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Copper-Catalyzed Radical-Promoted Aminocyclization of Acrylamides with *N*-Fluorobenzenesulfonimide

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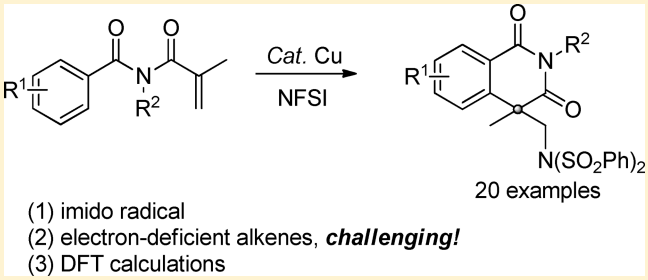
Supporting Information

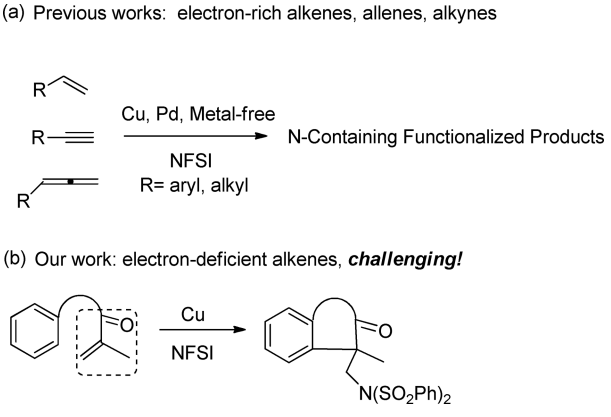
ABSTRACT: A facile copper-catalyzed radical aminoarylation of acrylamide with *N*-fluorobenzenesulfonimide (NFSI) is described. In the presence of copper acetate and 1,10-phenanthroline, a range of isoquinoline-1,3-diones can be constructed in moderate to good yields using NFSI as the amination reagent. Mechanistic studies demonstrated the reaction went through a sequential radical addition and cyclization pathway, which was supported by DFT calculations.



Isoquinoline-1,3-diones are important structural motifs that are widely present in plant alkaloids, natural products, and pharmaceuticals with certain biological properties.[1] Developing convenient and versatile methods for the synthesis of such molecules has attracted great attention from medicinal and synthetic chemists. Recently, radical addition/tandem cyclization reactions for the construction of isoquinoline-1,3-diones have been rapidly developed.[2] Several radical precursors such as carbon-, sulfur-, and phosphorus-containing radicals have been used to initiate this intriguing reaction. In 2013, Nevado et al. first presented a metal-free trifluoromethylation of acrylamides to construct isoquinolinediones in excellent yields.[2a] Afterward, a similar trifluoromethylated isoquinolinedione was synthesized by the Liu group under metal-free conditions using inexpensive $TMSCF_3$ as the CF_3 source.[2b] In 2015, the Tang group reported a visible-light-induced carboperfluoroalkylation for the synthesis of perfluorinated isoquinoline-1,3-diones.[2c] Xia and co-workers also described an elegant approach to trifluoromethylated isoquinoline-1,3-diones by visible-light photoredox catalysis.[2d] A cascade of couplings of acrylamides with benzenesulfonohydrazides to generate arylsulfonyl-substituted isoquinoline-1,3(2*H*,4*H*)-dione has been realized by the Zhou group.[2e] Very recently, our group has also developed some efficient alkyl radical addition/cyclization reaction, leading to alkylated isoquinoline-1,3-diones.[2f] Meanwhile, an efficient method for the synthesis of phosphono-isoquinolinediones from methacryloylbenzamides has been studied by the Zhao group.[2g] However, in sharp contrast, the unstable imide radical was rarely successfully introduced into such skeletons to date.

Structurally, *N*-fluorobenzenesulfonimide (NFSI) contains a N−F bond; thus, it can be used as an electrophilic fluorination agent and also as an efficient nitrogen source. During the past several years, a rapidly growing number of amination reactions exploring NFSI as a source of nucleophilic nitrogen,[3] electrophilic nitrogen,[4] or nitrogen radicals for the formation of C−N bonds have been reported by Liu, Zhang, Studer, and other groups. For example, Zhang and co-workers realized the imination of alkenes, allenes, and alkynes successively using copper as the catalyst.[5a,b,d,e,h] Studer et al. recently reported a TEMPONa intriguing radical aminooxygenation of alkenes with NFSI (Scheme 1a).[5g] Although electron-rich alkenes such as styrenes have been normally applied as radical acceptors in amination reactions, the applications of electron-deficient alkenes in such a reaction still remain a huge challenge for activity of the imine radical. Considering NFSI could produce

Scheme 1. Methods for the Synthesis of N-Containing Functionalized Products Using NFSI



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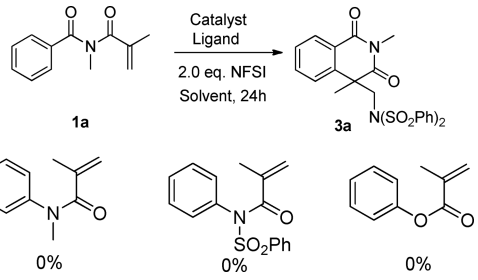
the imine radical and display multiple reaction modes, we were prompted to investigate the imine radical from NFSI in electron-deficient alkenes via radical addition/tandem cyclization reactions (Scheme 1b).

N-Methacryloyl-*N*-methylbenzamide (**1a**) was initially selected as the benchmark substrate to investigate the radical addition/cyclization reaction with NFSI as the nitrogen source. When the reaction of **1a** (0.2 mmol) and NFSI (2.0 equiv) was performed under atmospheric conditions at 80 °C in 1,2-dichloroethane (DCE, 2 mL) for 24 h, target product **3a** was obtained in 25% yield using $Pd(OAc)_2$ as the catalyst and 1,10-phenanthroline (phen) as the ligand (Table 1, entry 1). In

Table 1. Screening the Reaction Conditions[a]



entry	catalyst (%)	ligand (%)	solvent	yield[b]
1	10% $Pd(OAc)_2$	20% phen	DCE	25%
2	20% CuCl	20% phen	DCE	53%
3	20% CuBr	20% phen	DCE	27%
4	20% $Cu(OTf)_2$	20% phen	DCE	N.R.[c]
5	20% CuCl	20% phen	CH_3CN	57%
6	20% CuCl	20% phen	Dioxane	N.R.
7	20% CuI	20% phen	CH_3CN	32%
8	**20% $Cu(OAc)_2·H_2O$**	**20% phen**	**CH_3CN**	**70%**
9	20% $Cu(OAc)_2·H_2O$	20% DMAP	CH_3CN	47%
10	20% $Cu(OAc)_2·H_2O$	20% bpy	CH_3CN	48%
11	20% $Cu(OAc)_2·H_2O$	20% 6,6′-Me_2bpy	CH_3CN	52%
12	20% $Cu(OAc)_2·H_2O$	2,9-Me_2phen	CH_3CN	55%
13	20% $Cu(OAc)_2·H_2O$		CH_3CN	12%
14[d]	20% $Cu(OAc)_2·H_2O$	20% phen	CH_3CN	51%
15[e]	20% $Cu(OAc)_2·H_2O$	20% phen	CH_3CN	31%
16			CH_3CN	N.R.

[a]Reaction conditions: **1a** (0.2 mmol), NFSI (2.0 equiv), 1,2-dichloroethane (2 mL), 80 °C, 24 h, in air. [b]Isolated yield. [c]N.R. = no reaction. [d]Under 1 atm O_2. [e]Under 1 atm Ar.

addition, the structure of product **3a** was further confirmed by X-ray diffraction analysis (Figure 1).[6] To our delight, when the catalyst was switched to copper salts such as CuCl, the yield was increased to 53% (entry 2). Then, other copper catalysts, such as CuBr, $Cu(OTf)_2$, CuI, and $Cu(OAc)_2·H_2O$, were also screened, and $Cu(OAc)_2·H_2O$ can give a better result using CH_3CN as the solvent (entries 3−8). For the yield to be increased further, other N-containing ligands such as DMAP, bpy, 6,6′-Me_2bpy, and 2,9-Me_2phen were also explored; however, no better results were observed (entries 9−12). When the ligand was not involved, a very low yield was detected, which shows a huge rate-acceleration effect of ligand in this reaction (entry 13). When the reaction was conducted in an oxygen atmosphere, a slightly lower yield (51%) was separated, and only 31% product was obtained under the argon conditions (entries 14 and 15), which meant that the oxygen was very important for the transformation. Omitting the metal

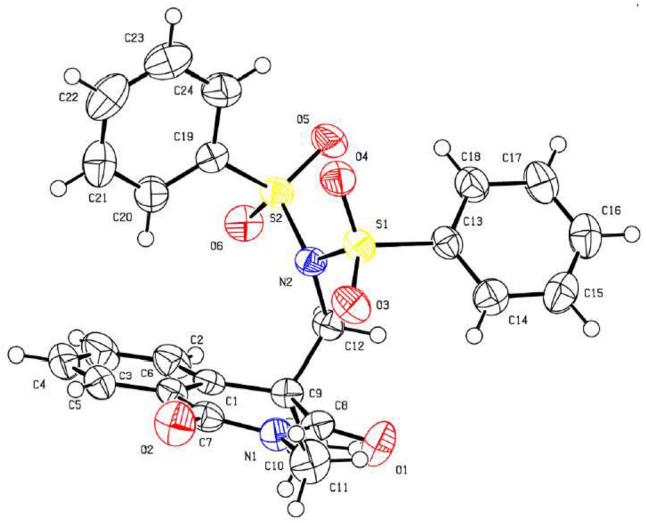


Figure 1. Structure of product **3a**.

catalysts, no reaction occurred (entry 16). Other substrates such as *N*-methyl-*N*-phenylmethacrylamide, *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide, and phenyl methacrylate were all not suitable for this radical addition reaction.

With the optimized reaction conditions in hand (Table 1, entry 8), the scope of the radical cascade imidation/cyclization reaction was shown in Scheme 2. The reaction of NFSI with various methacrylamides afforded the desired imidation products **3b−3t** in moderate to good yields. Several useful functional groups were tolerated, including chloro, bromo, fluoro, trifluoromethyl, cyano, and alkyl substituents at different positions of the phenyl moiety. Halo-substituents can be well tolerated in this copper-catalyzed imidation reaction (**3c−3e**). Electron-withdrawing groups such as CF_3 and CN afforded **3f** and **3h** in slightly lower yields. When the sterically demanding other-substituted methacrylamides were subject to the reaction, lower yields of the products (**3i**, **3k**, and **3m**) were obtained. When the substituent methyl was substituted in the meta position, a mixture of isomers was observed in approximately a 5:1 ratio (**3j**). Chloromethyl was also retained well without C−H imidation reactions (**3l**). Subsequently, the *N*-substituents of methacryloyl benzamides were investigated, and the ethyl, *n*-propyl, *n*-butyl, 1-propyl, and benzyl groups on the N atom were compatible with this radical addition. Interestingly, *N*-phenyl methacrylamide did not undergo the cyclization step, and a mixture of isomers were separated (**3t**, *Z*/*E* = 1:1). The heteroaryl substrate such as thienyl was also tolerated in this cyclization reaction (**3s**). In addition, olefins bearing *β*-substituted methyl groups or unsubstituted olefin were inefficient for the cascade process (**3u** and **3v**).

For more insight into the mechanism to be obtained, control experiments were performed (Scheme 3). When a stoichiometric amount of 1,1-diphenylethylene was used to trap the radical, no desired product was formed, and a 60% yield of **4a** was obtained. The cyclization reaction was found to be completely suppressed using 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the typical radical scavenger. These results indicated that an imine radical addition pathway might be involved in this transformation.

To further shed light on the reaction mechanism, we conducted several kinetic experiments (Scheme 4). First, a mixture of *N*-methacryloyl-*N*-methylbenzamide and 4-cyano-*N*-

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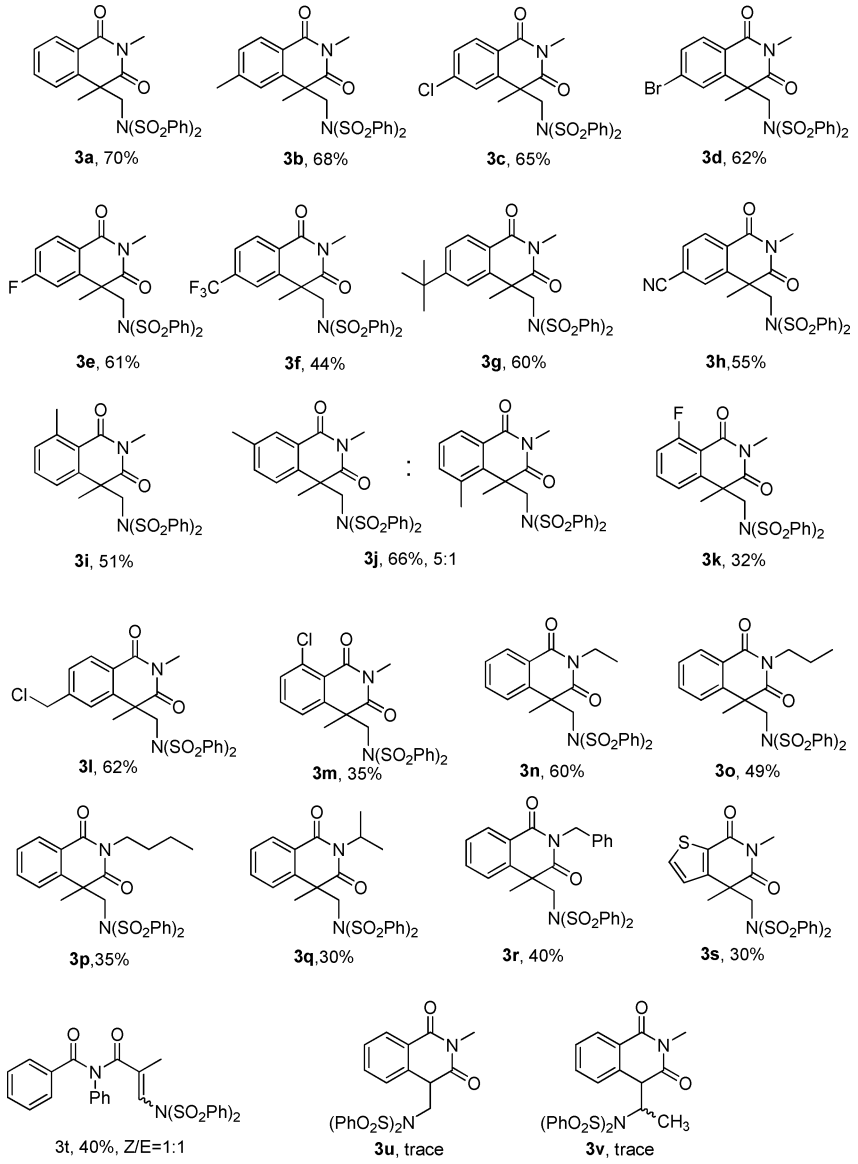
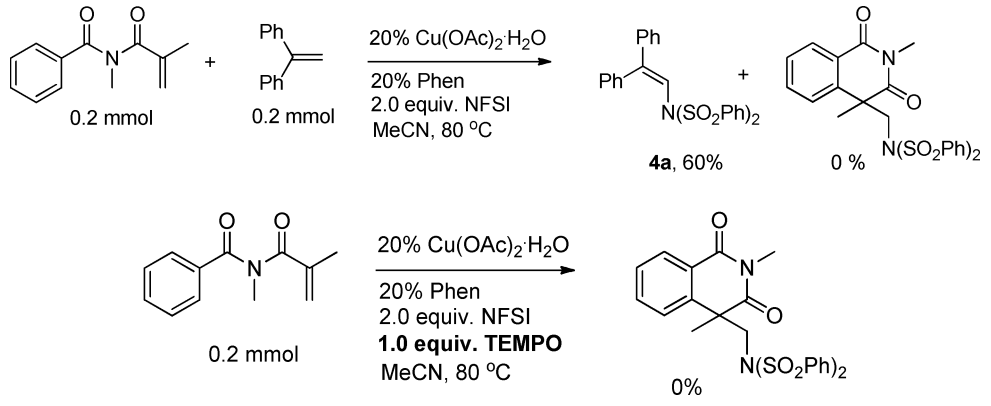
Scheme 2. Scope of Methacryloyl Benzamides



Scheme 3. Control experiments



methacryloyl-*N*-methylbenzamide with NFSI was subjected to the standard conditions to elucidate the electronic preference of the reacting arenes (eq 1). Under the competitive conditions, a 1.2:1 ratio of products was obtained, which meant an aromatic electrophilic substitution was not involved in the present cyclization. The deuterium labeling studies for the reactions of *N*-methacryloyl-*N*-methylbenzamide **1a** and its pentadeuterated analogue **1a**-d_5 were performed, and no kinetic isotope effect was observed (k_H/k_D = 1:1, eq 2). These results meant that C–

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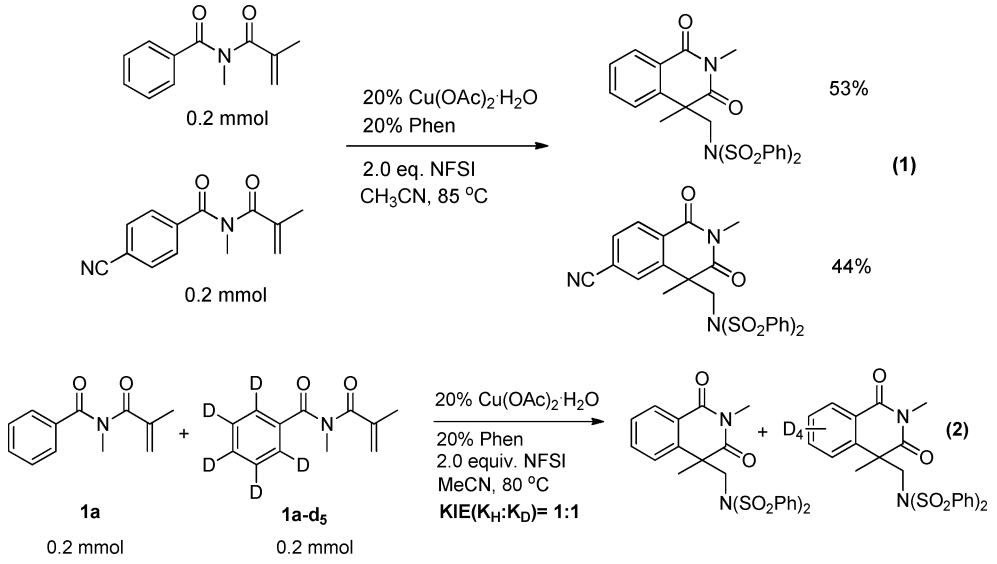
Scheme 4. kinetic experiments



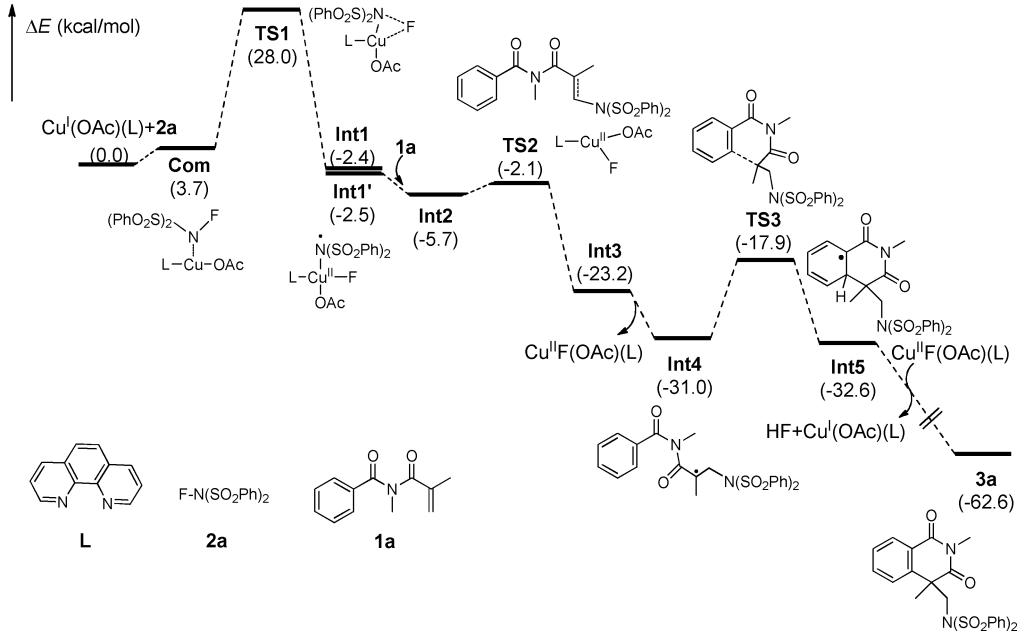


Figure 2. Energy profile of the overall catalytic cycle. Energies are relative to $Cu^{I}(OAc)(L)$ + **1a** and are mass balanced. All of the energies are in kcal mol^{-1}.

H bond cleavage was not the rate-determining step in this reaction.[7]

To gain more understanding of the mechanism of this process, we performed density functional theory (DFT) calculations at the B3LYP level using a mixed basis set of LANL2DZ for copper and 6-31G* for the other atoms. Geometry optimization and frequency calculations were performed using the Gaussian 09 package.[8] As shown in Figure 2, coordinations of phenanthroline ligand and *N*-fluorobenzenesulfonimide (NFSI) to the catalyst by N atoms form **Com** at first.[5f] The subsequent oxidative addition of copper(I) to the N−F bond leads to copper(III) intermediate (**Int1**) with a barrier of 28.0 kcal/mol. The resulting **Int1** could generate the copper(II)-stabilized radical **Int1′** through a fast equilibration. Compared with the metal−ligand bond lengths in **Int1**, there are remarkable bond elongations in **Int1′**. Upon complexation of acrylamide **1a**, intermolecular radical addition of **Int1′** to acrylamide results in **Int3** via **TS2** with a negligible energy barrier. The resulting radical **Int4** further undergoes cyclization by intramolecular radical addition with an energy barrier of 13.1 kcal/mol. Finally, reaction of **Int5** with $Cu^{II}F(OAc)(L)$ furnishes the product and regenerates the catalyst. This process has large thermodynamic driving forces as expected. On the basis of the experimental results presented above, a possible mechanism was proposed (Scheme 5).[9]

In summary, we have developed a novel copper-catalyzed radical addition/cyclization reaction between acrylamide and NFSI. A range of isoquinoline-1,3-diones can be constructed in moderate to good yields using NFSI as amination reagent. Preliminary mechanistic studies were confirmed by DFT calculations.

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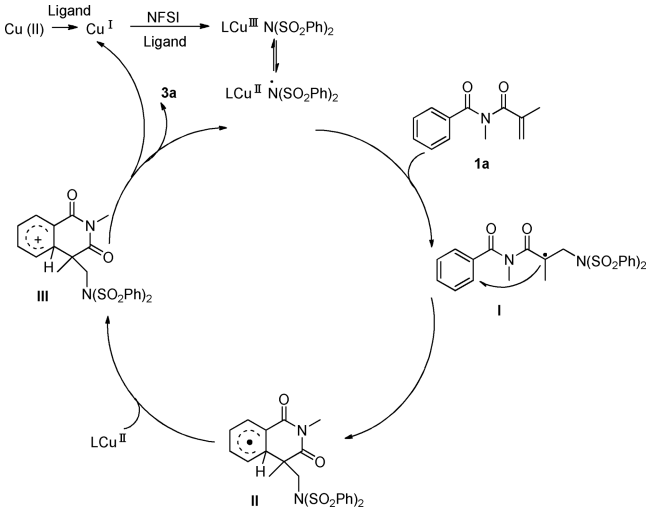
Scheme 5. Proposed Mechanism



EXPERIMENTAL SECTION

General Remarks. Column chromatography was carried out on silica gel. Unless noted; ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. IR spectra were recorded on an FT-IR spectrometer using the liquid-film method, and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by high-resolution mass spectra (HRMS), which were obtained on a micrOTOF-Q instrument equipped with an ESI source; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided.

Procedure for the Synthesis of Product 3. An oven-dried Schlenk tube (10 mL) was equipped with a magnetic stir bar, *N*-methacryloyl-*N*-methylbenzamide (**1a**, 0.3 mmol), NFSI (**2**, 0.6 mmol), 20% $Cu(OAc)_2{\cdot}H_2O$ (0.06 mmol, 12 mg), and 20% phen (0.06 mmol, 11.2 mg). Then, CH_3CN (2.0 mL) was added with a syringe. The reaction mixture was then stirred for 24 h at 80 °C. After the reaction, 6 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product (6:1 petroleum ether/ethyl acetate as eluent).

Characterization Data of Compounds 3 and 4a. *N*-((2,4-Dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3a**): 70%, 104.5 mg; mp 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.31−8.34 (m, 1 H), 7.59−7.62 (m, 1 H), 7.52−7.55 (m, 7 H), 7.48−7.49 (m, 1 H), 7.38−7.42 (m, 4 H), 4.51−4.55 (d, J = 16.0 Hz, 1 H), 4.18−4.22 (d, J = 16.0 Hz, 1 H), 3.43 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.2, 163.9, 139.5, 137.9, 133.6, 128.9, 128.8, 128.6, 127.9, 127.8, 125.8, 54.7, 47.8, 29.6, 27.4; IR (cm^{-1}) 3070, 2955, 1714, 1669, 1449, 1374, 1168, 1088, 756, 720, 687; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_6S_2^+$ (M + Na)$^+$ 521.0817, found 521.0841.

N-(Phenylsulfonyl)-*N*-((2,4,6-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzenesulfonamide (**3b**): 68%, 104.4 mg; mp 218−219 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.21−8.23 (d, J = 8.0 Hz, 1 H), 7.54−7.60 (m, 6 H), 7.48 (s, 1 H), 7.40−7.44 (m, 4 H), 7.29−7.31 (m, 1 H), 4.51−4.55 (d, J = 16.0 Hz, 1 H), 4.18−4.22 (d, J = 16.0 Hz, 1 H), 3.43 (s, 3 H), 2.33 (s, 3 H), 1.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.4, 163.9, 144.7, 138.1, 133.8, 128.5, 123.2, 54.6, 47.7, 29.7, 27.3, 21.6; IR (cm^{-1}) 2945, 1708, 1665, 1368, 1337, 1305, 1173, 1039, 790, 734; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_6S_2^+$ (M + H)$^+$ 513.1149, found 513.1144.

N-((6-Chloro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide, (**3c**): 65%, 104 mg; mp 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.22−8.24 (d, J = 8.0 Hz, 1 H), 7.59−7.67 (m, 7 H), 7.43−7.46 (m, 5 H), 4.51−4.55 (d, J = 16.0 Hz, 1 H), 4.20−4.24 (d, J = 16.0 Hz, 1 H), 3.43 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 163.1, 141.2, 140.3, 137.8, 134.0, 128.0, 124.2, 54.7, 47.9, 29.5, 27.5; IR (cm^{-1}) 3074, 2957, 1712, 1668, 1599, 1430, 1380, 1333, 1174, 1091, 1054, 737, 686; HRMS (ESI) m/z calcd for $C_{24}H_{22}ClN_2O_6S_2^+$ (M + H)$^+$ 533.0602, found 533.0601.

N-((6-Bromo-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3d**): 62%, 107 mg; mp 197−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.14−8.16 (d, J = 8.0 Hz, 1 H), 7.83−7.84 (m, 1 H), 7.60−7.63 (m, 7 H), 7.43−7.47 (m, 4 H), 4.51−4.55 (d, J = 16.0 Hz, 1 H), 4.19−4.23 (d, J = 16.0 Hz, 1 H), 3.42 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.6, 163.3, 141.2, 137.8, 134.0, 128.6, 124.6, 54.7, 47.9, 29.5, 27.5; IR (cm^{-1}) 3074, 2953, 1716, 1667, 1380, 1333, 1173, 770, 690; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrN_2O_6S_2^+$ (M + H)$^+$ 577.0097, found 577.0098.

N-((6-Fluoro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3e**): 61%, 94.4 mg; mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.29−8.33 (m, 1 H), 7.59−7.65 (m, 6 H), 7.43−7.47 (m, 4 H), 7.32−7.35 (m, 1 H), 7.13−7.17 (m, 1 H), 4.49−4.53 (d, J = 16.0 Hz, 1 H), 4.22−4.26 (d, J = 16.0 Hz, 1 H), 3.42 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.8, 167.1 (d, $^1J_{C-F}$ = 255 Hz), 164.5 (d, $^1J_{C-F}$ = 255 Hz), 163.1, 142.4 (d, $^3J_{C-F}$ = 8 Hz), 142.4, 137.9, 134.0, 128.6, 122.2 (d, $^4J_{C-F}$ = 3 Hz), 115.9 (d, $^2J_{C-F}$ = 22 Hz), 115.8 (d, $^2J_{C-F}$ = 22 Hz), 114.9 (d, $^2J_{C-F}$ = 23 Hz), 114.7 (d, $^2J_{C-F}$ = 23 Hz), 54.9, 48.1, 29.6, 27.5; IR (cm^{-1}) 3070, 2946, 1712, 1668, 1445, 1367, 1177, 1074, 796, 739; HRMS (ESI) m/z calcd for $C_{24}H_{22}FN_2O_6S_2^+$ (M + H)$^+$ 517.0898, found 517.0897.

N-((2,4-Dimethyl-1,3-dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3f**): 44%, 75 mg; mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.42−8.44 (d, J = 8.0 Hz, 1 H), 7.99 (s, 1 H), 7.74−7.76 (d, J = 8.0 Hz, 1 H), 7.58−7.60 (m, 2 H), 7.50−7.52 (m, 4 H), 7.40−7.44 (m, 4 H), 4.54−4.58 (d, J = 16.0 Hz, 1 H), 4.22−4.26 (d, J = 16.0 Hz, 1 H), 3.45 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.6, 162.9, 140.2, 137.7, 135.1 (q, J_{C-F} = 271.0 Hz), 134.1, 129.8, 128.5, 125.3 (d, J_{C-F} = 43.4 Hz), 124.9 (d, J_{C-F} = 43.4 Hz), 121.9, 54.9, 48.0, 29.5, 27.6; IR (cm^{-1}) 1711, 1669, 1370, 1313, 1172, 743, 689; HRMS (ESI) m/z calcd for $C_{25}H_{22}F_3N_2O_6S_2^+$ (M + H)$^+$ 567.0866, found 567.0866.

N-((6-(*tert*-Butyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3g**): 60%, 100 mg; mp 200−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.29−8.31 (m, 1 H), 7.69−7.70 (m, 1 H), 7.56−7.62 (m, 4 H), 7.45−7.46 (m, 4 H), 7.38−7.42 (m, 3 H), 4.59−4.63 (d, J = 16.0 Hz, 1 H), 4.18−4.22 (d, J = 16.0 Hz, 1 H), 3.43 (s, 3 H), 1.69 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.6, 163.9, 157.5, 139.1, 138.0, 133.8, 129.6, 129.4, 128.9, 128.8, 125.7, 125.3, 125.1, 123.3, 122.6, 54.2, 47.9, 35.4, 30.8, 27.3; IR (cm^{-1}) 2962, 1712, 1666, 1374, 1170, 743, 686; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_2O_6S_2^+$ (M + H)$^+$ 555.1618, found 555.1610.

N-((6-Cyano-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3h**): 55%, 86 mg; mp 181−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.39 (d, J = 8.0 Hz, 1 H), 7.96−7.97 (m, 1 H), 7.71−7.73 (m, 1 H), 7.60−7.64 (m, 2 H), 7.55−7.57 (m, 4 H), 7.42−7.46 (m, 4 H), 4.53−4.57 (d, J = 16.0 Hz, 1 H), 4.26−4.30 (d, J = 16.0 Hz, 1 H), 3.46 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.2, 162.5, 140.4, 137.5, 131.9, 129.7, 129.0, 128.4, 117.4, 117.0, 55.3, 47.9, 29.3, 27.7; IR (cm^{-1}) 3066, 2957, 1715, 1671, 1450, 1427, 1368, 1175, 1082, 1059, 792, 735, 691; HRMS (ESI) m/z calcd for $C_{25}H_{22}N_3O_6S_2^+$ (M + H)$^+$ 524.0945, found 524.0944.

N-(Phenylsulfonyl)-*N*-((2,4,8-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzenesulfonamide (**3i**): 51%, 78 mg; mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.58−7.63 (m, 6 H), 7.51−7.53 (m, 1 H), 7.41−7.46 (m, 5 H), 7.29−7.31 (m, 1 H), 4.45−4.49 (d, J = 16.0 Hz, 1 H), 4.14−4.18 (d, J = 16.0 Hz, 1 H), 3.39 (s, 3 H), 2.82 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 164.5, 142.5, 140.7, 138.2, 133.9, 132.5, 132.0, 128.8, 128.7, 125.9,

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124.2, 55.5, 47.8, 29.1, 27.5, 23.9; IR (cm^{-1}) 3068, 2961, 1708, 1667, 1450, 1372, 1174, 1049, 810, 747; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_6S_2^+$ $(M + H)^+$ 513.1149, found 513.1148.

N-(Phenylsulfonyl)-*N*-((2,4,5-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzenesulfonamide and *N*-(phenylsulfonyl)-*N*-((2,4,7-trimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-benzenesulfonamide (**3j**): 66%, 101 mg; mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.12 (d, 0.77 H), 7.68−7.70 (m, 1 H), 7.58−7.61 (m, 5 H), 7.51−7.53 (m, 1.3 H), 7.36−7.47 (m, 5 H), 4.49−4.53 (d, *J* = 16.0 Hz, 1 H), 4.15−4.19 (d, *J* = 16.0 Hz, 1 H), 3.43 (s, 3 H), 2.64 (s, 0.5 H), 2.45 (s, 2.5 H), 1.88 (s, 0.5 H), 1.65 (s, 2.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.3, 164.1, 138.1, 138.0, 136.5, 134.5, 133.9, 133.8, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 125.6, 54.8, 53.9, 49.6, 47.5, 29.5, 27.9, 27.4, 24.2, 23.8, 20.9; IR (cm^{-1}) 1708, 1666, 1370, 1174, 1052, 745, 683; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_6S_2^+(M + H)^+$ 513.1149, found 513.1148.

N-((8-Fluoro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3k**): 32%, 49.5 mg; mp 169−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.12−8.14 (m, 1 H), 7.72−7.75 (m, 3 H), 7.55−7.60 (m, 3 H), 7.41−7.48 (m, 5 H), 7.04−7.09 (m, 1 H), 4.71−4.75 (d, *J* = 16.0 Hz, 1 H), 4.23−4.27 (d, *J* = 16.0 Hz, 1 H), 3.40 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.5, 163.1, 161.3 (d, J_{C-F} = 250 Hz), 158.8 (d, J_{C-F} = 250 Hz), 138.3, 133.9, 128.7, 125.1, 121.1, 120.9, 54.3, 46.8, 30.8, 27.6, 25.9, 25.8; IR (cm^{-1}) 3070, 2953, 1716, 1669, 1450, 1374, 1172, 1083, 850, 819, 756; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}FN_2O_6S_2^+$ $(M + H)^+$ 517.0898, found 517.0895.

N-((6-(Chloromethyl)-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3l**): 62%, 102 mg; mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.32−8.34 (m, 1 H), 7.59 (s, 1 H), 7.51−7.57 (m, 7 H), 7.39−7.45 (m, 4 H), 4.50−4.58 (m, 3 H), 4.21−4.25 (m, 1 H), 3.43 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 163.5, 143.1, 137.9, 133.9, 129.6, 128.9, 128.6, 128.5, 128.1, 128.0, 125.6, 54.7, 47.9, 44.9, 29.7, 27.5; IR (cm^{-1}) 3066, 2952, 1713, 1667, 1614, 1370, 1172, 1088, 1056, 799, 740, 682; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}ClN_2O_6S_2^+$ $(M + H)^+$ 547.0759, found 547.0759.

N-((8-Chloro-2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3m**): 35%, 56 mg; mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56−7.64 (m, 7 H), 7.41−7.51 (m, 6 H), 4.42−4.46 (m, 1 H), 4.18−4.22 (m, 1 H), 3.40 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.8, 161.7, 142.4, 134.0, 129.1, 128.8, 126.7, 123.0, 55.5, 48.2, 28.9, 27.9; IR (cm^{-1}) 3070, 2952, 1715, 1671, 1449, 1371, 1172, 1086, 742, 682; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}ClN_2O_6S_2^+$ $(M + H)^+$ 533.0602, found 533.0600.

N-((2-Ethyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3n**): 60%, 92 mg; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.32−8.34 (m, 1 H), 7.55−7.66 (m, 8 H), 7.48−7.52 (m, 1 H), 7.40−7.44 (m, 4 H), 4.51−4.55 (d, *J* = 16.0 Hz, 1 H), 4.29−4.33 (d, *J* = 16.0 Hz, 1 H), 4.07−4.14 (m, 2 H), 1.66 (s, 3 H), 1.26−1.29 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.9, 163.5, 139.7, 138.1, 133.5, 129.0, 128.8, 128.6, 127.9, 127.8, 125.8, 54.4, 47.8, 36.3, 30.6, 12.9; IR (cm^{-1}) 2976, 2934, 1708, 1665, 1455, 1369, 1174, 1087, 824, 749; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_6S_2^+$ $(M + H)^+$ 513.1149, found 513.1147.

N-((4-Methyl-1,3-dioxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3o**): 49%, 77 mg; mp 106−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.31−8.34 (m, 1 H), 7.55−7.66 (m, 8 H), 7.48−7.52 (m, 1 H), 7.40−7.44 (m, 4 H), 4.50−4.54 (d, *J* = 16.0 Hz, 1 H), 4.29−4.33 (d, *J* = 16.0 Hz, 1 H), 3.99−4.03 (m, 2 H), 1.67−1.77 (m, 2 H), 1.64 (s, 3 H), 0.98 (t, *J* = 8.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 163.7, 139.7, 138.0, 133.5, 129.1, 128.8, 128.6, 127.8, 125.8, 54.4, 47.8, 42.6, 30.7, 20.9, 11.5; IR (cm^{-1}) 2968, 1708, 1664, 1457, 1367, 1172, 1082, 749, 684; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_2O_6S_2^+$ $(M + H)^+$ 527.1305, found 527.1306.

N-((2-Butyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3p**): 35%, 57 mg; mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.31−8.34 (m, 1 H), 7.55−7.66 (m, 8 H), 7.48−7.52 (m, 1 H), 7.40−7.44 (m, 4 H), 4.50−4.54 (d, *J* = 16.0 Hz, 1 H), 4.29−4.33 (d, *J* = 16.0 Hz, 1 H), 4.02−4.06 (m, 2 H), 1.66 (s, 3 H), 1.62−1.64 (m, 2 H), 1.38−1.43 (m, 2 H), 0.95 (t, *J* = 8.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 163.7, 139.7, 138.1, 133.5, 129.0, 128.8, 128.6, 127.9, 127.8, 125.9, 54.4, 47.8, 40.9, 30.6, 29.7, 20.4, 13.8; IR (cm^{-1}) 2957, 1708, 1665, 1456, 1368, 1174, 1086, 826, 749, 686; HRMS (ESI) *m/z* calcd for $C_{27}H_{29}N_2O_6S_2^+$ $(M + H)^+$ 541.1462, found 541.1466.

N-((2-Isopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3q**): 30%, 47 mg; mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.29−8.31 (m, 1 H), 7.55−7.61 (m, 7 H), 7.51−7.55 (m, 1 H), 7.45−7.49 (m, 1 H), 7.40−7.46 (m, 4 H), 5.17−5.24 (m, 1 H), 4.48−4.52 (d, *J* = 16.0 Hz, 1 H), 4.33−4.37 (d, *J* = 16.0 Hz, 1 H), 1.64 (s, 3 H), 1.53 (d, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.4, 164.0, 139.7, 138.1, 133.4, 128.9, 128.8, 128.6, 127.8, 127.5, 126.5, 54.2, 47.9, 46.1, 30.9, 19.6, 19.4; IR (cm^{-1}) 2977, 2938, 1706, 1663, 1368, 1264, 1172, 1088, 805, 746; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_2O_6S_2^+$ $(M + H)^+$ 527.1305, found 527.1306.

N-((2-Benzyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3r**): 40%, 69 mg; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.30−8.33 (m, 1 H), 7.63−7.65 (m, 1 H), 7.57−7.61 (m, 3 H), 7.53−7.56 (m, 4 H), 7.39−7.51 (m, 7 H), 7.26−7.30 (m, 2 H), 7.21−7.23 (m, 1 H), 5.20−5.30 (m, 2 H), 4.51−4.55 (d, *J* = 16.0 Hz, 1 H), 4.24−4.28 (d, *J* = 16.0 Hz, 1 H), 1.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.0, 163.7, 139.6, 138.0, 137.2, 133.9, 133.7, 128.8, 128.7, 128.6, 128.3, 127.9, 127.8, 127.2, 125.8, 54.5, 48.0, 44.1, 30.2; IR (cm^{-1}) 3066, 1709, 1669, 1369, 1172, 1080, 820, 745, 696; HRMS (ESI) *m/z* calcd for $C_{30}H_{27}N_2O_6S_2^+$ $(M + H)^+$ 575.1305, found 575.1304.

N-((4,6-Dimethyl-5,7-dioxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-4-yl)methyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**3s**): 30%, 45 mg, oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.95−7.97 (m, 4 H), 7.71−7.74 (m, 2 H), 7.57−7.60 (m, 4 H), 7.12−7.13 (d, *J* = 4.0 Hz, 1 H), 6.64−6.65 (d, *J* = 4.0 Hz, 1 H), 5.31−5.34 (m, 2 H), 3.38 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4, 166.7, 142.6, 142.5, 140.1, 138.3, 134.6, 131.6, 129.2, 128.7, 122.3, 33.6, 29.7, 18.8; IR (cm^{-1}) 3098, 2929, 1693, 1655, 1446, 1379, 1304, 1179, 1060, 874, 753; HRMS (ESI) *m/z* calcd for $C_{22}H_{21}N_2O_6S_3^+$ $(M + H)^+$ 505.0556, found 505.0555.

N-(2-Methyl-3-(*N*-(phenylsulfonyl)phenylsulfonamido)acryloyl)-*N*-phenylbenzamide (**3t**): 40%, 67 mg; mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.98 (s, 1 H), 7.85−7.87 (m, 3 H), 7.63−7.65 (m, 3 H), 7.52−7.56 (m, 4 H), 7.44−7.48 (m, 3 H), 7.30−7.38 (m, 5 H), 7.10−7.16 (m, 2 H), 5.78 (s, 1 H), 5.44 (s, 1 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.6, 165.8, 137.9, 134.9, 131.8, 129.0, 128.9, 128.7, 127.0, 124.5, 124.4, 120.2, 120.0, 119.7, 18.7; IR (cm^{-1}) 1656, 1525, 1439, 1321, 747, 686; Elemental Anal. Calcd for $C_{29}H_{24}N_2O_6S_2$ C 62.13, H 4.31, N 5.00, O 17.12, S 11.44; found C 62.17, H 4.33, N 5.01, O 17.15, S 11.34.

N-(2,2-Diphenylvinyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**4a**):[5g] 60%, 85.5 mg; mp 171−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.69−7.71 (m, 4 H), 7.54−7.58 (m, 2 H), 7.37−7.41 (m, 4 H), 7.29−7.34 (m, 3 H), 7.20−7.29 (m, 7 H), 6.13 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.2, 139.8, 138.6, 136.7, 133.7, 128.7, 128.3, 128.1, 116.2; IR (cm^{-1}) 3066, 2925, 1669, 1447, 1376, 1170, 1085, 899, 811, 756, 699.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02337.

^{1}H and ^{13}C NMR spectra of all of the compounds (PDF)

Optimized structures of the intermediates and transition states and Cartesian coordinates of all of the structures (PDF)

X-ray crystallographic data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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