnCl_2$ (68 mg, 10 mmol %) was added to a mixture of 2-methylbenzenesulfonamide (5 mmol, 855 mg) in Ac_2O (10 mL), the reaction mixture was stirred at 50 °C until all the starting material was consumed completely, and the residue was diluted with 30 mL of ethyl acetate, washed with 30 mL water, and extracted with ethyl acetate two times. Then the organic phase was combined, washed with brine, and dried over anhydrous Na_2SO_4. The organic phase was concentrated to give crude product **1a**, which was recrystallized from toluene to give the *N*-(*o*-tolylsulfonyl)acetamide **1a** (873 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.31−8.29 (m, 1H), 7.84−7.81 (m, 1H), 7.71−7.69 (m, 2H), 3.99 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.2, 137.8, 136.8, 134.3, 132.9, 131.0, 126.6, 23.4, 20.5.

Other *N*-Ac-substituted benzenesulfonamides were synthesized according to the synthesis of *N*-(*o*-tolylsulfonyl)acetamide.

*N-((2,4-Dimethoxyphenyl)sulfonyl)acetamide (**6a**) (987 mg, 87% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 8.8 Hz, 2.1 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 166.0, 158.6, 133.4, 118.4, 104.8, 99.7, 56.4, 56.0, 23.3.

*N-((4-Chloro-2,5-dimethylphenyl)sulfonyl)acetamide (**10a**) (1.1 g, 85% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 8.00 (s, 1H), 7.32 (s, 1H), 2.59 (s, 3H), 2.42 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.8, 140.7, 136.5, 134.9, 134.8, 133.3, 133.0, 23.6, 19.9, 19.8.

*N-((2-Fluorophenyl)sulfonyl)acetamide (**3a**) (922 mg, 85% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.08 (t, J = 7.3 Hz, 1H), 7.69−7.64 (m, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.27−7.22 (m, 1H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 159.1 (d, J = 255.5 Hz), 136.6 (d, J = 8.6 Hz), 131.9, 126.7 (d, J = 12.2 Hz), 124.7 (d, J = 3.8 Hz), 117.3 (d, J = 20.6 Hz), 23.5.

*N-((2,4-Dimethylphenyl)sulfonyl)acetamide (**4a**) (885 mg, 78% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.14 (s, 1H), 2.62 (s, 3H), 2.39 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 145.3, 137.7, 133.8, 133.6, 131.2, 127.2, 23.4, 21.6, 20.4.

*N-((2-Methoxy-4-methylphenyl)sulfonyl)acetamide (**5a**) (984 mg, 81% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 3.98 (s, 3H), 2.43 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 156.9, 147.7, 131.3, 123.6, 121.5, 113.2, 56.4, 23.3, 22.2.

*Methyl 2-(N-acetylsulfamoyl)benzoate (**2a**) (1.1 g, 86% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.32−8.28 (m, 1H), 7.86−7.81 (m, 1H), 7.72−7.68 (m, 2H), 3.99 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.4, 167.5, 137.9, 133.7, 131.8, 131.5, 131.1, 130.7, 53.6, 24.1.

*N-((3-Chloro-2-methylphenyl)sulfonyl)acetamide (**8a**) (988 mg, 80% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 2.70 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 138.7, 137.2, 135.7, 135.2, 130.0, 127.0, 23.6, 17.0.

*N-Tosylacetamide (**11a**) (937 mg, 88% yield).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.4, 145.4, 135.6, 129.8, 128.5, 23.6, 21.8.

*N-((5-Fluoro-2-methylphenyl)sulfonyl)acetamide (**9a**) (820 mg, 71% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.86 (dd, J = 8.4 Hz, 2.7 Hz, 1H), 7.32 (dd, J = 8.4 Hz, 5.3 Hz, 1H), 7.25 (dt, J = 8.3 Hz, 2.6 Hz, 1H), 2.63 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.19, 160.5 (d, J = 248.0 Hz), 138.0 (d, J = 6.9 Hz), 134.4 (d, J = 7.1 Hz), 133.4 (d, J = 3.8 Hz), 121.3 (d, J = 20.7 Hz), 118.3(d, J = 25.2 Hz), 23.52, 19.70.

*Methyl 4-(N-Acetylsulfamoyl)benzoate (**12a**) (1.13 mg, 88% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.21 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H), 3.97 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.5, 165.5, 142.3, 135.3, 130.4, 128.6, 52.9, 23.8.

*(R)-Methyl 2-acrylamidopropanoate (**19a**) (549 mg, 70% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (dd, J = 17.0 Hz, 1.5 Hz, 1H), 6.18 (dd, J = 17.0 Hz, 10.1 Hz, 1H), 5.66 (dd, J = 10.1 Hz, 1.5 Hz, 1H), 4.68 (p, J = 7.2 Hz, 1H), 3.76 (s, 3H), 1.44 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.6, 165.1, 130.5, 127.1, 52.6, 48.1, 18.4.

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*N,N-Dibenzylacrylamide (**21a**) (815 mg, 65% yield).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (ddd, J = 27.6 Hz, 14.2 Hz, 6.6 Hz, 8H), 7.19 (t, J = 12.3 Hz, 2H), 6.61 (dd, J = 16.7 Hz, 10.2 Hz, 1H), 6.49 (dd, J = 16.6 Hz, 2.1 Hz, 1H), 5.73 (dd, J = 10.2 Hz, 2.1 Hz, 1H), 4.66 (s, 2H), 4.51 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 137.3, 136.6, 129.1, 129.0, 128.7, 128.5, 127.8, 127.7, 127.6, 126.6, 50.0, 48.7, 40.2, 36.3, 29.8.

Synthesis of Methyl *o*-Tolylsulfonylcarbamate (12b). 2-Methylbenzenesulfonamide (5 mmol, 855 mg) was added to a mixture of Et_3N (3.0 equiv, 2 mL) in CH_3CN (100 mL), and then methyl chloroformate (1.5 equiv, 588 μL) was added slowly. The mixture was stirred at room temperature and monitored by LC−MS and TLC until all the starting material was consumed completely, and then CH_3CN was evaporated in vacuo. The residue was dissolved in ethyl acetate (30 mL), and then aqueous $NaHCO_3$ (30 mL) was added. The water phase was separated, and concentrated HCl was dropwise added with a mixture of ice to give a granular precipitate which slowly crystallized upon standing. The crystals were collected by filtration, washed with water, and dried to give methyl *o*-tolylsulfonylcarbamate (458 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.0 Hz, 1H), 7.55−7.49 (m, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 3.68 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.8, 137.9, 136.4, 134.2, 132.7, 131.5, 126.5, 53.8, 20.5.

Synthesis of *N*-Boc-Substituted 2-Methylbenzenesulfonamide (11b). 2-Methylbenzenesulfonamide (5 mmol, 855 mg) was added to a mixture of DMAP (10 mmol %, 62 mg) in CH_2Cl_2 (10 mL), then Et_3N (1.1 equiv, 765 μL) and Boc_2O (1.15 equiv, 1.32 mL) were added, and the reaction mixture was stirred at room temperature and monitored by LC−MS until all of the starting material was consumed completely. The reaction mixture was washed with water (50 mL × 2) and extracted with CH_2Cl_2 two times, and then the organic phase was combined and washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with silica gel column chromatography to afford white solid (1.016g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 1H), 7.54−7.50 (m, 2H), 7.38−7.33 (m, 2H), 2.67 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (150 MHz, CDCl3) δ 149.4, 137.6, 137.0, 133.9, 132.6, 131.3, 126.2, 84.4, 27.9, 20.3.

Synthesis of *N*-Trifluoroacetyl 2-Methylbenzenesulfonamide (13b). 2-Methylbenzenesulfonamide (5 mmol, 885 mg) was added a mixture of TFA (1.3 equiv, 910 μL) in toluene (15 mL), and the reaction mixture was heated to reflux and monitored by LC−MS until all of the starting material was consumed completely. Solvent was removed in vacuo, the residue was diluted with 30 mL of ethyl acetate and washed with 30 mL water, and then the organic phase was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated to afford a white solid without further purification (1.268 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.62−7.58 (m, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.4, 135.3, 135.0, 133.0, 132.1, 126.9, 58.7, 20.5, 18.6.

Synthesis of *N*-Methyl 2-Methylbenzenesulfonamide (15b). The mixture of 2-methylbenzenesulfonamide (5 mmol, 885 mg) and K_2CO_3 (1.1 equiv, 1.38 g) in CH_3OH was stirred for 5 min at room temperature, MeI (1.1 equiv, 342 μL) was added, and the reaction mixture was monitored by LC−MS until all the starting material was consumed completely. CH_3OH was evaporated in vacuo, the residue was diluted with 30 mL of ethyl acetate and washed with 30 mL water, and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified with silica gel column chromatography to afford white solid (276 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.96 (m, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 6.5 Hz, 2H), 4.41 (s, 1H), 2.65 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.2, 136.9, 133.0, 132.7, 130.0, 126.3, 29.2, 20.5.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of products. 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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