JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03305 • Publication Date (Web): 24 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Access to (*Z*)-1,2-Endiamides and 1,1-Endiamides via a Base-Promoted Tandem Reaction

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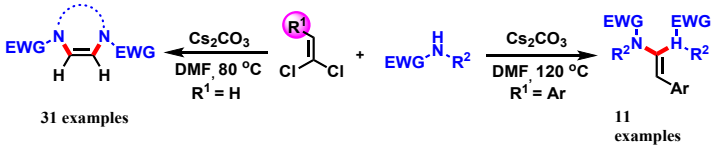
Supporting Information



ABSTRACT: An efficient base-promoted tandem reaction between vinyl 1,1-dichlorides and secondary sulfonamides with ynamide as the key intermediate is described. This method provides a facile approach to (*Z*)-1,2-endiamide and aryl 1,1-endiamide derivatives via the *β*-hydroamidation of terminal ynamides and the *α*-hydroamidation of internal ynamides, respectively. Moreover, this reaction proceeded through double elimination of vinyl chlorides and double addition of nucleophiles to alkynes. In addition, this transformation features readily available starting materials, mild reaction conditions, a broad substrate scope, a wide functional group tolerance, and an operational convenience.

■ INTRODUCTION

(*Z*)-1,2-Endiamides/1,1-endiamides are important structural motifs in many bioactive molecules and natural products (Figure 1).[1] Well-known examples of compounds containing the (*Z*)-1,2-endiamide unit include enkephalinase inhibitor (**A**)[2] and NK1 receptor (**B**)[3] as well as the antitubercular natural cyclic peptides Callyaerin (**C**)[4] and Viomycin (**D**).[5] In addition, the cell-cell adhesion inhibitor dibohemamine (**E**)[6] and insecticide (**F**)[7] contain the 1,1-endiamide skeleton. Furthermore, (*Z*)-1,2-endiamide and 1,1-endiamide compounds have also been used as building blocks in organic syntheses.[8] Although the usefulness of the motifs, only a few examples for the synthesis of (*Z*)-1,2-endiamide and 1,1-endiamide derivatives are available. Substitution reaction is the traditional synthetic strategy in this field,[9] but these methods are limited by complex substrates, a low stereoselectivity, and harsh reaction conditions.[10] Accordingly, the development of a novel strategy to achieve (*Z*)-1,2-endiamide and 1,1-endiamide analogues from readily available starting materials under simple and mild conditions is highly desirable.

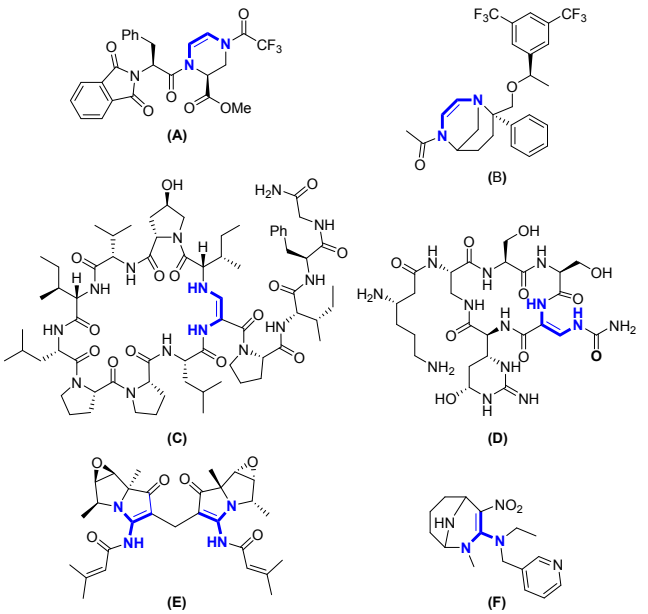
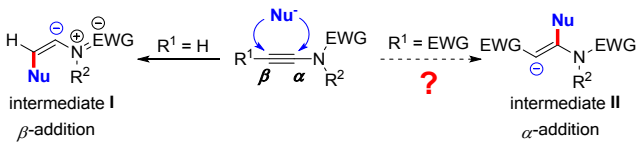


Figure 1. Bioactive compounds containing the (*Z*)-1,2-endiamide and 1,1-endiamide moieties.

Over the past few decades, the transformations of ynamides have been developed as a powerful tool for the construction of nitrogen-containing heterocycles and complex organic molecules.[11] For example, the addition of ynamides has attracted considerable attention due to the unique structure of ynamides.[12] However, precisely controlling of the regioselectivity and stereoselectivity of this transformation remains a challenge.[13] Theoretically, ynamides consist of two polar resonance structures, i.e., the keteniminium and yniminium structures.[14] The former, which undergoes *α*-addition with nucleophiles under acidic conditions or in the presence of transition metal catalysts, has been extensively studied.[15] In contrast, the "umpolung-type" *β*-addition of ynamides has been less explored,[16] although radical addition[17] and the carbometallation of ynamides[18] allow the *β*-addition reaction to take place.[19] Recently, Dodd[20] and our group[21] reported the base-promoted *β*-addition of ynamides for the synthesis of disubstituted (*Z*)-enamide derivatives with excellent regio- and stereoselectivities. However, these prior studies suggested that the *β*-addition reaction via this strategy is limited to terminal ynamides due to the steric hindrance and the stability of intermediate **I** originated from the yniminium resonance structure of the ynamide (Scheme 1, left). Thus, considering the steric hindrance and stability of the intermediate vinyl anion,[22] we reasoned that the *α*-addition



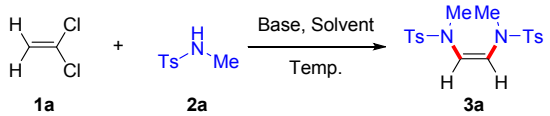
Scheme 1. Addition reactions of ynamides.

might also be possible for election-withdrawing group-containing internal ynamides via intermediate **II** (Scheme 1, right). Based on our previous studies on the preparation of ynamides from sulfonamides and vinyl 1,1-dichlorides,[23] we herein describe a robust one-pot strategy for the synthesis of 1,2-endiamides via the β-addition of terminal ynamides, in addition to the preparation of 1,1-endiamides via the α-addition of internal ynamides.

■ RESULTS AND DISCUSSION

We initially investigated the model tandem reaction between 1,1-dichloroethylene (**1a**) and *N*,4-dimethylbenzenesulfonamide (**2a**) to optimize the reaction conditions. The corresponding product 1,2-endiamide (**3a**) was obtained in 66% isolated yield with excellent regio- and stereoselectivities (*Z*:*E* > 99:1) using NaH (6 equiv) as the base in DMF at 80 °C (Table 1, entry 1). The screening of different bases revealed that Cs_2CO_3 was the most efficient, affording the desired product in 96% yield (Table 1, entries 2–6). No improvement was observed when DMSO, THF, EtOH, or MeCN was used as the solvent (Table 1, entries 7–10). Furthermore, shortening the reaction time or altering the reaction temperature was not beneficial to the reaction (Table 1, entries 11 and 14), and reducing the amount of base or substrate **2a** also gave poorer results (Table 1, entries 15 and 16).

Table 1. Optimization of the Reaction Conditions[a]



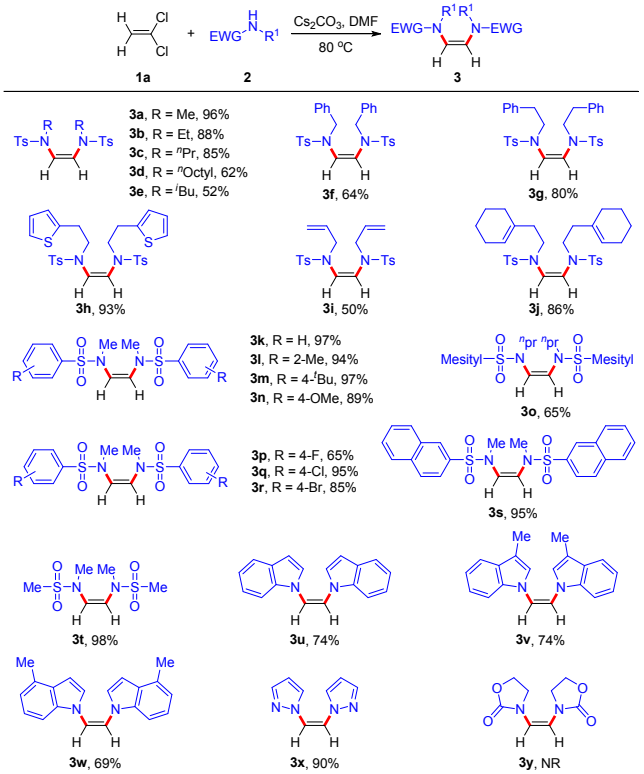
1a **2a** **3a**

entry	base (x equiv)	solvent	time (h)	temp. (°C)	yield (%)[b]
1	NaH (6)	DMF	24	80	66
2	DBU (6)	DMF	24	80	ND
3	K_2CO_3 (3)	DMF	24	80	15
4	CsOH (6)	DMF	24	80	trace
5	**Cs_2CO_3 (3)**	**DMF**	**24**	**80**	**96**
6	NaOH (6)	DMF	24	80	67
7	Cs_2CO_3 (3)	DMSO	24	80	53
8	Cs_2CO_3 (3)	THF	24	80	ND
9	Cs_2CO_3 (3)	EtOH	24	80	ND
10	Cs_2CO_3 (3)	MeCN	24	80	ND
11	Cs_2CO_3 (3)	DMF	18	80	92
12	Cs_2CO_3 (3)	DMF	12	80	73
13	Cs_2CO_3 (3)	DMF	24	100	72
14	Cs_2CO_3 (3)	DMF	24	60	64
15	Cs_2CO_3 (2)	DMF	24	80	78
16[c]	Cs_2CO_3 (3)	DMF	24	80	90

[a] Reaction condition: **1a** (0.2 mmol), **2a** (0.6 mmol), and base (0.6 mmol) in solvent (1.0 mL) at 80 °C for 24 h. [b]Isolated yields. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR spectroscopy). [c]**2a** (0.5 mmol) was used.

Having established the optimal reaction conditions, the reaction scope and limitations with respect to the secondary amides (**2**) were examined. As illustrated in Scheme 2, our results demonstrate that the tandem reaction exhibits good functional group tolerance with a broad substrate scope. Indeed, secondary sulfonamides **2** bearing linear alkyl, branched alkyl, and some unsaturated bond-containing groups afforded the corresponding products (**3a–3j**) in moderate to excellent yields. In addition, the presence of phenyl rings on the sulfonyl moiety bearing electron-donating groups such as 2-Me, 4-^{t}Bu, and 4-OMe were also compatible, affording the desired products (**3k–3n**) in 89–97% yields. It should be noted that the sterically hindered mesityl sulfonamide group also exhibited a good reactivity (**3o**). Substrates containing halogen atoms (i.e., -F, -Cl, and -Br) at the 4-position of the phenyl ring were also tolerated, giving the corresponding products (**3p–3r**) in good to excellent yields. Moreover, *N*-methylnaphthalene-2-sulfonamide and *N*-methylmethanesulfonamide afforded the target products (**3s** and **3t**) in excellent yields. Interestingly, the reaction was also amenable to nitrogen-containing heterocyclicaryl substrates such as indoles, substituted indoles, and pyrazoles under the standard reaction conditions. The structure of **3u** was confirmed by X-ray chromatography (See the Supporting Information for details). However, no reaction was observed with oxazolidin-2-one as substrate under the optimized conditions, it is could be due to the effect of carbonyl of oxazolidin-2-one.

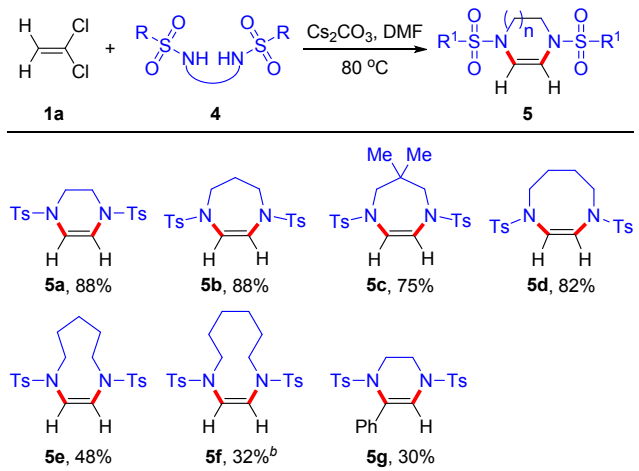
Scheme 2. Scope of the Secondary Amide Substrate[a]



[a]Reaction conditions: 1,1-Dichloroethylene **1a** (0.2 mmol), secondary amide **2** (0.6 mmol), and Cs_2CO_3 (0.6 mmol) in DMF (1.0 mL) at 80 °C for 24 h.

We subsequently evaluated the disulfonamide substrate scope of the tandem reaction for the synthesis of cycloendiamides **5** under the optimized conditions. As shown in Scheme 3, *N*,*N*′-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) underwent the tandem reaction with 1,1-dichloroethylene to give the 1,2,3,4-tetrahydropyrazine derivative **5a** in 88% yield. Products **5b** and **5c** bearing a seven-membered ring could also be synthesized in a high efficiency under this reaction system. Furthermore, the reaction of 1,4-butanedisulfonamide proceeded smoothly, delivering the desired eight-membered ring product **5d** in a good yield. The structure of **5d** was confirmed by X-ray chromatography (See the Supporting

Scheme 3. Scope of the Disulfonamide Substrate[a]



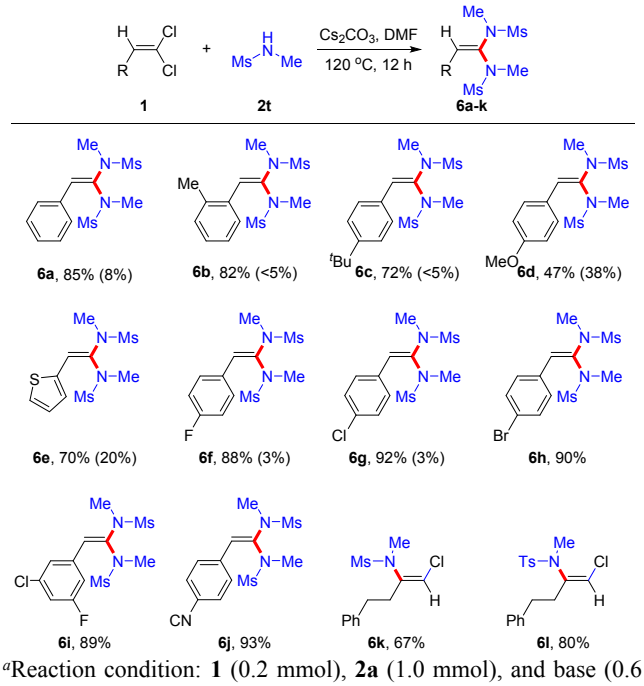
[a]Reaction conditions: 1,1-Dichloroethene **1a** (0.2 mmol), disulfonamide **4** (0.3 mmol), and Cs_2CO_3 (0.6 mmol, 3.0 equiv) in DMF (1.0 mL) at 80 °C for 24 h. [b]5 mL DMF was used.

Information for details). In addition, the synthesis of nine- and ten-membered ring products (**5e** and **5f**) was achieved in 48% and 32% yields, respectively. Importantly, aryl 1,1-dichloroethylene was found to be compatible with *N*,*N*′-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) under the standard reaction conditions to give the desired cyclization product **5g** albeit in 30% yield.

Subsequently, we examined the substrate scope of the aryl 1,1-dichloroethylenes under the optimized conditions. The reaction between (2,2-dichlorovinyl)benzene and *N*,4-dimethylbenzenesulfonamide (**2a**) provided a complex mixture. Pleasingly, after a number of attempts, the α-addition product 1,1-endiamide (**6a**) instead of β-addition product 1,2-endiamide was obtained in 40% yield by using *N*-methylmethanesulfonamide (**2t**) as the substrate under the standard reaction conditions. The structure of **6a** was confirmed by X-ray chromatography (See the Supporting Information for details). It was also found that the yield of **6a** could be increased to 85% with a high regioselectivity (α-**6a**/β-**6a** > 10/1, determined by crude ^{1}H NMR measurements) by increasing the amount of **2t** to 5.0 equiv and increasing the reaction temperature to 120 °C.

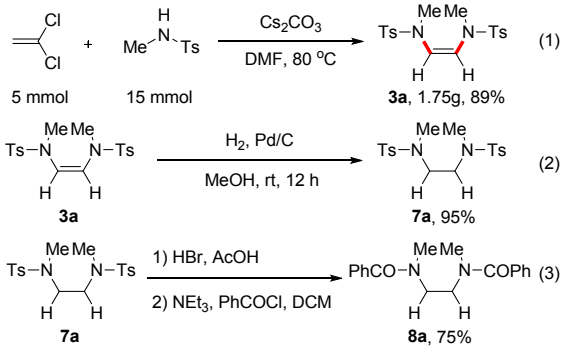
The substrate scope was then investigated with respect to the aryl 1,1-dichloroethylenes, and the results are summarized in Scheme 4. The substrates bearing weak electron-donating groups such as Me and ^{t}Bu on the phenyl ring were smoothly converted to the desired α-addition products (**6b** and **6c**) in good yields and high regioselectivities. However, when the strongly electron-donating OMe group (**6d**) was installed on the phenyl ring, the yield of the β-addition product 1,2-endiamide increased to 38% and a mixture of products was obtained in a total yield of 85%. A similar result was observed for the electron-rich substrate thiophenyl 1,1-dichloroethylene, which gave a mixture of products (**6e**) in a 90% total yield (α-**6e**/β-**6e** = 7/2). Furthermore, substrates bearing halogen atoms such as 4-F, 4-Cl, 4-Br, and 3-Cl-5-F on the phenyl ring delivered the corresponding 1,1-endiamide products (**6f** and **6i**) in high yields and high regioselectivities. For the electron-withdrawing groups 4-CN, the reactions could afford the corresponding products (**6j**) in high yields and excellent regioselectivities. Moreover, as expected, substrates bearing alkyl groups afforded vinyl chloride products (**6k** and **6l**) instead of the 1,2-endiamide or 1,1-endiamide products.

Scheme 4. Scope of the 1,1-Dichloroethylene Substrate for the Synthesis of 1,1-Endiamides[a]



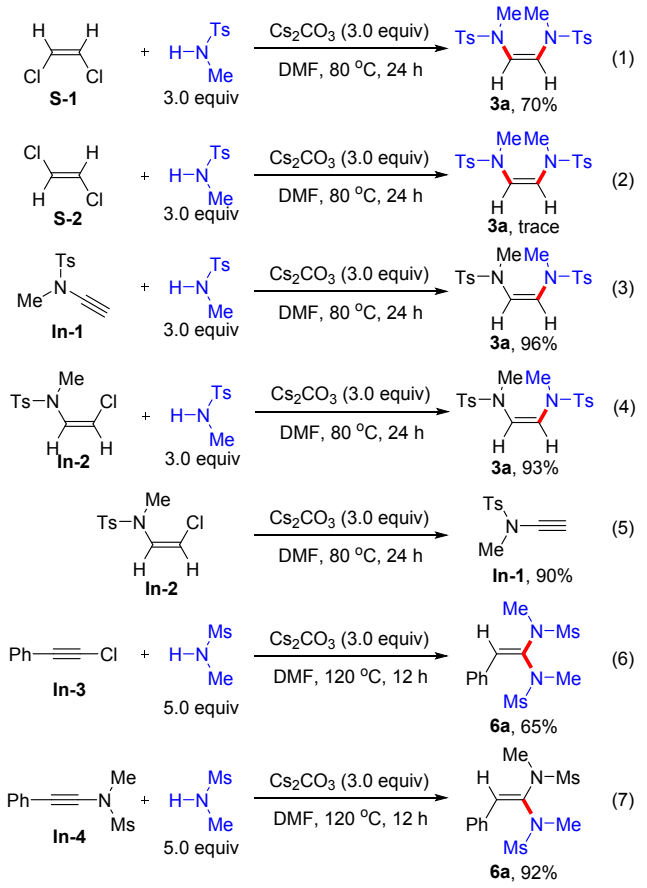
[a]Reaction condition: **1** (0.2 mmol), **2a** (1.0 mmol), and base (0.6 mmol) in DMF (1.0 mL) at 120 °C for 12 h. Yields of the β-addition product are shown in parentheses, and were determined by crude ^{1}H NMR measurements.

Scheme 5. Large-scale Synthesis and Application of the Method



Finally, we turned our attention to the scalability and potential application of this method (Scheme 5). First, a gram-scale operation was performed on 5 mmol of **1a**, affording 1,2-endiamide product **3a** in 89% yield (Scheme 5, eq 1). The subsequent hydrogenation of **3a** was then carried out in the presence of Pd/C to afford the desired 1,2-diamide **7a** in 95% yield (Scheme 5, eq 2). A one-pot two-step combined removal of the Ts group and subsequent acylation provided **8a** in a total yield of 75% (Scheme 5, eq 3),[24] thereby indicating the potential application of this reaction.

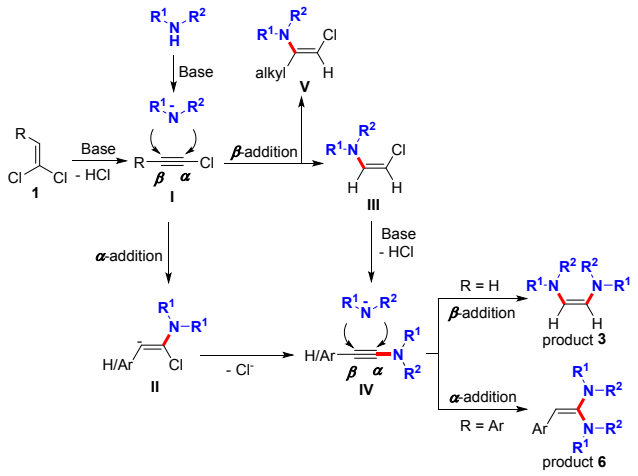
Scheme 6. Control Experiments



To understand the mechanistic pathway, a number of control experiments were carried out (Scheme 6). Under the standard reaction conditions, the tandem reaction using (*Z*)-1,2-dichloroethylene as a substrate resulted in smooth conversion to the 1,2-endiamide product **3a** in 70% yield (Scheme 6, eq 1), while the reaction using (*E*)-1,2-dichloroethylene failed to proceed (Scheme 6, eq 2). In addition, when ynamide **In-1** or vinyl chloride **In-2** were reacted with *N*,4-dimethylbenzenesulfonamide (**2a**) under the standard reaction conditions (Scheme 6, eqs 3 and 4), 1,2-endiamide product **3a** was obtained in excellent yields of 96% and 93%, respectively. Furthermore, ynamide **In-1** was obtained in 90% yield by the direct reaction of vinyl chloride **In-2** under the standard conditions (Scheme 6, eq 5). Moreover, when (chloroethynyl)benzene **In-3** and ynamide **In-4** were employed as substrates, the corresponding 1,1-endiamide product **6a** was obtained in 65% and 92% yields, respectively (Scheme 6, eqs 6 and 7). These results suggested that the ynamide, the vinyl chloride, and the alkynyl chloride could all be key intermediates in this tandem reaction.

Based on the above results, a possible mechanism for this base-promoted tandem reaction of 1,1-dichloroethylenes and secondary amides is presented in Scheme 7. Under basic reaction conditions, an initial elimination of the 1,1-dichloroethylenes would generate intermediate chloroalkyne **I**. Ynamide **IV** could then be obtained through the second elimination of either intermediate **II** from the α-addition of nucleophile $R^1R^2N^-$ to chloroalkyne **I** when the R group of the 1,1-dichloroethylene is Ar or H, or intermediate **III** from the

Scheme 7. Plausible Reaction Mechanism



β-addition of nucleophile $R^1R^2N^-$ to chloroalkyne **I** when the R group of the 1,1-dichloroethylene is H. Subsequently, the second addition of nucleophile $R^1R^2N^-$ to ynamide **IV** affords the corresponding tandem product **3** or **6**. When the R group is H, the β-addition product **3** is obtained due to steric factors, while α-addition product **6** is obtained when the R group is Ar due to electronic factors. In contrast, when the 1,1-dichloroethylenes bear an alkyl R group, the β-addition of nucleophile $R^1R^2N^-$ to intermediate chloroalkyne **I** takes place to directly afford the tri-substituted vinyl chloride product **V** that cannot undergo a second elimination.

■ CONCLUSIONS

In conclusion, we successfully developed an efficient method for the synthesis of 1,2-endiamide and 1,1-endiamide derivatives via a base-promoted tandem reaction of vinyl 1,1-dichlorides and secondary amides where ynamide acts as the key intermediate. It was found that the product regioselectivity could be switched by the introduction of different substituents on the vinyl 1,1-dichloride substrates. In addition, the results of control experiments showed that this unprecedented tandem reaction takes place through the double elimination reactions of vinyl chlorides and the double addition reactions of alkynes. Furthermore, this process is particularly attractive due to the absence of transition metals, the mild reaction conditions, the broad substrate scope, a good functional group tolerance, and its operational simplicity, thereby rendering it a useful method for application in organic syntheses.

■ EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware and were monitored by thin-layer chromatography (TLC). All reagents and solvents were purchased from commercial vendors and used without further purification. Starting material vinyl dichlorides and secondary amides were either purchased from commercial vendors or synthesized following our previous works.[23a]

$^1H/^{13}C$ NMR spectra were recorded on Bruker Avance 400 MHz and Bruker AMX 400 MHz spectrometer at 400/100 MHz, respectively, in $CDCl_3$ or DMSO-d_6, using either TMS or the undeuterated solvent residual signal as the reference. Chemical shifts are given in ppm and are measured relative to $CDCl_3$ or

DMSO-d_6 as an internal standard. High resolution mass spectra (HRMS) were obtained by the electrospray ionization time-of-flight (ESI-TOF) mass spectrometry. Flash column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) in light petroleum ether (PE).

General procedure for the synthesis of 1,2-endiamides in Scheme 1. To a mixture of secondary amide (0.6 mmol, 3.0 equiv), and Cs_2CO_3 (0.6 mmol, 3.0 equiv) was added a solution of 1,1-dichloroethylene (0.2 mmol, 1.0 equiv) in DMF (1.0 mL). The mixture was stirred at 80 °C (heating mantle) for 24 h and the reaction was cooled to room temperature. Then the reaction was quenched by water and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with petroleum ether/ethyl acetate.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N,4-dimethylbenzenesulfonamide) (**3a**)*. Yield 96% (75.6 mg); white solid, Mp: 156–158 °C; TLC R_f = 0.3 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.0 Hz, 4H), 5.54 (s, 2H), 2.99 (s, 6H), 2.43 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.1, 133.7, 129.8, 127.6, 118.3, 36.6, 21.6. IR (KBr) $\tilde{\nu}$ 2923, 1662, 1600, 1347, 1162, 811, 547 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_4S_2$ [M + Na]$^+$ 417.0913, found 417.0907.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-ethyl-4-methylbenzenesulfonamide) (**3b**)*. Yield 88% (74.3 mg); yellow solid, Mp: 83–85 °C; TLC R_f = 0.5 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.0 Hz, 4H), 5.49 (s, 2H), 3.46 (q, J = 7.2 Hz, 4H), 2.42 (s, 6H), 1.08 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):: δ 143.9, 135.3, 129.6, 127.6, 117.1, 43.9, 21.5, 13.7. IR (KBr) $\tilde{\nu}$ 3029, 2931, 2869, 1656, 1351, 1159, 680 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_4S_2$ [M + Na]$^+$ 445.1226, found 445.1221.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(4-methyl-N-propylbenzenesulfonamide) (**3c**)*. Yield 85% (76.5 mg); white solid, Mp: 73–75 °C; TLC R_f = 0.3 (PE/EA = 10:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.3 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 5.47 (s, 2H), 3.33–3.29 (m, 4H), 2.42 (s, 6H), 1.57–1.47 (m, 4H), 0.81 (t, J = 7.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.8, 135.4, 129.5, 127.6, 117.5, 50.9, 21.6, 21.5, 11.1. IR (KBr) $\tilde{\nu}$ 2927, 2852, 1351, 1662, 813, 673, 545 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{31}N_2O_4S_2$ [M + H]$^+$ 451.1720, found 451.1717.

*(Z)-N,N′-(ethene-1,2-diyl)bis(4-methyl-N-octylbenzenesulfonamide) (**3d**)*. Yield 62% (73.2 mg); white solid, Mp: 108–110 °C; TLC R_f = 0.8 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, CDCl3): δ 7.64 (d, J = 8.2 Hz, 4H), 7.29 (d, J = 8.0 Hz, 4H), 5.45 (s, 2H), 3.38–3.30 (m, 4H), 2.41 (s, 6H), 1.49–1.45 (m, 4H), 1.29–1.23 (m, 20H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, CDCl3): δ 143.8, 135.4, 129.6, 127.6, 117.3, 49.3, 31.8, 29.3, 29.2, 28.5, 26.8, 22.6, 21.5, 14.0. IR (KBr) $\tilde{\nu}$ 2956, 2854, 1698, 1600, 1353, 1159, 815, 590, 549 cm^{-1}. HRMS (ESI) calcd for $C_{32}H_{50}N_2NaO_4S_2$ [M + Na]$^+$ 613.3104, found 613.3101.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-isobutyl-4-methylbenzenesulfonamide) (**3e**)*. Yield 52% (49.7 mg); white solid, Mp: 74–76 °C; TLC R_f = 0.6 (PE/EA = 10:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.2 Hz, 4H), 7.27 (d, J = 8.0 Hz, 4H), 5.43 (s, 2H), 3.17 (d, J = 7.4 Hz, 4H), 2.40 (s, 6H), 1.83–1.76 (m, 2H), 0.80 (d, J = 6.6 Hz, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.7, 135.9, 129.5, 127.6, 118.5, 57.1, 27.4, 21.5, 20.1. IR (KBr) $\tilde{\nu}$ 2964, 2875, 1600, 1338, 1168, 811, 663 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{35}N_2O_4S_2$ [M + H]$^+$ 479.2033, found 479.2032.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-benzyl-4-methylbenzenesulfonamide) (**3f**)*. Yield 64% (70.1 mg); white solid, Mp: 163–165 °C; TLC R_f = 0.7 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 4H), 7.22 (d, J = 8.1 Hz, 4H), 7.12–7.09 (m, 6H), 6.93 (d, J = 6.8 Hz, 4H), 5.51 (s, 2H), 4.44 (s, 4H), 2.39 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.9, 135.6, 135.5, 129.5, 128.3, 128.2, 127.6, 127.4, 117.1, 52.5, 21.5. IR (KBr) $\tilde{\nu}$ 2921, 2852, 1590, 1490, 1157, 931, 674, 619, 545 cm^{-1}. HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO_4S_2$ [M + Na]$^+$ 569.1539, found 569.1545.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(4-methyl-N-phenethylbenzenesulfonamide) (**3g**)*. Yield 80% (91.8mg); yellow solid, Mp: 104–106 °C; TLC R_f = 0.6 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 4H), 7.28–7.23 (m, 8H), 7.20–7.13 (m, 6H), 5.62 (s, 2H), 3.64–3.60 (m, 4H), 2.82–2.78 (m, 4H), 2.36 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.2, 138.1, 134.9, 129.8, 128.6, 127.7, 126.5, 117.8, 50.7, 34.7, 21.5. IR (KBr) $\tilde{\nu}$ 3025, 2933, 1658, 1498, 1159, 757, 549 cm^{-1}. HRMS (ESI) calcd for $C_{32}H_{35}N_2O_4S_2$ [M + H]$^+$ 575.2033, found 575.2031.

*(Z)-4-Methyl-N-(2-((4-methyl-N-(2-(thiophen-2-yl)ethyl)phenyl)sulfonamido)vinyl)-N-(2-(thiophen-2-yl)ethyl)benzenesulfonamide (**3h**)*. Yield 93% (109.1 mg); white solid, Mp: 80–82 °C; TLC R_f = 0.5 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 4H), 7.29 (d, J = 8.1 Hz, 4H), 7.11 (dd, J = 5.1, 1.1 Hz, 2H), 6.89 (dd, J = 5.1, 3.4 Hz, 2H), 6.79 (dd, J = 3.3, 0.8 Hz, 2H), 5.58 (s, 2H), 3.67–3.63 (m, 4H), 3.04–3.00 (m, 4H), 2.39 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.3, 139.9, 134.7, 129.8, 127.7, 127.0, 125.5, 123.9, 117.7, 50.6, 28.8, 21.6. IR (KBr) $\tilde{\nu}$ 2927, 2854, 1658, 1353, 1087, 811, 545 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{31}N_2O_4S_4$ [M + H]$^+$ 587.1161, found 587.1162.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-allyl-4-methylbenzenesulfonamide) (**3i**)*. Yield 50% (44.6 mg); white solid, Mp: 99–101 °C; TLC R_f = 0.4 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 5.69–5.59 (m, 2H), 5.51 (s, 2H), 5.14–5.06 (m, 4H), 4.07 (d, J = 6.1 Hz, 4H), 2.42 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.0, 135.2, 132.3, 129.6, 127.7, 118.5, 117.0, 51.6, 21.5. IR (KBr) $\tilde{\nu}$ 3085, 2929, 1658, 1180, 937, 607, 545 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{26}N_2O_4S_2Na$ [M + Na]$^+$ 469.1226, found 469.1221.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide) (**3j**)*. Yield 86% (100.1 mg); white solid, Mp: 178–180 °C; TLC R_f = 0.7 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 5.47 (s, 2H), 5.36 (s, 2H), 3.49–3.44 (m, 4H), 2.42 (s, 6H), 2.12 (t, J = 8.0 Hz, 4H), 1.97–1.92 (m, 4H) , 1.89–1.84 (m, 4H), 1.60–1.56 (m, 4H), 1.54–1.50 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.8, 135.2, 134.2, 129.6, 127.7, 123.3, 117.3, 48.2, 36.3, 28.5, 25.2, 22.9, 22.3, 21.5. IR (KBr) $\tilde{\nu}$ 2931, 2857, 1600, 1332, 1162, 811, 553 cm^{-1}. HRMS (ESI) calcd for $C_{32}H_{43}N_2O_4S_2$ [M + H]$^+$ 583.2659, found 583.2661.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N-methylbenzenesulfonamide) (**3k**)*. Yield 97% (71.1 mg); yellow solid, Mp: 115–117 °C; TLC R_f = 0.5 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.3 Hz, 4H), 7.61 (t, J = 7.2 Hz, 2H), 5.54 (t, J = 7.5 Hz, 4H), 5.56 (s, 2H), 3.00 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 136.7, 133.2, 129.1, 127.5, 118.4, 36.6. IR (KBr) $\tilde{\nu}$ 3062, 2929, 1654, 1344, 1091, 838, 578 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_4S_2$ [M + Na]$^+$ 389.0600, found 389.0592.

*(Z)-N,N′-(Ethene-1,2-diyl)bis(N,2-dimethylbenzenesulfonamide) (**3l**)*. Yield 94% (74.1 mg); yellow liquid, TLC R_f = 0.8 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 1.6 Hz, J = 8.8 Hz, 2H), 7.49–7.45 (m, 2H), 7.33 (d, J = 7.4 Hz, 4H), 5.63 (s, 2H), 3.08 (s, 6H), 2.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.1, 135.7, 133.1, 130.0, 130.0, 126.3, 117.4, 36.6, 21.0. IR (KBr) $\tilde{\nu}$ 2931, 2859,

1704, 1346, 1166, 1093, 815, 713 549 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{23}N_2O_4S_2$ $[M + H]^+$ 395.1094, found 395.1085.

(Z)-N,N′-(Ethene-1,2-diyl)bis(4-(tert-butyl)-N-methylbenzenesulfonamide) ***(3m)***. Yield 97% (92.7 mg); white solid, Mp: 180–182 °C; TLC R_f = 0.5 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.6 Hz, 4H), 7.54 (d, J = 8.4 Hz, 4H), 5.57 (s, 2H), 3.01 (s, 6H), 1.34 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.0, 133.8, 127.5, 126.1, 118.4, 36.7, 35.2, 31.1. IR (KBr) $\tilde{\nu}$ 2962, 2871, 1860, 1594, 1346, 1172, 759, 659 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{34}N_2O_4S_2Na$ $[M + Na]^+$ 501.1852, found 501.1846.

(Z)-N,N′-(Ethene-1,2-diyl)bis(4-methoxy-N-methylbenzenesulfonamide) ***(3n)***. Yield 89% (75.8 mg); white solid, Mp: 115–157 °C; TLC R_f = 0.5 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.9 Hz, 4H), 7.00 (d, J = 8.9 Hz, 4H), 5.54 (s, 2H), 3.87 (s, 6H), 2.98 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.3, 129.7, 128.3, 118.2, 114.3, 55.7, 36.6. IR (KBr) $\tilde{\nu}$ 3075, 2923, 1658, 1351, 1022, 836, 557 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_6S_2Na$ $[M + Na]^+$ 449.0811, found 449.0804.

(Z)-N,N′-(Ethene-1,2-diyl)bis(2,4,6-trimethyl-N-propylbenzenesulfonamide) ***(3o)***. Yield 65% (65.8 mg); yellow solid, Mp: 75–77 °C; TLC R_f = 0.5 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 4H), 5.70 (s, 2H), 3.33 (t, J = 8.0 Hz, 4H), 2.57 (s, 12H), 2.27 (s, 6H), 1.36–1.31 (m, 4H), 0.68 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.7, 139.7, 133.3, 132.1, 116.5, 50.1, 23.5, 21.4, 20.9, 11.1. IR (KBr) $\tilde{\nu}$ 2969, 2940, 1604, 1332, 989, 674 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{38}N_2NaO_4S_2$ $[M + Na]^+$ 529.2165, found 529.2150.

(Z)-N,N′-(Ethene-1,2-diyl)bis(4-fluoro-N-methylbenzenesulfonamide) ***(3p)***. Yield 65% (52.2 mg); white solid, Mp: 118–120 °C; TLC R_f = 0.5 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.78 (m, 4H), 7.27–7.20 (m, 4H), 5.54 (s, 2H), 3.01 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.7 ($J_{C\text{-}F}$ = 254.2 Hz), 132.8, 130.3 ($J_{C\text{-}F}$ = 9.4 Hz), 118.3, 116.6 ($J_{C\text{-}F}$ = 22.4 Hz), 36.6. IR (KBr) $\tilde{\nu}$ 3102, 2919, 2850, 1662, 1492, 1351, 979, 842, 649 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{17}F_2N_2O_4S_2$ $[M + H]^+$ 403.0592, found 403.0586.

(Z)-N,N′-(Ethene-1,2-diyl)bis(4-chloro-N-methylbenzenesulfonamide) ***(3q)***. Yield 95% (82.4 mg); white solid, Mp: 145–147 °C; TLC R_f = 0.5 (PE/EA = 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 4H), 7.52 (d, J = 8.3 Hz, 4H), 5.54 (s, 2H), 3.01 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.9, 135.2, 129.5, 129.0, 118.3, 36.6. IR (KBr) $\tilde{\nu}$ 3091, 2925, 1662, 1355, 1168, 761, 601, 480 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{17}Cl_2N_2O_4S_2$ $[M + H]^+$ 435.0001, found 434.9997.

(Z)-N,N′-(Ethene-1,2-diyl)bis(4-bromo-N-methylbenzenesulfonamide) ***(3r)***. Yield 85% (88.7 mg); white solid, Mp: 130–132 °C; TLC R_f = 0.6 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (m, 4H), 7.64–7.62 (m, 4H), 5.56 (s, 2H), 2.99 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 135.7, 132.5, 129.0, 128.4, 118.3, 36.6. IR (KBr) $\tilde{\nu}$ 3093, 2925, 2958, 1660, 1361, 1178, 748, 592 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{16}Br_2N_2NaO_4S_2$ $[M + Na]^+$ 544.8810, found 544.8828.

(Z)-N,N′-(Ethene-1,2-diyl)bis(N-methylnaphthalene-2-sulfonamide) ***(3s)***. Yield 95% (88.5 mg); white solid, Mp: 138–140 °C; TLC R_f = 0.6 (PE/EA = 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 1.0 Hz, 2H), 7.89–7.87 (m, 4H), 7.82 (d, J = 7.9 Hz, 2H), 7.67 (dd, J = 1.8 Hz, J = 8.7 Hz, 2H), 7.59–7.51 (m, 4H), 5.56 (s, 2H), 2.99 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 135.0, 133.8, 132.1, 129.4, 129.3, 129.0 (2C), 128.0, 127.7, 122.6, 118.4, 36.8. IR (KBr) $\tilde{\nu}$ 3060, 2923, 1662, 1347, 1166, 674, 545, 482 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{22}N_2O_4S_2Na$ $[M + Na]^+$ 489.0913, found 489.0905.

(Z)-N,N′-(Ethene-1,2-diyl)bis(N-methylmethanesulfonamide) ***(3t)***. Yield 98% (47.4 mg); white solid, Mp: 104–106 °C; TLC R_f = 0.4 (PE/EA = 5:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$)*:* δ 5.70 (d, J = 2.8 Hz, 2H), 3.16 (d, J = 2.8 Hz, 6H), 2.89 (d, J = 2.7 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 119.0, 36.4, 36.2. IR (KBr) $\tilde{\nu}$ 3014, 2935, 1662, 1330, 1159, 759, 518 cm^{-1}. HRMS (ESI) calcd for $C_6H_{15}N_2O_4S_2$ $[M + H]^+$ 243.0468, found 243.0465.

(Z)-1,2-Di(1H-indol-1-yl)ethene ***(3u)***. Yield 74% (38.2 mg); brown solid, Mp: 141–143 °C; TLC R_f = 0.8 (PE/EA = 40:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.7 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 6.77 (s, 2H), 6.75 (d, J = 3.3 Hz, 2H), 6.49 (d, J = 3.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.2, 128.5, 126.6, 122.8, 121.1, 121.0, 115.0, 109.9, 105.0. IR (KBr) $\tilde{\nu}$ 3102 3048, 2929, 1673, 1461, 1160, 767, 736, 505 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}N_2$ $[M + H]^+$ 259.1230, found 259.1226.

(Z)-1,2-Bis(3-methyl-1H-indol-1-yl)ethene ***(3v)***. Yield 79% (45.2 mg); yellow solid, Mp: 127–129 °C; TLC R_f = 0.4 (PE/EA = 40:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.25–7.16 (m, 4H), 6.63 (s, 2H), 6.62 (s, 2H), 2.20 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.7, 129.0, 124.1, 122.7, 120.4, 119.1, 114.0, 113.9, 109.9, 9.6. IR (KBr) $\tilde{\nu}$ 3048, 2921, 2852, 1675, 1459, 1095, 1018, 736, 599 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{19}N_2$ $[M + H]^+$ 287.1543, found 287.1537.

(Z)-1,2-Bis(4-methyl-1H-indol-1-yl)ethene ***(3w)***. Yield 69% (39.4 mg); yellow solid, Mp: 121–123 °C; TLC R_f = 0.5 (PE/EA = 40:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 8.0 Hz, 2H), 6.97 (d, J = 6.8 Hz, 2H), 6.75 (s, 2H), 6.74 (d, J = 4.4 Hz, 2H), 6.51 (d, J = 3.9 Hz, 2H), 2.53 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.0, 130.6, 128.2, 126.0, 122.9, 121.3, 115.0, 107.5, 103.4, 18.6. IR (KBr) $\tilde{\nu}$ 3048, 2929, 2856, 1673, 1436, 1311, 1159, 746, 715 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{19}N_2$ $[M + H]^+$ 287.1543, found 287.1539.

(Z)-1,2-Di(1H-pyrazol-1-yl)ethene ***(3x)***. Yield 90% (28.8 mg); yellow liquid, TLC R_f = 0.2 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 2H), 7.41 (d, J = 2.0 Hz, 2H), 6.78 (s, 2H), 6.34 (t, J = 2.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.1, 130.4, 118.1, 107.6. IR (KBr) $\tilde{\nu}$ 3035, 2925, 2850, 1885, 1440, 1403, 1047, 792, 620 cm^{-1}. HRMS (ESI) calcd for $C_8H_9N_4$ $[M + H]^+$ 161.0822, found 161.0820.

General procedure for the synthesis of cycloendiamides in Scheme 2: To a mixture of disulfonamide (0.3 mmol, 1.5 equiv), and Cs_2CO_3 (0.6 mmol, 3.0 equiv) was added a solution of 1,1-dichloroethylene (0.2 mmol, 1.0 equiv) in DMF (1.0 mL). The mixture was stirred at 80 °C (heating mantle) for 24 h and the reaction was cooled to room temperature. Then the reaction was quenched by water and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with petroleum ether/ethyl acetate.

1,4-Ditosyl-1,2,3,4-tetrahydropyrazine ***(5a)***. Yield 88% (69.1 mg); white solid, Mp: 191–193 °C; TLC R_f = 0.7 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.2 Hz, 4H), 7.25 (d, J = 8.5 Hz, 4H), 6.20 (s, 2H), 3.07 (s, 4H), 2.43 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.2, 133.8, 129.9, 127.1, 110.7, 41.7, 21.6. IR (KBr) $\tilde{\nu}$ 2925, 2854, 1648, 1353, 1166, 958, 727, 619 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_4S_2$ $[M + H]^+$ 393.0937, found 393.0934.

1,4-Ditosyl-4,5,6,7-tetrahydro-1H-1,4-diazepine ***(5b)***. Yield 88% (71.4 mg); white solid, Mp: 144–146 °C; TLC R_f = 0.6 (PE/EA = 4:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.3 Hz, 4H), 7.29 (d, J = 8.1 Hz, 4H), 5.94 (s, 2H), 3.40 (t, J = 6.3 Hz, 4H), 2.42 (s, 6H), 1.69–1.61 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.0, 135.8, 129.9, 126.9, 114.5, 47.9, 25.9, 21.5. IR (KBr) $\tilde{\nu}$ 3097, 2925, 2854, 1353, 1648, 1166, 958, 727, 619 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{23}N_2O_4S_2$ $[M + H]^+$ 407.1094, found 407.1092.

6,6-Dimethyl-1,4-ditosyl-4,5,6,7-tetrahydro-1H-1,4-diazepine ***(5c)***. Yield 75% (65.1 mg); white solid, Mp: 159–161 °C; TLC R_f = 0.4 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.2 Hz, 4H), 7.29 (d, J = 8.1 Hz, 4H), 5.82 (s, 2H), 3.26 (s, 4H), 2.42 (s, 6H), 1.05 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.1, 135.3, 130.0, 127.0, 114.1, 59.6, 34.2, 24.4, 21.5. IR (KBr) $\tilde{\nu}$ 2960, 2923, 2854, 1353, 1160, 1087, 892, 671, 547 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{27}N_2O_4S_2$ [M + H]$^+$ 435.1407, found 435.1402.

(Z)-1,4-Ditosyl-1,4,5,6,7,8-hexahydro-1,4-diazocine ***(5d)***. Yield 82% (68.9 mg); white solid, Mp: 139–141 °C; TLC R_f = 0.9 (PE/EA = 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.2 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 5.80 (s, 2H), 3.56 (s, 4H), 2.43 (s, 6H), 1.78 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.0, 135.1, 130.0, 127.2, 115.2, 47.9, 25.7, 21.5. IR (KBr) $\tilde{\nu}$ 3069, 2971, 2854, 1643, 1340, 1159, 925, 549 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{24}N_2O_4S_2Na$ [M + Na]$^+$ 443.1070, found 443.1076.

(Z)-1,4-Ditosyl-4,5,6,7,8,9-hexahydro-1H-1,4-diazonine ***(5e)***. Yield 48% (41.7 mg); yellow solid, Mp: 140–141 °C; TLC R_f = 0.6 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.2 Hz, 4H), 7.32 (d, J = 8.0 Hz, 4H), 5.68 (s, 2H), 3.54–3.51 (m, 4H), 2.43 (s, 6H), 1.80–1.76 (m, 4H), 1.67–1.63 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.9, 135.0, 129.8, 127.3, 117.4, 49.6, 30.4, 23.8, 21.6. IR (KBr) $\tilde{\nu}$ 2927, 2850, 1731, 1450, 1338, 1164, 1087, 970, 671, 620, 549 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{27}N_2O_4S_2$ [M + H]$^+$ 435.1407, found 435.1407.

(Z)-1,4-Ditosyl-1,4,5,6,7,8,9,10-octahydro-1,4-diazecine ***(5f)***. Yield 32% (28.6 mg); yellow solid, Mp: 151–153 °C; TLC R_f = 0.8 (PE/EA = 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 4H), 7.32 (d, J = 8.2 Hz, 4H), 5.51 (s, 2H), 3.50 (t, J = 6.2 Hz, 4H), 2.43 (s, 6H), 1.67–1.62 (m, 4H), 1.59–1.53 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.8, 135.2, 129.6, 127.6, 117.4, 47.7, 24.0, 22.7, 21.6. IR (KBr) $\tilde{\nu}$ 2927, 2856, 1650, 1347, 1164, 1093, 817, 711, 545 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{29}N_2O_4S_2$ [M + H]$^+$ 449.1563, found 449.1556.

5-Phenyl-1,4-ditosyl-1,2,3,4-tetrahydropyrazine ***(5g)***. Yield 30% (28.1 mg); yellow solid, Mp: 48–50 °C; TLC R_f = 0.5 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.7 Hz, 4H), 7.35 (t, J = 6.6 Hz, 4H), 7.29 (d, J = 7.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.63 (s, 1H), 3.57 (t, J = 4.2 Hz, 2H), 2.75 (t, J = 4.2 Hz, 2H), 2.46 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 144.8, 144.6, 137.9, 134.0, 133.7, 130.6, 130.2, 128.4, 127.8, 127.6, 127.2, 126.8, 121.4, 116.6, 43.8, 40.7, 21.6, 21.5. IR (KBr) $\tilde{\nu}$ 2919, 2854, 1635, 1349, 1166, 692, 658, 553 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{25}N_2O_4S_2$ [M + H]$^+$ 469.1250, found 469.1248.

General procedure for the synthesis of 1,1-endiamides in Scheme 3. To a mixture of *N*-methylmethanesulfonamide (1.0 mmol, 5.0 equiv), aryl 1,1-dichloroethylene (0.2 mmol, 1.0 equiv), and Cs_2CO_3 (0.6 mmol, 3.0 equiv) was added to DMF (1.0 mL). The mixture was stirred at 120 °C (heating mantle) for 12 h and the reaction was cooled to room temperature. Then the reaction was quenched by water and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with petroleum ether/ethyl acetate.

N,N'-(2-Phenylethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6a)***. Yield 85% (54.1 mg); white solid, Mp: 89–91 °C; TLC R_f = 0.3 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 6.10 (s, 1H) , 3.23 (s, 3H), 3.06 (s, 3H), 3.04 (s, 3H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.0, 132.6, 128.9, 128.7, 128.3, 122.5, 40.1, 39.7, 36.4, 34.4. IR (KBr) $\tilde{\nu}$ 3025, 2929, 2852, 1643, 1332, 1147, 962, 800, 601, 518 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{18}N_2NaO_4S_2$ [M + Na]$^+$ 341.0600, found 341.0595.

N,N'-(2-(o-Tolyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6b)***. Yield 82% (54.5 mg); yellow solid, Mp: 79–81 °C; TLC R_f = 0.3 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (t, J = 4.0 Hz, 1H), 7.24–7.22 (m, 3H), 6.55 (s, 1H), 3.21 (s, 3H), 3.15 (s, 3H), 2.84 (s, 3H), 2.66 (s, 3H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 138.5, 136.8, 133.3, 130.4, 128.5, 127.9, 126.4, 121.8, 40.0, 38.6, 36.1, 35.6, 19.9. IR (KBr) $\tilde{\nu}$ 3023, 2929, 1641, 1328, 1143, 1072, 960, 815, 518 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{21}N_2O_4S_2$ [M + H]$^+$ 333.0937, found 333.0931.

N,N'-(2-(4-(tert-Butyl)phenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6c)***. Yield 72% (53.9 mg); white solid, Mp: 109–111 °C; TLC R_f = 0.2 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 4H), 6.07 (s, 1H), 3.29 (s, 3H), 3.07 (s, 3H), 3.02 (s, 3H), 2.96 (s, 3H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.1, 137.2, 129.5, 128.2, 125.9, 122.6, 40.1, 39.9, 36.4, 34.8, 34.2, 31.2. IR (KBr) $\tilde{\nu}$ 2929, 2962, 2852, 1639, 1459, 1340, 1145, 960, 796, 771, 514 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{26}N_2NaO_4S_2$ [M + Na]$^+$ 397.1226, found 397.1221.

N,N'-(2-(4-Methoxyphenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6d)***. Yield 50% (34.8 mg); yellow solid, Mp: 150–152 °C; TLC R_f = 0.2 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.04 (s, 1H), 3.83 (s, 3H), 3.29 (s, 3H), 3.09 (s, 3H), 3.02 (s, 3H), 2.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.9, 136.2, 129.8, 124.8, 122.5, 114.3, 55.3, 40.0 (double), 36.3, 34.1. IR (KBr) $\tilde{\nu}$ 3008, 2935, 2842, 1338, 1149, 1251, 958, 773, 514 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{21}N_2O_5S_2$ [M + H]$^+$ 349.0886, found 349.0882.

N,N'-(2-(Thiophen-2-yl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6e)***. Yield 70% (45.4 mg); yellow solid, Mp: 174–176 °C; TLC R_f = 0.2 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.12 (t, J = 4.0 Hz, 1H), 6.94 (s, 1H), 3.17 (s, 6H), 3.12 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 135.8, 134.8, 130.5, 129.5, 127.4, 120.8, 40.3, 39.2, 37.1, 35.4 cm^{-1}. HRMS (ESI) calcd for $C_{10}H_{17}N_2O_4S_3$ [M + H]$^+$ 325.0345, found 325.0336.

N,N'-(2-(4-Fluorophenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6f)***. Yield 88% (59.1 mg); yellow solid, Mp: 149–151 °C; TLC R_f = 0.4 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (q, J = 3.6 Hz, J = 8.4 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.51 (s, 1H), 3.19 (s, 3H), 3.15 (s, 3H), 3.08 (s, 3H), 2.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 163.33 (d, J = 245 Hz), 137.62 (d, J = 2 Hz), 130.73 (d, J = 8 Hz), 130.18 (d, J = 4 Hz), 122.0, 116.24 (d, J = 21 Hz), 39.57, 36.30, 35.29 (double). IR (KBr) $\tilde{\nu}$ 3025, 2927, 2852, 1509, 1334, 1151, 962, 779, 559, 512 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{17}FN_2NaO_4S_2$ [M + Na]$^+$ 359.0506, found 359.0500.

N,N'-(2-(4-Chlorophenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6g)***. Yield 92% (64.8 mg); yellow solid, Mp: 139–141 °C; TLC R_f = 0.4 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.85 (s, 1H), 3.07 (s, 3H), 2.87 (s, 3H), 2.82 (s, 3H), 2.69 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.6, 134.4, 131.1, 129.6, 129.1, 121.1, 40.1, 39.8, 36.4, 34.3. IR (KBr) $\tilde{\nu}$ 3015, 2933, 2850, 1643, 1492, 1342, 1143, 1008, 962, 800, 539, 518 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{18}ClN_2O_4S_2$ [M + H]$^+$ 353.0391, found 353.0388.

N,N'-(2-(4-Bromophenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6h)***. Yield 90% (71.2 mg); white solid, Mp: 147–149 °C; TLC R_f = 0.2 (PE/EA = 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.03 (s, 1H), 3.29 (s, 3H), 3.08 (s, 3H), 3.03 (s, 3H),

2.91 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 138.7, 132.1, 131.5, 129.8, 122.7, 121.1, 40.2, 39.8, 36.5, 34.3. IR (KBr) $\tilde{\nu}$ 3019, 2929, 2850, 1639, 1340, 1153, 1010, 516, 746, 615 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{17}BrN_2NaO_4S_2$ $[M + Na]^+$ 418.9705, found 418.9699.

N,N'-(2-(3-Chloro-5-fluorophenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6i)***. Yield 89% (65.9 mg); yellow solid, Mp: 148–150 °C; TLC R_f = 0.4 (PE/EA = 2:1, v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 7.16 (d, J = 9.6 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.02 (s, 1H), 3.28 (s, 3H), 3.09 (s, 3H), 3.04 (s, 3H), 2.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1 (d, J = 249 Hz), 140.2, 136.0 (d, J = 9 Hz), 135.6 (d, J = 11 Hz), 124.5 (d, J = 3 Hz), 119.7, 116.3 (d, J = 25 Hz), 113.4 (d, J = 23 Hz), 40.1, 39.5, 36.6, 34.7. IR (KBr) $\tilde{\nu}$ 3081, 2938, 1639, 1432, 1155, 962, 674, 514 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{17}ClFN_2O_4S_2$ $[M + H]^+$ 371.0297, found 371.0291.

N,N'-(2-(4-Cyanophenyl)ethene-1,1-diyl)bis(N-methylmethanesulfonamide) ***(6j)***. Yield 93% (63.8 mg); white solid, Mp: 158–160 °C; TLC R_f = 0.1 (PE/EA = 2:1, v/v); ^1H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 6.57 (s, 1H), 3.23 (s, 3H), 3.16 (s, 3H), 3.11 (s, 3H), 2.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 140.1, 138.8, 133.0, 129.2, 121.0, 119.2, 110.7, 40.1, 39.3, 36.5, 35.5. IR (KBr) $\tilde{\nu}$ 2925, 2854, 2229, 1639, 1340, 1149, 1012, 960, 612 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{17}N_3NaO_4S_2$ $[M + Na]^+$ 366.0553, found 366.0551.

(Z)-N-(1-Chloro-4-phenylbut-1-en-2-yl)-N-methylmethanesulfonamide ***(6k)***. Yield 67% (36.7 mg); colorless liquid; ^1H NMR (400 MHz, DMSO-d_6): δ 7.31 (t, J = 7.2 Hz, 2H), 7.25–7.20 (m, 3H), 6.24 (s, 1H), 3.09 (s, 3H), 3.01 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 142.5, 141.1, 128.8, 128.7, 126.5, 116.8, 40.0, 36.3, 36.3, 32.9. HRMS (ESI) calcd for $C_{12}H_{16}ClNNaO_2S$ $[M + Na]^+$ 296.0482, found 296.0484.

(Z)-N-(1-Chloro-4-phenylbut-1-en-2-yl)-N,4-dimethylbenzenesulfonamide ***(6l)***.[42] Yield 80% (56.0 mg); colorless liquid; TLC R_f = 0.3 (PE/EA = 10:1, v/v); ^1H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 6.38 (s, 1H), 2.97 (s, 3H), 2.69–2.65 (m, 2H), 2.62–2.58 (m, 2H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 144.0, 142.2, 140.9, 136.9, 130.3, 128.8, 128.6, 127.5, 126.5, 117.3, 36.9, 36.4, 33.0, 21.5.

Procedure for Large Scale Reaction. To a mixture of *N*,4-dimethylbenzenesulfonamide (**2a**) (15.0 mmol, 2.77 g, 3.0 equiv), and Cs_2CO_3 (15 mmol, 4.88 g, 3.0 equiv) was added a solution of 1,1-dichloroethylene (5.0 mmol, 0.40 mL, 1.0 equiv) in DMF (20.0 mL). The mixture was stirred at 80 °C (heating mantle) for 24 h and the reaction was cooled to room temperature. Then the reaction was quenched by water and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The desired products were obtained in 89%yield after purification by flash chromatography on silica gel with petroleum ether/ethyl acetate.

Hydrogenation of product 3a. To the solution of **3a** (0.2 mmol) in MeOH was added Pd/C (0.02 mmol), and then the reaction mixture was stirred at room temperature for 12 h under a balloon pressure of H_2. The reaction mixture was concentrated and purified by silica gel chromatography to afford the product **7a** in 95% yield.

N,N'-(Ethane-1,2-diyl)bis(N,4-dimethylbenzenesulfonamide) ***(7a)***.[37] Yield 95% (79.4 mg); White soild, mp 173–174 °C; purification by chromatography (petroleum ether/EtOAc = 8:1); ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, J = 8.0 Hz, 4H), 7.43 (d, J = 8.0 Hz, 4H), 3.08 (s, 4H), 2.67 (s, 6H), 2.40 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 143.8, 134.5, 130.3, 127.6, 47.9, 35.3, 21.4.

Procedure for the removal of Ts group of 7a. To a solution of sulfonamide **7a** (38.0 mg, 0.1 mmol, 1 eq), NaH_2PO_4 (240.0 mg, 20 eq) and 120 mg of 20% w/w Na/Hg amalgam in THF (1 mL) at 0 °C was added MeOH (1 mL) dropwise. The reaction mixture was stirred for 12 hours at room temperature. The solvent was removed under vacuum. NEt_3 (0.1 mL) was added to the residue in an ice-water bath, and then benzoyl chloride (70.0 mg, 5 eq) in DCM (1 mL) was added slowly. After stirred for 2 h, the reaction mixture was concentrated and purified by silica gel chromatography to afford the product **8a** in 70% yield (two-step).

N,N'-(Ethane-1,2-diyl)bis(N-methylbenzamide) ***(8a)***.[25] Yield 70% (20.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.36 (m, 10H), 3.90 (s, 4H), 3.09 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 136.3, 129.5, 128.4, 126.8, 44.5, 37.9.

Procedure for the synthesis of ynamide In-1 and In-4. To an oven-dried Schlenk tube equipped with a magnetic stir bar was added sulfonamide (0.5 mmol, 1.0 equiv), 1,1-dichloroethene (1.0 mmol, 2.0 equiv), NaH (2.5 mmol, 5.0 equiv) in DMF (2.5 mL) at 80 °C (heating mantle). Upon the reaction completion (monitored by TLC), the residue was purified by silica gel chromatography to afford the desired products **In-1** and **In-4**.

N-Ethynyl-N,4-dimethylbenzenesulfonamide ***(In-1)***.[23a] Yield 95% (99.3 mg); white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 3.06 (s, 3H), 2.70 (s, 1H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.0, 133.2, 129.9, 127.8, 77.6, 57.5, 38.9, 21.7.

N-Methyl-N-(phenylethynyl)methanesulfonamide ***(In-4)***.[23a] Yield 90% (94.0 mg); yellow solid; ^1H NMR (400 MHz, DMSO-d_6): δ 7.42–7.40 (m, 2H), 7.38–7.35 (m, 3H), 3.30 (s, 3H), 3.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 131.6, 129.1, 128.6, 122.6, 84.8, 68.6, 39.6, 36.9.

Procedure for the synthesis of In-2. To an oven-dried Schlenk tube equipped with a magnetic stir bar was added *N*,4-dimethylbenzenesulfonamide (1.0 mmol, 1.0 equiv), 1,1-dichloroethene (1.0 mmol, 1.0 equiv), NaH (2.0 mmol, 2.0 equiv) in DMF (2.5 mL) at 80 °C (heating mantle) for 12 h. Upon the reaction completion (monitored by TLC), the residue was purified by silica gel chromatography to afford the desired products **In-2**.

(Z)-N-(2-Chlorovinyl)-N,4-dimethylbenzenesulfonamide ***(In-2)***. Yield 40% (98.0 mg); yellow liquid; ^1H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 6.66 (d, J = 6.1, Hz, 1H), 5.91 (d, J = 6.1 Hz, 1H), 3.08 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 144.8, 134.3, 130.6, 128.6, 127.6, 107.2, 36.0, 21.5. HRMS (ESI) calcd for $C_{10}H_{13}ClNO_2S$ $[M + H]^+$ 246.0350, found 246.0346.

Procedure for the synthesis of In-3. To the mixture of ethynylbenzene (10 mmol), TBAF·$3H_2O$ (1 mmol), K_2CO_3 (10 mmol), and CCl_4 (6 mL) was added and the mixture was stirred at room temperature for two hours. After completion of the reaction, the solution concentrated under reduced pressure. The residue was purified by column chromatography to give alkynyl chlorides **In-3**.

(Chloroethynyl)benzene ***(In-3)***.[23b] Yield 85% (1.16 g), colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.34–7.27 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 132.0 128.6, 128.4, 122.2, 69.4, 68.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Copies of ^1H and ^{13}C NMR spectra for all compounds
Crystallographic data for **3u** (CIF)
Crystallographic data for **5d** (CIF)
Crystallographic data for **6a** (CIF)

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Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (21778025 and 21762021), and the Science and Technology Project of Jiangxi Provincial Education Department (GJJ150297and GJJ150324).

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